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BRIEF ARTICLE

Effectiveness of circumferential endoscopic mucosal resection with a novel tissue-anchoring device

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Abstract

AIM: To evaluate the efficacy of circumferential endoscopic mucosal resection (EMR) with a tissue-anchoring device in comparison to forceps precut EMR and conventional endoscopic submucosal dissection (ESD).

METHODS: The study was designed as a prospective, randomized, *ex vivo* study. Fresh *ex vivo* specimens were harvested from adult white Yorkshire pigs weighing 30-50 kg. Seventy-five standardized, artificial lesions measuring 3 cm × 3 cm were created by methylene blue tattoo at the greater curvature in fresh *ex vivo* stomachs using the EASIE-R simulator platform (Endosim LLC, Berlin, MA, United States). The three advanced endoscopists performed the three resection techniques such as circumferential EMR using the tissue-anchoring device (TA-EMR), forceps precut EMR (FP-EMR), and endoscopic submucosal dissection. The endoscopists and the type of cutting methods were determined randomly by grouped randomized selection. The resection bed was grossly inspected to determine whether the lesion was resected "*en-bloc*" (defined as no remaining mucosal tattoo remaining on specimen). The resection bed was also probed for evidence of perforation. The procedural time of circumferential resection, submucosal dissection, and injection frequency were recorded by an independent observer.

RESULTS: All 75 created lesions were successfully resected by three advanced endoscopists using the three techniques. The mean ± SD size of resected specimens (long axis) were 39.5 ± 5.6 mm, 36.5 ± 7.3 mm, and 44.6 ± 5.6 mm for TA-EMR, FP-EMR, and ESD respectively. The overall mean dissection time of both the TA-EMR and FP-EMR was significant shorter than ESD (TA-EMR: 5.1 ± 3.3 min, FP-EMR: 3.5 ± 2.0 min *vs* ESD: 15.8 ± 9.5 min, $P < 0.001$, $P < 0.001$). The overall mean total procedure time of both the tissue-anchoring and forceps circumferential EMR was significantly shorter than ESD (TA-EMR: 17.5 ± 6.0 min, FP-EMR: 16.6 ± 6.6 min *vs* ESD: 28.6 ± 13.9 min, $P < 0.001$, $P < 0.001$). The *en-bloc* resection rate of ESD was 100% (25/25) and the *en-bloc* resection rate of the TA-EMR (84.0%, 21/25) was higher than for the FP-EMR (60.0%, 15/25), yet not statistically significant ($P = 0.18$). The perforation rate of each technique was 8.0% (2/25).

CONCLUSION: TA-EMR appears to be quicker than ESD, and there was a trend towards improved *en bloc* resection rate with the TA-EMR when compared to the FP-EMR.

Key words: Endoscopic mucosal resection; Endoscopic submucosal dissection; *En bloc* resection; Perforation

Core tip: The recently introduced tissue anchor device has the capability of deploying three spikes into the tissue that allow a reliable fixation of the tissue and facilitate retraction into snare. We demonstrated the efficacy of circumferential endoscopic mucosal resection (EMR)

with a novel tissue-anchoring device in comparison with circumferential EMR using conventional forceps, and endoscopic submucosal dissection.

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INTRODUCTION

Endoscopic mucosal resection (EMR) is widely employed for the local treatment of early superficial cancer and dysplasia. Due to its simplicity and safety, it is one of the most common endoscopic techniques for resecting superficial lesions of the esophagus, stomach or colon. Various techniques of EMR such as ligation-EMR (EMRL), cap-EMR (EMRC), and strip-biopsy EMR (SB-EMR) have been developed. With these conventional techniques, however, the specimen size obtained from a one-piece resection is limited in size, with mean maximum resction sizes in the 10-15 mm range[1-5]. The precut-EMR (EMR-P) method, in which lesions are resected using a snare after circumferential precutting, allows *en-bloc* resection of lesion with a maximum diameter of 20 mm[6,7]. This snare technique is not reliable for lesions greater than 20 mm in diameter because of the difficulty of capturing and effectively ligating the significant amount of submucosal tissue in these lesions, even after successful circumferential precutting[3,8,9]. Endoscopic submucosal dissection (ESD) has a potential for a high rate of *en-bloc* resection, regardless of tumor size, leading to a more precise histological evaluation of the specimen and a lower recurrence rate at long-term follow up[10,11]. ESD, however, is a technically difficult procedure, and it can frequently cause serious complications such as significant bleeding or perforation. Thus, development of new endoscopic tools and the simplification of endoscopic resection techniques are necessary to enhance safety. Von Renteln and colleagues recently published a pilot study demonstrating the feasibility of grasp-and-snare circumferential EMR using a novel tissue-anchoring device ("Tissue Anchor", Ovesco Endoscopy AG, Tübingen, Germany) for large-sized lesions[12]. To date, there is no study that compares circumferential EMR with this novel tissue-anchoring device and other resection techniques, including circumferential EMR with a conventional strip-biopsy technique and ESD. Therefore, the aim of this study is to evaluate of the efficacy of these three methods.

MATERIALS AND METHODS

The study was designed as a prospective, randomized, *ex vivo* study. Fresh *ex vivo* specimens containing esophagus, stomach and duodenum were harvested from adult white Yorkshire pigs weighing 30-50 kg (from a commercial livestock vendor) and used with the EASIE-R simulator platform (Endosim, LLC, Berlin, MA, United States) (Figure 1). Institutional review board (IRB) review for human subject and/or live animal research was not required as there were no human research subjects or live animals involved in the study. A total of 75 procedures were performed by three advanced endoscopists. Prior to the study, the participants each practiced five cases of circumferential EMR using the novel tissue-anchoring device. Each endoscopist then performed eight to nine recorded cases of each: circumferential EMR using the tissue-anchoring device (TA-EMR), forceps precut EMR (FP-EMR), and endoscopic submucosal dissection (ESD).

Creation of lesions

Seventy-five standardized, artificial lesions measuring 3 cm × 3 cm were created by methylene blue tattoo in the mucosa of fresh *ex vivo* stomachs at the anterior and posterior wall in the proximity of the greater curvature (Figure 2). The endoscopists and the type of cutting methods were determined randomly by grouped randomized selection (*i.e.*, each endoscopist performed the same number of each procedure, but the order was randomized).

Tissue resection

A double-channel endoscope (GIF-2T 160; Olympus America Inc, Center Valley, PA, United States) was used for all resections. A normal saline and methylene blue solution was injected to provide tissue separation between the mucosal and submucosal layers. For the circumferential TA-EMR, the tissue anchor was used to grasp the mucosal flap after circumferential cutting. For FP-EMR, a foreign body retrieval forceps (Olympus, Tokyo, Japan) was used to grasp the mucosal flap after circumferential cutting. For ESD, conventional ESD technique was used. All cases of direct circumferential resection were carried out with the hook knife, needle knife and IT knife, after repeated injection of the saline/methylene blue cushion solution (Figure 3A). The separation of the circumferential cutting area was carefully inspected (Figure 3B). The anchor and forceps accessories were used in the left channel of the double-channel endoscope for their respective resection techniques, and a 25 mm standard oval-shaped disposable electrosurgical snare (SD-210U-25, Olympus, Tokyo, Japan) was used in the right channel. Following injection with normal saline solution, the tissue anchor and forceps were then retracted into the endoscope to lift the mucosa, and the snare was placed into the circular pre-cut incision (Figure 4). The snare was subsequently closed and the specimen resected with electrocautery (UES-30 generator, 40 W output; Olympus America Inc, Center Valley, PA, United States) (Figure 5). For conventional ESD, a circular precut was made with the IT knife after an initial incision with the conventional needle knife. The lesion was then resected with a conventional needle

Figure 1 Simulation platform using the EASIE-R simulator with an *ex-vivo* porcine stomach specimen.

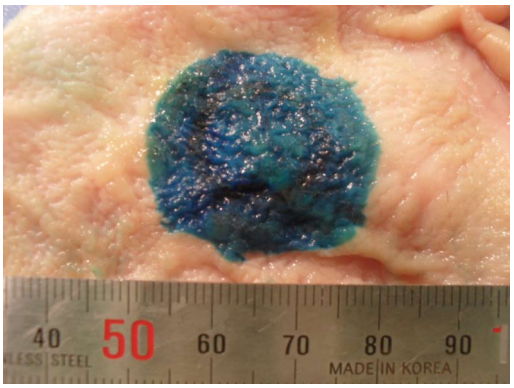

Figure 2 3 cm × 3 cm target lesions created by methylene blue tattoo in the mucosa of fresh *ex-vivo* stomachs.

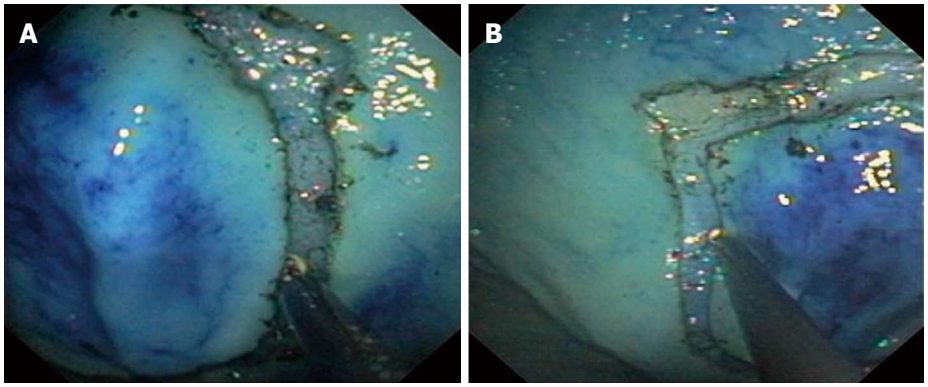

Figure 3 Endoscopic images. A: Circumferential resection with the IT knife after injection; B: The separation of the circumferential cutting area being carefully inspected.

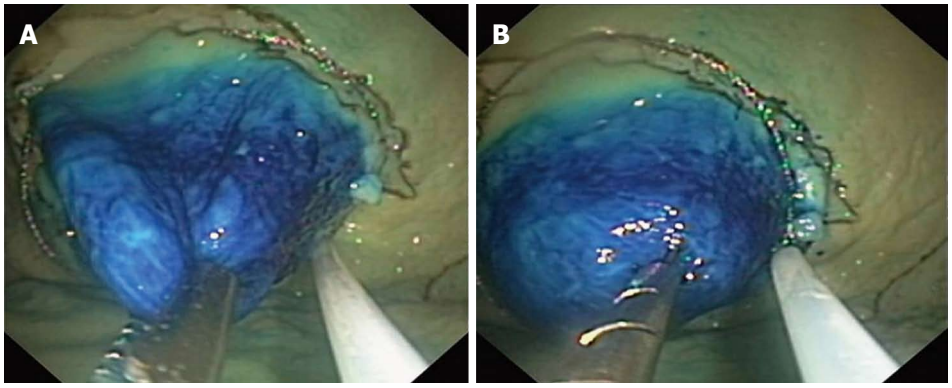

Figure 4 Endoscopic images. A: The mucosal retraction with regular forceps (unipolar traction); B: Mucosal retraction with the tissue-anchoring device (retracting tissue from three anchor points).

knife and hook knife following injection to separate the mucosa and submucosa.

Assessment of complications

Immediately after retrieving the excised specimens, the lesions were spread and pinned on flat cork plates. The length and area of each excision specimen were measured. The resection bed was grossly inspected to determine whether the lesion was resected "*en-bloc*" (defined as no remaining mucosal tattoo remaining on specimen). The resection bed was also probed for evidence of perforation. The procedural time of circumferential resection, submucosal dissection, and injection frequency were recorded by an independent observer.

Statistical analysis

The sample size was calculated by 10 cases of initial data of each group (TA-EMR: 21.1 ± 6.4 min, FP-EMR: 20.1 ± 7.8 min, and ESD: 35.1 ± 18.5 min). We used the one-Way ANOVA method to estimate sample size, with an

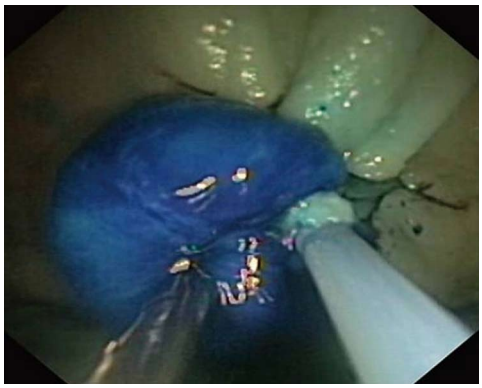

Figure 5 The snare being subsequently closed and the specimen resected by application of electrocautery.

Table 1 Resection results of tissue-anchoring circumferential endoscopic mucosal resection

Endoscopist	Margin (min)	Dissection (min)	Total time (min)	Perforation (rate)	*En-bloc* (rate)
1st	7.3 ± 2.4	5.2 ± 3.8	17.8 ± 4.7	1/9 (11.1%)	9/9 (100%)
2nd	9.0 ± 4.5	6.0 ± 3.7	21.5 ± 6.7	0/8 (0%)	6/8 (75%)
3rd	5.8 ± 2.2	4.1 ± 2.1	13.2 ± 3.5	1/8 (12.5%)	6/8 (75%)
Total	7.4 ±3.3	5.1 ± 3.3	17.5 ± 6.0	2/25 (8.0%)	21/25 (84.0%)

alpha of 0.05, a power of 80% and calculated an estimated sample size of 25 cases for each group. Data were analyzed by using SPSS software, version 18.0 (SPSS Inc Headquarters, Chicago, Ill). Statistical comparisons were made between the groups using the One-Way ANOVA test and statistical significance was defined as $P < 0.05$.

RESULTS

All 75 created lesions were successfully resected by three advanced endoscopists using the three techniques. All parameters (procedure time, specimen size, *en-bloc* resection status, and perforation) were successfully recorded by an independent observer for each procedure. The mean ± SD size of resected specimens (long axis) were 39.5 ± 5.6 mm, 36.5 ± 7.3 mm, and 44.6 ± 5.6 mm for the tissue-anchoring circumferential EMR (TA-EMR), forceps precut EMR (FP-EMR), and ESD respectively.

The overall mean total procedure time of TA-EMR was 17.5 ± 6.0 min (circumferential cutting: 7.4 ± 3.3 min, dissection: 5.1 ± 3.3 min) and the *en-bloc* resection rate was 84.0% (21/25) (Table 1).

The overall mean total procedure time of the forceps circumferential EMR was 16.6 ± 6.6 min (circumferential cutting: 7.9 ± 4.0 min, dissection: 3.5 ± 2.0 min) and the *en-bloc* rate was 60.0% (15/25). Two of the piecemeal resections (non *en-bloc*) resulted in 3 and 4 individual resection pieces, respectively (Table 2).

The overall mean total procedure time of the ESD was 28.6 ± 13.9 min (circumferential cutting: 6.9 ± 4.9 min, dissection: 15.8 ± 9.5 min) and the *en-bloc* rate was 100% (25/25). The perforation rate of each technique

Table 2 Resection results of forceps precut endoscopic mucosal resection

Endoscopist	Margin (min)	Dissection (min)	Total time (min)	Perforation (rate)	*En-bloc* (rate)
1st	9.6 ± 4.1	3.8 ± 2.4	19.1 ± 9.2	0/8 (0%)	5/8 (62.5%)
2nd	8.4 ± 2.9	3.6 ± 1.7	18.0 ± 3.8	0/9 (0%)	4/9 (44.4%)
3rd	5.6 ± 2.3	3.0 ± 2.1	12.6 ± 4.3	2/8 (25%)	6/8 (75%)
Total	7.9 ± 4.0	3.5 ± 2.0	16.6 ± 6.6	2/25 (8.0%)	15/25 (60.0%)

Table 3 Resection results of endoscopic submucosal dissection

Endoscopist	Margin (min)	Dissection (min)	Total time (min)	Perforation (rate)	*En-bloc* (rate)
1st	7.2 ± 2.3	16.1 ± 7.0	30.5 ± 9.2	1/8 (12.5%)	8/8 (100%)
2nd	8.3 ± 6.1	18.7 ± 12.1	33.1 ± 16.6	1/8 (12.5%)	8/8 (100%)
3rd	5.5 ± 1.9	12.9 ± 7.0	22.9 ± 10.0	0/9 (0%)	9/9 (100%)
Total	6.9 ± 4.9	15.8 ± 9.5	28.6 ± 13.9	2/25 (8.0%)	25/25 (100%)

was 8.0% (2/25) (Table 3). The overall mean dissection time of both the TA-EMR and FP-EMR was significant shorter than ESD (TA-EMR: 5.1 ± 3.3 min, FP-EMR: 3.5 ± 2.0 min *vs* ESD: 15.8 ± 9.5 min, $P < 0.001$, $P < 0.001$) (Figure 6A). The overall mean total procedure time of both the tissue-anchoring and forceps circumferential EMR was significantly shorter than ESD (TA-EMR: 17.5 ± 6.0 min, FP-EMR: 16.6 ± 6.6 min *vs* ESD: 28.6 ± 13.9 min, $P < 0.001$, $P < 0.001$) (Figure 6B).

DISCUSSION

The ability to perform an *en-bloc* endoscopic resection of superficial cancerous and pre-malignant lesions may lead to an improvement of patient outcomes, since it provides an accurate and reliable histopathological evaluation. An inaccurate histopathological assessment from piece-meal resection may result in an inaccurate decision for further treatment and ultimately, local tumor recurrence[6,13]. EMR is used world-wide as the first-choice therapy for patients with early gastric cancer (EGC) who meet indications for this technique. The appropriate indication for EMR for EGC is considered to be an intramucosal differentiated type adenocarcinoma without ulceration or scarring, that is no more than 15 mm in size, regardless of macroscopic type[14]. The most common technique for upper gastrointestinal EMR include A) the strip biopsy method, also referred to as grasp-and-pull technique, using a double-channel endoscope, and B) the aspiration mucosectomy technique which uses a clear cap fitted onto the end of the endoscope. Using these techniques, only lesions of up to 10 mm in diameter can be reliably removed *en-bloc* with a sufficiently clear margin[15-18]. A definite histological diagnosis of the depth of invasion and the tumor margin from these resected specimens is frequently challenging, since the lesions measure only 10 mm or less in size. Circumferential incision with a tool such as the IT-knife, followed by snare resection (EMR-P), has been used to overcome such obstacles. Studies have demonstrated that

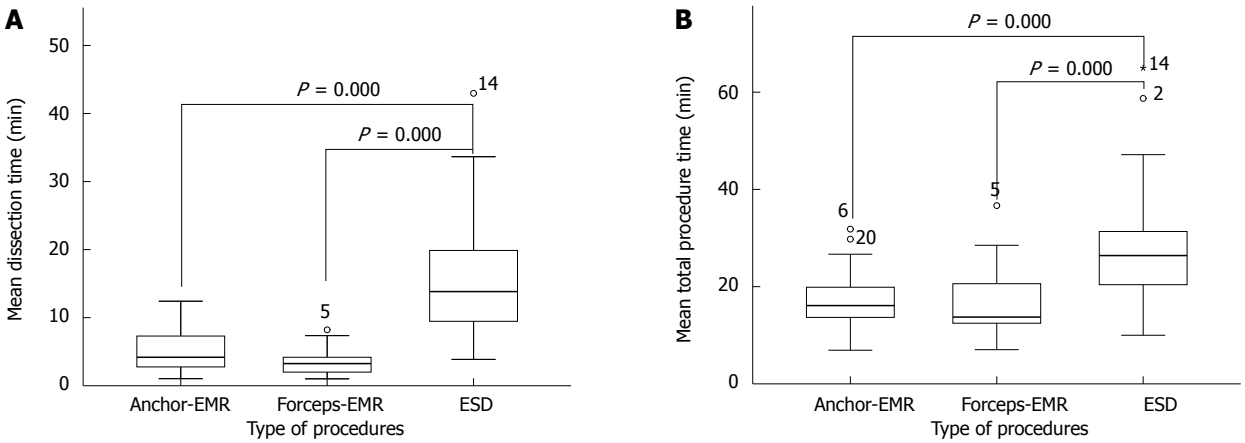

Figure 6 The overall mean total procedure time. A: Overall mean dissection time; B: Mean total procedure time. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

Figure 7 Detail of the novel tissue-anchoring device.

the *en-bloc* resection rates of the EMR-P technique are 82% for lesions of 10 mm or less, 54%-75% for those between 11 and 20 mm, 14%-38% for those of over 20 mm. They showed that snaring a lesion of over 20 mm using this technique was difficult, even after successful circumferential incision by IT-knife[3,8,9].

The concept of tissue grasping in combination with snare resection, after circumferential cutting, may enable the performace of EMR to be expanded further. Ovesco's recently introduced tissue anchor device has the capability of deploying three spikes into the tissue (Figure 7) that allow a reliable fixation of the tissue and facilitate retraction into snare. von Renteln *et al*[12] demonstrated that grasp-and-snare EMR using this tissue anchor, in combination with a 25 mm monofilament snare, is feasible and results in reliable *en-bloc* resections of up to 40 mm × 42 mm specimens. The group achieved 90% (9/10) complete *en-bloc* resections. They demonstrated an improved time-efficiency of this method (average of 32 min) when compared to ESD (average of 78 min). However, the study lacked a control group and allowed no direct comparison between various EMR/ESD methods.

In this study, we compared the efficacy (as defined by *en bloc* resection rate) and efficiency (as defined by time of total procedure) of grasp-and-snare circumferential EMR using a novel tissue-anchoring device in comparison to circumferential EMR with strip biopsy and direct ESD, using *ex vivo* porcine endoscopy simulator. Our results demonstrated that the overall mean total procedure time of TA-EMR was significantly shorter than ESD. Mean total procedure times of the anchor and forceps circumferential EMR were shorter than ESD. The overall mean total procedure time of TA-EMR was not significantly different from FP-EMR. The perforation rate of both TA-EMR and FP-EMR were comparable. However, the *en-bloc* rate of the TA-EMR (84.0%) was higher than for FP-EMR (60.0%), although this difference did not hold statistical significance ($P = 0.18$).

Based on our experience, the tissue-anchoring device was able to retract the mucosal flap into the snare easier and more efficiently than regular forceps since pulling the tissue with forceps resulted in a triangle shape of the mucosal flap as it only uses one point of traction. However, the tissue anchor is capable of retracting tissue from three anchor points (Figure 7). Therefore, it pulls the mucosal flap more efficiently into the snare thus avoiding a deformity of the lesion from unipolar traction. There is a theoretical potential for the three spikes of the tissue anchor to result in more injury of the resection specimen than the regular forceps since the spikes penetrate into the tissue. We did not, however, observe any injury of the specimens from the tissue anchor in any of the specimens retrieved. We believe that clear circumferential cutting is the most important factor for successful *en-bloc* resection. The operator should examine the adequate separation of the circumferential cutting area carefully before using the tissue-anchoring device for resection. A generous submucosal cushion should be injected and confirmed prior to retraction-assisted resection.

Limitations of this study include the fact that bleeding is not able to be accounted for as a complication in this simulation model. Of course, bleeding is a significant complication that must be managed in ESD and also occasionally in EMR. Furthermore, our study did not compare different sizes of lesions or compare multiple different anatomical resection locations.

In conclusion, the grasp-and-snare EMR using a

novel tissue-anchoring device after circumferential cutting appears to be equivalent in performance to EMR using forceps, with a trend towards increased *en bloc* resection rate. When comparing the EMR techniques, we confirmed a known trade-off between techniques: ESD has more predictably successful *en bloc* resection of specimens, while the EMR techniques were significantly quicker to perform.

COMMENTS

Background

To date, there is no reliable endoscopic mucosal resection (EMR) method for *en-bloc* resection for lesions greater than 20 mm in diameter. Recently, a novel tissue-anchoring device was introduced to improve grasping and retraction of tissue for endoscopic resection.

Research frontiers

This concept of tissue grasping in combination with snare resection after circumferential cutting is not new. However, the recently introduced tissue-anchoring device has the capability of deploying three spikes into the tissue that allow a reliable fixation of the tissue and facilitate retraction into snare. A pilot study demonstrated the feasibility of the grasp-and-snare EMR technique using a tissue-anchoring device for the resection of large-sized lesions.

Innovations and breakthroughs

The pilot study demonstrated that grasp-and-snare EMR using the tissue-anchoring device in combination with a 25 mm monofilament snare is feasible and results in reliable *en-bloc* resections of up to 40 mm x 42 mm specimens. The group achieved 90% complete *en-bloc* resections and time-efficiency of this method (average of 32 min) compared to the endoscopic submucosal dissection (ESD) (average of 78 min).

Applications

This study may represent another strategy for therapeutic intervention in the treatment of patients with large sized early gastric cancer or adenoma.

Terminology

En-bloc was defined as no remaining mucosal tattoo on resected specimen.

Peer review

Grasp-and-snare endoscopic mucosal resection using a novel tissue-anchoring device (TA-EMR) appears to be quicker than ESD, and there was a trend towards improved *en bloc* resection rate with the TA-EMR when compared to the conventional EMR technique.

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BRIEF ARTICLE

Clinical outcomes and risk factors for perforation in gastric endoscopic submucosal dissection: A prospective pilot study

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Abstract

AIM: To evaluate clinical outcomes and risk factors for endoscopic perforation during endoscopic submucosal dissection (ESD) in a prospective study.

METHODS: We investigated the clinical outcomes and risk factors for the development of perforation in 98 consecutive gastric neoplasms undergoing ESD regarding. Demographic and clinical parameters including patient-, tumor-, and treatment-related factors, clinical parameters, and duration of hospital stay were analyzed for risk factors for perforation. In subgroup analysis, we also compared the clinical outcomes between perforation and "silent" free air without endoscopically visible perforation detected only by computed tomography.

RESULTS: Perforation was identified in 8.2% of patients. All patients were managed conservatively by the administration of antibiotics. The mean procedure time was significantly longer in patients with endoscopic perforation than in those without. According to the receiver-operating characteristic analysis, the resulting cutoff value of the procedure time for perforation was 115 min (87.5% sensitivity, 56.7% specificity). Prolonged procedure time (≥ 115 min) was associated with an increased risk of perforation (odds ratio 9.15; 95%CI: 1.08-77.54; P = 0.04). Following ESD, body temperature and C-reactive protein level were significantly higher in patients with perforation than in those without (P = 0.02), whereas there was no difference between these patient groups on the starting day of oral intake or of hospitalization. In subgroup analysis, the post-ESD clinical course was not different between endoscopic perforation and silent free air.

CONCLUSION: Only prolonged procedure time (≥ 115 min) was significantly associated with perforation. The clinical outcomes of perforation are favorable and are comparable to those of patients with or without silent free air.

Key words: Gastric cancer; Endoscopic submucosal dissection; Perforation; Risk factors; Treatment outcome

Core tip: There has been little prospective study on the clinical outcomes of endoscopic perforation in endoscopic submucosal dissection for gastric neoplasia. In the current study, we investigated clinical outcomes of perforation during gastric endoscopic submucosal dissection, and analyzed various demographic and clinical parameters for risk factors. The results clearly demonstrated that prolonged procedure time (≥ 115 min),

but not tumor location, was significantly associated with endoscopic perforation. The clinical outcomes of perforation are favorable and comparable to those with or without silent free air without endoscopic perforation as detected only by computed tomography.

Watari J, Tomita T, Toyoshima F, Sakurai J, Kondo T, Asano H, Yamasaki T, Okugawa T, Ikehara H, Oshima T, Fukui H, Miwa H. Clinical outcomes and risk factors for perforation in gastric endoscopic submucosal dissection: A prospective pilot study. *World J Gastrointest Endosc* 2013; 5(6): 281-287 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i6/281.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i6.281

INTRODUCTION

Endoscopic submucosal dissection (ESD) is indicated for early gastric cancer in Japan, and enables *en bloc* resection regardless of lesion size[1,2]. Besides its positive outcomes, ESD carries controversial risks, such as perforation, bleeding, aspiration pneumonia, and technical difficulties[1-6]. According to a recent meta-analysis, although ESD had higher *en bloc* and curative resection rates than endoscopic mucosal resection (EMR), operation time was longer, with higher risks of complications compared to EMR[7].

Previous reports showed that large tumor size, location of the lesion in an upper region of the stomach, and long procedure time are risk factors for perforation following ESD[8-13]. Although perforation may be the most serious complication in the ESD procedure, most studies have reported recovery from perforation with conservative management such as endoscopic clipping, fasting, nasogastric aspiration, and broad-spectrum antibiotics[1,14]. However, the previous reports regarding clinical outcomes of perforation during ESD are retrospective analyses[5,8,9,13-15]. More recently, prospective studies by Onogi *et al*[16] and our group[17] found that "transmural air leak" or "silent" free air without endoscopically visible perforation detected only by computed tomography (CT) did not affect the post-ESD clinical course. In contrast, there has been little prospective research regarding clinical outcomes of perforation during the ESD procedure. In this study, we prospectively evaluated clinical outcomes and factors of endoscopic perforation during ESD.

MATERIALS AND METHODS

Patients

Between November 2010 and January 2012, 94 consecutive patients with a total of 98 gastric adenomas or cancers treated with ESD were enrolled in this study. In patients with multiple gastric neoplasms, each of the lesions was treated separately at an interval of at least 1 mo. The indications for ESD for gastric neoplasms, such as intramucosal gastric cancer and adenoma, include intramucosal differentiated tubular adenocarcinoma of any size without ulceration or signs of submucosal invasion and intramucosal differentiated-type adenocarcinoma of less than 3 cm with an ulcer scar. The histology, tumor location, and depth of invasion fulfilled the criteria of the Japanese Research Society for Gastric Cancer[18]. The histological criteria for the ESD to be considered curative were as follows: (1) margins negative for a lesion; and (2) an intramucosal lesion or minute submucosal invasion (up to 500 m invasion into the submucosal layer) without any venous or lymphatic invasion[16].

All patients were admitted on the day before ESD, and were usually discharged 9 d after the procedure. Oral intake was started 3 d after ESD. The hospital stay for patients without any clinical complications was basically 10 d, in line with the clinical protocol at our hospital (Figure 1).

Written informed consent was obtained from all patients prior to the start of the study, and all patients provided written informed consent for publication of individual clinical details. The study design was approved by the ethics committee of Hyogo College of Medicine.

ESD procedure

The ESD procedure was performed under conscious sedation using midazolam and pethidine with or without propofol. ESD was performed using an insulation-tipped diathermic (IT-2) knife (KD-610L; Olympus Medical Systems, Tokyo, Japan) or FlushKnife BT (Fujifilm, Tokyo, Japan) for *en bloc* resection. We marked the normal mucosa about 5 mm outside the tumor edge with a needle knife (KD-1L-1; Olympus Medical Systems). Saline with adrenaline (1:10000 solution in saline) was injected into the submucosa, and the initial incision was made outside the marked line. Next, the diathermic knife was inserted into the initial incision, and the mucosa 5 mm outside the mark was cut circumferentially using a VIO electrosurgical generator (Erbe, Tübingen, Germany). After tumor resection, all visible vessels in the created ulcer were coagulated using coagulation forceps (Olympus Medical Systems) to reduce the risk of delayed bleeding, according to a report by Takizawa and colleagues[5]. During the ESD procedure, carbon dioxide (CO_2) insufflation was used.

ESD complications

Endoscopic perforation was diagnosed by direct endoscopic observation of the extramural organ or fat through the muscle layer during ESD. When perforation occurred, the perforation site was immediately closed using endoclips (Olympus Medical Systems). However, endoclips sometimes make it difficult to obtain a sufficient resection margin or perform *en bloc* resection. In such cases, it is desirable to apply clips to perforated areas after an incision has been made or an exfoliation performed and after sufficient space for complete resection has been created. All patients with endoscopic perforation were administered antibiotics. In cases with severe pneumoperitonium such as that caused respiratory failure, de-

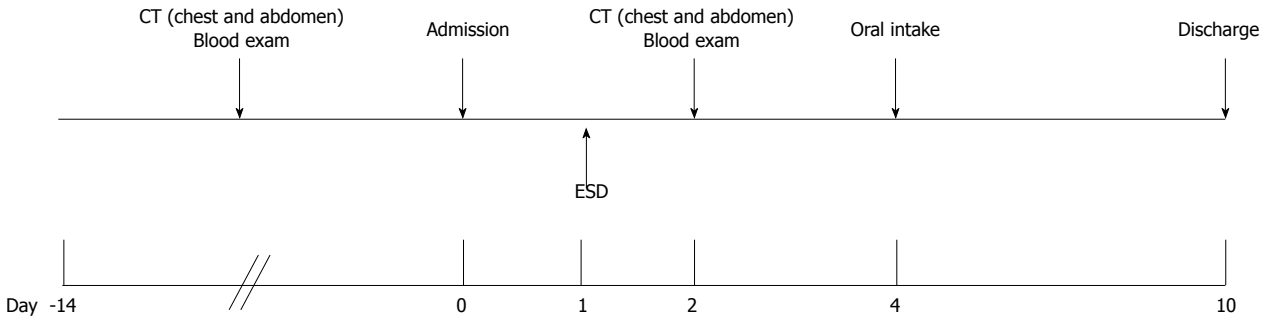

Figure 1 Clinical protocol of endoscopic submucosal dissection. ESD: Endoscopic submucosal dissection; CT: Computed tomography.

creased blood pressure or increased abdominal fullness, after which centesis was performed with an 18-gauge puncture needle to remove air from the abdominal cavity. Patients with this condition received a nasogastric tube for 1 to 2 d. In patients with perforation, oral intake was started once the white blood cell (WBC) count fell to the normal range.

Data analysis

We evaluated the following demographic and clinical parameters: patient-related factors (age, sex, use of alcohol and tobacco, and body mass index), tumor-related factors (macroscopic type, tumor location, presence or absence of scarring in the tumor, invasion depth, and histology), treatment-related factors (operator's skill, mean dimension (cm^2) of the resected specimen, and procedure time), clinical parameters (body temperature, WBC count, and serum C-reactive protein (CRP) level at one day before and after ESD), and duration of hospital stay. The procedure time was recorded from the start of the marking around the tumor to the removal of the endoscope.

The operator's skill is thought to affect the total procedure time and the treatment complications of ESD, according to previous reports[1-6]. Thus, differences in these outcomes between experienced and less-experienced endoscopists should be assessed. Japanese endoscopists receive board certification from the Japan Gastroenterological Endoscopy Society (JGES) after 5 years of training in a JGES-approved educational institution of endoscopy, and must also pass an examination administered by JGES. In the present study, the doctors who were defined as experienced endoscopists had board certification from the JGES and had each performed more than 30 ESD procedures for early gastric cancers[5,19,20].

Statistical analysis

The data were assessed using the Mann-Whitney *U*-test for comparisons between two independent groups and the χ^2 test or Fisher's exact test for comparisons between two proportions. Patient-, tumor-, and treatment-related factors were included as potential risk factors for endoscopic perforation in univariate analysis. Risk factors with a *P* value of < 0.05 in univariate analysis were included in the multiple logistic regression model and analyzed using the backward approach. Odds ratios (OR) and 95%CI were calculated for risk factors. The 95%CI of the OR was used to assess statistical significance at the conventional level of 0.05. Statistical analysis was performed using StatView version 5.0 (SAS Institute, Cary, NC, United States).

To identify the ESD procedure time that was associated with the highest diagnostic performance in terms of perforation development, we used receiver operating characteristic (ROC) curve analysis. The ROC curve for procedure time was plotted by using SPSS 11.0 for Windows (SPSS, Chicago, IL, United States). The area under the ROC curve (AUC) was calculated. The point with the largest AUC was defined as the point having the greatest association with perforation. Optimal cutoff points were determined on the basis of maximum values of the Youden index, calculated as [sensitivity + specificity-1], and the minimum values of the square root of [(1 - sensitivity)^2 + (1 - specificity)^2], which indicates the minimum distance from the upper left corner to the point on the ROC curve[21].

RESULTS

A total of 98 gastric lesions in 94 patients were evaluated, including 6 adenomas and 92 gastric cancers. The mean age of the patients was 70.9 ± 9.1 years (range, 48-87 years), and women accounted for 24.5% (23 of 94) of the patients. The curative *en bloc* resection rate was 88.8% (87 of 98), and endoscopic perforation during ESD occurred in 8.2% (8 lesions).

Factors predicting development of endoscopic perforation

The mean procedure time was significantly longer in patients with perforation than in those without (controls) (*P* = 0.02), but the tumor location and lesion with scar were not associated with perforation (Table 1). Also, the perforation rate did not differ between experienced and less-experienced operators.

The association between endoscopic perforation and procedure time was evaluated using ROC curve analysis (Figure 2). According to this analysis, cutoff points showing optimal performance were chosen by the distance to the ROC curve and the Youden index for the procedure time. The resulting cutoff value of the procedure time

Table 1 Relationship between perforation and various factors

	Control (n = 90)	Perforation (n = 8)	P value
Patient-related factors			
Age (yr)	70.8 ± 9.2	72.4 ± 7.5	NS
Sex, male/female	69/21	6/2	NS
Active alcohol drinking	40/50	4/4	NS
Positive/negative			
Active smoking	16/74	2/6	NS
Positive/negative			
Body mass index (kg/m^2)	23.2 ± 2.9	23.0 ± 3.3	NS
Tumor-related factors			
Macroscopic type: Ⅰ/Ⅱa/Ⅱb/Ⅱc	9/43/2/36	0/5/0/3	NS
Location: Upper/middle/lower	12/48/30	2/6/0	NS
Scar: Positive/negative	9/81	0/8	NS
Depth of invasion: M/SM and beyond	77/13	5/3	NS
Histology: DAC/poorly DAC/adenoma	5/6/1979	7/1/0	NS
Treatment-related factors			
Operator: Experienced/less-experienced	32/58	2/6	NS
Resected dimensions (cm^2)	9.7 ± 6.0	24.0 ± 24.9	NS
Procedure time (min)	122.5 ± 75.6	203.1 ± 114.3	0.02
Clinical parameters			
Body temperature	36.9 ± 0.5	37.3 ± 0.6	NS
White blood cell (/mL)	10566.9 ± 2903.6	9898.8 ± 3149.4	NS
C-reactive protein (mg/dL)	1.5 ± 1.4	2.4 ± 1.3	0.04
Hospital stay (d)	10.5 ± 2.4	10.9 ± 1.5	NS

Data are expressed as mean ± SD. M: Intramucosal cancer and adenoma; SM: Submucosal invasive cancer; DAC: Differentiated-type adenocarcinoma; Poorly DAC: Poorly differentiated-type adenocarcinoma; NS: Not significant.

for perforation was 115 min (sensitivity, 87.5%; specificity, 56.7%) for patients who underwent gastric ESD.

Based on the ROC curve analysis and optimal cutoff points of the procedure time of gastric ESD determined above, a procedure time of ⩾ 115 min was used in the analyses. We analyzed the strength of the association between perforation development and procedure time (⩾ 115 min). As a result, procedure time (⩾ 115 min) was significantly associated with increased endoscopic perforation (OR = 9.15, 95%CI: 1.08-77.54; P = 0.04).

Clinical course in patients with perforation

Following ESD, only the CRP level was significantly higher in patients with perforation than in those without (P = 0.04) (Table 1). The clinical courses of patients with perforation are summarized in Table 2. Four patients with endoscopic perforation received a nasogastric tube for a mean of 1.3 d. None of the patients with this condition required surgery, and there was no perforation-related mortality. Oral intake was started from a mean of 4.0 d after ESD (range, 3-7 d). Patients with perforation were discharged after a mean stay of 10.9 d (9.9 d after ESD); this did not differ significantly from the average stays of patients without perforation (Table 1).

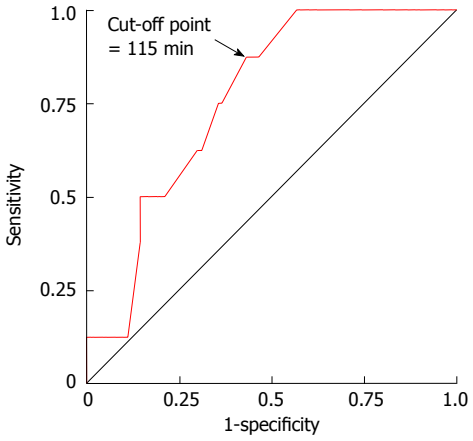

Figure 2 Receiver-operating characteristic curve of perforation development after endoscopic submucosal dissection. The curve is plotted with sensitivity (y-axis) and (1-specificity) (x-axis). The resulting cut-off value of the procedure time for perforation was 115 min (sensitivity, 87.5%; specificity, 56.7%).

Subgroup analysis: Comparison of clinical outcomes between patients with perforation and those with silent free air

All patients underwent plain abdominal CT on the day after ESD. If free air close to the stomach was detected by CT on the day after ESD even though no evidence of endoscopic perforation was seen during ESD and peritonitis, the case was defined as silent free air as reported previously[17]. We compared the clinical outcomes between patients with perforation and silent free air.

Silent free air was observed in 35.7% (35 lesions) in this period. Body temperature and CRP levels following ESD were significantly higher in patients with endoscopic perforation than in those with silent free air (P = 0.04 and P = 0.03, respectively) (Table 3). Oral intake was started from 3 d after ESD in all patients with silent free air, as scheduled based on the clinical protocol (Figure 1), but no significant difference in the starting day of oral intake was found between these conditions.

DISCUSSION

Even though ESD is widely accepted and performed worldwide in patients with gastric cancer, perforation is a common and serious complication. In contrast, many retrospective studies show that conservative management by immediate endoscopic closure with endoclips is effective in most patients with perforation[1,14]. Recently in prospective studies, Onogi *et al*[16] and we reported that an "air leak" after gastric ESD, detected only by CT in patients without endoscopically visible perforation, was observed frequently, and this asymptomatic (silent) free air does not affect the post-ESD clinical course. Likewise, the current work, which is based on our recent study[17], clearly demonstrated that perforation was not associated with clinically significant complications, and showed clinical outcomes similar to those of cases without perfora-

Table 2 Clinical courses after perforation

Age (yr)	Sex	Macroscopic type	Location	Depth of invasion	Scar	Resected dimensions (cm^2)	Procedure time (min)	Nasogastric tube (d)	Beginning of oral intake after ESD (d)	Hospitalization (d)
62	Male	IIa	Upper	M	-	69.1	460	1	4	10
63	Male	IIc	Middle	M	-	5.5	130	-	3	10
77	Male	IIb + IIa	Middle	SM	-	18.8	220	1	3	11
71	Male	IIa	Middle	M	-	8.2	160	2	3	10
83	Female	IIc	Lower	SM	-	56.1	220	-	5	12
72	Female	IIa	Middle	M	-	22.0	215	-	3	10
80	Male	IIa	Upper	M	-	3.1	100	-	3	10
71	Male	IIc	Lower	SM	-	9.4	120	1	7	14

Data are expressed as mean ± SD. M: Intramucosal cancer and adenoma; SM: Submucosal invasive cancer; ESD: Endoscopic submucosal dissection.

Table 3 Subgroup analysis: Comparison in various factors between perforation and silent free air

	Perforation (n = 8)	Silent free air on CT (n = 35)	P value
Tumor-related factors			
Location: Upper/middle/lower	2/6/0	9/21/5	NS
Scar: Positive/negative	0/6	5/30	NS
Depth of invasion: M/SM and beyond	5/3	5/30	NS
Treatment-related factors			
Operator: Experienced/less-experienced	2/6	16/19	NS
Resected dimensions (cm^2)	24.0 ± 24.9	10.4 ± 7.2	NS
Procedure time (min)	203.1 ± 114.3	145.1 ± 76.5	NS
Clinical parameters			
Body temperature	37.3 ± 0.6	36.8 ± 0.6	0.04
White blood cell ($/mm^3$)	9898.8 ± 3149.4	10658.0 ± 3119.3	NS
C-reactive protein (mg/dL)	2.4 ± 1.3	1.4 ± 1.0	0.03
Oral intake (d)	3.0	4.0 ± 1.5	NS
Hospital stay (d)	10.9 ± 1.5	10.7 ± 2.1	NS

Data are expressed as mean ± SD. CT: Computed tomography; M: Intramucosal cancer and adenoma; SM: Submucosal invasive cancer; NS: Not significant.

tion. Therefore, perforations might be considered part of the procedure and not as a complication[22].

In the current study, a procedure time exceeding 115 min was considered to be a reliable marker associated with perforation development by ROC curve analysis. Thus, prolonged procedure time was a highly significant factor for endoscopic perforation; this finding is consistent with those of other studies[9,11-13,16]. However, tumor location was not related to perforation. In our previous study[17], tumor location was also not an independent risk factor for silent free air. Previous studies showed that tumor location (the upper portion of the stomach) was a significant and independent predictor of perforation by multivariate analysis[8-13,16,17]. A possible explanation for the discrepancy may be the difference in the number of patients with perforation investigated between ours and other studies. Indeed, only 8 of the patients in our study had perforation. In reports from Japan and South Korea, perforation was observed in 1.2% to 6.1% of patients[8-15]. Our perforation rate (8.2%) was slightly higher than in the other studies. Of the 8 cases with endoscopic perforation, 6 were treated by less-experienced operators. However, operator skill was not associated with either perforation or silent free air (Tables 1 and 2). This was attributed to the fact that more experienced endoscopists were more likely to perform ESD in patients with larger tumors or tumors with scars than were less-experienced endoscopists. Actually, the features of the lesions, *i.e.*, ulcer scarring, tumor size, and tumor location, in addition to technical skill, may be significant risk factors for perforation, as many reports have pointed out.

Silent free air was detected in 35.7% of the cases in this study. Jeon *et al*[14] recently reported a similar study, which compared the clinical outcomes of treatment for macro- and micro-perforations with ESD and determined the short-term prognosis after ESD. Those authors defined micro-perforation as a perforation identified by a pneumoperitoneum seen on plain radiographs after ESD. According to their report, a micro-perforation, resembling the silent free air in our study, was observed in only 0.76% (13 of 1711) of the patients undergoing gastric ESD, an extremely lower incidence than we found in our study. The difference may be attributable to different sensitivities between plain radiograph and CT.

With regards to inflammatory markers after ESD, such as body temperature, WBC level, and CRP level, only CRP level was significantly higher in perforation patients than in controls (P = 0.04). All the patients with endoscopic perforation were exposed to antibiotics, and 4 patients received a nasogastric tube. By conservative treatments, these patients with perforation were able to start oral intake from a mean of 4 d following ESD; this time to resume oral intake was not significantly different from that in patients with or without silent free air. Furthermore, the hospital stay did not differ according to the presence or absence of perforation or silent free air. These results indicate that immediate closure of the perforation site, intravenous antibiotic therapy, or brief nasogastric tube replacement may be important for favorable outcomes. In our clinical protocol of ESD, the hospital stay was 10 d, and oral intake was started 3 d after ESD; these may be slightly longer than in other hospitals. It remains possible, therefore, that this longer hospitalization in our protocol affected the present results.

In our series, we used CO_2 insufflation during the ESD procedure. It has been reported that ESD with CO_2

insufflation is safe and reduces both abdominal discomfort and the risk of perforation after ESD[9,23,24]. Hereafter, ESD with CO_2 insufflation should be performed during lengthy endoscopic treatment procedures to avoid complications during and after ESD.

In the present study, there has been no evidence of peritoneal seeding after endoscopic perforation with short follow-up periods by CT or ultrasonography, and this was consistent with previous results[10,14]. Similarly, Ikehara *et al*[25] reported that perforation associated with EMR and ESD does not lead to peritoneal dissemination even in the long term (median 53.6 mo, range 7.0-136.6 mo). Further studies are needed before definitive conclusions can be drawn about the risk of peritoneal seeding after perforation or silent free air[10].

The limitation of this study is the small number of patients with perforation in a single center, limiting our ability to draw conclusions, as mentioned previously[8,9,13,14]. Our results do not necessarily mean, therefore, that perforation during ESD can be managed conservatively. Seewald *et al*[22] previously showed an algorithm for endoscopic management of gastrointestinal perforation. Therefore further studies with larger numbers of patients will be needed to clarify the long-term outcomes of patients with endoscopic perforation.

In conclusion, the current prospective pilot study showed that prolonged procedure time (≥ 115 min) was associated with an increased risk of perforation. However, conservative management of perforation was successful and did not affect the post-ESD clinical course. Therefore, clinical outcomes of endoscopic perforation are favorable and comparable to those with or without silent free air.

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COMMENTS

Background

Endoscopic submucosal dissection (ESD) is indicated for early gastric cancer in Japan, and enables *en bloc* resection regardless of lesion size. Besides its positive outcomes, ESD carries controversial risks, such as perforation, bleeding, aspiration pneumonia, and technical difficulties.

Research frontiers

Even though ESD is widely accepted and performed worldwide in patients with gastric cancer, perforation is a common and serious complication. In contrast, many retrospective studies show that conservative management by immediate endoscopic closure with endoclips is effective in most patients with perforation.

Innovations and breakthroughs

There has been little prospective study on the clinical outcomes of endoscopic perforation in endoscopic submucosal dissection for gastric neoplasia. In the current study, authors investigated clinical outcomes of perforation during gastric endoscopic submucosal dissection, and analyzed various demographic and clinical parameters for risk factors.

Applications

The clinical outcomes of perforation are favorable and comparable to those with or without silent free air without endoscopic perforation as detected only by computed tomography.

Peer review

Generally, this is an interesting and well written prospective study about clinical outcomes and risk factors for perforation in gastric ESD. Authors prospectively investigated 98 consecutive gastric neoplasms undergoing ESD regarding the clinical outcomes and risk factors for development of perforation. They clearly showed that prolonged procedure time was associated with an increased risk of perforation.

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BRIEF ARTICLE

Failure of sequential biliary stenting for unsuccessful common bile duct stone removal

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Abstract

AIM: To determine the factors associated with the failure of stone removal by a biliary stenting strategy.

METHODS: We retrospectively reviewed 645 patients with common bile duct (CBD) stones who underwent endoscopic retrograde cholangiography for stone removal in Siriraj GI Endoscopy center, Siriraj Hospital from June 2009 to June 2012. A total of 42 patients with unsuccessful initial removal of large CBD stones that underwent sequential biliary stenting were enrolled in the present study. The demographic data, laboratory results, stone characteristics, procedure details, and clinical outcomes were recorded and analyzed. In addition, the patients were classified into two groups based on outcome, successful or failed sequential biliary stenting, and the above factors were compared.

RESULTS: Among the initial 42 patients with unsuccessful initial removal of large CBD stones, there were 37 successful biliary stenting cases and five failed cases. Complete CBD clearance was achieved in 88.0% of cases. The average number of sessions needed before complete stone removal was achieved was 2.43 at an average of 25 wk after the first procedure. Complications during the follow-up period occurred in 19.1% of cases, comprising ascending cholangitis (14.3%) and pancreatitis (4.8%). The factors associated with failure of complete CBD stone clearance in the biliary stenting group were unchanged CBD stone size after the first biliary stenting attempt (10.2 wk) and a greater number of endoscopic retrograde cholangio-pancreatography sessions performed (4.2 sessions).

CONCLUSION: The sequential biliary stenting is an effective management strategy for the failure of initial large CBD stone removal.

Key words: Endoscopic retrograde cholangiography; Common bile duct stone; Biliary stenting; Large common bile duct stone; Biliary stenting failure

Core tip: This study was a retrospective review of 42 patients who underwent sequential biliary stenting following a failed removal of a large common bile duct stone by endoscopic retrograde cholangiopancreatography. Complete common bile duct (CBD) clearance was achieved in 88% of the patients at 25 wk after the first procedure, while 19% reported complications. The common complications were cholangitis and pancreatitis. The factors associated with the failure of this strategy were unchanged CBD stone size at the second biliary stenting attempt, and more endoscopic retrograde cholangio-pancreatography sessions performed.

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INTRODUCTION

Patients with untreated common bile duct (CBD) stones, irrespective of the presence of symptoms, are at high risk of experiencing further symptoms or complications. Given the potentially serious complications of CBD stones such as ascending cholangitis or acute pancreatitis, specific therapy is usually required[1]. Choledocholithiasis is one of the most common indications for performing therapeutic endoscopic retrograde cholangiography (ERC)[1].

The majority (80%-90%) of simple CBD stones, specifically those that are < 1 cm, are removed by ERC *via* endoscopic sphincterotomy by using a basket or balloon catheter[2,3]. However, from references[4-15], we know that approximately 10%-15% of patients have bile duct stones that cannot be removed using standard techniques. These stones are generally larger than 1-1.5 cm, impacted, located proximal to strictures, or associated with the duodenal diverticulum, and are frequently successfully removed by mechanical lithotripsy or large balloon sphincteroplasty[16]. However, the removal of large CBD stones is not possible by using these techniques. Therefore, most endoscopists prefer to place a biliary stent as a temporary measure to maintain biliary drainage and prevent stone impaction[17]. Biliary stenting is an effective method of reducing the size of CBD stones because the stone-stent friction force can lead to stone fragmentation inside the CBD[18,19]. Therefore, sequential biliary stenting is still the most common technique for large CBD stone removal. However, this technique can be time-consuming for complete stone removal and is associated with a higher complication rate during the follow-up period, particularly from cholangitis. Thorough studies examining the success factors for this treatments strategy are incomplete or lacking[18-20]. Thus, the aim of this study was to determine the factors that can potentially predict a high failure rate of the first CBD clearance, in turn providing a clearer picture of patients who can be managed conservatively by sequential biliary stenting.

MATERIALS AND METHODS

The medical records and endoscopic reports of patients who underwent ERC for choledocholithiasis from June 2009 to June 2012 were retrospectively reviewed (645 total records). The siriraj institutional review board gave approval for the study. Experienced endoscopists or gastroenterology fellows under the supervision of experienced endoscopists performed all ERC procedures. The inclusion criteria were as follows: (1) large CBD stones (diameter of > 15 mm); (2) failure of complete stone removal during the initial attempt and biliary stent insertion; and (3) follow-up and subsequent ERC procedures performed in our institution. Patients were classified into two groups: group one comprised patients who underwent repeated short-term biliary stenting after failure of CBD clearance (with standard techniques or mechanical lithotripsy or balloon sphincteroplasty) until achievement of complete CBD clearance; group two comprised patients who underwent failed biliary stenting. Patients who were unable to be contacted for a follow-up or who did not undergo further procedures in our institute were excluded. The study design is presented in Figure 1. Five dedicated endoscopists, each performing more than 200 cases annually, performed the ERC procedures with biliary stenting. We used a therapeutic duodenoscope (Olympus TJF-140 or TJF-160; Olympus America, Central Valley, PA, United States) with patients under intravenous sedation or general anesthesia with full anesthetic monitoring. Patients with ascending cholangitis received pre-procedural antibiotics. The first treatment attempt was standard endoscopic sphincterotomy, stone retrieval *via* balloon retrieval catheter or basket extraction catheter, and crushing by mechanical lithotripsy (Soehendra Lithotriptor; Wilson-Cook Medical Inc., Winston-Salem, NC, United States) at the discretion of the endoscopists. After the initial clearance attempts failed, patients underwent biliary stenting and were scheduled for repeated ERC. Straight plastic stents (Cotton-Leung Biliary Endoprosthesis; Wilson-Cook Medical Inc., United States) or double pigtail plastic stents (C-flex Biliary; Boston Scientific, Spencer, IN, United States) were used. The clearance of the biliary tract was documented using a cholangiogram. The success of biliary clearance, cost of the procedures, degree of complications, time interval between the initial attempt and complete CBD clearance of the stones, surgical procedures, and complications during follow-up were assessed. The follow-up period extended to the last recorded medical visit. Descriptive statistics were used to summarize patients' baseline demographics, clinical characteristics, and radiographic data. Continuous variables were reported as means or medians (min, max).

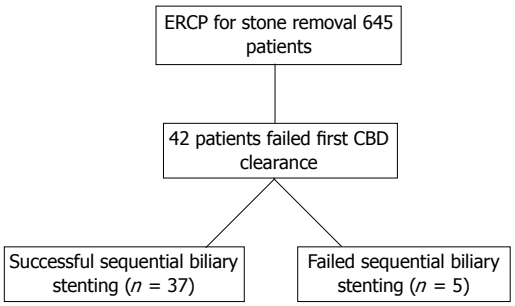

Figure 1 Diagram of the study population. CBD: Common bile duct; ERCP: Endoscopic retrograde cholangio-pancreatography.

Statistical analysis

The compared data were analyzed using a χ^2 or Mann-Whitney *U* test. A value of $P < 0.05$ was considered significant. All statistical evaluations were performed using SPSS version 11.5 software.

RESULTS

A total of 645 medical records and electronic endoscopy records were retrospectively reviewed, and 42 patients

Table 1 Baseline characteristics and cholangiographic findings of enrolled patients in both groups, including the comparison of procedural details, stone characteristics, and complications *n* (%)

Details	Total (*n* = 42)	Success group (*n* = 37)	Failed group (*n* = 5)	*P* value
Male sex	34 (81.0)	6 (16.2)	2 (40.0)	NS
Age in years	71.9 ± 14.2	71.9 ± 14.3	72.0 ± 15.5	NS
Indications for ERC				
Cholangitis	22 (52.4)	20 (54.1)	2 (40.0)	NS
Biliary pain	10 (23.8)	8 (21.6)	2 (40.0)	
Obstructive jaundice	4 (9.5)	3 (8.1)	1 (20.0)	
Acute pancreatitis	2 (4.8)	2 (5.4)	0 (0.0)	
Asymptomatic	4 (9.5)	4 (9.5)	0 (0.0)	
CBD size in mm	1.83 ± 0.45	1.80 ± 0.44	2.06 ± 0.56	NS
Stone size in mm	1.86 ± 0.43	1.85 ± 0.41	2.04 ± 0.58	NS
Stone number	1.50 ± 1.06	1.51 ± 1.12	1.40 ± 0.55	NS
Stone fit to CBD	37 (88.1)	32 (86.5)	5 (100)	NS
Stone shape				NS
Irregular		7 (18.9)	1 (20.0)	
Geometric (oval, cube)		30 (81.1)	4 (80.0)	
Stone characteristics				NS
Mixed stone		17 (45.9)	3 (60.0)	
Cholesterol stone		20 (54.1)	2 (40.0)	
Change in stone size				
Decrease		25 (67.6)	1 (20.0)	0.04
Stable		12 (32.4)	4 (80.0)	
Balloon sphincteroplasty		9 (24.3)	3 (60.0)	0.13
Use of mechanical lithotripsy		14 (37.8)	2 (40.0)	NS
Time to successful procedures in weeks		25.42 ± 40.42	None	NA
Sessions carried out		2.43 ± 0.80	2.80 ± 1.30	NS
Average follow-up time in months		13.10 ± 13.79	10.70 ± 8.81	NS
Complications during follow-up period				NS
Ascending cholangitis	6 (14.3)	6 (16.2)	0 (0.0)	
Acute pancreatitis	2 (4.8)	1 (2.7)	1 (20.0)	
None	34 (80.9)	30 (81.1)	4 (80.0)	

CBD: Common bile duct; ERC: Endoscopic retrograde cholangiography; NS: No statistical significance as $P > 0.5$; NA: Not analyzed.

who met the inclusion criteria were enrolled in the study. Thirty-seven patients achieved successful sequential biliary stenting after the failure of initial stone extraction, whereas this strategy failed in five patients. Of the 42 patients were enrolled, 81% were women, and the mean age was 71.9 ± 14.2 years (range: 33-97 years). Almost 90% of patients were symptomatic, presenting with ascending cholangitis, biliary pain, obstructive jaundice, or acute pancreatitis (52.4%, 23.8%, 9.5%, and 4.8%, respectively). The stones were located at the distal, middle, and proximal portions of the CBD in 47.6%, 47.6%, and 4.8% of cases, respectively. Eight-eight percent were fit to the duct. The mean number of stones per patient was 1.5 ± 1.1 stones (range: 1-6 stones), the mean stone maximum diameter was 1.86 ± 0.43 cm (range: 1.5-3.0 cm), and the average CBD maximum diameter was 1.83 ± 0.45 cm (range: 1.2-3.5 cm). Patients who underwent biliary stenting were followed for an average of 12.8 mo (range: 2-54 mo) after the initial stone removal attempt. Biliary clearance was achieved in 88.0% of cases, with an average time between each attempt of 10.2 wk (range: 5-24 wk), and an average time to complete duct clearance of 26.8 wk (range: 6-216 wk). The average number of sessions for complete biliary clearance was 2.5 ± 0.86 procedures (range: 2-6 procedures). The baseline characteristics of the patients and procedural details (including cholangiographic findings) are shown in Table 1.

Table 1 compares the clinical characteristics, cholangiographic features, and procedure details between the two groups of patients. Stone shape, size, and characteristics were similar between the groups. For patients with failed sequential biliary stenting, the average time interval after the first endoscopic retrograde cholangio-pancreatography (ERCP) to surgery was 71 wk (range: 28-184 wk), and the average number of sessions performed before surgery was 4.2 sessions (range: 3-6 sessions). The surgical outcomes were satisfactory without significant complications. The patients who underwent successful sequential biliary stenting had an average time interval between the first attempt and complete CBD clearance of 25.4 wk (range: 6-216 wk), and the average number of sessions performed was 2.43 sessions (range: 2-6 sessions). The factors that may be related to the failure of sequential biliary stenting were no reduction of CBD stone size at the second procedure ($P = 0.04$) and a greater number of sessions performed ($P < 0.001$). Another factor that may contribute to the failure of sequential biliary stenting, albeit insignificant in our study ($P = 0.13$), is the failure of balloon sphincteroplasty at the first attempt. A study in a larger cohort may be required to confirm this result.

DISCUSSION

Almost 7% of the patients in this study had large CBD stones that were not completely cleared using standard techniques at the first attempt, which is consistent with reports from other endoscopy centers[1-3,16,17]. Almost 90% of all patients in this study were symptomatic, and the most common clinical presentation was ascending cholangitis. Stones were located throughout the CBD, but more prominently in the distal and mid portions. The conventional management of large CBD stones that fail to be completely removed at the first attempt is sequential biliary stenting, which reduces stone size by stent-stone friction force. We observed that leaving the stent inside the CBD for an average of 10 wk resulted in stone size reduction in 45% of the cases and complete disappearance in 16% of the enrolled patients. Furthermore, we speculated that the CBD might have been completely cleared in 85.7% of patients by further serial sessions combined with the use of mechanical lithotripsy. Nineteen percent of patients suffered from complications during the follow-up period, which were primarily related to ascending cholangitis. Chan *et al*[20] reported on a total of 46 patients with large CBD stones who were treated with plastic stent insertion, among which 28 cases underwent repeated ERC. Stones were extracted after a median of 63 d, and the repeated procedures achieved complete duct clearance in 25 (89%) of the patients. Similar results have also been reported by Maxton *et al*[21] and Jain *et al*[22]. The most common complications we observed were cholangitis and pancreatitis (14.3% and 4.8%, respectively). This result is in agreement with data reported from a Japanese study in which 13% of patients suffered cholangitis during biliary stenting[23]. Comparing this with long-term biliary stenting, Ang *et al*[24] reported up to 22% mortality among patients treated by long-term biliary stenting for an average of 12 mo (range: 1-54 mo), which accounted for 3.5% of biliary-related mortality. However, there was no mortality in the present study. Therefore, in the majority of patients, sequential biliary stenting was a safer and more effective procedure for treating difficult CBD stones than long-term biliary stenting. However, there were five cases (11.9%) where sequential biliary stenting failed in this study. The factors associated with the failure to achieve complete CBD stone clearance were unchanged CBD stone size at an average of 10 wk after the first biliary stenting attempt and a greater number of sessions performed (particularly for > 4 sessions). In cases presenting these particular factors, the therapeutic strategy should be changed from sequential biliary stenting to other alternative treatments such as intraductal lithotripsy (EHL or laser) or surgery. However, the current study did have some limitations similar to those in the other studies that included a retrospective case series of a limited number of patients. A multicenter study for a larger population should be conducted in the future.

In conclusion, sequential biliary stenting was an effective management strategy for large CBD stones that failed initial complete CBD clearance. The factors associated with failure were unchanged CBD stone size after the first biliary stenting procedure and a greater number of ERCP sessions performed.

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COMMENTS

Background

Common bile duct (CBD) stones and related complications are one of the most common pancreatobiliary diseases in daily practice. The treatment of choice for CBD stone removal is endoscopic retrograde cholangiopancreatography (ERCP) with an 85%-90% success rate of complete stone removal. Complete removal is therefore not achieved for 10%-15% of CBD stones-particularly large stones-by the standard technique, and these may be managed conservatively by biliary stenting. The factors associated with the failure of this strategy are not well established.

Research frontiers

Sequential biliary stenting has been used as an option for common bile duct stones that were not completely successfully removed following the first ERCP. The stent-stone friction force could lead to size-reduction or fragmentation of the stone.

Innovations and breakthroughs

The goal of this study was to determine the factors that are associated with the failure of ERCP. These factors will potentially aid endoscopists in making decisions of referring the patient for other treatment options such as laser choledochoscopy, electrohydraulic lithotripsy or even surgery.

Applications

This study suggested that the treatment strategies should be changed if the size of the CBD stone was not changed at 10 wk after the first procedure or failure of complete stone removal at the second attempt.

Terminology

Sequential biliary stenting was the strategy of insertion the plastic stent over the CBD stone for two major reasons. First to maintain the drainage and second to aid in stone fragmentation after the stent was placed for more than 4-6 wk. The common interval for each procedure was 6-12 wk.

Peer review

The present study demonstrated the parameters associated with the failure of sequential biliary stenting following unsuccessful stone removal from the large common bile duct. The authors found that sequential biliary stenting is an effective management strategy for treating failed initial large CBD stone removal.

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CASE REPORT

Carcinoma in gut-associated lymphoid tissue in ulcerative colitis: Case report and review of literature

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Abstract

The colorectal mucosa includes two quantitatively, structurally and functionally dissimilar areas: one, built with columnar and goblet cells, covers the vast majority of the mucosa, and the other consists of scattered minute gut-associated lymphoid tissue (GALT). The overwhelming majority of colorectal carcinomas evolve in GALT-free mucosal areas and very rarely in GALT aggregates. Remarkably, the colonic mucosa in patients with ulcerative colitis (UC) displays a high number of newly formed GALT-aggregates. The patient here described is a 68-year-old female with a history of UC since 1984. At surveillance colonoscopy in 2012, one of two detected polyps was a tubular adenoma with high-grade dysplasia. Beneath this adenoma, a well-circumscribed GALT sheltering a carcinoma was found. Serial sections revealed no connection between the villous adenoma and the GALT-carcinoma. The GALT-carcinoma here reported seems to have evolved in a newly formed, UC-dependent, GALT complex. This notion is substantiated by the fact that 27% or 4 out of the 15 cases of GALT-carcinomas in the colon reported in the literature (including the present case) evolved in patients with UC.

Key words: Colon; Advanced adenoma; Gut-associated lymphoid tissue; Carcinoma; Ulcerative colitis

Core tip: Of the 15 cases of gut-associated lymphoid tissue (GALT)-carcinomas in the colon reported in the literature (including the present case) 27% (n = 4) have evolved in patients with ulcerative colitis. The possibilities that the advanced adenoma on top had invaded the GALT-complex underneath or that the GALT-carcinoma was a metastasis from the adenoma on top were rejected, since serial sections revealed neither continuity between the adenoma and the GALT-carcinoma, nor invasive growth in the adenoma.

Rubio CA, Befrits R, Ericsson J. Carcinoma in gut-associated lymphoid tissue in ulcerative colitis: Case report and review of literature. *World J Gastrointest Endosc* 2013; 5(6): 293-296 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i6/293.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i6.293

INTRODUCTION

The colorectal mucosa can be divided into two quantitatively, structurally and functionally dissimilar areas[1]. One comprises the vast majority of the colorectal mucosa: it is built with mucus producing goblet cells and columnar cells exhibiting microvilli covered with glycocalix. The function of this huge mucosal area is to protect the underlying structures, to allow free passage into the host,

of water and other fluids (encouraged by aquaporin 8, a water channel protein[2]), ions, vitamins and some nutrients, as well as to produce lysozyme, the innate antibacterial enzyme that annihilates pathogenic bacteria[3]. The other mucosal area, called gut-associated lymphoid tissue (GALT), is composed of tiny mucosal fractions scattered in the colorectal mucosa. O'Leary *et al*[4] found only 36 GALT aggregates (also called cryptopatches or lymphoglandular complexes) per colectomy in 27 specimens without ulcerative colitis. A single layer of cubic cells and few or no goblet cells build the epithelium covering GALT aggregates. Electron-microscopic studies show an epithelium with a poorly developed brush border, but clear-cut micro-ridges (thereof the M designation). In addition, invaginations in the surface of M cells create intraepithelial pockets[5]. The function of M cells is to absorb luminal antigens such as macromolecules and microorganisms *via* clathrin-mediated endocytosis[6] and to haul these antigens into the underlying collection of gut-indigenous, thymus-independent lymphoid tissue for immediate immunological processing. Hence, the M cell-lymphoid tissue assemblage (that is GALT) is a lymphoepithelial immunological unit that coordinates antigen recognition and processing in the gut mucosa[5].

Nearly all-colorectal carcinomas (CRC), the third most frequent cancer worldwide[7], evolve in GALT-free mucosal areas. In contrast, CRC arising in GALT-associated mucosa are very rare.

Patients with extensive ulcerative colitis (UC) are at increased risk of developing a CRC[7]. It is generally accepted that CRC in UC also originates in GALT-free colorectal mucosa: either from UC-related non-protruding dysplastic crypts (known as dysplasia in flat mucosa[8]), from protruding, or non-protruding adenomatous lesions, or from age-dependent, UC-unrelated, sporadic adenomas[9].

Dukes[10] described in colitic patients a histological lesion, usually in the submucosa, characterized by "misplaced" colonic epithelium surrounded by nodular lymphoid tissue. Dukes[10] believed that this epithelium was the result of mucosal repair following regeneration of a mucosal ulcer and that the epithelium detached and buried in the submucosa encouraged cancer development. Hultén *et al*[11] also considered this phenomenon, a precancerous lesion. Their descriptions fit well with the notion of GALT-mucosa.

Searching for a confirmation of the hypothesis of Cuthbert Dukes, we reported and illustrated in 1984, the first case of GALT-carcinoma of the colon in the literature[12]. In 2002, Rubio and Talbot reported another case of GALT-carcinoma in a patient with UC[13]. Of note, of the two cases of GALT-carcinoma reported by Stewart *et al*[14], one occurred in a patient with UC.

de Petris *et al*[15] reported a case of sporadic GALT-carcinoma in the colon of a patient without UC. Because of its protruding shape, these authors proposed to call it dome carcinoma (DC). Since then, six new cases of sporadic DC in patients without UC appeared in the literature[14,16-19] (Table 1). In addition 3 DC were found in a colectomy specimen in a patient with Lynch syndrome[20].

Table 1 Colon carcinomas evolving in gut-associated lymphoid tissue reported in the literature

Ref.	Clinical data	GALT-carcinomas
Rubio[12]	UC	1
Rubio *et al*[13]	UC	1
Stewart *et al*[14]	UC (in 1 of 2 cases)	2
De Petris *et al*[15]	HNPCC	1
Jass *et al*[16]		1
Clouston *et al*[17]		2
Asmussen *et al*[18]		2
Rubio *et al*[19]	Lynch	3
Yamada *et al*[20]		1
Present communication	UC	1

UC: Ulcerative colitis; GALT: Gut-associated lymphoid tissue; HNPCC: Hereditary nonpolyposis colon cancer.

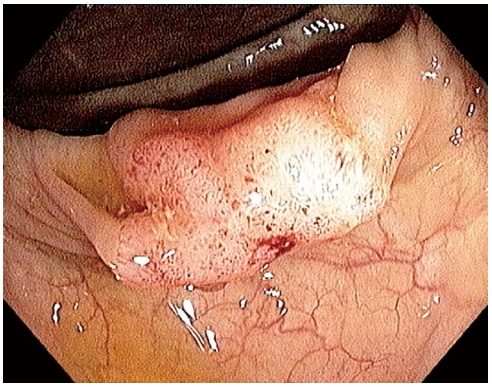

Figure 1 Endoscopic image showing a polypoid lesion in the transverse colon.

The purpose of this communication is to report a new case of GALT-carcinoma in a patient with UC.

CASE REPORT

The patient is a 68-year-old female, with a history of UC since 1984. She has been under colonoscopic-histologic surveillance since 1985. In 2004 one of 11 biopsies exhibited low-grade dysplasia (LGD) in flat mucosa. In 2005, an aggressive breast ductal cancer was diagnosed and treated with surgery and chemotherapy. Despite treatment, the disease progressed, and several skeletal metastases were detected. In September 2011, numerous polyps in the right colon were found at a colonoscopic-histologic séance; two of these polyps were reported as tubular adenomas with LGD. A new colonoscopy in February 2012 revealed two new polyps, this time in the transverse colon (Figure 1).

Biopsies were stained with hematoxylin and eosin (HE), and immuno-histochemically stained with MNF 116, Actin SM (Leica Microsystems AB, Bromma, Sweden), Ki67 (clone MIB1, Leica Microsystems AB, Bromma, Sweden), p53 (BD Products, Franklin Lakes, United States), p21WAF1 (Oncogene Science, Chicago, United States), and histochemically stained with Alcian blue pH 2.5, periodic acid-Schiff (PAS) and PAS-D.

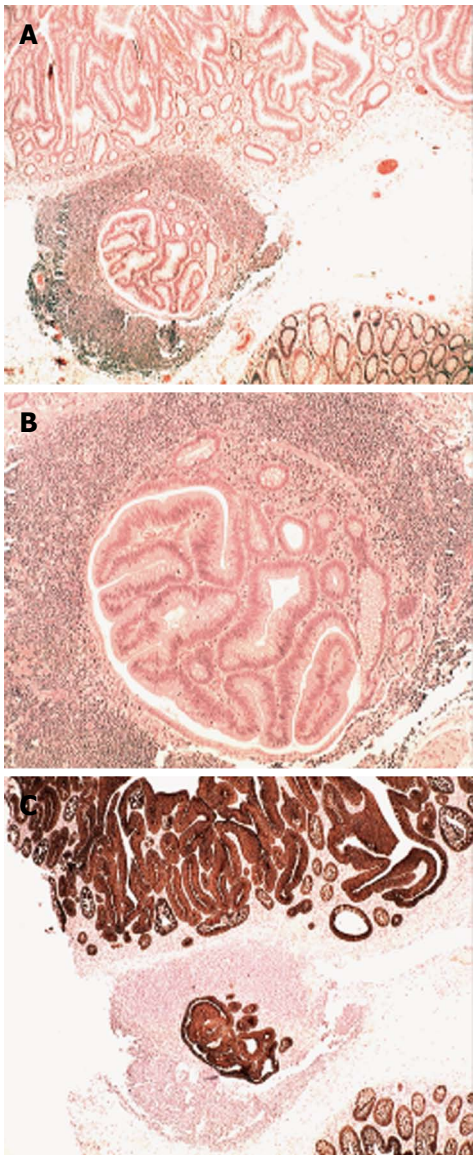

Figure 2 Low-power view. A: A villous adenoma on top of a gut-associated lymphoid tissue (GALT) with carcinoma [hematoxylin and eosin (HE) × 4]; B: Detail showing carcinoma in GALT (HE × 10); C: A villous adenoma on top of a GALT with carcinoma (MNF 116 × 4).

The histological examination showed in one of the two polyps in the transverse colon a GALT-carcinoma roofed by a tubular adenoma with high-grade dysplasia (Figure 2A). Beneath the adenoma, a well-circumscribed GALT-carcinoma was found (Figure 2B). Serial sections revealed no connection between the villous adenoma and the GALT-carcinoma. MNF 116 immunostain labelled all epithelial cells in the villous adenoma on top and in the subjacent GALT-carcinoma (Figure 2C). MIB1 disclosed high cell proliferation in the villous adenoma (Figure 3A); cell proliferation was comparatively lower in the GALT-carcinoma (Figure 3B).

Neither the GALT-carcinoma nor the advanced adenoma expressed p53. The neoplastic cells displayed sialomucins (Alcian blue stain) and mucopolysaccharides (PAS stain) were demonstrated, both in the villous adenoma and in the GALT-carcinoma.

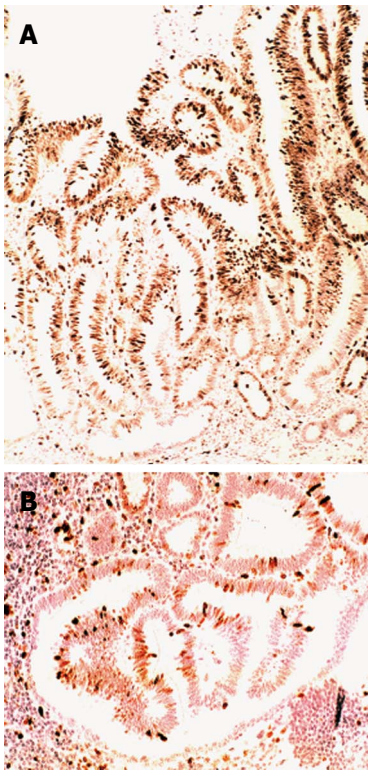

Figure 3 High-power view. A: The villous adenoma showing high cell proliferation (Ki67, clone MIB1 × 10); B: Gut-associated lymphoid tissue with carcinoma showing lower cell proliferation than in the villous adenoma on top (Ki67, clone MIB1 × 20).

DISCUSSION

The lymphoid tissue in the colorectal mucosa is found in three different compartments: in the epithelium, in the lamina propria mucosa, and in GALT aggregates. GALT aggregates may be found as minute lymphoid collections or larger collections of lymphoid tissues, known as Peyer's patches. It goes without saying that the possibility for a neoplasia to evolve in the minute mucosal area that covers a GALT aggregate might be a fortuitous event.

While investigating colorectal neoplasias in Japanese patients[21] we found GALT aggregates underneath 38% of non-protruding adenomas. Puzzlingly, GALT-carcinomas are a common finding in the colon of rats treated with 1,2-dimethylhydrazine[22]. Following 27 wk treatment, subjacent lymphoid aggregates were found in as many as 36% of the flat (non-protruding) colon adenomas and early flat adenocarcinomas in rats[22]. In contrast, only 9% subjacent lymphoid aggregates were found in exophytic (protruding) colon adenomas and early flat adenocarcinomas. When only adenomas were considered, subjacent lymphoid aggregates were present in 50.0% of the flat adenomas, but only in 14.0% of the 50 protruding adenomas[22]. This is surprising, considering that in these animals, only a mean of 1.9 GALT aggregates per colon was recorded. Thus, it would appear that in humans and in rats, non-protruding colonic adenomas evolve not only in the GALT-free colonic mucosa but also in the GALT-associated mucosa.

Table 1 shows that 27% (4/15) of the reported cases of GALT-carcinoma of the colon evolved in patients with UC. In this context, O'Leary *et al*[23] found, 36 GALT foci per colectomy in patients without UC, but as many as 168 GALT foci per colectomy in patients with UC that is 4.7 times more frequently. Obviously, in the colon of patients with UC, newly GALTs are being formed. It is therefore not inconceivable that the GALT-carcinoma here reported might have evolved in a newly formed, UC-dependent, GALT complex.

Immunohistochemistry showed that cell proliferation was lower in the GALT-carcinoma than in the villous adenoma on top. These findings are in concert with those obtained by Anjomshoaa *et al*[24]. These authors found decreased tumour proliferation in metastatic lymph nodes from colon carcinomas.

This report is limited by the rarity of these tumors. Notwithstanding, the awareness that colonic carcinomas may evolve in mucosa-associated lymphoid tissue should encourage endoscopists to methodically examine areas with GALT complexes, particularly in patients with UC.

The possibilities that the advanced adenoma on top had invaded the GALT-complex underneath or that the GALT-carcinoma was a metastasis from the adenoma on top were rejected, since serial sections revealed neither continuity between the adenoma and the GALT-carcinoma, nor invasive growth in the adenoma. In light of these considerations it is submitted that the GALT-carcinoma here described evolved in a newly formed GALT aggregate in a patient with UC. A similar conclusion was drawn in 1984, when searching for a confirmation of the hypothesis of Cuthbert Dukes[10], the first case of GALT-associated carcinoma was detected[12].

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CASE REPORT

Use of a novel covered self-expandable metal stent with an anti-migration system for endoscopic ultrasound-guided drainage of a pseudocyst

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Author contributions: Téllez-Ávila FI and Vilalobos-Garita A designed the report; Téllez-Ávila FI, Villalobos-Garita A and Ramírez-Luna M were attending doctors for patient; Téllez-Ávila FI performed endoscopy procedure; Téllez-Ávila FI and Villalobos-Garita A organized the report; Téllez-Ávila FI and Villalobos-Garita A wrote paper.
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Abstract

The development of pseudocysts in patients with chronic pancreatitis has been reported in 23%-60% of cases and drainage is indicated when they become symptomatic. Endoscopic ultrasound-guided drainage with the placement of plastic or metallic stents to create a cystogastric anastomosis has been shown to be a reliable and efficacious maneuver. Metallic stent use appears to be a safe and effective alternative that shortens the length of time of the procedure and maintains a greater diameter in the cystogastric communication. However, important migration rates have been reported. The use of new metallic stents that are specially designed to prevent migration represents a promising development in the treatment of these group of patients that appears to be safe and effective for pseudocyst drainage and could importantly reduce migration rates, while at the same time having the advantage of a single step procedure and a larger fistula diameter in the endoscopic cystogastric anastomosis.

Key words: Pancreatic pseudocyst; Metallic stents; Endoscopic ultrasound

Core tip: The use of novel covered self-expanding metallic stents that are specially designed to prevent migration represents a promising development in the treatment of patients with pancreatic pseudocysts that appears to be safe and effective for drainage and could importantly reduce migration rates, while at the same time having the advantage of a single step procedure and a larger fistula diameter in the endoscopic cystogastric anastomosis.

Téllez-Ávila FI, Villalobos-Garita Á, Ramírez-Luna MÁ. Use of a novel covered self-expandable metal stent with an anti-migration system for endoscopic ultrasound-guided drainage of a pseudocyst. *World J Gastrointest Endosc* 2013; 5(6): 297-299 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i6/297.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i6.297

INTRODUCTION

Standard procedure for endoscopic ultrasound-guided drainage of peripancreatic collections includes the use of various plastic endoprostheses in the same endoscopic procedure and the need for programmed replacement to preclude their dysfunction. The use of completely covered self-expanding metallic stents (CSEMS) has recently been shown to be a safe and effective alternative that reduces the number of procedures[1]. However, there are

high migration rates (up to 15%)[1,2]. The use of metallic stents designed to prevent migration are an interesting option in these patients that reduces procedure duration and provides a larger fistula diameter.

CASE REPORT

A 51-year-old man presented with chronic pancreatitis (CP) due to alcohol overuse and had a past 3-year history of obstructive jaundice with a pseudotumor at the level of the pancreatic head, along with common bile duct stricture. Cytology consistent with CP without evidence of cancer was obtained through endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNA). The patient underwent a number of endoscopic treatment sessions for the placement of multiple plastic stents and pneumatic dilatation 4 times a year for 3 years with no adequate response. During the last year of disease progression, he presented with a pseudocyst associated with early postprandial fullness and abdominal pain.

The patient rejected surgical treatment of the pseudocyst and the biliary stricture. Due to symptom persistence, the patient underwent endoscopic placement of a CSEMS in the biliary tract and endoscopic ultrasound-guided drainage of the pseudocyst with the placement of a 3 cm long "NAGI" CSEMS (Taewoong-Medical Co, Seoul, South Korea) with a 10 mm diameter in the center and 20 mm ends, for an endoscopic cystogastric anastomosis (Figure 1).

Biliary diversion

Using a duodenoscope (GIF-140, Olympus America, Melville, NY, United States), endoscopic retrograde cholangiopancreatography (ERCP) was performed. There was evidence of intrapancreatic bile duct stricture and a 6 cm long CSEMS with a 10 mm diameter (Taewoong-Medical Co, Seoul, South Korea) was placed. Pancreatography revealed an area of stricture, at the level of the neck of the pancreas, through which the passage of 0.035", 0.025", and 0.018" guidewires (Boston Scientific, Natick, MA, United States) was not possible. The body and tail of the pancreas were dilated and there was contrast medium leakage (Figure 2).

Endoscopic ultrasound-guided pseudocyst drainage

A pseudocyst with a 6 cm × 5 cm diameter was then seen with a GF-UCT140AL5 echo endoscope (Olympus America, Melville, NY, United States). Under endosonographic vision, and after using the Doppler mode to detect blood vessels in the tract, the pseudocyst was punctured through the gastric wall with a 19G-caliber Echotip® needle (Cook Endoscopy, Winston-Salem, NC, United States) followed by the introduction of a 0.035" Hydra Jagwire® (Boston Scientific, Natick, MA, United States). The needle-knife (Boston Scientific, Natick, MA, United States), 6, 7, 8.5, and 10 F Soehendra® catheters (Cook Endoscopy, Winston-Salem, NC, United States), and lastly, a Max Force® balloon dilator (Boston Scientific, Galway, Ireland) were progressively advanced along the guidewire to dilate the puncture tract up to 8 mm. A "NAGI" CSEMS was put in place under fluoroscopic vision to provide support to the cystogastrostomy (Figure 3).

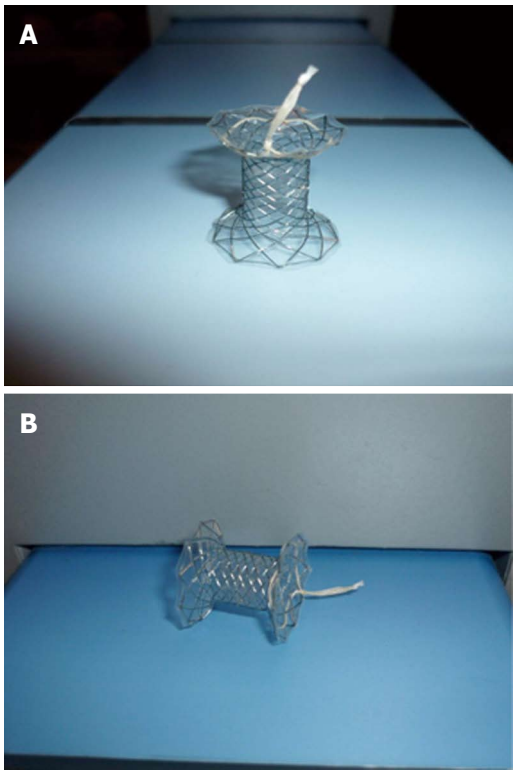

Figure 1 Novel "NAGI" covered self-expanding metallic stents with a 10 mm center and 20 mm ends (A and B).

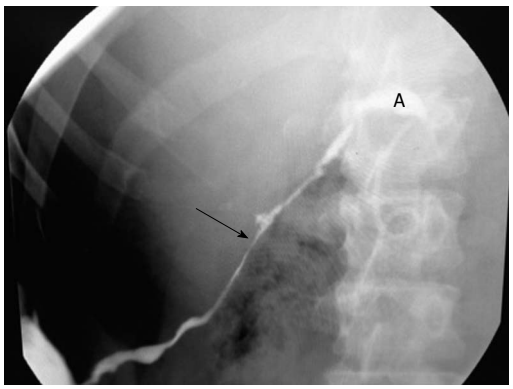

Figure 2 Presence of stenosis (arrow) and leak (A) of the main pancreatic duct.

At 6 mo of outpatient evaluation, the patient is asymptomatic and his liver function tests are normal (Table 1).

DISCUSSION

High success rates have been reported for ultrasound-guided pseudocyst drainage since 2001 and this procedure has shown advantages over the surgical option in relation to hospital stay and costs[3,4].

The placement of multiple plastic stents is technically difficult and so the use of a single CSEMS has been proposed[1]. Procedure duration and resolution time is lower

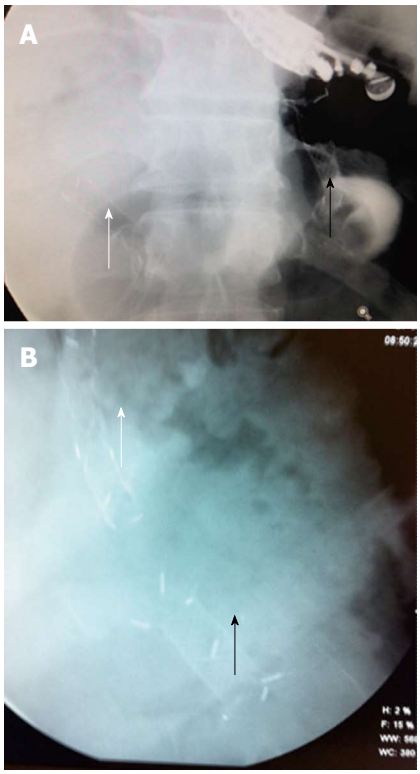

Figure 3 Fluoroscopy image at basal (A) and at after 6 mo (B) of follow-up: Biliary stent (white arrows) and Nagi stent through cystogastrostomy (black arrows).

with CSEMSs and this is probably related to the larger fistula diameter, while the technical success, clinical outcome, and complications are similar[5]. Nevertheless, the probability of stent migration in 15% of the patients is a concern[1,2]. In the present case, a stent with a specially designed feature to reduce the high migration rate was used. The design of the "NAGI" stent, with 20 mm large and acute angled flare ends, implies a decrease in the migration rates due to better anchoring in the gastric and pseudocyst extremes. Besides this is fully covered with silicone that prevents leakage and tissue ingrowth and with retrieval string allows for easy removal. With a reduced migration rate, severe complications such as gastrointestinal tract obstruction, impaction, and/or perforation of the gastrointestinal tract wall could be prevented[6-11].

In conclusion, the use of CSEMSs that are designed with an anti-migration system is an alternative that appears to be safe and effective for pseudocyst drainage and could importantly reduce migration rates, while at the same time having the advantage of a single step procedure and a larger fistula diameter in the endoscopic cystogastric anastomosis.

Table 1 Liver function test before and after procedure

Parameter	Before procedure	12-wk after procedure
Total bilirubin	5.66	0.45
Direct bilirubin	4.09	0.08
ALT	351	49
AST	271	25
ALP	391	112

ALT: Alanine amino transferase; AST: Aspartate amino transferase; ALP: Alkaline phosphatase.

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CASE REPORT

Youngest case of an early gastric cancer after successful eradication therapy

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Abstract

A 28-year-old woman visited our clinic with a chief complaint of epigastralgia. She had received successful *Helicobacter pylori* (*H. pylori*) eradication therapy 5 years before. We repeated esophagogastroduodenoscopy, and a discolored depressed area with reddish spots and converging folds, 20 mm in size, was detected. No atrophic change including intestinal metaplasia or nodular gastritis was seen endoscopically. Two endoscopic biopsies revealed undifferentiated adenocarcinoma. No *H. pylori* was found, and the ^{13}C-urea breath test was also negative. Abdominal computed tomography demonstrated no nodal involvement, distant metastasis or fluid collection. She underwent a laparoscopy-assisted distal gastrectomy. Histologically, the resected specimen revealed an early undifferentiated gastric cancer that had invaded deeply into the submucosal layer. Nodal involvement was histologically confirmed. No atrophic change or *H. pylori* infection was evident histologically. This is the youngest patient ever reported to have developed a node-positive early gastric cancer after eradication of *H. pylori*.

Key words: Early gastric cancer; *Helicobacter pylori*; Eradication therapy; Undifferentiated adenocarcinoma; Intestinal-type adenocarcinoma; Point of no return theory

Core tip: Although, earlier eradication of *Helicobacter pylori* (*H. pylori*) is considered to be more effective for prevention of gastric cancer by inhibiting the progression of mucosal atrophy, this youngest case developed an invasive gastric cancer with nodal involvement. From the viewpoint of the "point of no return" theory, future research should focus on the appropriate time of life at which to treat ideal candidates who would benefit from preventive eradication therapy. At present, it appears that cure of *H. pylori* infection still cannot prevent all gastric cancers, clinical studies are needed to clarify how to follow up patients after successful eradication therapy.

Konuma H, Konuma I, Fu K, Yamada S, Suzuki Y, Miyazaki A. Youngest case of an early gastric cancer after successful eradication therapy. *World J Gastrointest Endosc* 2013; 5(6): 300-303 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i6/300.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i6.300

INTRODUCTION

Helicobacter pylori (*H. pylori*) infection plays an important role in the development of gastric cancer. Therefore, *H. pylori* eradication is considered an important approach for prevention of gastric cancer. *H. pylori* infection has been

shown to induce gastric adenocarcinoma in animal models[1,2]. Furthermore, a number of studies in humans have demonstrated that *H. pylori* eradication has the potential to prevent gastric cancer[3-7]. Unfortunately, however, gastric cancers can still arise after *H. pylori* eradication therapy[8]. We herein report a case of diffuse-type early gastric cancer that developed in a young woman 5 years after successful *H. pylori* eradication.

CASE REPORT

A 28-year-old woman visited our clinic with a chief complaint of epigastralgia that had lasted for 10 d. She had undergone esophagogastroduodenoscopy (EGD) at another outpatient clinic because of epigastralgia 5 years previously. At that time, she had received successful *H. pylori* eradication therapy, as histologic examination of the endoscopic biopsy specimen had revealed *H. pylori* positivity. Her family history included a hepatocellular carcinoma in her father at the age of 31-year-old, a gastric cancer in her grandmother at the age of 67-year-old, and an esophageal squamous cell carcinoma in her grandfather at the age of 76-year-old. We repeated EGD at our clinic for further investigation, and a depressed area, 20 mm in size, was detected at the anterior wall in the greater curvature of the gastric body (Figure 1). The depressed area was discolored with a reddish spot, and converging folds were also evident endoscopically. The endoscopic diagnosis was early-stage undifferentiated adenocarcinoma (submucosal invasive carcinoma). No atrophic change including intestinal metaplasia or nodular gastritis was seen during the first and second endoscopy examinations. Two endoscopic biopsies were performed for histological evaluation, and the specimens revealed undifferentiated adenocarcinoma. However, no *H. pylori* was found, and the ^{13}C-urea breath test was also negative. Abdominal computed tomography demonstrated no nodal involvement, distant metastasis or fluid collection suggestive of ascites. A final clinical diagnosis of localized early gastric cancer with undifferentiated histology was established, and the patient was sent for surgical treatment. She underwent a laparoscopy-assisted distal gastrectomy with D2 dissection of lymph nodes. Histologically, the resected specimen revealed an early undifferentiated gastric cancer that had invaded deeply into the submucosal layer, and marked lymphatic permeation (Figures 2, 3). Nodal involvement was histologically confirmed in one out of 24 dissected lymph nodes. No atrophic change or *H. pylori* infection was evident histologically. The pathological staging was T1bN1M0 (stage IB) according to the TNM classification. The postoperative course was uneventful, and no recurrence of gastric cancer was recognized thereafter.

DISCUSSION

To our knowledge, the present patient is the youngest ever reported to have developed a node-positive early gastric cancer after eradication of *H. pylori*. Until now, most reported patients developing gastric cancer after *H. pylori* eradication therapy have been 50 years old or more[8,9]. Characteristically, such gastric cancers have been discovered at an advanced stage significantly less frequently in Japanese patients than in patients elsewhere[8]. Most of the Japanese cases were detected at an early stage, had a depressed form, and showed an intestinal-type dominant histology[8,9]. The risk factors for gastric cancer after *H.*

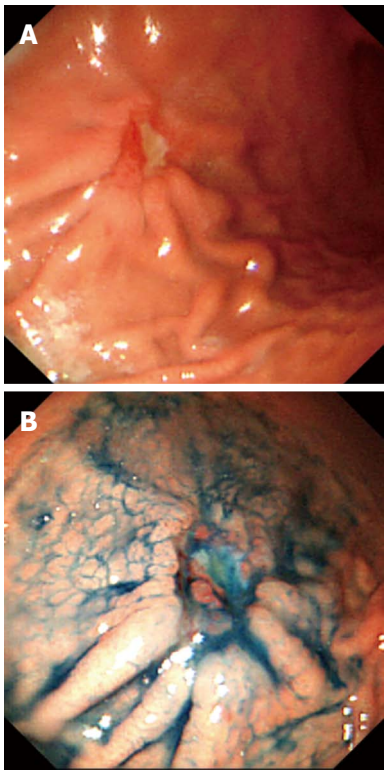

Figure 1 Endoscopic views. A: Conventional endoscopy before dye spraying showed a depressed area, 20 mm in size, was detected at the anterior wall in the greater curvature of the gastric body. The depressed area was discolored with a reddish spot, and converging folds were also evident endoscopically; B: Chromoendoscopy after 0.4% indigo-carmine dye spraying better defined the depressed area.

Figure 2 Surgical specimens obtained by a laparoscopy-assisted distal gastrectomy revealed an depressed cancer with fold convergence (white arrow).

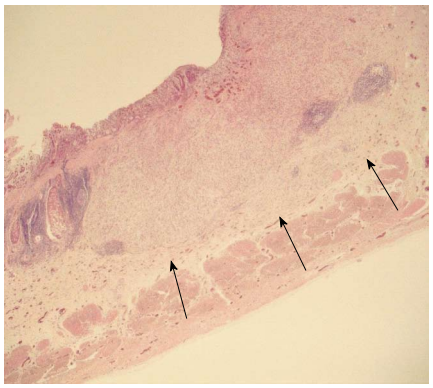

Figure 3 Histologically, it was an early undifferentiated gastric cancer that had invaded deeply into the submucosal layer (black arrow), and marked lymphatic permeation.

pylori eradication therapy are reportedly older age and advanced atrophic change in the gastric corpus, neither of which characterized the present case[8,10]. In the multistep pathogenesis of intestinal-type gastric cancer, *H. pylori*-induced chronic active gastritis slowly progresses through the premalignant stages of atrophic gastritis, intestinal metaplasia, and dysplasia to gastric adenocarcinoma. No similar sequence has been described for the diffuse type. Theoretically, *H. pylori* eradication stops the natural progression of premalignant lesions, and thus stabilizes the risk of gastric cancer. In the present young female patient, however, an early diffuse-type gastric cancer was detected even after *H. pylori* had been eradicated. The incidence of *H. pylori*-negative gastric cancer is extremely low (less than 1%)[10]. Recently, a prospective study reported that infection with *H. pylori* is associated with the development of both intestinal- and diffuse-type gastric cancer[4]. Furthermore, a close relationship between *H. pylori* and diffuse-type cancer has also been described, especially in younger individuals[11].

Previous reports have indicated that *H. pylori* eradication does not prevent the development of gastric cancer in all patients during long-term follow-up[12]. The risk of developing gastric cancer reportedly depends on the level of severity and extent of atrophic gastritis and gastric atrophy at the time of eradication. In a study from China, a beneficial effect of *H. pylori* eradication was seen only among those with a low baseline risk (without atrophy), and it was concluded that the chemopreventive effect of eradication is achieved during the earlier phases of carcinogenesis, before preneoplastic lesions have developed[13]. Therefore, earlier eradication of *H. pylori* is considered to be more effective for prevention of gastric cancer by inhibiting the progression of mucosal atrophy. Despite undergoing successful eradication therapy in her early 20s in the absence of any premalignant lesions such as mucosal atrophy or intestinal metaplasia identified endoscopically and histologically, this young woman unfortunately developed an invasive gastric cancer with nodal involvement. From the viewpoint of the "point of no return" theory (when the development of gastric cancer can no longer be prevented by *H. pylori* eradication), future clinical research should focus on the appropriate time of life at which to treat ideal candidates who would benefit from preventive eradication therapy. At the present time, however, it appears that cure of *H. pylori* infection still cannot prevent the development of gastric cancer in all patients. More data such as the optimal interval for surveillance endoscopy are needed for patients even after successful eradication of *H. pylori*.

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CASE REPORT

Incarceration of a colonoscope in an inguinal hernia: Case report and literature review

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Key words: Colonoscopy; Inguinal hernia; Fluoroscopy

Core tip: Incarceration of a colonoscope in an inguinal hernia is likely an under reported occurrence. The authors present a case report and literature review of incarceration of a colonoscope in an inguinal hernia and a suggested management algorithm.

Tan VP, Lee YT, Poon JTC. Incarceration of a colonoscope in an inguinal hernia: Case report and literature review. *World J Gastrointest Endosc* 2013; 5(6): 304-307 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i6/304.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i6.304

Abstract

Incarceration of an endoscope in an inguinal hernia may occur during the course of routine colonoscopy. The incarceration may occur on insertion or withdrawal and frequently the hernia is not suspected prior to the colonoscopy. Most commonly, a left sided inguinal hernia is involved, however right inguinal hernias may be implicated in subjects with altered anatomy post abdominal surgery. Incarceration of an endoscope in an inguinal hernia has been seldom reported in the literature which is likely to be related to under reporting. A range of techniques have been suggested by various authors over the last four decades to manage this unusual complication of colonoscopy. These techniques include utilizing fluoroscopy, manual external pressure and/or the fitting of a cap onto the tip of the colonoscope to facilitate colonoscopic navigation. The authors present a case report of incarceration of the colonoscope on withdrawal in an unsuspected left inguinal hernia with a review of the literature on the management of this colonoscopic complication. A management strategy is suggested.

INTRODUCTION

A 76-year-old man presented for colonoscopy for follow up of previously diagnosed colonic polyps. A colonoscopy had been performed one month prior where a significant 1.2 cm sessile polyp was found in the mid transverse colon, however at that juncture given the patient's co morbid conditions and the lack of recent clotting profile and platelet count, the decision was made to repeat the colonoscopy with polypectomy after relevant blood work was performed. During the original colonoscopy no complications were encountered and the patient did not require much sedation (midazolam 4 mg and pethidine 37.5 mg).

CASE REPORT

The colonoscope was inserted without difficulty or significant abdominal discomfort to the terminal ileum at 100 cm. The procedure was performed under conscious sedation and the patient had received 2 mg of midazolam and 25 mg of pethidine at this juncture. Multiple polyps in the caecum, hepatic flexure and transverse colon had

Figure 1 Incarcerated colonoscope bulging into the left inguinal hernia during colonoscopy.

been noted on insertion and were removed on with snare polypectomy on withdrawal. In the mid transverse colon at 60 cm the colonoscope could not longer be withdrawn and appeared to be "frozen" in position, although the patient did not experience significant discomfort. Despite clockwise and counter clockwise rotation with gentle traction as well as positioning the patient into the supine position the colonoscope was unable to be withdrawn. During these manoeuvres the lumen of the transverse colon could be clearly seen. An examination of the patient's left inguinal hernia orifice revealed a bulge in the left scrotum consistent with incarceration of the colonoscope in the inguinal hernia sac (Figure 1).

The patient was given further midazolam and pethidine to a total of 5 mg and 62.5 mg, respectively, to ensure adequate analgesia and the incarcerated colonoscope was attempted to be reduced manually through external manual pressure and clockwise and counter clockwise torque with gentle traction. This was unsuccessful and the patient was immediately wheeled into the fluoroscopy suite and under direct radiographic guidance, the loop in the hernial sac was minimized and the colonoscope withdrawn by gentle traction without complication (Figure 2). The patient remained well throughout the reduction of the incarcerated colonoscope. On further withdrawal of the endoscope, a large 1-1.5 cm flat polyp was seen in the mid transverse colon which had been seen at the original endoscopy. A saline lift was attempted but the lesion did not lift the polyp which suggested sub-mucosal infiltration. Biopsies were taken, the lesion tattooed and the colonoscope withdrawn without complication. The histopathology of the lesion returned adenocarcinoma of the transverse colon. The patient was subsequently referred to the surgeons for a right hemi-colectomy and left inguinal hernia repair. An examination of the patient post colonoscopy indicated that the patient had a large sliding indirect inguinal hernia. We now present a review of the literature regarding the complication of incarceration of the colonoscope within an inguinal hernia.

DISCUSSION

Due to under reporting, the occurrence of colonoscope incarceration in an abdominal hernia is probably un-

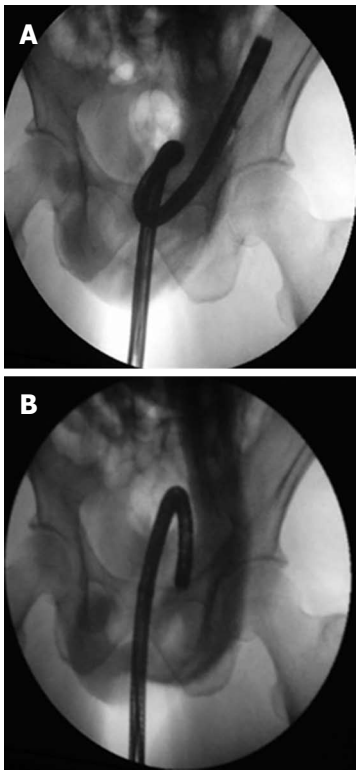

Figure 2 Colonoscopic loop in the process reduction under fluoroscopic guidance and fluoroscopic image of complete reduction of colonoscopic loop respectively. A: Fluoroscopic image of incarcerated colonoscope in left inguinal hernia; B: Fluoroscopic image of incarcerated colonoscope post reduction.

derestimated as evidenced by the scant number of case reports published in the English language. A total of 12 case reports involving 15 cases have been identified by the authors published to date (Table 1). The incarceration occurs both on insertion and withdrawal, usually when the endoscope is 60-80 cm from the anal verge and involves left inguinal hernias exclusively. One exception was a case published by Koltun *et al*[1], where the incarceration occurred in the right inguinal hernia however the patient had slightly altered abdominal anatomy due to a prior right hemi-colectomy. In only four of the cases were the presence of an inguinal hernia known prior to colonoscopy.

The neck of an indirect inguinal hernia is usually the site of obstruction when loops of bowel become incarcerated. In cases where the colonoscope becomes unable to progress on insertion, this is likely to occur due to three scenarios, firstly, a loop of bowel has become incarcerated in an inguinal hernial sac which has a small neck, the aperture of which is insufficient to permit the entry of the colonoscope[2]. In this specific scenario the hernia may only be suspected on imaging, in this case, a barium enema revealed a constriction at the level of the sigmoid colon. The second scenario occurs in patients with moderate sized inguinal hernias sufficient to permit the entry of the colonoscope into the hernial sac but not simultaneous entry and exit of the colonoscope side by side[3]. In this scenario, the tip of the colonoscope enters the

Table 1 Published case reports of incarcerated colonoscopes in inguinal hernia and strategy utilized to remove the scope

Ref.	No. of cases	Inguinal hernia (side)	Method of scope removal	Distance from anus at obstruction	Obstruction on insertion *vs* withdrawal
Waye[5]	1	Unknown	NA	NA	NA
Leichtmann *et al*[6]	3	× 2 Unknown × 1 Known	× 2 Manual reduction × 1 Hernial reduction before and maintenance during procedure	NA	NA
Fulp *et al*[7]	1	Known, Left	Withdrawl of endoscope	Sigmoid colon	Insertion
Leisser *et al*[8]	1	Unknown, Left	Manual reduction	60 cm	Insertion
Koltun *et al*[1]	2	Known, Right	Failed fluoroscopic reduction Manual reduction utilizing "Pulley" technique	NA	Withdrawal
Yamamoto *et al*[4]	1	Unknown, Left	Failed manual reduction, Reduction under fluoroscopic guidance	70cm	Insertion
Saunder[9]	1	Unknown	NA	NA	NA
Punnam *et al*[10]	1	Known Left	Failed manual reduction Surgical Dissection of Hernial Sac	NA	Withdrawal
Lee *et al*[2]	1	Unknown, Left	Manual reduction	NA	Insertion
Iser *et al*[11]	1	Unknown, Left	Manual reduction under deep sedation	NA	NA
Fan *et al*[3]	1	Unknown, Left	Reduction under fluoroscopy and external manual pressure	60 cm	Withdrawal
Kume *et al*[12]	1	Unknown, Left	Reduction under fluoroscopy	60 cm	Withdrawal

NA: Not available.

hernial sac very easily but when the colonoscope forms a loop and attempts to exit the hernial sac it becomes obstructed with bulging and pain in the lower abdomen/scrotum. In the third scenario, the hernial sac is sufficiently wide enough to accommodate both the entry and exit of the two segments of colonoscope, however further insertion creates a large loop in the scrotum resulting in pain, "freezing" of the scope and inability to progress the examination[4]. For the first two scenarios, should it be necessary to proceed with the colonoscopy, use of a cap attached to the tip of the colonoscope may facilitate passage of colonoscope through the loop of bowel which has prolapsed into the hernia (unpublished data). In the third scenario, manual pressure externally may enable the colonoscopy to be completed.

However, in half of the published case studies, incarceration of the colonoscope occurs during withdrawal. Here, during the advancement phase of the colonoscope a loop forms bulging into the hernial sac. The hernial orifice is sufficiently wide to comfortably permit the entry and exit of the two segments of colonoscope, with prolapse of the colonoscope and colon into the scrotum. It is only on withdrawal of the colonoscope that a tight loop, usually a gamma loop, is formed which becomes incarcerated if the maximum diameter of the loop exceeds that of the hernial orifice, which occurred in our case.

A variety of methods have been published to reduce the incarcerated colonoscope which included manual reduction after deepened sedation, a "pulley" method of manual reduction, reduction under direct fluoroscopic guidance, surgical reduction or some combination of the aforementioned methods[1,3,4]. The authors suggest that in the event of an incarcerated colonoscope in an inguinal hernia, clinicians should proceed directly to fluoroscopic guidance if available. The benefits of fluoroscopic guidance includes the ability to minimize the colonoscope loop in the scrotal sac and an estimation of the hernial orifice to determine if removal of an incarcerate colonscope with a loop *in situ* is feasible. After the retraction of the loop from the scrotal sac, fluoroscopy can enable the straightening of the colonoscope before the procedure is completed[3]. Simultaneous gentle manual pressure to encourage the loop through the hernial orifice is recommended. Failing this, the authors suggest trying the "pulley" method if the hernial orifice is so small it will not permit the exit of the smallest loop feasible with the colonoscope[1]. Should this fail surgery is most likely indicated.

Some clinicians have suggested the presence of a large inguinal hernia is a relative contra-indication to colonoscopy[1]. We suggest that in the event a colonoscopy is clinically necessary prior to repair of moderate to large inguinal hernia, the option of computerized tomography colonoscopy be explored. Should a colonoscopy still be necessary, the authors suggest that the risk of incarceration may be reduced by reducing the hernia prior to colonoscopy and maintaining reduction manually whilst the scope is advanced. The use of cap assisted colonoscopy may also aid the negotiation of the endoscope through the herniated bowel loop (unpublished data). However as most of these case studies demonstrate, most cases of incarcerated colonoscopes are the first presentation of the patient with an inguinal hernia.

In summary, incarcerated colonoscopes in an inguinal hernia are, thankfully, a rare event. In patients with known inguinal hernias, consideration must be given to computed tomography colonoscopy and in the event the colonoscopy must proceed, strategies employed to reduce the risk of complication. However as our literature review has demonstrated the incarcerated scope is usually

the first sign of an inguinal hernia in a patient and in this situation should be reduced under direct fluoroscopic guidance with gentle manual pressure and adequate sedation, followed by an attempt at the "pulley" system and finally, surgery, if all else fails.

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In press

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

Organization as author

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

Both personal authors and an organization as author

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

No author given

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

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

Issue with no volume

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

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

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Personal author(s)

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

Conference proceedings

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

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

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

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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

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