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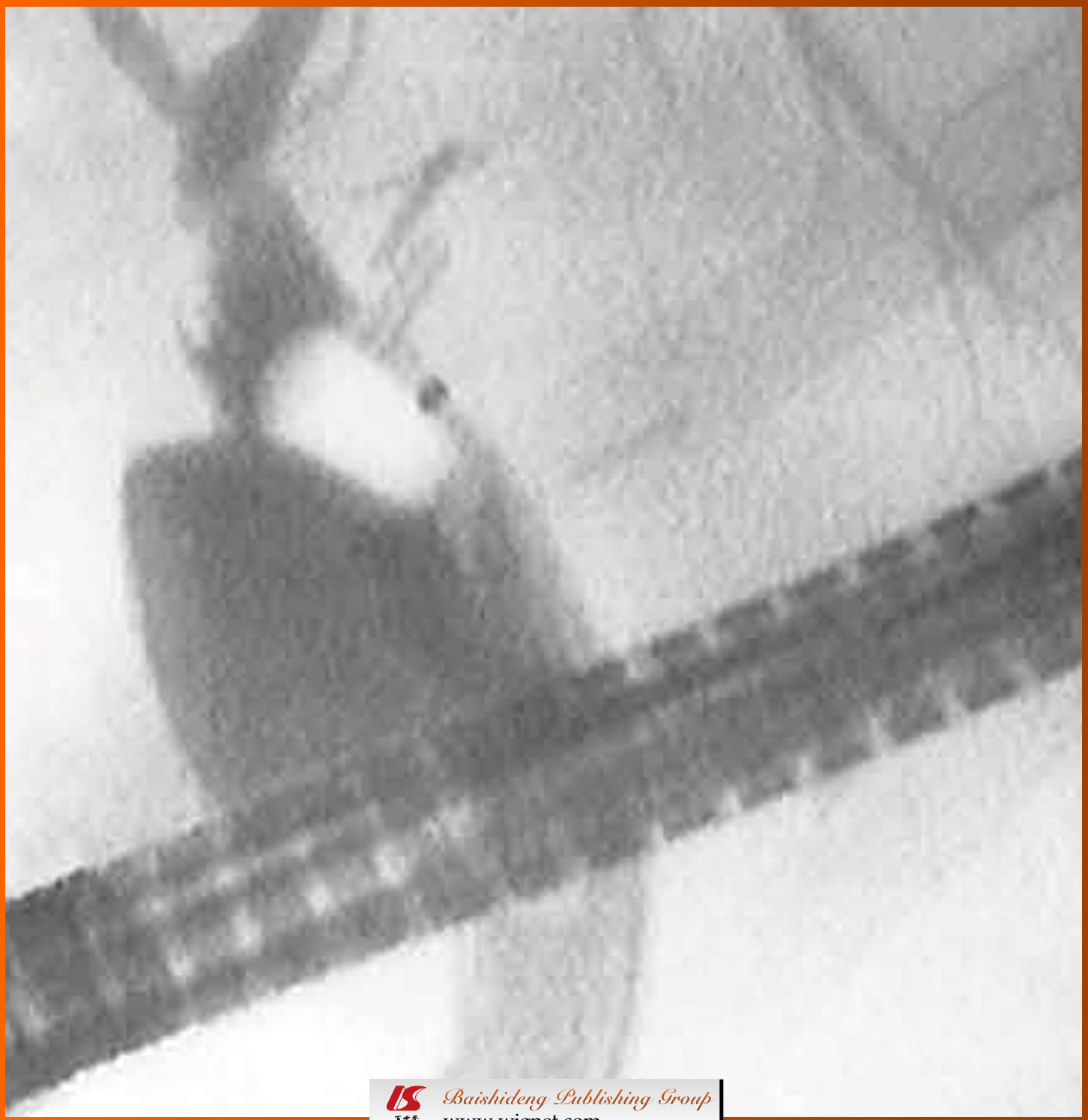

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EDITORIAL

Endoscopic treatments for chronic radiation proctitis

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Abstract

Chronic radiation proctitis is a complication that occurs in patients who receive radiation therapy for pelvic malignancies. The common presentation is with rectal bleeding, but also rectal pain, diarrhea, tenesmus and even passage of mucus can occur. The optimal treatment of bleeding due to radiation proctitis remains unclear. Among various therapeutic options, medical management is generally ineffective and surgical intervention has a high incidence of morbidity. Promising advances have been made in endoscopic therapy, including argon plasma coagulation (APC), formalin application as well as new techniques such as radiofrequency ablation and cryoablation. APC is a safe, highly effective and long-lasting therapy in patients with rectal bleeding associated with radiation proctitis. It has been shown that several sessions of APC reduce the rate of bleeding and therefore the blood transfusion requirements. Moreover, the effect of treatment is long lasting. However, best results are achieved in patients with mild to moderate radiation proctitis, leaving space for alternative treatments for patients with more severe disease. In patients with severe or refractory radiation proctitis intra rectal formalin application is an appropriate treatment option. Radiofrequency ablation and cryoablation have shown efficacy as alternative methods in a limited number of patients with refractory chronic radiation proctitis.

Key words: Radiation proctitis; Endoscopic treatment; Argon plasma coagulation; Formalin application; Cryoablation; Radiofrequency ablation

Core tip: Chronic radiation proctitis presents with rectal bleeding, pain, diarrhea, tenesmus and passage of mucus. Among other therapeutic options, endoscopic therapy with argon plasma coagulation (APC) is a safe and highly effective in patients with rectal bleeding associated with radiation proctitis. Although best results are achieved in patients with mild to moderate lesions, APC therapy reduces the rate of bleeding and blood transfusion requirements and its effect last for long. In patients with severe or refractory radiation proctitis intra rectal formalin application,radiofrequency ablation and cryoablation have shown efficacy in a limited number of patients.

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INTRODUCTION

The rectum is often injured during pelvic radiation due to its fixed position and its anatomical proximity to the radiated target organ such as prostate and cervix. Radiation proctitis, usually mild, is a complication that occurs in up to 15% of patients who receive radiation therapy for pelvic malignancies. Radiation damage may occur in

acute or chronic form. Acute complications are seen during or up to 6 wk after radiotherapy, whereas late radiation injury usually occurs in the first 2-3 years after treatment[1-3]. A change in the treatment practices has recently occurred toward escalating radiation doses with improved local control. Conformal radiotherapy of pelvic tumors focuses on reducing irradiation of organs at risk such as rectum[4,5]. Although the incidence of complications has been reduced using this new technology, rectal wall damage continues to be an important side effect of pelvic radiotherapy[6-9].

CLINICAL FEATURES AND TREATMENT OPTIONS

The common presentation of radiation proctitis is with rectal bleeding, but also rectal pain, diarrhea, tenesmus and even passage of mucus can occur. In approximately 35% of patients the symptoms are mild and settle spontaneously over several months without any treatment. However, rectal bleeding due to chronic radiation proctitis may lead to anemia and necessitate repeated blood transfusions. Medical treatment with salicylates, sucralfate or corticosteroids enemas is usually not beneficial[10-14]. Thus, alternative treatments including endoscopic ones have been used. Among endoscopic treatments, argon plasma coagulation (APC), a nontouch thermo ablative therapy, is increasingly recommended as first line treatment for patients with radiation proctitis.

APC

For evaluation of endoscopic severity of radiation proctitis, a scoring system with measurement of three independent factors (telangiectasia distribution, surface area involved and the presence of fresh blood) was proposed[15] (Table 1). A cumulative score was calculated and three categories of endoscopic severity of radiation proctitis were derived: grade A (mild, 2 points), grade B (moderate, 3 points), and grade C (severe 4/5 points).

Recently, we prospectively investigated in a large number of patients the effectiveness of APC in treating patients with various endoscopic grading of radiation proctitis (mild, moderate, and severe) using a modified scoring system with measurement of two independent factors for evaluation of endoscopic severity: telangiectasia distribution and surface area involved[16]. For APC application, an ERBE APC 300 (ERBE Elektromedizin, Tubingen, Germany) argon delivery unit and a 2.3 mm diameter front-firing APC probe inserted through the working channel of the flexible sigmoidoscopy were used. The argon flow rate and the electrical power were set at 2.0 L/min and 40 W, respectively.

Our results showed that APC was successful in all patients with mild and in almost all patients with moderate radiation proctitis. In contrary, in the presence of severe mucosal damage APC failed in 50% of patients. Patients with mild proctitis required 1-2 sessions of APC, while patients with moderately to severe form required a statistically significantly higher number of APC sessions. Our results were in accordance with the existing literature; APC is the preferred method in patients with rectal bleeding associated with mild to moderate radiation proctitis, while in cases of severe and diffuse involvement of the rectum multiple treatments sessions are required and success is less certain[17-26]. We also presented long-term follow up of patients successfully treated with APC and showed that during a follow-up of a mean of 17.9 mo (range 6-33 mo) about 90% of these patients remain in clinical remission.

Table 1 Endoscopic classification of radiation proctitis

Distribution of telangiectasias	Surface area covered by telangiectasias	Presence of fresh blood
Distal rectum (within 10 cm from anal verge): 1 point Entire rectum +/- sigmoid (more than 10 cm from anal verge: 2 points	Less than 50%: 1 point More than 50%: 2 points	No fresh blood: 0 points Fresh blood : 1 point

APC parameters: Number of APC sessions

Till now there is no consensus for the optimal APC settings (power and gas flow rate) for successful and safe coagulation. In the literature the power setting for APC ranged from 25-80 W and for the argon flow rate ranged from 0.6-2 L/min[21]. In our study low-power settings (argon flow rate and electrical power were set at 2.0 L/min and 40 W, respectively) were used. Although these settings were among the lowest reported in the literature seemed adequate for successful coagulation and also carried low rate of complications.

The optimal number of treatment sessions is still unknown. APC is traditionally not applied in 1 treatment session, particularly in patients with severe disease, because of the concern regarding strictures formation. For therapeutic success, the median number of sessions per patient was ranged from 1 to 3.7[27]. Similarly to previous reports, multiple sessions of APC were performed in our patients with a maximum of eight sessions in a patient with severe radiation proctitis.

FORMALIN APPLICATION

In severe cases of radiation proctitis and in cases resistant to other treatment modalities intra-rectal formalin is a useful strategy[28]. Formalin is a mixture of methanol and formaldehyde which covalently binds to proteins, and causes cell necrosis. It acts as a haemostatic agent causing chemical cauterization to control bleeding from telengiectatic mucosal and submucosal vessels. Most used 4% dilute formalin applied to the rectum mucosa either by direct application of formalin-soaked gauze or by 'instilling' the solution in single or multiple aliquots down the operating channel of a colonoscope. Various volumes of formalin and different mucosal contact time were re-

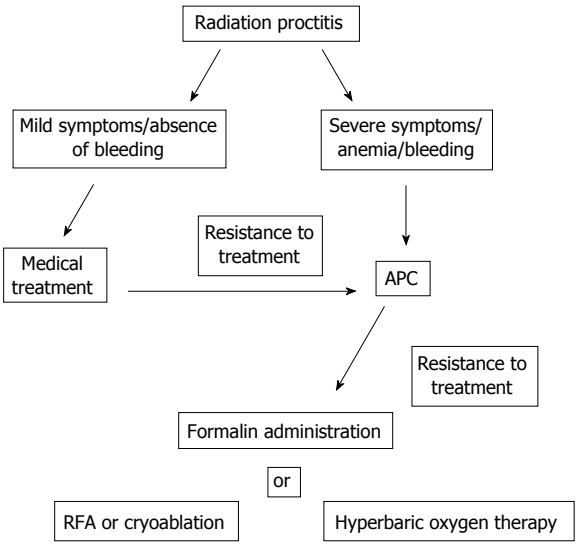

Figure 1 Treatment options for patients with radiation proctitis. APC: Argon plasma coagulation; RFA: Radiofrequency ablation.

ported. Mean number of treatment ranged from 1.1-3.4 per patient. Cessation of bleeding occurred in most studies in the range of 60%-100%[28-38]. Median follow ups to a period of two years have shown only a minimal relapse among responders. Reported side effects include anal stenosis, fissures, fecal incontinence and ulceration of mucosa.

RADIOFREQUENCY ABLATION

The theoretical benefits of radiofrequency ablation are extrapolated are studies treating gastric antral vascular ectasia and Barrett's esophagus. Effective control of lower gastrointestinal bleeding in patients with refractory chronic radiation proctitis using radiofrequency ablation (RFA) with the Halo90 system has been recently reported[39-41]. RFA was performed in an outpatient practice using a single use Halo90 electrode catheter that was fit on the distal end of a standard flexible sigmoidoscope. An energy density of 12 J/cm^2 at a power density of 40 W/cm^2 was chosen based on previous studies performed, which showed no transmural injury at these settings. In all cases, the procedure was well tolerated and hemostasis was achieved after 1 or 2 RFA sessions. Re-epithelialization of squamous mucosa was observed over areas of prior hemorrhage. Patients were symptom free on follow-up up to 19 mo after treatment.

CRYOABLATION

Cryoablation involves noncontact application of liquid nitrogen or carbon dioxide gas to tissue for superficial ablation[42]. Cryospray ablation has been used to treat esophageal high-grade dysplasia and early cancer. In two recent studies endoscopic cryoablation was performed in 20 patients with hemorrhagic radiation proctitis[43,44]. Endoscopic severity and subjective clinical scores improved in all patients. Cryoablation was performed with a catheter placed through the endoscope under direct endoscopic visualization to approximately 0.5 to 1.0 cm from the tip of the endoscope. The spray was applied for 5 s and the treatment area was then allowed to thaw no less than 45 s before initiating subsequent cryospray applications. Required sessions ranged from one to four and endoscopic score significantly improved, as well as, rectal pain and rectal bleeding. Although patients tolerated the procedure well, one patient experienced a cecal perforation[43] after therapy probably due to over insufflation during the procedure.

ALTERNATIVE TREATMENT OPTIONS (HYPERBARIC OXYGEN THERAPY)

Hyperbaric oxygen therapy (HBOT) is the use of 100% oxygen at pressures greater than atmospheric pressure. The patient breathes 100% oxygen intermittently, while the pressure of the treatment chamber is increased to greater than 1 atmosphere absolute. HBOT promotes angiogenesis and hyperoxygenation to the irradiated tissues. Increasing the oxygen content to the surrounding tissues markedly increases the overall oxygen gradient between these tissues and the central hypoxic area. The increased oxygen gradient is the essential catalytic factor for angiogenesis[45].

Unfortunately, the research into the use of HBOT in radiation proctitis is heterogeneous in terms of duration of treatment, number of treatments and pressures of HBOT used. Warren *et al*[46] reported a response rate of 64%, with complete symptomatic resolution in 57%, in 14 cases of radiation proctitis treated with varying doses of HBOT. Girnius *et al*[47] reported nine patients with refractory haemorrhagic proctitis who had failed previous therapy; all patients had some response to HBOT and seven had complete resolution of their rectal bleeding. Jones *et al*[48] also found that 8 out of 10 patients with refractory radiation proctitis responded to HBOT. Dall'Era *et al*[49] found that a total of 48% of 27 patients with treatment-resistant radiation proctitis had complete resolution of bleeding and 28% of them had significantly fewer bleeding episodes. Similarly, a recent study reported that HBOT significantly improved the healing responses in patients with refractory radiation proctitis, generating an absolute risk reduction of 32% (number needed to treat of 3)[50]. Although HBOT appears to be of value for refractory radiation proctitis, the quality of current data is poor with marked variability between studies. Moreover, the cost of HBO is high enough, and it is not widely applicable.

CONCLUSION

Based on currently data, APC is the favored treatment for bleeding from chronic radiation proctitis. APC is a safe, highly effective and long-lasting therapy in patients with rectal bleeding associated with endoscopic mild

radiation proctitis. In severe radiation proctitis multiple APC applications are usually required and success is likely to be more limited. In these patients other treatment options such as intra rectal formalin application should be considered. New therapeutic endoscopic modalities, including radiofrequency ablation and cryoablation, showed effective control of lower gastrointestinal bleeding in patients with refractory chronic radiation proctitis. As the number of patients treated with these new modalities was limited, further studies are needed to identify their safety and efficacy. Figure 1 summarized the treatment modalities available for patients with radiation proctitis.

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ORIGINAL ARTICLE

Implementation of a polling protocol for predicting celiac disease in videocapsule analysis

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Abstract

AIM: To investigate the presence of small intestinal villous atrophy in celiac disease patients from quantitative analysis of videocapsule image sequences.

METHODS: Nine celiac patient data with biopsy-proven villous atrophy and seven control patient data lacking villous atrophy were used for analysis. Celiacs had biopsy-proven disease with scores of Marsh Ⅱ-ⅢC except in the case of one hemophiliac patient. At four small intestinal levels (duodenal bulb, distal duodenum, jejunum, and ileum), video clips of length 200 frames (100 s) were analyzed. Twenty-four measurements were used for image characterization. These measurements were determined by quantitatively processing the videocapsule images *via* techniques for texture analysis, motility estimation, volumetric reconstruction using shape-from-shading principles, and image transformation. Each automated measurement method, or automaton, was polled as to whether or not villous atrophy was present in the small intestine, indicating celiac disease. Each automaton's vote was determined based upon an optimized parameter threshold level, with the threshold levels being determined from prior data. A prediction of villous atrophy was made if it received the majority of votes ($\geqslant$ 13), while no prediction was made for tie votes (12-12). Thus each set of images was classified as being from either a celiac disease patient or from a control patient.

RESULTS: Separated by intestinal level, the overall sensitivity of automata polling for predicting villous atrophy and hence celiac disease was 83.9%, while the specificity was 92.9%, and the overall accuracy of automata-based polling was 88.1%. The method of image transformation yielded the highest sensitivity at 93.8%, while the method of texture analysis using subbands had the highest specificity at 76.0%. Similar results of prediction were observed at all four small intestinal locations, but there were more tie votes at location 4 (ileum). Incorrect prediction which reduced sensitivity occurred for two celiac patients with Marsh type Ⅱ pattern, which is characterized by crypt hyperplasia, but normal villous architecture. Pooled from all levels, there was a mean of 14.31 ± 3.28 automaton votes for celiac *vs* 9.67 ± 3.31 automaton votes for control when celiac patient data was analyzed ($P < 0.001$). Pooled from all levels, there was a mean of 9.71 ± 2.8128 automaton votes for celiac *vs* 14.32 ± 2.7931 automaton votes for control when control patient data was analyzed ($P < 0.001$).

CONCLUSION: Automata-based polling may be useful to indicate presence of mucosal atrophy, indicative of celiac disease, across the entire small bowel, though this must be confirmed in a larger patient set. Since the method is quantitative and automated, it can potentially eliminate observer bias and enable the detection

of subtle abnormality in patients lacking a clear diagnosis. Our paradigm was found to be more efficacious at proximal small intestinal locations, which may suggest a greater presence and severity of villous atrophy at proximal as compared with distal locations.

Key words: Automata; Celiac disease; Small intestine; Videocapsule; Villous atrophy

Core tip: Videocapsule endoscopy images from celiac disease patients and controls were extracted from video clips and compared using image processing. The image processor consists of 24 automated measurements, or automata. The values of these automata were polled for yes or no vote, which depended on a predetermined threshold value set for each measurement. The polling process predicted whether the patient had celiac disease, based on majority vote from the 24 automata. Celiac patients with even subtle villous atrophy were distinguished from controls by this method. For 16 patients, the overall sensitivity, specificity, and accuracy of the method was 83.9%, 92.9%, and 88.1%, respectively.

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INTRODUCTION

Videocapsule endoscopy has been used in clinical practice for over 10 years as a way to visualize the entire small intestine in patients with known or suspected celiac disease, inflammatory bowel disease, and other diseases where lesions are likely to be present in this region[1-5]. The capsule is swallowed and then provides two high resolution images per second from all regions of the gastrointestinal system, including distal areas where standard endoscopy cannot be used. Based on findings that show the videocapsule to be helpful in the identification of abnormalities consistent with celiac disease[6-9], there is increasing use in clinical practice.

When villous atrophy is present in the small intestine, as confirmed using standard endoscopy with biopsy, abnormalities are often evident in the endoscopic images including fissuring, mosaic pattern, and scalloping of mucosal folds[10-14]. These abnormalities are often patchy in location, being interspersed with more normal-appearing mucosal surface. We have developed quantitative analyses of videocapsule endoscopy images[15-19]. In these studies, it was hypothesized that patchy small intestinal abnormality would result in quantitative differences in the digital images. In patient image sequences with substantial heterogeneity, caused by visually evident abnormalities including fissuring, mosaic pattern, and scalloping of mucosal folds in celiac patients, the image texture, which is the pixel-to-pixel variability in brightness level, would be expected to increase. Furthermore, it was hypothesized that in celiac patients, small bowel regions with villous atrophy may have abnormal motility, manifested as changes in oscillations in videocapsule image brightness. These hypotheses were validated in our initial studies[15-19], and it was determined that patients with active celiac disease *vs* controls could be classified using threshold levels of the quantitative parameters used to measure image texture and oscillations in image brightness levels.

Although in prior work, classification of celiac *vs* control image sequences was done using several variables and multidimensional nonlinear discriminant functions[15-19], development of such functions without user intervention is computationally intensive. Herein, a means to automatically classify celiac *vs* control image sequences using quantitative texture and oscillation variables is described using automata-based polling[20].

MATERIALS AND METHODS

Clinical procedure and data acquisition

Retrospective videocapsule endoscopy data was obtained from 9 celiac patients and 7 control patients. In all except one patient, six biopsy specimens were obtained during endoscopy and then analyzed using light microscopy. In one hemophiliac patient, biopsies were not obtained. The celiac patients had recently begun a gluten-free diet, except for one patient with hemophilia and positive anti-endomysial antibody who had not yet started the diet. These patients had a diagnostic biopsy with Marsh grade Ⅱ-ⅢC lesions, and positive serology for celiac disease upon diagnosis. These patients were still considered to have active celiac disease due to the fact that a period of months is often needed for the diet to cause a reduction in small intestinal villous atrophy[1-4].

For the videocapsule endoscopy study, informed consent was obtained. Exclusion criteria were age under 18 years, history of or suspected small bowel obstruction, dysphagia, presence of electromedical implants, previous gastrointestinal surgery, pregnancy, or nonsteroidal anti-inflammatory drug use during the previous month. For analysis, only complete videocapsule endoscopy studies, reaching the colon, were used. The study was approved by the Internal Review Board at Columbia University Medical Center, with all patients being evaluated from May 1, 2008 to July 31, 2009.

The PillCam videocapsule (ver. SB2, 2007, Given Imaging, Yoqneam, Israel)[21] was used for imaging. The device includes a recorder unit, battery pack, wireless interface, and real-time viewer. The capsule acquires digital image frames at a 2/second rate, with a resolution of 576 × 576 pixels, and it is a single-use pill-sized device[21]. For each patient undergoing the procedure, abdominal leads were placed on the upper, mid, and lower abdomen, and a belt containing the data recorder was positioned at waist

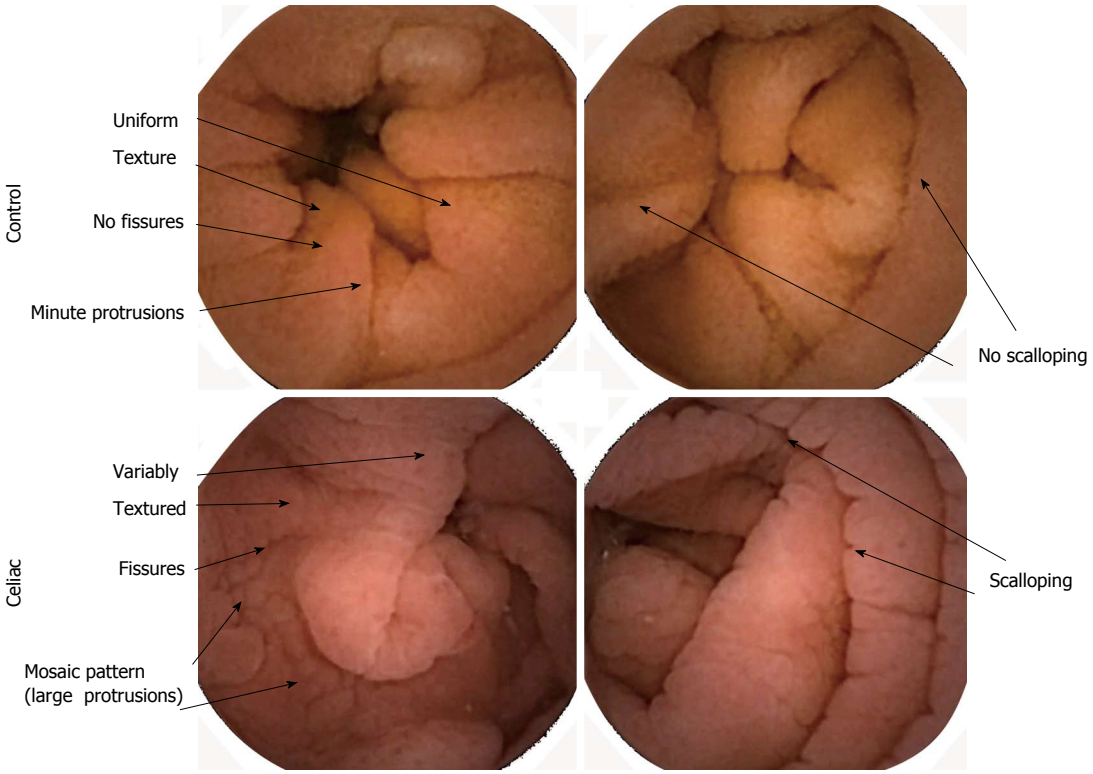

Figure 1 Color images from videocapsule device. Differences in celiac images where villous atrophy is present are shown *vs* control. Control images have a more uniform texture at the mucosal surfaces. Celiac surfaces have a rougher appearance, with more fissuring, large protrusions, and scalloping along the folds.

level. All subjects swallowed the videocapsule with radio transmitter in the early morning with approximately 200 cc's of water and 80 mg simethicone after an overnight fast without bowel preparation. Subjects were allowed to drink water two hours after capsule ingestion, and to eat a light meal four hours after capsule ingestion. The recorder was then removed, and the data downloaded to a HIPAA-compliant PC-based computer console equipped with RAPID software (ver. 5, 2008, Given Imaging, Yoqneam, Israel). The RAPID software was used for review and clinical report generation during the videocapsule endoscopy studies. Videos were interpreted by three experienced gastroenterologists. Selected video clips, 200 image frames in length (100 s of data), were exported to external media without patient identifiers for quantitative analysis. Images were acquired immediately distal to the pylorus corresponding to the proximal duodenum (location 1). The total small bowel transit time of the videocapsule was divided into tertiles. Video clips were also acquired from each of the three tertiles for each patient (locations 2, 3, and 4, roughly corresponding to the distal duodenum, the jejunum, and the proximal ileum, respectively).

Data preprocessing

From each color videoclip, 200 grayscale images (*i.e.*, 256 brightness levels, 0 = black, 255 = white) were extracted using Matlab Ver. 7.7, 2008 (The MathWorks, Natick, MA, United States). The image data were ported into software created by the authors, which was coded using the Intel Visual Fortran Compiler (ver. 9.0, 2005, Intel Corporation, Santa Clara, CA, United States).

Implementation of automata-based polling

A procedure termed automata-based polling[20] was implemented for analysis of videocapsule images. Automata are defined as functional nodes in a computational network, and they are used for quantitative analysis of a physiological system. At each node, a calculation is done based on a predefined set of rules and equations. Quantitative measurements devised previously were used to develop the network of automata for polling[15-19]. The following methods were used:

Texture analysis: Texture analysis[15] is based on measurement in 10 × 10 subimage regions from each 576 × 576 pixel image in the sequence, excluding edge pixels. Texture was defined by the measurement of standard deviation in pixel grayscale level in each subimage. The average grayscale level (brightness) and the standard deviation in grayscale level (image texture) of each subimage were averaged for all subimages in each image. The mean in brightness and texture over 200 frames (100 s) were used as automata measurements. It was expected that brightness would decrease with increase in abnormal features due to villous atrophy in active celiac images. Similarly, it was expected that texture would increase in celiac patient images due to heterogeneity in the mucosal surface characteristics. In Figure 1 are shown examples of control and celiac images in color. The control images have uniform texture, no fissures, and minute protrusions. There are few folds and no scalloping of folds. In

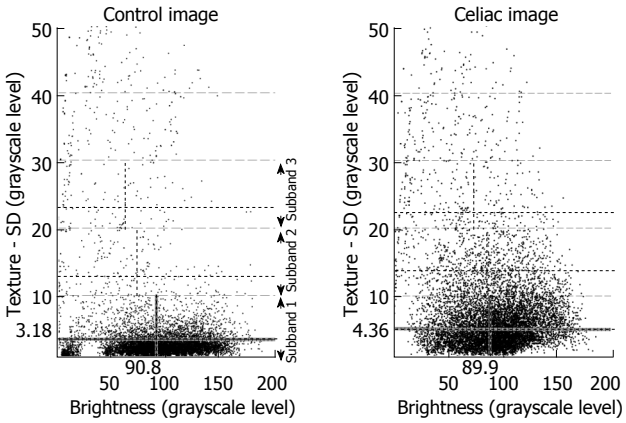

Figure 2 The method of using subbands in the standard deviation of image texture. Subbands are shown to the right of the control scatterplot. Mean values for each of the two variables are noted as hatched lines in each subband. The subband characteristics differ in celiac *vs* control videoclip series. In the control scatterplot the points are concentrated at low values of standard deviation in texture. In the celiac scatterplot the points are concentrated at higher values of standard deviation in texture. Thus the celiac image data has a greater variability of pixel gray level, which can be used to distinguish it from the control image data.

contrast, the celiac images have variable texture, presence of fissuring, and a mosaic pattern of large protrusions. There are more folds and scalloping of folds.

A third parameter was derived from the variability in frame-to-frame mean image brightness over the sequence of 200 images. The largest peak in the frequency spectrum of this measurement is termed the dominant frequency[15]. Its inverse, the dominant period, was used as a third automaton measurement, and it is reflective of oscillations in image brightness over the 200 image sequence. Thus three automata were developed from the texture analysis method. Mean values for celiac and control from the prior study[15] were used to develop threshold levels for classification. The threshold levels used were the midpoints between celiac and control data. An input videoclip sequence with a measured value closer to the celiac mean as compared with the threshold level would be counted as a vote for celiac. An input videoclip sequence with a measurement value closer to the control mean as compared with the threshold level would be counted as a vote for control.

Extraction from texture subbands: These measurements are made by plotting the brightness and texture of individual subimages. In the scatterplot, subimage values for all 200 images are included. The scatterplot is then divided into subbands. This is shown in Figure 2. Subband 1 is defined as including those subimages having a texture of 0-10 as measured by the standard deviation in pixel brightness. The average texture and the average brightness level within this subband, shown as hatched lines in the figure, along with the number of subimage values contained in the subband, are used as measurement values. This is repeated for subband 2 (texture of 10-20 as measured by the standard deviation in pixel brightness) and subband 3 (texture of 20-30 as measured by the standard deviation in pixel brightness). Thus there are 9 measurements in all, 8 of which were used for automata. The texture for subband 3 was not used as an automaton, since the mean values from previous data for celiac and controls overlapped. Threshold levels for classification of celiacs *vs* controls were determined from previous data[16]. The scatterplots of Figure 2 suggest that celiacs tend to have greater texture in the 0-10 subband, which is the subband consisting of most of the subimages. Also, as shown in Figure 2, celiacs tend to have less total pixels in the 0-10 subband but more total pixels in the 10-20 and 20-30 subbands, suggesting that celiac subimages have greater texture variability (their presence is at the higher variability subbands) as compared with controls.

Motility estimation: The darkest 10000 pixels per image were selected as an approximation of the view along the luminal axis of the small intestine. Variation in the centroid of this region (mean pixel location along the x and y axes), and variation in the maximum width of the region, were used as estimates of motility. The threshold values for the three automata to distinguish celiac from control data were based on a prior study[17]. In the prior study it was found that celiacs tend to have more variability in the x and y position of the lumen, perhaps due to irregular motility.

Volumetric method: Two-dimensional images were converted to three dimensions using shape-from-shading principles[18]. The third dimension is formed according to the grayscale level of each pixel. The principle is shown in Figure 3. Darker pixels and darker image regions are at greater depth along the z-axis in the three-dimensional representation at right, while brighter pixels and image regions are at shallower depth. Examples of corresponding locations in two and three dimensions are noted by asterisks. The text at left in the two-dimensional image is shown for reference in the three-dimensional representation. Based on the three-dimensional structure, a syntax was developed to detect and measure luminal wall protrusions. Protrusions were quantified according to their height, width, and number per image. Means and standard deviations for each 200 image sequence were used as automata values. Threshold values for polling were obtained from a prior study[18]. In this study it was shown that active celiac patients tend to have less protrusions per image, and that these protrusions are greater in width and height, and in the standard deviation, or variability, in the width and height dimensions[18]. This may be due the blunted and perhaps clumped nature of villi when there is atrophy.

Image transformation to basis images: Transformed images contain salient features from the sequence of original videocapsule images and are termed basis images[19]. The purpose of transformation is to retain repetitive components in the sequence of images, while

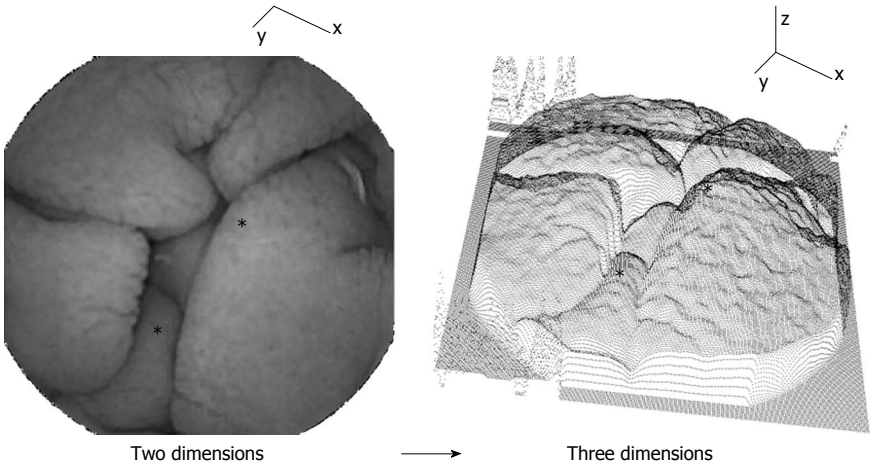

Figure 3 Image transformation from two to three dimensions. Coordinate axes are shown for reference. Examples of corresponding landmark locations are noted by asterisks. The gray levels of the two-dimensional endoscopic image at left are converted to a depth along the z axis in the three-dimensional projection at right. The characteristics of the surface protrusions in the three-dimensional image are used for distinguishing celiac from control patient data.

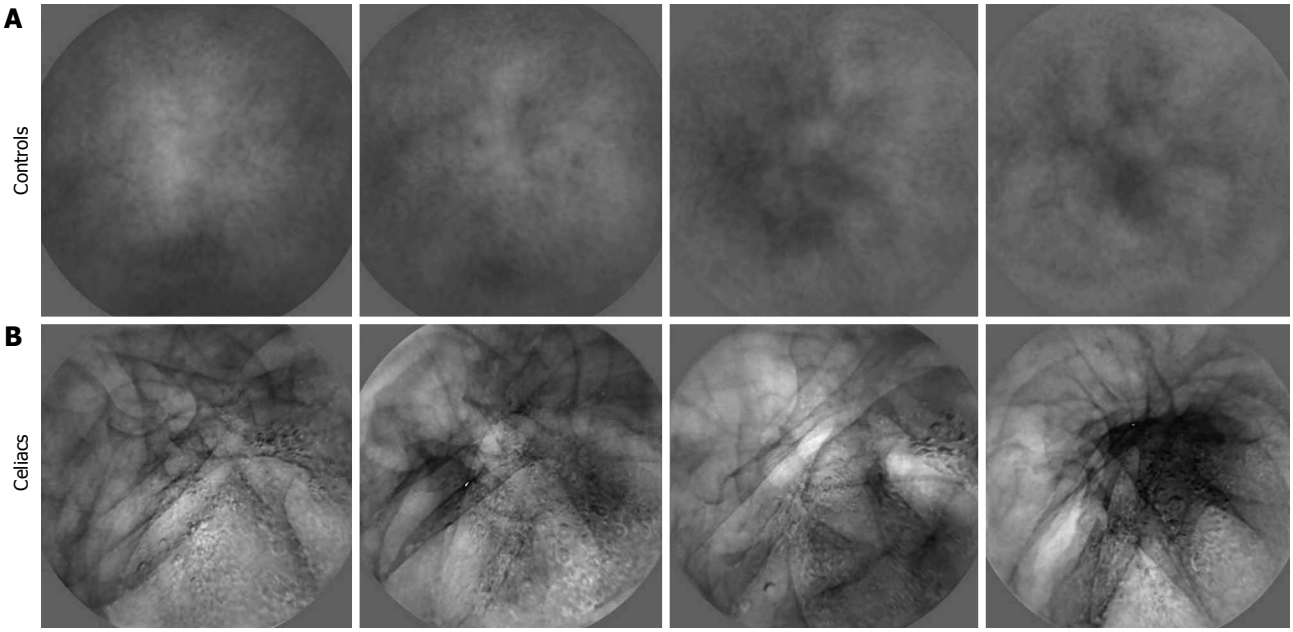

Figure 4 Examples of basis images derived from celiac *vs* control videoclip series. A: Control; B: Celiacs. The celiac basis has more heterogeneous structure. There are dark lines running through the celiac basis images as well as black and white blotches. In contrast, the control basis images are mostly uniform, with only diffuse features being evident.

removing noise and extraneous substances such as air bubbles and opaque fluids[19]. Analysis of basis images rather than the original images makes the measurements more robust to features that were not a part of the actual luminal surface. Examples of basis images are shown in Figure 4. Note that the control basis images appear smoother and with less change in content as compared with the celiac basis images. The control basis contains more uniform homogeneous structure. The celiac basis images vary substantially in content and brightness. These basis images are indicative of the original salient content in each series of images. The parameters measured from basis images were the mean texture and standard deviation in brightness over the basis image series. The dominant period was also measured, as calculated from the original 200 image sequence. A separate spectrum was constructed for each x, y pixel location (576 × 576 pixels in total)[19]. These separate spectra were then averaged to form a mean spectrum from which the dominant period was determined. An example is shown in Figure 5. Control spectra generated from image series acquired from locations 3 and 4 have highest peak (dominant period) at 4.0-4.5 s. Celiac spectra generated from image series acquired from locations 3 and 4 have highest peak (dominant period) at 6-8.5 s. This was typical of all spectra-celiacs tended to have longer dominant periods, perhaps due to an increase in motility at areas of injury. The threshold values for vote-casting to classify the data were

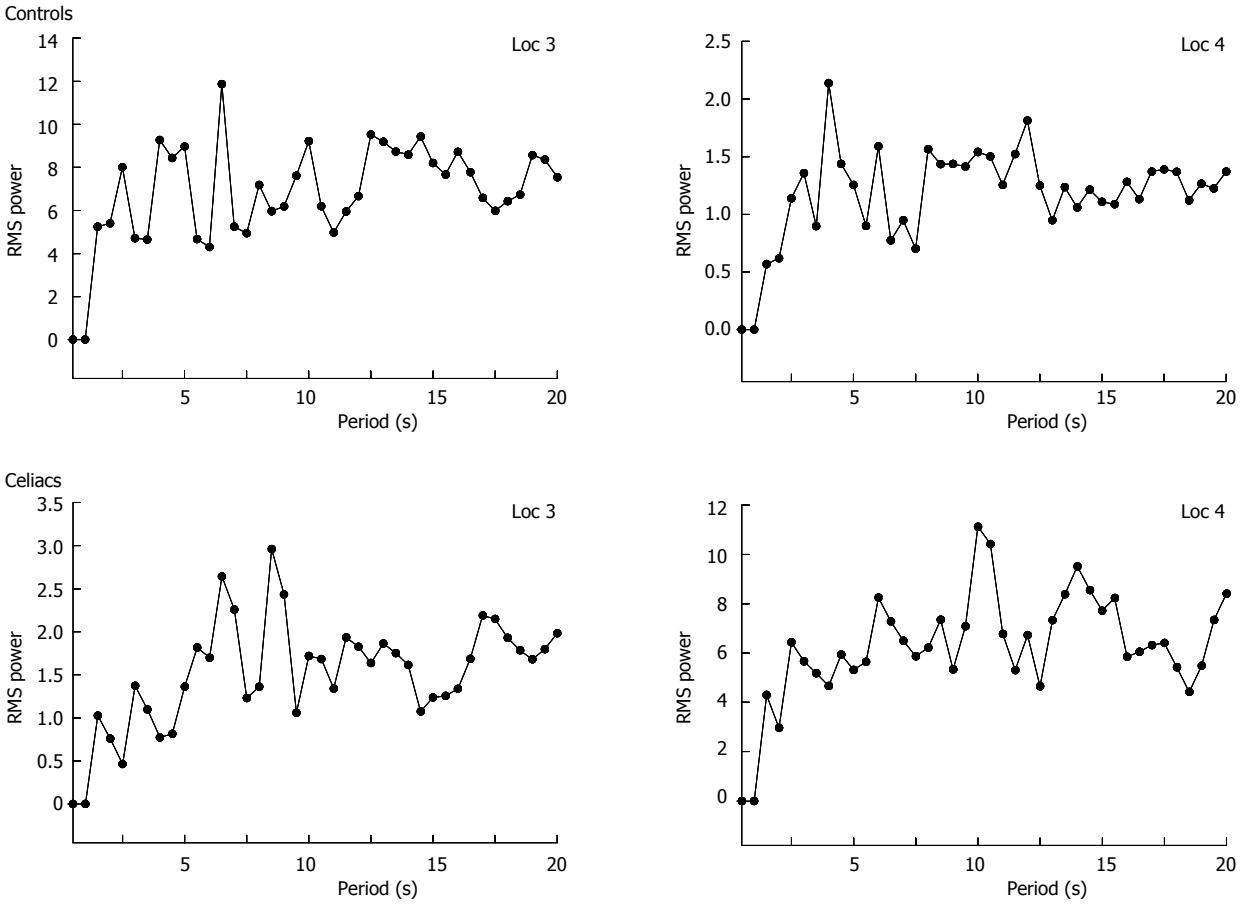

Figure 5 Examples of frequency spectra for celiac *vs* control. The dominant period (DP) is the highest peak in the physiologic range, taken as 1-20 s per oscillation. The graphs are shown for locations 3 and 4 in the small intestine. In the control patient the DP is 6 and 5 s for location 3 and 4, respectively. In the celiac patient the DP is 9 and 10 s for location 3 and 4, respectively. Thus the DP is higher for the celiac patient.

again midpoints between means for celiacs and controls from prior data[19].

Overall a total of 24 automata from the five measurement methods outlined above were incorporated as functional nodes into the computational network. Each automaton was given one vote, and all automata were then polled to decide whether the sequences of images being analyzed was acquired from a patient with active celiac disease or not. Thus there were 24 vote-casting nodes, each having equal weight.

Statistical analysis

Votes for celiac and for control were tallied at all four intestinal levels for both celiac and control video clips. Summary results in terms of the number of votes cast were also expressed as mean ± SD, and the statistical significance based on the unpaired *t*-test was determined for each small intestinal level (SigmaPlot 2004, ver. 9.01, Systat Software, Chicago, IL, United States). The sensitivity, specificity, and accuracy of the method was then determined. The sensitivity was defined as the number of videoclip image sequences determined to be celiac out of the total number of actual celiac video clips that were classified. The sensitivity was defined as the number of video clips determined to be controls out of the total number of actual control videoclip sequences that were classified. The accuracy was defined as the total number of correct classifications out of the total number of video clips classified. Video clips that were not classified by the automata-based polling protocol were not included in the sensitivity, specificity, and accuracy statistical calculations. The statistical calculations were done separately for each of the small intestinal locations 1-4, and also for all four locations combined.

RESULTS

Automata-based voting and prediction are summarized in Table 1 for celiac and control patients. Votes are shown for locations 1 to 4, and by patient. More votes in the celiac as compared with the non-celiac column are predictive of a celiac patient, while more votes for non-celiac is predictive of a control patient. A tie indicates that no prediction was made. For most locations and patients, prediction by the automata-based polling protocol was correct. All predictions were correct for Marsh type ⅢC celiac patients. However for the two celiac patients with Marsh type Ⅱ pathology, prediction was incorrect at two locations, there was no prediction at location 4, and at only one location out of four was the prediction correct.

Table 1 Number of votes cast by automata, celiac patient data

Mar	C1	N1	Vote	C2	N2	Vote	C3	N3	Vote	C4	N4	Vote
Celiac patients												
ⅢC	13	11	C	13	11	C	20	4	C	18	6	C
ⅢC	13	11	C	16	6	C	17	7	C	16	8	C
ⅢC	13	11	C	21	3	C	13	11	C	15	9	C
ⅢA	17	7	C	16	8	C	19	5	C	14	10	C
ⅢA	16	8	C	16	8	C	14	10	C	12	12	-
ND	16	8	C	17	7	C	16	9	C	12	12	-
ⅢA	14	10	C	15	9	C	9	15	N	12	12	-
Ⅱ	10	14	N	14	10	C	9	15	N	12	12	-
Ⅱ	19	5	C	10	14	N	6	18	N	12	12	-
Mean ± SD	14.56 ± 2.70	9.44 ± 2.70	$P = 0.022$	15.33 ± 3.00	8.44 ± 3.13	$P = 0.009$	13.67 ± 4.85	10.44 ± 4.80	$P = 0.345$	13.67 ± 2.24	10.33 ± 2.24	$P = 0.056$
Control patients												
0	9	15	N	11	13	N	5	19	N	8	16	N
0	9	15	N	8	16	N	6	18	N	8	16	N
0	10	14	N	12	13	N	9	15	N	9	15	N
0	11	13	N	10	14	N	4	20	N	11	13	N
0	16	8	C	10	14	N	9	15	N	6	18	N
0	16	8	C	11	13	N	10	14	N	9	15	N
0	10	14	N	10	14	N	10	14	N	15	9	C
Mean ± SD	11.57 ± 3.10	12.43 ± 3.10	$P = 0.727$	10.29 ± 1.25	13.86 ± 1.07	$P = 0.006$	7.57 ± 2.51	16.43 ± 2.51	$P = 0.003$	9.43 ± 2.88	14.57 ± 2.88	$P = 0.056$

Automata vote tallies for celiac (C) and non-celiac controls (N). The number of votes for each are shown for small intestinal levels 1, 2, 3, and 4. Vote = the overall vote for celiac, non-celiac, or tie (-) based on the tally for each. The vote tallies for celiac patients with villous atrophy and control patients lacking villous atrophy confirmed by intestinal biopsy. The Marsh score based on the intestinal biopsy is given (Mar) except in one patient who was a hemophiliac it was not determined (ND). Means and standard deviations are provided in the lower two rows, with significances based on the paired *t*-test shown.

For two of the Marsh type ⅢA celiac patients, and for the patient lacking biopsy, no prediction was also made at location 4, suggesting that images acquired from this location (ileum) are more difficult to evaluate, or that there is a lesser degree of villous atrophy, as compared with more proximal small intestinal locations. The results for control patients are shown in Table 1. In 4/7 control patients, predictions at all four levels were correct, indicating no celiac disease. In 3/7 control patients, prediction at three of the four locations was correct.

The mean and standard deviations for number of votes cast by automata are noted in the last row of each portion of the table. The significance of the difference based upon the paired t-test is also provided. At intestinal levels 1 and 2, there is significance for all but level 1 of control patients. At intestinal levels 3 and 4, there is significance only at level 1 of control patients. Thus there is a tendency for greater significance in the automated classification procedure at more proximate levels of the small intestine as compared to distal levels. When the data of Table 1 was pooled from all levels, for actual celiacs there was a mean of 14.31 ± 3.28 celiac votes cast, *vs* 9.67 ± 3.31 control votes cast ($P < 0.001$). When the data of Table 1 was pooled from all levels, for actual controls there was a mean of 9.71 ± 2.81 celiac votes cast *vs* 14.32 ± 2.79 control votes cast ($P < 0.001$).

The sensitivity, specificity, and accuracy of the automata-based polling protocol described in this study are shown in Table 2. At top are the results for sensitivity. Provided are the values for each method type alone and also based on location, as well as the value for data pooled from all locations. The method of first transforming the data into a series of basis vectors had the highest sensitivity at 93.8% (Table 2), while textural measurement without transformation being the second most sensitive method, at 77.8%. The other methods had approximately the same sensitivity. Values for specificity are also shown in Table 2. For data pooled from all locations, the subband method is the most specific at 76.0%. The transformation into basis vectors is least specific at 27.8%. The accuracy of the methods are also shown in Table 2. The transformation into basis vectors method is the most accurate at 70.8% for pooled data. The texture, subband, and volume methods have approximately equal accuracy overall.

In Table 2 at the bottom is shown the overall sensitivity, specificity, and accuracy of the automata-based polling protocol. Similar efficacy is evident at each small intestinal location. For pooled values from all locations, the overall sensitivity of vote-casting was 83.9%, the specificity was 92.9%, and the accuracy was 88.1%.

DISCUSSION

Videocapsule data was acquired from the small intestine of celiac patients with biopsy-proven active disease, and from control patients without mucosal lesions. Using an automata-based polling protocol to classify celiac *vs* control video clips, the overall specificity and accuracy were 92.9% and 88.1%, with the sensitivity being 83.9%. The method of transformation to basis vectors had the best overall sensitivity and accuracy for prediction, although the specificity using this method was reduced. Several tie votes were cast at location 4 (ileum) suggesting that

Table 2 Statistics of automata polling to correctly classify videocapsule data

Sensitivity	1st	2nd	3rd	4th	All locations
Sensitivity					
Texture	88.9	88.9	55.6	77.8	77.8
Subband	55.6	50.0	42.9	83.3	56.7
Motility	42.9	100.0	50.0	37.5	84.2
Volume	44.4	77.8	55.6	44.4	55.6
Basis	100.0	100.0	75.0	100.0	93.3
Specificity					
Texture	0.0	42.9	71.4	71.4	46.4
Subband	80.0	83.3	71.4	71.4	76.0
Motility	100.0	25.0	83.3	60.0	64.7
Volume	71.4	85.7	85.7	71.4	78.6
Basis	0.0	33.3	100.0	40.0	27.8
Accuracy					
Texture	50.0	68.8	62.5	75.0	64.1
Subband	64.3	64.3	57.1	76.9	65.4
Motility	55.6	70.0	64.3	46.2	58.7
Volume	56.3	81.3	68.8	56.3	64.1
Basis	50.0	80.0	81.8	76.9	70.8
Overall					
Sensitivity	88.9	88.9	66.7	100.0	83.9
Specificity	85.7	100.0	100.0	85.7	92.9
Accuracy	87.5	93.8	81.3	90.9	88.1

The sensitivity, specificity, and accuracy of the method at locations, and for all locations combined, separated by the measurement type (texture, subband coding, motility, volumetric analysis, and reconstruction using basis vectors.

videocapsule images acquired from this region are less differentiable as being active celiac or control data. Prediction using the automata-based polling protocol is an improved technique because votes are polled from many independent automata. Although extraneous features and random and phasic noise may degrade quantitative comparisons of videocapsule data, the methodology has been shown to be relatively robust to these external influences[22,23].

As compared to prior analyses[15-19], the automata-based polling protocol tended to improve prediction. Although the methods as introduced previously tended to be quite predictive of celiac and control patients, they made use of nonlinear discriminant functions which were specifically tailored to the data at hand. This previous methodology was computationally intensive and was developed for a specific data set. The texture method, the subband method, and the motility method by themselves all make use of manually-derived three-dimensional classifiers and nonlinear discriminant functions[15-17]. In contrast, the automata-based polling protocol described in this study does not use three-dimensional classifiers nor complex nonlinear discriminant functions. Rather, each measurement method is used independently for calculation. The threshold for determining whether the measurement is likely to have been from data acquired from an active celiac or a control patient was based on a predetermined threshold level from data analyzed previously. Pooled voting from all measurements was used for prediction, making the method robust to outliers in the individual measurements.

Other measurement methods may be useful to incorporate into the automata polling procedure for improved efficacy. These include texture-based methods[24-28]. Yet equally important will be the need for advances in videocapsule technology[29-32] and image resolution[33-36].

Limitations

The number of video clips analyzed was relatively small, and validation should be done in a prospective double-blinded study with larger data set. Our results suggest in part that classification of celiacs *vs* controls can be used for dynamic estimates of wall motility. Inclusion of a control group with severe intestinal motility disorders would be helpful for validation. The number of automata used for classification was 24. Classification accuracy may increase with a larger computational network, the subject of future study. The technique presented in the study presumed that camera angle and distance to the mucosal surface is uniform, and that coverage of the surface area of the small intestinal lumen is relatively constant during transit of the videocapsule. However, continual variation in these parameters actually occurs. These variations may act as random and phasic noise to reduce accuracy in quantitatively comparing celiac *vs* control videoclip images. Yet, these quantitative methods have been shown to be relatively robust to additive random and phasic noise[22]. Removal of extraneous image features prior to analysis[23] can potentially improve efficacy further. Capsule motion may also be erratic, further limiting analysis. The study was also performed with only one type of capsule endoscope and it is unclear if these results would be different with the use of a different capsule endoscopy system. Since there was no gold standard of biopsy specimen for levels 3 and 4 analysis, villous atrophy may have been absent from these regions in celiac patients, which would result in classification error. The findings were determined with a relatively small patient population, and should be confirmed in a larger study.

In conclusion, video clips from four small intestinal locations in the duodenum, jejunum, and ileum can be used to differentiate data acquired from active celiacs from controls. Several methods that were introduced previously, namely texture-based analysis, use of subbands, syntactic analysis of volumetric properties, estimation of motility, and use of transformed basis vectors to extract salient information, were all found to be useful for prediction. The system was implemented as an automata-based polling protocol, with pooling of the votes cast from a network of 24 automata. The findings of this study suggest that the technique may be useful for discerning images of celiac patients with villous atrophy from images of control patients lacking atrophy, though this must be confirmed with a larger data set that includes different Marsh grades of intestinal damage. The sensitivity of the method was less accurate due to the fact that Marsh type Ⅱ celiac patients were not as readily discerned by the quantitative analysis.

COMMENTS

Background

In celiac disease patients and in other patients with gastrointestinal malady there may be atrophy of the small intestinal villi. Changes in the villi and other abnormalities of the intestinal mucosa may be detectable by quantitative analysis of videocapsule images.

Research frontiers

Quantitative biomedical image processing is becoming an important means to assist gastroenterologists during their evaluation of videocapsule images for the detection of gastrointestinal abnormalities.

Innovations and breakthroughs

In this study an automated, unbiased method was developed to quantify changes in videocapsule images of the small intestine. The method was found useful to distinguish images of celiac disease patients with biopsy-proven villous atrophy, *vs* control patients lacking villous atrophy.

Applications

The method is potentially useful as a real-time analysis tool during videocapsule image acquisition and playback at the clinical analysis console. The degree of abnormality can be posted on-screen with each image in the set of patient data.

Terminology

The method determines the degree of abnormality in videocapsule imagery by polling of specialized measurement automata. Each automaton is an independent measurement that is calculated without user intervention. By referring to threshold values from prior analysis, each automaton casts a vote as to whether their particular measurement value is indicative of abnormality, and the votes are tallied, or pooled. Classification as to whether villous atrophy is present or not at each small intestinal level is determined by which of the two classes garners the greater number of votes.

Peer review

This study outlines an approach for analysis of videocapsule endoscopy data to assess patients with celiac disease. In particular, the benefit of automated quantitative analysis is investigated. It is concluded from the findings that the method is useful in the detection of villous atrophy, especially in proximal locations of the small intestine.

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ORIGINAL ARTICLE

Reliability in endoscopic diagnosis of portal hypertensive gastropathy

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Abstract

AIM: To analyze reliability among endoscopists in diagnosing portal hypertensive gastropathy (PHG) and to determine which criteria from the most utilized classifications are the most suitable.

METHODS: From January to July 2009, in an academic quaternary referral center at Santa Casa of São Paulo Endoscopy Service, Brazil, we performed this single-center prospective study. In this period, we included 100 patients, including 50 sequential patients who had portal hypertension of various etiologies; who were previously diagnosed based on clinical, laboratory and imaging exams; and who presented with esophageal varices. In addition, our study included 50 sequential patients who had dyspeptic symptoms and were referred for upper digestive endoscopy without portal hypertension. All subjects underwent upper digestive endoscopy, and the images of the exam were digitally recorded. Five endoscopists with more than 15 years of experience answered an electronic questionnaire, which included endoscopic criteria from the 3 most commonly used Portal Hypertensive Gastropathy classifications (McCormack, NIEC and Baveno) and the presence of elevated or flat antral erosive gastritis. All five endoscopists were blinded to the patients' clinical information, and all images of varices were deliberately excluded for the analysis.

RESULTS: The three most common etiologies of portal hypertension were schistosomiasis (36%), alcoholic cirrhosis (20%) and viral cirrhosis (14%). Of the 50 patients with portal hypertension, 84% were Child A, 12% were Child B, 4% were Child C, 64% exhibited previous variceal bleeding and 66% were previously endoscopic treated. The endoscopic parameters, presence or absence of mosaic-like pattern, red point lesions and cherry-red spots were associated with high inter-observer reliability and high specificity for diagnosing Portal Hypertensive Gastropathy. Sensitivity, specificity and reliability for the diagnosis of PHG (%) were as follows: mosaic-like pattern (100; 92.21; High); fine pink speckling (56; 76.62; Unsatisfactory); superficial reddening (69.57; 66.23; Unsatisfactory); red-point lesions (47.83; 90.91; High); cherry-red spots (39.13; 96.10; High); isolated red marks (43.48; 88.31; High); and confluent red marks (21.74; 100; Unsatisfactory). Antral elevated erosive gastritis exhibited high reliability and high specificity with respect to the presence of portal hypertension (92%) and the diagnosis of portal hypertensive gastropathy (88.31%).

CONCLUSION: The most suitable endoscopic criteria for the diagnosis of PHG were mosaic-like pattern, red-point lesions and cherry-red spots with no subdivisions,

which were associated with a high rate of inter-observer reliability.

Key words: Endoscopy; Cirrhosis; Portal hypertension; Portal hypertensive gastropathy; Stomach

Core tip: This article proposes a simplified approach for the diagnosis of portal hypertensive gastropathy, considering the presence or the absence of mosaic-like pattern, red point lesions and cherry-red spots, without subdivisions, as those criteria exhibit high agreement among observers and high specificity. This simplified approach is useful for future research on the natural history of this disease and its related factors, thus helping to clarify some of the current controversies due to the lack of homogeneity on the diagnostic criteria of portal hypertensive gastropathy.

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INTRODUCTION

Portal hypertensive gastropathy (PHG) is characterized by an alteration in gastric mucosa that causes digestive hemorrhage in patients with portal hypertension (PH) of any etiology. Its incidence varies in the medical literature from 4% to 80% owing to a lack of consensus on endoscopic criteria for diagnosis[1-6].

PHG is histologically characterized by the dilation and tortuosity of the sub mucosal vessels, the thinning of the vascular wall and the increased areas of gastric mucosa occupied by vessels[7-11]. These alterations stem from hemodynamic modifications caused by portal hypertension syndrome and are not related to inflammatory infiltration[7-18].

McCormack *et al*[7] first described PHG in 1985 and proposed the first classification, attributing a risk of bleeding of 38% to 62% for severe forms and 3.5% to 31% for mild forms of PHG. Although simplified, this classification is problematic for grading intermediate endoscopic findings.

In 1994, the New Italian Endoscopy Club (NIEC) proposed an alternative classification including a moderate aspect of PHG for grading intermediate endoscopic findings[19].

Shortly after, in 1996, the Baveno Consensus, a scoring system for the most relevant aspects of PHG (the Baveno Score System), was developed and attributed a higher risk of bleeding in patients with the severe form of PHG and an odds ratio of 2.56[20].

The medical literature is not in agreement regarding the best classification and endoscopic criteria for diagnosing PHG, nor is there a consensus on its therapeutic management[21-28].

The purpose of this study was to analyze reliability among endoscopists in diagnosing PHG and to determine which endoscopic criteria, from the most utilized classifications (McCormack, NIEC and Baveno), are most suitable for diagnosing PHG.

MATERIALS AND METHODS

In a prospective study, a total of 100 patients were selected from those undergoing upper digestive endoscopy between January and July 2009 at the Endoscopy Service - Santa Casa School of Medical Sciences (Santa Casa de São Paulo Medical School), São Paulo, Brazil. This study was approved by the local Research Ethics Committee, and patients were included only after signing informed consent forms.

Fifty sequential patients with portal hypertension of various etiologies previously diagnosed based on clinical, laboratory and imaging exams who presented with esophageal varices were selected (Table 1). All patients with clinical or endoscopic signs of upper hemorrhage were included in this study. A control group was formed, consisting of 50 sequential patients with dyspeptic symptoms referred for upper digestive endoscopy without portal hypertension or a previous history of hepatopathy or congestive cardiopathy, abdominal ultrasounds disclosing normal liver and spleen, and a portal vein caliber of less than 12 mm.

Exams were performed under sedation and digitally recorded. Six images were selected from recordings, consisting of two from the antrum, two from the gastric body and two from the gastric fundus (not showing varices). The images were then analyzed by five independent expert endoscopists with over 15 years of experience in our service. First, the examiners were familiarized with the standards used in this trial and subsequently evaluated the selected images of each patient while blinded to patients' clinical information. The varices were deliberately excluded from the images that were presented in sequential order to each endoscopist. The endoscopists were also blinded to each other's comments and evaluations.

An electronic questionnaire, which included endoscopic criteria from PHG classifications (McCormack, NIEC and Baveno) and recorded the presence or otherwise of elevated or flat antral erosive gastritis, was used to collect and collate the results (Figure 1). The results were independently analyzed to determine their relationship with PHG.

Figures 2-4 compare endoscopic aspects with their classifications.

Due to inconsistencies in the medical literature on the role of histological analysis of standard endoscopic biopsies for diagnosing PHG, we decided not to perform

Table 1 Group with portal hypertension and esophageal varices *n* (%)

Character	*n* = 50
Mean age (52.7 yr)	
Sex	
Male	28 (56)
Female	22 (44)
Etiology	
Alcohol	10 (20)
Schistosomiasis	18 (36)
Hepatitis B	2 (4)
Hepatitis C	5 (10)
Alcohol and schistosomiasis	1 (2)
Alcohol, schistosomiasis and Hepatitis B	1 (2)
Autoimmune hepatitis	1 (2)
Portal vein thrombosis	1 (2)
Non-alcoholic hepatic steatosis	1 (2)
Budd-Chiari Syndrome	1 (2)
Biliary cirrhosis	1 (2)
Idiopathic or not yet identified	8 (16)
Child-pugh classification	
A	42 (84)
B	6 (12)
C	2 (4)
Previous digestive bleeding	32 (64)
Previous endoscopic treatment	33 (66)
Using propanolol	25 (50)

biopsies in this study[29-31]. Due to the absence of an established gold standard for diagnosing PHG, the statistical analysis was performed in two stages. The first stage verified the correlation between each endoscopic criterion and the presence of PH, with the group of 50 patients without PH serving as a control. The second stage determined the correlation between each endoscopic criterion and the diagnosis of PHG. The establishment of a relationship between the endoscopic criterion and the presence of PH was a prerequisite for the potential correlation between the same criterion and PHG. If any criterion demonstrated an apparent relationship with PHG but not with PH, then it was deemed logically false.

The Statistical Package for Social Sciences version 17.0 was utilized for statistical analysis, adopting a 5% level of significance on Fisher's Exact Test. Cronbach's alpha was used to determine reliability among the five endoscopists, with values between 0 and 0.60 considered Unsatisfactory, values between 0.60 to 0.69 as Satisfactory, and values between 0.70 to 1.00 as a High degree of reliability.

RESULTS

For criteria from the McCormack classification (Table 2), the mosaic-like pattern was associated with high reliability, specificity (90%) and positive predictive value (82.76%) for the presence of PH, as well as sensitivity and negative predictive values of 100% for the diagnosis of PHG. Fine pink speckling and superficial reddening both exhibited unsatisfactory reliability, as well as low specificity (86%) and high false positive values (7%) for the presence of PH. In addition, these criteria exhibited low specificity (76.62%) and high false positive values (18%) for the diagnosis of PHG.

On the NIEC classification (Table 3), pink and red mosaic-like patterns were associated with unsatisfactory reliability, but red center mosaic-like patterns exhibited high reliability, thus defining PHG as moderate.

For criteria from the Baveno classification (Table 4), only red marks demonstrated high reliability and specificity (92%) for the presence of PH and high reliability for the diagnosis of PHG.

Table 5 depicts the results of the statistical analysis of antral erosive gastritis and its variations, flat and elevated, in relation to the presence of portal hypertension and the diagnosis of portal hypertensive gastropathy. Antral elevated erosive gastritis exhibited high reliability and high specificity with respect to the presence of PH (92%) and the diagnosis of PHG (88.31%).

DISCUSSION

The analyzed classifications (McCormack, NIEC and BAVENO) comprise several common endoscopic aspects, albeit aspects that are occasionally analyzed from different perspectives, thereby affecting the level of agreement among the observers. Others classifications have been published, including pre- and post-treatment evaluations, but these classifications have been reported without exclusive diagnostic aspects[21-22].

The presence of any mosaic-like pattern, defined as polygonal areas with whitish reticular borders, is utilized in all three classifications studied. The McCormack Classification considers only its presence or absence but not variations in its inner polygonal area. In the present study, the mosaic-like pattern was associated with high reliability, specificity and positive predictive value for the presence of PH, as well as sensitivity and negative predictive values of 100% for the diagnosis of PHG, where its absence almost excluded this diagnosis. This finding corroborates the results of the study by Stewart *et al*[24] in which, out of the 100 patients diagnosed with PHG, 96 exhibited mosaic-like patterns.

Based on the NIEC classification, the mosaic-like pattern is subdivided into three and classified according to the color of the inner polygonal area as either pink, red center or red. In the present study, pink and red mosaic-like patterns were associated with unsatisfactory reliability, whereas a red center mosaic-like pattern had high reliability, defining PHG as moderate. Nevertheless, the red center may also be considered a red-point lesion or a cherry-red spot, characterizing the PHG as severe, thereby rendering this stratification of the pattern ambiguous and the NIEC classification inconsistent.

The Baveno Score System subdivides the mosaic-like pattern into two aspects: mild, corresponding to a pink mosaic-like pattern, and severe, which corresponds to a red mosaic-like pattern, which as mentioned above, was found to exhibit Unsatisfactory reliability and thus low agreement among observers. Although Stewart *et al*[24]

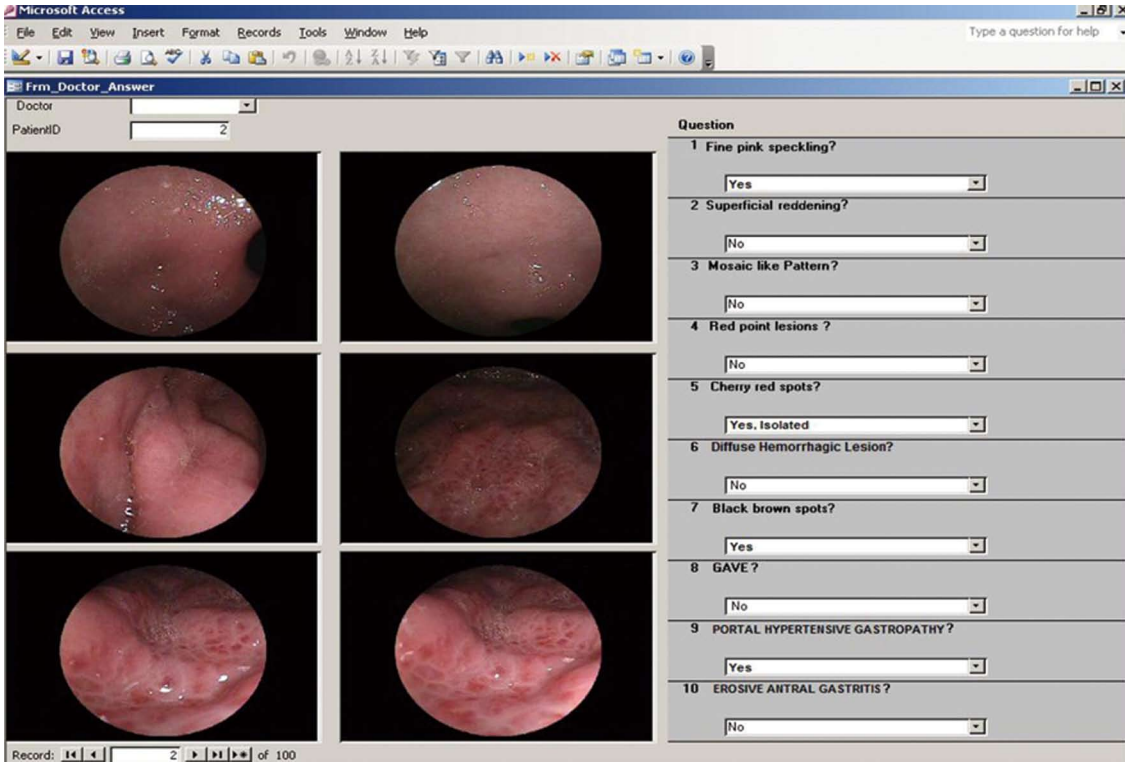

Figure 1 Electronic questionnaire.

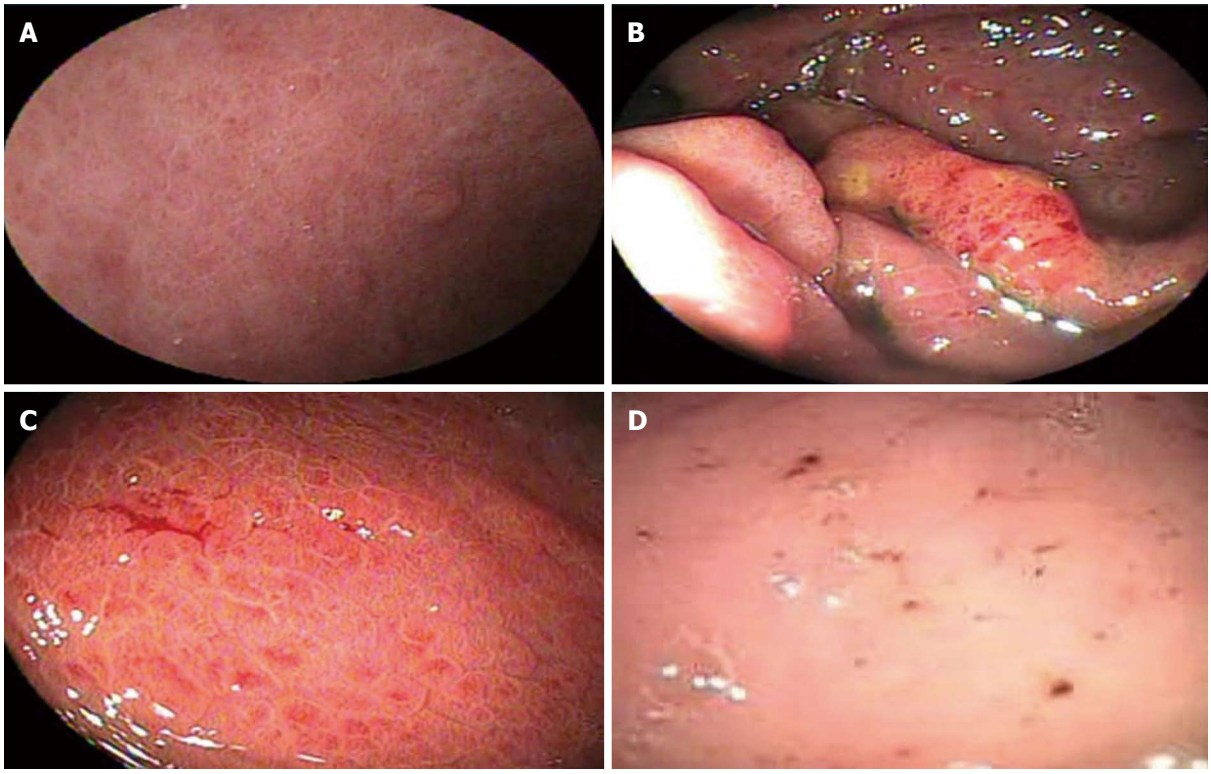

Figure 2 Endoscopic aspects of portal hypertensive gastropathy considered in the study and their corresponding classifications. A: Fine pink speckling - McCormack; B: Superficial reddening - McCormack; C: Diffuse hemorrhagic lesion - McCormack; D: Black brown spots - New Italian Endoscopy Club.

also demonstrated agreement among observers analyzing the presence or absence of the mosaic-like pattern, with a Kappa Index of greater than 0.75, concordance decreased when this aspect was subdivided according to variation in the inner polygonal area.

The present results demonstrated that fine pink

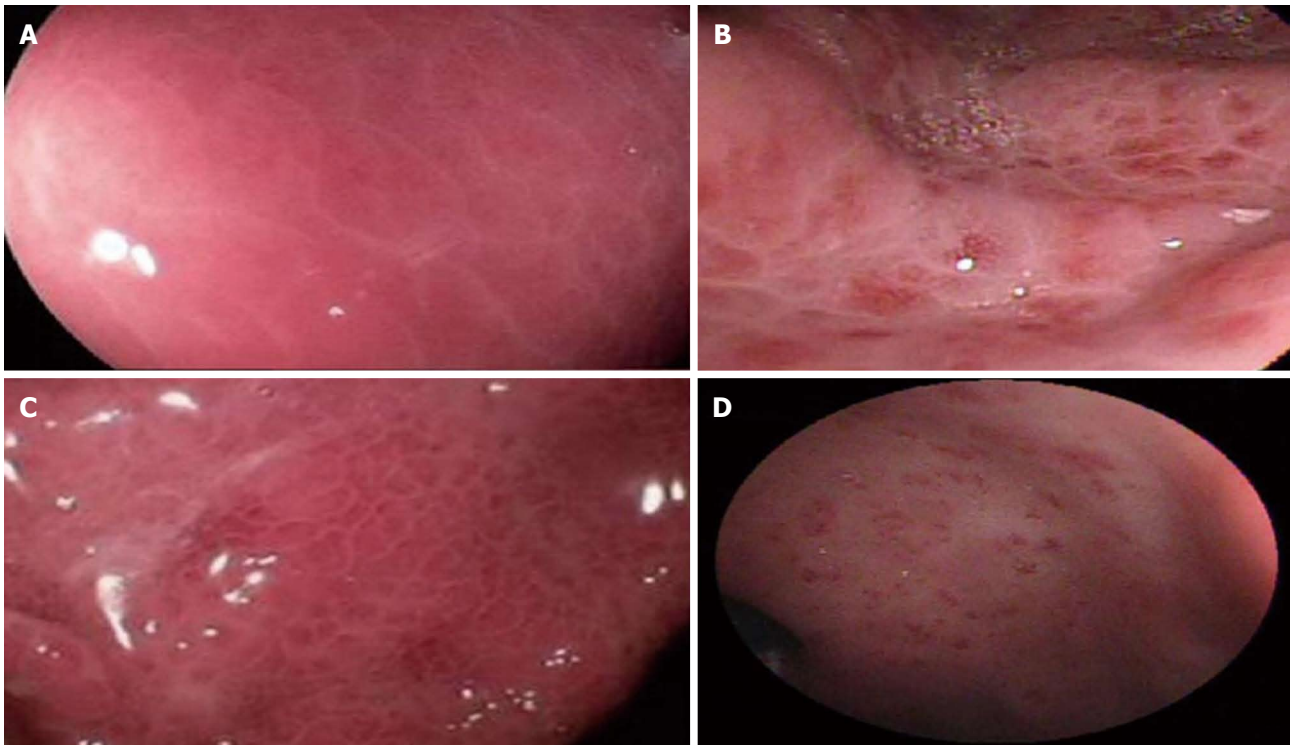

Figure 3 Endoscopic aspects of portal hypertensive gastropathy considered in the study and their corresponding classifications. A: Corresponds to "mosaic-like pattern" with different nomenclature in each classification as follows: mosaic-like pattern - McCormack; mild mosaic-like pattern - New Italian Endoscopy Club (NIEC); mild mosaic-like pattern - Baveno; B: Corresponds to "mosaic-like pattern" with different nomenclature in each classification as follows: red center mosaic-like pattern - McCormack; moderate mosaic-like pattern - NIEC; C: Corresponds to "mosaic-like pattern" with different nomenclature in each classification as follows: mosaic-like pattern - McCormack; severe mosaic-like pattern - NIEC; severe mosaic-like pattern - Baveno; D: GAVE - Baveno.

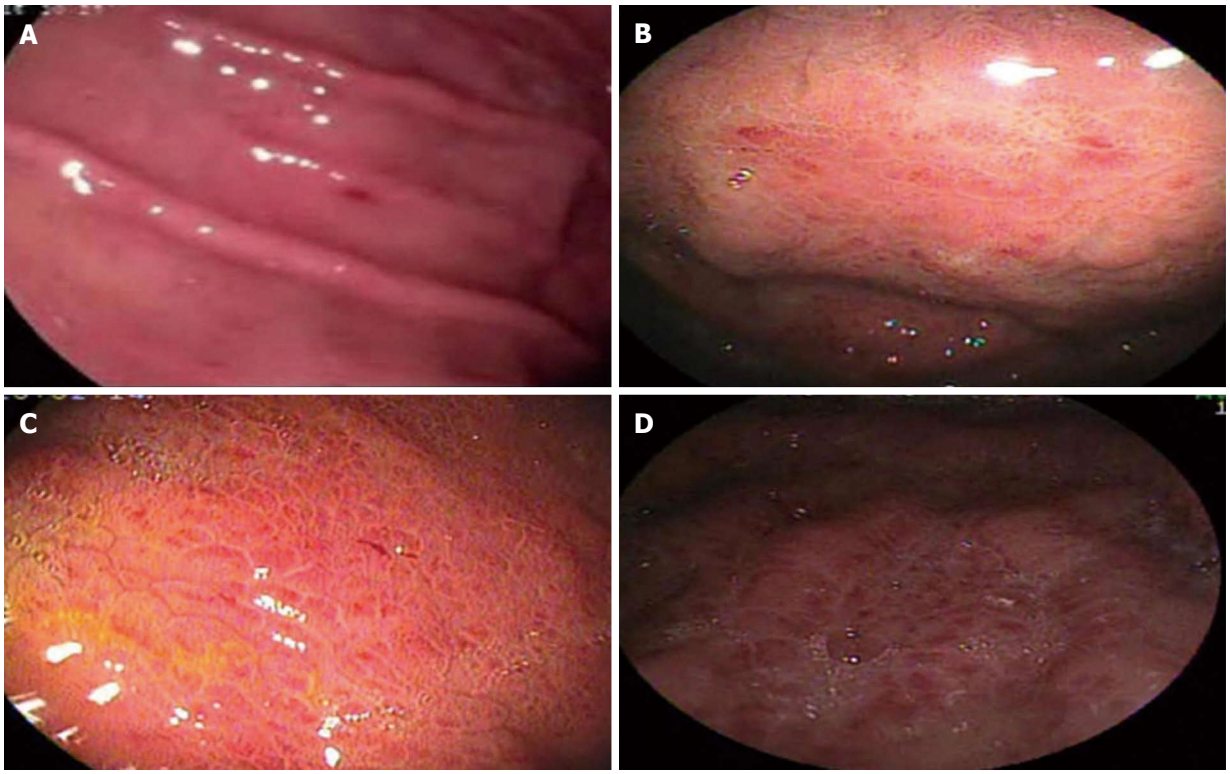

Figure 4 Endoscopic aspects of portal hypertensive gastropathy considered in the study and their corresponding classifications. A: Corresponds to "cherry-red spots" with different nomenclature in each classification as follows: discrete red spots - McCormack; cherry-red spots - New Italian Endoscopy Club (NIEC); B: Red-point lesions - NIEC; C: Isolated red marks - Baveno; D: Confluent red marks - Baveno.

Table 2 Analysis of the criteria from the McCormack classification for the presence of portal hypertension and portal hypertensive gastropathy

	Fine pink speckling		Superficial reddening		Mosaic-like pattern		Cherry-red spots		Diffuse hemorrhagic lesion	
Diagnosis	PH	PHG	PH	PHG	PH	PHG	PH	PHG	PH	PHG
Sensitivity	48.00%	56.52%	64.00%	69.57%	48.00%	100.00%	22.00%	39.13%	8.00%	17.39%
Specificity	86.00%	76.62%	80.00%	66.23%	90.00%	92.21%	98.00%	96.10%	100.00%	100.00%
PPV	77.42%	41.94%	76.19%	38.10%	82.76%	79.31%	91.67%	75.00%	100.00%	100.00%
NPV	62.32%	85.51%	68.97%	87.93%	63.38%	100.00%	55.68%	84.09%	52.08%	80.21%
Accuracy	67.00%	72.00%	72.00%	67.00%	69.00%	94.00%	60.00%	83.00%	54.00%	81.00%
False negative	26.00%	10.00%	18.00%	7.00%	26.00%	0.00%	39.00%	14.00%	46.00%	19.00%
False positive	7.00%	18.00%	10.00%	26.00%	5.00%	6.00%	1.00%	3.00%	0.00%	0.00%
Significance	$P < 0.001$	$P = 0.03$	$P < 0.001$	$P = 0.002$	$P < 0.001$	$P < 0.001$	$P = 0.002$	$P < 0.001$	$P = 0.059$	$P = 0.002$
Reliability (α)	0.430[1]	0.430[1]	0.532[1]	0.532[1]	0.799[2]	0.799[2]	0.753[2]	0.753[2]	0.574[1]	0.574[1]

[1]Unsatisfactory; [2]High. PPV: Positive predictive value; NPV: Negative predictive value; PH: Portal hypertension; PHG: Portal hypertensive gastropathy.

Table 3 Analysis of the criteria from the New Italian Endoscopy Club classification for the presence of portal hypertension and portal hypertensive gastropathy

	Pink mosaic-like pattern		Red center mosaic-like pattern		Red mosaic-like pattern		Red-point lesions		Cherry-red spots		Black-brown spots	
Diagnosis	PH	PHG	PH	PHG	PH	PHG	PH	PHG	PH	PHG	PH	PHG
Sensitivity	26.00%	52.17%	16.00%	34.78%	6.00%	13.04%	28.00%	47.83%	22.00%	39.13%	2.00%	4.35%
Specificity	90.00%	92.21%	100.00%	100.00%	100.00%	100.00%	92.00%	90.91%	98.00%	96.10%	98.00%	98.70%
PPV	72.22%	66.67%	100.00%	100.00%	100.00%	100.00%	77.78%	61.11%	91.67%	75.00%	50.00%	50.00%
NPV	54.88%	86.59%	54.35%	83.70%	51.55%	79.38%	56.10%	85.37%	55.68%	84.09%	50.00%	77.55%
Accuracy	58.00%	83.00%	58.00%	85.00%	53.00%	80.00%	60.00%	81.00%	60.00%	83.00%	50.00%	77.00%
False negative	37.00%	11.00%	42.00%	15.00%	47.00%	20.00%	36.00%	12.00%	39.00%	14.00%	49.00%	22.00%
False positive	5.00%	6.00%	0.00%	0.00%	0.00%	0.00%	4.00%	7.00%	1.00%	3.00%	1.00%	1.00%
Significance	$P = 0.033$	$P < 0.001$	$P = 0.003$	$P < 0.001$	$P = 0.121$	$P = 0.011$	$P = 0.009$	$P < 0.001$	$P = 0.002$	$P < 0.001$	$P = 0.753$	$P = 0.358$
Reliability (α)	0.569[1]	0.569[1]	0.727[2]	0.727[2]	0.079[2]	0.079[2]	0.752[2]	0.752[2]	0.753[2]	0.753[2]	0.408[1]	0.408[1]

[1]Unsatisfactory; [2]High. PPV: Positive predictive value; NPV: Negative predictive value; PH: Portal hypertension; PHG: Portal hypertensive gastropathy.

speckling and superficial reddening from the McCormack classification were associated with unsatisfactory reliability and, thus, the low agreement among observers. These criteria also exhibited low specificity and high false positive values for the presence of PH, as well as low specificity and high false positive values for the diagnosis of PHG. This result indicated that fine pink speckling and superficial reddening also occurred in the group without PH, possibly corresponding to enanthematous mucosal alterations unrelated to portal hypertension. McCormack *et al*[7], in his original article, emphasized that with the exception of the cherry-red spots, the endoscopic aspects he described for the diagnosis now called PHG were indistinguishable from gastritis.

PHG is classified according to its tendency to bleed. Nonetheless, diffuse hemorrhagic lesions and black brown spots (old mucosal hemorrhage) are utilized in the McCormack and NIEC classifications. This use reveals incoherence because these aspects are, concomitantly, both a cause (PHG) and a consequence (hemorrhage). Additionally, these parameters exhibited unsatisfactory reliability in the present study due to low inter-observer agreement. Occasionally, these tenuous hemorrhages may exhibit discrete clinical manifestations[2,18]. In our study, patients with suspected digestive bleeding were excluded. The exclusion of these cases may partly explain the low statistical significance of these criteria.

Mucosal delimited red alterations are utilized in all three classifications. Red-point lesions are employed in the NIEC classification whereas cherry-red spots are used in both the McCormack (called discrete red spots) and NIEC classification. The Baveno score system groups red-point lesions and cherry-red spots together under red marks. We found that the presence or absence of red alterations was associated with high reliability due to high agreement among the endoscopists, high specificity and high positive predictive value in relation to the presence of PH and the diagnosis of PHG (Tables 2-4), thus demonstrating that these endoscopic aspects are related to PH and PHG.

The Baveno score system splits these parameters by grouping the alterations as either isolated or confluent. Nevertheless, there is no definition of the confluence criterion, thus leading to subjective interpretation and unsatisfactory reliability in the present study. Stewart *et al*[24] studying patients with PHG, demonstrated high inter-observer agreement in relation to the presence or absence of red marks and a kappa index of greater than 0.75, indicating desirable agreement. However, this level became unsatisfactory when used with the confluence criterion, splitting the red marks of the endoscopic aspect into isolated and confluent categories.

Table 4 Analysis of the criteria from the Baveno classification for the presence of portal hypertension and portal hypertensive gastropathy

	Pink mosaic-like pattern		Red mosaic-like pattern		Isolated red marks		Confluent red marks		GAVE	
Diagnosis	PH	PHG	PH	PHG	PH	PHG	PH	PHG	PH	PHG
Sensitivity	26.00%	52.17%	6.00%	13.04%	30.00%	43.48%	10.00%	21.74%	8.00%	4.35%
Specificity	90.00%	92.21%	100.00%	100.00%	92.00%	88.31%	100.00%	100.00%	100.00%	96.10%
PPV	72.22%	66.67%	100.00%	100.00%	78.95%	52.63%	100.00%	100.00%	100.00%	25.00%
NPV	54.88%	86.59%	51.55%	79.38%	56.79%	83.95%	52.63%	81.05%	52.08%	77.08%
Accuracy	58.00%	83.00%	53.00%	80.00%	61.00%	78.00%	55.00%	82.00%	54.00%	75.00%
False negative	37.00%	11.00%	47.00%	20.00%	35.00%	13.00%	45.00%	18.00%	46.00%	22.00%
False positive	5.00%	6.00%	0.00%	0.00%	4.00%	9.00%	0.00%	0.00%	0.00%	3.00%
Significance	$P = 0.033$	$P < 0.001$	$P = 0.121$	$P = 0.011$	$P = 0.005$	$P = 0.0014$	$P = 0.028$	$P < 0.001$	$P = 0.059$	$P = 0.429$
Reliability (α)	0.569[1]	0.569[1]	0.079[1]	0.079[1]	0.753[2]	0.753[2]	0.558[1]	0.558[1]	0.514[1]	0.514[1]

[1]Unsatisfactory; [2]High. PPV: Positive predictive value; NPV: Negative predictive value; PH: Portal hypertension; PHG: Portal hypertensive gastropathy.

Table 5 Analysis of antral erosive gastritis in the presence of portal hypertension and portal hypertensive gastropathy

	Antral erosive gastritis		Antral elevated erosive gastritis		Antral flat erosive gastritis	
Diagnosis	PH	PHG	PH	PHG	PH	PHG
Sensitivity	34.00%	39.13%	26.00%	34.78%	8.00%	4.35%
Specificity	84.00%	79.22%	92.00%	88.31%	92.00%	90.91%
PPV	68.00%	36.00%	76.47%	47.06%	50.00%	12.50%
NPV	56.00%	81.33%	55.42%	81.93%	50.00%	76.09%
Accuracy	59.00%	70.00%	59.00%	76.00%	50.00%	71.00%
False negative	33.00%	14.00%	37.00%	15.00%	46.00%	22.00%
False positive	8.00%	16.00%	4.00%	9.00%	4.00%	7.00%
Significance	$P = 0.032$	$P = 0.046$	$P = 0.016$	$P = 0.012$	$P = 0.643$	$P = 0.297$
Reliability (α)	0.840[2]	0.840[2]	0.862[2]	0.862[2]	0.641[1]	0.641[1]

[1]Satisfactory; [2]High. PPV: Positive predictive value; NPV: Negative predictive value; PH: Portal hypertension; PHG: Portal hypertensive gastropathy.

Although the current study demonstrated that GAVE (Baveno score system) exhibited 100% specificity and 0% false positive results, suggesting a strong association with portal hypertension and PHG, this relationship failed to reach statistical significance. Some authors claim that PHG and GAVE are distinct entities with no correlations between them[32-34].

Analysis of antral erosive gastritis and its variations, flat and elevated, revealed that antral elevated erosive gastritis exhibited high reliability and high specificity with relation to the presence of PH and the diagnosis of PHG, thereby suggesting an association with PHG. Assef *et al*[35] observed a 37.5% rate of antral elevated erosive gastritis in patients with PHG. Using multivariate analysis, Auroux *et al*[36] demonstrated that 31.2% of patients with portal hypertension had gastric erosions related to PHG and not to the presence of *Helicobacter pylori*, alcohol abuse, Child classification or the severity of esophageal varices. Further studies including histological analyses are warranted to confirm this association.

All endoscopic parameters analyzed exhibited low accuracy for the presence of PH (Tables 2-4). This low accuracy is due to the low negative predictive values of each separate parameter. Therefore, it is important to analyze all of the endoscopic parameters in conjunction with PH.

Regarding criteria for the diagnosis of PHG, the mosaic-like pattern, pink mosaic-like pattern, mosaic-like pattern with red center, cherry-red spots and red-point lesions showed accuracies of 94%, 83%, 85%, 83% and 81%, respectively. Of these criteria, only the mosaic like-pattern offered high sensitivity (100%). As explained earlier, the subdivision of the mosaic-like pattern leads to low inter-observer agreement, whereas the mosaic-like pattern with red center is an incoherent subdivision, at the same time representing a mosaic-like pattern and a red point lesion or cherry red spot.

The unsatisfactory reliability and low inter-observer agreement of the analyzed classifications corroborate the findings reported in other studies. Yoo *et al*[25] analyzed McCormack and NIEC classifications and observed low kappa indices of 0.52 and 0.44, respectively, indicating low inter-observer agreement given that a desirable Kappa index is greater than 0.75. Stewart *et al*[24] analyzing the Baveno classification, found an unsatisfactory rate of agreement when mosaic-like patterns and red marks were subdivided.

It is clear that all three investigated classifications have inadequate endoscopic parameters. Nevertheless, analyzing binary criteria such as the presence or the absence of the mosaic-like pattern, red-point lesions and cherry-red spots, the diagnosis of PHG yields high inter-observer agreement and high specificity. This approach can prove useful for future research on the natural history of this disease and related factors, thus helping to clarify some of the current controversies, including studies with his-

tologic findings and comparisons with the endoscopic criteria of the classifications that we have already begun.

In conclusion, the most suitable endoscopic criteria for the diagnosis of portal hypertensive gastropathy were mosaic-like pattern, red-point lesions and cherry-red spots (without subdivisions), all of which were associated with a high rate of inter-observer reliability.

COMMENTS

Background

Portal hypertensive gastropathy (PHG) is an alteration of gastric mucosa causing occult and sometimes massive digestive hemorrhage in patients with portal hypertension of any etiology.

Research frontiers

PHG remains an endoscopic diagnosis, and there are many endoscopic classifications. No histologic correspondence was proven, leading to an individual observer opinion in diagnosis and grading, with a low level of reliability among endoscopists.

Innovations and breakthroughs

The most used classifications of PHG comprise several common endoscopic aspects, albeit aspects that are sometimes analyzed from different perspectives, thereby affecting the level of agreement among observers and leading to no consensus on endoscopic diagnosis and grading.

Applications

By separating the most suitable endoscopic criteria for the diagnosis of PHG, authors found that mosaic-like pattern, red-point lesions and cherry-red spots (without subdivisions) were associated with high inter-observer reliability and should be used to simplify and standardize the PHG diagnosis and severity.

Peer review

PHG is frequently observed on an upper gastrointestinal endoscopy in patients of portal hypertension. However, there are no objective criteria to diagnose PHG, and there is no consensus on the best classification and endoscopic criteria in the medical literature. The authors have attempted to analyze the data regarding reliability of various endoscopic morphological features among different endoscopists based on the criteria of McCormack, New Italian Endoscopy Club and Baveno. The authors concluded that most suitable endoscopic criteria for the diagnosis of PHG are mosaic-like pattern, red point lesions and cherry red spot.

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BRIEF ARTICLE

Evaluation of fully covered self-expanding metal stents in benign biliary strictures and bile leaks

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Abstract

AIM: To investigate the use of fully covered metal stents in benign biliary strictures (BBS) and bile leaks.

METHODS: We studied 17 patients, at Harbor-UCLA Medical center (Los Angeles), with BBS (*n* = 12) and bile leaks (*n* = 5) from July 2007 to February 2012 that had received placement of fully covered self-expanding metal stents (FCSEMs). Fourteen patients had endoscopic placement of VIABIL® (Conmed, Utica, New York, United States) stents and three had Wallflex® (Boston Scientific, Mass) stents. FCSEMS were 8 mm or 10 mm in diameter and 4 cm to 10 cm in length. Patients were followed at regular intervals to evaluate for symptoms and liver function tests. FCSEMS were removed after 4 or more weeks. Resolution of BBS and leak was documented cholangiographically following stent removal. Stent patency can be defined as adequate bile and contrast flow from the stent and into the ampulla during endoscopic retrograde cholangiopancreatography (ERCP) without clinical signs and/or symptoms of biliary obstruction. Criterion for bile leak resolution at ERCP is defined as absence of contrast extravasation from the common bile duct, cystic duct remanent, or gall bladder fossa. Rate of complications such as migration, and in-stent occlusion were recorded. Failure of endoscopic therapy was defined as persistent biliary stenosis or continuous biliary leakage after 12 mo of stent placement.

RESULTS: All 17 patients underwent successful FCSEMS placement and removal. Etiologies of BBS included: cholecystectomies (*n* = 8), cholelithiasis (*n* = 2), hepatic artery compression (*n* = 1), pancreatitis (*n* = 2), and Whipple procedure (*n* = 1). All bile leaks occurred following cholecystectomy. The anatomic location of BBS varied: distal common bile duct (*n* = 7), common hepatic duct (*n* = 1), hepaticojejunal anastomosis (*n* = 2), right intrahepatic duct (*n* = 1), and choledochoduodenal anastomatic junction (*n* = 1). All bile leaks were found to be at the cystic duct. Twelve of 17 patients had failed prior stent placement or exchange. Resolution of the biliary strictures and bile leaks was achieved in 16 of 17 patients (94%). The overall median stent time was 63 d (range 27-251 d). The median stent time for the BBS group and bile leak group was 62 ± 58 d (range 27-199 d) and 92 ± 81 d (range 48-251 d), respectively. All 17 patients underwent successful FCSEMS removal. Long term follow-up was obtained for a median of 575 d (range 28-1435 d). Complications occurred in 5 of 17 patients (29%) and included: migration (*n* = 2), stent clogging (*n* = 1), cholangitis (*n* = 1), and sepsis with hepatic abscess (*n* = 1).

CONCLUSION: Placement of fully covered self-expanding metal stents may be used in the management of benign biliary strictures and bile leaks with a low rate of complications.

Key words: Bile leaks; Benign biliary stricture; Fully covered metal stents; Biliary disease

Core tip: We studied 17 patients with Benign Biliary

Strictures (BBS) (n = 12) and bile leaks (n = 5) from July 2007 to February 2012 that had fully covered self-expanding metal stents (FCSEMs) placed. Twelve of 17 patients had failed prior stent placement or exchange. After a median stent time of 63 d, we found 16 of 17 patients (94%) had complete resolution of biliary strictures and bile leaks. We reported complications in 5 of 17 patients (29%) which included: migration (n = 2), stent clogging (n = 1), cholangitis (n = 1), and sepsis with hepatic abscess (n = 1).

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INTRODUCTION

Benign biliary diseases, including benign biliary strictures (BBS) and bile duct leaks, are common and management can be potentially challenging. BBS may occur as a result of chronic pancreatitis, postoperative anastomotic strictures following cholecystectomy and liver transplantation, choledocholithiasis, sclerosing cholangitis and other cholangiopathies[1-3]. Complications of biliary strictures include cholangitis, secondary biliary cirrhosis and end stage liver disease (ESLD). Because of the severity of these complications urgent decompression of strictures is required.

Bile leaks occur after abdominal surgery classically following cholecystectomy, traumatic injury[4], liver transplantation or hepatic resection[5,6]. The most common location of bile leaks is the cystic duct stump followed by the duct of Luschka[6]. Many of these patients require external biliary drainage or develop an internal biliary leak resulting in a biloma, peritonitis or abscess formation[6]. The first-line intervention in treatment of bile leaks involves placement of transpapillary biliary plastic stents and/or sphincterotomy[7,8]. Stent placement has been effective in the closure of 70%-100% of postcholecystectomy bile leaks[8].

Complex leaks are defined as those that are refractory to endoscopic intervention with biliary sphincterotomy or plastic stent placement, bile leaks following orthotopic liver transplantation or complicated cholecystectomy with large leaks. Previous studies have shown single large diameter or multiple stents across the site of the leak are superior in complex leaks[6,8]. Bile leaks can further be classified by endoscopic retrograde cholangiography (ERC) into low grade (leak identified only after intrahepatic opacification) or high grade (leak observed before intrahepatic opacification)[8]. In a study by Sandha *et al*[8] of 204 patients with bile leaks, transpapillary biliary stenting was found to be more effective than sphincterotomy alone in patients with high grade leaks.

Management of BBS includes decompression by endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy and stent placement, and ultimately choledochojejunostomy. Recent studies have shown that therapeutic ERC with stent placement in BBS is a potential, although not equivalent, alternative to surgery. Compared with surgery, stent placement has lower rates of stricture recurrence, lower cost, and lower overall morbidity and mortality[9]. The standard of care for repairing bile leaks involves placement of transpapillary biliary stents with or without sphincterotomy.

Currently, plastic stents are the only Food and Drug Administration (FDA) approved therapy used in benign biliary conditions to treat biliary strictures and bile leaks. Plastic stent patency, usually 3-4 mo in malignant strictures, has been limited secondary to occlusion due to deposition of a bacterial biofilm within the stent lumen[10,11]. Self-expanding metal stents (SEMS) provide prolonged stent patency of up to 9 mo and can be deployed from a small diameter delivery system that can expand to a large diameter (10 mm) permitting improved biliary drainage. Initially, SEMS were bare metal (uncovered) meaning they had no coating material covering the metal stent. A major challenge with uncovered SEMS was in-stent epithelial hyperplasia accounting for the difficult removability of the stents and poor long term patency[2]. Partially covered self-expanding metal stents (PCSEMS) have had some success in BBS and bile leaks but were limited by the susceptibility to in-stent hyperplasia, migration, and difficultly in extraction due to mucosal hyperplasia at the uncovered proximal ends[1,2]. Advances in the development of endoprosthesis led to Fully Covered SEMS (FCSEMS) which are coated circumferentially with a material that prevents stent occlusion and imbedding due to bacterial colonization, tissue hyperplasia, and tumor ingrowth thereby increasing the duration of stent patency and permitting easier stent retrieval. Moreover, FCSEMS use in BBS and bile leaks may result in fewer endoscopic sessions and not require placement of multiple plastic stents[12]. Previous studies have shown successful outcomes of FCSEMS used in malignant biliary strictures however the data for use in benign biliary disease remains limited and conflicting (Table 1). Our studies primary aim was to evaluate the efficacy, patency and rate of complications with placement of FCSEMS for BBS and bile leaks.

MATERIALS AND METHODS

From July 2007 and February 2012, seventeen patients diagnosed at Harbor-UCLA Medical center with BBS and bile leaks who had undergone endoscopic placement of a FCSEMS were included in this study. Twelve patients were females and five patients were males; the mean age was 50.5 ± 16.5 years (range 27-77 years). Patient records were reviewed retrospectively. The most common presenting symptom among patients was abdominal pain. All strictures had brushings and biopsies to rule out malignancy. Fourteen patients had endoscopic placement of VIABIL® (Conmed, Utica, New York, United States) stents and three had Wallflex® (Boston Scientific,

Table 1 Studies reporting placement of covered metal stent in benign biliary strictures and bile leaks

Ref.	No. of patients/ No. stents	BBS or bile leaks	Etiology	Stent type	Time to removal	Results (success rate)	Complications
Benign biliary strictures							
Deviere *et al*[18]	20/20	BBS	CP	Wallstent FCSEMS	NA[1]	90%	Epithelial hyperplasia (2)
Cantù *et al*[19]	14/14	BBS	CP	pCSEMS	21 mo (median)	37.5% at 30-mo fu	Cholestasis (7), cholangitis (5), duodenal migration (2), cholecystitis (1)
Kuo *et al*[20]	3/4	BBS	OLT	FCSEMS	32 d (median)	100%	Septicemia (1), misplacement (1)
Kahaleh *et al*[2]	79/79	BBS	CP, OLT, BC, INF, surgical	pCSEMS	4 mo (median)	90% ITT 75%	Migrations (11)
Cahen *et al*[21]	6/6	BBS	CP	FCSEMS	3-6 mo (median)	66%	Migration (2), recurrent stricture (1)
Mahajan[3]	44/44	BBS	CP, gallstone related, OLT, AP, PSC	FCSEMS	3.3 mo (median)s	83% 77% ITT (3 patients died)	Post ERCP pancreatitis (1), mucousal ulceration and bleeding (1)
Garcia-Cano[22]	20/20	BBS	Biliary fistula, perforation of papilla, to remove uncovered stents, benign strictures, CBD stones	Wallstent FCSEMS	132 d (median)	70%	Pancreatitis (3)
Sauer *et al*[23]	19/19	BBS and bile leaks	Liver transplant	Wallflex	11.7 wk (mean)	79%	Proximal migration (1), distal migration (5), occlusion (1), *de novo* stricture (2)
Bile leaks							
Wang *et al*[24]	13	Complex bile leaks	Chole and OLT	Viabil FCSEMS	103 d	85% ITT	Mucousal ulcerations (4), *de novo* choledocholithiasis/ luminal debris (10), strictures (2)
Sandha *et al*[8]	97	High grade leaks	Chole	FCSEMS	42 d	100%	Post ERCP pancreatitis (2), duodenal perforation (1)
Kahaleh *et al*[1]	16/16	Bile leaks	Chole, OLT	Wallstent FCSEMS	3 mo	93%	Stent migration (2)
Sauer *et al*[23]	19/19	BBS and bile leaks	Liver transplant	Wallflex	11.7 wk (mean)	79%	Proximal migration (1), distal migration (5), occlusion (1), *de novo* stricture (2)

[1]Stents not extracted in the study. OLT: Orthotopic liver transplant; Chole: Cholecystectomy; AP: Autoimmune pancreatitis; PSC: Primary sclerosing cholangitis; ITT: Intent to treat; pCSEMS: Partially covered self-expanding metal stent; FCSEMS: Fully covered self-expanding metal stent; BBS: Benign biliary strictures; CP: Cholangiopancreatography.

Mass) stents. An 8 or 10 mm diameter FCSEM Viabil® (Conmed, Utica, New York, United States) or Wallflex® (Boston Scientific, Mass) was deployed over a guidewire under endoscopic and fluoroscopic visualization across the biliary stricture or bile leak. The length of the stents varied ranging from 4 to 10 cm. When the gallbladder was present FCSEMS were placed below the cystic duct to avoid cholecystitis. All patients had undergone a biliary sphincterotomy prior to placement of FCSEMS.

Stent patency can be defined as adequate bile and contrast flow from the stent and into the ampulla during ERCP without clinical signs and/or symptoms of biliary obstruction (*e.g.*, RUQ pain/tenderness, elevated alkaline phosphatase ± bilirubin, *ect.*). Stent placement was confirmed fluoroscopically and endoscopically. Repeat cholangiogram after stent deployment revealed the absence of a leak. Criterion for bile leak resolution at ERCP is defined as absence of contrast extravasation from the CBD, cystic duct remanent, or gall bladder fossa.

Stents were removed after at least a month, only after liver function test (LFT) normalization and resolution of symptoms, using rat-tooth forceps or a snare. After stent removal, a cholangiogram was performed to document resolution of BBS and sealed leaks. In time of follow-up, LFTs were reviewed after stent extraction and routinely during follow up course. Stent duration was expressed as median ± SD. All patients were contacted by a physician after stent removal, as a follow-up to evaluate for biliary pain and jaundice. Any patients who developed signs of biliary obstruction underwent follow-up ERCP to re-evaluate for stricture re-occurrence. Failure of endoscopic therapy was defined as persistent biliary stenosis or continuous biliary leakage after 12 mo of stent placement. Patients who failed stent therapy were referred for surgical intervention.

RESULTS

From July 2007 to February 2012, seventeen patients with BBS (12 patients) or bile leaks (5 patients) under-

Table 2 Patient characteristics and demographics

Case No.	Age, yr	Sex	Etiology	Location	FCSEMS (mm), type	Complications	Duration of stenting (d)	Follow-up after removal (d)	Results
Benign biliary strictures									
1	47	M	Biliary anastomosis/ Whipple	Choledocho-duodenal anastomosis	10 mm × 0 mm Viabil	None	89	1435	Patent
2	77	F	Cholecystectomy	Distal CBD	10 mm × 10 cm wallstent	None	92	1210	Patent
3	36	F	Cholelithiasis	Distal CBD	10 mm × 6 cm Viabil	None	37	1138	Patent
4	51	F	Cholelithiasis	Distal CBD	10 mm × 6 cm Viabil	None	161	1131	Patent
5	73	M	Cholecystectomy	Right intrahepatic duct	10 mm × 10 cm Viabil	Solid debris in lumen	160	1112	Patent
6	76	F	Cholecystectomy	H-J anastomosis	8 mm × 6 cm Viabil	None	29	55	Patent
7	27	F	Cholecystectomy	H-J anastomosis	10 mm × 4 cm Viabil	None	42	176	Patent
8	47	F	Compression by hepatic artery	CHD	80 mm × 8 cm wallstent	None	35	302	Patent
9	36	F	Cholecystectomy	CBD	10 mm × 80 mm Viabil	Migration	27	463	Not patent
10	45	F	Chronic pancreatitis/ cholecystectomy	Distal CBD	10 mm × 10 cm Viabil	None	63	36	Patent
11	42	F	Pancretitis and pancreatic head necrosis	Distal CBD	10 mm × 6 cm wallstent	Recurrent cholangitis (n = 2), migration	199	122	Patent
12	35	M	Cholecystectomy	Distal CBD	10 mm × 8 cm Viabil	Abd pain following day of stent placement; repeat ERCP showed residual bile duct stones	57	41	Patent
Bile leaks									
13	75	F	Cholecystectomy	Bile leak (high grade); complex	10 mm × 80 mm Viabil	None	99	1364	Sealed
14	49	F	Cholecystectomy	Bile Leak (high grade)	10 mm × 10 cm Viabil	None	92	1294	Sealed
15	30	F	Cholecystectomy	Bile leak (low grade); complex	10 mm × 80 mm Viabil	Occluded stent after lost to follow-up (eight and a half months)	251	1007	Sealed
16	64	M	Cholecystectomy	Bile leak (high grade)	8 mm × 8 cm Viabil	None	62	575	Sealed
17	50	M	Cholecystectomy	Bile leak (low grade)	10 mm × 80 mm Viabil	Hepatic abscess and Sepsis	48	28	Sealed

M: Male; F: Female; FCSEMS: Fully covered self-expandible metallic stents; Chole: Cholecystectomy; CBD: Common bile duct; H-J: Hepaticojejunostomy; CHD: Common hepatic duct; ERCP: Endoscopic retrograde cholangiopancreatography.

went successful placement of FCSEMS. Etiologies of BBS included: cholecystectomies (n = 8), cholelithiasis (n = 2), hepatic artery compression (n = 1), pancreatitis (n = 2), and Whipple procedure (n = 1). All bile leaks occurred following cholecystectomy. Etiologies of BBS and bile leaks are shown in Table 2. The anatomic location of BBS varied: distal common bile duct (n = 7), common hepatic duct (n = 1), hepaticojejunal anastomosis (n = 2), right intrahepatic duct (n = 1), and choledochoduodenal anastomatic junction (n = 1). All bile leaks were found to be at the cystic duct. One patient was had a previous ERCP with intraductal ultrasonography (IDUS) showing possible hepatic artery compression leading to the common hepatic duct stricture. A repeat ERCP with IDUS for stent placement demonstrated a normal hepatic artery. Twelve of 17 patients had failed prior stent placement or exchange with plastic and/or metal stents (seven having multiple stents). Because several of our subjects were referred to us who had stents placed at other facilities we were unable to determine the length of previous stenting. In patients with hepaticojejunal anastomotic strictures stents were placed percutaneously.

The median stent time was for all subjects was 63 d (mean 90.7 ± 65 d; range 27-199 d). The median stent time for the BBS group and bile leak group was 62 ± 58 d (range 27-199 d) and 92 ± 81 d (range 48-251 d), respectively. All 17 patients underwent successful FCSEMS removal. Resolution of biliary strictures and bile leaks was achieved in 16 of 17 patients (94%) (Figure 1). One patient with a bile leak did not have her stent removed until eight and a half months after placement due to loss of follow-up. An ERCP showed a sealed bile leak but an occluded stent which was extracted. One patient who failed stent therapy for BBS was referred to surgery. Long term follow-up, which included labs and symptom assessment, was obtained for a median of 575 d (range 28-1435

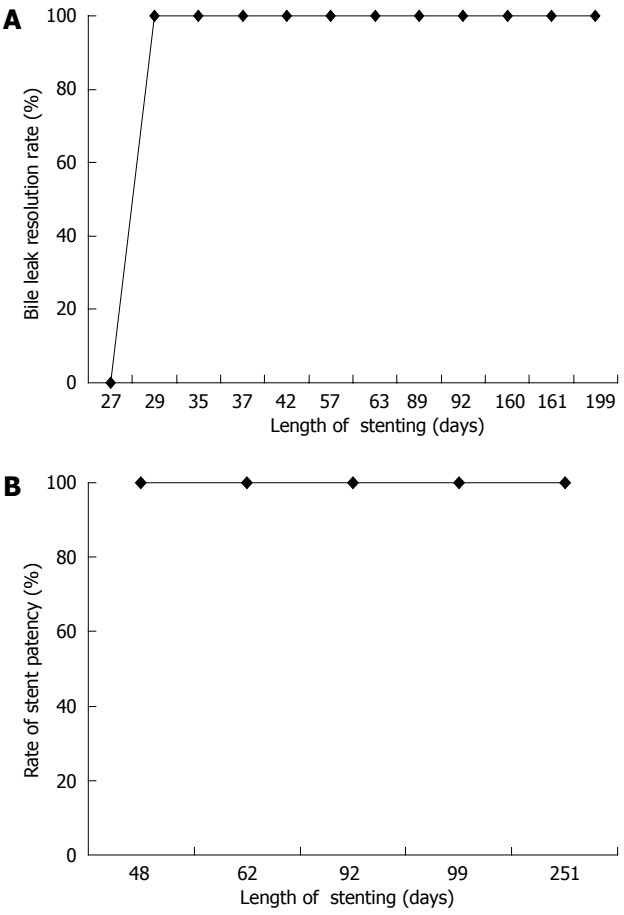

Figure 1 Stent patency rate (%) in patients with benign biliary strictures after insertion of fully covered self-expanding metal stents plotted against stent duration (d). A: Stent patency rate (%) in 12 patients with benign biliary strictures after insertion of fully covered self-expanding metal stents plotted against stent duration; B: Bile leak resolution rate (%) in 5 patients with bile leaks after insertion of fully covered self-expanding metal stents plotted against stent duration (d).

d). Follow-up was longer than one year in 10 cases (58%). No patients reported recurrent biliary pain or jaundice on follow-up. All patients liver function tests normalized. Figure 2 demonstrate stent placement for BBS and bile leaks.

FCSEMS related complications

Complications occurred in 5 of 17 patients (29%). Two patients were found to have proximal stent migration. The first was a Viabil metal stent seen to have migrated proximally. The time elapsed from stent placement to migration of FCSEMS was 27 d. Using rat-toothed forcepts the migrated stent was grasped at the distal end and removed. Prior to removal of the stent because the stent had migrated inwards, dilation of the sphincterotomy site was performed after which the distal end of the stent could be seen. The CBD stricture had resolved at the time of extraction. The second migration involved a Wallstent that migrated proximally. The time elapsed from the stent placement to migration was 66 d. A second Wallstent was placed into a migrated Wallstent. Both Wallstents were removed after 133 d.

Two additional patients had stent occlusion caused by intraluminal debris and bile duct stones. The time elapsed from stent placement to occlusion caused by intraluminal debris and bile duct stones were 160 and 251 d, respectively.

One patient developed recurrent cholangitis due to stent occlusion. One patient was found to have a hepatic abscess of the right liver lobe after stent placement for a bile leak. He later developed sepsis and was transferred to the intensive care unit (ICU). Overall, two patients had *de novo* choledocholithiasis and/or lumen debris that required multiple balloon sweeps and irrigation of the bile duct.

DISCUSSION

Placement of plastic stents with or without sphincterotomy is the most popular and accepted therapy for treatment of BBS and bile leaks in most centers. Short-term patency rates, limited stent diameter and requirement of multiple endoscopic sessions with stenting have led to the development of SEMS[13-15].

The overall success rate in our study for BBS and bile leaks was 94% (16/17). In the subset of patients with only BBS the success rate was 92% (11/12) (Figure 1A). Our results compare favorably to past results including a case series by Mahajan *et al*[5] of 44 patients with BBS who were treated with FCSEMS (Viabil, Conmed) and demonstrated a success rate of 83% (34/41) after median stent time of 3.3 mo (Table 1).

In our study, FCSEMS were removed only when all criteria described earlier in methods were met. All stents were able to be removed without any difficulty with median duration of 89 d (range 29-428 d). Although there is no consensus on the optimal duration of biliary stenting some advocate for no longer than 6 mo[2]. Several randomized trials have shown that FCSEMS remained patent for up to a median of 9 mo[16,17]. Our stricture recurrence rate was 0% after a median follow-up of 575 d. Dumonceau *et al*[5] reported a stricture recurrence was 19% on 36 patients who underwent plastic stent placement for BBS during a mean follow-up period of 44 mo.

Patients presenting with bile leaks had placement of Viabil FCSEMS. Viabil stents (Conmed, Utica, NY) are entirely covered with polytetrafluoroethylene and fluorinated ethylene propylene (ePTFE/FEP) liner that acts as a barrier to tissue ingrowth permitting long stent duration and easier extraction. Moreover, the anchoring fins placed on each tail end aid in prevent stent migration. Although our results are limited by the small sample size we were able to achieve 100% success rate in resolution of biliary leaks with temporary placement of FCSEMS for a mean of 110 ± 81 d (range, 48-251 d) (Figure 1B). The overall success rate for the subset of patients with bile leaks was 100%. Our results again compare favorably to past studies (Table 1). Three of 5 patients had high grade leaks and two of 5 patients had complex bile leaks refractory to previous stenting (Table 2). One patient had a biloma

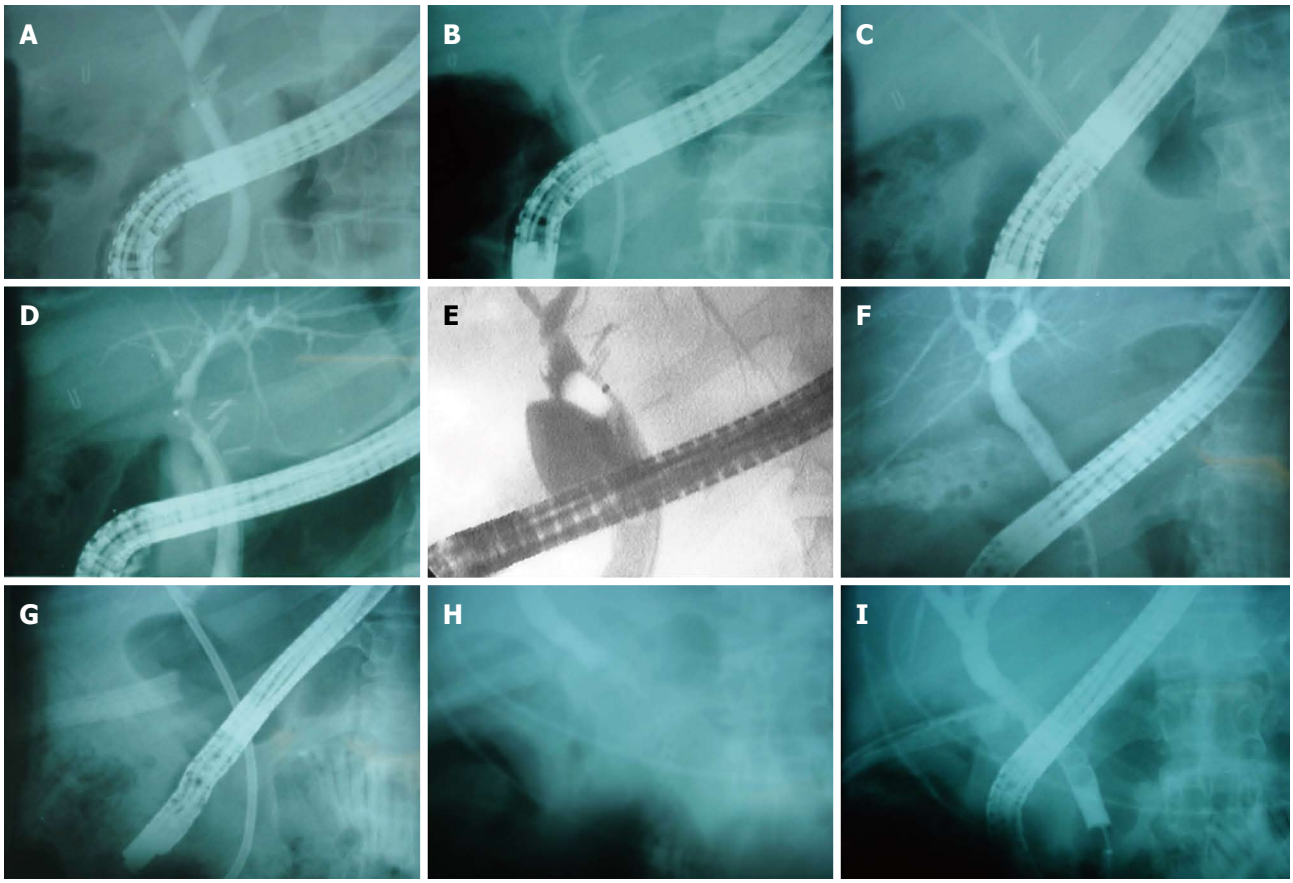

Figure 2 Stent placement for benign biliary strictures and bile leaks. A: A Left intrahepatic duct stricture after cholecystectomy and repair; B: Placement of biliary plastic stent for intrahepatic duct stricture; C: Placement of 2 plastic stents for persistent intrahepatic duct stricture; D: Persistent intrahepatic stricture after placement of 2 plastic biliary stents every 3 mo for 2 years. This stricture did not resolve therefore plastic stents were extracted and a Viabil fully covered metal stent was later placed; E: Intrahepatic stricture resolution following Viabil stent removal after 5 mo; F: Bile leak in a patient with a cystic stump and gangrenous gallbladder; G: Placement of plastic biliary stent in patient with bile leak; H: Placement of viabil stent since bile leak did not resolve with plastic stents; I: Resolution of bile leak following Viabil stent removal after 1 mo.

secondary to bile leak in the cystic duct and required percutaneous drain. She was lost to follow-up after eight and a half months and returned with abdominal pain. An ERCP revealed an occluded stent and intrahepatic ductal dilation. The stent was removed and a follow-up ERCP revealed a sealed bile leak.

Twelve patients had failed prior plastic stent placement and were referred to Harbor UCLA for refractory strictures (seven having had ≥ 2 stents). These subjects had fully covered metal stents placed for recurrent strictures. Because several of our subjects had stents placed at outside hospitals we are unable to determine the length of stenting, diameter or type of stent placed for all of these twelve patients. We did not encounter technical difficulties of FCSEMS placement in patients who had failed prior plastic stent therapy. There was no significant difference in total stenting time for patients that had failed prior plastic stenting and new onset strictures or bile leaks.

Upon stent removal, three patients were found to have biliary sludge and/or luminal debris requiring multiple balloon sweeps and irrigation. The incidence of sludge/luminal debris was noted to be proportional to the duration of stenting. One patient was found to have a hepatic abscess of the right liver lobe on computed tomography scan after stent placement for a bile leak proximal to the cystic duct. The patient was transferred to the ICU for sepsis. It is unclear whether the abscess developed as a result of ERCP or secondary to an underlying infection. One patient had developed cholangitis due to an occluded stent. This patient was treated successfully with placement of another stent within the original stent, multiple balloon sweeps to remove sludge, and a course of antibiotics. This compares favorably to rates of cholangitis observed with plastic stent placement for BBS of 18%[5]. The patient with stenting of a BBS localized to the right hepatic duct had an additional anastomosis done by surgery between the other hepatic duct and the duodenum. It is important to mention that unilateral placement of FCSEMS beyond the hepatic hilum harbors the risk of occluding the contralateral hepatic duct and side branches of the right or left hepatic ducts (depending on Bismuth stage of stricture). All complications in our study were treated conservatively.

Overall, our study showed that temporary placement of FCSEMS successfully treated BBS and bile leaks with

excellent long-term patency rates and relatively few complications. FCSEMS may provide an effective method in management of BBS and bile leaks while allowing easy endoscopic removability. FCSEMS can be easily removed after insertion and remain in place for several months although there is insufficient data as to what the optimal duration of placement is. The high cost of FCSEMS may be offset by a reduction in ERCP sessions and recurrent stenting for recurrent strictures[14,15].

COMMENTS

Background

Management of bile leaks and benign biliary strictures (BBS) involves placement of plastic and uncovered metal stents which have been associated with limited long term stent patency secondary to stent lumen occlusion and epithelial hyperplasia, respectively.

Research frontiers

Recent advances in development of endoprosthesis have led to the development of fully covered self-expanding metal stents (FCSEMs) which are coated circumferentially with a material that prevents stent occlusion due to bacterial colonization, tissue hyperplasia, and tumor in growth thereby increasing the duration of stent patency in BBS and bile leaks.

Innovations and breakthroughs

In this retrospective review of patients with BBS and Bile leaks treated with FCSEMS, stricture and bile leak resolution was achieved in 16 of 17 patients after a median follow-up time of 575 d after stent extraction.

Applications

This study demonstrated that temporary placement of FCSEMS successfully treated BBS and bile leaks with excellent long-term patency rates and relatively few complications.

Peer review

The manuscript entitled "An evaluation of fully covered self-expanding metal stents in benign biliary strictures and complex bile leaks" provided valuable data about the safety and efficacy of FCSEMS for endoscopic treatment of benign biliary strictures and bile leaks.

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BRIEF ARTICLE

Successful treatment of cervical esophageal leakage by endoscopic-vacuum assisted closure therapy

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Abstract

AIM: To evaluate the efficacy and safety of endoscopic-vacuum assisted closure (E-VAC) therapy in the treatment of cervical esophageal leakage.

METHODS: Between May and November 2012, three male patients who developed post-operative cervical esophageal leakage were treated with E-VAC therapy. One patient had undergone surgical excision of a pharyngo-cervical liposarcoma with partial esophageal resection, and the other two patients had received surgical treatment for symptomatic Zenker's diverticulum. Following endoscopic verification of the leakage, a trimmed polyurethane sponge was fixed to the distal end of a nasogastric silicone tube and endoscopically positioned into the wound cavity, and with decreasing cavity size the sponge was positioned intraluminally to cover the leak. Continuous suction was applied, and the vacuum drainage system was changed twice a week.

RESULTS: The initial E-VAC placement was technically successful for all three patients, and complete closure of the esophageal leak was achieved without any procedure-related complications. In all three patients, the insufficiencies were located either above or slightly below the upper esophageal sphincter. The median duration of the E-VAC drainage was 29 d (range: 19-49 d), with a median of seven sponge exchanges (range: 5-12 sponge exchanges). In addition, the E-VAC therapy reduced inflammatory markers to within normal range for all three patients. Two of the patients were immediately fitted with a percutaneous enteral gastric feeding tube with jejunal extension, and the third patient received parenteral feeding. All three patients showed normal swallow function and no evidence of stricture after completion of the E-VAC therapy.

CONCLUSION: E-VAC therapy for cervical esophageal leakage was well tolerated by patients. This safe and effective procedure may significantly reduce morbidity and mortality following cervical esophageal leakage.

Key words: Endoscopic-vacuum assisted closure therapy; Vacuum therapy; Negative pressure wound therapy; Cervical esophageal leakage; Anastomotic leakage

Core tip: Traditional methods to treat cervical esophageal leakage close to the upper esophageal sphincter are associated with high morbidity and mortality. The newly developed method of endoscopic-vacuum assisted closure (E-VAC) therapy using polyurethane sponges has been demonstrated as efficacious for treating gastrointestinal tract leakages. We applied E-VAC therapy to three patients with post-operative cervical leakage and achieved complete closure in all, without any procedure-related complications. The E-VAC therapy was well tolerated by patients with cervical esophageal leakage, and its application in this patient population may contribute to a significant reduction in morbidity

and mortality.

Lenzen H, Negm AA, Erichsen TJ, Manns MP, Wedemeyer J, Lankisch TO. Successful treatment of cervical esophageal leakage by endoscopic-vacuum assisted closure therapy. *World J Gastrointest Endosc* 2013; 5(7): 340-345 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i7/340.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i7.340

INTRODUCTION

Anastomotic leakage is a potentially life-threatening complication that may follow esophageal surgery. The leakage may range in severity from a minor anastomotic defect to a fulminant leak with systemic sepsis and multiple organ failure[1-3]. Cervical anastomoses have been associated with leakage rates as high as 40% and a mortality rate of 5%[4-6]. The treatment of cervical anastomotic leakage above the upper esophageal sphincter is particularly challenging, and only limited treatment options are available. Traditionally, the repair of cervical leakage has involved surgical intervention[7]; however, re-operation is associated with high morbidity and mortality rates[8]. Placement of self-expandable metal stents in such situations is difficult or even impossible and is associated with a high rate of procedure-related complications, such as globus sensation and/or respiratory insufficiency. Therefore, the procedure is often not performed[9-11].

Over the last decade, several endoscopic treatment options for repair of esophageal anastomotic leakages have emerged, including fibrin glue injection, endoscopic transluminal drainage and self-expanding metal stents[12-14]. Endoscopic treatment using self-expandable metal or plastic stents has become the treatment of choice for anastomotic esophageal leakage, and its reported success rates are above 80%[12,15-18]. Most recently, endoscopic-vacuum assisted closure (E-VAC) has been suggested as an effective treatment modality for esophageal anastomotic leakage in the upper gastrointestinal tract[19]. E-VAC therapy involves placing polyurethane sponges into the wound cavity that was induced by the leak, followed by application of an external vacuum through a transnasal tube to drain the infected fluid and induce the formation of granulation tissue. Recent studies of E-VAC therapy for the treatment of leaks following esophageal anastomoses have demonstrated that the procedure is capable of achieving successful wound closure with no associated mortality[20-23]. However, these studies have mainly examined intrathoracic anastomotic leakages. Here, we report the successful application of E-VAC therapy to treat cervical anastomotic leakages in three patients.

MATERIALS AND METHODS

Patients and procedure description

Between May and November 2012, three male patients with post-operative cervical esophageal leakage were treated with E-VAC therapy at the Endoscopy Unit of the Hannover Medical School (Hannover, Germany). E-VAC placement was performed as described previously[22] as the modified form of the VAC technique, which is an established treatment modality for chronic and infected cutaneous wounds[24,25]. Briefly, a trimmed polyurethane sponge, pore size 400-600 μm (KCI, Wiesbaden, Germany) was fixed to the distal end of a nasogastric silicone tube (Freka 15 Ch; Fresenius Kabi, Bad Homburg, Germany) and introduced into the cavity under endoscopic vision. With decreasing cavity size, the sponge was placed endoluminally to cover the entire esophageal defect. A continuous negative pressure of 125 mmHg was applied using a vacuum pump (KCI). The vacuum drainage system was endoscopically changed two times per week. All endoscopic interventions were performed either under general anesthesia or conscious sedation with propofol and midazolam. All three patients gave informed consent for publication of their case, and retrospective analysis was performed in accordance with the Declaration of Helsinki.

Descriptive statistics were used to evaluate the patients' demographic and clinical characteristics. The data are presented as individual values, median, and ranges.

RESULTS

Characteristics of patients

We used E-VAC therapy to treat three male patients with post-operative cervical esophageal leakage. The patients were 69-, 71- and 80-year-old (Table 1). Patient 1 had undergone surgical excision of a pharyngo-cervical liposarcoma with partial esophageal resection followed by an insufficiency 3 cm below the upper esophageal sphincter (17 cm from the incisors). Patients 2 and 3 had suffered from cervical esophageal perforation following surgical treatment of a symptomatic Zenker´s diverticulum. Patient 2 had open surgery with a diverticulectomy and myotomy (Figure 1). Patient 3 suffered from recurrent Zenker´s diverticulum and was treated with transoral endoluminal mucomyotomy. The insufficiency in these two cases was located above the upper esophageal sphincter, at 17 cm from the incisors in patient 2 and at 19 cm from the incisors in patient 3.

Results of E-VAC therapy

All three patients had endoscopically diagnosed esophageal leakage and their initial E-VAC placement was technically successful. In all three cases, the sponge was initially placed into the extraluminal cavity (intracavitary), which was changed to intraluminal placement with decreasing cavity size. Two patients immediately received a percutaneous enteral gastric feeding tube with jejunal extension (PEG-J tube) and the third patient received parenteral feeding (Table 2). The median duration of E-VAC therapy was 29 d (range: 19-49 d) with a median of seven sponge exchanges (range: 5-12 sponge exchanges) (Table

Table 1 Characteristics of three patients who underwent endoscopic-vacuum assisted closure treatment

Patient	Sex	Age, yr	Diagnosis	Surgical procedure	Cause of leakage	Distance from the dental arch, cm	Time interval from diagnosis to start of E-VAC therapy, d	Time interval from surgery to start of E-VAC therapy, d
1	Male	80	Liposarcoma	Thoracic esophageal resection	Anastomotic insufficiency	17	11	25
2	Male	71	Zenker´s diverticulum	Diverticulectomy and myotomy	Anastomotic insufficiency	17	0	13
3	Male	69	Zenker´s diverticulum	Mucomyotomy	Iatrogenic perforation	19	0	2

E-VAC: Endoscopic-vacuum assisted closure.

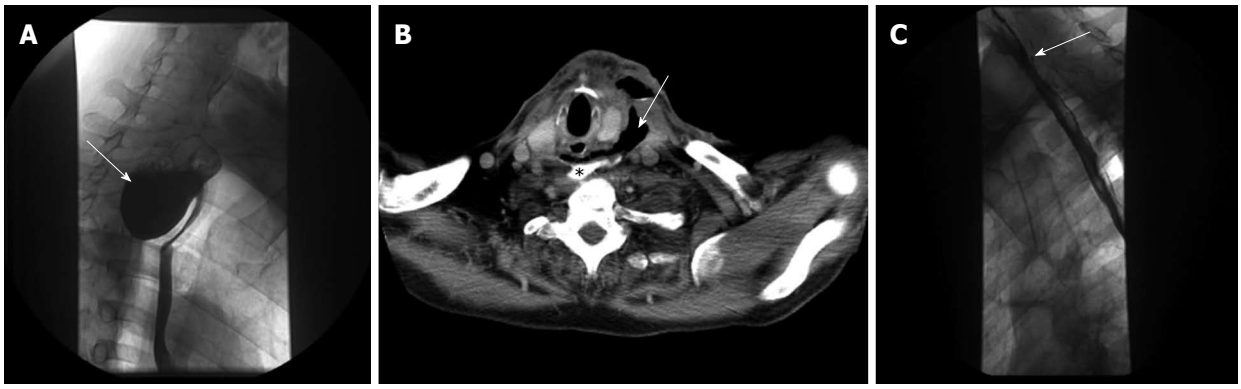

Figure 1 Radiographic findings of the second patient with Zenker's diverticulum. A: Barium swallow showing the Zenker's diverticulum (arrow) out-pouching from the posterior wall of the esophagus. Computed tomography scan showing the cervical esophageal leakage with periesophageal mediastinal abscess and extraluminal air (arrow); B: Contrasted esophagus (asterisk) with extravasation; C: Gastrografin swallow after endoscopic-vacuum assisted closure treatment showing a small residual saccular protrusion (arrow), but no leakage and no stenosis, clip *in situ*.

Table 2 Endoscopic-vacuum assisted closure treatment characteristics

Patient	Treatment type	Sponge exchanges, *n*	E-VAC treatment duration, d	Hospitalization duration, d	Endoscopic follow-up[2] duration, d	Feeding method
1[1]	Intracavitary/ intraluminal	1 × 9 1 × 3	1 × 34 1 × 15	108	None	PEG-J tube
2	Intracavitary/ intraluminal	5	19	42	47	Intravenously
3	Intracavitary/ intraluminal	7	29	46	206	PEG-J tube

[1]Patient did not achieve complete healing after the first treatment cycle and underwent a second treatment; [2]Days after sponge removal. E-VAC: Endoscopic-vacuum assisted closure; PEG-J tube: Percutaneous endoscopic gastrostomy with jejunal extension.

2). Median hospitalization time was 46 d (range: 42-108 d). In all three patients, complete closure of the leakage was achieved without any procedure-related complications and without the need for surgical re-intervention (Figure 2). Sponge therapy was well tolerated and there was no evidence of residual leakage either clinically or after Gastrografin swallow in patients 2 and 3. Inflammation was assessed by measuring white blood cell (WBC) counts and C-reactive protein (CRP) levels. In two patients, the WBC count was initially elevated but decreased to within the normal range following E-VAC therapy. All three patients had markedly elevated CRP levels (range: 152-296 mg/L) at the beginning of the treatment, which were reduced to almost normal (range: 3-34 mg/L) by the time of discharge (Table 3). Patients were clinically followed-up after hospital discharge and endoscopy was performed in two patients at post-discharge days 47 and 206. All three patients had normal swallow function and no evidence of stenosis after completion of the E-VAC therapy.

DISCUSSION

Esophageal anastomotic leakage is associated with high morbidity and mortality rates, particularly when surgical repair is required[1,4,8]. Consequently, efforts have been made to devise less invasive treatment modalities. A number of endoscopic techniques have emerged in recent years, including E-VAC therapy. Here, we report the successful use of E-VAC therapy for the treatment of post-

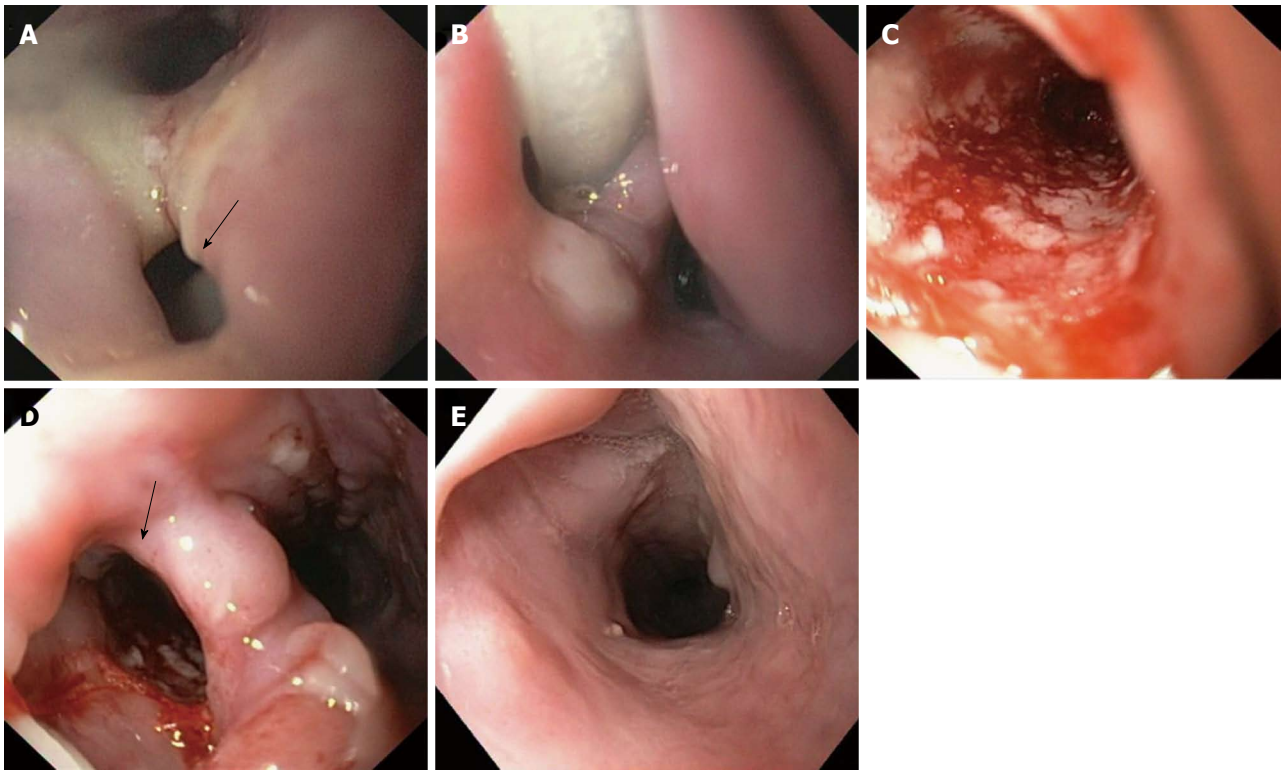

Figure 2 Endoscopic images of cervical esophageal leakage after surgical diverticulectomy and cricopharyngeal myotomy and subsequent treatment with endoscopic-vacuum assisted closure. A: The defect was large enough to be intubated with a standard endoscope (arrow); B: Sponge positioned in the extraluminal wound cavity and connected to a drainage tube; C: Clean wound ground and formation of fresh granulation tissue with good vascularisation at 3 d after the endoscopic-vacuum assisted closure (E-VAC) therapy; D: Appearance of esophageal defect (arrow) at 11 d after the E-VAC therapy; E: Complete healing of the leakage at 47 d after completion of the E-VAC treatment.

Table 3 Inflammation markers monitored during the endoscopic-vacuum assisted closure treatment

Patient	WBC		CRP	
	1st sponge placement	Sponge removal	1st sponge placement	Sponge removal
1	11.6	4.3	152	34
2	8.2	8.8	244	34
3	14.3	9.9	296	3

WBC: White blood cell count, normal range: 4.4-11.3 Tsd/μL; CRP: C-reactive protein, normal range: < 8 mg/L.

operative cervical esophageal leakage.

Previous studies of E-VAC treatment were mainly concerned with the management of thoracoabdominal esophageal leakages; although, cervical esophagogastric anastomoses have a higher incidence of leaks compared to thoracic anastomoses[5]. Cervical leakages treated with E-VAC therapy have been rarely described[20,26]. Here, we examined two cases of Zenker´s diverticulum perforation with insufficiencies above the upper esophageal sphincter and one case of surgical excision of a pharyngo-cervical liposarcoma with partial esophageal resection followed by an insufficiency just below the upper esophageal sphincter. Due to high cervical localization of the perforation, stent placement was not considered. In all three patients, complete closure of the leakage was achieved without any procedure-related complications. None of the patients required further surgical intervention, and all three patients displayed regular swallow function after completion of the E-VAC therapy. Follow-up endoscopy in patients 2 and 3 demonstrated complete healing of the esophagus.

These case series indicate that E-VAC therapy has clinical utility in the repair of cervical esophageal leakage. These data justify conducting further studies to examine the potential of E-VAC therapy for treating other iatrogenic cervical esophageal perforations, such as perforations after transesophageal echocardiography, foreign body impaction, or endoscopic and surgical procedures. Compared to the previous studies of E-VAC therapy for treating thoracic esophageal leakage[20,26], our case studies of E-VAC therapy for treating cervical esophageal leakage required longer treatment times and a higher number of sponge changes. Therefore, we recommend early PEG placement for enteral feeding. However, despite the longer treatment times, the E-VAC therapy was well tolerated by all of our patients.

Our case studies suggest that use of E-VAC therapy allows for rapid removal of infected tissue. Prior to E-VAC therapy, all three patients displayed high levels of inflammatory markers that were indicative of systemic inflammatory complications from the esophageal leakage. Notably, a considerable reduction in the levels of these inflammatory markers was observed following treatment,

which suggests that the E-VAC therapy resulted in rapid drainage of the infected wound cavity and control of inflammation.

In summary, we report that E-VAC therapy is a safe and efficacious treatment option for cervical esophageal leakage. E-VAC therapy appears to provide adequate wound drainage, promotion of tissue granulation within the wound cavity, and closure of the cervical esophageal defect. Despite the high localization of the vacuum placement, sponge therapy was well tolerated by our patients. Application of this therapy may contribute a significant improvement in morbidity and mortality. A multidisciplinary approach, involving the coordinated efforts of abdominal and/or ear-nose-throat surgeons, may further enhance E-VAC therapy as a treatment modality for cervical esophageal leakage.

COMMENTS

Background

Traditionally, the repair of cervical esophageal leakage has involved surgical intervention, as placement of self-expandable metal stents in this situation is difficult or even impossible. Most recently, endoscopic-vacuum assisted closure (E-VAC) has been suggested as an effective treatment modality for esophageal leakage. Therefore, the authors investigated the efficacy of E-VAC therapy for cervical leakage above or slightly below the upper esophageal sphincter.

Research frontiers

Cervical esophageal leakage is associated with high morbidity and mortality rates, particularly when surgical repair is required. Therefore, this study evaluated the effectiveness and safety of a non-invasive endoscopic treatment using E-VAC therapy for treating cervical esophageal leakage.

Innovations and breakthroughs

This study demonstrates that E-VAC therapy is an efficacious and safe treatment option for treating cervical esophageal leakage. Despite the high localization of the vacuum placement, the sponge therapy is well tolerated.

Applications

E-VAC therapy can be used as an alternative treatment option for cervical esophageal leakages above or slightly below the upper esophageal sphincter. These findings indicate the benefit of future studies addressing whether E-VAC therapy may also be useful for treatment of other iatrogenic cervical esophageal perforations, such as perforations after transesophageal echocardiography, foreign body impaction, or endoscopic and surgical procedures.

Terminology

The VAC technique is an established treatment modality for chronic and infected cutaneous wounds. Recently, the endoscopic placement of a vacuum-assisted closure system (endoscopic-vacuum assisted closure, E-VAC) in the gastrointestinal tract has been shown to be an effective treatment option for anastomotic leaks. The trimmed polyurethane foam with an open-cell structure (sponge) is fixed to the distal end of a silicone duodenal tube and endoscopically introduced into the necrotic cavity of the upper or the lower gastrointestinal tract. A continuous negative pressure of 125 mmHg is applied using a vacuum pump and the sponge is replaced two to three times per week.

Peer review

The authors conclude that E-VAC therapy is a safe and effective treatment option for cervical esophageal leakage.

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BRIEF ARTICLE

Ultrathin endoscope flexibility can predict discomfort associated with unsedated transnasal esophagogastroduodenoscopy

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Abstract

AIM: To evaluate the effects of choice of insertion route and ultrathin endoscope types.

METHODS: This prospective study (January-June 2012) included 882 consecutive patients who underwent annual health checkups. Transnasal esophagogastroduodenoscopy (EGD) was performed in 503 patients and transoral EGD in 235 patients using six types of ultrathin endoscopes. Patients were given a choice of insertion route, either transoral or transnasal, prior to EGD examination. For transoral insertion, the endoscope was equipped with a thin-type mouthpiece and tongue depressor. Conscious sedation was not used for any patient. EGD-associated discomfort was assessed using a visual analog scale (VAS; no discomfort 0-maximum discomfort 10).

RESULTS: Rates of preference for transnasal insertion were significantly higher in male (male/female 299/204 *vs* 118/117) and younger patients (56.8 ± 11.2 years *vs* 61.3 ± 13.0 years), although no significant difference was found in VAS scores between transoral and transnasal insertion (3.9 ± 2.3 *vs* 4.1 ± 2.5). Multivariate analysis revealed that gender, age, operator, and endoscope were independent significant predictors of VAS for transnasal insertion, although gender, age, and endoscope were those for transoral insertion. Further analysis revealed only the endoscopic flexibility index (EFI) as an independent significant predictor of VAS for transnasal insertion. Both EFI and tip diameter were independent significant predictors of VAS for transoral insertion.

CONCLUSION: Flexibility of ultrathin endoscopes can be a predictor of EGD-associated discomfort, especially in transnasal insertion.

Key words: Esophagogastroduodenoscopy; Ultrathin endoscope; Visual analog scale; Discomfort; Surveillance

Core tip: To evaluate the effects of choice of insertion route and ultrathin endoscope types for unsedated surveillance esophagogastroduodenoscopy (EGD), this prospective study was conducted including 882 consecutive patients who underwent annual health checkup using six types of ultrathin endoscopes in a single in-

stitute. EGD-associated discomfort was assessed using a visual analog scale (VAS) by patients themselves. Statistical analysis of VAS revealed the following two points; Transnasal insertion of ultrathin endoscopy for unsedated EGD can be preferable for younger males rather than elder females. Flexibility of ultrathin endoscopes can be a reliable predictor of reduction in transnasal EGD-associated discomfort rather than thinness of tip.

Ono S, Niimi K, Fujishiro M, Nakao T, Suzuki K, Ohike Y, Kodashima S, Yamamichi N, Yamazaki T, Koike K. Ultrathin endoscope flexibility can predict discomfort associated with unsedated transnasal esophagogastroduodenoscopy. *World J Gastrointest Endosc* 2013; 5(7): 346-351 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i7/346.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i7.346

INTRODUCTION

With improvements in resolution and image enhancement, gastrointestinal endoscopic technology has advanced considerably, detecting an increasing number of superficial neoplasms during surveillance esophagogastroduodenoscopy (EGD)[1-5]. New endoscopic treatments for superficial neoplasms, including endoscopic submucosal dissection, have been reported to be effective and less invasive compared with traditional open surgical exploration and treatment[6-10]. Against the backdrop of such concerns, importance of detecting them in early stage has been emphasized more than ever to achieve curative resection endoscopically.

Although identification of patients at high risk for superficial esophageal squamous cell carcinoma (SESCC) and early gastric cancer (EGC) has been reported as useful, diagnoses must still be confirmed by histopathological assessment of biopsy specimens obtained via endoscopy[11-13]. However, EGD-associated discomfort is a major problem for many patients, who are reluctant to undergo subsequent EGD procedures. Although sedation is possible for reduction of EGD-associated discomfort, cost and various adverse events associated with use of sedative agents must be considered among the risks and benefits of this option[14-17].

Use of an ultrathin endoscope may also reduce unsedated EGD-associated discomfort. Transnasal insertion of ultrathin endoscopes is reported to be a promising alternative in terms of patient satisfaction and cardiopulmonary function[18-21]. Although various types of ultrathin endoscopes are available at present, predictors of discomfort associated with EGD performed using ultrathin endoscopes have not been determined.

This prospective study was conducted to identify predictors of discomfort associated with unsedated EGD performed using ultrathin endoscopes.

MATERIALS AND METHODS

This study was conducted at the Center for Epidemiology and Preventive Medicine of the University of Tokyo after receiving ethics committee approval. From January to June 2012, 882 consecutive patients who underwent annual health checkups were included in this study. Subjects were given a choice of insertion route, either transoral or transnasal, prior to EGD examination. The subjects were prepared for transnasal insertion using the modified spray method, which involves spraying 0.05% naphazoline nitrate into each nostril, followed by injection of a viscous gel of 2% lidocaine hydrochloride[22]. Conscious sedation was not used for any patient.

Six ultrathin endoscopes (A: GIF-XP260N, B: GIF-XP260NS, C: EG-530NW, D: EG-580NW, E: EG16-K10, and F: prototype EG17-K10) from three manufacturers (Olympus Corp., Tokyo, Japan; Fujifilm Holdings Corp., Tokyo, Japan; and Hoya Corp., Tokyo, Japan) were utilized in this study. Prototype EG17-K10 was equipped as part of a collaborative effort by the University of Tokyo Hospital and Hoya Corporation. Profiles of these endoscopies are shown in Table 1. All endoscopes were utilized for this study after being used for more than one hundred EGDs.

The flexibility of each endoscope was evaluated as follows. We fixed the middle portion of the endoscope to a flat surface, and allowed the tip of the endoscope to bend freely under the influence of gravity. After adjusting the length of endoscope from 150 to 400 mm allowed free movement under the influence of gravity, we mapped the position of the tip of the endoscope on a two dimensional grid. Continuous two-dimensional horizontal and vertical distances were plotted, as shown in Figure 1. The mean horizontal distances at the fixed points of 200, 250, 300, 350 and 400 mm were utilized as an endoscopic flexibility index (EFI) to provide a surrogate value of flexibility for each endoscope. Measurements of EFI for each endoscope were performed at room temperature.

The combination of endoscopes changed depending on the day of the week. Consequently, the patients were randomly allocated to six endoscope groups.

All examinations were performed by two operators who had been certified by the Japanese Gastroenterological Endoscopy Society. For transoral insertion, the endoscope was equipped with a thin-type mouthpiece and tongue depressor (Endo-leader; Top Corp.; Tokyo, Japan)[23]. In cases where transnasal insertion failed due to narrowness of nasal cavity or intolerable discomfort, transoral insertion was performed continuously after confirmation with the patient. After completion of the examination, EGD-associated discomfort was evaluated using a visual analogue scale (VAS) by patients themselves in another room from 0 to 10, which were minimum and maximum of discomfort respectively.

Parameters analyzed in this study were examination

Table 1 Profiles of six endoscopes and outcomes for transnasal insertion

	A	B	C	D	E	F
EFI (mm)	224	192.4	175.2	174.8	146	166.6
Tip diameter (mm)	5	5.4	5.9	5.9	5.2	5.4
Transnasal insertion						
Insertion success rate	58/59	110/112	119/123	112/118	47/47	57/57
Nasal bleeding rate	0/58	2/110	2/119	2/112	1/47	0/57
VAS	4.2 ± 2.7	4.0 ± 2.1	4.0 ± 2.4	4.0 ± 2.3	3.2 ± 2.2	3.8 ± 2.3
Examination time (s)	351.0 ± 58.8	345.8 ± 62.2	324.9 ± 61.1	340.0 ± 48.1	376.7 ± 61.7	349.1 ± 57.3

VAS: Visual analog scale; EFI: Endoscopic flexibility index.

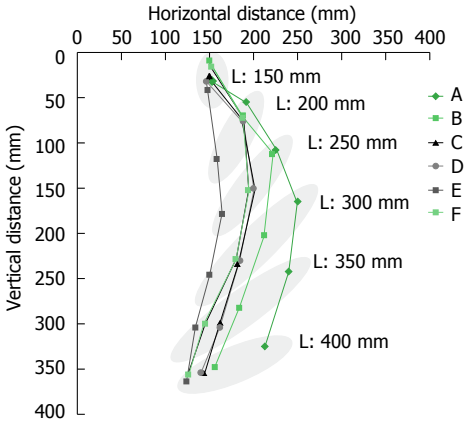

Figure 1 A two-dimensional plot of the transition from the tip of the endoscope. L: The length of endoscope allowed free movement under the influence of gravity.

time and VAS score. Moreover, the insertion success rate and nasal bleeding rate were evaluated for each endoscope for transnasal insertion. Patients with a past history of surgical resection in the upper gastrointestinal tract and those in whom biopsy or another procedure had been performed were excluded from the analyses to avoid effects of these factors on examination time or VAS scores.

Statistical analysis

Statistical analyses were performed using Student's *t*-test, χ^2 test, and Fisher's exact test. For multivariate analysis, the least-squares method was employed using dummy variables for nominal variables. All analyses were performed using JMP software (SAS Institute Inc., Cary, NC, United States). $P < 0.05$ was considered significant.

RESULTS

Among the 882 patients, 91 patients were excluded because of invalid responses or missing data. Thirty-nine patients were excluded because of past history of surgery in the upper gastrointestinal tract (n = 19) and biopsy during the examination (n = 20). One asymptomatic patient in whom anisakiasis was coincidentally discovered and who underwent endoscopy for removal of this parasite was also excluded from the analysis. In total, data of 751 patients were analyzed, as shown in Figure 2. Among

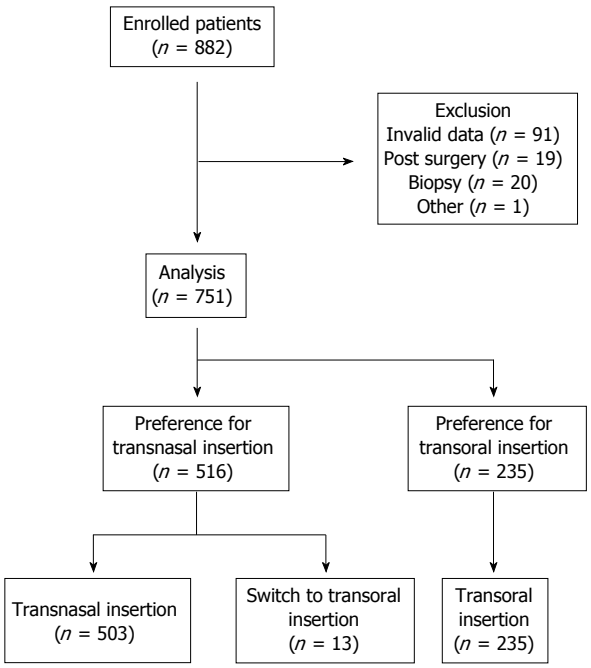

Figure 2 Flowchart of patient involvement in this study.

them, 516 patients (68.7%) preferred transnasal insertion and 235 patients (31.3%) preferred transoral insertion. Thirteen patients who preferred transnasal insertion were switched to transoral insertion after failure of transnasal insertion. EGD was performed more than once in 665 patients (88.5%).

Characteristics of patients and outcomes are shown in Table 2. Rates of preference for transnasal insertion were significantly higher in male patients (male/female 299/204 *vs* 118/117 for transnasal *vs* transoral insertion, respectively; $P < 0.05$) and younger patients (56.8 ± 11.2 years *vs* 61.3 ± 13.0 years; $P < 0.05$). Examination time for transnasal insertion was significantly longer than that for transoral insertion, although no significant difference was found between VAS scores for transnasal and transoral insertion (3.9 ± 2.3 *vs* 4.1 ± 2.5; NS).

For multivariate analysis of VAS scores, six parameters were employed: gender, age, experience of previous EGD, operator, type of endoscope, and examination time. Results of multivariate analysis of VAS scores for transnasal and transoral insertion are shown in Tables 3 and 4, respectively. For transnasal insertion, gender (posi-

Table 2 Characteristics of patients

	Transnasal insertion (n = 503)	Transoral insertion (n = 235)	P value
Gender M/F	299/204	118/117	< 0.05
Age (yr)	56.8 ± 11.2 (25-84)	61.3 ± 13.0 (27-88)	< 0.05
1st examination Y/N	54/449	19/216	0.29
Operator A/B	326/177	143/92	0.32
Endoscope			0.36
A	58	31	
B	110	52	
C	119	58	
D	112	61	
E	47	17	
F	57	16	
Examination time (s)	343.4 ± 59.4 (210-630)	324.5 ± 59.8 (196-600)	< 0.05
VAS	3.9 ± 2.3 (0-10)	4.1 ± 2.5 (0-10)	0.90

VAS: Visual analog scale; M: Male; F: Female.

Table 3 Multivariate analysis for visual analog scale in transnasal insertion

	Parameter estimate ± SE	P value
Gender (F)	0.780 ± 0.100	< 0.05
Age	-0.0193 ± 0.00886	< 0.05
1st examination (N)	0.252 ± 0.160	0.12
Operator (A)	-0.341 ± 0.110	< 0.05
Scope (E)	-0.719 ± 0.281	< 0.05
Examination time	0.00270 ± 0.00180	0.134

tive correlation with female gender), age, operator, and endoscope (negative correlation with endoscope E) were independent significant predictors of VAS scores. On the other hand, gender (positive correlation with female gender), age, and endoscope (positive correlation with endoscope C) were independent significant predictors of VAS scores for transoral insertion.

Multivariate analysis was also performed using EFI and tip diameter as alternative features of the endoscopes. Although both EFI and tip diameter were independent significant predictors of VAS scores for transoral insertion, only EFI was an independent significant predictor of VAS scores for transnasal insertion as shown in Table 5.

DISCUSSION

The appropriate usage of ultrathin endoscopes in the transoral and transnasal insertion techniques remains controversial[24]. In addition, although various ultrathin endoscopes are presently available, predictors of EGD-associated discomfort are unclear. This study demonstrated that both tip diameter and flexibility of ultrathin endoscopes can be predictors in reducing EGD-associated discomfort, especially for transnasal insertion.

Greater flexibility of the endoscope may lead to poorer handleability, resulting in prolonged examination time, which may in turn increase the discomfort accompanying EGD. However, although the most flexible endoscope (endoscope E) in this study required the longest

Table 4 Results of multivariate analysis of visual analog scale scores for transoral insertion

	Parameter estimate ± SE	P value
Gender (F)	0.575 ± 0.156	< 0.05
Age	-0.0343 ± 0.0125	< 0.05
1st examination (N)	-0.00289 ± 0.294	0.99
Operator (A)	-0.297 ± 0.177	0.10
Scope (C)	0.634 ± 0.313	< 0.05
Examination time	-0.00159 ± 0.00291	0.59

Table 5 Parameters of endoscopic flexibility index and tip diameter by multivariate analysis for visual analog scale

	Transnasal insertion	Transoral insertion
EFI	0.0125 ± 0.00563 (P < 0.05)	0.0212 ± 0.00966 (P < 0.05)
Tip diameter	0.450 ± 0.338 (P = 0.18)	1.33 ± 0.561 (P < 0.05)

EFI: Endoscopic flexibility index.

examination time among the six endoscopes, VAS scores were lowest for EGD using this endoscope for transnasal insertion. This result indicates that prolonging the examination for a certain amount of time may be acceptable in terms of the level of tolerable discomfort.

In a high proportion of regular patients in this study, EGD had been periodically performed in the past. Almost all patients selected the insertion route based on their experience with discomfort in previous examinations. Consequently, although no significant difference in VAS scores was observed between transoral and transnasal insertion, patient characteristics and preferences showed their propensity for discomfort with either one technique or the other. Table 2 shows the trend toward preference for transnasal insertion among males and younger patients. We speculate that younger patients preferred transnasal insertion to suppress a stronger gagging reflex that is reported by Enomoto *et al*[25]. By contrast, smaller female patients may have preferred transoral insertion because of their narrower nasal cavities, which are more prone to discomfort caused by transnasal insertion. However, VAS scores are reported to be affected by gender[26]. Additionally, there might be a gender deference in diminishing of gagging reflex or nasal pain by aging. We need further accumulation of data for appropriate insertion route in each gender or age-groups.

One limitation of this study is its unequal allocation of patients to each endoscope because of the system utilized in our institute. Moreover, the objectivity and reproducibility of VAS and EFI are questionable. EFI is affected by the weight of the endoscope, whose mass/length is not homogenous. However, this parameter can be a surrogate marker that can be evaluated simply and non-destructively.

In summary, this study demonstrated that flexibility of the ultrathin endoscope can be a reliable predictor of reduction in transnasal EGD-associated discomfort. Although further analysis of details concerning appropriate location and degree of flexibility is required, patient com-

pliance can be improved for follow-up and surveillance EGD by utilizing less uncomfortable tools.

COMMENTS

Background

As gastrointestinal endoscopic technology has advanced considerably with improvements in resolution and image enhancement, importance of surveillance esophagogastroduodenoscopy (EGD) to detect superficial neoplasms in early stage has been emphasized more than ever to achieve curative resection.

Research frontiers

Although EGD using an ultrathin endoscope has been accepted as a minimally invasive modality, the effects of choice of insertion route and ultrathin endoscope types have not been evaluated.

Innovations and breakthroughs

The authors' study using six types of ultrathin endoscopes demonstrated that flexibility of the ultrathin endoscope can be a reliable predictor of reduction in transnasal EGD-associated discomfort.

Applications

To decrease unsedated EGD-associated discomfort, transnasal insertion of ultrathin endoscopy should be chosen for younger males. A flexible ultrathin endoscope can reduce transnasal EGD-associated discomfort for the other people.

Terminology

Endoscopic flexibility index is a surrogate marker that can be evaluated simply and non-destructively.

Peer review

This is the first report of comparison of the difference between several models of ultrathin endoscope. The conclusion that the discomfort is associated with the flexibility of the endoscope is a novel and unique.

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CASE REPORT

Longest duration of retention of video capsule: A case report and literature review

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Key words: Video capsule endoscopy; Obscure gastrointestinal bleeding; Capsule retention; Crohn's disease; Enteropathy

Core tip: We present the longest case of asymptomatic video capsule retention in the literature. With our case we would like to highlight that asymptomatic video capsule retention is not an indication for surgical retrieval. Capsule can retain for long time without harm. Surgical retrieval should be reserved for those patients in whom the expectant management, medical management and endoscopic therapy fails or in patients who are symptomatic with intestinal obstruction or perforation.

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Abstract

Video capsule endoscopy (VCE) is a safe innovative tool for investigating obscure gastrointestinal bleeding, Crohn's disease and other small bowel pathologies. The capsule is usually excreted with faeces within 24-48 h. Retention of capsule rarely occurs, and it usually depends on the indication of VCE. The longest reported case of capsule retention in the literature is 2.5 years. Surgical approach is considered effective to retrieve the retained capsule. We present a case of asymptomatic retention of capsule for four and half years in a 49-year-old man who underwent VCE to explore the cause of obscure gastrointestinal bleeding. It was successfully retrieved endoscopically. We will also briefly review the literature regarding the causes, different presentations and management of capsule retention.

INTRODUCTION

Video capsule endoscopy (VCE) since its approval from Food and Drug Administration in August 2001 has become the innovative tool for investigating small bowel pathology mainly to determine the cause of obscure gastrointestinal bleeding, Crohn's disease, polyposis syndromes and evaluation of patients with complicated celiac disease, *etc*[1]. VCE is noninvasive and is considered a safe procedure because the capsule is usually excreted with the feces within 24-48 h[2]. However, if capsule retention occurs, it would help determine the underlying cause of gastrointestinal pathology. But there is always a concern of capsule retention which could potentially lead to acute intestinal obstruction and perforation requiring surgery who otherwise would have been treated medically[3,4]. Furthermore, it is rare for video capsule

to stay in the GI tract for long duration without any symptoms. We report a case of the longest duration of retention of video capsule which was retrieved successfully with an endoscope.

CASE REPORT

A 49-year-old man with history of ulcerative colitis-status post subtotal colectomy done 13 years ago was referred to gastroenterology clinic by his family physician for evaluation of occasional gastrointestinal bleeding with drop in his hemoglobin to 8.4 g/dL from baseline of 10-11 g/dL. Since the time of subtotal colectomy, his underlying colitis remained stable. His past medical history included Ankylosing Spondylitis for which he was following rheumatology. He was managed only with physical therapy not requiring medication.

His daily medications included iron, folic acid and B12 supplements. He denied use of any Non-steroidal anti-inflammatory drugs (NSAIDs). There was no history of smoking and alcohol abuse in the past. His family history was significant for ulcerative colitis in father; however, no history of bowel cancer was reported. The patient did not admit to have abdominal pain, nausea, vomiting. There was no history of change in bowel movements. Initially he was losing weight following surgery but for last two years his weight has been stable.

He then underwent upper endogastroduodenoscopy (EGD), flexible sigmoidoscopy later followed by colonoscopy which did not reveal the cause of the gastrointestinal bleed. He was planned for VCE. First he underwent small bowel follow through (SBFT) which demonstrated all normal appearing small bowel loops with patent ileorectal anastomosis. Subsequently, he underwent VCE uneventfully. He did not report spontaneous passage of the capsule in one week which was confirmed by abdominal X-ray revealing retained capsule in right lower quadrant of abdomen as shown in Figure 1A. The result of VCE did not reveal any pathology causing obscure gastrointestinal bleeding and retained capsule. He did not have features of bowel obstruction both clinically and radiographically. He followed up periodically for 2 mo with serial imaging studies which showed capsule in different parts of the loops of bowel (Figure 1B).

Then he lost to follow up with our gastroenterology department as he moved out from the area. Subsequently, he returned for follow up for his ulcerative colitis after 4 years. Even at this time he did not report to have any symptoms of intestinal obstruction such as nausea, vomiting, abdominal pain, diarrhoea, *etc*. His abdominal X-ray at this time again demonstrated persistent retained capsule overlying the right upper quadrant of abdomen without any evidence of intestinal obstruction (Figure 1C). He was discussed with several options of management including surgery to retrieve the retained capsule. But he preferred non-surgical approach as he explained that he was not having symptoms due to the retained capsule. Computed tomography (CT) abdomen reported the capsule in the bowel lumen at anastomotic site in the right upper quadrant (Figure 2). He then underwent colonoscopy with successful retrieval of the intact 4 year 5 mo 21 d-old retained capsule by a roth net basket (Figure 3) from patent surgical anastomosis at the site of prior diverting loop ileostomy located at 120 cm proximal to the anal verge. During the follow up after two months, the patient did not report to have any consequences from the capsule retrieval procedure.

DISCUSSION

VCE is a simple, safe, non-invasive, reliable procedure which is well accepted and tolerated by the patient, without requiring any sedation, surgery or radiation exposure[5]. Though rare, capsule retention is the major risk following VCE. The International Conference on Capsule Endoscopy (ICCE) 2005 defines capsule retention as having a capsule endoscope remain in the digestive tract for minimum 2 wk. Capsule retention is further defined as the capsule remaining in the bowel lumen unless it is recovered medically, endoscopically or surgically[6].

Retention rate of video capsule is variable depending mostly on the clinical indication for VCE[7-10]. It ranges from 0% in healthy subjects, to 1.5% in patients with obscure gastrointestinal bleeding, to 5% in patients with suspected Crohn's disease and 21% in patients with intestinal obstruction[7,8]. In a recently published systematic review by Liao *et al*[9], there were 184 capsule retentions in both prospective and retrospective studies of total 22840 procedures giving a pooled retention rate of 1.4%. The retention rate in obscure gastrointestinal bleeding, Crohn's disease, neoplastic lesions are 1.2%, 2.6% and 2.1% respectively[9]. The other causes of retention are NSAID induced enteropathy, post-surgical stenosis, adhesions, tuberculosis, ischemia and radiation enteritis[9,11]. Furthermore, rare causes include Meckel's diverticulum, peptic ulcer, cryptogenic multifocal stenosing enteritis with frequencies of less than 2% of total capsule retention[7]. Based on these studies, the probability of capsule retention is higher in Crohn's disease, NSAIDs induced enteropathy and history of abdominal surgeries. Our patient also had the history of abdominal surgery such as subtotal colectomy which increased the risk of capsule retention. Thus obtaining the good medical history is essential to prevent the capsule retention. There are no other accepted methods including the imaging studies prior to VCE are useful to prevent occurrence of capsule retention[6,12].

Retention of capsule is mostly asymptomatic or sometimes it causes partial bowel obstruction[4,10,13,14]. Retention usually helps identify the etiology and site of obstruction by indicating the presence of underlying pathology. There are some studies in which VCE was done in the patients who already had symptoms of partial bowel obstruction. Even in those studies, the patients did not develop symptoms of acute intestinal obstruction rather

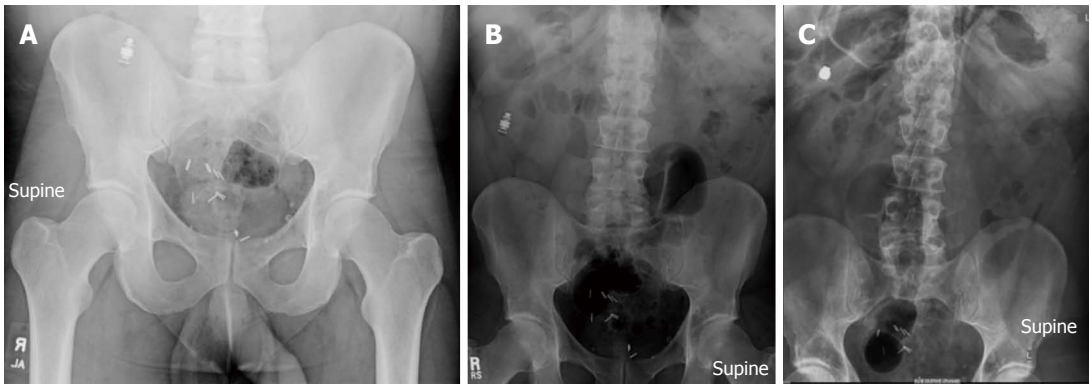

Figure 1 Abdominal X rays done at several time intervals following video capsule endoscopy showing retention of video capsule. Several surgical clips are also present at pelvis. A: Follow up in 1 wk showing capsule in right lower quadrant of abdomen; B: Follow up in two months showing capsule in right mid abdomen laterally; C: Follow up after 4 years showing capsule in right upper quadrant of abdomen.

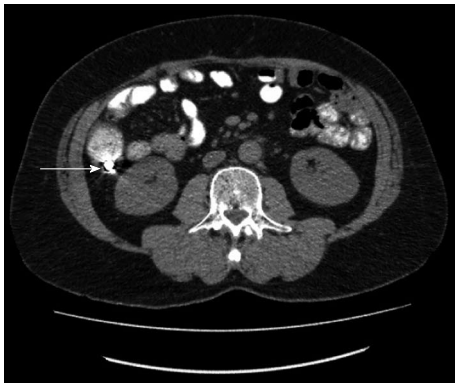

Figure 2 Computer tomography abdomen done for further evaluation of retained capsule which is present in bowel lumen (arrow).

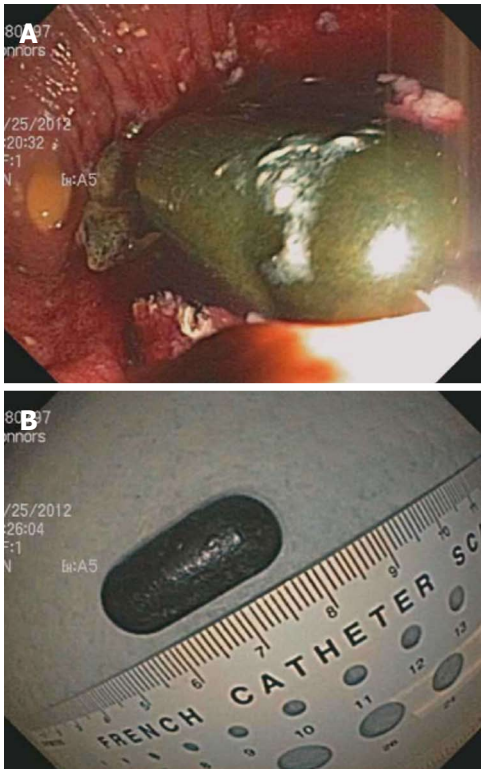

Figure 3 Capsule seen in colonoscopy (A) and video capsule was retrieved intact after 4 year 5 mo and 21 d with endoscopically (B).

the retention of capsule helped the clinician to determine the etiology[4]. The retrospective study of 1000 capsule endoscopies by Li *et al*[10] demonstrated 1.4% retention rate which all were asymptomatic. Similarly another study revealed development of partial small bowel obstruction in 15% of patients who had capsule retention; the remaining 85% were asymptomatic[13]. In the study from Cheifetz *et al*[4] with 19 cases and Yang *et al*[14] with 31 cases of capsule study in patients of underlying suspected small bowel obstruction, none of the patients with retained capsule developed acute intestinal obstruction requiring surgery.

The studies have suggested that asymptomatic capsule retention can undergo expectant, medical and endoscopic management or even surgical intervention[14-17]. Meanwhile, the longest duration of retention is 2.5 years reported by ICCE without reporting the sequelae associated with long term retention of capsule[6]. But the patient should not undergo magnetic resonance imaging[17]. Authors have advocated that surgical intervention not only allows removal of the capsule but also can remove the offending pathology causing capsule retention[9,14-16]. In a systematic review of 184 capsule retentions from Liao *et al*[9], retained capsules were excreted spontaneously or by pharmaceutical manipulation in 15%, endoscopically in 12% and the majority 58.7% were removed surgically. Baichi *et al*[16] studies five permanent capsule retention out of which two cases had successful endoscopic retrieval and remaining three cases required surgical intervention. Another study presented three cases of capsule retention out of which two patients needed surgery for retrieval and other patient passed capsule spontaneously in six months with medical treatment[14]. Therefore, these studies have demonstrated that majority of patients eventually require surgical retrieval but non-surgical management could be the best option to begin with in a patient without symptoms of acute intestinal obstruction. This is also shown in another large study in which out of 32 retained capsules, 21 (65.6%) patients received medical treatment resulting in spontaneous passage

of the capsule in 11 (34.4%). Rest 10 (31.3%) patients ultimately underwent surgical intervention to retrieve the capsule[15]. Medical management usually consists of use of anti-inflammatory agents and colonoscopy preparation fluids or enemas[10,18]. There are few case reports of capsule retention causing intestinal obstruction in patients with underlying Crohn's disease and history of abdominal surgeries who were successfully treated with disimpaction with intravenous steroids and diatrizoate upper GI series and enemas[17,18].

Nevertheless, there are only few cases of complication reported in the literature due to retained capsule. In a recent analysis of 2300 capsule examinations, six patients had acute obstructive symptoms and also reported one death related to complications after acute surgical capsule retrieval[3]. There is also a case report of retained capsule causing intestinal perforation after two months following VCE in an elderly man who underwent VCE for evaluation of anemia[19]. There is another case of capsule impaction and subsequent fracture of the capsule in the small bowel six months following VCE[20]. Thus, though rare, we need to keep in mind that there is a possibility of acute complication of capsule retention.

With our case we would like to make physicians aware of the possibility of asymptomatic capsule retention even after four to five years following VCE. We also highlight that retained capsule can be retrieved non surgically even if it is retained for long period of time in the patient who is asymptomatic.

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CASE REPORT

Oldest biliary endoprosthesis *in situ*

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Author contributions: Familiari L and Consolo P performed the ERCP; Pallio S, Scalisi G, Cintolo M, Tortora A and Giacobbe G managed the patient during and after hospitalisation; Crinò SF performed the US; Crinò SF and Scalisi G wrote the paper and revised the English in the paper.
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Abstract

The advantages of endoscopic retrograde cholangiopancreatography over open surgery have made it the predominant method of treating patients with choledocholithiasis. After sphincterotomy, however, 10%-15% of common bile duct stones cannot be removed with a basket or balloon. The methods for managing "irretrievable stones" include surgery, mechanical lithotripsy, intraductal or extracorporeal shock wave lithotripsy and biliary stenting. The case presented was a referred 82-year-old Caucasian woman with a 7-year-old plastic biliary endoprosthesis *in situ*. To the best of our knowledge the examined endoprosthesis is the oldest endoprosthesis *in situ* reported in the literature. Endoscopic biliary endoprosthesis placement remains a simple and safe procedure for patients with stones that are difficult to manage by conventional endoscopic methods and for patients who are unfit for surgery or who are high surgical risks. To date no consensus has been reached regarding how long a biliary prosthesis should remain *in situ*. Long-term biliary stenting may have a role in selected elderly patients if stones extraction has failed because the procedure may prevent stones impaction and cholangitis.

Key words: Common bile duct stones; Cholangitis; Biliary endoprosthesis; Endoscopic retrograde cholangiopancreatography; Endoscopic sphincterotomy

Core tip: Endoscopic extraction of biliary tract stones is safe and effective. When the procedure is not successful the placement of a plastic biliary endoprosthesis can be a solution. To date no consensus has been reached regarding how long the biliary prosthesis should remain *in situ*. This case report represents the oldest *in situ* plastic biliary endoprosthesis ever reported in the literature. Despite the fact that endoprostheses will inevitably occlude after 3 to 5 mo *in situ*, they may still prevent impaction of stones in the distal part of the common bile duct and ensure free flow of bile even if the endoprostheses are obstructed, calcified and have a bilious coat.

Consolo P, Scalisi G, Crinò SF, Tortora A, Giacobbe G, Cintolo M, Familiari L, Pallio S. Oldest biliary endoprosthesis *in situ*. *World J Gastrointest Endosc* 2013; 5(7): 356-358 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i7/356.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i7.356

INTRODUCTION

Nearly a third of patients with common bile duct (CBD) stones are at risk of developing recurrent cholangitis or pancreatitis[1]. These complications are associated with significant mortality in elderly or infirm patients. Therefore a prompt intervention to remove the stones (or at least establish an uninterrupted flow of bile) is required. Whit a success rate of over 90% endoscopic sphincterotomy and stones extraction comprise the treatment of choice for patients of all ages affected by choledocholithiasis. Large stones that cannot be extracted with the conventional endoscopic means present a greater challenge,

and a variety of surgical and non-surgical techniques are now available to remove these stones. Endoscopic insertion of biliary endoprosthesis has been proposed as an alternative for such high-risk patients and primarily in the case of failed stones extraction. Biliary stenting aims to prevent stone impaction by perpetuation of bile flow and helps to avoid subsequent life-threatening complications such as cholangitis and even cholangiosepsis[2].

CASE REPORT

An 82-year-old Caucasian woman complaining of symptoms characterised by itch and recurrent episodes of fever (maximum body temperature 38.5 ℃) for approximately 6 mo and treated using quinolone and cholestyramine respectively was referred to our unit. The patient underwent cholecystectomy for gallstones in 2000 and in 2005, at a non referral centre, the patient underwent endoscopic-retrograde-cholangiopancreatography (ERCP), which revealed dilatation and multiple stones of the CBD. After the sphincterotomy, because of the failure of stones extraction, a biliary endoprosthesis was implanted to avoid cholangitis. ERCP was not repeated and the endoprosthesis remained *in situ* until this admission. During hospitalisation at our unit, the patient underwent abdominal ultrasonography that revealed hyperechoic streaks along the CBD and a computed tomography abdominal scan that revealed moderate dilatation of the CBD and intrahepatic bile ducts with aerobilia. The routine blood parameters were all normal except for gamma glutamyl transferase (GGT) (101 U/L; normal value: 10-54 U/L). It was decided that another ERCP would be performed. The old double pigtail endoprosthesis was removed, the sphincterotomy was extended and the stones were extracted using a Dormia basket. The original prosthesis was obstructed, calcified and had a bilious coat (Figure 1). The post-operative course was complicated by the occurrence of fever (maximum body temperature 38.5 ℃), which cleared up after treatment with quinolone.

DISCUSSION

Choledocholithiasis is one of the most common gastrointestinal diseases encountered in clinical therapeutic endoscopy practice. Endoscopic sphincterotomy and stone extraction are widely performed as the primary treatment methods for patients with CBD stones, with an 80% to 90% success rate and a complication rate of less than 10%[3]. Approximately 10% to 15% of CBD stones are difficult to remove using conventional endoscopic sphincterotomy and balloon/basket extraction techniques, including mechanical lithotripsy. Multiple or large CBD stones (> 20 mm in diameter), the presence of periampullary diverticula, narrowing or stricture of the distal CBD, limited sphincterotomy caused by small papillae and no visible intramural course of the CBD in the duodenal wall all influence the probability of successful stone extraction[4]. In such cases, temporary biliary stenting is a safe and effective bridge therapy. This stenting

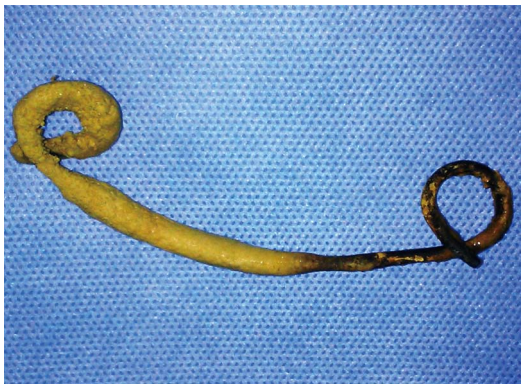

Figure 1 The oldest biliary endoprosthesis.

has several advantages, primarily the prevention of the incarceration of the stone at the ampulla of Vater and maintenance of biliary drainage. In addition, stenting can reduce the possibility of unnecessary surgery in patients exhibiting technical difficulties in stone removal[5-7]. Furthermore, friction between the stones and the prosthesis induces fragmentation, decreasing stone size, and thus facilitating removal[8]. To date, no consensus has been reached regarding how long the biliary prosthesis should remain *in situ*. Despite the fact that the endoprosthesis will inevitably occlude after 3 to 5 mo *in situ*, it is believed to work by splinting the stones or preventing impaction in the distal common bile duct or both, thus ensuring free flow of bile. The most serious drawback of a long-term indwelling biliary endoprosthesis is the risk of recurrent cholangitis, which is reported in 3.5% to 40% of patients. The median time to onset of cholangitis appears to be approximately 16 wk and occurs mainly in patients with an *in situ* gallbladder or in cases of prosthesis insertion without sphincterotomy[9-12]. Several previous studies have suggested that permanent biliary stenting may be a definitive therapy for endoscopically unextractable common duct stones in selected elderly patients who are poor surgical candidates. When biliary symptoms do recur, they can usually be treated conservatively with antibiotics, a prosthesis change, or both[2,13].

To the best of our knowledge, our case report represents the oldest *in situ* plastic biliary endoprosthesis ever reported in the literature. Other studies have reported stent survival up to 6 years[12,14]. These reports confirm that biliary endoprostheses may prevent impaction of stones in the distal part of the common bile duct and maintain biliary flow despite being obstructed, calcified and having a bilious coat. The stent may function as a wick around to drain the bile, rather than as a conduit for bile. The present case demonstrates that in high-risk patients, a regular endoprosthesis exchange might be delayed according to the patient's individual needs without fearing inevitable complications. However, further case-controlled studies are needed.

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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]

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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]

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

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

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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

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

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

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

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