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INDEXING/ABSTRACTING

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Robot-assisted laparoscopic gastrectomy for gastric cancer

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Abstract

Phase Ⅲ evidence in the shape of a series of randomized controlled trials and meta-analyses has shown that laparoscopic gastrectomy is safe and gives better short-term results with respect to the traditional open technique for early-stage gastric cancer. In fact, in the East laparoscopic gastrectomy has become routine for early-stage gastric cancer. In contrast, the treatment of advanced gastric cancer through a minimally invasive way is still a debated issue, mostly due to worries about its oncological efficacy and the difficulty of carrying out an extended lymphadenectomy and intestinal reconstruction after total gastrectomy laparoscopically. Over the last ten years the introduction of robotic surgery has implied overcoming some intrinsic drawbacks found to be present in the conventional laparoscopic procedure. Robot-assisted gastrectomy with D2 lymphadenectomy has been shown to be safe and feasible for the treatment of gastric cancer patients. But unfortunately, most available studies investigating the robotic gastrectomy for gastric cancer compared to laparoscopic and open technique are so far retrospective and there have not been phase III trials. In the present review we looked at scientific evidence available today regarding the new high-tech surgical robotic approach, and we attempted to bring to light the real advantages of robot-assisted gastrectomy compared to the traditional laparoscopic and open technique for the treatment of gastric cancer.

Core tip: Laparoscopic gastrectomy has been shown to be a viable option for early gastric cancer, showing survival rates comparable to those of open procedure. However, there has been criticism concerning the routine use of laparoscopy in patients with advanced gastric cancer, principally because it adapts poorly to complex maneuvers like D2 lymphadenectomy. Robotic surgery has been shown to make certain laparoscopic procedures easier and safer. Reports have recently shown the ever increasing feasibility and safety of robotic assisted laparoscopic gastrectomy for gastric cancer, in some cases even proving superior to traditional laparoscopy.

INTRODUCTION

In 1991, Kitano *et al*[1] performed the first laparoscopically assisted gastrectomy for gastric cancer. Subsequently, under the impulse of level III studies providing the evidence of the safety of laparoscopic assisted distal gastrectomy (LADG) for distal early-stage gastric cancer, several authors reported comparative studies with better short-term results in favor of this technique with respect to traditional open[2]. As a consequence laparoscopic gastrectomy (LG) has progressively spread worldwide, especially in the East, for the treatment of early gastric cancer[3,4]. On the other hand, the treatment of patients with advanced gastric cancer has always been considered difficult laparoscopically, thus techniques such as laparoscopic assisted total gastrectomy (LATG) and laparoscopic extended lymphadenectomy did not meet the same enthusiasm. As a result, the spread of laparoscopic surgery as a means of performing total gastrectomy and managing advanced gastric cancer was limited. This was mainly due to the technical difficulties and complexity of the D2 lymphadenectomy and the intestinal reconstruction after total gastrectomy[5,6].

Robot-assisted techniques have brought about improvements to certain surgical procedures, particularly those which require precise dissection, making it possible to resolve some of the innate limitations of laparoscopy. So over the years, robot-assisted gastrectomy (RAG) has become increasingly considered as a valid, yet still debatable, alternative to executing gastrectomy for gastric cancer, in particular for total gastric resection and extended lymph node dissection in advanced tumours[7-9].

We analyzed high-quality clinical trials by systematically reviewing the literature published so far in Pubmed comprehending robotic case series, as well as those studies that have compared RAG with LG and/or open gastrectomy for gastric cancer. Our intent is to verify if at present there is actual evidence of an advantage to robotic compared to laparoscopic and traditional open gastrectomy for gastric cancer.

Rational basis of robotic surgery as improvement of laparoscopy

Areas of surgery necessitating precise movements have employed Robotic technology. In 1994 the da Vinci® Surgical System (Intuitive Surgical, Sunnyvale, California, United States) gained the approval of the United States Food and Drug Administration (FDA). The da Vinci® Surgical Robotic has undergone constant improvement over recent years, and now includes additional features including near-infrared technology, and facilitated set-up. The latest generation, which was released in 2014 and is known as the da Vinci Xi™ system, is less bulky and its arms are more ergonomic (Figure 1).

Robotic surgery eliminates some of the disadvantages of conventional laparoscopy. The principal drawbacks of conventional laparoscopy from a technical standpoint are: The instability of the two-dimensional (2D) camera; instruments with limited movement which augment the physiologic tremor of the surgeon's hand, therefore limiting manipulative actions and increasing ergonomic discomfort.

The robotic surgery system has the upper hand over laparoscopy when fine dissection is needed, eliminating the traces of physiologic human tremor, increasing dexterity through its typical internal articulated endoscopic wrist (EndoWrist™ System), and providing stereoscopic vision with 3D high-resolution images[10]. This allows surgeons to perform minimally invasive surgery with greater ease and safety, and more ergonomically. As a consequence it probably makes it possible for more surgeons to complete complex procedure in a minimally invasive fashion.

Moreover, even if laparoscopic surgery may have an effect on the robotic gastrectomy learning process, robotic surgery appears to globally need less time to master compared to a laparoscopic procedure traditionally requiring a steep learning curve[11-14].

Main drawbacks of conventional laparoscopy in gastric cancer surgery

Delicate maneuvers which necessitate excellent visualization and total precision such as intra-corporeal anastomosis and dissection of extra-perigastric lymph nodes along the major arterial structures are the principal pitfalls of conventional laparoscopic gastrectomy for gastric cancer.

The far from perfect and often shallow angulation of the traditional unergonomic laparoscopic technique render the D2 lymphadenectomy especially hard and

Figure 1 New-generation da Vinci Xi™; the system is more versatile and better manoeuvrable, the robotic arms are thinner and arranged in a more ergonomic way, enabling multiquadrant procedures without repositioning the system.

demanding even for minimally-invasive surgeons who have been solidly trained. Areas which are quite hard to reach during laparoscopic lymphadenectomy include lymph node stations 4, 6, 9, 11p and 12a[15]. It may be linked to the risk of important blood loss which can occur particularly during the lymph node dissection around the infra pyloric area and the inferior mesenteric vein, including stations 6 and 14, and the supra pancreatic area including stations 7, 8, and 9[16]. Miura *et al*[15] indicated a far inferior amount of harvested lymph nodes obtained by laparoscopy in comparison to open surgery along the major gastric curvature (Nos. 4 and 6) and second tier nodes along the celiac and splenic arteries (Nos. 9 and 11). Similarly, Bouras *et al*[17] showed a greatly inferior amount of lymph nodes harvested along the common hepatic artery in a series of laparoscopic distal gastrectomy procedures compared to open distal gastrectomy (ODG).

Main technical advantages of robotics over traditional laparoscopy in gastric cancer

The majority of resectable gastric cancer patients are advised to undergo gastrectomy with D2 lymph node dissection surgical procedure[18]. Thus, in gastric cancer treatment, in order to fit oncological criteria, minimally invasive procedures must entail proper lymphadenectomy, as in its traditional open counterpart.

It is widely accepted that D2 lympadenectomy is one of the most difficult steps of the laparoscopic gastrectomy procedure for gastric cancer. The certain

advantage produced by the robotic system could be decisive in gastric cancer surgery, mainly ensuring an extremely precise and safe lymphadenectomy with reduced risk of vessel injury[19], thus making this phase a principal indicator for the robot-assisted technique. The advantages of robotic surgery, such as tremor filtration and articulated function of wristed instruments, would be particularly suitable for enabling more complete dissection in demanding areas such as the dorsal part of the pancreas and behind splenic vessels at the hilum, which are not easily identified and are difficult to reach with current laparoscopic instruments and camera system[20]. It is extremely hard to reach the back of the suprapancreatic lymphatic area laparoscopically, and the downward compression of the pancreas which is particular prominent through the laparoscopic instruments may lead to pancreatic damage and pancreatitis. In these sites especially, the EndoWrist® robotic property and a far more stable vision allow the surgeon to complete this surgical step more easily and safely in comparison to the laparoscopic counterpart.

Robotic surgery also has the advantage of making intra-corporeal anastomosis easier, and therefore over-comes one of the greatest limitations of traditional laparoscopy from a technical standpoint in carrying out digestive restoration. This is particularly true after total gastrectomy, otherwise made possible by extracorporeal anastomosis with a small mini-laparotomy. Placing a hand-sewn purse-string suture on the esophagus is made easier by using robotic assistance, and esophageal

anastomosis can subsequently be carried out by using a circular stapler, as in open surgery[7,19]. Another option would be to carry out a full robotic hand-sewn eso-phagojejunal anastomosis[21], possible because the robotic system gives surgeons the chance to suture more easily and with greater precision compared to laparoscopy, particularly in deep and narrow areas. Thus, increased know-how and confidence with the robotic system will enable the surgeon to perform high-precision and safer intra-corporeal sutures for patients undergoing digestive anastomosis.

LITERATURE EVIDENCE

Studies of feasibility and safety
The earliest reports of robot-assisted gastrectomy (RAG) were published in 2003 by Hashizume *et al*[22] and Giulianotti *et al*[23]. Recent reports have shown the safety and viability of robotic gastrectomy for treating gastric cancer[24,25]. Table 1 summarizes some of the robotic case series published to date[7-9,26-34]. Most of the experience so far derives from non-randomized retrospective studies, while only one available clinical trial to date has been prospectively conducted[34]. The studies mainly hail from the East. In the western countries, reports on RAG are fewer and usually limited to smaller series. In 2007, in the United States Anderson *et al*[7] reported the results of the first western series including 7 gastric cancer patients who were submitted to robot-assisted subtotal gastrectomy, demonstrating that robotic gastrectomy was viable, even if no direct comparison with laparoscopy was made[7].

Several authors worldwide reported their experience on RAG for cancer and the largest single institution series investigating clinical and oncological outcomes so far include (Table 1): Song *et al*[9] in 2009, Jiang *et al*[29] in 2012, Liu *et al*[31] and Park *et al*[32] in 2013, Tokunaga *et al*[34] in 2015, which included respectively 100, 120, 104, 200 and 120 patients. These studies confirmed the safety and feasibility of RAG for cancer, essentially reporting a suitable amount of lymph nodes retrieved, but they did not furnish long-term survival data. Globally, among these various studies RAG appears to be safe in terms of the incidence and severity of postoperative complications. The morbidity rate ranges between 4.9% to 13%, with a mortality rate of 0%-6%, comparable to those of conventional gastric cancer surgery. Among reported potential advantages of the robotic procedure, Tokunaga *et al*[34] noted a very low incidence of intra-abdominal infectious complications (3.3%) in a large cohort of gastric cancer patients (*n* = 120) submitted to total or subtotal gastrectomy.

Comparative studies
Despite the existence of numerous reports regarding the safety and feasibility of RAG, only few robotic comparative analysis investigated RAG *vs* laparoscopic and/or open gastrectomy (Table 2)[11,12,24,25,35-50]. Most

studies comparing robotic gastrectomy with open and laparoscopic surgery are retrospective case-control studies, almost all of these with sample sizes of fewer than 100 cases. Only one multi-centre comparative study was prospectively conducted: Kim *et al*[50], compared a total of 434 gastric cancer patients submitted to robotic and laparoscopic gastrectomy (223 *vs* 211 respectively), and showed similar overall complications rate with no operative mortality in either group, at the expense of significantly higher operative time and higher costs of the robotic group.

However, initial outcome demonstrated comparable or superior short-term results of RAG than the results achieved by open and laparoscopic procedures, at the price of generally longer operation time, as well as higher cost. The prolonged operation time is attributable also to the additional time docking the robotic system, however that time decreases gradually as the expertise of the team increases, and robotic devices are upgraded[9]. Multiple series have reported various ranges in morbidity (5%-17%) after RAG (Table 2). Essentially, outcomes shown in these studies are satisfactory and similar to those of traditional surgical procedures (Table 2). Aforementioned outcomes demonstrate the clinical feasibility in using robotic radical gastrectomy for gastric adenocarcinoma in comparison with the conventional open and traditional minimally invasive laparoscopic approach, in some cases with potential clinical advantages also. For example, Kim *et al*[44] and Suda *et al*[49] showed a statistically significant improvement of the postoperative morbidity rate in gastric cancer patients submitted to RAG compared to LAG. In particular, Suda *et al*[49] noted that local (particularly pancreatic fistula, robotic 0% *vs* conventional laparoscopy 4.3%, *P* = 0.029) rather than systemic complication rates were attenuated using the surgical robot. Also Seo *et al*[47] reported an advantages of RAG in comparison to LAG in terms of a reduction of the incidence of postoperative pancreatitis or pancreatic fistula, which has been attributed to what is assumed to be a more gentle and steady pancreatic compression through the robotic system compared to laparoscopy during the suprapancreatic lymph nodes dissection.

For the first time Kim *et al*[36] reported the results achieved with robotic surgery with respect to laparoscopic and open gastrectomy for the treatment of early gastric cancer. They compared 16 patients who underwent robotic procedure with 11 and 12 laparoscopic and open gastrectomy respectively, revealing longer operative times of the robotic group, but less bleeding and reduced length of hospital stay. With regards to number of har-vested lymph nodes and post-operative outcomes am-ongst the groups no difference was demonstrated.

The biggest (not meta-analyzed) comparative study so far was carried out by Kim *et al*[41]. They retrospectively looked at data on surgical complications of 5839 gastric cancer patients (4542 open, 861 laparo-scopic and 436 robotic gastrectomies), and found no

Table 1 Robot-assisted laparoscopic gastrectomy series for treatment of gastric cancer

Ref.	Country	Patients (n)	Stage disease	Resection type Total	Subtotal	Operative time[1] (min ± SD)	Blood loss[1] (mL ± SD)	Open conversion (%)	Harvested nodes[1] (n ± SD)	Morbidity (%)	Mortality (%)	Hospital stay[1] (d ± SD)
Anderson *et al*[7]	United States	7	0- I -II	-	7	420 ± NR	300 ± NR	0	24 ± NR	11.1	0	4 ± NR
Patriti *et al*[8]	Italy	13	I - II - III	4	9	286 ± 32.6	103 ± 87.5	0	28.1 ± 8.3	7.7	0	11.2 ± 4.3
Song *et al*[9]	South Korea	100	I - II - III	33	67	231.3 ± 43.2	128.2 ± 217.5	0	36.7 ± NR	13	1	7.8 ± 17.1
Pugliese *et al*[26]	Italy	18	All stages	-	18	344 ± 62	90 ± 48	12	25 ± 4.5	6	6	10 ± 3
Lee *et al*[27]	South Korea	12	I	-	12	253.7 ± 53.0	135.8 ± 133.9	0	46.0 ± 25.5	8.3	0	6.6 ± 1.6
D'Annibale *et al*[28]	Italy	24	I - II - III	11	13	267.5 ± NR	30 ± NR	0	28 ± NR	8.3	0	6 ± NR
Jiang *et al*[29]	China	120	I - II - III	35	85	245 ± 50	70 ± 45	0.9	22.5 ± 10.7	5	0	6.3 ± 2.6
Isogaki *et al*[30]	Japan	61	Not reported	14	47	520 ± 177 TG 388 ± 85 SDG	150 ± 234 TG 61.8 ± 46.5 SDG	0	43 ± 14 TG 42 ± 18 SDG	4.9	1.6	13.3 ± NR
Liu *et al*[31]	China	104	I - II - III	54	50	272.52 ± 53.91	80.78 ± 32.37	2	23.1 ± 5.3	11.5	0	6.2 ± 2.5
Park *et al*[32]	South Korea	200	All stages	46	154	248.8 ± 55.6	146.1 ± 130.3	7	37.9 ± NR	10	0.5	8.0 ± 3.7
Coratti *et al*[33]	Itlay	98	All stages	38	60	296.1 ± NR	105.4 ± NR	7.1	30.6 ± NR	12.1	4.1	8.7 ± NR
Tokunaga *et al*[34]	Japan	120	I	12	108	348.5 ± NR	19 ± NR	2.5	44 ± NR	14.2	0	9 ± NR

[1]Mean value. SD: Standard deviation; NR: Not reported; TG: Total gastrectomy; SDG: Subtotal distal gastrectomy.

significant differences between the three groups with regards to post-operative complication and morbidity.

In another large single institute comparative study[25] the authors made a comparison between 236 patients who had undergone robotic curative resection of gastric cancer and 591 laparoscopic surgery patients (Table 2). The authors revealed a statistical significance difference, the mean duration of surgery was 49 min longer in the robotic group, whereas blood loss was 56.3 mL less. Morbidity, mortality and number of lymph nodes retrieved per level were comparable.

In yet another large comparative study (39 patients with gastric cancer undergoing robotic, 586 open and 64 laparoscopic gastrectomies)[39], RAG was linked to diminished bleeding and reduced hospital stay, but with longer operative time than was necessary for both open and laparoscopic gastrectomy. The amount of harvested lymph nodes was also similar between the open and robotic groups, but less in the laparoscopic group (Table 2). The authors especially underlined that robotic instruments made it a great deal more simple to carry out the lymph node dissection, rather than the conventional laparoscopic approach, more so in the infra-pyloric and supra-pancreatic stations.

Junfeng *et al*[24] retrospectively compared 120 *vs* 394 gastric cancer patients who had undergone RAG and laparoscopic assisted gastrectomy (LAG) respectively, revealing similar results. However, it is interesting to note that the authors showed, in addition to once more less intra operative bleeding and longer RAG operative time compared to the laparoscopic counterpart, that the numbers of harvested lymph nodes were notably

superior in the RAG group at tier 2. In the same way, Kim *et al*[44] commented that, with regard to their experience achieved on 87 gastric cancer patients who had undergone robot-assisted distal gastrectomy (RADG) compared to 288 submitted to LADG, RADG seemed to be advantageous over LADG in performing the dissection of the second level lymph nodes, in particular those located in the suprapancreatic space and those around the splenic artery. Also Son's *et al*[45] showed that robotic gastric surgery gave a much larger amount of harvested lymph nodes around splenic vessels in comparison to lymph nodes retrieved during laparoscopic procedure. This current medical research evidence, albeit initial, seems to consolidate the advantage of robotic surgery over LAG in its ability to perform a more complete D2 lymphadenectomy, probably making it possible to overcome one of the greatest surgical drawbacks of the laparoscopy in the treatment of gastric cancer.

An advantage of RAG compared to LAG has been reported in terms of a reduction of the incidence of postoperative pancreatitis or pancreatic fistula. This has been attributed to what is assumed to be a more gentle and constant pancreatic compression obtained using the robotic system compared to laparoscopy during the suprapancreatic lymph nodes dissection, *i.e.*, at station 9 and 11[47].

Review and meta-analysis studies

To date, several review articles[10,19,51-55] have been published which provide a critical appraisal of the effectiveness of RAG for gastric cancer, but they are not systematic research and do not actually supply any statistical

Table 2 Comparative case-control studies of robot-assisted gastrectomy *vs* laparoscopic assisted gastrectomy and/or open gastrectomy

Ref.	Subject	Stage disease	Patients (*n*) RAG	LAG	OG	Operation time (min)[1]	Blood loss (mL)[1]	Harvested nodes (*n*)[1]	Morbidity (%)	Mortality (%)	Hospital stay (d)[1]
Song *et al*[35]	RAG *vs* iLAG2 *vs* rLAG2	I - II	20[2]	20[2] 20[2]	-	230 *vs* 289.5 *vs* 134.1 (RAG < iLAG > rLAG)[3]	94.8 RAG *vs* 39.5 rLAG (NS)	35.3 *vs* 31.5 *vs* 42.7 (NS)	5 *vs* 5 *vs* 10 (NS)	0 *vs* 0 *vs* 0	5.7 *vs* 7.7 *vs* 6.2 (RAG < iLAG)[3] (RAG~rLAG, NS)
Kim *et al*[36]	RAG *vs* LAG *vs* OG	I - II - III	16	11	12	259.2 *vs* 203.9 *vs* 126.7 (RAG > LAG > OG)[3]	30.3 *vs* 44.7 *vs* 78.8 (RAG < LAG < OG)[3]	41.1 *vs* 37.4 *vs* 43.3 (NS)	0 *vs* 10 *vs* 20 (NS)	0 *vs* 0 *vs* 0	5.1 *vs* 6.5 *vs* 6.7 (RAG < LAG < OG)[3]
Eom *et al*[37]	RAG *vs* LAG	I - II - III	30	62	-	229.1 *vs* 189.4 (RAG > LAG)[3]	152.8 *vs* 88.3 (NS)	30.2 *vs* 33.4 (NS)	13.3 *vs* 6.6 (NS)	0 *vs* 0	7.9 *vs* 7.8 (NS)
Woo *et al*[25]	RAG *vs* LAG	I - II - III	236	591	-	219.5 *vs* 170.7 (RAG > LAG)[3]	91.6 *vs* 147.9 (RAG < LAG)[3]	39.0 *vs* 37.4 (NS)	11 *vs* 13.7 (NS)	0.4 *vs* 0.3 (NS)	7.7 *vs* 7.0 (RAG > LAG)[3]
Caruso *et al*[38]	RAG *vs* OG	All stages	29	-	120	290 *vs* 222 (RAG > OG)[3]	197.6 *vs* 386.1 (RAG < OG)[3]	28.0 *vs* 31.7 (RAG~OG)	10.34 *vs* 10.0[4] (NS)	0 *vs* 3.3 (NS)	9.6 *vs* 13.4 (RAG < OG)[3]
Huang *et al*[39]	RAG *vs* LAG *vs* OG	I - II - III	39	64	586	430 *vs* 350 *vs* 320 (RAG > LAG > OG)[3]	50 *vs* 100 *vs* 400 (RAG < LAG < OG)[3]	32 *vs* 26 *vs* 34 (RAG = OG > LAG)[3]	15.4 *vs* 15.6 *vs* 14.7 (NS)	1.4 *vs* 1.6 *vs* 2.6 (NS)	7 *vs* 11 *vs* 12 (RAG < LAG < OG)[3]
Uyama *et al*[40]	RAG *vs* LAG	All stages	25	225	-	361 *vs* 345 (NS)	51.8 *vs* 81.0 (RAG < LAG)[3]	44.3 *vs* 43.2 (NS)	11.2 *vs* 16.9 (NS)	0 *vs* 0	12.1 *vs* 17.3 (RAG < LAG)[3]
Kang *et al*[12]	RAG *vs* LAG	I - II - III	100	282	-	202.05 *vs* 173.45 (RAG > LAG)[3]	93.25 *vs* 173.45 (RAG < LAG)[3]	NR	14.0 *vs* 10.3 (NS)	0 *vs* 0	9.81 *vs* 8.11 (RAG > LAG)[3]
Kim *et al*[41]	RAG *vs* LAG *vs* OG	0- I - II - III	436	861	4542	226 *vs* 176 *vs* 158 (RAG > LAG > OG)[3]	85 *vs* 112 *vs* 192 (RAG = LAG < OG)[3]	40.2 *vs* 37.6 *vs* 40.5 (RAG = OG > LAG)[3]	10.1 *vs* 10.4 *vs* 10.7 (NS)	0.5 *vs* 0.3 *vs* 0.5 (NS)	7.5 *vs* 7.8 *vs* 10.2 (RAG = LAG < OG)[3]
Yoon *et al*[42]	RAG *vs* LAG	I - II - III	36	65	-	305.8 *vs* 210.2 (RAG > LAG)[3]	NR	42.8 *vs* 39.4 (NS)	16.7 *vs* 15.4 (NS)	0 *vs* 0	8.8 *vs* 10.3 (NS)
Hyun *et al*[43]	RAG *vs* LAG	I - II - III	38	83	-	234.4 *vs* 220.0 (NS)	131.3 *vs* 130.48 (NS)	32.8 *vs* 32.8 (NS)	13.1[4] *vs* 16.8[4] (NS)	0 *vs* 0	10.5 *vs* 11.9 (NS)
Kim *et al*[11]	RAG *vs* LAG	I - II - III	172	481	-	206.4 *vs* 167.1 (RAG > LAG)[3]	59.8 *vs* 134.9 (RAG < OG)[3]	37.3 *vs* 36.8 (NS)	5.2 *vs* 4.2 (NS)	0 *vs* 0.6 (NS)	7.1 *vs* 6.7 (NS)
Kim *et al*[44]	RAG *vs* LAG	I - II - III	87	288	-	248.4 *vs* 230.0 (RAG > LAG)[3]	NR	37.1 *vs* 34.1 (RAG > LAG)[3]	5.7 *vs* 9.0 (RAG < LAG)[3]	1.1 *vs* 0.3 (NS)	6.7 *vs* 7.4 (RAG < LAG)[3]
Son *et al*[45]	RAG *vs* LAG	I - II - III	51	58	-	264.1 *vs* 210.3 (RAG > LAG)[3]	163.4 *vs* 210.7 (NS)	47.2 *vs* 42.8 (NS)	16 *vs* 22 (NS)	1.9 *vs* 0 (NS)	8.6 *vs* 7.9 (NS)
Park *et al*[46]	RAG *vs* LAG	I - II - III	30	120	-	218 *vs* 140 (RAG > LAG)[3]	75 *vs* 60 (NS)	34 *vs* 35 (NS)	17 *vs* 7.5 (NS)	0 *vs* 0	7.0 *vs* 7.0 (NS)
Junfeng *et al*[24]	RAG *vs* LAG	I - II - III	120	394	-	234.8 *vs* 221.3 (RAG > LAG)[3]	118.3 *vs* 137.6 (RAG < LAG)[3]	34.6 *vs* 32.7 (RAG > LAG)[3]	5.8 *vs* 4.3 (NS)	NR	7.8 *vs* 7.9 (NS)
Seo *et al*[47]	RAG *vs* LAG	I - II - III	40	40	-	243 *vs* 224 (NS)	76 *vs* 227 (RAG < LAG)[3]	40.4 *vs* 35.4 (NS)	NR	NR	6.75 *vs* 7.37 (RAG < LAG)[3]
Shen *et al*[48]	RAG *vs* LAG	I - II - III	93	330	-	257.1 *vs* 226.2 (RAG > LAG)[3]	176.6 *vs* 212.5 (RAG < LAG)[3]	33.0 *vs* 31.3 (RAG > LAG)[3]	9.8 *vs* 10.0 (NS)	NR	9.4 *vs* 10.6 (NS)
Suda *et al*[49]	RAG *vs* LAG	All stages	88	438	-	381 *vs* 361 (RAG > LAG)[3]	46 *vs* 34 (RAG > LAG)[3]	40 *vs* 38 (NS)	2.3 *vs* 11.4 (RAG < LAG)[3]	1.1 *vs* 0.2 (NS)	14 *vs* 15 (RAG < LAG)[3]
Kim *et al*[50]	RAG *vs* LAG	I - II - III	223	211	-	226 *vs* 180 (RAG > LAG)[3]	50 *vs* 60 (NS)	33 *vs* 32 (NS)	13.5 *vs* 14.2 (NS)	0 *vs* 0	7.8 *vs* 7.9 (NS)

[1]Mean value; [2]The authors compared 20 gastric cancer patients who underwent robotic gastrectomy with 20 initial patients who underwent laparoscopic subtotal gastrectomy (iLAG) and 20 recent laparoscopic subtotal gastrectomy performed during the same period as the 20 robotic gastrectomy (rLAG); [3]Difference statistically significant, $P < 0.05$; [4]Major complications rate base on Clavien-Dindo classification $\geqslant$ 3, such as anastomotic and duodenal leakage. RAG: Robot-assisted laparoscopic gastrectomy; LAG: Laparoscopic assisted gastrectomy; OG: Open gastrectomy; NR: Not reported; NS: Not statistically significant difference.

comparative analysis. Thus, the usefulness of these articles is essentially of scientific expounding and debating, they do not add any new knowledge to that so far evidenced by clinical studies.

On the other hand, 9 meta-analysis[20,56-63] conducted using a systematic method have been published to date in literature trying to focus on RAG utility in treating gastric cancer (Table 3). One meta-analysis included certain reports which compared RAG to OG[57]; 5 meta-analyses utilized high quality studies which compared RAG and LG[56,59-61,63]; and the remaining 3 meta-analyses contained a systematic review and meta-analysis of studies investigating short-term results of RAG *vs* LG and OG[20,58,62]. Exclusively prospective and retrospective

Table 3 Meta-analysis comparing robot-assisted gastrectomy with laparoscopic assisted gastrectomy and/or open gastrectomy in the treatment gastric cancer

Ref.	Subject	Patients (n)			Operation time (min)[1]	Blood loss (mL)[1]	Harvested nodes (n)[1]	Morbidity (%)	Mortality (%)	Hospital stay (d)[1]
		RAG	LAG	OG						
Hyun et al[56]	RAG vs LAG	268	650	-	68.77[2] (RAG > LAG)[3]	-41.88[2] (RAG < LAG)[3]	-0.71[2] (NS)	0.74[4] (NS)	1.80[4] (NS)	-0.54[2] (NS)
Liao et al[57]	RAG vs OG	520	-	5260	65.73[2] (RAG > LAG)[3]	-126.08[2] (RAG < LAG)[3]	-0.78[2] (NS)	0.98[4] (NS)	0.98[4] (NS)	-2.87[2] (RAG < LAG)[3]
Xiong et al[58]	RAG vs LAG	634	1236	-	61.99[2] (RAG > LAG)[3]	-6.08[2] (NS)	-0.25[2] (NS)	1.12[4] (NS)	NR	-0.60[2] (NS)
	RAG vs OG	558	-	5301	65.73[2] (RAG > OG)[3]	-154.18[2] (RAG < OG)[3]	-1.13[2] (NS)	1.37[4] (NS)	NR	-2.18[2] (RAG < OG)[3]
Marano et al[20]	RAG vs OG	404	-	718	95.83[2] (RAG > OG)[3]	-225.58[2] (NS)	-2.68[2] (NS)	0.93[4] (NS)	NR	-2.92[2] (RAG < OG)[3]
	RAG vs LAG	404	845	-	63.70[2] (RAG > LAG)[3]	-35.53[2] (RAG < LAG)[3]	0.50[2] (NS)	0.87[4] (NS)	NR	-0.60[2] (NS)
Xiong et al[59]	RAG vs LAG	736	1759	-	48.64[2] (RAG > LAG)[3]	-33.56[2] (RAG < LAG)[3]	1.28[2] (NS)	1.13[4] (NS)	1.66[4] (NS)	-1.16[2] (NS)
Liao et al[60]	RAG vs LAG	762	1473	-	50.0[2] (RAG > LAG)[3]	-46.97[2] (RAG < LAG)[3]	1.61[2] (NS)	0.88[4] (NS)	0.45[4] (NS)	-0.5[2] (NS)
Shen et al[61]	RAG vs LAG	506	1369	-	48.46[2] (RAG > LAG)[3]	-38.43[2] (RAG < LAG)[3]	1.06[2] (NS)	0.95[4] (NS)	NR	-1.0[2] (NS)
Zong et al[62]	RAG vs OG	481	-	4674	68.47[2] (RAG > OG)[3]	-106.63[2] (RAG < OG)[3]	-0.78[2] (NS)	0.92[4] (NS)	0.72[4] (NS)	-2.49[2] (RAG < OG)[3]
	RAG vs LAG	997	2207	-	57.15[2] (RAG > LAG)[3]	-28.59[2] (NS)	-0.63[2] (NS)	1.06[4] (NS)	1.05[4] (NS)	-0.16[2] (NS)
Chuan et al[63]	RAG vs LAG	551	1245	-	42.9[2] (RAG > LAG)[3]	-16.07[2] (RAG < LAG)[3]	2.45[2] (NS)	1.05[4] (NS)	NR	-1.98[2] (RAG < LAG)[3]

[1]Mean value; [2]Weighted mean difference; [3]Difference statistically significant, $P < 0.05$; [4]Odds ratio. RAG: Robot-assisted laparoscopic gastrectomy; LAG: Laparoscopic assisted gastrectomy; OG: Open gastrectomy; NR: Not reported; NS: Not statistically significant difference.

studies were included in these meta-analysis, while no randomized controlled trials (RCTs) were found. The aforementioned meta-analysis showed that the RAG short-term clinical results were basically to be compared to LG and OG results. In terms of bleeding in particular, RAG was superior to both LG and OG, in spite of longer operation time. In addition RAG and LG groups did not show differences with regards to the number of harvested lymph nodes and conversion to open rates; RAG comported slightly inferior hospital stay or similar to that for LAG, but much less than OG; complications occurring after the operation were similar for all three operating methods.

Robotic surgery lasts longer mainly because of the additional set-up and docking-time necessary for the robotic system. However, it must be said that operating time noticeably diminished as surgical experience in robotic gastrectomy increased[9,32,46]. Moreover, there are major limits to how these meta-analysis are interpreted. All data came from non-randomized controlled trials, and the included studies are essentially limited in number and with small sample sizes. Moreover, significant heterogeneity exists among the included studies deriving from several factors, such as different surgeon skill levels, different types of gastrectomy, different extent of lymph node dissection, different tumour stage, different rate of adjuvant treatment, and different protocols of post-operative management and discharge of patients. Thus, the overall level of clinical evidence of this pooled data was low and, since there have been no randomized comparative studies, even if a meta-analysis is performed, it seems difficult to reach a clear conclusion.

Long term outcome
At the present time, long-term benefits of RAG for the treatment of gastric cancer are under reported in literature. Pugliese et al[26] are among the few who have reported long term results in their minimally invasive surgical experience in gastric cancer patients. Among a cohort-case study of 70 patients who underwent minimally invasive subtotal gastrectomy with D2 lymphadenectomy, the authors included also 18 patients submitted to the robotic procedure. The authors did not provide data specifically referred to the robotic group only, however, always on the basis of analogous short-term results between groups undergoing laparoscopic and robotic procedures, the reported 5-year survival was 81% for the whole cohort. Coratti et al[33] were the first to report long-term survival data specifically referring to gastric cancer patients submitted to robot-assisted gastrectomies. They analyzed survival results in a group of 98 patients with either early and advanced gastric cancer submitted to RAG. In a mean follow-up of 46.9 mo, they registered a cumulative 5-year survival rate of 73.3%. Son et al[45] carried out the longest follow-up study till now available. They evaluated the survival rates in a cohort-study group of 51 gastric cancer patients submitted to robotic total gastrectomy with D2 lymph nodes dissection and compared it to 58 patients who underwent analogous surgery but through the laparoscopic approach. In a median long-term follow-up of 70 mo, the authors did not find significant differences

in overall survival and disease-free survival between the two groups. Specifically, the authors reported a 5-year overall survival rate of 89.5% for the robotic group, which was not statistically significant different with respect to the rate revealed in the laparoscopic group (91.1%).

The aforementioned results are comforting, but it must be said that the case studies were limited, and selection bias is a real worry as it was a non-randomized study design. Follow-up periods longer than 5 years are needed to show oncological results, and so further RCTs are required in order to validate definitive conclusions.

DISCUSSION

The relative new technological advance in surgery through the introduction of minimally invasive technique can be accepted as an alternative to open surgery, which usually confers better short-term post-operative results, only if the oncologic parameters are as sufficiently respected as for the traditional open approach. Obviously, at the same time the long-term survival rates should not be adversely affected either.

With specific reference to gastric cancer one of the most important oncological criterion is the quality of lymphadenectomy, thus in order for laparoscopic or robot-assisted laparoscopic gastric surgery to be considered adequate, at least the same extent of lymph node dissection as in traditional surgery should be achieved, and moreover favorable postoperative results should also be evident.

Over the last two decades LG with lymph node dissection has developed as minimally invasive surgery for gastric cancer and it has been principally applied to early gastric cancer. Certain RCTs and meta-analysis showed that laparoscopic gastrectomy did not have inferior oncologic results compared to open surgery for early-stage gastric cancer, with instead improved results in the short term[3,64,65]. In fact, laparoscopic extended D1 lymphadenectomy may be seen as sufficient for almost all early gastric cancer in which lymph node metastases rarely occur, and is today the recommended approach in the East. On the other hand, only few high quality reports investigating the oncological adequacy of laparoscopic minimally invasive techniques for advanced gastric cancer are available to date. Recently, some meta-analyses related to this have been published, but there have been contrasting outcomes, particularly regarding complications after total gastrectomy and the actual adequacy of D2 lymphadenectomy in patients affected by advanced-stage of gastric cancer[4,64,66-69]. Even though a complete LG and extended lymph nodes dissection has been demonstrated by several experts to be feasible laparoscopically[5,6,26,70], due to some intrinsic limiting drawbacks of the laparoscopic technique, important oncologic preoccupations have been raised. When in the meta-analysis studies data not restricted to LADG solely for early gastric cancer was considered, but instead included advanced-stage tumour too, it was not possible to guarantee the same amount of lymph node dissection

as in conventional surgical procedures[71,72]. Thus, the laparoscopic techniques cannot be considered a standard validated procedure for all gastric cancer sufferers.

Certain inherent drawbacks of conventional laparoscopy may be eliminated by robotics by increasing the use of minimally invasive procedures, especially when more extended lymph nodes dissection and complicated reconstruction are required. In light of this, the introduction of robotic technologies could lead to the improvement of health care and final results. Particularly during typical difficult maneuvers in laparocopy, such as the dissection of the lymphatic tissue around major abdominal vessels (gastric, gastroepiploic, common hepatic, and celiac artery lymph nodes), robotics offers some indisputable advantages, which make it possible to perform the dissection more safely and easily. Consequently, robotic techniques should be viewed more as a technical advancement and auxiliary tool of the traditional minimally invasive laparoscopic approach, rather than an independent device system.

Most surgeons who are experts in robotics reported in their experience amounts of retrieved lymph nodes during RAG similar to those obtainable by the classic open counterpart procedure and sometimes more than those achieved by laparoscopy[8,20,38,56-63]. However, it must be said that the explanation of available comparable data among RAG, LG and OG has notable limitations. The principal issue that could affect the interpretation of these data is essentially the lack of a comprehensive comparative RCT. However, we have also to consider that the number of published high quality observational and retrospective studies is limited, and globally the sample sizes in each singular trial is poor. Ultimately, but not less importantly from the point of view of oncological adequacy, the duration of follow up is almost always limited.

CONCLUSION

RAG appears to be a safe and feasible alternative to conventional open or laparoscopic gastrectomy for the treatment of early stage gastric carcinoma, having demonstrated satisfactory perioperative outcomes and oncological adequacy. The number of collected lymph nodes when comparing RAG to open and laparoscopic gastrectomy are essentially similar when considering early-stage gastric cancer only, while an advantageous lower blood loss estimation was revealed in comparison with the other two approaches.

Basically the robotic system simplifies certain hard conventional laparoscopy techniques and renders them safer, in addition simultaneously possessing a learning curve and reproducibility that appear to be briefer than conventional laparoscopy[11-14]. These results, albeit initial, are promising, but the superiority of robotic gastric surgery over the traditional laparoscopic approach has not yet been solidly proved and its validation is still a long way off for all gastric cancer patients. The main controversial issue regards the possibility of

demonstrating that the supposed superiority of RAG with respect to laparoscopy in carrying out a more adequate extended lymphadenectomy could lead to potential oncological benefit, probably true in gastric cancer of a more advanced stage.

Unfortunately, due to inadequate long-term follow-up results and a limited number of studies to date available, larger and randomized prospective trials are required to draw definitive conclusion.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Efficacy of multiple biliary stenting for refractory benign biliary strictures due to chronic calcifying pancreatitis

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Abstract

AIM
To investigate endoscopic therapy efficacy for refractory benign biliary strictures (BBS) with multiple biliary stenting and clarify predictors.

METHODS
Ten consecutive patients with stones in the pancreatic head and BBS due to chronic pancreatitis who underwent endoscopic therapy were evaluated. Endoscopic insertion of a single stent failed in all patients. We used plastic stents (7F, 8.5F, and 10F) and increased stents at intervals of 2 or 3 mo. Stents were removed approximately 1 year after initial stenting. BBS and common bile duct (CBD) diameter were evaluated using cholangiography. Patients were followed for ≥ 6 mo after therapy, interviewed for cholestasis symptoms, and underwent liver function testing every visit. Patients with complete and incomplete stricture dilations were compared.

RESULTS
Endoscopic therapy was completed in 8 (80%) patients, whereas 2 (20%) patients could not continue therapy because of severe acute cholangitis and abdominal

abscess, respectively. The mean number of stents was 4.1 ± 1.2. In two (20%) patients, BBS did not improve; thus, a biliary stent was inserted. BBS improved in six (60%) patients. CBD diameter improved more significantly in the complete group than in the incomplete group (6.1 ± 1.8 mm *vs* 13.7 ± 2.2 mm, respectively, *P* = 0.010). Stricture length was significantly associated with complete stricture dilation (complete group; 20.5 ± 3.0 mm, incomplete group; 29.0 ± 5.1 mm, *P* = 0.011). Acute cholangitis did not recur during the mean follow-up period of 20.6 ± 7.3 mo.

CONCLUSION
Sequential endoscopic insertion of multiple stents is effective for refractory BBS caused by chronic calcifying pancreatitis. BBS length calculation can improve patient selection procedure for therapy.

Key words: Chronic pancreatitis; Biliary stricture; Biliary stent; Pancreatic stone; Endoscopy

Core tip: Endoscopic biliary stenting for benign biliary strictures (BBS) is useful for symptom relief and less invasive than surgery. Therefore, BBS caused by chronic pancreatitis (CP) is often managed by biliary stenting. However, subsequent treatment for refractory BBS caused by CP is unclear and no predictive factors for therapeutic success have been defined. The results of the present study indicated that endoscopic therapy with multiple biliary stenting was effective against the refractory BBS caused by chronic calcifying pancreatitis. Moreover, our study indicated that stricture length was correlated with therapeutic outcome.

INTRODUCTION

Chronic pancreatitis (CP) is characterized by progressive inflammation of the pancreas, which leads to permanent damage of pancreatic structure, function, or both, resulting in episodic or intractable abdominal pain with progressive exocrine and endocrine insufficiency[1]. Inflammation associated with CP occurs in 2.7% to 45.6% of cases and leads to stricture formation in the common bile duct (CBD)[2]. The stasis of bile caused by strictures increases intraluminal pressure in the CBD and induces cholangitis, choledocholithiasis, and secondary biliary cirrhosis[2,3]. Therefore, to reduce CBD pressure, biliary dilation for benign biliary stricture (BBS) should be

attempted, while pressure increase as a result of CP can be managed by surgery or endoscopic therapy.

Nealon *et al*[4] reported that surgical intervention offered a definitive solution for BBS, but was associated with significant morbidity and mortality. Endoscopic biliary dilation by endoscopic retrograde cholangio-pancreatography (ERCP) is less invasive than surgery and is the most successful option for patients who are not candidates for surgery[5-7]. Thus, the European Society of Gastrointestinal Endoscopy (ESGE) has recommended endoscopic therapy as a useful therapeutic approach for BBS[8].

A previous study reported the effectiveness of endoscopic therapy with a single stent for BBS due to CP[9]. By comparing single *vs* multiple simultaneous biliary stenting for treatment of strictures, use of multiple stents appeared to be superior to use of a single stent[10]. Other studies suggest that sequential endoscopic insertion of multiple biliary stents leads to medium and long-term success of stricture dilation[11,12]. Patients with calcifications of the pancreatic head were identified as a group nonresponsive to endoscopic single stent insertion[9] and BBS with pancreatic stones was reported as intractable to therapy with multiple biliary stenting[12]. However, the efficacy of multiple biliary stenting for patients with pancreatic stones has not been investigated in detail and predictive factors of therapeutic success remain undefined. The aim of this study was to assess the usefulness of endoscopic therapy for refractory BBS as a result of chronic calcifying pancreatitis with multiple biliary stenting, and to clarify predictors.

MATERIALS AND METHODS

Patients

From November 2012 to April 2014, 50 patients with CP visited at the Chiba University Hospital. Of these 50 patients, ten consecutive patients for whom endoscopic therapy with a single stent was unsuccessful were evaluated. Patients aged < 20 years and with a diagnosis of malignant diseases, existence of coagulopathy, a history of biliary surgery, inability to provide informed consent, or medical contraindications for multiple biliary stenting were excluded from the study. Patients were followed after therapy and interviewed for symptoms of cholestasis. Biochemical testing of liver function was performed at each visit. Written informed consent was obtained from all patients who underwent endoscopic therapy. The study protocol was approved by the institutional review board of Chiba University.

Procedure

Side-viewing duodenoscopes (JF-240/260V, TJF-260V; Olympus Medical Systems, Tokyo, Japan) were used to perform all endoscopic procedures. Endoscopic sphincterotomy was performed for all patients. After insertion of a catheter into the CBD, the existence of a BBS was evaluated and the length of the stricture and CBD diameter,

Table 1 Baseline patient characteristics, imaging findings, and interventions before treatment (*n* = 10)

Variable	Value
Patient characteristics	
Sex, *n* (%)	
Male	10 (100.0)
Female	0 (0.0)
Age, mean ± SD, yr	56.9 ± 6.9
BMI, mean ± SD, kg/m²	19.2 ± 2.6
Etiology, *n* (%)	
Alcohol	9 (90.0)
Other	1 (10.0)
Alcohol abuse, *n* (%)	
Presence	8 (80.0)
Absence	2 (20.0)
Duration of CP, mean ± SD, mo	106.4 ± 72.4
Treatment period, mean ± SD, d	350.6 ± 61.0
Follow up period, mean ± SD, mo (complete group)	20.6 ± 7.3
Imaging findings	
CBD diameter, mean ± SD, mm	12.5 ± 2.7
Length of stricture, mean ± SD, mm	23.9 ± 5.7
No. of pancreatic stones, *n* (%)	
Single	5 (50.0)
Multiple	5 (50.0)
Pancreatic stone location, *n* (%)	
Head	10 (100.0)
Body + Tail	0 (0.0)
Pancreatic stone diameter, mean ± SD, mm	10.2 ± 5.5
Interventions	
No. of ERCP sessions, mean ± SD	4.5 ± 1.0
No. of stents, mean ± SD	4.1 ± 1.2
Dilation of CBD stricture, *n* (%)	
Presence	0 (0.0)
Absence	10 (100.0)

BMI: Body mass index; CBD: Common bile duct; CP: Chronic pancreatitis; ERCP: Endoscopic retrograde cholangiopancreatography.

which was upstream of the stricture, was measured by cholangiography in all patients. A flexible guide wire was passed through the stricture and a single plastic stent was inserted beyond the stricture. Plastic stents (7F, 8.5F, and 10F) and increased stents at intervals of 2 or 3 mo were used to avoid clogging and development of cholangitis[13]. When symptoms and abnormal liver function test results following cholestasis appeared, stents or exchanged stents were inserted. All stents were removed approximately one year after initial stenting. Then, the stricture and CBD diameter were evaluated by comparisons with values before therapy.

Outcomes and definitions
The main study outcome was the usefulness of multiple biliary stenting for refractory BBSs for symptom relief and maintenance. Diagnosis of CP was based on clinical history and morphological abnormalities of the pancreas, as identified by computed tomography, magnetic resonance cholangiopancreatography, ERCP, and endoscopic ultrasound[14]. Diagnosis of a BBS was based on signs and symptoms of biliary obstruction and evidence of upstream biliary dilatation on imaging[15]. Symptomatic biliary obstruction was defined by clinical and laboratory findings

of obstructive jaundice. The stricture was considered sufficiently dilated if there was easy passage of an 8.5 mm balloon and rapid emptying of contrast was evident fluoroscopically[12]. Accordingly, patients with complete stricture dilation were included in the complete group and those with incomplete stricture dilation were included in the incomplete group. Characteristics of the two groups were compared to identify therapeutic predictors. Patient sex, age, body mass index (BMI), etiology, history of alcohol abuse, duration of CP, treatment period, CBD diameter, length of stricture, number of pancreatic stones, pancreatic stone location, pancreatic stone diameter, number of ERCP sessions, and number of biliary stents were evaluated as potential predictors. During the follow-up period, symptom relapse was defined as the appearance of symptomatic biliary obstruction. Complications related to endoscopic therapy were recorded. The severity of these complications was defined and graded according to the consensus criteria proposed by Cotton *et al*[16].

Statistical analysis
The Mann-Whitney *U* test was used to compare continuous variables, while the Fisher's exact test was used for comparison of categorical variables. The Wilcoxon signed-rank test was used to identify differences in the median values of proposed predictors. A probability (*P*) value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software version 20.0 (IBM-SPSS, Inc., Chicago, IL, United States).

RESULTS

Patients
Baseline patient characteristics, imaging findings, and interventions of all patients enrolled in this study are summarized in Table 1. ERCP procedures were tolerated in all patients. The mean number of biliary stents was 4.1 ± 1.2. Completion of endoscopic therapy was achieved in eight (80.0%) patients. Complete stricture dilation after therapy was achieved in six (60.0%) patients. BBS was not improved in two (20%) patients, thus biliary stents were inserted. CBD diameter was significantly improved after therapy (before therapy; 12.5 ± 2.7 mm, after therapy; 8.7 ± 3.9 mm, *P* = 0.022).

Outcomes
All patients were male and had pancreatic stones in the pancreatic head. Therefore, patient sex and pancreatic stone location were excluded from analysis of therapeutic outcome predictors. Patients' age, BMI, etiology history of alcohol abuse, duration of CP, treatment period, number of pancreatic stones, pancreatic stone diameter, number of ERCP sessions, and number of biliary stents were similar in complete and incomplete groups. CBD diameter improvement was more significant in the complete group than the incomplete group (6.1 ± 1.8 mm *vs* 13.7 ± 2.2 mm, respectively, *P* = 0.010). Furthermore, only the stricture length was significantly associated with

Table 2 Univariate analysis of factors predicting complete stricture improvement

Variable	Complete (*n* = 6)	Incomplete (*n* = 4)	*P* value
Patient characteristics			
Sex, *n* (%)			
Male	6 (100.0)	4 (100.0)	
Female	0 (0.0)	0 (0.0)	
Age, mean ± SD, yr	58.8 ± 8.2	54.0 ± 3.4	0.61
BMI, mean ± SD, kg/m^2	18.0 ± 1.7	20.6 ± 3.1	0.114
Etiology, *n* (%)			0.6
Alcohol	5 (83.3)	4 (100.0)	
Other	1 (16.7)	0 (0.0)	
Alcohol abuse, *n* (%)			0.667
Presence	1 (16.7)	1 (25.0)	
Absence	5 (83.3)	3 (75.0)	
Duration of CP, mean ± SD, mo	83.7 ± 79.4	140.5 ± 51.4	0.257
Treatment period, mean ± SD, d	384.5 ± 16.4	299.8 ± 70.6	0.171
Imaging findings			
CBD diameter before therapy, mean ± SD, mm	12.4 ± 2.3	12.8 ± 3.7	0.762
Length of stricture, mean ± SD, mm	20.5 ± 3.0	29.0 ± 5.1	0.011
No. of pancreatic stones, *n* (%)			0.738
Single	3 (50.0)	2 (50.0)	
Multiple	3 (50.0)	2 (50.0)	
Pancreatic stone location, *n* (%)			
Head	6 (100.0)	4 (100.0)	
Body + Tail	0 (0.0)	0 (0.0)	
Pancreatic stone diameter, mean ± SD, mm	7.4 ± 3.7	14.2 ± 6.2	0.067
Interventions			
No. of ERCP sessions, mean ± SD	4.5 ± 0.8	4.5 ± 1.3	> 0.999
No. of biliary stents, mean ± SD	4.0 ± 0.9	4.3 ± 1.7	0.767

BMI: Body mass index; CBD: Common bile duct; CP: Chronic pancreatitis; ERCP: Endoscopic retrograde cholangio-pancreatography.

complete stricture dilation (complete group; 20.5 ± 3.0 mm, incomplete group; 29.0 ± 5.1 mm, *P* = 0.011) (Table 2). Successful results were obtained only in patients with a stricture length of less than 24.0 mm (Table 3, Figures 1 and 2).

All six patients who achieved complete stricture dilation at least 6 mo after therapy were followed-up for a mean period of 20.6 ± 7.3 mo. During the follow-up period, there was no incidence of recurrence of symptomatic biliary obstruction.

Complications
Endoscopic therapy could not be completed in two (20%) patients because of acute cholangitis and abdominal abscess, respectively. Therefore, each underwent endoscopic biliary stenting and both recovered following conservative therapy. There were no complications related to ERCP. No instance of severe complication or patient death was noted during the follow-up period.

DISCUSSION
BBS formation is a common complication from either hepato-biliary surgery or diseases, such as CP and primary sclerosing cholangitis, among others[17]. BBS complicates the course of CP in 3% to 23% of patients[18]. BBS causes cholestasis that frequently results in cholangitis. Therefore, endoscopic therapy or surgery for BBS should be attempted. A postoperative BBS is managed with endoscopic therapy, which can improve long-term and very long-term results[12,19,20]. According to the ESGE guidelines, if endoscopic therapy is selected for BBS caused by CP, temporary (one-year) placement of multiple, side-by-side, plastic biliary stents is recommended[8]. Therefore, many patients with BBS caused by CP are managed with multiple biliary stenting. However, Draganov *et al*[12] reported that endoscopic therapy for these patients tended to be more unsuccessful than for patients with postoperative stricture and the results are worse for those with pancreatic stones. This study aimed to evaluate the efficacy of endoscopic therapy for refractory BBS caused by chronic calcifying pancreatitis with multiple biliary stenting and to clarify predictors of therapeutic success.

Alcohol is the most common cause of CP in Japan[21] and is regarded as the leading cause of CP in Western countries[14]. Disease in patients with alcoholic CP often progresses to pancreatic degeneration and pancreatic stone formation occurs more rapidly than in those with idiopathic CP[22]. Moreover, patient compliance tends to be poor[8]. Our study had a relatively larger proportion of patients with alcoholic CP (90.0%) than reported in previous studies (54.1%-69.0%)[6,9]. Since all patients in our study had refractory BBS, those with alcoholic CP were likely the majority. Although alcoholic CP mainly affects men[14], prognosis of all patients in this study might be generally consistent with that of males.
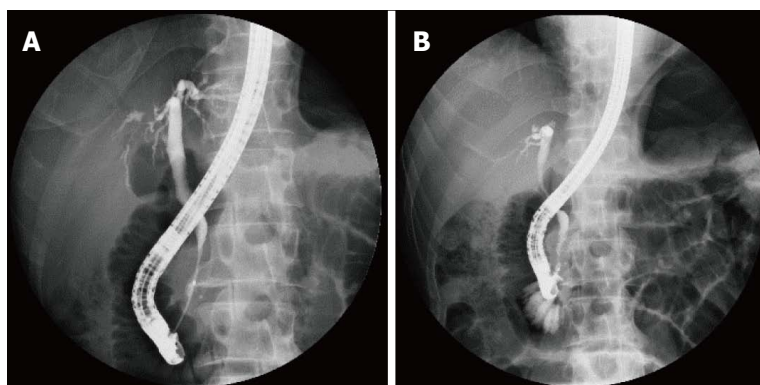
Figure 1 Endoscopic retrograde cholangiopancreatography pictures of successful endoscopic stenting in a male patient with a short stricture (19.3 mm). A: Before stent therapy; B: After 1 year of stent therapy.
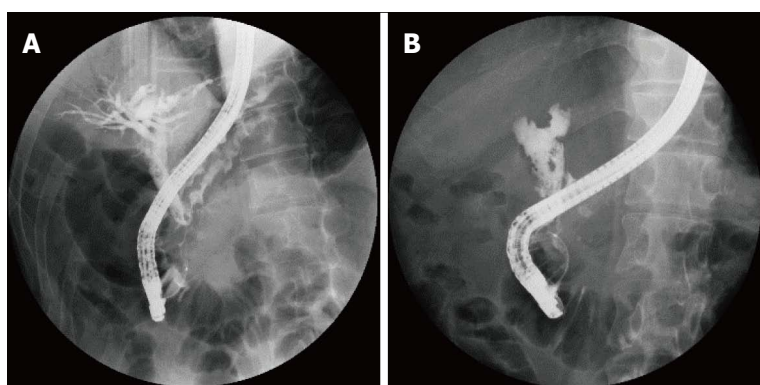

Figure 2 Failure of endoscopic stenting of common bile duct stricture demonstrated by endoscopic retrograde cholangiopancreatography findings in a male patient with a long stricture (36.0 mm). A: Before stent therapy; B: After 1 year of stent therapy.

Table 3 Outcomes of multiple biliary stenting in association with stricture length

Patient No.	Length of stricture (mm)	Outcomes of stricture dilation
1	23.2	Complete
2	20.7	Complete
3	19.3	Complete
4	36	Incomplete
5	20.4	Complete
6	24.9	Incomplete
7	29.4	Incomplete
8	25.5	Incomplete
9	24	Complete
10	15.5	Complete

Biliary stenting was routinely exchanged every 3 mo to avoid clogging and resulting cholangitis based on a study by Dumonceau *et al*[8] and supported by findings of Greiner's group[13,23]. Besides, the ESGE recommends temporary (one-year) placement of multiple, side-by-side, plastic biliary stents. In our study, the mean number of biliary stents was 4.1 ± 1.2 and the mean number of ERCP sessions was 4.5 ± 1.0, similar to those reported in previous studies[5,6,10-12,19,24].

Patients with BBS caused by CP were previously treated by single stent insertion to dilate the stricture, according to the recommendations of Kahl *et al*[9]. Endoscopic therapy was successful for some patients, especially those with a short BBS length. Although the presence of calcification in the pancreatic head and stricture location according to the Bismuth classification was used to predict complete stricture dilation in previous studies[9,12], no report has investigated the relevance of BBS length. Therefore, we evaluated the impact of BBS length on treatment outcome and found that BBS length was indeed a prognostic factor for procedural success. Calculation of BBS length improves the patient selection procedure for therapy. Although it is important to select patients who are likely to achieve favorable outcomes with complete stricture dilation, alternative therapies, including surgery, and avoidance of repetitive therapies could improve the quality of life of others.

In this study, complete stricture dilation was observed in 60% of patients, consistent with previous studies (44%-92%)[6,10-12]. The results suggest that multiple biliary stenting is a useful procedure for treatment of refractory BBS.

Complications were observed in two (20.0%) patients: one developed cholangitis and the other an abdominal abscess. Both recovered by conservative therapy and biliary stent insertion. Moreover, the frequency of these findings was comparable with other reports[6,9,10,12].

In our study, the sample size was small and the patients were all male. In addition, this study was investigated by a single center. Additional multicenter studies with large number of patients involving both male and female patient population are needed to confirm our study.

In conclusion, the results of the present study indicated that endoscopic therapy with multiple biliary stenting was effective against refractory BBS caused by chronic calcifying pancreatitis. Moreover, the stricture length was correlated with therapeutic outcomes. A stricture length of < 24.0 mm is a predictor of good prognosis of complete

stricture dilation. Therefore, the use of this threshold could help in the planning of alternative therapeutic options for patients for whom incomplete stricture dilation is likely.

ACKNOWLEDGMENTS

COMMENTS

Background

To reduce common bile duct (CBD) pressure, biliary dilation for benign biliary stricture (BBS) is often attempted by endoscopic therapy with multiple biliary stenting. However, the efficacy of multiple biliary stenting for patients with pancreatic stones has not been investigated in detail and predictive factors of therapeutic success remain undefined.

Research frontiers

Identifying predictors of good prognosis of complete stricture dilation may help in the planning of alternative therapeutic options for patients for whom incomplete stricture dilation is likely.

Innovations and breakthrough

Endoscopic therapy with multiple biliary stenting was effective against refractory BBS caused by chronic calcifying pancreatitis. Moreover, the stricture length was correlated with therapeutic outcomes.

Applications

This study suggests that calculation of BBS length improves the patient selection procedure for therapy.

Terminology

BBS refers to benign biliary stricture. Inflammation associated with chronic pancreatitis leads to stricture formation in the CBD. The stasis of bile caused by BBS induces cholangitis, choledocholithiasis, and secondary biliary cirrhosis.

Peer-review

This is a meaningful and innovative manuscript based on endoscopic retrograde cholangiopancreatography stenting and BBS therapy. This is an interesting cohort study with small group of patients. However, the data presented is important in identifying a large cohort group involving both male and female patient population in future studies. The studies including the patient selection has been carefully performed. Data analysis was performed carefully and could have been improved with a larger cohort.

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ORIGINAL ARTICLE

Retrospective Study

Gastric antral webs in adults: A case series characterizing their clinical presentation and management in the modern endoscopic era

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Abstract

AIM
To investigate the current management of gastric antral webs (GAWs) among adults and identify optimal endoscopic and/or surgical management for these patients.

METHODS
We reviewed our endoscopy database seeking to identify patients in whom a GAW was visualized among 24640 esophagogastroduodenoscopies (EGD) over a seven-year period (2006-2013) at a single tertiary care center. The diagnosis of GAW was suspected during EGD if aperture size of the antrum did not vary with peristalsis or if a "double bulb" sign was present on upper gastrointestinal series. Confirmation of the diagnosis was made by demonstrating a normal pylorus distal to the GAW.

RESULTS
We identified 34 patients who met our inclusion criteria (incidence 0.14%). Of these, five patients presented with gastric outlet obstruction (GOO), four of whom underwent repeated sequential balloon dilations and/or needle-knife incisions with steroid injection for alleviation of GOO. The other 29 patients were incidentally found to have a non-obstructing GAW. Age at diagnosis ranged from 30-87 years. Non-obstructing GAWs are mostly

incidental findings. The most frequently observed symptom prompting endoscopic work-up was refractory gastroesophageal reflux (n = 24, 70.6%) followed by abdominal pain (n = 11, 33.4%), nausea and vomiting (n = 9, 26.5%), dysphagia (n = 6, 17.6%), unexplained weight loss, (n = 4, 11.8%), early satiety (n = 4, 11.8%), and melena of unclear etiology (n = 3, 8.82%). Four of five GOO patients were treated with balloon dilation (n = 4), four-quadrant needle-knife incision (n = 3), and triamcinolone injection (n = 2). Three of these patients required repeat intervention. One patient had a significant complication of perforation after needle-knife incision.

CONCLUSION

Endoscopic intervention for GAW using balloon dilation or needle-knife incision is generally safe and effective in relieving symptoms, however repeat treatment may be needed and a risk of perforation exists with thermal therapies.

Core tip: Gastric antral webs (GAWs) in adults are rare, likely often overlooked, and when seen, considered to be incidental findings on upper endoscopy. They can, however, cause symptoms including gastric outlet obstruction. Herein, we review management of 34 such patients that underwent treatment at our tertiary institution. Our findings indicate that GAWs can be managed safely and effectively *via* endoscopic intervention with balloon dilation and endoscopic incision with needle knife, although repeat procedures were required in some cases, and a small risk of perforation exists. Standards for appropriate surveillance and appropriate indications for surgical intervention are yet to be defined.

INTRODUCTION

Gastric antral web (GAW), or antral diaphragm, is an uncommon endoscopic finding and a rare cause of gastric outlet obstruction (GOO). Evans and Sarani define GAW as a layer of submucosa and that runs perpendicular to the axis of the stomach[1]. The diagnosis of GAW is suspected during esophagogastroduodenoscopy (EGD) if aperture size of the antrum does not vary with peristalsis and is confirmed by demonstrating a normal pylorus distal to the GAW. To date, the majority of cases have been reported in the pediatric population ranging from

premature neonates to teenagers[2-4]. The first case in an adult patient was reported by Sames *et al* in 1949, and very few have been described in the last thirty years[5]. Thus, the clinical setting in which GAW is likely to arise, as well as the optimal endoscopic and/or surgical interventions are poorly defined.

The differential diagnosis of a GAW is broad and includes "distal gastrospasm", redundant gastric mucosa, hypertrophic gastric rugae, heterotrophic pancreatic tissue and cholecystogastrocolic bands and perigastric adhesions[6,7]. Historically, upper gastrointestinal (UGI) series were the imaging modality of choice for patients suspected of having GAW or other obstructive pathology. Interestingly, the radiographic incidence of GAW far exceeds that reported in medical and surgical literature with almost half the cases being incidental findings in "asymptomatic" individuals[8]. The characteristic radiographic findings are thin, knife-like linear septae 2-3 mm thick seen as radiolucent lines 1-2 cm proximal to the pylorus projecting from the greater and lesser curvature[6]. The antrum distal to the web may fill giving the appearance of a "double duodenal bulb", and contrast exiting through the central orifice gives a "jet effect"[7]. However, a GAW may easily be confused with the pylorus despite the use of double-contrast radiographs, and it is recommended that right anterior oblique and left posterior oblique views be obtained[7]. A contrast-enhanced computed tomography (CT) scan may demonstrate the cutoff proximal to the pylorus and a normal caliber pylorus and duodenum downstream with greater accuracy. Rarely has a duodenal web been described[9].

In adults, patients with GAW often develop symptoms when the aperture size is less than 1 centimeter in diameter[10]. Symptoms are usually worse post-prandially and include water brash, dysphagia, odynophagia, abdominal distention, nausea, forced or spontaneous vomiting, early satiety, weight loss, epigastric or right upper quadrant abdominal pain, anterior chest pain and non-bloody, watery diarrhea[5,9,11,12]. Historically, most cases are diagnosed during an endoscopic or radiographic work-up to explain various upper gastrointestinal symptoms[1,13].

MATERIALS AND METHODS

Patient characteristics

We evaluated patients with a diagnosis of GAW by EGD performed at Medstar Georgetown University Hospital between 2007 and 2013. In all cases, the diagnosis of GAW was suspected during EGD if aperture size of the antrum does not vary with peristalsis or if a "double bulb" sign is present on upper gastrointestinal (UGI) series. Confirmation of the diagnosis was made by demonstrating a normal pylorus distal to the GAW.

Data collection

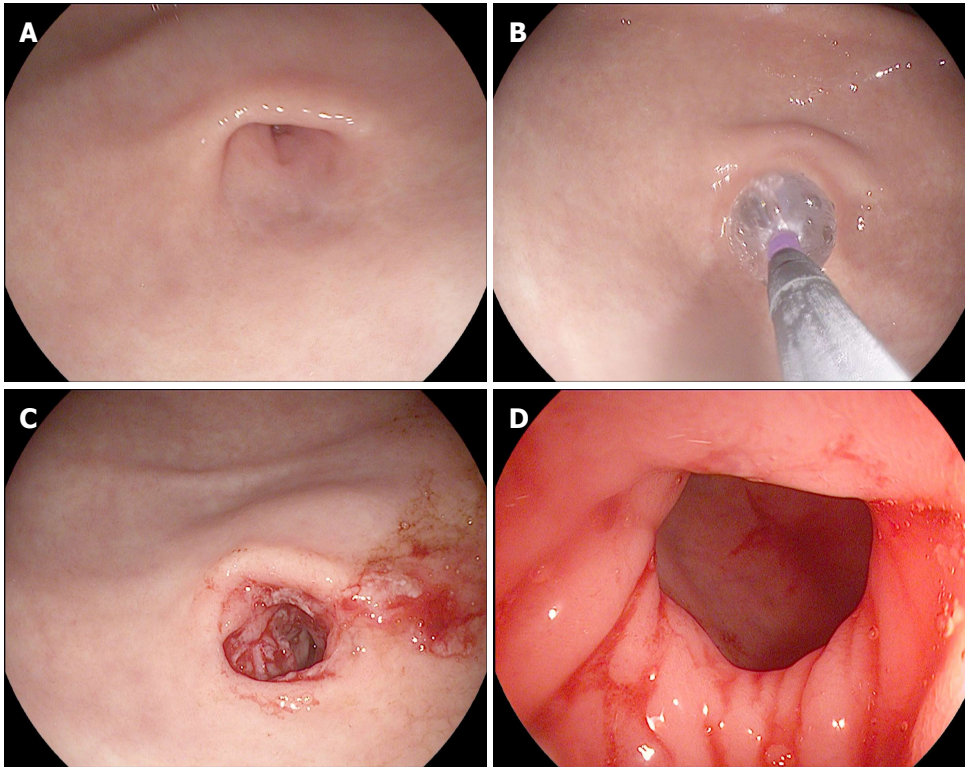For all patients, data were collected retrospectively,

Figure 1 Endoscopic images from Case 1. A: An obstructing gastric antral web (GAW); B: Balloon dilation of the GAW; C: The appearance of the GAW following balloon dilation; D: A normal pylorus seen distally to the GAW.

including demographic data, presenting symptoms, imaging prior to EGD, endoscopic findings, endoscopic interventions, and course following index EGD. These data were gathered *via* a review of procedure reports and other materials found in our electronic medical records systems.

Statistical analysis

Univariate analyses were conducted to describe the distributions of demographic data, presenting symptoms and need for intervention. Significance statements refer to *P* values of two-tailed tests that were < 0.05.

RESULTS

We identified 34 cases of GAW encountered among 24640 EGDs performed at our institution from 2007-2013 for an incidence of 0.14%. These cases included five instances in which GAW was complicated by GOO as described below. There were no significant differences in presenting symptoms between patients with GAW with GOO and non-obstructing GAW.

Case 1

A 60-year-old Caucasian female with hypothyroidism, hyperlipidemia, and functional constipation was evaluated for a three-month history of gastroesophageal reflux. She had been experiencing odynophagia and retrosternal pressure after eating solid foods. Her symptoms were not alleviated with omeprazole, cimetidine, or bismuth subsalicylate. Laboratory testing, including thyroid function

tests, were normal. EGD revealed retained food in the stomach and an obstructing antral web (Figure 1A). Balloon dilation to 12 mmHg was performed (Figure 1B and C), allowing visualization of a normal pylorus beyond the narrowing (Figure 1D). Following balloon dilation, needle-knife cuts were made in four quadrants (Figure 2) and 80 mg triamcinolone was injected. The patient remained asymptomatic for five years, at which time symptoms similar to those at initial presentation returned. She underwent a repeat EGD which showed recurrence of the obstructing antral web. The GAW was sequentially balloon dilated to 15 mmHg, followed by repeat four quadrant needle-knife cuts and reinjection of 80 mg triamcinolone. The patient remained asymptomatic for two years at which time EGD showed a third recurrence of the GAW, requiring repeat balloon dilation, four-quadrant needle-knife cuts, and triamcinolone injection. Although her symptoms were alleviated, the patient was advised to seek surgical evaluation for more permanent intervention, should her symptoms recur.

Case 2

A 80-year-old African-American female with hypertension, emphysema and prior breast and lung cancer presented with dysphagia to solids and liquids, persistent nausea and vomiting, and abdominal fullness. CT scan showed a partial GOO without evidence of external compression or intrinsic mass at the pylorus, while UGI series suggested a near complete gastric outlet obstruction. EGD revealed retained food in the body and antrum of the stomach,
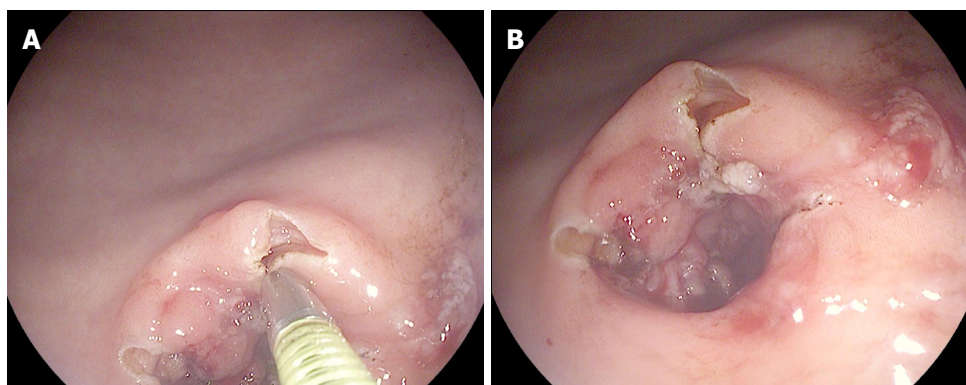
Figure 2 Needle-knife incision of a gastric antral web. A: Four-quadrant needle-knife incision of a gastric antral web (GAW); B: The final appearance of a GAW following balloon dilation, four-quadrant needle-knife incision, and triamcinolone injection.

severe antral erosions, and an obstructing GAW. Sequential balloon dilation to 10 mmHg was performed, allowing the regular 9.8 mm endoscope to be advanced without resistance. Given the partial return of symptoms within two weeks, EGD was repeated, and the GAW was incised using needle-knife cautery. Subsequently, the patient noted alleviation in her symptoms, and during follow-up EGD a week later, the endoscope traversed the antral web with minimal resistance.

Case 3

A 68-year-old Hispanic male with diabetes mellitus, coronary artery disease, and chronic kidney disease was evaluated for a ten-year history of nausea, frequent regurgitation and early satiety with a 90 pound weight. Screening colonoscopy two years prior was unremarkable, as was an UGI series and CT scan of the abdomen. EGD at the time showed antral narrowing, complicated by post biopsy bleeding. After a two year course of esomeprazole, repeat EGD showed retained gastric contents and an obstructing GAW with 6 mm aperture. Balloon dilation to 15 mm was performed, allowing a 9 mm endoscope to be advanced. The patient was seen in our clinic three weeks later and reported a five pound weight gain in the interim with no recurrence of his symptoms.

Case 4

A 74-year-old Caucasian female with hypertension, arthritis and gastroesophageal reflux disease was admitted to the inpatient service for a six-week history of abdominal cramping and diarrhea with intermittent melena. She reported no fever, nausea, vomiting, early satiety, weight loss, recent travel, or recent antibiotic use. Stool studies were unremarkable for enteric pathogens or fecal leukocytes. CT scan of the abdomen and pelvis showed pancolitis and a thickened antrum. The patient was empirically started on budesonide and the frequency of her bowel movements decreased. A colonoscopy performed three weeks later was unremarkable, and biopsies were negative for inflammatory bowel disease or microscopic colitis suggesting a possible transient infectious or ischemic colitis. EGD performed at the same time showed an

obstructing GAW, but no intervention was performed given the lack of symptoms suggesting GOO. Of note, an EGD performed five years earlier showed a gastric ulcer, but a GAW was not described. The patient's symptoms continued to improve over the next several weeks.

Case 5

An 81-year-old Caucasian woman with scleroderma and gastric antral vascular ectasia (GAVE) treated previously with argon plasma coagulation presented with persistent nausea and vomiting. A GAW causing GOO had been identified at an outside institution, and she was referred for endoscopic management. Upon our initial EGD, the patient was treated with needle-knife incision and injection of 80 mg of triamcinolone. Following this procedure, her symptoms improved, but did not resolve, and she returned for further endoscopic management 8 wk later. At that time, we again performed needle-knife incision, however a complication of perforation was noted with direct visualization of small bowel through the gastric defect. Three endoscopic clips were placed to close the defect, but CT of the abdomen revealed a large pneumoperitoneum. The patient was then taken emergently to the operating room, where a 1.5 cm perforation in the distal aspect of the lesser curvature of the stomach was identified laparoscopically and closed with full-thickness surgical sutures. On post-operative day five, the patient underwent an UGI series that revealed no evidence of persistent perforation and only mild narrowing in the gastric antrum. She was discharged home the following day, and upon follow-up in clinic reported that she was no longer experiencing her symptoms of GOO.

Summary of all cases

Among the 34 cases of GAW, 19 (55.9%) occurred in women and 15 (44.1%) in men. Ages at the time of diagnosis ranged from 30 to 87 years (mean 65.3, St.dev 12.9). Five patients had an obstructing GAW (14.7%, discussed above) and 29 patients were incidentally found to a have non-obstructing GAW (85.3%). The most frequently reported symptom was chronic gastro-esophageal reflux in 24 patients (70.6%), each of whom

Table 1 Age, sex, and symptoms of thirty-three patients found to have gastric antral web on esophagogastroduodenoscopy

Patient No.	Age	Sex	Year of diagnosis	Obstructing GAW	Reflux symptoms	PPI course	Dysphagia	Nausea/ vomiting	Abdominal discomfort	Weight loss
1[1]	60	F	2006	Yes	Yes	Yes	Solid	Yes	No	No
2[1]	80	F	2008	Yes	Yes	Yes	Solid/liquid	Yes	No	No
3[1]	68	M	2013	Yes	Yes	Yes	No	Yes	No	Yes
4	74	F	2011	Yes	No	No	No	No	Diffuse	No
5[1]	81	F	2015	Yes	Yes	Yes	No	Yes	No	No
6	85	F	2003	No	No	No	No	No	Diffuse	No
7	62	F	2003	No	No	No	No	No	Diffuse	No
8	56	M	2003	No	No	No	No	No	No	No
9	38	M	2004	No	Yes	Yes	No	No	No	No
10	49	M	2004	No	Yes	Yes	No	No	No	No
11	68	M	2004	No	Yes	Yes	No	No	No	No
12	53	M	2004	No	Yes	Yes	No	No	No	No
13	61	F	2005	No	Yes	Yes	No	No	No	No
14	67	M	2006	No	No	No	No	No	No	Yes
15	69	M	2006	No	Yes	Yes	No	No	No	No
16	82	M	2007	No	Yes	Yes	No	No	No	No
17	63	F	2007	No	Yes	Yes	No	No	No	No
18	66	F	2007	No	No	No	No	Yes	Diffuse	Yes
19	54	F	2007	No	Yes	Yes	Solid	No	Substernal	No
20	76	F	2007	No	Yes	Yes	No	No	No	No
21	58	F	2007	No	Yes	Yes	No	Yes	No	No
22	70	F	2009	No	Yes	Yes	No	No	Diffuse	No
23	67	F	2009	No	No	No	No	No	Diffuse	No
24	56	F	2010	No	No	No	No	No	Diffuse	No
25	30	F	2010	No	Yes	Yes	No	Yes	No	Yes
26	57	M	2011	No	Yes	Yes	No	No	No	No
27	73	M	2011	No	Yes	Yes	No	Yes	No	No
28	52	F	2011	No	Yes	Yes	No	No	No	No
29	71	M	2011	No	Yes	Yes	No	No	Diffuse	No
30	67	M	2012	No	Yes	Yes	Solid	No	Epigastric	No
31	68	F	2012	No	Yes	Yes	Solid	No	No	No
32	66	M	2013	No	No	No	No	Yes	Diffuse	No
33	87	F	2013	No	Yes	Yes	No	No	No	No
34	86	M	2014	No	No	Yes	Solid	No	No	No

[1]Indicates intervention was performed during esophagogastroduodenoscopy. GAW: Gastric antral web; F: Female; M: Male.

had taken proton-pump inhibitor therapy for various periods without significant improvement. Nine patients complained of diffuse abdominal pain (26.5%), one of epigastric pain (2.94%), and one of substernal discomfort (2.94%). Eight patients reported nausea and vomiting (23.5%). Six patients had dysphagia to solids (17.6%) and one to solids and liquids (2.9%). Four patients complained of early satiety (11.8%), three of whom also experienced weight loss (Table 1).

Among patients undergoing further work-up for their chronic gastroesophageal reflux, eight of 24 were found to have a hiatal hernia on endoscopy (33.3%), four had duodenal ulcers (18.2%), one had an antral ulcer (4.17%), and one had a Schatzki ring in addition to the GAW (4.17%). Of note, eight of the 34 patients in this series had prior endoscopies performed three to 14 years prior without description of a GAW (23.5%).

DISCUSSION

While the cause of GAW in adults is poorly understood, in 1965 Rhind et al[12] theorized that GAW was "acquired" in adults, and resulted from scarring as circumferential

pyloric and pre-pyloric peptic ulcers heal. This theory fits well with our Case 5 where GAW was likely the result of antral scarring from prior APC treatment of GAVE. Given the higher reported incidence in children, many authors believed the "congenital" theory that rapid proliferation of epithelial cells in the gut lumen was not followed by vacuole formation, fusion and recanalization during early development[11,14]. It was further speculated in the past that a congenital GAW may manifest only in adulthood as a result of a decline in efficacy of mastication from fewer teeth, dentures, or diminished muscle strength, or, alternatively, from hypertrophy and decompensation of the stomach chronically forcing food through a narrowed opening, although to our knowledge, these theories were never validated[5,6,14].

Given the prevalence of chronic gastroesophageal reflux in this cohort, we believe the association between this acidity and GAW may be significant. Two-thirds of our patients had reflux symptoms, five of whom had duodenal or gastric ulcers visualized during endoscopy. This is similar to historical reports of GAWs in three adult patients with gastric ulcer of the lesser curvature, and three others who had a duodenal ulcer[5,7,12]. Eight of our

patients had prior endoscopies in which a GAW was not described, and while this might argue against the notion that GAW is a congenital anomaly, it is equally possible that the web simply may have been missed, as they can easily be overlooked or confused with other entities.

Diagnosis

In our patients, GAW was identified on EGD and fulfilled the criteria set forth by Sokol *et al*[15] in 1965: fixed size aperture or "pseudopylorus"; smooth GAW mucosa devoid of folds; and normal peristalsis to the GAW that stops abruptly but continues beyond in a concordant fashion. Evidence of gastric retention was seen in 14.7% of the patients in our series, further confirming the clinical picture.

Treatment

Conservative management with acid suppression, such as proton-pump inhibitors, has been reported to provide temporary relief, but does not result in a permanent cure. Most of the published literature describing GAW dates back 30-40 years and predates modern endoscopic approaches to treatment. Following preliminary exploratory laparotomy or duodenotomy, an incision of the GAW to the central aperture; enlargement of the aperture *via* lysis with transverse gastroplasty or pyloroplasty; or a finger fracture of the GAW and pyloromyotomy were the most common surgical procedures utilized[11]. Although such surgery successfully restored a functional gastric outlet and alleviated symptoms, an endoscopic "webotomy", first suggested by Swartz and Shepard in 1956, heralded the minimally invasive options currently deemed safe given the lack of a muscularis propia in GAWs, and a low risk of perforation[14]. Endoscopic balloon dilation to 10 mm was first described in 1984, and has proven to be effective and safe to repeat[10,16]. However, frequent recurrence led to the development of more permanent interventions. Endoscopic snaring was used successfully in treating an obstructing GAW in an infant[9], and three radial incisions with a papillotome relieved symptoms from a partially obstructing GAW in a 14-year-old female[17]. In 1988, Al-Kawas reported the use of Nd: YAG laser therapy in a 64-year-old symptomatic woman with an obstructing GAW to create a 14 mm lumen, which alleviated symptoms in 48 h, although she later required surgery[9]. This technique has also proven effective in treating an obstructing duodenal web[9]. In 2013, Salah reported a case of obstructing GAW in an 11 year old boy treated with snare resection, electroincision and balloon dilation[18]. Several cases, including ours, have shown long-term resolution of symptoms after radial incisions using needle-knife electrocautery, but the use of empiric triamcinolone acetate for its anti-inflammatory effects has not been previously reported. However, we believe that a combination of balloon dilation and/or needle knife incisions remain the primary endoscopic management tools with low risk of perforation or significant bleeding. In our series, perforation following needle-knife incision

occurred in one patient who was likely predisposed by antral scarring from prio APC treatment. In our practice, interventions were only performed after biopsies had confirmed the absence of malignancy. In addition, interventions were only performed in patients with clinically significant symptoms of GOO that were refractory to medical management. The role of surgical intervention for adults with GAWs refractory to endoscopic treatment remains incompletely defined in the endoscopic era.

In conclusion, GAW is a rare endoscopic finding among adults undergoing endoscopy (0.14% in this series over a 7 year period). It is likely often overlooked and is considered an incidental finding when seen, but may be associated with GOO, refractory GERD or gastric or duodenal ulceration. Through-the-scope balloon dilation with or without a needle-knife incision of the web appears to be effective in many patients, although the need for repeat endoscopic treatment was frequent among those with high-grade GOO. The current role for surgical intervention remains to be defined, as it appears to be less necessary in adults than in the past.

COMMENTS

Background

Gastric antral webs (GAWs) are rare entities in adults which can cause gastric outlet obstruction (GOO). In the endoscopic era, interventional endoscopic techniques have been employed in the management of these patients.

Research frontiers

Optimal technique and devices for intervention on GAWs with GOO have yet to be defined, however several techniques have been described in the literature.

Innovations and breakthrough

Herein, the authors report their experience with GAWs at the tertiary institution. The authors found that endoscopic intervention for GAW using balloon dilation or needle-knife incision is generally safe and effective, however repeat treatment may be required and a risk of perforation exists with thermal therapies.

Applications

These techniques, including needle-knife incision, balloon dilation, and triamcinolone injection are generally safe and effective endoscopic interventions, however repeat treatment may be needed and a risk of perforation exists with thermal therapies. These treatment modalities can be used to treat gastric antral webs associated with gastric outlet obstruction.

Peer-review

It's a quite extensive manuscript especially for a case series.

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Recurrence of choledocholithiasis following endoscopic bile duct clearance: Long term results and factors associated with recurrent bile duct stones

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Abstract

AIM
To evaluate the rate of recurrence of symptomatic choledocholithiasis and identify factors associated with the recurrence of bile duct stones in patients who underwent endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (EST) for bile duct stone disease.

METHODS
All patients who underwent ERCP and EST for bile duct stone disease and had their bile duct cleared from 1/1/2005 until 31/12/2008 was enrolled. All symptomatic recurrences during the study period (until 31/12/2015) were recorded. Clinical and laboratory data potentially associated with common bile duct (CBD) stone recurrence

were retrospectively retrieved from patients' files.

RESULTS
A total of 495 patients were included. Sixty seven (67) out of 495 patients (13.5%) presented with recurrent symptomatic choledocholithiasis after 35.28 ± 16.9 mo while twenty two (22) of these patients (32.8%) experienced a second recurrence after 35.19 ± 23.2 mo. Factors associated with recurrence were size (diameter) of the largest CBD stone found at first presentation (10.2 ± 6.9 mm *vs* 7.2 ± 4.1 mm, $P = 0.024$), diameter of the CBD at the first examination (15.5 ± 6.3 mm *vs* 12.0 ± 4.6 mm, $P = 0.005$), use of mechanical lithotripsy (ML) ($P = 0.04$) and presence of difficult lithiasis ($P = 0.04$). Periampullary diverticula showed a trend towards significance ($P = 0.066$). On the contrary, number of stones, angulation of the CBD, number of ERCP sessions required to clear the CBD at first presentation, more than one ERCP session needed to clear the bile duct initially and a gallbladder in situ did not influence recurrence.

CONCLUSION
Bile duct stone recurrence is a possible late complication following endoscopic stone extraction and CBD clearance. It appears to be associated with anatomical parameters (CBD diameter) and stone characteristics (stone size, use of ML, difficult lithiasis) at first presentation.

Key words: Bile duct stone disease; Common bile duct angulation; Choledocholithiasis; Endoscopic retrograde cholangiopancreatography; Endoscopic sphincterotomy; Recurrence of choledocholithiasis

Core tip: Recurrence of choledocholithiasis is considered a late complication following endoscopic extraction of bile duct stones. There are various factors associated with the risk of recurrence. In our study the rate of recurrence was 13.5%. Although univariate analysis identified four different risk factors associated with both anatomical parameters (common bile duct diameter) and stone characteristics (stone size, use of mechanical lithotripsy, difficult lithiasis), multivariate analysis confirmed only bile duct diameter as being important. The underlying pathogenetic mechanism of recurrence is likely multi-factorial in nature. Bile stasis, duodenal - biliary reflux and unfavorable stone characteristics probably contribute towards stone reformation.

INTRODUCTION
Endoscopic retrograde cholangiopancreatography (ERCP) is widely accepted as the modality of choice for the endoscopic removal of bile duct stones. Endoscopic sphincterotomy (EST) since its introduction in 1974[1,2], has been extensively used for the endoscopic extraction of bile duct stones. Endoscopic techniques for stone removal are generally considered both safe and effective but, their invasive nature cannot preclude the possibility of complications. In fact complications can occur even in the hands of the most seasoned expert[3]. They can be broadly classified, depending on their timing, as early (up to 3 d post-procedure) or late (> 3 d)[4]. Early complications are mostly related with sedation and endoscopy like bleeding, infection, pancreatitis, perforation, cardiopulmonary events, while late complications concern mainly stent infections due to long-term/permanent stent deployment and post-procedural duct/sphincter of Oddi (SO) inflammatory changes (*i.e.,* ampullary stenosis) because of ductal/SO manipulation[4]. Although not officially listed as a late complication of ERCP in various guidelines[3], recurrence of choledocholithiasis is considered to be one by many authors[5-7]. Rates of recurrence vary across different studies, ranging from 4% to 24% (variable intervals of follow-up of up to 15 years)[8-10]. The goal of this paper is to evaluate the rate of recurrence of symptomatic choledocholithiasis and identify factors associated with the recurrence of bile duct stones in patients who underwent endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (EST) for bile duct stone disease.

MATERIALS AND METHODS
Patients
We retrospectively studied a group of patients who underwent ERCP and EST for bile duct stone disease at a tertiary center, Department of Gastroenterology of the University hospital of Patras from 1/1/2005 until 31/12/2008. Only patients in whom complete and successful clearance of the common bile duct (CBD) from stones was achieved were included in the study irrespectively of the number of sessions required to fulfill that requirement. Patients with difficult bile duct stones (large bile duct stones (> 10 mm) and/or multiple stones (≥ 3) or impacted stones)[11] or residual choledocholithiasis were included in the study as long as a patent CBD was achieved in their baseline or any of their subsequent follow-up examinations. Patients with known residual CBD stones (unable to be extracted or referred for surgical treatment), pancreatic/biliary malignant disorders and benign biliary strictures (usually post - surgery) were excluded from the study, finally patients with indwelling biliary stents (permanent or long standing) and patients that were lost to follow - up

were also excluded. Every patient with gallbladder stones was instructed to remove his/her gallbladder surgically after the first (baseline) clearance of the bile duct (if a cholocystectomy was not already performed). All patients were followed up until either termination of the study (31/12/2015) or when they died.

For the purpose of studying recurrence associated risk factors we created two (2) groups. In the first group all patients with a history of symptomatic recurrence were enrolled (after applying exclusion criteria). An equal number (1:1) of age / gender - matched control patients was selected from the pool of recurrent free patients (group two).

Endoscopic treatment
Written informed consent for the ERCP was obtained from all the patients undergoing the procedure. Preparation included local anesthesia of the pharynx using 10% xylocaine, and conscious sedation of the patient with the use of (IV) midazolam - pethidine. Reversal agents (flumazenil) were used when indicated. Antibiotic prophylaxis was used in accordance with published guidelines at the time, the exact regimen depending on the appropriate clinical indication[12]. ERCP was performed using a side-view endoscope (Olympus Optical Corporation, Tokyo, Japan). In patients with native papilla EST was performed, after deep cannullation of the CBD with the help of a guidewire, using a standard pull-type papillotome according to the standard technique. Before performing the EST a cholangiogram (using a diluted contrast medium) was attainted to confirm CBD stones. Under fluoroscopic/endoscopic guidance stones were removed from the CBD, mainly with the use of ballon catheters and occasionally with dormia retrieval baskets. Patients with difficult stones were treated with either mechanical lithotripsy at the same session or use of temporary plastic stents. Patency of the CBD/clearance of stones was evaluated by absence of any filling defects at the final cholangiogram. During the enrollment period (2005-2008) large balloon dilation was not a common practice. As such it was not exercised by our unit.

Study of the cholangiograms
Size and number of CBD stones were assessed on the cholangiogram after optimum opacification of the CBD. Stone size was assessed by comparing the diameter of the stone to the (relevant size of the) shaft of the endoscope on the cholangiogram. CBD diameter was measured in a similar manner. Likewise CBD angulation(s) were also calculated from postoperative cholangiograms. All calculations were independently validated by a second observer and any interobserver differences were expressed as mean values.

Data collection and definitions
All data was extracted from the first (baseline) ERCP of all patients.

The following parameters were recorded and investigated for the purpose of studying risk factors. (1) Basic demographics: sex and age; (2) Diameter of the CBD (mm); (3) Stone characteristics: Size (mm) (defined as the diameter of the largest stone), number of stones, difficult CBD lithiasis (defined as presence of large bile duct stone (> 10 mm) and/or multiple stones ($\geq$ 3) and/or impacted stones[11]); (4) Angulation of the CBD: Two (2) different angulation scores were assessed (Figure 1)[13,14]; (5) Juxtapapillary duodenal diverticula; (6) Timing of recurrences (early *vs* late); (7) Use of mechanical lithotripsy (ML); (8) Number of ERCP session required to clear the Bile Duct; and (9) Past medical history: Surgical (mainly hepatobililiary/ pancreatic): (1) Biliary - enteric anastomosis (BEA); (2) Altered stomach anatomy (gastrectomy or other); and (3) Cholocystectomy/remaining gallbladder (gallbladder that was not surgically removed, termed gallbladder *in situ*)/ gallbladder stones (chololithiasis).

Stone recurrence, for the purpose of this study, was defined by the confirmation of the presence of a CBD stone in the appropriate clinical context at least 6 mo after previous (complete) CBD stone removal by ERCP was achieved. Thus we evaluated only clinically significant recurrences (patients exhibiting relevant hepatobiliary symptoms like pain and jaundice).

Multiple recurrences were defined as 2 or more stone recurrences after the first ERCP. In this study early recurrence was defined as a recurrence that occurred up to (and including) 24 mo after the baseline ERCP that CBD patency was achieved (this term applies only to first recurrence episodes). A recurrence after the first 24 month was termed a late one.

Follow-up
Clinical and laboratory data potentially associated with common bile duct (CBD) stone recurrence were retrospectively retrieved from patients' files. Our department belongs in a tertiary hospital. Our hepatobiliary unit acts as regional referral center. The likelihood of patients being referred to another unit would be truly improbable.

Statistical analysis
Clinical and ERCP related factors that might have contributed to the recurrence of common bile duct stones were evaluated. All these parameters were correlated with recurrence, initially by using univariate analysis. Continuous variables were expressed as mean ± SD and were compared by using Student's *t*-test. Categorical variables were expressed as percentages and differences between groups were tested for significance by using the χ^2 test. Variables found to be significant in the univariate analysis (*P*-value less than 0.05) were included in a multivariate stepwise logistic regression model. All analyses were conducted by using statistical software SPSS, version 20 (SPSS, Inc, Chicago, IL,
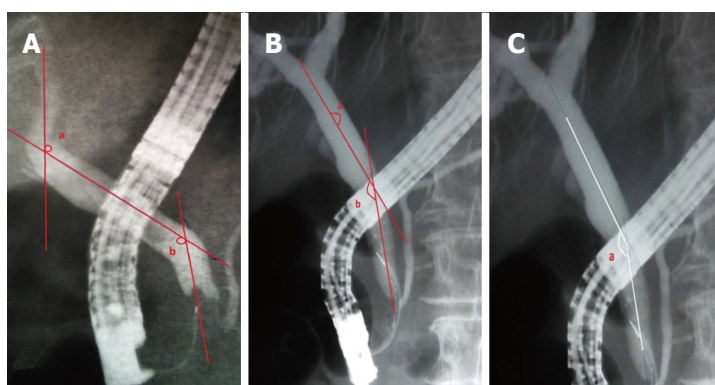
Figure 1 Common bile duct angulation calculation methods. Accumulative score (A and B): The axis (red line) runs through the center of the CBD. Each internal angle was measured at the angulation of the proximal (A) and distal (B) bile duct level respectively. The values of both angles were added (A + B). If either part of the CBD was not angulated a set score of 180 was used[13]. Minimal angle score (C): Angulation (A) was measured as the sharpest angle along the CBD from 1 cm below the bifurcation to 1 cm above the papilla[14]. CBD: Common bile duct.
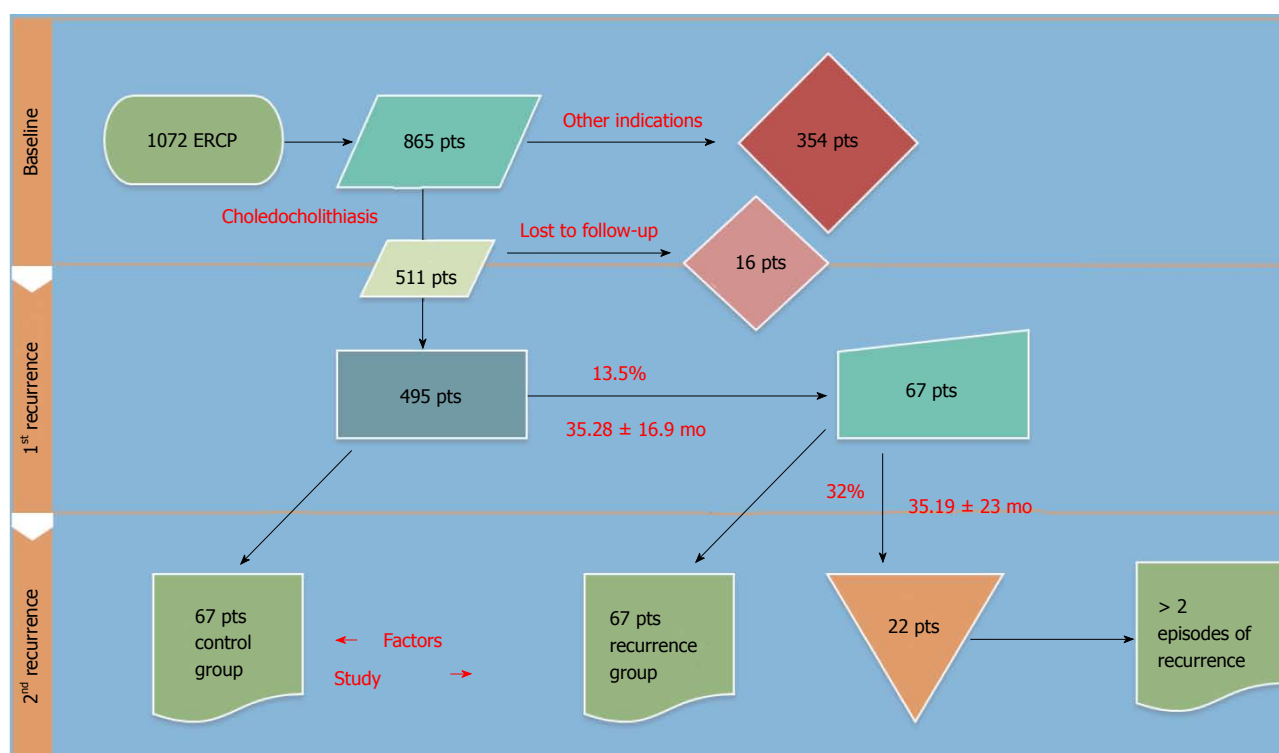

Figure 2 Study flowchart. ERCP: Endoscopic retrograde cholangiopancreatography.

RESULTS

Between January 2005 and (including) December 2008, 511 unique patients were treated in our center for choledocholithiasis/microcholedocholithiasis (Figure 2). All symptomatic recurrences for the study period (until December 2015) were recorded, after applying exclusion criteria. Sixteen patients that were lost to follow - up were dropped from the study. Sixty-seven (67) out of 495 patients (13.5%) presented with recurrent symptomatic choledocholithiasis after 35.28 ± 16.909 (7-96) mo while twenty-two (22) of these patients (32.83% of the recurrent) experienced a second recurrence after 35.19 ± 23.22 (9-78) mo. A 3rd recurrence occurred to 6 (8.9%) of the recurrent patients at 16.83 ± 15.3 mo (Table 1).

The number of procedures/ERCPs required to treat the recurrent population (baseline ERCP, recurrence examinations including any follow-up procedures that were required to achieve CDB patency) is summarized in Table 2. An impressive total of 199 ERPCs was required to treat the 67 recurrent patients over time. On the other hand for the 67 controls a total of 89 ERCP sessions was needed.

Early recurrences (recurrence during the first 24 mo after the baseline ERCP) occurred in 21/67 patients (46/67 late).

Multiple recurrences occurred in 22 patients (Table 1). We have found that an early recurrence predisposes to multiple recurrences more often than a late one. Thirteen (13) out of the 21 early recurrent patients (13/21) had a second recurrence, while only 14/46 of those with late recurrence suffered from a second episode ($P = 0.0025$).

For the purpose of studying risk factors, the 67 patients with a history of symptomatic recurrence were

United State).

Table 1 Number and percentage of patients who experienced one or more (up to five) symptomatic recurrences

No. of recurrences	Patients (*n* = 67) *n* (%)
1	45 (67.1)
2	16 (23.8)
3	4 (5.9)
4	1 (1.5)
5	1 (1.5)

Most of the patients experienced only a single episode (67%).

Table 2 Number and percentage of endoscopic retrograde chol-angiopancreatography required to treat patients with recurrence

No. of ERCP sessions	Patients (*n* = 67) *n* (%)
2	31 (46)
3	16 (23.8)
4	13 (19)
5	5 (7.46)
6	2 (2.98)

ERCP: Endoscopic retrograde cholangiopancreatography.

Table 3 Baseline characteristics of the study groups

Variable	Recurrence group (*n* = 67)	Control group (*n* = 67)	*P* value
Age, yr	71.2 ± 12.4	71.9 ± 12.6	0.82
Sex, male	26/67	28/67	0.86
History of cholecystectomy before first ERCP	37	40	0.73
BEA/gastric surgery	4 (2 billroth, 2 BEA)	2 (1 billroth, 1 BEA)	0.68
Mean follow-up time, mo	70,1 ± 31.7 (2-121)	68.5 ± 36.1 (1-129)	0.8

Recurrence group: Patients with a history of recurrent common bile duct stones; Control group: Patients with a history of non recurrent common bile duct stones; BEA: Biliary enteric anastomosis.

compared to a group of 67 age/gender - matched control patients that were selected from a pool of 428 patients with a recurrent free history. Baseline characteristics for both groups are presented in Table 3.

No significant differences were found with regard to age, sex, previous surgical history (including cholecystectomy before the baseline (first) ERCP and biliary, gastric surgery) and mean follow -up time between the groups.

Table 4 summarizes the risk factors for recurrence that were evaluated.

Logistic regression analyses were performed to identify the risk factors for stone recurrence, including both baseline characteristics and ERCP-related parameters. Univariate analysis revealed that diameter of the CBD, size (diameter) of the largest CBD stone, use of ML and difficult lithiasis were associated with stone recurrence. Multivariate analysis revealed that CBD diameter was the only independent risk factor associated with CBD stone recurrence (OR = 1.116, 95%CI: 1.005-1.277, *P* = 002).

DISCUSSION

The recurrence of CBD stones is a possible outcome following endoscopic clearance[5,6]. Rates of recurrence in the literature vary with some authors estimating them being as high as 24%[8-10]. So although it is considered a late complication of stone extraction, it certainly is not a rare one. Many authors report that most recurrences of bile duct stones take place in the first 3 years[15,16], the limit between recurrence and residual stone disease is somewhat arbitrary with many authors advocating for the threshold of 5[16] to 6[15] mo.

Bile duct stones (and as a result also recurrent stones) are classified as primary or secondary stones, both with different pathogenesis and etiologies[17]. A stone is termed primary when located at the site of its formation, while a secondary stone is a stone that has migrated from the site of its origin (in this case usually the gallbladder). Thus, primary CBD stones form de novo in the CBD, these are usually brown pigment (calcium bilirubinate) stones, where they remain either uneventfully or until they are implicated in a clinical sequela (*e.g.,* cholangitis)[18]. Secondary CBD stones are commonly associated with migrating gallbladder (or rarely intrahepatic) stones and thus consist mainly of cholesterol.

There's a plethora of risk factors related with recurrence of choledocholithiasis proposed in the literature; many of these are summarized in Table 5.

The putative mechanism responsible for stone recurrences still eludes us. In some cases, like secondary CBD stones in patients with concurrent chololithiasis, the underlying cause is in most probability also the most obvious one (*i.e.,* stone migration from the stone-ridden gallbladder to the CBD). After reviewing the literature it is obvious that there is no consensus reached in the scientific community on the exact mechanism. We could argue that at the present there are two dominating theories.

Endobiliary bile stasis (endo - Bi.S.)[18,19,22,31]

The term endobiliary bile stasis encloses a variety of risk factors that predispose to biliary stasis, delayed biliary emptying and/or impaired biliary flow. Acute distal CBD angulation, oblique CBD angulation, CBD dilation, periampullary diverticula, billiary strictures, papillary stenosis, cirrhosis, cholocystectomy, possibly genetic factors (like variations of the ABCB4, ABCB11 genes) have been associated with biliary stasis and the formation of primary CBD stones and their recurrence. Mechanical obstruction/blockage as well as variations in the (patho)physiology of bile secretion (bile viscosity, bile secretion rate, loss of bile flushing due to cholocystectomy) could help to explain why a bile duct system exhibiting any number of these anatomic/physiology abnormalities could be predisposed to stone recurrence.

Table 4 Parameters of the first endoscopic retrograde cholangiopancreatography/risk factors for recurrence in patients with or without a history of recurrent common bile duct stones

Variable	Recurrence group (n = 67)	Control group (n = 67)	P value
Stone size, mm	11.0 ± 7.0	7.5 ± 4.5	0.007
Stone number, n	4.9 ± 4.4	4.3 ± 4.7	0.53
CBD diameter, mm	16.03 ± 6.1	12.0 ± 4.6	0.001
CBD angulation method 1 (accumulative score)	303.97 ± 34.41	304.84 ± 31.61	0.91
CBD angulation method 2 (minimal angle score)	137.03 ± 17.0	138.41 ± 14.18	0.71
Difficult bile duct stones	24	14	0.04
Use of mechanical lithotripsy	13	5	0.04
No. of ERCP sessions required to clear the bile duct	1.33 ± 0.6	1.34 ± 0.7	0.95
More than one ERCP needed to clear the bile duct initially	14	11	0.43
Gallbladder *in situ*	2	5	1
Periampullary diverticula	25	16	0.066

Gallbladder *in situ* (remaining gallbladder): Patients who did not/could not conform to the instructions to perform cholocystectomy after the first ERCP, or a cholocystectomy was not indicated. ERCP: Endoscopic retrograde cholangiopancreatography; CBD: Common bile duct.

Table 5 Risk factors for recurrence of choledocholithiasis proposed in the literature

Proposed risk factor	Ref.	Comment section
DBR	[19-21]	DBR
Pneumobilia	[19]	Indicative of DBR
Acute distal CBD angulation	[19]	Promotes bile stasis
CBD dilation	[19]	Promotes bile stasis
Periampullary diverticulum	[19]	Promotes bile stasis
Prior EST	[22,23]	Promotes DBR
Intact gallbladder with stones *in situ*	[22]	(Secondary) stone CBD migration
Billiary stricture	[22]	Promotes bile stasis
Papillary stenosis	[22]	Promotes bile stasis
ML	[22]	Small residual microlithiasis acts as nidi for stone formation
Stone size	[24]	Size of the largest stone
Cirrhosis	[22]	Delayed biliary emptying/bile stasis
Delayed biliary emptying	[22]	Promotes bile stasis
Bacterial infection/colonization of the CBD. Bacterial count	[25,26]	Promotes chronic infection, and inflammation, promotes stone formating
Impaired biliary flow	[25]	Scintigraphic study
Cholecystectomy (without stones)	[27]	Impede flushing of nidus/residual stones
Post-procedural sphincter function impaired	[6,27]	EST *vs* EPBD/EPLBD *vs* EPSBD, promote DBR
Number of sessions to clear duct at first presentation	[6]	# of ERCPs required to achieve a patent CBD
Age	[6]	Old age
Previous cholecystectomy (open or lap)	[6]	
Serum lvls of chol	[24]	Lithogenic properties
EST size	[24]	Minimal size is protective
Inflammation CBD	[24]	
Parasites of the CBD	[24]	Parasitic infection
Foreign bodies in the CBD	[24]	
Concurrent cholecystolithiasis and cholelithiasis	[28]	
Post stone removal CBD diameter	[21]	At 72 h after stones removal, cholangiogram *via* nasobiliary tube
EPLBD > 10 mm	[29]	Disruption of SO, DBR
Variations of the *ABCB4*, *ABCB11* genes	[30]	Affect composition of bile. Associated with cholestasis, cholelithiasis and formation of primary intrahepatic stones
Excessive dilation of the CBD	[31]	Recurrence rate was 40% when maximum CBD diameter was more than 20 mm, whereas recurrence rate was 18% when maximum CBD diameter was 20 mm or less

The level of evidence varies. DBR: Duodenal-biliary reflux; CBD: Common bile duct; EST: Endoscopic sphincterotomy; ML: Mechanical lithotripsy; EPBD: Endoscopic papillary balloon dilation; EPLBD: Endoscopic papillary large balloon dilation; EPSBD: Endoscopic papillary small balloon dilation; ERCP: Endoscopic retrograde cholangiopancreatography; Llv: Level; Chol: Cholesterol; SO: Sphincter of Oddi.

Duodenal - biliary reflux[6,19-23,27]

This term encompasses a number of factors that are associated with the reflux of enteric contents (fluid and/or solid chime) inside the biliary tract. Pneumobilia[19], post-procedural impaired sphincter function (EST/ EPLBD), bacterial infection/colonization of the CBD, EST size are all factors that have been related to duodenal reflux. Recent studies have drawn our focus towards the role that post - procedural sphincter functional adequacy has in Duodenal - Biliary Reflux (DBR) in particular and in

stone recurrence in general. It has been suggested that sphincter preserving procedures (small size EST, EPSBD) exert a protective role, reducing the risk of recurrence. Permanent sphincter function disruption by EST or EPLBD could result in duodenobiliary reflux.

The underlying pathogenesis of stone recurrence is not yet fully elucidated. To a great extent clinical practice has proceeded basic research[32]. A multifactorial model where chronic inflammation of the bile ducts plays a central role could help to better explain it. Bile stagnation, reflux of duodenal content, bacterial colonization and chronic infection of the CBD as well as mechanical and chemical damaging effects of chronic irritants (from the enteric content) could all contribute to sustain chronic inflammation[25,26].

In our study we found that CBD dilation, stone size at first presentation, difficult lithiasis and use of mechanical lithotripsy were all risk factors for stone recurrence in the univariate analysis. These findings are similar to those of previous reports[6,19,22,24,31]. We could argue that large stone size, presence of difficult lithiasis and need for mechanical lithotripsy is all different aspects of the same factor. In a way they serve to prove that patients with certain "unfavorable stone characteristics" recur more often than others. Multivariate analysis revealed that the diameter of the common bile duct was the only independent risk factor associated with stone recurrence. It has been suggested before that CBD dilation above a certain threshold (13 mm)[21] and especially excessive dilation (> 20 mm)[31] predispose to stone reformation. In our study, the issue of a cut-off value of CBD diameter that predisposes to higher rates of recurrence was addressed but we did not reach a statistically significant result (probably due to the sample size). Periampullary diverticula showed a trend towards significance in our study (P = 0.066), unlike the clear association reported by other authors[19,29]. This is probably so because of the small sample in our study.

It has been proposed that patients with recurring CBD stones are at increased risk for a subsequent recurrence[7]. Data from our study is also in support. Patients who suffered from a recurrence were in a much greater danger. Thirty-two percent of the recurrent population had at least a second episode, while the recurrence rate for a patient who has not experienced a recurrence before was 13.5%. Data from the aforementioned study[7] identified an interval of ≤ 5 years between initial EST and repeat ERCP as a risk factor for re - recurrence. Likewise, patients from our cohort who suffered from an early (≤ 24 mo) recurrence attack, were at increased risk for consequent episodes.

There are several limitations in this study including its retrospective design, single-center site and the relative small sample size. We acknowledge that because of both the retrospective design and the often asymptomatic nature of CBD stones, several methodological issues concerning mainly the follow-up of patients and data collection could arise. A prospective multi center cohort study needs to be conducted to investigate further the association between these risks factors and stone recurrence. This study needs to be powered by both a large sample size and a long follow-up (longer than five years)[29]. Last but not least future studies need to focus more on possible clinical applications. Bedside questions that need to be answered like which patients should we follow-up? Is there any patient group with specific characteristics (*e.g.,* CBD dilation above a certain threshold) that justify more intensive follow-up? What is the importance of asymptomatic stones in multi-recurring patients, can these patients benefit from pre-emptive/prophylactic ERCP, what's the hazard/benefit ratio?

In conclusion, bile duct stone recurrence is a likely late complication following endoscopic stone extraction and CBD clearance. In our study the rate of recurrent symptomatic choledocholithiasis was 13.5%. It appears to be associated with both anatomical parameters (CBD diameter) and stone characteristics (stone size, use of ML, difficult lithiasis) at first presentation.

COMMENTS

Background
Endoscopic retrograde cholangiopancreatography (ERCP) is widely accepted as the modality of choice for the endoscopic removal of bile duct stones. Endoscopic sphincterotomy (EST) since its introduction in 1974, has been extensively used for the endoscopic extraction of bile duct stones. Endoscopic techniques for stone removal are generally considered both safe and effective but, their invasive nature cannot preclude the possibility of complications.

Research frontiers
Many authors report that most recurrences of bile duct stones take place in the first 3 years the limit between recurrence and residual stone disease is somewhat arbitrary with many authors advocating for the threshold of 5 to 6 mo.

Innovations and breakthroughs
In this study, the issue of a cut-off value of common bile duct diameter that predisposes to higher rates of recurrence was addressed but the authors did not reach a statistically significant result (probably due to the sample size). Periampullary diverticula showed a trend towards significance in the study (P = 0.066), unlike the clear association reported by other authors.

Peer-review
This manuscript is very well designed, the authors did a great effort in selecting the articles to be included in the meta-analysis with a proper quality scoring of selected articles. This manuscript is suitable for publication.

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ORIGINAL ARTICLE

Retrospective Study

Essential role of small bowel capsule endoscopy in reclassification of colonic inflammatory bowel disease type unclassified

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Institutional review board statement: This retrospective study was performed without direct contact with either patients or providers and no individual patient information was revealed. Therefore this study was not previously reviewed by the Local Ethics Committee.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to procedure by written consent.

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at sara.s.o.monteiro@gmail.com. Consent was not obtained but the presented data are anonymized and risk of identification is low.

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Abstract

AIM
To evaluate the role of small bowel capsule endoscopy (SBCE) on the reclassification of colonic inflammatory bowel disease type unclassified (IBDU).

METHODS
We performed a multicenter, retrospective study including patients with IBDU undergoing SBCE, between 2002 and 2014. SBCE studies were reviewed and the inflammatory activity was evaluated by determining the Lewis score (LS). Inflammatory activity was considered significant and consistent with Crohn's disease (CD) when the LS $\geq$ 135. The definitive diagnosis during follow-up (minimum 12 mo following SBCE) was based on the combination of clinical, analytical, imaging, endoscopic and histological elements.

RESULTS
Thirty-six patients were included, 21 females (58%) with mean age at diagnosis of 33 ± 13 (15-64) years. The mean follow-up time after the SBCE was 52 ± 41 (12-156) mo. The SBCE revealed findings consistent with significant inflammatory activity in the small bowel (LS $\geq$ 135) in 9 patients (25%); in all of them the diagnosis of CD was confirmed during follow-up. In 27 patients (75%), the SBCE revealed no significant inflammatory activity (LS < 135); among these patients, the diagnosis of Ulcerative Colitis (UC) was established in 16 cases (59.3%), CD in 1 case (3.7%) and 10 patients (37%) maintained a diagnosis of IBDU during follow-up. A LS $\geq$ 135 at SBCE had a sensitivity = 90%, specificity = 100%, positive predictive value = 100% and negative predictive value = 94% for the diagnosis of CD.

CONCLUSION
SBCE proved to be fundamental in the reclassification of patients with IBDU. Absence of significant inflammatory activity in the small intestine allowed exclusion of CD in 94% of cases.

Key words: Inflammatory bowel disease; Inflammatory bowel disease type unclassified; Capsule endoscopy; Crohn's disease; Lewis score; Reclassification

Core tip: This is a retrospective study to evaluate the role of small bowel capsule endoscopy (SBCE) on the reclassification of colonic inflammatory bowel disease type unclassified (IBDU). The SBCE revealed findings consistent with significant inflammatory activity in the small bowel, Lewis score (LS) $\geq$ 135, in 9 patients (25%); in all of them the diagnosis of Crohn's disease (CD) was confirmed during follow-up. In 27 patients (75%) without significant inflammatory activity (LS < 135), the diagnosis of ulcerative colitis was established in 16 cases (59.3%), CD in 1 case (3.7%) and 10 patients (37%) maintained a diagnosis of IBDU during follow-up.

INTRODUCTION

The differential diagnosis of Crohn's disease (CD) and ulcerative colitis (UC) relies on a combination of clinical, analytical, imaging, endoscopic and histologic data[1,2]. In 5% of patients with inflammatory bowel disease limited to the colon is not possible to establish a definitive diagnosis into CD or UC[3]. In 1978, Price introduced the concept of indeterminate colitis to describe cases in which colonic resections had been undertaken for chronic inflammatory bowel disease but a definitive diagnosis of either of UC and CD was not possible[4]. In 2005, the Montreal Working Party proposed that the term "indeterminate colitis" should be reserved for patients in whom surgical specimen is available and the term "colonic IBD type unclassified" (IBDU) for patients with no surgical specimen available and for whom the endoscopy is inconclusive and histology reveals chronic inflammation with absence of definite diagnostic features of either CD or UC[5]. Actually, for most patients, IBDU represents a temporary diagnosis, as it has been estimated that 80% of them will be reclassified to either CD or UC within 8 years[6].

The correct diagnosis of inflammatory bowel disease is extremely important to define prognosis, therapeutic orientation and surgical intervention[7,8]. Since Small Bowel Capsule Endoscopy (SBCE) enables a direct endoscopic visualization of throughout the small intestine with higher diagnostic yield compared to conventional endoscopy or imaging studies[9,10], it may be expected to contribute for the reclassification of IBDU. We report a multicenter study that aimed to evaluate the role of SBCE to reclassify patients with IBDU.

MATERIALS AND METHODS

We performed a multicenter study including consecutive patients undergoing SBCE between 2002 and 2014 for IBDU, ASCA negative/pANCA negative.

All patients had undergone an ileocolonoscopy prior to SBCE. Inclusion criteria were as follows: Patients with clinical features of chronic IBD, without previously known small bowel involvement, in whom endoscopic type and/or distribution of lesions did not allow a definite diagnosis of CD or UC, microscopy indicating active and patchy transmucosal chronic inflammation with minimal or moderate architectural distortion and absence of unequivocal diagnostic features for either CD or UC, after exclusion of infectious colitis[5]. Subjects were excluded from entering the study if they had nonsteroidal anti-inflammatory drugs intake within 4 wk prior to capsule endoscopy[11], clinical or imaging evidence of bowel stenosis or occlusion, or a follow-up of less than 12 mo.

Patients underwent SBCE with PillCam® SB1/SB2/

Table 1 Demographics and clinical characteristics of the inflammatory bowel disease type unclassified patients

No. of patients, *n* (%)	36 (100)
Gender	
Female	21 (58.3)
Male	15 (41.7)
Age (yr) (mean ± SD) at diagnosis	33.2 ± 13.1 (15-64)
Age (yr) (mean ± SD) at SBCE	35.9 ± 13.3 (18-64)
Device (no. patients), *n* (%)	
PillCam® SB1	13 (36.1)
PillCam® SB2	16 (44.4)
PillCam® SB3	1 (2.8)
Mirocam®	5 (13.9)
Endocapsule®	1 (2.8)
Gastric transit time (min)	38.6 ± 44.7 (2–257)
Small bowel transit time (min)	290.4 ± 101.5 (52-480)
Incomplete SBCE	1 (2.8)
Capsule retention	0
Follow-up (mo) before SBCE	30.2 ± 29.9 (1-108)
Follow-up (mo) after SBCE	51.9 ± 40.5 (12-156)

IBDU: Inflammatory bowel disease type unclassified; SB: Small bowel; SBCE: Small bowel capsule endoscopy.

SB3 (Given® Imaging, Yoqneam, Israel), Endocapsule® (Olympus Medical Systems Corporation, Tokyo, Japan) or Mirocam® (Intromedic Co., Ltd., Seoul, South Korea) receiving a clear liquid diet the day before capsule ingestion and an overnight 12 h fast. No bowel purge was administered prior to capsule ingestion.

SBCE videos were reviewed by two experienced gastroenterologists in each center. In case of disagreement, the findings were reviewed by investigators until a consensus was reached. Inflammatory activity was objectively assessed by determining the Lewis score (LS)[12]. Inflammatory activity was considered significant and consistent with CD when the LS $\geq$ 135[13].

The mean, SD, and range were calculated for continuous data. Categorical data analysis was conducted using the Fisher exact test. Data analysis was performed using SPSS version 20.0 (IBM, Armonk, New York, United States). Test characteristics were determined using a 2 × 2 table and calculating the sensitivity, specificity, positive predictive value and negative predictive value.

Statistical significance was considered when the *P* value was less than 0.05.

RESULTS

A total of 36 consecutive patients with IBDU underwent SBCE procedures between October 2002 and August 2014, with a mean follow-up before the exam of 30 mo (1-108 mo).

The mean age of patients at the time of diagnosis of IBDU and at time of SBCE was 33 years and 36 years, respectively, with 58% being of female gender.

Table 1 summarizes the demographic and clinical characteristics of the study population. The capsule was ingested without difficulty by all of the 36 subjects. There were no cases of capsule retention or reported adverse events in any of the subjects included in this study.

A complete small-bowel examination was achieved in 97.2% of studies. The mean follow-up after SBCE was 52 mo (12-156 mo).

At the moment of SBCE thirty four patients had clinically active disease and received anti-inflammatory treatment, as summarized in Tables 2 and 3. SBCE revealed small bowel lesions in 13 of patients (36.1%) and 23 (63.9%) patients had no lesions detected on SBCE. The distribution of the lesions in the small intestine were as follows: Two patients had multiple ulcerations ($n \geq 8$) throughout the entire small bowel, 1 patients had ulcerations in first and second tertiles, 1 patient had ulcerations only in the second tertile, 5 patients had multiples ulcerations in the third tertile. In 4 patients the capsule revealed subtle findings of focal edema in a single short segment of the small bowel (Table 2).

Nine patients (25%) had inflammatory lesions considered significant (LS $\geq$ 135) and consistent with a diagnosis of CD (Table 2). In 4 of those patients (44.4%) a subsequent ileocolonoscopy showed, by this occasion, lesions compatible with CD in the terminal ileum and histology of colonic lesions was unspecific. In the remaining 5 patients (55.6%), the histology of colonic lesions was unspecific and ileoscopy detected no lesions.

In 27 patients (75%), the SBCE revealed no significant inflammatory activity (LS < 135). Among these patients, no lesion was detected in 23 patients and subtle lesions were found in 4 cases (Tables 2 and 3).

One patient (4.3%) with no lesions at SBCE had on follow-up a subsequent ileoscopy which revealed lesions compatible with CD (Table 3).

In 12 of 23 patients (52.2%) with no lesions at SBCE, a diagnosis of UC was established on follow-up, on average 38.3 mo after SBCE (Table 3). Four patients (25%) with a final diagnosis of UC had subtle lesions (focal edema) on SBCE (Table 2). In all of these patients the endoscopic and histological findings were consistent with the diagnosis of UC, which remained in clinical and analytical remission on follow-up.

Ten patients (27.8%) remained with a diagnosis of IBDU after a mean follow-up of 42 mo (Table 3). Considering the endoscopic criterion of significant inflammatory activity to predict a diagnosis of CD, using a cut-off for LS $\geq$ 135[13], it would result in no false positive and only one false negative examinations, corresponding to a sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 90%, 100%, 100% and 94%, respectively.

In 6 of 9 patients (66.7%) with significant inflammatory activity detected in SBCE, the treatment during the follow-up was escalated to immunosuppressive drugs or biological therapy (Table 2). In 3 of 16 (18.8%) patients with a definitive diagnosis of UC and in 4 of 10 (40%) patients who remained with a diagnosis of IBDU on follow-up, a new IBD medication was introduced during the follow-up.

The start of treatment with thiopurines and/or biologics in patients who were previously naïve to those medications

Table 2 Clinical characteristics and outcome of the patients with positive small bowel capsule

Case	Sex	Age	SBCE Findings	LS	Treatment pre-SBCE	Treatment post-SBCE	Diagnostic at follow-up
1	F	38	Multiple jejuno-ileal ulcerations	1404	5ASA	5 ASA + AZT	CD
2	F	18	Ulcer (n = 1) and edema of 3° tertile	143	AZT	Anti-TNF	CD
3	M	23	Ulcer (n = 1) and edema of 3° tertile	143	5ASA	5ASA	CD
4	F	20	Ulcerations (n = 2) and edema of 3° tertile	233	5ASA	5ASA	CD
5	F	33	Ulcer (n = 3) of 2° tertile	225	5ASA	5ASA	CD
6	F	19	Multiple ulcerations and edema of 3° tertile	908	5ASA	AZT	CD
7	M	60	Focal edema of 1° tertile	8	No treatment	5ASA	UC
8	M	22	Multiple jejuno-ileal ulcerations	2080	5ASA	5ASA + AZT	CD
9	F	32	Multiple ulcerations and edema of 3° tertile	908	5ASA	AZT	CD
10	F	27	Focal edema of 3° tertile	8	Prednisolone	anti-TNF	UC
11	F	47	Focal edema of 2° tertile	8	5ASA	5ASA	UC
12	F	31	Ulceration and edema of 1° (n = 5) and 2° tertile (n = 6)	879	5ASA+Prednisolone	AZT	CD
13	M	44	Focal edema of 3º tertile	8	5ASA	5ASA	UC

5ASA: Mesalamine; anti-TNF: Anti-tumor necrosis factor drug; AZT: Azathioprine; CD: Crohn's disease; SBCE: Small bowel capsule endoscopy; LS: Lewis score; UC: Ulcerative colitis.

Table 3 Clinical characteristics and outcome of the patients with negative small bowel capsule

Case	Sex	Age	Treatment pre-SBCE	Treatment post-SBCE	Diagnostic at follow-up
1	M	45	5ASA	5ASA	IBDU
2	F	15	Prednisolone, 5ASA	5ASA	UC
3	F	27	AZT, 5ASA	AZT	UC
4	F	26	5ASA	5ASA	UC
5	M	31	5ASA	5ASA	IBDU
6	F	34	5ASA	5ASA	IBDU
7	M	21	5ASA	5ASA	IBDU
8	F	22	5ASA	5ASA, AZT	IBDU
9	F	56	5ASA	5ASA	UC
10	F	27	AZT, anti-TNF	AZT, anti-TNF	UC
11	F	30	5ASA	5ASA	UC
12	M	24	5ASA	5ASA	CD
13	M	49	5ASA	5ASA	UC
14	M	43	5ASA	5ASA	UC
15	F	30	5ASA + AZT	Anti-TNF	IBDU
16	M	24	5ASA	5ASA	UC
17	F	20	5ASA	5ASA	UC
18	M	55	5ASA	5ASA	IBDU
19	F	31	5ASA	5ASA, AZT, Anti-TNF	UC
20	F	48	5ASA	5ASA, AZT	IBDU
21	M	64	5ASA	5ASA	UC
22	M	44	No treatment	5ASA	IBDU
23	M	53	5ASA	5ASA	IBDU

5ASA: Mesalamine; anti-TNF: Anti-tumor necrosis factor drug; AZT: Azathioprine; CD: Crohn's disease; IBDU: Colonic inflammatory bowel disease type unclassified; SBCE: Small bowel capsule endoscopy; UC: Ulcerative colitis.

occurred in 6/9 (66.7%) *vs* 5/27 (18.5%) patients with or without significant inflammatory activity detected at the SBCE, respectively (P = 0.012).

DISCUSSION

Ileocolonoscopy remains the first line exam to achieve the diagnosis in patients with suspected IBD[14]. Nonetheless, ileocolonoscopy can miss CD and result in false negative results due to skip lesions throughout the terminal ileum[15].

Upper endoscopy, SBCE, computed tomography enterography (CTE) and magnetic resonance entero-graphy (MRE) can provide important information and may be useful to establish a definitive diagnosis[14].

In patients with suspected CD and negative ileocolonoscopy findings, recent European guidelines recommends SBCE as the next diagnostic exam for small bowel investigation, in the absence of obstructive symptoms or known stenosis[11].

SBCE has proven its superiority in identifying inflammatory lesions consistent with the diagnosis of CD in the small intestine when compared to CTE[9,16] or MRE[10], thus it has assumed an important role on the evaluation of patients with suspected CD[13,17-19], having a high negative predictive value for the absence of significant

inflammatory activity[13]. However, there is still limited evidence for the role of SBCE in patients with IBDU[11].

Most studies[20-22] used the non-validated diagnostic criteria for small-bowel CD proposed by Mow *et al*[23] (presence of more than three ulcerations).

Meanwhile, two scoring systems have been developed to standardize the quantification of inflammatory activity in the small bowel. The Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) is based on evaluation of the following parameters: Inflammation, extent of disease and presence of a stricture, while the LS evaluates villous appearance, ulcers and strictures[12]. The LS has shown a better performance than the CECDAI at describing small-bowel inflammation[24].

Indeed, LS has been shown a strong interobserver agreement for the determination of the inflammatory activity, and it is validated for the reporting small-bowel inflammatory activity[25,26].

In our study, the findings revealed by SBCE were consistent with a diagnosis of CD, based upon LS ≥ 135, in 9 of 36 (25%) of the subjects with IBDU, which is in line with the 16%-50% range described in other previous series[20-22,27-29]. An even higher percentage has been reported in pediatric patients[14].

In the present study, 4 patients (25%) with final diagnosis of UC had subtle small bowel lesions, such as focal edema, without a significant inflammatory activity, LS < 135, and with clinical and analytical remission during follow-up. Indeed, previous studies already reported a significantly higher frequency of small-bowel lesions in UC patients as compared with that in the control healthy volunteers[30]. The significance of the presence of these lesions and the possible risk of misdiagnosis is still indeterminate[31].

Although a negative SBCE study did not allow to definitely exclude a future diagnosis of small bowel CD, as further investigation and biopsies on follow-up led to a diagnosis of CD in one patient, the absence of significant inflammatory activity (LS < 135) in the small intestine actually allowed exclusion of CD in 94% of cases.

Based on our findings, SBCE may lead to reclassification of disease from suspected IBDU to definitive CD in 25% of cases. Furthermore, treatment with thiopurines and/or biologics was initiated more often in patients with significant inflammatory activity detected on SBCE (66.7% *vs* 18.5%, *P* = 0.012). This association suggests that capsule findings may be helpful in the clinical management of these patients, as already been proven in other series[28,32-34].

There are some limitations of this study, including its retrospective design, a limited number of subjects, and no direct comparison of SBCE with alternative small bowel diagnostic imaging, however, the last was not an aim of this study.

Nevertheless, to our knowledge this is one of the studies with larger number of patients included to evaluate this particular issue[20-22,27-29].

There are no definite diagnostic criteria for IBDU, as it must be considered a provisional diagnosis until more information (clinical, endoscopic, radiologic or pathologic) or data on follow-up enable a definitive reclassification[35]. Mucosal biopsy samples before treatment can be useful to distinguish UC from CD, but this distinction is based primarily on the pattern, type and location (distribution) of the disease, rather than specific histological features, for which there is much overlap between the two diseases[36]. Therefore, SBCE has a valuable role in the reclassification of patients with IBDU, may also contribute to establish the strategy for clinical management, and should be performed in the undefined diagnosis, which IBDU represents, in order to contribute to a definite diagnosis.

COMMENTS

Background
Colonic inflammatory bowel disease type unclassified (IBDU) is defined as a chronic idiopathic inflammatory bowel disease limited to the colon, whose combination of clinical, analytical, imaging, endoscopic and histological elements does not allow a differential diagnosis between Crohn's disease (CD) and ulcerative colitis.

Research frontiers
In patients with suspected CD and negative ileocolonoscopy findings, small bowel capsule endoscopy (SBCE) is the next diagnostic exam for small bowel investigation, in the absence of obstructive symptoms or known stenosis. Since SBCE enables a direct endoscopic visualization of throughout the small intestine, it may be expected to contribute for the reclassification of IBDU. However, the role of SBCE in IBDU has not been clearly established. In this study, the authors evaluate the role of SBCE on the reclassification of IBDU.

Innovations and breakthroughs
In this study, inflammatory activity on SBCE was objectively assessed by determining the Lewis score (LS). SBCE lead to reclassification of disease from IBDU to definitive CD in 25% of cases. Although a negative SBCE study did not allow to definitely exclude a future diagnosis of small bowel CD, as further investigation and biopsies on follow-up led to a diagnosis of CD in one patient, the absence of significant inflammatory activity (LS < 135) in the small intestine actually allowed exclusion of CD in 94% of cases.

Applications
This study suggests that SBCE is useful in the reclassification of patients with IBDU. Facing a patient with IBDU, a SBCE should be performed in order to diagnosis or exclude a CD.

Peer-review
This manuscript "Essential role of small bowel capsule endoscopy in reclassification of colonic inflammatory bowel disease type unclassified" is well written.

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Endoscopy-guided ablation of pancreatic lesions: Technical possibilities and clinical outlook

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Abstract

Endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP)-guided ablation procedures are emerging as a minimally invasive therapeutic alternative to radiological and surgical treatments for locally advanced pancreatic cancer (LAPC), pancreatic neuroendocrine tumours (PNETs), and pancreatic cystic lesions (PCLs). The advantages of treatment under endoscopic control are the real-time imaging guidance and the possibility to reach a deep target like the pancreas. Currently, radiofrequency probes specifically designed for ERCP or EUS ablation are available as well as hybrid cryotherm probe combining radiofrequency with cryotechnology. To date, many reports and case series have confirmed the safety and feasibility of that kind of ablation technique in the pancreatic setting. Moreover, EUS-guided fine-needle injection is emerging as a method to deliver ablative and anti-tumoral agents inside the tumuor. Ethanol injection has been proposed mostly for the treatment of PCLs and for symptomatic functioning PNETs, and the use of gemcitabine and paclitaxel is also interesting in this setting. EUS-guided injection of chemical or biological agents including mixed lymphocyte culture, oncolytic viruses, and immature dendritic cells has been investigated for the treatment of LAPC. Data on the long-term efficacy of these approaches, and large prospective randomized studies are needed to confirm the real clinical benefits of these techniques for the management of pancreatic lesions.

Key words: Endoscopic ablation; Radiofrequency ablation; Cryoablation; Endoscopic ultrasound-guided ablation; Ethanol; Alcohol ablation; Chemoablation; Endoscopic ultrasound; Pancreatic cancer; Endoscopic

retrograde cholagiopancreatography; Pancreatic cystic neoplasm; Pancreatic endocrine tumours

Core tip: Endoscopic ablation is a procedure with interesting potential for the treatment of locally advanced pancreatic ductal adenocarcinoma, functioning pancreatic endocrine tumours, and pancreatic cystic neoplasms in patients unfit for surgery. There is limited evidence regarding the feasibility, safety, and efficacy of such treatments. Both endoscopic ultrasound and endoscopic retrograde cholangiopancreatography have been employed to guide ablation with several chemo-physical agents (including alcohol-chemo ablation, radiofrequency ablation, and cryo-therm-ablation). However, evidence regarding the best treatment and the ideal clinical setting for ablation strategies is still lacking. In the multidisciplinary approach to pancreatic cancers, these emerging local ablation techniques will probably be the future for individualized patient treatments.

INTRODUCTION

The technical possibilities for treating pancreatic tumours under endoscopic retrograde colangiopancreatography (ERCP) and endosonographic (EUS) guidance have been evolving thanks to the development of biotechnologies applied to endoscopy. During the last 15 years, EUS has expanded more and more into a therapeutic tool and many studies have tested new probes and devices, especially in porcine models. The EUS-guided delivery of anti-tumour agents has been proposed as an alternative method to treat pancreatic cancer[1]. The concept is that if you can get in with a needle to acquire tissue, you can also insert a needle to release drugs or you can insert a probe to ablate tissues by using physical agents. Among the techniques proposed, the most promising are delivery of antitumoural drugs like TNF-erade[2], local immunotherapy with Cytoimplant[3], modified viruses[4], alcohol[5,6], and physical agents like monopolar or bipolar radiofrequency probes[7,8], cryotherm probes[9,10], and Nd:YAG laser[11,12]. All the studies carried out in *in vivo* animal models have demonstrated that the EUS-guided ablation of the pancreas is feasible, efficient and safe, but they all concluded that its clinical application in humans requires further evaluation in future studies. However, while a number of technologies for the local treatment of pancreatic masses are available, the real clinical indications and the outcomes of treatment still need to be elucidated. The current review will present different kinds of technologies, how they work, and their possible present and future applications in the treatment of different types of pancreatic lesions.

Locally advanced pancreatic cancer

Pancreatic cancer has a poor prognosis, with a 5-years survival rate < 10% for all stages[13]. Radical resection is the only treatment for resectable disease, but, unfortunately, at diagnosis only 15%-20% of patients are candidates for surgery[14]. About 40% of pancreatic cancer patients have locally advanced unresectable disease[15]. An autopsy series identified 30% of patients with pancreatic cancer who died because of locally destructive disease, without evidence of distant progression. The authors of this study concluded that the determination of *DPC4* gene status at diagnosis might play a role in the choice of patient's treatment: Systemic *vs* loco-regional[16].

Several studies have shown improved outcomes and survival when a multidisciplinary team evaluates patients[17]. In this context, EUS plays a role as a diagnostic and staging tool, but it becomes also an alternative/additional therapeutic approach to pancreatic cancer, and the gastroenterologist can join the oncology team in the treatment of patients with pancreatic cancer by administering anticancer drugs.

Patients who would benefit more from loco-regional treatment are those with unresectable locally advanced pancreatic cancer (LAPC). LAPC is defined by the National Comprehensive Cancer Network as a local disease, with no distant metastasis, with a contact with the superior mesenteric artery (SMA) or the celiac artery (CA) > 180° (head-uncinate process cancer), or a contact > 180° with the SMA or CA, or CA and aortic involvement (body and tail cancer)[18]. This vascular involvement makes the surgery ineffective and impossible even in case of small solid masses. Usually, LAPC is classified into borderline resectable (< 10% of pancreatic cancers) and unresectable disease (20%-30%)[19]. The American Society of Clinical Oncology Clinical Practice Guidelines suggest that "for patients who have tumours that are anatomically resectable but are characterized by a high likelihood of metastatic disease or margin-positive resection, a preoperative strategy is appealing because the results of an initial surgical strategy are particularly poor"[20].

A local ablative treatment that allows selective destruction of the tumour might improve the efficacy of chemo-radiation therapy in patients with vascular involvement that precludes resection as a first treatment (Table 1). EUS-guided ablation allows a minimally invasive approach to target pancreatic lesions that are extremely difficult to reach by a percutaneous approach by obtaining real-time imaging.

Pancreatic neuroendocrine tumours

Pancreatic neuroendocrine tumours (PNETs) are usually

Table 1 Characteristics and findings of studies of endoscopy-guided ablation for locally advanced pancreatic adenocarcinoma

Ref.	Year	No.	Endoscopy technique	Type of ablation	Stage of PDAC *n* (%)	Median survival (mo)	Complications *n* (%)	Response rate *n* (%)
Chang *et al*[3]	2000	8	EUS-FNI	EUS-FNI Cytoimplant	4 (50) II 3 (37) III 1 (12.5) IV	13.2	8 (86) fever, 3 (37.5) GI toxicities, 3 (37.5) hyperbilirubinemia	3 (37) PR
Irisawa *et al*[85]	2007	7	EUS-FNI	EUS-FNI DCs	7 (100) IV	9.9	None	1 (14) CR 3 (43) PR
Hirooka *et al*[86]	2009	5	EUS-FNI	EUS-FNI DCs plus systemic GEM	5 (100) III	15.9	None	1 (20) PR
Hecht *et al*[4]	2003	21	EUS-FNI	ONYX-015 plus systemic GEM	3 (48) III 2 (52) IV	7.5	2 (10) sepsis, 2 (10) duodenal perforation, 2 (10) cystic fluid collection, 1 (5) fever	2 (10) PR
Hecht *et al*[87]	2012	50	EUS-FNI or percutaneous	TNFerade plus radiation and 5-FU	(100) III	13.2	6 (12) GI bleeding, 6 (12) deep vein thrombosis, 2 (4) pulmonary embolism, 9 (18) abdominal pain, 2 (4) pancreatitis, 1 (2) cholangitis	1 (2) CR 3 (6) PR
Herman *et al*[88]	2013	304	EUS-FNI or percutaneous	TNFerade plus radiation (180 pts) and 5-FU *vs* radiation and 5-FU (90 pts)	NR (Unresectable PDAC)	10 (the same in two groups) NR (7 pts alive at 6 mo and 2 at 12 mo)	34 (20) *vs* 10 (11) GI toxicities grade 3-4, 60 (33) *vs* 32 (35) hematologic toxicities grade 3-4, 22 (12) *vs* 7 (10), non-GI/nonhematologic toxicities (*e.g.*, fever, fatigue) grade 3-4	8 (8.2) *vs* 6 (12) PR 3 PR
Hanna *et al*[89]	2012	9	EUS-FNI or percutaneous (TC-guided)	BC-819	8 (88.9) III 1 (10.1) IV		4 (44) gastrointestinal disorders, 2 (22) abdominal pain, 1 (11) influenza like illness, 1 (11) fatigue, 2 (22) back pain, 2 (22) hypertension 2 (22) metabolic disorders, 1 (11) syncope	
Facciorusso *et al*[81]	2016	123	EUS-FNI	CPN plus ethanol (65 pts) *vs* CPN alone (58 pts)	25 (20.4) IV 98 (79.6) III	8.3 *vs* 6.5	16 (25) *vs* 14 (24) diarrhoea 31 (48) *vs* 11 (19) fever	NR
Waung *et al*[51]	2016	3	EUS-guided	RFA	3 (100) III	NR	30 (46) *vs* 20 (34) abdominal pain None	NR (14% mean reduction in size)
Song *et al*[48]	2016	6	EUS-guided	RFA	4 (67) III 2 (33) IV	NR	2 (33) abdominal pain	NR
Figueroa-Barojas *et al*[44]	2013	22	ERCP-guided	RFA	7 III plus 16 CHR 1 HGD IPMN	NR	5 (23) (1 pancreatitis post ERCP with cholecystitis, 5 abdominal pain)	NR
Kallis *et al*[45]	2015	69	ERCP-guided	RFA plus SEMS stenting (23 pts) *vs* SEMS stenting alone (46 pts)	100% III	7.5 *vs* 4.1	1 (1.4) cholangitis, 1 (1.4) asymptomatic hyperamylasaemia	NR

PDAC: Pancreatic ductal adenocarcinoma; EUS: Endoscopic ultrasound; ERCP: Endoscopic retrograde cholagiopancreatography; EUS-FNI: Endoscopic ultrasound fine-needle injection; RFA: Radiofrequency ablation; CHR: Cholangiocarcinoma; DCs: Dendritics cells; GEM: Gemcitabine; IPMN: Intraductal papillary mucinous neoplasia; SEMS: Self-expandable metal stent; NR: Not reported; CR: Complete response; PR: Partial response; 5-FU: 5-fluorouracil; CPN: Celiac plexus neurolysis; GI: Gastrointestinal; HGD: High grade dysplasia.

considered rare neoplasms, but their incidence has steadily increased over the past decades[21]. Furthermore, as the prognosis of PNETs is good even in the advanced disease setting, they represent about 10% of all pancreatic neoplasms by prevalence[22]. PNETs are categorized according to their diagnosis as sporadic or as genetically determined in the setting of inherited syndromes. They are further classified depending on the disease stage and histological grade, which depends on ki67 immunostaining, and, from a clinical viewpoint, based on the presence or absence of symptoms due to the secretion of hormones. Functioning PNETs produce hormones such as insulin, gastrin, and glucagon that can determine specific syndromes[23]. However, the majority of PNETs are non-functioning. All the above-mentioned features of PNETs are important to plan the most appropriate therapeutic strategy[24]. Most functioning PNETs present with a resectable disease and therefore have an indication for surgery. Given the high risks related with pancreatic surgery, however, some patients might benefit from alternative treatments able to reduce the symptoms due to hormone hypersecretion. Endoscopic-guided ablative techniques might therefore have a role in this setting, although limited data are available so far (Table 2).

Pancreatic cystic lesions
Pancreatic cystic lesions (PCLs) are extremely common,

Table 2 Characteristics and findings of studies of endoscopic ultrasound-guided ablation of pancreatic neuroendocrine tumours

Ref.	Year	No.	Endoscopy technique	Type of ablation	Tumour type *n* (%)	Clinical response (mo)	Complications *n* (%)	Morphological response *n* (%)
Pai *et al*[8]	2015	2	EUS guided	RFA	2 NF-PNET	NR	2 abdominal pain	Complete necrosis of NF-PNET
Armellini *et al*[49]	2015	1	EUS guided	RFA	NF-PNET G2 (the patient refused surgery)	NR	No complications	CA on CT scan (one month later)
Lakhatia *et al*[50]	2016	3	EUS guided	RFA	Symptomatic insulinomas in patients unfit for surgery	All patients asymptomatic 12 mo after the procedure	No complications	1 disease free at 8 mo, 1 residual asymptomatic disease at 12 mo, 1 CA and asymptomatic at 11 mo
Waung *et al*[51]	2016	1	EUS-guided	3 consecutive RFA sessions	Symptomatic insulinoma (resistant to medical therapy)	Asymptomatic at 10 mo FU	No complications	NR
Levy *et al*[82]	2012	8	EUS-guided or intraoperative US (IOUS) guided	Ethanol	8 (100) insulinomas	5 patients asymptomatic, 3 clinical improvement	1 minor peritumoural bleeding (IOUS)	NR
Park *et al*[83]	2015	10 (13 tumours)	EUS-guided	Ethanol	10 NF-PNETs 4 insulinomas	2 asymptomatic pts with insulinomas	3 mild pancreatitis, 1 abdominal pain	13 (61.5) CA
Paik *et al*[84]	2016	8	EUS-guided	Ethanol	2 NF-PNETs, 3 insulinomas, 1 gastrinoma, 2 SPN	4 patients asymptomatic	1 severe acute pancreatitis, 2 abdominal pain, 1 fever	6 CA
Deprez *et al*[90]	2008	1	EUS-guided	Ethanol	1 insulinoma	Asynmptomatic	Ulceration of duodenal wall	CA
Jürgensen *et al*[6]	2006	1	EUS-guided	Ethanol	1 insulinoma	Asynmptomatic	1 mild acute pancreatitis	CA
Muscatiello *et al*[91]	2008	1	EUS-guided	Ethanol	1 insulinoma		1 pancreatic necroting lesion	CA

EUS: Endoscopic ultrasound; RFA: Radiofrequency ablation; MCN: Mucinous cystic lesions; IPMN: Intraductal papillary mucinous neoplasia; SPN: Solid pseudopapillary tumours; NET: Pancreatic endocrine tumour; NF-PNET: Non-functioning pancreatic neuroendocrine tumour; FU: Follow-up; NR: Not reported; CT: Computed tomography; CA: Complete ablation.

being incidentally diagnosed in about 10% of subjects undergoing abdominal imaging[25]. EUS imaging is an important method to evaluate PCLs and to determine the internal structure such as the presence of septa, wall thickness, and mural nodules or masses[26]. The epithelium of mucinous cystic lesions of the pancreas, which include intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs), can undergo dysplastic changes ranging from benign to borderline or malignant. Others cystic lesions such as serous cystadenomas (SCA) instead have a negligible malignant potential and surgery is required only in case of mass-related symptoms[27]. As a large part of patients diagnosed with PCLs are elderly and/or not good surgical candidates, the interest in a minimally invasive approach such as an endoscopic-guided one to treat such lesions has increased considerably in the past few years (Table 3).

RADIOFREQUENCY ABLATION

Physical and biological considerations

Radiofrequency ablation (RFA) works at high local temperatures to induce irreversible cellular damage, cellular apoptosis, and the coagulative necrosis of the tissue[28]. The technical advantages of loco-regional thermo-ablative techniques, when compared to surgical procedures, are lower rates of morbidity, the preservation of healthy surrounding tissues, shorter hospital stay and overall lower costs. In addition to that, evidence supports a possible immuno-modulation with an additional overall anti-cancer effect[29]. Radiofrequencies cause hyper-thermal damage through the delivery of high energies eventually resulting in a destruction of the tumour micro-environment, damages to the cell membrane, and sub-cellular injuries[30].

It is noteworthy that cancer cells are more heat-sensitive when compared to normal tissue probably due to a higher metabolic stress, a lower thermal con-ductance, and a lower cancer microenvironment pH[31].

Inside the ablated field, three areas can be easily recognised: (1) a zone of coagulative necrosis in direct contact with the probe; (2) a surrounding peripheral zone with a sub-lethal injury (whose final destiny is either apoptosis or complete "*restitutio ad integrum*"); and (3)

Table 3 Characteristics and findings of studies of endoscopic ultrasound-guided alcohol ablation in pancreatic cystic lesions

Ref.	Year	No.	Ablative agent	Clinical diagnosis (%)	Size mm (range)	Septated cysts n (%)	Follow-up months (range)	Complications	Percentage of ablated cysts
Gan *et al*[5]	2005	25	Ethanol	MCN 56%, IPMN 12%, SCA 12%, PCs 4%, unknown 8%	19.4 mean (6-37)	7 (28)	6-12	0%	35%
Oh *et al*[72]	2008	14	Ethanol and paclitaxel	MCN 14%, SCA 2%, lymphangioma 21%, unknown 43%	25.5 median (17-52)	3 (21.4)	9 median (6-23)	AP (7%)	79%
Oh *et al*[73]	2009	10	Ethanol and paclitaxel	MCN 30%, SCA 40%, unknown 30%	29.5 median (20-68)	10 (100)	8.5 median (6-18)	AP (10%)	60%
DeWitt *et al*[75]	2009	42	Ethanol *vs* saline	MCN 40%, IPMN 40%, SCA 12%, PCs 7%	20.5 (10-40)	17 (40.5)	3-4 mo after 2nd lavage	AP (2.4%), intracystic bleeding (2.4%), abdominal pain (24%), major complications, (24%)	33% (ethanol) 0% (saline)
Oh *et al*[74]	2011	52	Ethanol and paclitaxel	MCN 17%, SCA 29% PCs 4%, unknown 50%	31.8 (17-68)	20 (38.5)	21.7 mean (2-44)	Fever (2%), AP (2%), abdominal pain (2%), splenic vein obliteration (2%)	62%
DiMaio *et al*[76]	2011	13	Ethanol	IPMN 100%	20.1 mean (13-27.2)	7 (54)	3-6 mo after 2nd lavage	Abdominal pain (15%)	38%
Park *et al*[77]	2016	91	Ethanol	Indeterminate	30 (20-50)	64 (70)	40 median (13-117)	Fever (9%), abdominal pain (20%) AP (3%)	45%
Moyer *et al*[78]	2016	10	Ethanol or saline plus paclitaxel and gemcitabine	MCN 70%, IPMN 30%, unknown 10%	30	Unilocular predominantly	12	AP (10 %)	75% (ethanol plus paclitaxel and gemcitabine) 67% (alcohol free harm)

MCN: Mucinous cystic neoplasm; IPMN: Intraductal papillary mucinous neoplasm; SCA: Serous cystadenoma; PC: Pseudocyst; AP: Acute pancreatitis.

a healthy, surrounding, non-ablated zone. The process that leads to tumoural destruction takes place in two phases: One direct and the other indirect. In fact, cellular damages occur in parallel at multiple levels, either sub-cellular and tissutal. In general, the thermal-mediated toxicity varies according to the amount of energy delivered and to the thermal sensitivity of the treated tissue. In addition, other processes, such as the loss of membrane integrity, the occurrence of mitochondrial dysfunction, and the inhibition of the replication, play also a role in the killing process[30]. Finally, indirect hits such as oxidative stress and inflammatory processes also occur. The former is due to ischemia-reperfusion injury, while the latter is due to the strong infiltration of the marginal zone by neutrophils, macrophages, dendritic cells, natural killer lymphocytes, T and B lymphocyte[32].

These inflammatory cells have been also highlighted in the blood stream at a distance from the tumour, reflecting a possible systemic, autoimmune reaction triggered by RFA and mediated by the interplay of various interleukins. The levels of heat shock proteins (particularly HSP70) seem also to be increased after RFA, being recognised as a potential early marker of good therapeutic response.

From a physical point of view, temperatures ranging between 60 ℃ and 100 ℃ are generated by high frequency alternating currents that induce frictional heating, which is also known as resistive heating.

Interestingly, temperatures above 100 ℃ are less efficient in local ablation, probably due to a process of the immediate vaporization and drying of the tissue surrounding the probe, which finally leads to a higher thermal impedance and ultimately a lower ablative efficiency.

Another limitation of RFA is the heat-shrink effect, a phenomenon occurring when the heat is absorbed by the blood stream of an adjacent vessel, dissipating hyperthermia and thus limiting the effectiveness of treatment[33].

From a technical point of view, two different types of radiofrequency probes are available on the market: Monopolar and bipolar. Monopolar probes include a gene-rator, a delivering electrode, and a dispersive electrode (ground pad). The delivering electrode releases high-density current providing localized heating. The ground pad disperses energy in order to avoid possible thermal injury on the skin. Bipolar probes include two interstitial electrodes (in the middle of which, the electrical pulses oscillate) and the ground pad. In bipolar probes, energy delivering is confined between the two electrodes with the advantage of a more rapid and focal heating, overall

with less perfusion conductance, potentially less injuries to the surrounding tissue but an overall minor ablative capacity[34].

Previous applications

RFA is a polyhedral technique, interestingly applied in many different oncological setting. Particularly it has been described for obtaining local control of lesions potentially evolving into high grade, as in cases of Barrett's oesophagus for which RFA is considered the ablative procedure of choice[35].

RFA has also been widely studied with curative intent in hepatocellular carcinoma (HCC). Currently, clinical practice guidelines for the management of HCC support the use of loco-regional ablation with RFA as a standard of care in patients with Barcelona Clinic Liver Cancer stage 0 unsuitable for surgery. Particularly, the treatment is recommended in most instances, as the ablation of masses < 5 cm leads to a significant better control of the disease[36].

RFAs have been employed elsewhere, with palliative aims, in case of lung and bone metastasis, breast, adrenal cancer, head and neck lesions, and cholangiocarcinoma[37,38].

Pancreatic applications

Despite numerous applications in different settings, pancreatic RFA *per se* has always been regarded with reluctance by clinicians, for the fear of adverse events such as thermal induced pancreatitis, thermal injury to adjacent structures (*e.g.,* the duodenum, stomach, mesenteric artery and vein, and bile duct), as well as for technical limitations, due to the fact that pancreatic cancer has generally poorly defined margins, making it difficult to ablate all the tumoural mass in a single session[39].

Although most of the clinical experiences with thermo-ablative procedures on the pancreas continue to be confined to a surgical setting[40], the potential use of an endoscopic guided approach provides undoubted advantages, such as the possibility of real-time imaging during the procedure, the ability to monitor the evolution of the treated lesion, and the possibility, compared to percutaneous approaches, to reach extremely distant and inaccessible anatomical areas[41].

On the other hand, the pancreas is a highly thermo-sensitive organ, with a potential susceptibility to iatrogenic injury leading to pancreatitis, peripancreatic fluid collections, stomach or intestinal perforation, and peritonitis, as suggested by some studies conducted on animal models[7].

In fact, initial clinical studies on animal models showed a high rate of mortality (25%). Anyway, it is noteworthy that all these preliminary studies were performed by applying high temperatures above 90 ℃ and treating large tumours[42].

Interestingly, the previous surgical experiences suggest that the iatrogenic injuries might be limited by applying some technical precautions, such as the reduction of the ablation temperature (< 90 ℃), the maintenance of a safety margin from major vessels or from the duodenum (which can also be irrigated by cold saline), and the use of a step-up approach in case of large size lesions[28,38].

So far, some studies on animal models or in small surgical human series have been performed to assess the feasibility and safety profile of the procedure.

Goldberg *et al*[7] conducted preliminary studies on the effect of RFA on normal pancreatic tissue on Yorkshire pigs (500 kHz for 6 min in order to obtain a temperature of 90 ℃). Histological examination was performed immediately after the procedure or 15 d later, showing respectively a bleeding zone surrounding the central coagulative necrotic area that after 2 wk was organized in fibrotic scar tissue.

Gaidhane *et al*[43] performed EUS-guided RFA in the normal pancreas of 5 Yucatan pigs by testing different powers (4, 5, 6 Watt), different exposure times (12-300 s) and application lengths (6 mm *vs* 10 mm). They reported no mortality and a mild pancreatitis rate of 25%, without other major complications.

For pancreatic applications, the currently available commercial probes have been designed to be used during either ERCP or EUS. ERCP probe (Habib EndoHBP catheter, EMcision London United Kingdom) has a catheter compatible with standard Duodenoscopes (3.2 mm working reeds) and can be passed over a 0.035 inch guidewire and connected to an RFA generator which delivers energy at 400 kHz (1500 RF generator; RITA Medical Systems, Inc., Fremont, CA, United States).

The clinical experience with this kind of probe comes mostly from the palliative treatment of inoperable cholangiocarcinomas, while "pure" pancreatic applications have been less extensively studied and pancreatic duct treatment has not been described so far.

Figueroa-Barojas *et al*[44] reported the palliation of obstructive jaundice, in a small series of pancreatic cancers and cholangiocarcinomas. They treated 22 patients with obstructive jaundice, including 16 with cholagiocarcinomas, 7 with stage Ⅲ pancreatic cancer and 1 with high-grade dysplasia IPMN, with RFA of the bile duct. The outcome of the study was the assessment of efficacy and safety profile. The procedure was effective in 100% of cases. Overall complications have been reported in 5 patients, 1 of whom required a surgical drainage. In contrast to what described in animal studies, no major complications on the surrounding organs were observed.

Kallis *et al*[45] performed a retrospective case-control analysis on 23 patients with malignant biliary obstruction and unresectable pancreatic carcinoma and undergoing endoscopic SEMS positioning and RFA and 46 controls (matched for sex, age, metastases, ASA score, and comorbidities). The median survival was 226 d in the RFA group *vs* 123.5 d in controls (P = 0.010). RFA was found to be an independent predictor of survival at 90 d and 180 d (respectively OR = 21.07, 95%CI: 1.45-306.64, and OR = 4.48, 95%CI: 1.04-19.30), potentially conferring a concrete early survival benefit.

Currently, three commercial probes specifically designed for EUS are available on the market[46]: (1) EUS RFA System (STARMED, Koyang, South Korea), which consists of a prototype 19 g, 140 cm long needle electrode, with an inner internal part, isolated in all its length except for the distal centimetre which delivers energy. It is provided with an internal cooling system and can be connected to a RF generator (VIVA, STARMED, Seoul, South Korea); (2) habib EUS-monopolar RFA catheter (EMcision Ltd, London, United Kingdom), which is a 1 Fr wire (0.33 mm, with a working length of 190 cm) which can be connected to RITA (Electrosurgical RF Generator). The catheter is placed through EUS control through a 19-gauge biopsy needle with a stylet and RF energy is then generally applied for 90-120 s; and (3) mixed radio-cryoablation probes, which are a flexible bipolar hybrid ablation device (ERBE Elektromedizin, Tübingen, Germany) combining bipolar RF ablation with cryotechnology.

EUS guided pancreatic RFA has been applied in small human case series (mostly stage III pancreatic cancer or neuroendocrine tumours).

Wang *et al*[47] reported a series of three patients with stage III pancreatic cancers treated by EUS guided RFA through a 22 gauge needle, delivering a 10 watts to 15 watts current for 2 min. Multiple EUS-RFA procedures were performed when needed, according to the size of tumour with a mean reduction in tumour size of 13.94%, a significant reduction in CA19-9 and without any complications.

Song *et al*[48] performed an ablation procedure by applying radiofrequency 20-50 W, for 10 s on a total of six patients with pancreatic cancer, either locally advanced (four patients) or metastatic (two patients). The procedure was successfully performed in 100% of the patients without major complications such as pancreatitis, bleeding, duodenal lesions, portal vein thrombosis, or splenoportal vein. Even in this small series, mortality was 0%.

Interestingly a preliminary application of RFA to treat pancreatic cystic neoplasms has also been recently described.

Pai *et al*[8] performed a multi-center, pilot safety and feasibility study describing RFA in eight patients, including six with cystic lesions (four mucinous cysts, one intraductal papillary mucinous neoplasm, and one microcystic adenoma) and two with neuroendocrine tumours of the pancreatic head. EUS-RFA was successfully completed in 100% of cases, with a complete resolution in 2/6 patients and a 50% size reduction in 3/6 patients with pancreatic cystic neoplasms. PNET also displayed a change in vascularity, with central necrosis after EUS-RFA. No major complications occurred. Two patients developed mild, self-limiting abdominal pain.

In addition to that, other clinical experiences with RFA of neuroendocrine tumours have been reported so far. Armellini *et al*[49] successfully treated a 20 mm G2 endocrine tumour by EUS-guided RFA in an asymptomatic 76-year-old patient who had refused surgery. The lesion was completely ablated without complications and one month computed tomography (CT) scan confirmed the efficacy of treatment.

A small series of three patients, unfit for surgery, with symptomatic neuroendocrine tumours successfully treated by EUS guided RFA has also been described by Lakhtakia *et al*[50]. No procedure related complications occurred. Similarly, Waung *et al*[51] reported the successful treatment of a symptomatic 18 mm insulinoma in a patient unfit for surgery (due to comorbidity) in which other medical treatments had failed. The patient underwent three consecutive treatments and eventually the full control of hypoglicaemic symptoms was obtained.

With a similar purpose, radiofrequency treatment has also recently been proposed as an additional treatment to endoscopic resection margins after ampullectomy, in case of recurring intraductal growing ampullary adenoma[52].

RFA for locally advanced or metastatic pancreatic cancer, functional neuroendocrine tumours and potentially in the future, pancreatic cystic tumours, through a mini-invasive ERCP or EUS-guided approach, can reasonably be an effective, not curative, cytoreductive treatment. In a multidisciplinary setting, those approaches might confer a better response to therapy, palliation of symptoms, and survival improvement in patients unfit for surgery.

CRYO-THERM ABLATION

Previous applications

A hybrid bipolar cryotherm probe (CTP) has been developed (ERBE Elektromedizin, Tübingen, Germany). The choice to create a bipolar device was sustained by the fact that bipolar systems ablate with less collateral thermal damage than monopolar systems but with the trade-off of less efficiency overall[53,54].

By combining the effects of the two technologies (RFA and cryotechnology), this flexible ablation device increases the effects of the two approaches and overcomes the disadvantage of less efficiency. It is known that the interstitial devitalization of tissues induced by radiofrequency is increased by the cooling effect of cryogenic gas[55].

Cryoablation has been used successfully for many years for the local treatment of many cancers (kidney, prostate, breast, and skin).

Besides the local tissue ablation, a systemic inflammatory response to cryoablation has been postulated as a reaction that can lead to an antitumour response, not only in the treated area, but also, in distant metastasis.

Most of these effects have been studied in mouse tumour models. Joosten *et al*[56] implanted subcutaneously two fragments of colon 26-B tumours into the thigh and flank of BALB/c mice. The thigh tumours were treated by either cryoablation or resection. Cryoablation clearly induced the inhibition of adjacent tumour growth, compared to the mere excision of the primary tumour. Plasma levels of TNF and IL-1 were significantly elevated after cryoablation. The authors concluded that cryosurgery leads to a systemic inflammatory response that can lead

to the inhibition of tumour growth. Another experiment in mice with MT-901 mammary adenocarcinoma demonstrated that cryoablation prior to surgical resection of breast cancer generated tumour specific T-cells. This immune response could be used for adjuvant adoptive cellular immunotherapy[57].

The CTP developed by ERBE is a hybrid RFA probe that is internally cooled with carbon dioxide, which allows efficient cooling because of the Joule-Thomson effect. The probe has been created on the model of a 19G needle for EUS-fine needle aspiration, with the distal tip that is sharp and stiff enough to penetrate the gastric and duodenal wall and pancreatic parenchyma with no need to apply current. The electrically active part of the CTP has a diameter of 1.8 mm.

A protective tube covers the entire probe so that it can be safely passed through the operative channel of the echoendoscope without the risk of damaging the instrument. The commercially available generator VIO 300D (ERBE) is used for power delivery, together with the ERBOKRYO CA system (ERBE) which is used for cooling. The pressure of the gas exiting through the expansion vessel, the power setting of the generator, and the duration of application can be varied independently. In the initial study in an *in vivo* animal model, the power and pressure settings were standardized according to previous laboratory experiments (respectively 16 W and 650 psi) and the application time ranged from 120 to 900 s[9]. The probe was applied under real-time EUS guidance in the pancreas of 14 pigs. Some of them received more than one application. The CTP was easily recognized during the ablation as a hyperchoic line. During the power delivery, a hyperechoic elliptic area was visualized around the distal tip of the probe, surrounded by a hypoechoic margin. The study demonstrated the ability of EUS to guide the placement of the probe and to measure the ablated area. There was a positive correlation between the size of the ablated area and the duration of application. The procedure was safe and the mortality was zero, while the morbidity was significant due to gastric wall burns and gut adhesions. There was one major complication (7%), while the overall rate for minor complications was 43%. The complications were clearly dose-dependent: The pig with the major complication (necrotic pancreatitis with peritonitis) was treated for more than 900 s.

At histological evaluation two weeks after ablation, the ablated area was clearly demarcated from the surrounding pancreatic parenchyma. An inflammatory wall with a remarkable number of lymphocytes and polymorphonucleated neutrophil granulocytes, and granulation tissue with fibroblastic reaction and new blood vessels surrounded a central necrosis (cellular debris and amorphous material).

The CTP was applied also in the liver and spleen of the pigs with no complications and with a good correlation between the application time and the size of the ablated area[58].

Pancreatic applications

Based on the results of the preliminary study in pigs, the CTP was used for the first time under EUS guidance in a pilot compassionate study in patients with LAPC with disease progression after standard chemotherapy ± radiotherapy[10].

Twenty-two patients were enrolled. The cryotherm ablation was feasible in 16 patients, but in six, it was not possible to apply the probe because of the stiffness of the gastro-duodenal wall and of the tumour due to desmoplastic reaction or fibrosis after radiation. The power (heating) was set at 18 W; the pressure (cooling) was set at 650 psi; the mean application time was 107 ± 86 s (range 10-360 s). Before the calculated application time, a computer connected to the energy delivery system automatically stopped the power when a rapid increase of electric resistance induced by fast desiccation and devitalization of the tumour tissue occurred. The probe was well visible inside the tumour and the effect of the ablation was followed under real-time EUS guidance.

There were no complications during or immediately after the ablation. Late complications were mostly related to tumour progression. One major limitation of this study is the difficulty of objectifying the size of the ablated area by CT scan. The low specificity of imaging techniques like B-mode EUS cannot distinguish between reactive oedema and the persistence of tumour. Some studies have demonstrated the role of contrast-enhanced ultrasonography (CEUS) in the surveillance of radiofrequency-ablated renal tumours[59]. Other studies have focused on the image fusion, demonstrating that the CEUS-CT/RM image fusion is feasible also intraoperatively during ablation of HCC and can improve the ablated margins by guiding supplementary ablation of margins[60]. Such good results are expected by the use of contrast-enhanced endoscopic ultrasound in the evaluation of devitalized tissues, but more studies are required.

ALCOHOL/CHEMO ABLATION

Previous applications

Ethanol is a low viscosity, cost effective chemical agent that induces coagulative necrosis, and subsequent fibrosis, small vessel thrombosis and granulomatous tissue formation[61]. It can be easily injectable through a small gauge needle. Percutaneous ethanol injection therapy, indeed, has been used for the ablation of several solid and cystic lesions.

Ethanol is the most common sclerosing material used for cyst ablation. After the initial success in the sclerosis of renal cysts[62], ethanol has been also used for the percutaneous ablation of hepatic cysts. US-guided aspiration with ethanol sclerosis is a relatively non-invasive, safe and effective procedure with low complication rates (that potentially can range from mild fever and loco-regional pain to systematic reactions

such as shock and intoxication)[61]. The 95%, 96% and 99% alcohol solutions are equally safe and effective without a dose-related adverse event[63].

Ethanol has been administered percutaneously as a safe therapeutic modality for patients with solid neoplastic lesions such as small HCC[64] and adrenal tumours[65]. In HCCs, the toxic effect of ethanol is facilitated by the hypervascularity and soft consistency of the tumour (softer compared to surrounding cirrhotic liver) that permit a selectively diffusion of alcohol within the nodule. EUS-guided fine needle injection (EIUS-FNI) is a safe and minimally invasive therapeutic EUS technique. It has been used for precise delivery of antitumour agents into target lesion. However, to date, there are few data regarding the use of chemotherapeutic and biologic agents, limited to animal feasibility studies, human case series, and phase I / II studies (see pancreatic application). As regards EUS-guided ethanol injection, it has been previously reported for celiac necrolysis[66] and more recently it has also been used for ablation of abdominal tumour such as gastrointestinal stromal tumour of the stomach[67], solid hepatic metastasis[68], metastatic pelvic lymph nodes[69], and adrenal metastatic carcinoma[70].

Pancreatic applications

EUS-guided ethanol ablation therapy: Some clinical trials of PCL ablation have been published so far (Table 3). To date, all studies about EUS-guided pancreatic cyst ablation have used a 22-gauge needle under EUS guidance to aspirate the cystic fluid. Through the needle, ethanol is injected in the collapsed cyst using a volume equal to the aspirate. The cavity can be alternately filled and emptied for 5 min[71].

Gan *et al*[5] first showed that EUS-guided ethanol injection for the ablation of pancreatic cysts is a feasible and safe procedure. They treated 25 patients with pancreatic cysts (13 MCN, 4 IPMN, 3 SCA, 3 pseudocysts, and 2 of unknown origin) and cyst resolution was achieved in 35% of patients during the follow-up (6-12 mo). Five patients (33%) underwent surgical resection and a variable degree of epithelial ablation (up to complete) was described on pathology.

Oh *et al*[72] evaluated the results of EUS-guided pancreatic cyst ablation after injection of ethanol and paclitaxel that was injected into the cyst after alcohol lavage and left in place. Paclitaxel is chemotherapeutic agent (viscous and hydrophobic) which interferes with G2 mitotic-phase cell replication by the arrest of cellular microtubule assembly.

An initial study[72] on 14 patients found that complete resolution of pancreatic cystic tumours was achieved in 11 out of 14 patients followed for more than 6 mo. After treatment, minor complications were observed in one patient (including hyperamylasemia and abdominal pain). The same authors reported the results of 10 patients with septated cysts[73]. They observed a 60% rate of complete radiological cyst resolution, proving that the presence of septations within the cyst is not an absolute contraindication to injection therapy. The same

group published a subsequent study in 2011 involving a larger population ($n = 52$)[74], reporting a complete resolution in 62% of the patients without any major complications.

DeWitt *et al*[75] conducted a randomized double-blind trial comparing ethanol with saline lavage in 42 patients. The study showed that EUS-guided lavage with 80% ethanol achieved a greater reduction in cystic size compared with saline solution injection, providing further evidence for pancreatic cyst ablation efficacy. As demonstrated by a CT scan, complete resolution was obtained in 33% of patients. Epithelial ablation was observed from 0% (with saline solution injection) to 50% or 100% (with one or two ethanol lavages, respectively) in the four patients who underwent surgery.

In 2011 the same group[76] analyzed retrospectively the efficacy of multiple EUS-guided lavages with ethanol for the treatment of pancreatic cystic tumours. The authors concluded that a complete cyst resolution was achieved in 38% of 13 patients who underwent two EUS-ethanol lavage sequential treatments.

Recently, Park *at al*[77] presented data on the longest follow-up and the largest number of patients with clinically indeterminate PCLs treated by EUS injection with 99% ethanol. They showed that the success rate of EUS-guided ethanol ablation therapy was significantly dependent upon findings of cystic fluid analyses (SCN, 58%; MCN, 50%; IPMN, 11%; uncategorized cyst, 39%; $P < 0.0001$). Another prognostic factor determining success rate of EUS-guided ethanol ablation therapy was the size of the cyst (smaller diameters had a significantly higher treatment success rate after EUS-guided ethanol ablation therapy).

Since complete ablation rates of 60%-79% have been reached in studies that added paclitaxel to ethanol, Moyer *et al*[78] recently published a prospective randomized trial pilot study (CHARM). The authors compared the efficacy of either an ablation with saline plus a chemotherapy cocktail of gemcitabine and paclitaxel or of an alcohol-free regimen with saline and the same chemotherapeutic agents in 10 patients with PLCs. Similar ablation rates were found in the two groups (a 67% complete ablation rate in the alcohol-free arm compared to 75% in the ethanol group), showing the efficacy of EUS-FNI of chemotherapeutic agents alone in treating PCLs.

Heterotopic pancreatic tissue and pancreatic tumours also have been directly injected with absolute ethanol without reported major complication as showed by porcine animal studies[79,80]. The role of contrast-enhanced EUS has been also described in a porcine model showing that this procedure can be used not only in the detection of small pancreatic lesions but also for monitoring necrosis after pancreatic tissue ablation[80]. Phase I and II studies will be necessary on this topic.

Facciorusso *et al*[81] prospectively enrolled 123 patients with advanced PDAC to compare the efficacy and safety of EUS-FNI ethanol ablation combined with EUS-guided celiac plexus neurolysis (EUS-CPN) with respect to EUS-CPN alone for pain management. They also reported data

about ablation rate of the tumour and the overall survival. At 48-h CT-scan imaging, ablation was confirmed in 55 patients (84.6%) treated with the combined approach and, at 3 mo, the response was maintained in 13 patients (20%). Moreover, a significantly longer median overall survival was observed after the combined therapy (8.3 mo *vs* 6.5 mo; *P* = 0.05).

In patients with a small endocrine tumour, EUS-guided ethanol injection could also be an alternative to surgery (Table 2). A retrospective study was conducted by Levy *et al*[82] that reported the data of eight patients with symptomatic insulinomas who received EUS and intraoperative US ethanol ablation after incomplete surgical resection. In five patients who underwent EUS-guided ethanol injection, hypoglycemia-related symptoms completely disappeared without complications.

Ethanol ablation was also successfully performed in a South Korean pilot study performed in 14 neuroendocrine tumours[83] (4 insulinomas) with a response rate of 53.8%, and three cases of mild pancreatitis were observed after treatment. After multiple treatment sessions performed in other three patients with residual enhancing tumours, the successful rate increased to 61.5%.

A recent study[84] reported a success rate of 75% in a cohort of six PNETs less than 2 cm (2 cases of non-functioning NETs, 3 cases of insulinomas, and 1 case of gastrinoma). Complete remission was obtained in five patients (the median follow-up period was 16.5 mo). Moreover, four patients with functioning NETs reported complete relief from tumour-related symptoms. Three mild adverse events were reported after the procedure: One case of abdominal pain, self-limiting fever, and acute pancreatitis each.

EUS-guided injection of anti-tumoural agents: Various anti-tumoural agents have been considered for the treatment of pancreatic adenocarcinoma trough EUS injection such as mixed lymphocyte culture, oncolytic viruses, and immature dendritic cells.

Allogenic Mixed Lymphocyte Culture (Cytoimplant): The first phase I trial was published in 2000 by Chang *et al*[3] who used EUS-FNI to deliver allogenic mixed lymphocyte culture (Cytoimplant) in eight patients with advanced pancreatic adenocarcinoma to induce cytokine production and activate the host immune effector mechanism. They reported no adverse events and a median survival of 13.2 mo, with 2 partial responses (> 50% reduction in tumour size measured on imaging) and 1 minor response (< 50%).

Immunotherapy/dendritic cells: To date two pilot trials evaluated EUS injection of immature dendritics cells to stimulate primary T-cell response against tumour antigens in 7 and 5 patients with unresectable pancreatic cancer[85,86], respectively. The first study reported a median survival of 9.9 mo with one complete response, three partial remissions while 3 out of 5 patients demonstrated effective response (1 partial response and 2 stable disease over 6 mo) in the later trial that combined systemic gemcitabine with EUS injection.

Adenovirus ONYX-015: Intravenous gemcitabine and EUS-guided ONYX-015[4] injection was observed in 21 patients with unresectable pancreatic cancers. ONYX-015 is a modified adenovirus (deletion in the E1B gene) which replicates preferentially in tumour cells, leading to cell death. In this phase I/II trial, no patients showed tumour regression with the injection alone after five weeks while two partial responses were described when administrated in combination with gemcitabine. Two patients had sepsis and two others duodenal perforation.

Tumour necrosis factor erade: Hecht *et al*[87] published a phase I/II study about the efficacy of TNFerade (replication-deficient adenovirus vector that expresses human TNF-alpha gene, which is inducible by chemotherapy and radiation) EUS injected in 50 patients with locally advanced PDAC. They reported three cases of partial response, one case of complete response and 12 cases of stable disease (median survival of 297 d). Dose-limiting toxicities were observed in three patients (pancreatitis and cholangitis). Although one case of complete pathologic response and six clear margins were observed among the seven patients surgically treated after treatment, the subsequent large randomized multi-center phase III study[88] involving 304 patients reported no survival benefit of adding intratumoural TNFerade injection to 5-fluorouracil and radiotherapy compared with chemotherapy alone.

BC-819: A phase I/II a trial[89-91] assessed the safety and tolerability and preliminary efficacy of a DNA plasmid that targets the expression of diphtheria-toxin gene under the control of H19 regulatory sequences that can potentially treat pancreatic adenocarcinoma overexpressing the H19 gene. It was injected into unresectable non-metastatic PDAC under EUS (six patients) or TC guidance (three patients). No serious major complications occurred. Two patients were successfully down-staged for surgery and three achieved partial response.

CONCLUSION

The rapid improvement in the development of devices for pancreaticobiliary endoscopy, particularly for EUS, has led to an increasing number of indications for endoscopically guided pancreatic lesions ablation. As regards pancreatic adenocarcinoma, the recent improvement of survival obtained thanks to more efficient chemotherapy regimens will most likely lead to a more widespread use of different ablative techniques, with EUS presenting the advantage of a minimally invasive technique with low risk and direct imaging of the lesions. The most efficient treatment has yet to be identified and there is a need of well-designed randomized controlled trials. Pancreatic cystic lesions are epidemic, and most of them require follow-up as potential preneoplastic lesions[25,27]. The use of cyst ablation in incidentally identified lesions or those that may not meet the criteria for surgical resection is controversial, while it could be proposed to those patients with high-risk stigmata or symptomatic pancreatic cysts who either refuse or are not fit for surgery.

In this setting, although EUS-guided ethanol injection has proved to be a safe and minimally invasive procedure, the total ablation of cystic epithelium was not always reached and it seemed less effective in IPMNs that are the most common lesions and those with a preneoplastic potential. The intracystic treatment with paclitaxel and gemcitabine is an interesting option that requires further evaluation.

EUS-guided ethanol ablation therapy for PNETs seems to be a promising technique for patients with functioning tumours who refuse or are unfit for surgery. Nevertheless one should notice that all the above-mentioned local ablative techniques are not completely free from complications. The decision to treat a pancreatic lesion by a loco-regional ablation technique can sometimes represent a very difficult task, particularly in cases of cystic lesions, demanding the need of well-trained operators and high volume centers. Clinical trials enrolling more patients with longer follow-up are required in order to better understand the complete ablation rate as well as the risk of metastasis after ablation.

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Overdiagnosis of gastric cancer by endoscopic screening

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Abstract

Gastric cancer screening using endoscopy has recently spread in Eastern Asian countries showing increasing evidence of its effectiveness. However, despite the benefits of endoscopic screening for gastric cancer, its major harms include infection, complications, false-negative results, false-positive results, and overdiagnosis. The most serious harm of endoscopic screening is over-diagnosis and this can occur in any cancer screening programs. Overdiagnosis is defined as the detection of cancers that would never have been found if there is no cancer screening. Overdiagnosis has been estimated from randomized controlled trials, observational studies, and modeling. It can be calculated on the basis of a comparison of the incidence of cancer between screened and unscreened individuals after the follow-up. Although the estimation method for overdiagnosis has not yet been standardized, estimation of overdiagnosis is needed in endoscopic screening for gastric cancer. To minimize overdiagnosis, the target age group and screening interval should be appropriately defined. Moreover, the balance of benefits and harms must be carefully considered to effectively introduce endoscopic screening in communities. Further research regarding overdiagnosis is warranted when evaluating the effectiveness of endoscopic screening.

Key words: Gastric cancer; Cancer screening; Upper gastrointestinal endoscopy; Overdiagnosis; Harm

Core tip: Overdiagnosis is the most serious harm of cancer screening and this can occur in any cancer screening programs. It is defined as the detection of cancers that would never have been found if there is no screening. Despite the lack of standardization of the estimation method for overdiagnosis, its estimation is necessary in endoscopic screening for gastric cancer. To minimize overdiagnosis, the target age group and screening interval should be appropriately defined. Consideration of the balance of benefits and harms of endoscopic screening is imperative for its effective introduction in communities.

INTRODUCTION

Endoscopic examination has been increasingly performed for gastric cancer screening in Eastern Asian countries[1]. Although national programs for gastric cancer screening have already been started in South Korea and Japan, endoscopic screening has been mainly performed in clinical settings as opportunistic screening[2]. Since 1999, endoscopic screening for gastric cancer has been performed in South Korea[3]. In 2016, the Japanese government decided to introduce endoscopic screening for gastric cancer as a national program based on the guidelines published by the National Cancer Center in Japan[4]. Although evidence for reduction in mortality from gastric cancer by endoscopic screening was insufficient when this method was initially introduced in South Korea, evidence regarding its effectiveness has gradually increased in South Korea, China, and Japan[5-8]. Gastric cancer screening by endoscopy has been increasingly anticipated because early stage cancer can be more definitively diagnosed than by radiographic screening using upper gastrointestinal series with barium meal.

Despite the benefits of endoscopic screening for gastric cancer, the major harms of this technique include infection, complications, false-negative results, false-positive results, and overdiagnosis[4]. Although complications and infection are highly probable in endoscopic screening, these can be minimized by appropriate safety management. On the other hand, false-positive results and overdiagnosis frequently occur in all cancer screenings. The false-positive rate can be managed using a quality assurance system to some extent[9]. However, because of the high sensitivity of endoscopic examination which can detect many early stage cancers, overdiagnosis cannot be avoided. To effectively introduce endoscopic screening in communities, the balance of benefits and harms should be prudently analyzed. Therefore, comprehensive knowledge of overdiagnosis in endoscopic screening is crucial as well as effective strategies for its management.

BASIC CONCEPT OF OVERDIAGNOSIS

When we consider the harms of endoscopic screening, overdiagnosis cannot be ignored because it occurs in this procedure and in all cancer screening programs[10]. Overdiagnosis represents the actual cancer detected by screening which would never have been found if there is no cancer screening. In cancer screening, it is not possible to distinguish between an overdiagnosis of cancer and a diagnosis of cancer that will progress[10]. Overdiagnosis leads to unnecessary examinations and treatments, the results of which can cause psychological problems[11].

Mammographic screening provides an easily understood example of the basic concept of overdiagnosis. Since the late 1990s, mammographic screening for breast cancer has rapidly spread nationwide in the United States. Women aged 40-69 years were the major target of mammographic screening. In Figure 1A, the upper graph shows a large impact of mammographic screening during the 1980s and early 1990s among women aged 40 years or older in the United States[12]. In the same Figure 1A, the lower graph shows a rapid increase in the incidence of early stage breast cancer according to the dissemination of mammographic screening. However, a small decrease in the incidence of late-stage breast cancer is observed.

In Figure 1B, breast cancer incidence flattened in women younger than 40 years of age because they did not have any opportunity to have mammographic screening. These trends of breast cancer in women aged 40 years and over suggested that the detected early stage cancer included cases of overdiagnosis.

There have also been developments of new techniques which can diagnose cancers that do not progress and are not fatal even if left untreated. The growth rates of cancer vary and are divided into 4 categories: Rapid, slow, very slow, and non-progressive. Periodic screening detects slow-growing (Tumor B) and non-progressive (Tumor A) cancers early, and finds some progressive cancer (Tumor C) early (Figure 2)[13]. Without screening, Tumor A remains undetectable and causes no morbidity during the patient's lifetime. However, rapid-growing cancer (Tumor D) which is a fatal tumor cannot be screened earlier and may cause death even with treatment. The benefit of screening is limited to true-positive results when earlier treatment works better. Even if the screening result is true-positive, there are no benefits for Tumors A, D and partly C[13]. When screening starts, this screening cascade cannot be stopped[14].

Overdiagnosis is not limited to the harms of cancer screening and it can occur in any diagnostic examinations. However, the frequency of overdiagnosis varies among examinations and diseases. The target of cancer screening is asymptomatic persons without any health problems. Therefore, in cancer screening, harms should be minimized and benefits should outweigh harms[14]. Importantly, the harms of cancer screening are often ignored because the screening benefits are usually emphasized. Although there is a possibility that endoscopic screening has made a large impact in terms of reducing mortality from gastric cancer, we have to consider minimizing its harms, particularly overdiagnosis. Therefore, estimation of the frequency of overdiagnosis is a key issue in considering the balance of benefits and harms of endoscopic screening.

ESTIMATION OF OVERDIAGNOSIS

Overdiagnosis has been estimated from randomized

Essernanl *et al*. *JAMA* 2009

Figure 2 Screen detection capability based on tumor biology and growth rates[13]. The growth rates of cancer vary and are divided into 4 categories: Rapid, slow, very slow, and non-progressive. Periodic screening detects slow-growing (Tumor B) and non-progressive (Tumor A) cancers early, and finds some progressive cancer (Tumor C) early. Tumor A remains undetectable and causes no morbidity during the patients' lifetime without screening. However, rapid-growing cancer (Tumor D) which is a fatal tumor is not screened earlier and can cause death even with treatment.
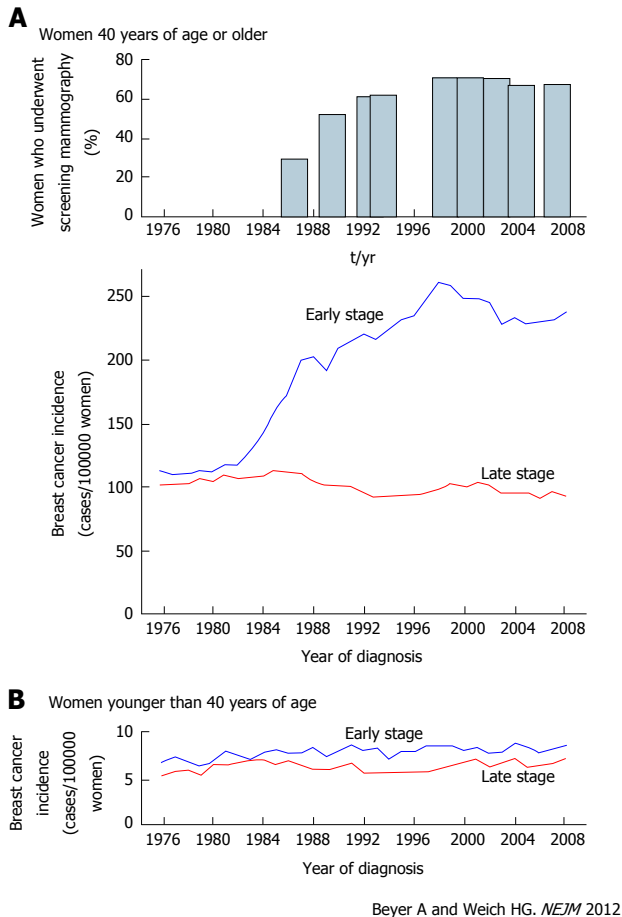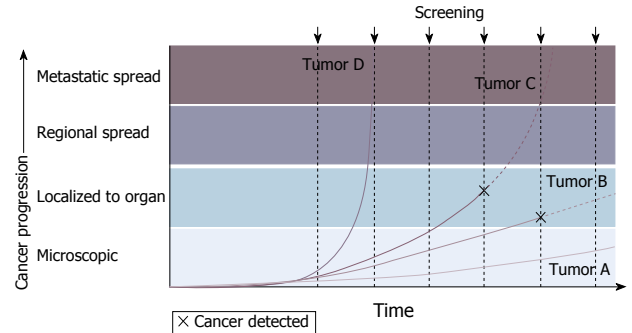

Beyer A and Weich HG. *NEJM* 2012

Figure 1 Trends of breast cancer incidence before and after mammographic screenings in the United States. A: Use of mammographic screening and incidence of stage-specific breast cancer among women 40 years of age and older; B: Incidence of stage-specific breast cancer among women younger than 40 years of age[12].

controlled trials (RCTs), ecological and cohort studies, pathological and imaging studies, and modeling[15]. The frequency of overdiagnosis is calculated on the basis of the difference in the incidence of cancer between screened and unscreened individuals after the follow-up. Although the estimation method has not yet been standardized, there is a high divergence, for example, 0%-50% in mammographic screening[16].

The frequency of overdiagnosis was previously estimated on the basis of RCTs without the provision of mammographic screening at the end of the screening phases. In the Independent United Kingdom Panel on Breast Cancer Screening, the overdiagnosis rate was calculated from the Canadian and Malmo studies for mammographic screening using 4 methods with different denominators as follows (Figure 3)[16]: (1) excess cancers as the frequency of cancers diagnosed over the whole follow-up period in unscreened women; (2) excess cancers as the frequency of cancers diagnosed over the whole follow-up period in women invited for screening; (3) excess cancers as the frequency of cancers diagnosed during the screening period in women invited for screening; and (4) excess cancers as the
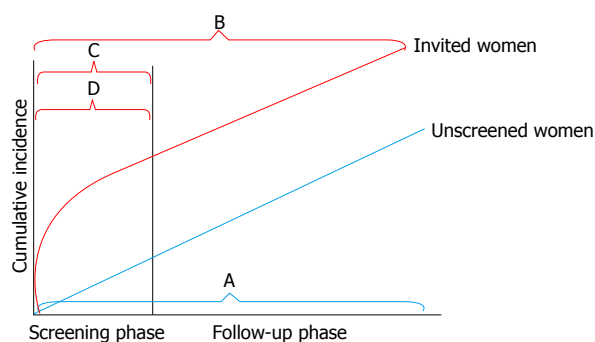
frequency of cancers detected at screening in women invited for screening. The frequency of overdiagnosis was estimated to be higher when the follow-up periods were limited to the screening phases. In the conclusions, the overdiagnosis rate for mammographic screening was in the range of 10%-20% based on the estimation using the data from 2 RCTs. Recently, a Canadian study has reported an overdiagnosis frequency of 22% based on 25 years of follow-up[17].

On the other hand, ecological and cohort studies have been commonly used to estimate the frequency of overdiagnosis. These studies can directly answer questions in real world settings and compare results from different settings[15]. Carter *et al*[15] have suggested that ecological and cohort studies in multiple settings are the most appropriate approaches for qualifying and monitoring overdiagnosis in cancer screening programs.

OVERDIAGNOSIS OF GASTRIC CANCER BY ENDOSCOPIC SCREENING

The frequency of overdiagnosis of gastric cancer by endoscopic screening has not yet been estimated. Excess rate was calculated on the basis of the results of endoscopic screening for gastric cancer which indicated that the observed number of detected cancer was twice the expected number (Table 1)[18]. However, the excess cancers included both early detection cases which progress into fatal cancers and overdignosis cases.

The calculation of sensitivity is affected by the number of overdiagnosis cases. The detection method is the most common and simplest procedure for calculating sensitivity in which the numerator includes all detected cancers and the denominator is the sum of detected cancers and interval cancers. In the detection method, sensitivity is often overestimated, whereas in the incidence method, overdiagnosis cases can be avoided[19]. Sensitivity calculation by the incidence method was adopted in

	A	B	C	D
Numerator	Excess cancers	Excess cancers	Excess cancers	Excess cancers
Denomibator	Cancer diagnosed over the whole follow-up period in unscreened women	Cancer diagnosed over the whole follow-up period in women invited for screening	Cancer diagnosed during the screening period in women invited for screening (screen-detected cancers and interval cancers)	Cancers detected at screening in women invited for screening (screen-detected cancers)
Malmö I (55-59 yr)	11.7% (82/698)	10.5% (82/780)	18.7% (82/438)	29.1% (82/282)
Canada 1	14.1% (82/581)	12.4% (82/663)	22.7% (82/361)	29.4% (82/279)
Canada 2	10.7% (67/626)	9.7% (67/693)	16.0% (67/420)	19.8% (67/338)

Marmot MG Br J Cancer 2013

Figure 3 Estimation of frequency of overdiagnosis on the basis of the results of Malmö and Canadian studies. The frequency of overdiagnosis was calculated on the basis of 2 randomized controlled trials for mammographic screening using 4 methods with different denominators as follows: A: Excess cancers as the frequency of cancers diagnosed over the whole follow-up period in unscreened women; B: Excess cancers as the frequency of cancers diagnosed over the whole follow-up period in women invited for screening; C: Excess cancers as the frequency of cancers diagnosed during the screening period in women invited for screening; D: Excess cancers as the frequency of cancers detected at screening in women invited for screening[16].

Table 1 Comparison of results from cohort studies of endoscopic screening for gastric cancer							

Target for cancer screening	Method	Male			Female		
		Observed number	Expected number	O/E	Observed number	Expected number	O/E
Stomach	Endoscopy	28	15.31	1.83	7	3.69	1.9
Colon and rectum	Barium enema	4	2.25	1.78	4	1.08	3.7
	Total colonoscopy	26	21.9	1.19	15	7.64	1.96
Lung	CT	14	10.86	1.29	18	2.38	7.56
Prostate	PSA	24	7	3.43	-	-	-
Breast	Combination of mammography, ultrasonography and physical examination	-	-	-	15	6.22	2.41

Available from Hamashima et al[18], 2006. O: Observed number; E: Expected number; CT: Computed tomography; PSA: Prostate specific antigen.

Table 2 Sensitivities and specificities of endoscopy and radiography for gastric cancer screening				

Screening round	Method	Sensitivity	Specificity	Sensitivity
		By the detection method	By the detection method	By the incidence method
Prevalence screening	Endoscopic screening	0.955 (95%CI: 0.875-0.991)	0.851 (95%CI: 0.843-0.859)	0.886 (95%CI: 0.698-0.976)
	Radiographic screening	0.893 (95%CI: 0.718-0.977)	0.856 (95%CI: 0.846-0.865)	0.831 (95%CI: 0.586-0.964)
Incidence screening	Endoscopic screening	0.977 (95%CI: 0.919-0.997)	0.888 (95%CI: 0.883-0.892)	0.954 (95%CI: 0.842-0.994)
	Radiographic screening	0.885 (95%CI: 0.664-0.972)	0.891 (95%CI: 0.885-0.896)	0.855 (95%CI: 0.637-0.970)

Available from Hamashima et al[23], 2013.

breast, lung, and colorectal cancer screenings[20-22]. In prevalence screening for using endoscopic screening for gastric cancer, the sensitivity was reportedly 0.955 (95%CI: 0.875-0.991) by the detection method and 0.886 (95%CI: 0.698-0.976) by the incidence method (Table 2)[23]. In incidence screening using endoscopic screening for gastric cancer, the sensitivity was reportedly 0.977 (95%CI: 0.919-0.997) by the detection method and 0.954 (95%CI: 0.842-0.994) by the incidence method[23]. The discrepancy between the results calculated by the detection method and the incidence method was small. It might be suggested that the frequency of overdiagnosis on endoscopic screening for gastric cancer is not very high.
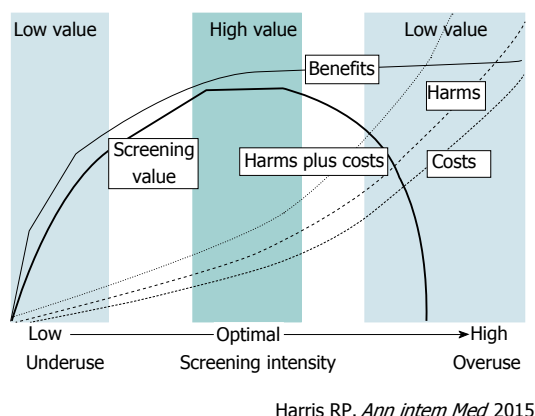
Harris RP. *Ann intem Med* 2015

Figure 4 A value framework for cancer screening. The value of cancer screening strategies is linked to the screening intensity (population screened, frequency, and sensitivity of the test used) and is determined by the balance among benefits (*e.g.*, cancer mortality reduction), harms (*e.g.*, anxiety from false-positive test results, harms of diagnostic procedures, labeling, and overdiagnosis leading to overtreatment), and costs. The value of cancer screening is determined by a trade-off between benefits *vs* harms and costs. As the intensity increases, the benefits of screening rapidly increase. However, as the intensity increases beyond an optimal level, the increase in benefits slows down whereas harms and costs increase rapidly, and the value decreases[14].

STRATEGIES FOR MANAGEMENT OF OVERDIAGNOSIS

Although frequent screenings can diagnose numerous cancers, the possibility of including overdiagnosis is high. In actuality, frequent screenings easily result in overdiagonsis. Therefore, the appropriate number of screenings should be considered in endoscopic screening for gastric cancer. The American College of Physicians has recommended high-value care based on the value framework (Figure 4)[14,24]. The value of cancer screening is determined by a trade-off between benefits *vs* harms and costs. As the intensity increases, the benefits of screening rapidly increase. However, as the intensity increases beyond an optimal level, the benefits decrease whereas the harms and costs increase rapidly thereby reducing the value of cancer screening. High-value care has been recommended which is defined as the lowest intensity threshold. On the basis of this concept, high-value and low-value screening strategies have been developed for 5 types of cancer. This framework can be adopted in endoscopic screening for gastric cancer. Since endoscopic screening has a high sensitivity, it has the same problems. To minimize harms including overdiagnosis and to maximize the benefits, the target age group and screening interval should be appropriately clarified. To decrease the harms of unnecessary examinations and treatments, the "Choosing Wisely" campaign has rapidly expanded collaboration with academic societies in the United States and other countries[25]. The basic concepts of the "Choosing Wisely" campaign are focused on the same goal of minimization of unnecessary examinations and treatments.

CONCLUSION

Overdiagnosis is the most serious harm of endoscopic screening for gastric cancer. Although the estimation method for the frequency of overdiagnosis has not yet been standardized, the present study is essential in further assessing the harms of endoscopic screening for gastric cancer in terms of overdiagnosis. To minimize overdiagnosis, the target age group and screening interval should be clearly defined in consideration of the balance of benefits and harms. Further research into overdiagnosis in endoscopic screening is warranted to realize its effective introduction in communities.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Gastric intestinal metaplasia is associated with gastric dysplasia but is inversely correlated with esophageal dysplasia

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Informed consent statement: Informed consent was obtained prior to all endoscopic procedures as part of routine patient care. However, this was a retrospective cohort study that involved materials (data, documents, or records) that were collected solely for non-research purposes (such as medical diagnosis and treatment). Therefore, informed consent was not required for the purposes of this study given minimal risk to subjects.

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Abstract

AIM

To determine which clinical factors might be associated with gastric intestinal metaplasia (IM) in a North American population.

METHODS

Pathology and endoscopy databases at an academic

medical center were reviewed to identify patients with and without gastric IM on biopsies for a retrospective cohort study. Patient demographics, insurance status, and other clinical factors were reviewed.

RESULTS
Four hundred and sixty-eight patients with gastric IM (mean age: 61.0 years ± 14.4 years, 55.5% female) and 171 without gastric IM (mean age: 48.8 years ± 20.8 years, 55.0% female) were compared. The endoscopic appearance of atrophic gastritis correlated with finding gastric IM on histopathology (OR = 2.05, P = 0.051). Gastric IM was associated with histologic findings of chronic gastritis (OR = 2.56, P < 0.001), gastric ulcer (OR = 6.97, P = 0.015), gastric dysplasia (OR = 6.11, P = 0.038), and gastric cancer (OR = 6.53, P = 0.027). Histologic findings of Barrett's esophagus (OR = 0.28, P = 0.003) and esophageal dysplasia (OR = 0.11, P = 0.014) were inversely associated with gastric IM. Tobacco use (OR = 1.73, P = 0.005) was associated with gastric IM.

CONCLUSION
Patients who smoke or have the endoscopic finding of atrophic gastritis are more likely to have gastric IM and should have screening gastric biopsies during esophagogastroduodenoscopy (EGD). Patients with gastric IM are at increased risk for having gastric dysplasia and cancer, and surveillance EGD with gastric biopsies in these patients might be reasonable.

Key words: Gastric; Intestinal metaplasia; Atrophic gastritis; Biopsies; Esophagogastroduodenoscopy

Core tip: Gastric intestinal metaplasia (IM) is a precursor to gastric adenocarcinoma. There are no North American consensus recommendations as to which patients might benefit from esophagogastroduodenoscopy (EGD) with biopsy for screening or surveillance for gastric IM. Patients who smoke or have the endoscopic finding of atrophic gastritis are more likely to have gastric IM and should have screening gastric biopsies during EGD. Patients with gastric IM are at increased risk for developing gastric dysplasia and cancer, and surveillance EGD with gastric biopsies in these patients might be reasonable.

INTRODUCTION
Gastric cancer is the fifth leading type of cancer worldwide, with 952000 new cases diagnosed in 2012. With 723000 reported deaths in 2012, gastric cancer is the third most common cause of cancer-related mortality[1,2]. The annual incidence of gastric cancer in 2013 based upon the SEER database was 7.5 per 100000 persons with an annual death rate of 3.5 cases per 100000 in the United States population[3]. The lower prevalence of gastric cancer in Western countries is also associated with the diagnosis of gastric cancer at a later stage, which results in a poor 5-year survival of 20% within the United States[4]. Patients diagnosed with early stage gastric carcinoma have a significantly better prognosis with 5-year survival rates approaching 90%[5,6].

The mechanisms responsible for gastric carcinogenesis are not completely known. However, gastric cancer is thought to arise from a premalignant cascade potentially initiated by *Helicobacter pylori* (*H. pylori*) infection[7-9]. In 1988, Correa[10] first described a pathway through which premalignant lesions could become gastric cancer. This cascade progresses from non-atrophic gastritis to atrophic gastritis, gastric intestinal metaplasia (IM), gastric dysplasia, and ultimately gastric carcinoma. Gastric IM has since become well established as a premalignant lesion that is associated with an increased risk of gastric carcinoma[11-13]. The largest observational study of patients with precancerous gastric lesions in the Western world included 61707 individuals with gastric IM and found an annual incidence of progression to gastric cancer of 0.25%[14].

Gastric IM is characterized by a change from the normal glandular epithelium found in the stomach to a small-intestinal phenotype. The pathogenesis of gastric IM remains unclear but is thought to involve environmental stimuli that lead to differentiation of the gastric stem cells towards an intestinal phenotype[15-17]. Pathologically, gastric IM can be recognized by the presence of a simple columnar epithelium containing Paneth cells, absorptive cells, and goblet cells[15]. Additionally, gastric IM may be classified further based on histologic appearance into complete (type Ⅰ) and incomplete (type Ⅱ or Ⅲ). Complete (type Ⅰ) gastric IM is recognized by the presence of a small intestinal mucosal phenotype with goblet cells containing sialomucins interspersed between absorptive cells and a well-defined brush border. Incomplete (type Ⅱ or Ⅲ) gastric IM is characterized by a colonic mucosal phenotype with tortuous crypts lined by tall columnar cells containing sulfomucins[18]. The incomplete pattern of gastric IM is associated with the greatest risk of progression to gastric cancer[19-25]. A study completed in Spain found that the incidence of gastric cancer in patients with incomplete IM was 16 (18.2%) out of 88 patients and 1 (0.96%) out of 104 patients with complete IM when followed for a mean of 12.8 years[26]. However, in practice pathologists, even

at most academic institutions, do not typically make the distinction between different types of gastric IM. The two types of incomplete IM are based on sulfomucin content, which cannot be determined by hematoxylin and eosin (H and E) staining alone. Pathologically, this distinction may be difficult to make as incomplete and complete gastric IM can coexist, and the finding of gastric IM can be very focal even on a small biopsy specimen.

The prevalence of gastric IM in the general population is difficult to assess due to the fact that it is an asymptomatic lesion that can only be found on histologic evaluation of gastric tissue, typically obtained by esophagogastroduodenoscopy (EGD). In 2010, Sonnenberg *et al*[27] published the results from a retrospective study of 78985 patients undergoing EGD and gastric biopsy in the United States and found that the prevalence of gastric IM was 7%. Within this patient population there was a continuous age-dependent rise in finding gastric IM from age 0 to 90 years. Furthermore, the frequency of gastric IM is geographically variable, as shown by a Chinese study that found gastric IM in 29.3% of 1630 consecutive patients with *H. pylori* infection presenting for a screening EGD[28,29].

Guidelines put forth by the European Society of Gastrointestinal Endoscopy (ESGE) in 2012 recommended that at least two biopsies from the antrum (greater and lesser curvature) and two biopsies from the corpus (greater and lesser curvature) be taken for adequate assessment of premalignant gastric conditions. These guidelines recommended that patients with extensive atrophic gastritis or gastric IM should be offered surveillance endoscopy every 3 years. They also recommended that if *H. pylori* infection is diagnosed, then eradication should be offered to decrease the progression to dysplasia and carcinoma[30]. Despite strong epidemiologic and molecular data linking gastric IM and gastric carcinoma, there are currently no North American consensus guidelines as to which patients might benefit from EGD with biopsy for screening or surveillance endoscopy[22]. The aim of this study was to determine what clinical factors might be associated with gastric IM in a United States population so as to identify potential indications for screening and/or surveillance by using EGD with gastric biopsies.

MATERIALS AND METHODS

This study was conducted at University of Virginia Medical Center, a single tertiary-care hospital that performs both outpatient and inpatient endoscopic procedures for patients from a wide geographic area (including significant portions of Virginia, West Virginia, and Tennessee). This study was approved by our institutional review board.

Pathology and endoscopy databases were reviewed to identify patients with and without gastric IM. Patients who had pathology-confirmed gastric IM from 2005-2011 were extracted from a dedicated pathology database. Using an endoscopic billing database, a control group of

patients was established by reviewing 300 consecutive patients who had undergone EGD with biopsies (186 patients had gastric biopsies) from March to June 2011, from which 171 patients were identified who had gastric biopsies without gastric IM. The rate of gastric IM in this control group of patients was 5%, which we have previously reported[31]. All upper endoscopies were performed by experienced gastrointestinal endoscopists, and all pathological diagnoses included in this study were made by academic pathologists at our institution. Diagnosis of gastric IM was made histologically on H and E-stained slides. Diagnosis of *H. pylori* infection was made histologically using immunohistochemical stains.

Electronic medical records, including pathology and endoscopy reports, were reviewed and information about patient demographics, insurance status, and possible risk factors for the development of gastric IM and gastric dysplasia was collected. Potential risk factors of interest included a first-degree family history of gastric cancer, presence of *H. pylori* infection on gastric biopsy, and certain clinical indications for endoscopy. Additional patient characteristics of interest included social factors such as lifetime history of tobacco use, alcohol use (if reported within the past year), and acid suppression therapy with proton-pump inhibitors or H_2-receptor antagonists. Unfortunately, ethnic background was not available for analysis, as data from earlier patients were derived from a different electronic medical record system that did not reliably capture this information.

Frequency data were summarized as percentages and analyzed by exact logistic regression. Continuous variables were summarized by the median and range of distribution. Univariate and age-adjusted multivariate analyses were conduct by way of exact logistic regression to compare patient outcomes between those with and without gastric IM. A two-sided $P \leqslant 0.05$ decision rule was established a priori as the null hypothesis rejection criterion, and 95%CI construction for the OR was based on the Mid-P method[32]. The exact statement of the SAS version 9.2 LOGISTIC procedure was utilized to conduct the exact logistic regression analyses (SAS Institute Inc., Cary, NC).

RESULTS

Patients and demographics
Four hundred and sixty-eight patients (mean age: 61.0 years ± 14.4 years, 55.5% female) with gastric IM diagnosed on gastric histopathology and 171 patients (mean age: 48.8 years ± 20.8 years, 55.0% female) without gastric IM on gastric biopsies were included in this study. Refer Table 1 for patient characteristics.

Patients with pathologically-diagnosed gastric IM were statistically more likely to be older (*P* < 0.001). When insurance status was evaluated, patients with Medicare were significantly more likely to have gastric IM [OR 1.94 (1.20, 3.17), *P* = 0.007], whereas patients with private insurance were less likely to have gastric IM [OR 0.66 (0.44, 0.99), *P* = 0.047]. We did not detect

Table 1 Patient characteristics and their associations with gastric intestinal metaplasia

	Gastric IM (+) n = 468	Gastric IM (-) n = 171	Univariate analysis	Multivariate analysis [OR (95%CI)]
Age (mean/median, yr)	61.0/64.0	48.8/53.0	*P* < 0.001	--
Male sex	208 (44.4%)	77 (45.0%)	*P* = 0.928	--
Family history of gastric cancer	23 (5.7%)[1]	5 (2.9%)	*P* = 0.557	1.38 (0.52, 4.25), *P* = 0.555
Tobacco use	214 (48.6%)[2]	61 (36.5%)[3]	*P* = 0.007	1.73 (1.18, 2.55), *P* = 0.005
Alcohol use	100 (22.7%)[2]	46 (26.9%)	*P* = 0.219	0.76 (0.50, 1.16), *P* = 0.199
H2-blocker use	21 (5.1%)[4]	13 (7.6%)	*P* = 0.251	0.74 (0.35, 1.59), *P* = 0.426
PPI use	258 (62.6%)[4]	94 (55.6%)	*P* = 0.088	1.23 (0.84, 1.79), *P* = 0.282
Medicare	245 (52.4%)	46 (26.9%)	*P* < 0.001	1.94 (1.20, 3.17), *P* = 0.007
Medicaid	24 (5.1%)	27 (15.8%)	*P* = 0.003	0.57 (0.30, 1.09), *P* = 0.090
Private insurance	118 (25.2%)	72 (42.1%)	*P* < 0.001	0.66 (0.44, 0.99), *P* = 0.047
Uninsured	68 (14.5%)	32 (18.7%)	*P* = 0.885	1.04 (0.64, 1.71), *P* = 0.885

[1]Information about family history was missing from 65 patients who had gastric intestinal metaplasia; [2]Information about social history was missing from 28 patients who had gastric intestinal metaplasia; [3]Information about tobacco use was missing from 4 patients who did not have gastric intestinal metaplasia; [4]Information about H2-blocker and/or PPI use was missing from 56 patients who had gastric intestinal metaplasia. IM: Intestinal metaplasia; PPI: Proton-pump inhibitor.

Table 2 Association among indications and gastric intestinal metaplasia

	Frequency in patients with gastric IM[1]	Frequency in patients without gastric IM[1]	Univariate analysis	Multivariate analysis [OR (95%CI)]
Abdominal pain	188 (41.7%)	93 (54.4%)	*P* = 0.005	0.81 (0.55, 1.18), *P* = 0.267
Weight loss	63 (13.5%)	21 (7.4%)	*P* = 0.014	1.81 (0.95, 3.66), *P* = 0.073
GI bleed	38 (8.4%)	13 (7.6%)	*P* = 0.755	1.23 (0.63, 2.52), *P* = 0.558
Nausea	60 (13.3%)	27 (15.8%)	*P* = 0.426	0.97 (0.58, 1.65), *P* = 0.903
Dysphagia	59 (13.1%)	26 (15.2%)	*P* = 0.490	0.74 (0.44, 1.26), *P* = 0.259
Barrett's esophagus	10 (2.2%)	8 (4.7%)	*P* = 0.123	0.32 (0.12, 0.92), *P* = 0.034

[1]The denominator (n) used to calculate the percentage of patients by indication (in each row) may vary depending on what was available from the clinical records. IM: Intestinal metaplasia; GI: Gastrointestinal.

a statistically significant association between a positive family history of gastric cancer and gastric IM. A history of recent alcohol abuse was not associated with gastric IM; whereas, a lifetime history of tobacco abuse was significantly associated with gastric IM [OR 1.73 (1.18, 2.55), *P* = 0.005].

Indication for endoscopy
Four hundred and eighteen patients with pathology-proven gastric IM and all 171 controls without gastric IM underwent EGD with gastric biopsies. Among indications for procedures (Table 2), Barrett's esophagus [OR 0.32 (0.12, 0.92), *P* < 0.034] was associated with an inverse association with gastric IM on multivariate analysis. Whereas, weight loss correlated with a trend towards increased frequency of gastric IM [OR 1.81 (0.95, 3.66), *P* = 0.073].

Endoscopic findings
The two most frequent endoscopic findings (Table 3) on EGD (prior to any pathologic confirmation) in this patient population were gastritis (137/589, 23.3% for all patients) and gastric mucosal nodularity (104/589, 17.7%).

Endoscopic findings of a gastric mass [OR 8.84 (1.88, ∞), *P* = 0.005] and atrophic gastritis [OR 2.05 (1.00, 4.58), *P* = 0.051] were significantly associated

with finding gastric IM on histopathology by multivariate analysis. The endoscopic appearance of duodenal polyps [OR 4.21 (0.81, ∞), *P* = 0.081] trended towards an increased association with finding gastric IM on biopsies. On multivariate analysis, the esophageal abnormalities of an esophageal mass [OR 0.04 (0.01, 0.16), *P* < 0.001], esophagitis [OR 0.49 (0.26, 0.91), *P* = 0.023], and Barrett's esophagus [OR 0.56 (0.26, 1.21), *P* = 0.134] were found to inversely correlate with finding gastric IM on histopathology.

Histopathological diagnoses
When all patients with and without gastric IM were considered, the most frequent histologic diagnoses encountered were chronic gastritis (305/639, 47.7%) and gastric polyps (46/639, 7.2%). Histologic diagnoses and associations for patients with and without gastric IM found on surgical pathology are shown in Table 4.

On univariate and multivariate analyses, patients with biopsy-proven gastric IM were found to have an increased association with the following gastric histopathological diagnoses (multivariate odds ratios are reported): Chronic gastritis [OR 2.56 (1.75, 3.76), *P* < 0.001], gastric ulcer [OR 6.94 (1.47, ∞), *P* = 0.015], gastric dysplasia [OR 6.11 (1.07, 131.57), *P* = 0.038], gastric cancer [OR 6.53 (1.17, 139.41), *P* = 0.027], and autoimmune metaplastic atrophic gastritis [OR 5.64

Table 3 Associations among endoscopic findings (prior to or without histopathology) and gastric intestinal metaplasia

	Frequency in patients with gastric IM, *n* = 418	Frequency in patients without gastric IM, *n* = 171	Univariate analysis	Multivariate analysis (OR, 95%CI)
Gastritis	100 (23.9%)	37 (21.6%)	*P* = 0.557	1.34 (0.84, 2.08), *P* = 0.223
Atrophic gastritis	55 (13.2%)	9 (5.3%)	*P* = 0.004	2.05 (1.00, 4.58), *P* = 0.051
Gastric mass	20 (4.8%)	0 (0%)	*P* = 0.001	8.84 (1.88, ∞), *P* = 0.005
Gastric ulcer	42 (10.0%)	11 (6.4%)	*P* = 0.163	1.42 (0.71, 3.01), *P* = 0.339
Gastric nodularity	71 (17.0%)	33 (19.3%)	*P* = 0.503	0.74 (0.46, 1.20), *P* = 0.213
Linitis plastica	1 (0.2%)	0 (0%)	*P* = 0.710	0.27 (0.01, ∞), *P* = 0.788
Esophagitis	28 (6.7%)	23 (13.4%)	*P* = 0.011	0.49 (0.26, 0.91), *P* = 0.023
Esophageal mass	2 (0.5%)	13 (7.6%)	*P* < 0.001	0.04 (0.01-0.16), *P* < 0.001
Barrett's esophagus	21 (5.0%)	13 (7.6%)	*P* = 0.235	0.56 (0.26, 1.21), *P* = 0.134
Duodenitis	17 (4.1%)	11 (6.4%)	*P* = 0.234	0.69 (0.30, 1.60), *P* = 0.337
Duodenal polyp	8 (1.9%)	0 (0%)	*P* = 0.063	4.21 (0.81, ∞), *P* = 0.081
Duodenal mass	4 (1.0%)	0 (0%)	*P* = 0.253	1.58 (0.26, ∞), *P* = 0.353
Duodenal ulcer	2 (0.5%)	2 (1.2%)	*P* = 0.407	0.21 (0.02, 2.20), *P* = 0.179

IM: Intestinal metaplasia.

Table 4 Association among histopathological biopsy results and gastric intestinal metaplasia

	Frequency in patients with gastric IM, *n* = 468	Frequency in patients without gastric IM, *n* = 171	Univariate analysis	Multivariate analysis (OR)
Chronic gastritis	265 (56.6%)	55 (32.2%)	*P* < 0.001	2.56 (1.75, 3.76), *P* < 0.001
Gastric polyp	35 (7.5%)	11 (6.4%)	*P* = 0.669	1.07 (0.53, 2.31), *P* = 0.861
MALT lymphoma	5 (1.1%)	0 (0.0%)	*P* = 0.209	1.48 (0.26, ∞), *P* = 0.372
Erosive gastritis	1 (0.2%)	6 (3.5%)	*P* = 0.002	0.06 (0.0, 0.43), *P* = 0.003
H. pylori infection	46 (9.8%)	6 (3.5%)	*P* = 0.007	3.07 (1.33, 8.20), *P* = 0.007
Gastric ulcer	18 (3.8%)	0 (0%)	*P* = 0.003	6.97 (1.47, ∞), *P* = 0.015
Gastric dysplasia	19 (4.1%)	1 (0.6%)	*P* = 0.017	6.11 (1.07, 131.57), *P* = 0.038
Gastric cancer	21 (4.5%)	1 (0.6%)	*P* = 0.010	6.53 (1.17, 139.41), *P* = 0.027
Autoimmune metaplastic atrophic gastritis	12 (2.6%)	0 (0%)	*P* = 0.023	5.64 (1.36, ∞), *P* = 0.035
Esophagitis	5 (1.1%)	5 (2.9%)	*P* = 0.125	0.36 (0.09, 1.41), *P* = 0.138
Barrett's esophagus	14 (3.0%)	13 (7.6%)	*P* = 0.016	0.28 (0.12, 0.63), *P* = 0.003
Esophageal dysplasia	2 (0.4%)	4 (2.3%)	*P* = 0.053	0.11 (0.01, 0.64), *P* = 0.014
Esophageal cancer	1 (0.2%)	1 (0.6%)	*P* = 0.535	0.13 (0.01, 9.88), *P* = 0.402
Eosinophilic esophagitis	1 (0.2%)	6 (3.5%)	*P* = 0.002	0.10 (0.00, 0.74), *P* = 0.020
Carcinoid tumor	10 (2.1%)	0 (0%)	*P* = 0.043	5.13 (1.02, ∞), *P* = 0.047
Duodenitis	2 (0.4%)	6 (3.5%)	*P* = 0.006	0.13 (0.02, 0.65), *P* = 0.012
Duodenal polyp	5 (1.1%)	1 (0.6%)	*P* = 0.645	1.2 (0.16, 29.49), *P* = 0.944
Duodenal ulcer	2 (0.4%)	0 (0%)	*P* = 0.536	0.63 (0.07, ∞), *P* = 0.628

IM: Intestinal metaplasia; *H. pylori*: *Helicobacter pylori*; MALT: Mucosa-associated lymphoid tissue.

(1.36, ∞), *P* = 0.035]. Patients with *H. pylori* infection on gastric pathology also had a significant association with gastric IM [OR 3.07 (1.33, 8.20), *P* = 0.007].

Patients with gastric IM were found to have an inverse association with pathology-proven duodenitis [OR 0.13 (0.02, 0.65), *P* = 0.012]. Furthermore, gastric IM was inversely associated with several esophageal histopathological diagnoses including Barrett's esophagus [OR 0.28 (0.12, 0.63), *P* = 0.003], esophageal dysplasia [OR 0.11 (0.01, 0.64), *P* = 0.014], and eosinophilic esophagitis [OR 0.1 (0.0, 0.74), *P* = 0.02].

DISCUSSION

Although the incidence of gastric cancer is relatively low within the United States, the 5-year survival for this disease remains poor. In large part, this is because gastric neoplasia is frequently diagnosed at an advanced stage when endoscopic and surgical therapies are less effective. There is a relative paucity of data concerning the frequency and significance of premalignant gastric lesions within the United States population. Best estimates of the prevalence of gastric IM in patients undergoing EGD with biopsy is probably between 5%-7%[27,31]. With an estimated 7 million EGDs done each year in the United States[33], this represents at least 350000 patients with gastric IM who could be diagnosed by the addition of a just a few gastric biopsies to these routine procedures.

Gastric IM is widely accepted as a premalignant lesion that can lead to gastric carcinoma[10]. Uemura *et al*[34] followed 1246 patients with *H. pylori* and gastric IM over a mean of 7.8 years and found that gastric cancer developed in 36 patients with a relative risk of 6.4 (2.6, 16.1), *P* < 0.001. In the present study, gastric IM was similarly associated with a six-fold increased odds ratio of finding gastric cancer [OR 6.53 (1.17, 139.41), *P* =

0.027].

H. pylori infection is recognized as one of the primary risk factors leading to the development of atrophic gastritis and gastric IM[8,9,23], which is probably a consequence of having a long-term chronic inflammatory state. Our study demonstrated a statistically significant association between gastric IM and *H. pylori* infection [OR 3.07 (1.33, 8.19), *P* = 0.007], as might be expected. Several prior studies have attempted to induce regression of gastric IM through treatment of *H. pylori* infection with varying results. A recent metaanalysis by Wang *et al*[35] included 12 studies and a total of 2658 patients with atrophic gastritis and gastric IM. They found that atrophic gastritis in the antrum can be reduced through treatment of *H. pylori* infection; however, atrophic gastritis in the corpus or gastric IM regardless of location in the stomach failed to regress with eradication of *H. pylori*. This observation that once gastric IM develops that subsequent *H. pylori* treatment might be ineffective supports the hypothesis that gastric IM is likely a breakpoint in the carcinogenic pathway leading to gastric cancer.

A large Dutch study by de Vries *et al*[36] of 61707 patients with gastric IM found that 874 patients developed a new diagnosis gastric cancer when followed over 10 years. The annual incidence of gastric cancer among patients with gastric IM in this study was 0.25%. Although these patients were followed for a total of 10 years, the median interval between diagnosis of gastric IM and gastric cancer was only 0.9 years. These data take on new meaning when compared to the annual incidence of Barrett's esophagus progressing to adenocarcinoma, which is estimated to range between 0.12% and 0.5%[37]. Paradoxically, in the West, screening and surveillance guidelines for Barrett's esophagus have been in place for over a decade, and they are widely practiced; whereas multi-society or multi-national consensus on the screening and surveillance for gastric IM is lacking in Western nations. In 2002, Whiting *et al*[38] published a study conducted in the United Kingdom that examined if annual endoscopic surveillance could detect new cases of gastric cancer at an earlier and possibly curative stage. The study followed 1753 patients over 10 years, and 14 new cases of gastric cancer were diagnosed at earlier stages (67% were stage Ⅰ and Ⅱ *vs* 23% stage Ⅲ or Ⅳ; *P* < 0.05).

Part of the difficulty in reaching North American guidelines is the lack of consensus among practicing gastroenterologists in the United States regarding the management of gastric IM. Our group, in conjunction with University of Virginia Center for Survey Research, conducted a survey of American Society for Gastrointestinal Endoscopy (ASGE) members that resulted in 162 responding endoscopists (85% gastroenterologists, 82% men, from 32 states, 53% in private practice). This survey uncovered that while 56% of these physicians considered gastric IM to be a premalignant lesion, only 26% screen for gastric IM, but 42% survey for gastric IM (at a time interval anywhere between 6 mo and 5 years). Importantly, 97% of respondents felt that societal guidelines for management of premalignant gastric lesions would be beneficial to clinical practice[39]. These results were further supported by a study by Vance *et al*[40] that showed "variability in the knowledge and practice patterns of United States endoscopists related to surveillance of gastric intestinal metaplasia".

In the 2006 ASGE guideline, "the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract", it was stated that "endoscopic surveillance for gastric IM has not been extensively studied in the United States and therefore cannot be uniformly recommended". However, those guidelines did recommend that "patients at increased risk for gastric cancer due to ethnic background or family history may benefit from surveillance"[22]. In this present study, family history of gastric cancer had an increased odd of being associated with the presence of gastric IM, but this finding was not significant, which could be due to a lack of power. European/ESGE guidelines published in 2012 recommended surveillance endoscopy for patients with extensive atrophic gastritis or gastric IM based on evidence from strong systematic reviews and large cohort studies. They did, however, note that future prospective studies were required to assess the cost-effectiveness of surveillance endoscopy in this patient population[30]. In 2014, Areia *et al*[41] conducted a cost-utility economic analysis from a societal perspective in Portugal using a Markov model and found that endoscopic surveillance every 3 years for patients with premalignant gastric conditions such as extensive atrophy or IM was cost-effective. Recently, Kim *et al*[42] have advocated that "Gastric cancer screening with endoscopy should be considered in individuals who are immigrants from regions associated with a high risk of gastric cancer (East Asia, Russia, or South America) or who have a family history of gastric cancer. Those with findings of atrophic gastritis or intestinal metaplasia on screening endoscopy should undergo surveillance endoscopy every 1 to 2 years".

Limitations of this present study include that it was a retrospective study conducted at a single academic medical center and that we did not have complete data on patient ethnicity to review. Data from 2010 from the United States Census Bureau about Albemarle County, Virginia (which is where the University of Virginia is located) reports the following ethnic demographics for its residents: 63.7% are White, 16.3% are Hispanic or Latino, 12.6% are Black or African American, 4.8% are Asian, 0.9% are American Indian or Alaska Native, and 0.2% are Native Hawaiian or other Pacific Islander. As such, the vast majority of patients in our study were White, Hispanic, or Black. Despite including a large number of patients with gastric IM, which remains a somewhat uncommon finding in the United States, our study could still be limited by a lack of statistical power.

In this study, we demonstrated that patients with biopsy-proven gastric IM were significantly more likely to be cigarette smokers and to have endoscopic findings

of gastric atrophy, which should prompt at least gastric biopsies (preferably *via* systematic endoscopy for gastric mapping[43] and with multiple biopsies taken from the antrum, incisura, lesser curve, and gastric body) during EGD to histopathologically confirm atrophic gastritis and also to screen for gastric IM. When multifocal, extensive, or incomplete gastric IM are found, we believe that surveillance endoscopy is reasonable, which we and others[20] conduct at 3-year intervals in the absence of any dysplasia. If focal areas of dysplasia or early gastric cancers are found, then we offer endoscopic mucosal resection or endoscopic submucosal dissection[44,45], when appropriate[46], in addition to more frequent endoscopic surveillance. Again, in this context, our data demonstrated that the presence of gastric IM is clinically significant, as this condition was associated with the pathologic findings of gastric dysplasia and cancer.

Interestingly, our study showed that gastric IM appears to confer a protective effect against the development of esophageal pathology including esophagitis, Barrett's esophagus, and esophageal dysplasia. The most likely etiology for this inverse relationship among gastric IM and these esophageal pathologies is the reduction in gastric acid secretion found in patients with atrophic gastritis and gastric IM.

In summary, we hope that the data presented in this study might be of use as guidelines and recommendations concerning the screening and surveillance of gastric IM and other premalignant gastric lesions in a United States patient population are developed. Patients who smoke or have the endoscopic finding of atrophic gastritis are significantly more likely to also have gastric IM, and these risk factors should prompt screening gastric biopsies during EGD. Patients with gastric IM are at increased risk for developing gastric dysplasia and cancer, and a program of surveillance biopsies in these patients might be reasonable. Conversely, patients with gastric IM appear significantly less likely to be diagnosed with Barrett's esophagus and esophageal dysplasia.

COMMENTS

Background
Gastric intestinal metaplasia (IM) is a precursor to gastric adenocarcinoma. However, there are no North American consensus recommendations as to which patients might benefit from esophagogastroduodenoscopy (EGD) with biopsy for screening or surveillance for gastric IM.

Research frontiers
Endoscopic technology has advanced significantly in the past two decades, and high-definition white-light endoscopy and advanced optical imaging techniques now allow accurate real-time diagnosis of luminal gastrointestinal disorders, which formerly required formal histopathologic review of biopsy specimens. Careful endoscopic examination remains critical to the correct diagnosis of conditions such as atrophic gastritis, gastric intestinal metaplasia, and early gastric cancers.

Innovations and breakthroughs
In Western nations and populations, the epidemiological risk of gastric IM has been largely ignored given the lower prevalence of gastric cancer, as compared to Asian, South American, and Eastern European populations. However, data

are re-emerging that demonstrate that gastric IM can be an important problem in Western populations. In the present study, gastric IM was associated with a statistically significant six-fold increased odds ratio of finding gastric cancer. Being mindful of clinical demographic factors and findings on endoscopic evaluation of the stomach can assist in determining which patients might benefit from screening gastric biopsies. Proper diagnosis of gastric IM might also identify a patient population that might benefit from surveillance endoscopy.

Applications
Patients who smoke or have the endoscopic finding of atrophic gastritis are more likely to have gastric IM and should have screening gastric biopsies during EGD. Patients with gastric IM are at increased risk for having gastric dysplasia and cancer, and surveillance EGD with gastric biopsies in these patients might be reasonable.

Terminology
Gastric intestinal metaplasia is characterized by the replacement of the normal gastric glandular epithelium by a small-intestinal phenotype, and it often accompanies or follows chronic *Helicobacter pylori* infection of the stomach. Dysplasia is an abnormal change to tissue (in this case the gastric epithelium) that is considered premalignant. EGD is a procedure performed using a flexible endoscope whereby endoscopic views of the upper gastrointestinal tract (esophagus, stomach and duodenum) are obtained. EGD can also enable sampling of the mucosa of the upper gastrointestinal tract, often by using cold biopsy forceps.

Peer-review
This is a valuable attempt to analyze IM with the development of gastric cancer. It is a well conducted and well written study.

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ORIGINAL ARTICLE

Retrospective Study

Endoscopic submucosal dissection for small submucosal tumors of the rectum compared with endoscopic submucosal resection with a ligation device

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Abstract

AIM
To evaluate the efficacy and safety of endoscopic submucosal dissection (ESD) for small rectal submucosal tumors (SMTs).

METHODS
Between August 2008 and March 2016, 39 patients were treated with endoscopic submucosal resection with a ligation device (ESMR-L) (*n* = 21) or ESD (*n* = 18) for small rectal SMTs in this study. Twenty-five lesions were confirmed by histological evaluation of endoscopic biopsy prior to the procedure, and 14 lesions were not evaluated by endoscopic biopsy. The results for the ESMR-L group and the ESD group were retrospectively compared, including baseline characteristics and therapeutic outcomes.

RESULTS
The rate of *en bloc* resection was 100% in both groups. Although the rate of complete endoscopic resection

was higher in the ESD group than in the ESMR-L group (100% *vs* 95.2%), there were no significant differences between the two groups (*P* = 0.462). In one patient in the ESMR-L group with a previously biopsied tumor, histological complete resection with a vertical margin involvement of carcinoid tumor could not be achieved, whereas there was no incomplete resection in the ESD group. The mean length of the procedure was significantly greater in the ESD group than in the ESMR-L group (14.7 ± 6.4 min *vs* 5.4 ± 1.7 min, *P* < 0.05). The mean period of the hospitalization was also significantly longer in the ESD group than in the ESMR-L group (3.7 ± 0.9 d *vs* 2.8 ± 1.5 d, *P* < 0.05). Postoperative bleeding was occurred in one patient in the ESMR-L group.

CONCLUSION
Both ESMR-L and ESD were effective for treatment of small rectal SMTs. ESMR-L was simpler to perform than ESD and took less time.

Key words: Leiomyoma; Lipoma; Rectum; Submucosal tumor; Endoscopic submucosal resection with a ligation device; Endoscopic submucosal dissection; Carcinoid tumor

Core tip: This was a retrospective study to evaluate the efficacy and safety of endoscopic submucosal dissection (ESD) compared with endoscopic submucosal resection with a ligation device (ESMR-L) for small rectal submucosal tumors (SMTs). A total of 39 patients were treated with endoscopic resection for small rectal SMTs; 21 were treated with ESMR-L and 18 were treated with ESD. The results show that both ESMR-L and ESD were effective for treatment of small rectal SMTs. ESMR-L was simpler to perform than ESD and took less time.

INTRODUCTION
Submucosal tumors (SMTs) consist of neoplastic lesions covered by normal overlying mucosa. SMTs with an intramural origin include carcinoid tumors, leiomyoma, lipoma, lymphoma, and gastrointestinal stromal tumors (GISTs). Rectal SMTs are relatively rare and are occasionally detected by screening colonoscopy without any symptoms. Rectal carcinoid tumors smaller than 10 mm in diameter are candidates for local excision (*e.g.,* by endoscopic resection

or transanal endoscopic microsurgery). As previous studies of endoscopic resection for rectal carcinoid tumors have reported, conventional endoscopic resection, such as polypectomy or endoscopic mucosal resection (EMR), is associated with involvement of the resection margin that necessitates further intervention[1-3]. On the other hand, endoscopic submucosal resection with a ligation device (ESMR-L) or endoscopic submucosal dissection (ESD) achieves a high rate of complete resection for rectal carcinoid tumors without involvement of the resection margin[4-12]. Complete resection rates have been reported as ranging from 93.3% to 100% for ESMR-L[4-9] and from 80.6% to 100% for ESD[8-16]. Although both endoscopic procedures are excellent treatments for carcinoid tumors, ESD takes longer to perform and has a longer hospitalization period[8-10]. However, an advantage of ESD is that the submucosal layer beneath the tumors can be directly visualized during submucosal dissection[17].

Although some cases have been reported of ESD for other rectal SMTs, such as leiomyoma and GISTs, there have been few reports comparing the two procedures for treatment of small rectal SMTs. The aim of this study was to evaluate the efficacy and feasibility of ESD for small rectal SMTs compared with ESMR-L.

MATERIALS AND METHODS
Patients
A total of 39 patients were treated with endoscopic resection for small rectal SMTs (35 with carcinoid tumors, three with leiomyoma, and one with lipoma) at the New Tokyo Hospital between August 2008 and March 2016. Twenty-one patients were treated with ESMR-L and 18 patients were treated with ESD.

All lesions were incidentally found by screening colonoscopy and none of the patients had any symptoms, such as carcinoid syndrome or hematochezia. Twenty-five lesions were confirmed by histological evaluation of endoscopic biopsy prior to the procedure, and 14 lesions were not evaluated by endoscopic biopsy. All patients were evaluated by endoscopic ultrasonography before endoscopic treatment and also by computed tomography (CT) to rule out metastases. The indications for endoscopic treatment were a tumor less than 10 mm in diameter and confined to the submucosal layer, and no lymph node involvement or distant metastases.

All patients provided written informed consent before the treatment. Their clinical records were retrospectively reviewed after approval had been obtained from the institutional review board of the New Tokyo Hospital.

ESMR-L procedure
The ESMR-L procedure was performed with the use of a single-channel endoscope (GIF-Q260J; Olympus, Tokyo, Japan) with an attached a band-ligation device (pneumo-activate EVL device; Sumitomo Bakelite, Tokyo, Japan). The procedure was performed as follows (Figure
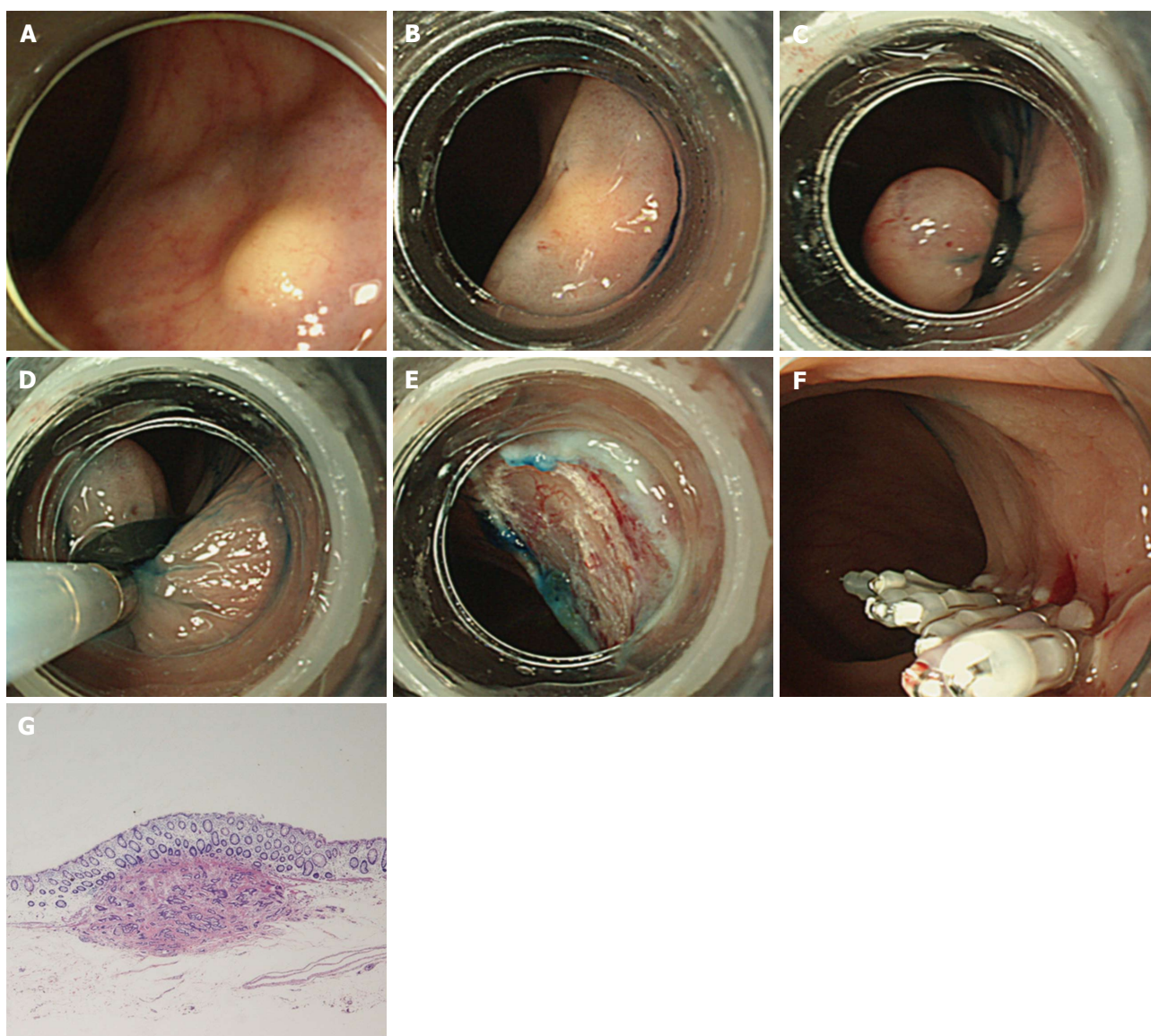
Figure 1 Endoscopic submucosal resection with a ligation device. A: Endoscopic view of a carcinoid tumor in the rectum; B: Submucosal injection beneath the tumor with glycerin solution; C: An elastic band was deployed, and then pseudopolyp was created; D: Snare resection was performed beneath the elastic band; E: An artificial ulcer was observed; F: Endoscopic plication was performed with the use of metal endoclips; G: Histopathological examination showed *en bloc* resection of the carcinoid tumor.

1). First, submucosal injection with a solution containing glycerin was performed to lift the submucosa off from the muscular layer. After the submucosa was lifted, the lesion was aspirated into a ligation device, followed by deployment of the elastic band. The shape of the lesion was changed to that of a pseudopolyp that was suitable for snare resection. Snare resection was then performed beneath the elastic band in an Endocut Q current (effect 3, cut duration 1, cut interval 6), which was generated with a VIO300D (ERBE, Türbingen, Germany). Finally, endoscopic plication was performed with the use of metal endoclips.

ESD procedure

The ESD procedure was performed with the use of a single-channel endoscope (GIF-Q240; Olympus, Tokyo, Japan). The procedure was performed as follows (Figure 2). After submucosal injection with sodium hyaluronate was

performed, a hemicircumferential mucosal incision was made from the anal side with the use of a FlushKnife BT (DK2618JB; Fujifilm, Tokyo, Japan). Next, a pocket of the submucosa was created to allow the endoscope to enter the submucosal layer while the submucosa was being dissected. In order to keep sufficient margin between the bottom of the tumor and the cutting margin, the submucosal dissection was performed just above the muscular layer using an Endocut I current (effect 2, cut duration 3, cut interval 2), which was generated by using a VIO300D. During the submucosal dissection, precoagulation was performed on visible vessels by using hemostatic forceps (FD-230U or FD-410LR; Olympus, Tokyo, Japan). After the submucosal dissection was performed beyond the tumor, the intact mucosa was cut by the electrosurgical knife. Finally, endoscopic plication was performed with the use of metal endoclips. For both of ESMR-L and ESD, the procedure time was defined as
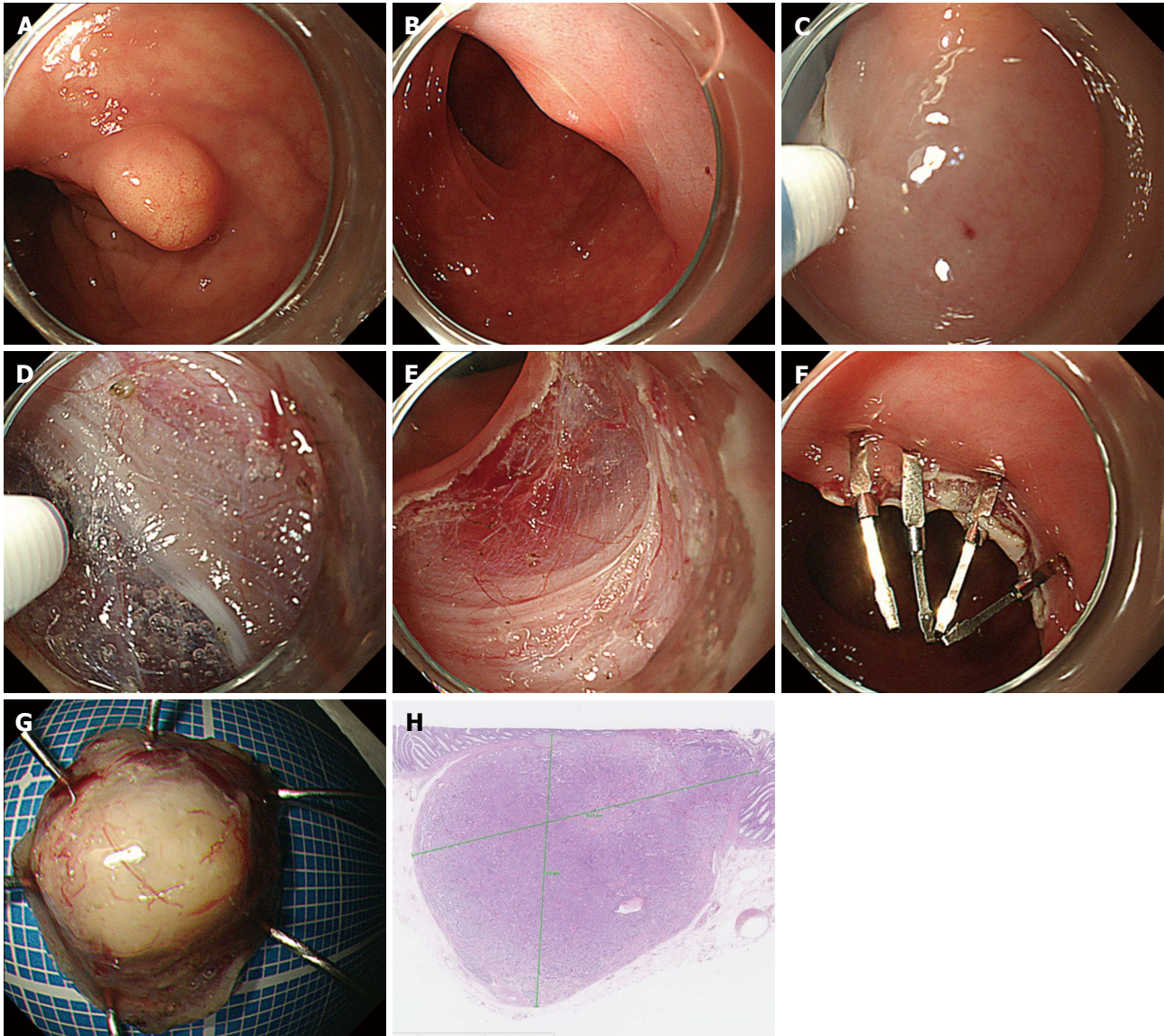
Figure 2 Endoscopic submucosal dissection. A: Endoscopic view of a carcinoid tumor in the rectum; B: Submucosal injection beneath the tumor with sodium hyaluronate; C: A hemicircumferential incision was performed with the use of the electrosurgical knife; D: A submucosal pocket was created during ESD. Submucosal dissection was performed just above the muscular layer; E: An artificial ulcer was observed; F: Endoscopic plication was performed with the use of metal endoclips; G: The specimen resected by ESD; H: Histopathological examination showed *en bloc* resection of the carcinoid tumor. ESD: Endoscopic submucosal dissection.

the time from the submucosal injection to the completion of endoscopic resection.

Histological evaluation

The resected specimens were carefully examined for histological evaluation by experienced pathologists. The resected specimens were evaluated microscopically for pathological type, depth of invasion, lateral and vertical margin involvement, and lymphovascular invasion. *En bloc* resection was defined as one-piece resection endoscopically. Endoscopic complete resection was defined as *en bloc* resection endoscopically without tumor involvement to the lateral and the vertical margins of the resected specimens.

Complications

Postoperative bleeding was defined as hematochezia after endoscopic resection that required simultaneous endoscopic hemostasis. Perforation was defined as a defect of the muscular layer during endoscopic resection or recognized free air on CT after endoscopic resection.

Follow-up

All patients were periodically followed up by colonoscopy between approximately 6 and 12 mo after endoscopic resection. If recurrent or remnant tumor was suspected, biopsy from the resected scar was performed. CT was performed annually to exclude lymph node metastases and distant metastases.

Statistical analysis

Continuous variables were expressed as the means and standard deviations. The χ^2 test or Fisher's exact test was used to analyze categorical variables. A P value < 0.05

Table 1 Clinical findings and characteristics between endoscopic submucosal resection with a ligation device and endoscopic submucosal dissection *n* (%)

	ESMR-L (*n* = 21)	ESD (*n* = 18)	*P* value
Age (yr, mean ± SD)	65.7 ± 14.2	61.2 ± 12.9	0.306
Sex (male/femal)	14/7	8/10	0.206
Tumor size (mm, mean ± SD)	4.9 ± 1.7	5.1 ± 2.1	0.681
Macroscopic type			
Sessile	21 (100)	17 (94.4)	0.462
Semipedunculated	0 (0)	1 (5.6)	
Location			
Rb	18 (85.7)	17 (94.4)	0.609
Ra	3 (14.3)	1 (5.6)	
History of previous biopsy	18 (85.7)	7 (38.9)	0.003

ESMR-L: Endoscopic submucosal resection with a ligation device; ESD: Endoscopic submucosal dissection.

Table 2 Clinical outcomes between endoscopic submucosal resection with a ligation device and endoscopic submucosal dissection *n* (%)

	ESMR-L (*n* = 21)	ESD (*n* = 18)	*P* value
En bloc resection	21 (100)	18 (100)	
Endoscopic complete resection	20 (95.2)	18 (100)	0.462
Histological evaluation			
Vertical margin involvement	1 (4.8)	0 (0)	0.717
Lymphovascular invasion	0 (0)	1 (5.6)	
Pathological findings			
Carcinoid	20 (95.2)	15 (83.3)	0.318
Others	1 (4.8)	3 (16.7)	
Complication			
Post-operative bleeding	1 (4.8)	0 (0)	0.462
Procedure time (min, mean ± SD)	5.4 ± 1.7	14.7 ± 6.4	< 0.001
Hospitalization (d, mean ± SD)	2.8 ± 1.5	3.7 ± 0.9	0.024
Local recurrence	0 (0)	0 (0)	
Distant recurrence	0 (0)	0 (0)	

ESMR-L: Endoscopic submucosal resection with a ligation device; ESD: Endoscopic submucosal dissection.

was considered to indicate statistical significance. Data analyses were performed with Stat View software Version 5.0 for Windows (SAS, Cary, NC, United States).

RESULTS

A total of 39 patients with small rectal SMTs were treated with endoscopic resection. The clinical findings and characteristics of these patients are shown in Table 1. No significant differences were observed between the ESMR-L group and the ESD group other than history of previous biopsy.

The clinical outcomes in the ESMR-L and the ESD groups are shown in Table 2. Three types of pathological findings were observed: Carcinoid tumors, leiomyoma, and lipoma. There were 20 lesions of carcinoid tumors and one lesion of lipoma in the ESMR-L group, and 15 lesions of carcinoid tumors and three lesions of leiomyoma in the ESD group.

The rate of *en bloc* resection was 100% in both groups. The rate of endoscopic complete resection was 95.2% (20/21) in the ESMR-L group and 100% (18/18) in the ESD group. There were no significant differences between the two groups (*P* = 0.462). Vertical margin involvement occurred in one carcinoid tumor in the ESMR-L group.

Lymphovascular invasion occurred in one carcinoid tumor in the ESD group. The tumor was 6 mm in diameter, located at Rb, and was an neuroendocrine tumor G2 with Ki-67 expression between 3% and 20%. The patient underwent additional surgical resection with lympha-denectomy. However, no remnant tumor or lymph node metastases were found.

The mean length of the procedure was significantly greater in the ESD group than in the ESMR-L group (14.7 ± 6.4 min *vs* 5.4 ± 1.7 min, *P* < 0.05). The mean length of the hospitalization was also significantly greater in the ESD group than in the ESMR-L group (3.7 ± 0.9 d *vs* 2.8 ± 1.5 d, *P* < 0.05). Postoperative bleeding occurred in one patient with carcinoid tumor in the ESMR-L group

after discharge from the hospital. The bleeding was successfully managed with emergency endoscopic hemostasis. There were no complications in the ESD group.

The average follow-up period after the treatment was 31.6 ± 21.9 mo in the ESMR-L group and 9.1 ± 5.8 mo in the ESD group. One patient in the ESMR-L group whose carcinoid tumor could not be resected completely was provided with careful follow-up by colonoscopy with biopsy and CT. There were no local recurrences or distant metastases during the follow-up period.

DISCUSSION

This study investigated the outcomes of endoscopic resection for small SMTs of the rectum. Although the rate of complete endoscopic resection was higher in the ESD group than in the ESMR-L group (100% *vs* 95.2%, *P* = 0.462), there were no significant differences in outcome between the two groups. Our results are similar to those of previous studies comparing ESD and ESMR-L for treatment of carcinoid tumors[7,9,10]. Previous studies reported that the length of the procedure and the period of hospitalization were greater in the ESD group than in the ESMR-L group. Although our study included other rectal SMTs, such as leiomyoma and lipoma, our results were also consistent with those of the previous studies of carcinoid tumors. In terms of procedure time and length of hospitalization, the ESMR-L procedure is a more favorable treatment than the ESD procedure.

One patient in the ESMR-L group had postoperative bleeding 3 d after undergoing ESMR-L. The patient received dual antiplatelet therapy (low-dose aspirin plus clopidogrel) for cardiovascular disease to prevent throm-bosis after percutaneous coronary intervention. Since the patient was treated with ESMR-L for carcinoid tumor with continuous use of low-dose aspirin after clopidogrel was

discontinued for 5 d before the treatment, the antiplatelet therapy probably contributed to the postoperative bleeding. The postoperative bleeding was successfully managed with endoscopic hemostasis with the use of metal endoclips.

One patient in the ESMR-L group had vertical margin involvement of the carcinoid tumor. Although the patient received no additional interventions, no local recurrence or distant metastases have occurred so far (24 mo after the resection). The patient had a diagnostic biopsy prior to ESMR-L. Im *et al*[18] reported that previously biopsied tumors remained independent significant predictors of histological incomplete resection of rectal carcinoid tumors. Previous endoscopic biopsy is likely to produce fibrosis around the lesion. The authors reported that ESMR-L for previously biopsied tumors had a significantly higher rate of complete resection than EMR. However, two patients in their study who were treated with ESMR-L for previously biopsied tumors had histological incomplete resection. The fibrosis caused by the previous biopsy probably contributed to the incomplete resection in the ESMR-L procedure. In our study, one patient in the ESMR-L group had histological incomplete resection of a previously biopsied tumor, whereas there were no incomplete resections in the ESD group. An advantage of ESD is that the surgeon can directly observe the submucosal layer during ESD and perform the submucosal dissection regardless of the fibrosis. We believe that this advantage contributed to the complete resection of the SMTs. However, since only seven of our patients underwent ESD for a previously biopsied tumor, no statistically significant conclusion can be drawn from these results.

The most importance of the endoscopic resection for SMTs, such as carcinoid tumors, is to achieve the complete resection of the deeper margins without involvement of the tumor. The submucosal dissection facilitates the complete resection of the SMTs by cutting just above the muscular layer. However, the rate of perforation with colorectal ESD is comparatively high because of the thin wall, sharp bends, and narrow lumen of the colorectum. To remedy with this situation, Hayashi *et al*[17] described the pocket-creation method (PCM). The authors reported that the PCM technique allows safe *en bloc* ESD and complete resection of tumors even in the presence of severe submucosal fibrosis, because creation of a submucosal pocket helps the endoscope to enter and stretch the submucosal layer and enables visualization of the line of dissection. We applied this method to the treatment of the rectal SMTs (Figure 2D).

The submucosal dissection is favorable to perform just above the muscular layer using an endocut mode rather than a coagulation mode, because it is likely to be the risk of a vertical margin involvement of the tumor caused by a burning effect during the submucosal dissection. Although the rate of perforation can be increased in the setting of an endocut mode during the submucosal dissection, an endocut mode would decrease the risk of the burning effect for the vertical margin of the tumor. On the other hand, using a coagulation mode would increase the risk of the burning effect for the vertical margin of the tumor. The PCM technique facilitated the submucosal dissection with the use of an endocut mode by preventing leakage of the submucosal injection and maintaining a thick submucosal layer owing to PCM technique. The creation of a submucosal pocket also facilitated the submucosal dissection of the rectal SMTs, regardless of the previous biopsy in this study. There was no vertical margin involvement in any of the specimens in the ESD group.

This study has some limitations. It was a retrospective study conducted in a single institution with a small sample size. A prospective study with a larger number of subjects will be expected.

In conclusion, both ESMR-L and ESD were effective for treatment of small rectal SMTs. ESMR-L was simpler to perform than ESD and took less time. However, the submucosal dissection using ESD could be effective for treatment of previously biopsied tumors.

COMMENTS

Background
Submucosal tumors (SMTs) consist of neoplastic lesions covered by normal overlying mucosa. SMTs with an intramural origin include carcinoid tumors, leiomyoma, lipoma, lymphoma and gastrointestinal stromal tumors. Rectal SMTs are relatively rare and are occasionally detected by screening colonoscopy without any symptoms. Rectal carcinoid tumors smaller than 10 mm in diameter are candidates for local excision (*e.g.*, by endoscopic resection or transanal endoscopic microsurgery). Endoscopic submucosal resection with a ligation device (ESMR-L) or endoscopic submucosal dissection (ESD) achieves a high rate of complete resection for rectal carcinoid tumors without involvement of the resection margin. In this study, the authors evaluated the efficacy and feasibility of ESD for small rectal SMTs compared with ESMR-L.

Research frontiers
Although ESMR-L and ESD are excellent treatments for carcinoid tumors, ESD takes longer to perform and has a longer hospitalization period.

Innovations and breakthroughs
Previous endoscopic biopsy is likely to produce fibrosis around the lesion. Fibrosis caused by the previous biopsy probably contributed to the incomplete resection. An advantage of ESD is that the surgeon can directly observe the submucosal layer during ESD and perform the submucosal dissection regardless of the fibrosis.

Applications
The submucosal dissection using ESD could be effective for treatment of previously biopsied tumors in patients with SMTs.

Terminology
ESMR-L is endoscopic submucosal resection with a ligation device. Pocket-creation method is pocket-creation method that the technique helps the endoscope to enter and stretch the submucosal layer and enables visualization of the line of dissection.

Peer-review
The study is original and timely. Although the study consist of relatively low number of patients the findings of this study will make contribution to the literature. The findings of this study are relevant to the focus of this journal and will be of interest to its readers.

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ORIGINAL ARTICLE

Clinical Trials Study

Clinical utility of 0.025-inch guidewire VisiGlide2™ in the endoscopic retrograde cholangiopancreatography-related procedures

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Abstract

AIM

To examine the result of the use of 0.025-inch guidewire (GW) VisiGlide2™ as the first choice in the endoscopic retrograde cholangiopancreatography (ERCP)-related procedures without selecting the patient in a multicenter prospective study.

METHODS

ERCP using 0.025-inch GW VisiGlide2™ as the first choice was conducted in patients who have needed ERCP, and its accomplishment rate of procedure, procedural time, incidence of accidental symptoms were compared with those of ERCP using 0.025-inch GW VisiGlide™.

RESULTS

The accomplishment rate of procedure was 97.5% (197/202), and procedural time was 23.930 ± 16.207 min. The accomplishment rate of procedure using 0.025-inch GW VisiGlide™ was 92.3% (183/195), and procedural time was 31.285 ± 19.122 min, thus the accomplishment rate of procedure was significantly improved and procedural time was significantly shortened ($P < 0.05$). Accidental symptoms by ERCP-related procedures were observed in 3.0% (6/202), and all were conservatively alleviated.

CONCLUSION

When 0.025-inch GW VisiGlide2™ was used for ERCP-related procedure as the first choice, it showed high accomplishment rate of procedure and low incidence of accidental symptoms, suggesting it can be used as the universal GW. Clinical Trial Registry (UMIN0000016042).

Key words: Endoscopic sphincterotomy; Endoscopic retrograde cholangiopancreatography; 0.025-inch guidewire

Core tip: When 0.025-inch guidewire (GW) VisiGlide2™ was used for endoscopic retrograde cholangiopancreatography-related procedure as the first choice, it showed high accomplishment rate of procedure and low incidence of accidental symptoms, suggesting it can be used as the universal GW.

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP)-related procedures have played a very important role for diagnosis/treatment of biliary and pancreatic disease. In ERCP-related procedures, it is needless to say that the guidewire (GW) is essential in performing the procedure safely, and elevating the accomplishment rate of the procedure. There are the GWs of various diameters, but the GW which has been used as the first choice was of 0.035 inches considering the stability of procedure[1-12]. The 0.025-inch GW is thin and excellent in breaking through the stenosis and selecting the branch but problematic in visibility and rigidity, which has not been used as the first choice[1-12]. It has been used in the case in which it was impossible to break through the stenosis even by using 0.035-inch GW, and in particular, peroral

Figure 1 0.025-inch guidewire VisiGlide2™. The tip of hydrophilic coating is flexible.

cholangioscopy (POCS) and placement of metallic stent (MS) have generally been conducted with 0.035-inch GW because of the problem of rigidity[8-12]. Previously, after 0.025-inch GW was used for breaking through the stenosis, GW was switched to 0.035 inch GW to stabilize the procedure, and the procedure was re-started. However, together with advancement of the endoscope, GW was improved, and it has become possible to use VisiGlide™ with excellent visibility and sufficient rigidity in spite of the external diameter of 0.025-inch in the clinical setting. As a result, we have treated a number of patients in whom ERCP-related procedure can be accomplished using only this GW. However, there remained still problems that GW must be changed due to seeking failure in some patients, and GW perforation comparatively frequently occurs[13]. After that, it has become possible to use VisiGlide2™ remodeled from VisiGlide™ in the clinical setting (Figure 1)[14]. VisiGlide2™ has excellent endoscopic visibility (Figure 2), and also has improved fluoroscopic visibility of GW using 2 radiopaque chips similarly to VisiGlide™ (Figure 3). Although it has thinness of 0.025-inch (0.63 mm), its special processing method ensures rigidity equivalent to that of 0.035 inch (0.89 mm) (Figure 4). It is the GW that was devised to reduce GW perforation, the accidental symptom observed in use of VisiGlide™, by making the tip flexible. The torque device for 0.025-inch GW VisiGlide™ was compliant to 0.035 inch previously, whereas that for 0.025-inch GW VisiGlide2™ has become compliant to 0.025-inch, thus torque transmissibility was improved.

We decided to examine the accomplishment rate of procedures and the incidence of accidental symptoms in the use of 0.025-inch GW VisiGlide2™ as the first-choice universal GW in the ERCP-related procedures.

MATERIALS AND METHODS

All the patients with biliary and pancreatic diseases, who were decided to undergo ERCP in 5 institutions participating in this clinical study in a month of December 2014, were included. A 0.025-inch GW (VisiGlide2: Olympus Corp. Japan straight type or angle type) was used. For cannulation, catheters PR-104Q, PR110Q-1,
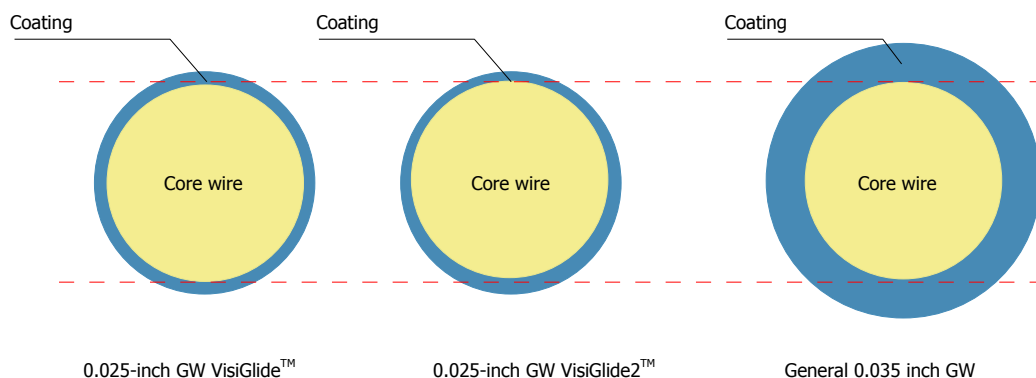
Figure 2 Comparison between 0.025-inch guidewire VisiGlide2™, 0.025-inch guidewire VisiGlide™, and 0.035 inch guidewire. Although it has thinness of 0.025-inch (0.63 mm), its special processing method ensures rigidity equivalent to that of 0.035 inch (0.89 mm). GW: Guidewire.
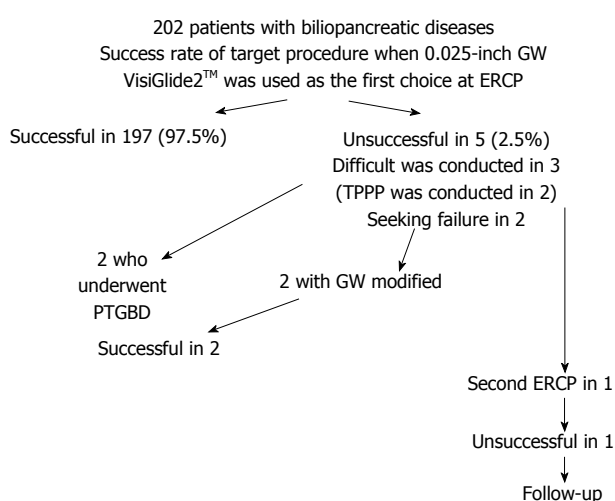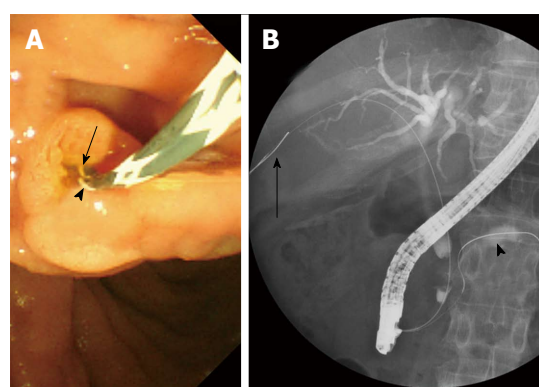

Figure 3 Result of use of 0.025-inch guidewire VisiGlide2™ in the endoscopic retrograde cholangiopancreatography as the first choice. ERCP: Endoscopic retrograde cholangiopancreatography; TPPP: Transpancreatic precut papillotomy; PTGBD: Percutaneous transhepatic gallbladder drainage; GW: Guidewire.

Figure 4 Although it has thinness of 0.025-inch (0.63 mm), its special processing method ensures rigidity equivalent to that of 0.035 inch (0.89 mm). A: 0.025-inch guidewire (GW) VisiGlide2™ placed in the bile duct (arrow)/pancreatic duct (arrow head). The visibility is good under endoscopy; B: 0.025-inch GW VisiGlide2™ placed in the bile duct (arrow)/pancreatic duct (arrow head). The visibility is good under radiography.

PR-233Q and Clever-Cut3V (Olympus Corp. Japan) were used. The endoscopes used were JF200, JF240, JF260V, and TJF260V (Olympus Corp. Japan). Prospective data collected in multicenter study were compared with those obtained from multicenter prospective study of 0.025-inch GW VisiGlide™ which we have already reported[13]. Patients treated using VisiGlide2™are shown. There were 202 patients including 122 males and 80 females, and the age was 72.9 (36 to 98) years old on average. The ERCP was conducted aiming at bile duct in 190 patients and pancreatic duct in 12 patients. There were 80 patients undergoing ERCP for the first time and 122 patients on whom papillary treatment has already been implemented. The case in which 0.025-inch guidewire VisiGlide2™ was used as a versatile GW and the scheduled procedure could be accomplished only with VisiGlide2™ at the ERCP was considered as the success of procedure, and the success rate and the incidence of accidental symptom were examined. Patients with difficulty in selective biliary cannulation were defined as patients who are considered by an investigator to be difficult cases for

biliary cannulation after over 10 min performing papilla cannulation through the frontal view. If such patients were observed, the following procedures were used to achieve biliary cannulation at the investigator's discretion: Needle knife precut papillotomy starting at orifice, transpancreatic precut papillotomy and pancreatic duct guidewire indwelling method. For patients with moderate or severe cholangitis, urgent ERCP was performed according to the Tokyo Guideline[15]. Iatrogenic morbidity was assessed according to the criteria of Cotton *et al*[16]. The observation period was 30 d after the procedure and any coincidental events noted during the period were considered as early coincidental events. All the treatment procedures were performed after obtaining the informed consent in writing from the patients. Assessment of this GW was performed based on approval of ethical committee of each institution, and registered at UMIN Clinical Trial Registry (UMIN0000016042-VIP2 study).

Statistical analysis
Person χ^2 test with Yates correction and Fisher's exact test, when appropriate, were used for statistical analysis of categorical variables. Data were Statistical analyses were performed with SPSS software version 18 (SPSS,

Table 1 Patients' background and disease background

		VisiGlide2™	VisiGlide™	*P* value
Sex		122 males	113 males	NS
		80 females	81 females	
Age		72.871 ± 11.403 (36-98)	70.834 ± 11.824 (38-95)	NS
Disease	Bile duct stone	113	103	NS
	Cholangiocarcinoma	31	26	NS
	Chronic pancreatitis	14	18	NS
	Pancreatic cancer	18	16	NS
	Gallbladder cancer	3	6	NS
	Hepatolithiasis	1	5	NS
	Metastatic biliary obstruction	5	5	NS
	IPMN	3	4	NS
	Benign biliary stenosis	4	3	NS
	Acute cholecystitis	5	3	NS
	PSC	2	2	NS
	Postoperative bile leakage	1	1	NS
	Pancreaticobiliary maljunction	1	1	NS
	Duodenal papillary cancer	1	1	NS
Target region	Bile duct	190	180	NS
	Pancreatic duct	12	14	NS
Stenosed lesion	Present	90	77	NS
	Absent	112	117	NS
Procedure	Scheduled ERCP	157	155	NS
	Emergency	45	39	NS
Purpose	Diagnosis	10	14	NS
	Diagnosis + treatment	15	9	NS
	Treatment	177	171	NS
Papillary treatment	None	80	81	NS
	Post EST	110	101	NS
	Post EPST	12	12	NS

IPMN: Intraductal papillary mucinous neoplasm; PSC: Primary sclerosing cholangitis; EST: Endoscopic sphincterotomy; EPST: Endoscopic pancreatic sphincterotomy; ERCP: Endoscopic retrograde cholangiopancreatography; NS: Not significant.

Table 2 Accomplishment rate of procedure and procedural time

	VisiGlide2™	VisiGlide™	*P* value
Success rate	97.5 (197/202)%	92.3 (180/195)%	0.034
Procedural time (min)	23.930 ± 16.207 (4-65)	31.285 ± 19.122 (4-117)	0.0001

Chicago, IL). A *P* value less than 0.05 was regarded as indicating a statistically significant.

RESULTS

Comparisons of patient background and disease background are shown (Table 1). There was no significant difference between VisiGlide2™ and VisiGlide™ in the patient background. The accomplishment rate of procedure only with VisiGlide2™ was 97.5% (197/202). The procedural time was 23.930 ± 16.207 (4-65) min. Use of VisiGlide2™ enabled significantly to elevate accomplishment rate of procedure and shorten procedural time compared with VisiGlide™ (*P* < 0.05) (Table 2). Of patients who failed accomplishment of the procedure, GW was changed in 2 patients. Of 2 patients, the procedure was successful in 1 patient using Radifocus™ (RF-GS25263 TERUMO Japan), and the procedure was also successful in 1 patient using Navipro™ (Boston Scientific Corp. Natick, MA).

Three patients had difficulty in selective bile duct insertion and 2 were acute cholecystitis patients to whom percutaneous transhepatic gallbladder drainage was inserted. One patient was clinically suspicious spontaneous passage of bile duct stone, and underwent unsuccessfully second ERCP, and followed-up. The final success rate of ERCP was 98.5% (199/202) (Figure 5). Among the patients succeeded in insertion into the bile duct and not undergoing papillary treatment, 74 patients underwent papillary treatment. The papillary treatment was successful in all the 74 patients conducted, the success rate of 100% (74/74) (Table 3). After papillary treatment, we underwent the procedure of purpose. The success rate was 99.4% (331/333) (Table 4). Accidental symptoms were observed at 3.0% (6/202). Bleeding, pancreatitis and perforation were observed at 1.0% (2/202), 1.5% (3/202) and 0.5% (1/202), respectively. Although there was no significant difference in accidental symptoms between VisiGlide2™ and VisiGlide™, GW perforation, which was observed in 2.1% (4/194) when

Table 3 Papillary treatment

Papillary treatment	VisiGlide2™		VisiGlide™		P-value
	n	Success rate of procedure	*n*	Success rate of procedure	
EST	67	100 (67/67)%	67	100 (67/67)%	NS
EST + EPLBD	3	100 (3/3)%	5	100 (5/5)%	NS
EPST	3	100 (3/3)%	3	100 (3/3)%	NS
EPBD	1	100 (1/1)%	4	100 (4/4)%	NS
Total	74	100 (74/74)%	79	100 (79/79)%	NS

EST: Endoscopic sphincterotomy; EPLBD: Endoscopic papillary large balloon dilation; EPST: Endoscopic pancreatic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; NS: Not significant.

Table 4 Procedure conducted after insertion into the bile duct and pancreatic duct

Procedure conducted	VisiGlide2™		VisiGlide™		P value
	n	Success rate of procedure	*n*	Success rate of procedure	
ENBD	60	98.3 (59/60)%	51	100 (51/51)%	NS
ENPD	5	100 (5/5)%	3	100 (3/3)%	NS
ENGBD	5	80.0 (4/5)%	1	100 (1/1)%	NS
EGBS	2	100 (2/2)%	1	0 (0/1)%	NS
EBS	95	100 (95/95)%	78	100 (78/78)%	NS
EPS	30	100 (30/30)%	22	100 (22/22)%	NS
EML	2	100 (2/2)%	2	100 (2/2)%	NS
Placement of MS	12	100 (12/12)%	8	100 (8/8)%	NS
Lithotomy	88	100 (88/88)%	69	100 (69/69)%	NS
Bile duct biopsy	8	100 (8/8)%	9	100 (9/9)%	NS
Pancreatic duct biopsy	0	-	1	100 (1/1)%	NS
Peroral cholangioscopy	2	100 (2/2)%	1	100 (1/1)%	NS
IDUS	10	100 (10/10)%	6	100 (6/6)%	NS
Bile duct brushing cytology	12	100 (12/12)%	9	100 (9/9)%	NS
Pancreatic duct brushing cytology	2	100 (2/2)%	2	100 (2/2)%	NS
		Total 333 99.4 (331/333)		Total 263 99.6 (262/263)%	NS
Guidewire type straight angle	127		34		NS
	75		0		NS

ENBD: Endoscopic nasobiliary drainage; ENPD: Endoscopic nasopancreatic drainage; ENGBD: Endoscopic nasogallbladder drainage; EGBS: Endoscopic gallbladder stenting; EBS: Endoscopic biliary stenting; EPS: Endoscopic pancreatic stenting; EML: Endoscopic mechanical lithotripsy; MS: Metallic stent; IDUS: Intraductal ultrasonography; NS: Not significant.

Table 5 Results of incidence of accidental symptoms

	VisiGlide2™ *n* = 202	VisiGlide™ *n* = 194	P value
Bleeding	2	4	NS
Pancreatitis	3	1	NS
Perforation	1	0	NS
Guidewire perforation	0	4	NS
Total (%)	6 (3.0%)	9 (4.6%)	NS

NS: Not significant.

VisiGlide™ was used, was not found when VisiGlide2™ was used (Table 5). All the accidental symptoms were mild and conservatively alleviated.

Figure 5 Placement of metallic stent using 0.025-inch guidewire VisiGlide2™. It was possible to break through the stenosis, to induce delivery and to place stents only with this guidewire.

DISCUSSION

GW is essential in conducting ERCP-related procedures to ensure the stable procedure. The functions required for the roles are visibility, insertion performance, rigidity and torqueability. Various types of GWs are available; there are a variety of differences including difference in thickness, hardness, or tip shape[17,18]. As for actual use of GW, at first the procedure was performed with 0.035-inch GW, and for patients whose stenosis cannot be broken through with 0.035-inch GW or patients with difficulty in selecting the branch, GW was switched to accomplish

the procedure. The ideal GW is the universal GW which can accomplish the procedure by itself. Therefore, we evaluated 0.025-inch GW VisiGlide™ (Olympus Corp. Japan) which has visibility and rigidity not inferior to those of 0.035 inch GW, retaining superiority of the conventional 0.025-inch GW in terms of stenosis break-through property and branch selectivity as the universal GW[13]. The success rate of procedure was very high. VisiGlide™ has a merit of thinness as 0.025-inches as well as good rigidity and visibility because of technical progress, which could be used for implementation of POCS which was difficult in the past and placement of MS with no problem. In addition to our reports, there appeared several reports using 0.025-inch GW VisiGlide™ for ordinary ERCP[19,20], which suggests that it may be one of choices as the first choice in using GW for ERCP. However, GW perforation was comparatively frequently observed, which is the problem to be improved hereafter[13]. Although it is reported that a few GW perforations are serious accidental symptoms which need operation[21], there is a report on portobiliary fistula from GW perforation, thus there is a possibility of progressing to a serious accidental symptom, and sufficient attention is required[20]. The core of 0.025-inch GW VisiGlide2™ is the same as that of 0.025-inch GW VisiGlide™, however, the tip of GW is improved to be flexible, which can reduce the risk of GW perforation, retaining rigidity of GW. Previously the torque device for 0.025-inch GW VisiGlide™ was compliant to 0.035 inch, however, it was improved so that torqueability is elevated, and the torque device for 0.025-inch GW VisiGlide2™ has become compliant to 0.025-inch. The advantage to use 0.025-inch GW as the first choice lies in that the free space within the forceps port is increased when compared with 0.035 inch GW, which provides higher degree of freedom at the time of operation and, in addition, enables the use of various devices, and may elevate accomplishment rate of procedure or shorten the procedural time. Recently a cannulation method to use multiple GWs at the time of performing cannulation as the double GW technique is reported[2,3]. In such a case, use of 0.025-inch GW may improve operationality when compared with insertion of multiple 0.035 inch GWs. Although it is needless to say that GW to fix papillary edge must have rigidity to some degree, the thinner the diameter of GW is, the greater the freedom of the procedure becomes, thus accomplishment rate of cannulation may be elevated. In such a sense, if it has rigidity to some degree, there is sufficient significance in using 0.025-inch GW as the first choice.

This review compared 0.025-inch GW VisiGlide™ and 0.025-inch GW VisiGlide2™. First of all, as for the procedure, the torque device for VisiGlide2™ has become compliant to 0.025-inch GW, thus torqueability was elevated, which led to elevation of seeking ability and enabled to accomplish the procedure using only one piece of GW, and furthermore, accomplishment rate of procedure was improved and procedural time was shortened.

As mentioned above, MS placement was not so frequently performed using 0.025-inch GW because it does not have sufficient rigidity. However, emergence of 0.025-inch GW VisiGlide™ changed the situation drastically. Currently, 0.025-inch GW sufficiently enables placement of MS, though it depends on type of GW. 0.025-inch GW VisiGlide2™ used in this study, has no adverse consequence regarding placement of MS. Since patients who need placement of MS often have severe stenoses, it is advantageous to use 0.025-inch GW in terms of stenosis breakthrough. In addition, since 0.025-inch GW VisiGlide2™ has a sufficient rigidity, it is possible to place MS without changing GW after breaking through the stenosis. Previously, in placement of MS, if it is impossible to break through the stenosis using 0.035 inch GW, it was switched to 0.025-inch GW to continue the procedure, and when stenosis breakthrough succeeded, GW was switched again to 0.035 inch GW to perform MS placement. The procedure is very complicated. In placement of MS, use of 0.025-inch GW VisiGlide2™ may be more useful than use of 0.035 inch GW as the first choice similarly to 0.025-inch GW VisiGlide™ in terms of shortening of procedural time, and reduction in total cost of treatment. In the partial stent in stent with a MS, the procedure used in unresectable malignant hilar biliary obstruction, particularly, examination by accumulation of cases is required, but it is possibly useful. First of all, the tip of this GW has an excellent visibility under fluoroscopic control (Figure 3). Therefore, it has an advantage that the position of GW can be identified easily even if GW is placed within the contrasted intrahepatic bile duct. In conducting this procedure, usually, the procedure has been accomplished by using landmark GW, leading GW or seeking GW differently[9,10]. In this procedure, when GW is firstly placed, the GW of thin diameter is advantageous in the aspect of breaking through the stenosis. Multiple GWs are placed after breaking through the stenosis. It is considered that a thin GW with good visibility is ideal as a landmark GW. Because the rigidity is adequate, this GW is considered useful as a leading GW because there is no problem in induction of delivery of MS. In placing the next stent after placement of a stent, moreover, the thinner GW is of course more advantageous as a seeking GW in passing through the void of mesh. As described before, the GW has the rigidity possible to place MS as it is after passing through the void of mesh, and this GW is considered an ideal GW in conducting the partial stent in stent. If this GW is used, it will be able to accomplish the procedure without requiring preparation of the GWs of various characteristics. Recently there is a placement method termed side by side as MS placement for unresectable malignant hilar biliary occlusion[22]. This is the procedure to place MS by placing multiple GWs over hilar bile duct stenosis. In this case, visibility of GW placed in the intrahepatic bile duct is excellent, and in terms of breaking through the stenosis, GW of thin diameter is advantageous, thus this may be an ideal GW even in this procedure. The procedure which we must review in the future is the special procedure such as gallbladder drainage. This is

the procedure to be performed for pathological evaluation in patients with suspected gallbladder cancer or in acute cholecystitis patients with hemorrhagic tendency for whom percutaneous approach is difficult[23,24]. Therefore, differently from ordinary drainage to the bile duct, chance of implementation is extremely few. According to the report so far, since the cystic duct is spirally-curved, in searching the cystic duct, GW with comparatively soft tip and high seeking ability such as Radifocus™ was comparatively frequently used[23,24]. This GW has a comparatively soft tip like Radifocus™, and has a high rigidity as a whole. Therefore, in attempting an approach to the cystic duct, flexibility or thinness of the tip of this GW and rigidity of GW itself may make it work for the procedure in patients in whom stones are incarcerated within the cystic duct. This review showed that although sample size is small, accomplishment rate of procedure to approach the cystic duct was as high as 86% (6/7). It may be necessary to review again with a large sample size in the future. Incidence of accidental symptoms was 3.0% (6/202). As for accidental symptoms, there was no significant difference when compared with the results in use of 0.025-inch GW VisiGlide™. Comparison with results using conventional GW showed that results of incidence of accidental symptoms were not so inferior. Although there was no significant difference, GW perforation was not observed in 0.025-inch GW VisiGlide2™. 0.025-inch GW VisiGlide2™ has high rigidity, however, its tip is flexible, which may have reduced potentiality for occurrence of GW perforation. 0.025-inch GW VisiGlide2™ has an advantage enabling the treatment comparatively safely because its tip is flexible, so breaking through of the stenosis is often conducted in the situation forming a loop (Figure 5). As mentioned above, elevation of accomplishment rate of procedure or shortening of procedural time may be caused by discontinuation of the procedure due to GW perforation or no transferring to other procedure. This study suggested that use of 0.025-inch GW VisiGlide2™ did not develop GW perforation, and showed a low incidence of accidental symptoms as a whole, thus it may be used as a universal GW. If 0.025-inch GW can be used as a universal GW, it is expected that ERCP related treatment instruments such as the delivery sheath of MS with a thinner diameter will be developed in the future. It suggests a possibility to be more advantageous for stenosis breakthrough or others.

In conclusion, when 0.025-inch GW VisiGlide2™ was used for ERCP-related procedure as the first choice, it showed high accomplishment rate of procedure and low incidence of accidental symptoms, suggesting it can be used as the universal GW.

COMMENTS

Background
In endoscopic retrograde cholangiopancreatography (ERCP)-related procedures, it is needless to say that the guidewire (GW) is essential in performing the procedure safely, and elevating the accomplishment rate of the procedure. The

authors decided to examine the accomplishment rate of procedures and the incidence of accidental symptoms in the use of 0.025-inch GW VisiGlide2™ as the first-choice universal GW in the ERCP-related procedures without selecting patients in a multicenter prospective study.

Research frontiers
All the patients with biliary and pancreatic diseases, who were decided to undergo ERCP in 5 institutions participating in this clinical study in a month of December 2014, were included. A 0.025-inch GW (VisiGlide2: Olympus Corp. Japan straight type or angle type) was used. Prospective data collected in multicenter study were compared with those obtained from multicenter prospective study of 0.025-inch GW VisiGlide™.

Innovations and breakthroughs
The accomplishment rate of procedure only with VisiGlide2™ was 97.5% (197/202). The procedural time was 23.930 ± 16.207 (4 to 65) min. Use of VisiGlide2™ enabled significantly to elevate accomplishment rate of procedure and shorten procedural time compared with VisiGlide™ ($P < 0.05$). There was no significant difference in accidental symptoms between VisiGlide2™ and VisiGlide™.

Applications
All the patients with biliary and pancreatic diseases, who were decided to undergo ERCP.

Terminology
0.025-inch GW VisiGlide2™ showed a high accomplishment rate of procedure and low incidence of accidental symptoms when used in ERCP-related procedures as the first choice.

Peer-review
This is a unique multicenter prospective study with a significant number of patients investigating an important topic, 0.025-inch guidewire VisiGlide2™ used for ERCP-related procedures as the first choice. The study results showed high accomplishment rate of procedure and low incidence of accidental symptoms. The results have a clinical impact on selecting the ideal guidewire that can accomplish the procedure by itself. This is a well-written article; the manuscript is concise, clear, comprehensive and convincing.

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CASE REPORT

Over-the-scope-clip closure of long lasting gastrocutaneous fistula after percutaneous endoscopic gastrostomy tube removal in immunocompromised patients: A single center case series

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Abstract

Over-the-scope-clips (OTSC®) have been shown to be an effective and safe endoscopic treatment option for the closure of gastrointestinal perforations, leakages and fistulae. Indications for endoscopic OTSC® treatment have grown in number and also include gastro cutaneous fistula (GCF) after percutaneous endoscopic gastrostomy (PEG) tube removal. Non-healing GCF is a rare complication after removal of PEG tubes and may especially develop in immunosuppressed patients with multiple comorbidities. There is growing evidence in the literature that OTSC® closure of GCF after PEG tube removal is emerging as an effective, simple and safe endoscopic treatment option. However current evidence is limited to the geriatric population and short standing GCF, while information on closure of long standing GCF after PEG tube removal in a younger population with significant comorbidities is lacking. In this retrospective single-center case-series we report on five patients undergoing OTSC® closure of chronic GCF after PEG tube removal. Four out of five patients were afflicted with long lasting, symptomatic fistulae. All five patients suffered from chronic disease associated with a catabolic metabolism (cystic fibrosis, chemotherapy for neoplasia, liver cirrhosis). The mean patient age was 43 years. The mean dwell time of PEG tubes in all five patients was 808 d. PEG tube dwell time was shortest in patient 5 (21 d). The mean duration from PEG tube removal to fistula closure in patients 1-4 was 360 d (range 144-850 d). The intervention was well

tolerated by all patients and no adverse events occured. Successful immediate and long-term fistula closure was accomplished in all five patients. This single center case series is the first to show successful endoscopic OTSC® closure of long lasting GCF in five consecutive middle-aged patients with significant comorbidities. Endoscopic closure of chronic persistent GCF after PEG tube removal using an OTSC® was achieved in all patients with no immediate or long-term complications. OTSC® is a promising endoscopic treatment option for this condition with a potentially high immediate and long term success rate in patients with multiple comorbidities.

Key words: Gastro cutaneous fistula; Endoscopic fistula closure; Over-the-scope-clips; Percutaneous endoscopic gastrostomy; Fistula in immmunosuppressed patients

Core tip: Over-the-scope-clips (OTSC®) are effective and safe for closure of gastrointestinal perforations, leakages and fistulae. There is growing evidence that OTSC® can be applied for the closure of gastrocutaneous fistula after percutaneous endoscopic gastrostomy (PEG) tube removal. In this retrospective single-center case-series we report on five middle-aged patients with multiple comorbidities undergoing OTSC® closure of chronic gastro cutaneous fistula after PEG tube removal. The mean dwell time of PEG tubes was 808 d. Successful immediate and long-term fistula closure was accomplished in all five patients. OTSC® is a promising treatment for this condition with a high immediate and long-term success rate.

INTRODUCTION

The application spectrum of the over-the-scope-clip (OTSC®) has continually evolved from hemostasis to closure of gastrointestinal perforations, leakages and fistulae including anorectal lesions[1-7]. OTSC®s have been proven to be an effective and safe endoscopic treatment option in these conditions[2,8-10]. Emerging indications include fixation of self-expandable metallic stent (SEMS) and diameter reduction of gastrojejunal anastomosis after gastric bypass.

Non-healing gastrocutaneous fistula (GCF) is a rare complication after removal of percutaneous endoscopic gastrostomy (PEG) tubes and can be treated surgically or endoscopically[11]. Clip application, suture, gluing, banding[12] and coagulation techniques have been de-

scribed as endoscopic therapeutic options[13-17]. Nevertheless, OTSC® application is emerging as a simple and safe endoscopic treatment for persistent GCF.

Even though various risk factors for the development of GCF such as stomal infection, delayed gastric emptying, acid hypersecretion, malnutrition, catabolic metabolism, tumors, immunosuppression and consecutive impaired wound healing have been discussed, the only evidence-based risk factor is a duration of gastrostomy > 6 mo leading to epithelialization and persistence of the gastrostomy channel[18,19]. Existing case series on OTSC® application for GCF closure generally focus on closure of short standing GCFs in the setting of infection in geriatric populations[2,8]. We here report on our experience with OTSC® closure of long standing GCF in middle-aged patients with significant comorbidities.

CASE REPORT

We report five cases of patients who were treated in one tertiary care center and underwent closure of persisting GCF after PEG tube removal. Since the OTSC® has been implemented into daily routine, five patients were referred to our clinic for endoscopic closure of persistent GCF after PEG tube removal. After thorough evaluation of each case and written informed consent by each patient, procedures were performed with flexible Olympus® endoscopes using carbon dioxide insufflation instead of ambient air.

The deployment of OTSC® has been published before[20]. A "bearclaw" like OTSC® clamped on a plastic cap is mounted onto the tip of the endoscope. The targeted lesion is then pulled into the plastic cap by suction. If the surrounding tissue is fibrotic and scarred a three-hook anchoring device (anchor® OVESCO Endoscopy AG, Tübingen) is used. The OTSC® is then deployed over the targeted lesion.

Primarily, the smallest, atraumatic (a) OTSC® (size 11 mm) was chosen in order to easily pass the upper esophageal sphincter and to minimize lacerations within the esophagus. In one patient, the largest OTSC® (size 14 mm) was necessary to achieve tight GCF closure after a size 12 OTSC® failed to do so. The small-sized OTSC® was removed with a standard rat-tooth forceps. No overtube was necessary to introduce the OTSC® mounted endoscope. Immediate evaluation of closure success was either proven endoscopically or utilizing contrast medium and inspection of the fistula orifice at skin level. Lasting closure success and subsequent complications were assessed clinically in the follow-up.

Between June 23rd 2009 and June 18th 2015, a total of 1373 PEG tubes were inserted at our clinic. We removed 231 of these PEG tubes in the follow-up. A total of 4 patients (0.29%) developed chronic GCF and were then referred to our unit for endoscopic closure (Table 1). Immediate OTSC® closure of the gastrostomy was performed upon PEG tube removal in a fifth patient due to ascitic fluid leakage. All 5 patients suffered

Table 1 Patients developed chronic gastro cutaneous fistula and were then referred to our unit for endoscopic closure

	Age	Gender	Underlying condition	No. of previous PEG's	Date of first PEG	Date of PEG removal	Duration of PEG treatment	PEG complication	Age of GC fistula (d)	Previous antibiotics	OTSC type	Date of OTSC placement	Method	Successful immediate closure	Long term resolution of leak	Follow-up (d)	Complications
Case 1	67	F	Cerebral ischemia, tongue carcinoma	3	23/07/09	20/01/11	546	Chronic, recurrent infections with gastrocutaneus fistula	203	Yes	11/3a	11/08/11	Suction and anchor	Yes	Yes	1875	No
Case 2	23	F	Cystic fibrosis	1	31/12/11	01/06/15	1248	Persisting gastrocutaneus fistula	241	No	11/6a	28/01/16	Suction	Yes	Yes	244	No
Case 3	23	M	Cystic fibrosis	1	30/07/12	18/06/15	1053	Persisting gastrocutaneus fistula	144	No	11/6a	09/11/15	Suction	Yes	Yes	324	No
Case 4	52	F	Oropharyngeal carcinoma	1	30/12/11	18/01/13	385	Persisting gastrocutaneus fistula	850	No	11/6a	18/05/15	Suction	Yes	Yes	499	No
Case 5	52	M	Tongue carcinoma liver cirrhosis	1	23/08/12	13/09/12	21	Leaking gastrostomy due to ascites	NA	No	14/6a	13/09/12	Suction	Yes	Yes	1476	No
Mean	43						808		360							884	

PEG: Percutaneous endoscopic gastrostomy; OTSC: Over-the-scope-clips; F: Female; M: Male; NA: Not applicable.

from chronic disease associated with a catabolic metabolism (cystic fibrosis, chemotherapy for neoplasia, liver cirrhosis). Patients 2 and 3 had cystic fibrosis and required additional feeding through a PEG tube due to malnutrition. Patient 1, patient 4 and patient 5 suffered from tongue or oropharyngeal carcinoma, respectively and needed PEG-feeding during radio-chemotherapy. Patient 5 additionally suffered from refractory ascites due to decompensated liver cirrhosis. The mean age of the patients was 43 years. The mean duration of prior PEG treatment was 808 d (d) in all 5 patients while the time period was shortest in patient 5 (21 d).

Patient 1 suffered from chronically infected PEG sites necessitating antibiotic treatment applying various different regimes and following two changings of the PEG site. Upon suction during OTSC® placement, pus drained through the fistula towards the endoscope (Figure 1). Three patients (patients 2-4) suffered from a chronically draining and persisting GCF after PEG tube removal. Patient 5 suffered from refractory ascites due to decompensated liver cirrhosis complicated by bacterial peritonitis following PEG insertion. Therefore, immediate and tight OTSC® closure of the gastrostomy was performed immediately after PEG tube removal.

The mean duration from PEG tube removal to fistula closure in patients 1-4 was 360 d (range 144-850 d).

A small sized OTSC® (size 11 mm) was sufficient in patients 1-4 to achieve successful and tight fistula closure. In patient 5, a size 12 mm OTSC® was chosen for the first closure attempt. After deployment, leakage of ascites into the stomach was noticed suggesting incomplete closure. Therefore, the 12 mm OTSC® was removed using a standard rat-tooth forceps. In a second attempt during the same procedure ascites-tight closure of the GCF was accomplished. In patient 1, we used suction and the anchoring device for appropriate clip deployment. Suction through the working channel of the endoscope alone was then sufficient for adequate clip placement in all the four cases that followed.

Successful immediate GCF closure was accomplished in all 5 patients. After a mean follow-up time of 746 d (range 186-1737 d), all five leaks showed persistent long-term fistula closure. All clips remained in place with some overgrowing granulation tissue, but patients were asymptomatic; no abdominal discomfort or pain was reported. No OTSC®-associated complications occurred and none of the clips had to be removed. On a skin level, scaring and retraction at the PEG site were minimal.

Figure 1 Upon suction during over-the-scope-clips placement, pus drained through the fistula towards the endoscope. A: Patient 1, arrow indicates pus; B: Patient 2; C: Patient 3; D: Patient 4; E: Patient 4, fistula after OTSC deployment; F: Patient 5, alignment of OTSC using a guide wire. OTSC: Over-the-scope-clip.

DISCUSSION

We present the first single-center case series showing successful endoscopic GCF closure using the OTSC® device in middle-aged patients suffering from severe comorbidities. Since the introduction of the PEG in 1980 by Gauderer *et al*[21] surgery has been the treatment of choice for persisting GCF. Before the introduction of the OTSC®, the endoscopic armamentarium for GCF closure comprised mainly clip application, suture, gluing and coagulation techniques[13-17]. Alongside with the evolution of interventional endoscopy, the OTSC® device has gained significant importance as a sophisticated closure tool for various gastrointestinal conditions. The classical indications for OTSC® treatment are gastrointestinal perforations[3], leakages[4], fistulae[5] and uncontrolled bleedings[22]. These classical indications have lately been broadened to include SEMS fixation[23], closure of Peroral Endoscopic Myotomy access[24] within the esophagus as well as diameter reduction of gastrojejunal anastomosis after gastric bypass[25]. As recently shown by our group in a large cohort[26], traumatic or inflammatory fistulae are the most challenging conditions in regards to closure success rate. OTSC® closure of persisting GCF after PEG tube removal is a specific subgroup within this fistula group and is thus not comparable to classic chronic GCF in other conditions in regards to closure efficacy. We argue, based on our results, that due to the removal of the inserted foreign body (PEG tube) and the absence of chronic inflammation, OTSC® closure in GCF is far more promising in regards to successful closure compared to self-developing inflammatory fistulae. Long-term immunosuppressive therapy is a known risk factor for impaired wound healing and might therefore promote persistence of GCF after PEG removal. Catabolic metabolism in chronically ill patients seems to have the same effect. Geriatric patients are prone to suffer from persisting GCF suggesting that age itself is a risk factor for impaired natural closure of the PEG tunnel. Our mean patient age (43 ± 24 years) was significantly lower compared to the only existing comparable case series by Singhal *et al*[2] (mean age 84.4 ± 8.75 years). Yet, all of our patients suffered from chronic disease associated with a catabolic metabolism. We therefore suggest, that the patients' tissue regeneration was compromised allowing the PEG tunnel to persist after tube removal. Once a chronic GCF is triggered by an immunocompromised state of any origin, the GCF still differs much from conventional inflammatory fistulae in the gastrointestinal tract. This fact might be due to the integrity of the tissue surrounding the fistula orifice in GCF compared to the damaged surrounding tissue in inflammatory fistulae. Therefore, effective clip placement and persistent attachment is far more challenging in inflammatory fistulae. In addition to the immunocompromised state, four out five patients underwent a long-term PEG treatment (> 6 mo) as the main risk factor for developing persistent GCF after PEG tube removal[18,19].

Portal hypertension with tense ascites is known

to hinder closure of abdominal wall fistulae[27,28]. We therefore decided to immediately close the GCF in patient 5 after PEG tube removal. Whether or not previous gastropexies play a role in this particular setting is unknown. Since we so far only treated one patient with ascites for closure after PEG tube removal, a general recommendation cannot be given yet. Until there will be more data available in the future, individual solutions will need to be sought for.

Even though the number of patients in our case series is relatively small, our high closure success rate (100%) is in accordance with the success rate presented by Singhal *et al*[2] (90%). These results stand in clear contrast to the low long-term success rate of 30% published by our group for inflammatory fistulae[26]. Compared to Singhal *et al*[2], our follow-up period was clearly longer and shows that there is a low rate of long term failures after endoscopic fistula closure. Although the OTSC® is a foreign body with a drop-off rate of 0% in our case series, the clips did not induce any symptoms and no need for removal arose.

No major complications connected to the OTSC® treatment were recorded in our study. In one case, a too small-sized OTSC® was chosen initially and failed to achieve tight GCF closure. The clip was easily removed with a standard forceps and did not interfere with a second deployment of a larger sized OTSC®. In case of strong clip adherence or any other indication for clip removal, OVESCO Endoscopy AG (Tübingen) has introduced an OTSC® clip cutter system. In our large OTSC® cohort published previously, only a few minor complications occurred (in 6 out of 233 cases)[26]. These included accidental deployment of the OTSC® on the patients' tongue in the very first cases and superficial mucosal laceration of the esophagus due to a too large-sized OTSC®.

In this case series, we adapted the clip size to the particular features of the GCF, the patient and the clinical setting. We used one size 14 clip, which can cause difficulties in passing the upper esophageal sphincter due to its large diameter. Compared to the study of Singhal *et al*[2] and Sulz *et al*[8], we included patients suffering from substantially more long standing GCF (mean fistula age = 360 d). Wright *et al*[29] performed electrocautery of the GCF before clip closure. Unfortunately, the authors did not discuss the reason for this step before OTSC® closure in their publication. One could hypothesize that the granulation tissue caused by electrocautery would promote GCF healing. Even though we did not perform this step, we were able to show that even epithelialized, long-lasting PEG fistulas should not be excluded from an endoscopic closure attempt using the OTSC® device.

In conclusion, endoscopic closure of persistent GCF after PEG tube removal using an OTSC® is a promising indication with a potentially high immediate and long term closure rate and with limited complications to be feared.

COMMENTS

Case characteristics
Five middle-aged patients with severe comorbidities developed gastro cutaneous fistula (GCF) after percutaneous endoscopic gastrostomy (PEG) tube removal. Four patients had long-standing symptomatic fistulas (mean PEG dwell time 808 d), while one patient developed a leaking gastrostomy due to ascites.

Research frontiers
Over-the-scope-clips (OTSC®) application in the gastrointestinal tract is safe and effective in large variety of indications. There is evidence in the literature that OTSC application is safe and effective for endoscopic closure for GCF after PEG tube removal. However this evidence is mostly limited to a geriatric population with short standing GCFs.

Innovations and applications
This case series is the first to our knowledge to show safe and effective closure of GCF after PEG tube removal in a middle-aged patient population with severe comorbidities and long standing GCF.

Terminology
OTSC application for GCF closure after PEG Tube removal.

Peer-review
The manuscript provides anecdotal support for the application of OTSC for long standing GCFs after PEG removal.

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CASE REPORT

Successful endoscopic fragmentation of large hardened fecaloma using jumbo forceps

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Abstract

We present a rare case of fecaloma, 7 cm in size, in the setting of systemic scleroderma. A colonoscopy revealed a giant brown fecaloma occupying the lumen of the colon and a colonic ulcer that was caused by the fecaloma. The surface of the fecaloma was hard, large and slippery, and fragmentation was not possible despite the use of various devices, including standard biopsy forceps, an injection needle, and a snare. However, jumbo forceps were able to shave the surface of the fecaloma and break it successfully by repeated biting for 6 h over 2 d. The ability of the jumbo forceps to collect large mucosal samples was also appropriate for achieving fragmentation of the giant fecaloma.

Key words: Fecaloma; Jumbo biopsy forceps; Systemic scleroderma; Mixed connective tissue disease

Core tip: A fecaloma can potentially cause intestinal obstruction or perforation. Reduced colonic peristaltic activity is present in systemic scleroderma and can lead to the formation of fecalomas, which are typically treated by surgery. Jumbo forceps, which have larger cups than standard capacity biopsy forceps, can collect large samples and have increased efficacy in diagnosis. To the best of our knowledge, this is the first case report of fecaloma cured by endoscopic fragmentation with jumbo forceps.

INTRODUCTION

A fecaloma is a hardened mass of food, discarded gastrointestinal cells, and digestive juice, which can become lodged in the gastrointestinal tract. A giant fecaloma must be removed because it can potentially cause intestinal obstruction, megacolon, and gastrointestinal perforation. Surgical removal is required if a fecaloma cannot be removed endoscopically. We report the successful fragmentation and removal of an extremely hardened fecaloma using jumbo forceps in a patient with gastrointestinal motility disorder resulting from mixed connective tissue disease (MCTD).

CASE REPORT

The patient is a 59-year-old woman who was diagnosed with MCTD at the age of 52. She had been largely affected by systemic scleroderma, which resulted in reduced gastrointestinal motility. At 55 years of age, she experienced the onset of superior mesenteric artery (SMA)-like syndrome. Since then, she had received oral drugs, such as a proton-pump inhibitor and prednisolone, and a small amount of water and was provided sustenance with a total parenteral nutrition solution. She presented at our hospital with queasiness and periumbilical abdominal pain, which had persisted for 3 mo. She was 159 cm in height and weighed 41 kg.

Abdominal computed tomography scans showed a highly absorbing round substance, which was 7 cm in size, with layered calcification in the transverse colon, resulting in a diagnosis of fecaloma (Figure 1). A colonoscopy revealed that a giant brown fecaloma occupied the lumen of the dilated transverse colon. A shallow 3-cm ulcer covered with a white coat was present near the fecaloma. The white coat was adherent to the fecaloma, suggesting it to be the cause of the ulcer (Figure 2).

As the fecaloma was huge and actually occupied the colonic lumen, endoscopic extraction was attempted without laxatives because it was thought that the oral administration of laxatives, such as polyethylene glycol, might cause an intestinal obstruction. The surface of the fecaloma was hard, large and slippery, and fragmentation was not possible despite the use of biopsy forceps (Radial Jaw 4 Biopsy Forceps Standard Capacity, Boston Scientific, United States), an injection needle for endoscopic treatment (Impact Flow, Top, Japan), a needle knife (KD-10Q-1-A, Olympus, Japan), and a snare for endoscopic mucosal resection (EMR) (Snare Master, Olympus,

Figure 1 Abdominal computed tomography-scan demonstrating 7 cm fecaloma in the transverse colon.

Figure 2 Lower gastrointestinal endoscopy revealed dilated colonic lumen and brown fecaloma in the transverse colon. There is 2 cm ulcer near the fecaloma.

Japan). Consequently, the surface of the fecaloma was shaved using jumbo forceps (Radial Jaw 4 Jumbo Cold Polypectomy Forceps, Boston Scientific, Japan) with about ten passes, which scraped the surface and made it possible to advance the forceps into the fecaloma. The same procedure was then repeated several hundred times, aiming for the center of the fecaloma and resulting in gradual fragmentation (Figure 3). A total of 6 h over 2 d were required to break the fecaloma into fragments of a size that could pass through the anus. We used the midazolam as a sedative and the pentazocine as an analgesic. Midazolam was administered intravenously according to the degree of affliction and administered 5 mg per time of the procedure. Pentazocine was administered 15 mg per each procedure. The fecaloma was then eliminated using laxatives (Figure 4).

DISCUSSION

Fecalomas, or hardened masses of food, discarded gastrointestinal cells, and digestive juice in the gastrointestinal tract, exceed fecal impactions in hardness[1]. Fecalomas commonly develop in the sigmoid colon and the rectum, which have a narrower lumen than that of the right colon[2]. Underlying diseases reported to result in fecalomas include chronic fecal impaction, Hirschsprung's disease, psychiatric

Figure 3 Same procedure was then repeated several hundred times, aiming for the center of the fecaloma and resulting in gradual fragmentation. A: Jumbo forceps scrape off the surface of hardened fecaloma; B: Jumbo forceps split the fecaloma; C: Fecaloma is separated into two blocks by biting the jumbo forceps.

Figure 4 Abdominal computed tomography reveal the disappearance of the fecaloma.

disorders, and intestinal tuberculosis[3,4]. Generally, fecalomas cause intestinal obstruction, megacolon, and gastrointestinal perforation, and can even result in deep vein thrombosis and urinary tract compression on rare occassions[5-7]. Fecalomas must be treated to prevent the onset of these complications. Initial treatments include administration of laxatives, enemas, and stool extraction. When patients do not respond to these treatments, surgical extraction becomes necessary[8].

Our patient had MCTD and presented mainly with systemic scleroderma as the underlying disease. The frequency of gastrointestinal lesions is the highest among internal organ lesions associated with scleroderma. With the combined atrophy of smooth muscle in the intrinsic muscle layer, replacement by collagen fibers, and a nervous system disorder, dilatation of the gastrointestinal tract and reduced peristaltic activity occur. The percentage of gastrointestinal tract lesions in patients with scleroderma listed as the cause of death reportedly range from 6% to 12%[9]. In our patient, reduced segmental movement and peristaltic activity of the colon attributable to MCTD led to fecal impaction that progressed to a fecaloma in the transverse colon before reaching the left colon. Her small amount of water intake, likely associated with the SMA-like syndrome due to a loss of peristasis with the scleroderma, may also have contributed to the hardened fecaloma formation.

Our patient also had pulmonary hypertension associated with MCTD and used steroids. Therefore, she was at high risk of respiratory failure associated with surgery under general anesthesia and at an increased risk of anastomotic leakage in the intestinal tract. Endoscopic extraction of the fecaloma is an ideal treatment to avoid surgery for such patients with serious comorbidities. However, there are few reports describing endoscopic extraction of a large fecaloma. In previous reports, endoscopic extraction was successfully performed using conventional forceps and a snare for polypectomy[2,4]. In our patient, however, the fecaloma could not be fragmented with forceps or a snare, presumably due to its hardness and the slipperiness of its surface.

One case of fecaloma that was too slippery and hard to grasp with forceps has been reported. That fecaloma was dissolved by a cola injection and was sufficiently softened to be removed[10]. Cola injection are often reported as the method for the removal of gastric bezoars. The mechanism of this method is considered the contribution of carbon dioxide bubble and the secretolic activity of sodium hydrogen carbonate. Jumbo forceps combined with a cola injection may be more efficient therapy for the removal of fecaloma endoscopically.

The fecaloma in this patient, which could not be fragmented with standard capacity forceps or a snare for EMR, was successfully grasped and fragmented with jumbo forceps. Jumbo forceps, which have larger cups than the standard capacity biopsy forceps, can collect large samples. Therefore, they are used in the resection of the colonic adenomas. When the routine biopsy forceps used at our institution are compared with the jumbo cold polypectomy forceps used in fecaloma fragmentation in the present patient, there are large differences in the dimensions of the outer diameter of the cup (2.2 mm and 2.8 mm, respectively), the maximum opening width (7.1 mm and 8.8 mm), and the quantities which can be removed (5.3 mm^3 and 12.4 mm^3). The size and shape of the jumbo forceps, for the collection of large quantities of fecaloma contents, was appropriate for achieving fragmentation of a giant fecaloma in our patient.

In summary, Jumbo forceps might be a useful device

for fragmenting hardened fecalomas.

COMMENTS

Case characteristics
A 59-year-old woman with abdominal pain, which had persisted for 3 mo.

Clinical diagnosis
Queasiness and peri-umbilical abdominal pain.

Differential diagnosis
Superior mesenteric artery syndrome, ileus, constipation, colonic cancer, volvulus of sigmoid colon.

Laboratory diagnosis
All labs were within normal limits.

Imaging diagnosis
Abdominal computed tomography scans showed a highly absorbing round substance, which was 7 cm in size, with layered calcification in the transverse colon.

Treatment
Endoscopic jumbo forceps break the fecaloma by repeated biting.

Related reports
Underlying diseases reported to result in fecalomas include chronic fecal impaction, Hirschsprung's disease, psychiatric disorders, and intestinal tuberculosis. Most of these cases needed the surgical treatments.

Term explanation
Jumbo forceps, which have larger cups than the standard capacity biopsy forceps, can collect large samples.

Experiences and lessons
Jumbo forceps might be a useful device for fragmenting hardened fecalomas.

Peer-review
This is a case report of a large faecaloma that was successfully fragmented by jumbo forceps.

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CASE REPORT

Endoscopic closure instead of surgery to close an ileal pouch fistula with the over-the-scope clip system

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Abstract

An ileal pouch fistula is an uncommon complication after an ileal pouch anal anastomosis. Most patients who suffer from an ileal pouch fistula will need surgical intervention. However, the surgery can be invasive and has a high risk compared to endoscopic treatment. The over-the-scope clip (OTSC) system was initially developed for hemostasis and leakage closure in the gastrointestinal tract during flexible endoscopy. There have been many successes in using this approach to apply perforations to the upper gastrointestinal tract. However, this approach has not been used for ileal pouch fistulas until currently. In this report, we describe one patient who suffered a leak from the tip of the "J" pouch and was successfully treated with endoscopic closure *via* the OTSC system. A 26-year-old male patient had an intestinal fistula at the tip of the "J" pouch after an ileal pouch anal anastomosis procedure. He received endoscopic treatment *via* OTSC under intravenous anesthesia, and the leak was closed successfully. Endoscopic closure of a pouch fistula could be a simpler alternative to surgery and could help avoid surgery-related complications.

Key words: Over-the-scope clip system; Endoscopic treatment; Restorative proctocolectomy; Ulcerative colitis; Ileal pouch fistula

Core tip: Leaks from the tip of the J-pouch are less likely to occur but are associated with pouch failure after ileal pouch-anal anastomosis. Salvage surgery has been commonly performed to resolve these leaks, and the surgery typically includes laparotomy with either pouch repair or pouch resection. In this report, we present a patient with a fistula on the tip of the "J" in the pouch who was successfully treated with the over-the-scope

clip system. We propose that this method could be used as an alternative to surgery to avoid surgery-related complications in patients with pouch fistula.

INTRODUCTION

A leak from the tip of the J-pouch was defined as a leak from the blind limb of the J-pouch with an endoscopic finding or imaging results, including a Gastrografin enema, computed tomography scan, magnetic resonance imaging, or intraoperative diagnosis made during reoperation[1-3]. Although leaks from the tip of the J-pouch are less likely to occur than leaks from anastomosis, these leaks are known to be associated with pouch failure after ileal pouch-anal anastomosis (IPAA). Salvage surgery has been commonly used for leaks and typically includes laparotomy with either pouch repair or pouch resection[3].

Recently, interventional endoscopy has evolved into an effective alternative to salvage surgery for leakages or perforations if the patient is not in a critical septic condition[4,5]. The over-the-scope clip (OTSC) system (Ovesco Endoscopy AG, Tübingen, Germany) was initially developed for hemostasis and leakage closure in the gastrointestinal tract during flexible endoscopy. These "bear claws" apply high compression forces on the tissue and facilitate stable closure[2]. In cases of sufficient closure, surgical intervention can be avoided. For acute endoscopy-associated perforations, the mean success rate is 90%. For postoperative leaks, the success rate is 68%[6]. However, the usage of OTSC in pouch fistula has not been reported yet. Due to the success of the technique and the opportunity to avoid the considerable risks of surgery, we tested the OTSC system in this patient and achieved success.

Endoscopic management of leakage and perforation in the upper gastrointestinal tract has gained prominence because it enables minimally invasive treatment of fistulas and avoids the morbidity and mortality of surgical intervention. However, it is important that the lesion is fresh, does not have fibrotic alterations or inflammation and is usually free from foreign bodies in the leakage area[1]. In this case, we used an active washing and drainage system for 4 wk to make the lesion of the fistula clear and reduce inflammation before the endoscopic closure.

CASE REPORT

A 26-year-old male patient was admitted to our hospital due to fever and severe bloody diarrhea. Endoscopy

Figure 1 Methylene blue was injected *via* the trocar site and flooded the enteric cavity to reveal a leak in the pouch.

Figure 2 Urografin was injected *via* the sinus, and the pouch was visualized to confirm a fistula on the top of the "J" pouch.

revealed acute ulcerative colitis with a Mayo score of 12. He failed to respond to intravenous corticosteroid therapy, and toxic megacolon appeared. He underwent a total laparoscopic restorative proctocolectomy with IPAA (with a loop ileostomy). After surgery, the patient recovered without complications and was discharged 10 d after the operation. Six weeks later, he was readmitted to our department for ileostomy reversal. Prior to the operation, pouch endoscopy, antegrade Gastrografin enema, and an abdominal computed tomography scan did not reveal an abnormality. A stapled side-to-side ileostomy reversal was performed, and he was discharged 3 d after the operation. One month after the final operation, he developed a high fever again (39.9 ℃) with stool leaking from the right lower abdominal trocar site. Colonoscopy and a Gastrografin enema confirmed there was a fistula on the tip of the "J" Pouch (Figures 1 and 2). He was treated with percutaneous drainage, total parenteral nutrition (TPN) and bowel rest. Signs of intra-abdominal sepsis were controlled after 4 wk of therapy. However, there was persistent feculent discharge from the fistula tract. The patient was comprehensively informed about the endoscopic procedure.

DISCUSSION

Alternatives, such as surgical treatment, were also

Figure 3 Fistula was closed by the over-the-scope clip system.

Figure 4 Gastrografin enema confirmed the fistula was closed.

discussed with the patient, and written informed consent was obtained. The patient was informed about the possible failure of the endoscopic procedure and the eventual need for an operation that may lead to pouch repair or even pouch resection. Endoscopic evaluation and a Methylene blue injection demonstrated a pouch-cutaneous fistula on the tip of the "J" pouch. Suction was used to draw the defect into the OTSC applicator cap, and the clip (12-mm OTSC) was applied, which completely closed the fistula tract (Figure 3). The complete procedure was performed in 21 min. After the procedure, he was given TPN and bowel rest for another 2 wk to allow the fistula to heal. Then, he resumed oral feeding without signs of a fistula or leakage. He was followed up with for another 2 mo and remained asymptomatic. A Gastrografin enema later confirmed that the fistula tract had healed (Figure 4).

In conclusion, although the OTSC system had mostly been used for treating upper gastrointestinal perfusion and fistulas and fistulas on the top of the pouch are rare and often are cured through surgery, we still suggest attempting OTSC to treat a pouch fistula due to the easy manipulation and reduction of immediate operative intervention rates, and length of hospitalization[7,8]. Even if the endoscopic closure failed, the salvage surgery would still be feasible.

ACKNOWLEDGMENTS

COMMENTS

Case characteristics
This was a young man with severe ulcerative colitis who received ileal pouch-anal anastomosis (IPAA) and developed a fistula after surgery.

Clinical diagnosis
Intestinal fistula.

Differential diagnosis
Leaks from the tip of the J-pouch, Anastomotic fistula, Crohn's disease, abscess.

Laboratory diagnosis
The patient had a high blood white cell count and fever; thus, he was diagnosed with an intra-abdominal infection.

Imaging diagnosis
Leaks from the tip of the J-pouch.

Pathological diagnosis
He was cured with non-surgical treatment, and there was no pathological diagnosis.

Treatment
Closed the fistula with the over-the-scope clip (OTSC) system.

Related reports
A J-pouch is the most common configuration of IPAA used currently. Risk factors for pouch-related sepsis complications include steroid use, a body mass index greater than 30, a patient older than 50 years, diagnosis of inflammatory bowel disease, and surgeon inexperience. Surgical approaches have always been used for pouch-related sepsis arising from pouch fistula.

Term explanation
Fistula is a pouch-related septic complication. There are 4 main pouch sources of fistula, including the appendage, pouch reservoir, inflow limb, and pouch-rectal anastomosis. Each can fistulize to different areas, including the abdominal wall, vagina, bladder, and other loops of the small bowel.

Experience and lessons
This was a successful application of OTSC to cure a patient with a pouch fistula that could partially replace surgery and avoid surgery-related complications. However, the authors must keep the tissue around the fistula fresh so percutaneous drainage, total parenteral nutrition and bowel rest were necessary.

Peer-review
The paper is well written.

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CASE REPORT

Combination of concurrent endoscopic submucosal dissection and modified peroral endoscopic myotomy for an achalasia patient with synchronous early esophageal neoplasms

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Abstract

Achalasia is generally accepted as a condition associated with an increased risk for developing esophageal squamous cell carcinoma. In our paper, we introduced an achalasia patient combined with synchronous early esophageal neoplasms. We performed a combination of concurrent endoscopic submucosal dissection (ESD) and peroral endoscopic myotomy (POEM). No complications other than postoperative pain that needed morphine treatment for two days had occurred. Dysphagia was significantly improved. Neither reflux nor cough occurred. The short-term efficacy and safety of our case is favor-able and suggests that concurrent ESD and POEM could be a treatment option to such patients.

Key words: Achalasia; Early esophageal neoplasm; Endoscopic submucosal dissection; Modified peroral endoscopic myotomy

Core tip: Achalasia is generally accepted as a condition associated with an increased risk for esophageal squamous cell carcinoma. However, cases of multiple synchronous neoplastic lesions in an achalasia patient had been rarely reported. In this paper, we performed a combination of concurrent endoscopic submucosal

dissection (ESD) and peroral endoscopic myotomy (POEM) on one patient suffering from esophageal achalasia for more than six years and esophageal neoplasia lesions for one month. The short-term efficacy and safety of our case is favorable and it suggests that concurrent ESD and POEM could be an option of treatment to this kind of patients.

INTRODUCTION

Peroral endoscopic myotomy (POEM) is used for treatment of achalasia as Endoscopic submucosal dissection (ESD) for treatment of early esophageal cancer. In this paper, we performed the two procedures on a patient suffering from esophageal achalasia for more than six years and early esophageal cancer for one month simultaneously. The symptoms of the patients relieved significantly while no intraoperative or postoperative complications occurred. The present report describes the safety and efficacy of the combination treatment of POEM and ESD for this kind of patients.

CASE REPORT

Before POEM, the patient was scored as Eckardt score 6 and Grade Ⅱ. Chest computed tomography showed an obviously dilated esophageal cavity with large amount fluid retention in the lumen. The cardiac muscle layer was significantly thickened (Figure 1). Esophago-gastroduodenoscopy also revealed significantly expanded esophageal lumen and remarkable fluid retention. After pumping the liquid and washing the lumen repeatedly, all of esophagus mucosa appeared edematous and turbid white. A reddish lesion (1.5 cm × 1.0 cm) was detected at 24 cm from the incisor. The lesion was identified as type Ⅳ of intra-epithelial papillary capillary loops (IPCLs) according to Inoue's classification by narrow-band imaging with magnification and background colorization was also seen. Biopsy histopathology showed normal tissue with inflammation. Another lesion (1.0 cm × 0.8 cm) was detected at 32 cm and identified as IPCLs type Ⅴ1, and the biopsy histopathology showed high-grade intraepithelial neoplasia. The third lesion (1.0 cm × 1.5 cm) was found at 34 cm disclosed type Ⅳ-Ⅴ1 IPCLs, and analysis of the biopsy revealed low-grade intraepithelial neoplasia. The neoplastic lesions were located in the anterior wall of the esophagus. The esophageal lumen below 30 cm was distorted and dilated. The cardia was tightly closed and the resistance was significant (Figure

2). According to the endoscope and pathology funding, the patient was diagnosed with Sigmoid-type achalasia combined with neoplastic lesions.

A combination treatment scheme of ESD and POEM was performed. The patient was fasted for over 24 h before procedure. Preoperative antibiotics were applied prophylactically. The patient was intubated and brought under intravenous anesthesia. Carbon dioxide insufflation was used throughout the procedure. First, ESD was conducted for both neoplastic lesions located at 32 cm and 34 cm. Immediately after ESD, a 2 cm longitudinal mucosal incision was made after submucosal injection at the opposite side wall of the ESD wound, the posterior wall. Meanwhile, a short-tunnel POEM surgery [about 35 cm from the esophagogastric junction (EGJ)] was performed; the muscularis propria was completely cut to 3 cm below the cardia. Owing to repeated injections of botulinum toxin and balloon dilatation, the submucosal tunnel creation was rather difficult. In the process of cutting the whole layer of muscularis propria, we found that the circular muscle of esophagus was obviously thickened (about 1 cm). We then exposed the esophageal fiber membrane and encountered the omentum in the cardia. After completing full-thickness myotomy, the entry site was closed using hemostatic clips (Figure 3). Subsequent histological evaluation combined with relevant immunohistochemistry produced a definitive diagnosis of high-grade intraepithelial neoplasia with a component of scattered low-grade intraepithelial neoplasia. The lateral and vertical margins were free (Figure 4). The patient was given liquid diet after 48 h of fasting. Because of the small perforation in the POEM, antibiotics were used to prevent infection. The patient felt severe pain and was given analgesic treatment. Two days later, the pain was relieved and pain medication was discontinued; three days later, the pain disappeared, antibiotics were stopped. Dysphagia was significantly improved. Neither reflux nor cough occurred. He was discharged 7 d later uneventfully. Two months after the procedures, the patient was largely asymptomatic with an increase of 3.5 kg body weight and was score as Eckardt 0. The Endoscopic examination showed the diameter of the esophageal lumen was significantly decreased. No food residual was found in the esophagus and the inflammatory mucosa turned normal. The ESD wounds healed completely. Gastroscope could pass through the EGJ without any resistance. Barium swallow examination showed that the emptying was smooth through the cardia. Due to the particularity of the patient, achalasia combined with neoplastic lesions, long time follow-up will be performed.

DISCUSSION

Esophageal achalasia is caused by esophageal neuromuscular dysfunction associated with lack of peristalsis of the esophagus, high pressure of lower esophageal sphincter and weakening response to the swallowing relaxation. Esophageal retention of foods and fluids,
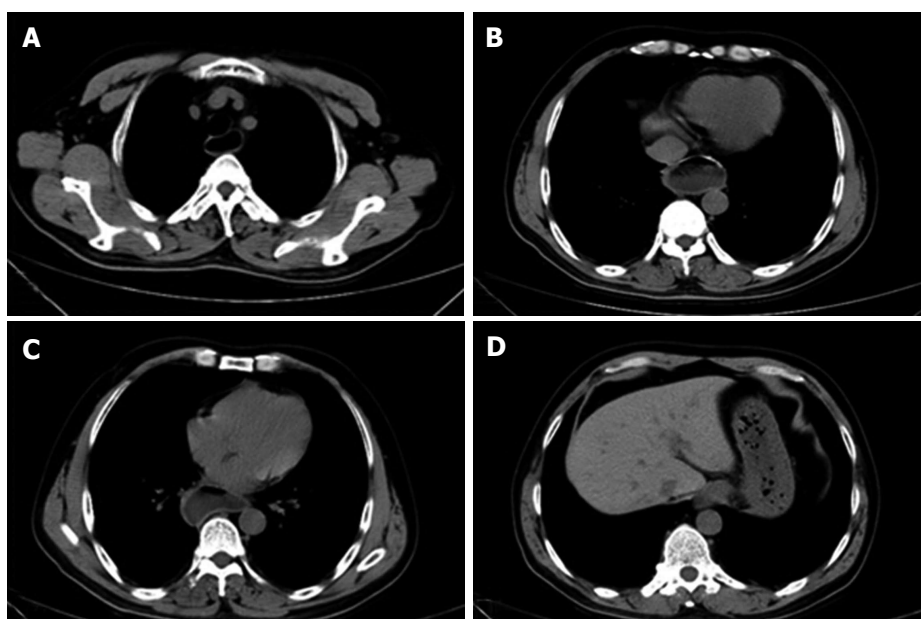
Figure 1 Chest computed tomography examination showed that the esophageal cavity was obviously expanded (A-C); large amount of fluid retention was seen in the lumen (D). The cardiac muscle layer was significantly thickened.
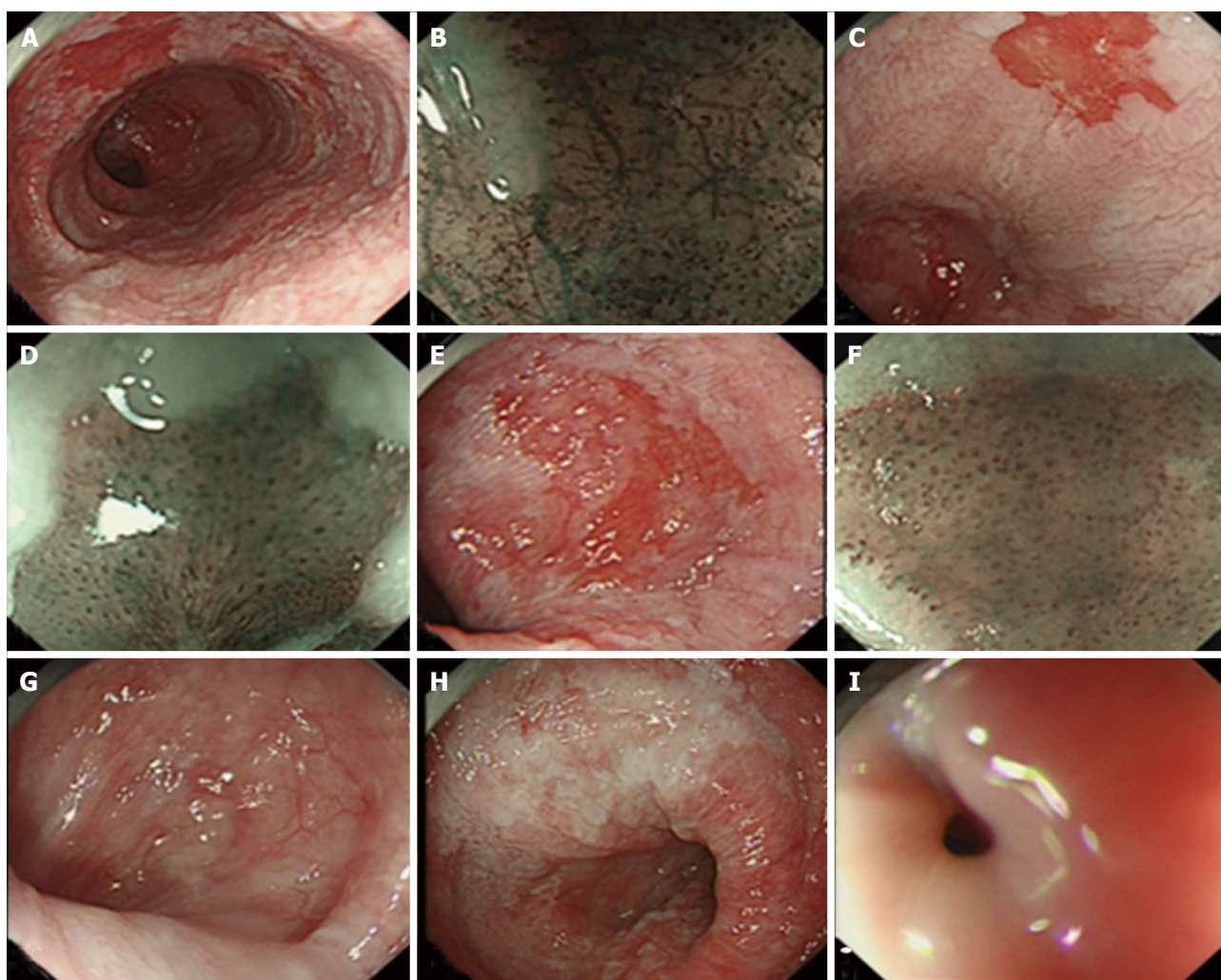

Figure 2 Cardia was tightly closed and the resistance. A, B: Lesion at 24 cm from the incisor and Narrow-band imaging (NBI) with magnification revealed type Ⅳ intra-epithelial papillary capillary loops (IPCLs) according to Inoue's classification; C, D: Another lesion at 32 cm, IPCLs were type Ⅴ1; E, F: The third lesion in 34 cm IPCLs were type Ⅳ-Ⅴ; G-I: The esophageal lumen below 30 cm was distorted and enlarged. The cardia was tightly closed; the resistance is significant.

Figure 3 Peroral endoscopic myotomy procedure. A: A 2-cm longitudinal incision was made into the mucosa after injection of natural saline with indigo carmine and epinephrine; B: A submucosal tunnel from the esophagus to the gastric cardia was created using a Dual knife; C: The submucosal tunnel was completed; D and E: The muscularis propria were dissected and the myotomy was completed using a Dual knife; F: The entry site in contralateral side of Endoscopic submucosal dissection wound was closed using hemostatic clips.

Figure 4 Endoscopic submucosal dissection procedure and pathological examination. A-D: Marking around the lesion using Dual knife; submucosal injection of 10 mL saline with 0.3% indigo carmine and 1:100000 epinephrine; cutting open the mucosa; the submucosa was stripped and the lesion was completely resected; E, F: Pathological examination of the resected specimen revealed high-grade intraepithelial neoplasia with a component of scattered low-grade intraepithelial neoplasia. Both of the lateral and vertical margins were negative of tumor.

bacterial overgrowth, and impaired clearance of regur-   which is potentially associated with an increased risk

of hyperplasia, dysplasia, and esophageal cancer[1-3]. Wychulis *et al*[4] have reported a 7-fold increased risk of esophageal squamous cell carcinomas in achalasia patients compared to the general population. However, cases of multiple synchronous neoplastic lesions in an achalasia patient had been rarely reported.

Tang *et al*[5] reported an achalasia patient with a small dysplastic lesion treated successfully with both of endoscopic mucosal resection (EMR) and POEM simultaneously. We performed ESD instead of EMR, as the size was larger than that of Tang's case and ESD was more suitable than EMR for resection.

One reason we chose the posterior wall as the position of the mucosal incision of POEM is that it is safe and effective. Now this operation is used for a lot of POEM. The other reason is to avoid the impact of ESD wound and incision of POEM. During the procedure, the patient was left decubitus. As the esophagus was distorted obviously, it was difficult to ensure that the tunnel was not deviated and lost. Aiming for a straight tunnel, the position of liquid concentration and the circular muscle layer were used as references. The tunnel direction was viewed repeatedly in the esophageal lumen.

The reasons that we did not perform ESD and POEM separately were as follows: First, the patient would need to take the risks associated with two times of general anesthesia. In addition, if POEM was performed first, it would result in submucosal fibrosis which might make the subsequent ESD difficult. If ESD first, large amount of fluid retention in the sigmoid-type achalasia would prolong the mucosal healing and even cause unfavorable complication such as bleeding in delayed fashion or systemic infection. As the esophageal cavity was obviously dilated, there was enough luminal space for both ESD and POEM conducted at a time. Recently, modified POEM with shorter submucosal tunnel was confirmed to have good safety and excellent short-term efficacy for achalasia, even for the sigmoid-type[6,7]. Therefore, to reduce operation duration, we generated a short submucosal tunnel for POEM after ESD. Moreover, considering the risk of metachronous neoplasms, long submucosal tunnel creation would result in extensive submucosal fibrosis and would make further if needed ESDs much more difficult and dangerous. Before the ESD mucosal incision, saline was injected into the submucosal layer. The lifting sign was good. We estimated that the lesion had no significant adhesions; the extent of the lesion was not large. There was little risk of perforation during ESD. Even if there was a small perforation, it was also relatively safe to establish a tunnel opening on the contralateral mucosa in case of that the perforation was closed by hemostatic clips and esophageal lumen was remarkably dilated. Fortunately, according to the location of the neoplastic lesions and good physical condition of the patient, two procedures were successfully performed simultaneously.

This is the first case of an achalasia patient with synchronous early esophageal neoplasms treated by a combination of concurrent ESD and POEM. The short-term efficacy and safety of our case is favorable and suggests that concurrent ESD and POEM could be an option of treatment to this kind of patients. More cases, however, are warranted to show its safety and efficacy.

COMMENTS

Case characteristics
A 50-year-old male suffering from esophageal achalasia and synchronous early esophageal neoplasms was treated by a combination of concurrent endoscopic submucosal dissection (ESD) and peroral endoscopic myotomy (POEM).

Clinical diagnosis
Esophageal achalasia, early esophageal neoplasms.

Differential diagnosis
Carcinoma of gastric cardia, reflux esophagitis, angina pectoris.

Laboratory diagnosis
All initial biochemical and hematological parameter results were within normal limits.

Imaging diagnosis
Chest computed tomography showed an obviously dilated esophageal cavity with large amount fluid retention in the lumen. The cardiac muscle layer was significantly thickened.

Pathological diagnosis
High-grade intraepithelial neoplasia.

Treatment
Combination of concurrent endoscopic submucosal dissection and modified peroral endoscopic myotomy.

Experiences and lessons
This is the authors' first case of an achalasia patient with synchronous early esophageal neoplasms treated by a combination of concurrent ESD and POEM. This case confirmed that it's safety and efficacy when there was no effect between the locations of the two operations.

Peer-review
This is the interesting case report describing combination of ESD and POEM for an achalasia patient with early esophageal neoplasms. As the authors mention, combination treatment of ESD and POEM seems to be effective in this case.

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FLYLEAF

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Endoluminal solutions to bariatric surgery complications: A review with a focus on technical aspects and results

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Abstract

Obesity is a growing problem in developed countries, and surgery is the most effective treatment in terms of weight loss and improving medical comorbidity in a high proportion of obese patients. Despite the advances in surgical techniques, some patients still develop acute and late postoperative complications, and an endoscopic evaluation is often required for diagnosis. Moreover, the high morbidity related to surgical reintervention, the important enhancement of endoscopic procedures and technological innovations introduced in endoscopic equipment have made the endoscopic approach a minimally-invasive alternative to surgery, and, in many cases, a suitable first-line treatment of bariatric surgery complications. There is now evidence in the literature supporting endoscopic management for some of these complications, such as gastrointestinal bleeding, stomal and marginal ulcers, stomal stenosis, leaks and fistulas or pancreatobiliary disorders. However, endoscopic treatment in this setting is not standardized, and there is no consensus on its optimal timing. In this article, we aim to analyze the secondary complications of the most expanded techniques of bariatric surgery with special emphasis on those where more solid evidence exists in favor of the endoscopic treatment. Based on a thorough review of the literature, we evaluated the performance and safety of different endoscopic options for every type of complication, highlighting the most recent innovations and including comparative data with surgical alternatives whenever feasible.

Key words: Bariatric surgery; Bariatric complications; Endoscopic treatment; Leaks; Stenosis; Sleeve gastrectomy; Gastric Roux-en-Y bypass

Core tip: In developed countries obesity is a prevalent and rising problem. Bariatric surgery is the most effective treatment to obtain sustainable weight loss but postoperative complications may be serious and challenging to treat. The minimally-invasive character of

endoscopic treatment has led endoscopic management of bariatric complications to become a suitable alternative to surgery. In this article, we discuss the indications of endoscopic treatment after bariatric surgery and the available endoscopic techniques.

INTRODUCTION

Obesity is a major health problem with significant morbidity and mortality. An estimated 3.4 million deaths worldwide were caused by obesity in 2010, and its prevalence rose by 27.5% for adults between 1980 and 2013[1]. Due to the far superior results of surgical treatment compared with obesity medical therapy, the American Society for Metabolic and Bariatric Surgery stated a grade A recommendation for bariatric surgery for patients with a body mass index (BMI) $\geqslant$ 40 kg/m^2 or those with a BMI $\geqslant$ 35 kg/m^2 and comorbid conditions who have failed to respond to prior medical intervention[2]. The most frequent bariatric operations performed worldwide are Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) (Figure 1). Although Gastric Roux-en-Y bypass (RYGB) is the most effective bariatric surgery, it is technically demanding, and, therefore, SG has been increasingly performed due to its simplicity. Laparoscopic adjustable gastric banding (LAGB) is now an outdated procedure despite its safety profile because of its poor long-term results. Other bariatric techniques, such as biliopancreatic diversion with or without duodenal switch (BD/DS) and jejunoileal bypass, have been abandoned due to severe metabolic complications[3].

Weight-loss surgery has been associated with an important reduction in obesity-related medical complications, such as diabetes mellitus and other cardiovascular risk factors[4]. The increased use of laparoscopy and improvements of surgical techniques have led to a significant decrease in surgical complications with a current mortality lower than 1% in centers of excellence. However, postoperative complications are still common, and minimally invasive endoscopic treatments have gained popularity to avoid surgical reinterventions.

In the literature, up to 30% of patients present symptoms in the perioperative setting requiring endoscopic evaluation[5]. The most common symptoms are abdominal pain, nausea, vomiting, dysphagia and gastrointestinal bleeding. These symptoms are predictive of pathologic findings at endoscopy, and, interestingly, this predictive potential depends on the time elapsed from surgery. In the first 6 mo following surgery, 85% of upper endoscopic explorations had, at least, one abnormal finding *vs* 47% after 6 mo. In addition, time elapsed from surgery also predicts the type of complication; in the first 6 mo after the surgery, the incidence of staple-line dehiscence is higher whereas stomal ulcerations or strictures are less probable[5]. Optimal management should be individualized because surgical reconstruction may make endoscopic access and resolution difficult or even impossible. In addition to these local complications directly related to the surgical procedure, other long-term metabolic consequences secondary to the rapid loss of weight, such as gallstones or hepatobiliary disease, may further complicate the clinical scenario and may also require endoscopic management[5].

Because the majority of symptomatic patients are endoscopically evaluated, the gastroenterologists must be familiar with post-surgical anatomy and complications, and their endoscopic management. In this review, we will briefly describe the most frequent complications related to every type of bariatric surgical technique and the most recent and remarkable results about the endoscopic procedures with proven effectiveness.

GASTROINTESTINAL BLEEDING

Gastrointestinal (GI) bleeding after bariatric surgery can occur in the first 30 d following surgery as an early complication, or afterwards as a delayed one. Early bleeding usually presents within the first 48 h in 1%-5% of patients after RYGB[6]. SG presents a variable rate of bleeding between 0% and 8%[7] whereas LAGB is almost never complicated with bleeding (0.1%)[8]. The risk of iatrogenic perforations at the surgical site along with the self-limited character in most cases are the reasons why minor bleeding is usually managed conservatively with fluid resuscitation or blood transfusion and proton pump inhibitors. In cases of severe bleeding, endoscopic exploration is mandatory, or even surgical intervention when no blood exteriorization is observed and after CT diagnosis of extraluminal bleeding[9,10]. Late bleeding is usually secondary to anastomotic ulceration and is almost never extraluminal.

Endoscopy must be performed with minimal insufflation with CO_2 if possible. Upper endoscopy is able to reach the gastrojejunal anastomosis but a balloon-assisted enteroscopy may be required to access the excluded gastric remnant, which carries a risk of perforation due to the immature anastomoses and the traction forces during enteroscopy. In this situation, if a skilled endoscopist is not available, surgical intervention should be the first option.

After bariatric surgery, the most common bleeding is at the staple-line of the anastomotic gastrojejunostomy in RYGB but it can occur anywhere in the gastrointestinal tract. There are few studies published on this subject but endoscopic management of bleeding at the gastrojejunal anastomosis has been successfully managed with

Figure 1 Bariatric surgery procedures. A: Adjustable gastric band; B: Roux-en-Y gastric bypass; C: Sleeve gastrectomy; D: Sleeve gastrectomy with biliopancreatic diversion.

the standard hemostatic modalities without more complications than in contexts other than bariatric surgery[11]. Injection of epinephrine or polidocanol[12], thermal methods[13] and endoclips have been used with success[14]. Nevertheless, mechanical methods, especially endoscopic clips, should be favored. Thermal techniques must be avoided at the staple-line and the anastomosis as for other surgical settings to prevent tissue injury. Hemostatic powder might be another option although no case has been reported thus far.

STOMAL AND MARGINAL ULCERS

Ulceration is a late complication that typically occurs 1 to 6 mo after surgery. In patients with epigastric pain after RYGB, ulceration at the gastrojejunal anastomosis is the most frequent finding during endoscopy and is also one of the most common complications after RYGB appearing in up to 16% of patients[15]. Other symptoms at diagnosis are nausea, vomiting, and bleeding, either overt or occult. Ulcerations on the gastric side of the anastomosis are referred to as stomal ulcers and those on the jejunal side as marginal ulcers[16].

The cause of stomal ulcers is known to be ischemia whereas the mechanism for marginal ulcers is not well understood. Local ischemia, acidic gastric secretions, NSAID use, alcohol intake, smoking, or a foreign body, such as non-absorbable suture material, have been suggested as plausible causes[17]. After resecting the duodenum, there is no longer a pH buffering function, and acidic secretions are poorly tolerated at the jejunum; however, refractory ulcers should raise the suspicion of a gastrogastric fistula causing continuous

acid exposure. The role of *Helicobacter pylori* (*H. pylori*) is controversial in this setting, and there is no consensus regarding preoperative screening for *H. pylori* and subsequent eradication therapy in patients undergoing bariatric surgery[18]. However, some authors have suggested that *H. pylori*-related mucosal damage before surgery may result in postoperative ulceration even after eradication. The efficacy of proton pump inhibitors (PPI) in preventing marginal ulcers is controversial[19]. After ulcer development, most authors advocate indefinite PPI treatment but if aspiration of gastric pouch fluid reveals a non-acidic pH, then acid suppression is less effective and sucralfate may be the treatment of choice[20].

The endoscopic intervention is especially indicated when a foreign body is suspected to be the underlying cause. Embedded sutures or staples can promote an inflammatory reaction exposed to the irritating lumen environment; thus, large amounts of sutures should be removed even in asymptomatic patients[21]. A double channel endoscope may be useful to introduce grasping or rat tooth forceps, loop cutters, endoscopic scissors or argon plasma coagulation probes. In some series that use these endoscopic accessories to manage foreign bodies, over 70% of patients reported clinical improvement[22]. Endoscopy should be repeated at 8 wk to confirm ulcer resolution. In cases of unhealed or recurrent ulcers, a gastrogastric fistula or staple-line dehiscence should be investigated.

A particular type of ulceration is related to gastric band erosion, which occurs in 1%-4% of patients 1 or 2 years after LAGB[23]. Traditionally, surgical removal performing another bariatric surgical reconstruction during the same procedure was the classical approach.

Nevertheless, endoscopic extraction of gastric bands is feasible and is especially useful in patients not suitable for a new bariatric intervention. The procedure usually involves several steps. First, partially migrated bands must become more accessible from the gastric cavity and this is achieved by placement of a fully covered self-expanding metal stent (FCSEMS) inducing mucosal necrosis[24,25]. Next, the band must be transected before band removal transorally. Although different endoscopic procedures have been described to cut the band, such as band transection using argon plasma, neodymium-YAG laser or endoscopic scissors, the easiest method is the wire-cutting technique. In this technique, a guide-wire is passed through the band and the distal end of the wire is caught and pulled back on the other extremity forming a loop. Then, the band transection is accomplished using a mechanical lithotripter. Before band extraction, the subcutaneous port must be disconnected. The technical success range from 80% to 100%, and failures are mainly related to adherences between perigastric tissues and the gastric band[25-28].

STOMAL STENOSES

Stenoses are usually secondary to stricture development although they may be due to a malfunction of prosthetic devices. Although LAGB and SG may be complicated with stenosis, this complication is more commonly observed after RYGB and more often located at the gastrojejunal anastomosis. Less frequent locations are the jejunojejunal anastomosis and sites of passage through the mesocolon or intestinal adhesions. Stomal stenosis occurs in as many as 3% to 28% of patients who have undergone RYGB[29-32] and are defined as stomas that are smaller than 10 mm in diameter or as stomas that prevent the passage of the standard gastroscope[33]. The clinical presentation consists of dysphagia, nausea, vomiting and early satiety without abdominal pain. They develop gradually; therefore, they are usually late complications presenting several weeks after the surgical intervention. Medical factors, such as the use of NSAIDs, smoking or alcohol intake, can promote stenosis development. Moreover, surgical factors, including the method for anastomosis creation and mechanical tension or ischemia at the anastomosis, are also associated. Anastomoses performed with a circular stapler resulted in a higher stricture rate than those hand-sewn or performed with a linear stapler[34].

RYGB

The most common endoscopic approach is dilation with a through-the-scope balloon (TTS balloon). Although the use of fluoroscopy is advisable to avoid entry into the blind limb in cases of non-traversable stenosis with the gastroscope, balloon dilation without fluoroscopy guidance has been reported to be safe. In a series of 22 patients with a stomal stenosis, balloon dilation was performed without fluoroscopy and achieved a success

rate of 100% without any perforation[35]. Based on these results, the authors concluded that fluoroscopy is not always required for positioning the balloon and recommended the use of fluoroscopy liberally in difficult cases.

Balloon dilation to 15 mm in the first session has been shown to be safe although several dilations, every 2 or 3 wk with balloon diameters gradually increased from 12 to 20 mm, are often needed to achieve resolution and to prevent perforation and weight regain secondary to the loss of volume restriction[36]. Overall, the most recent studies in the literature have reported a success rate higher than 90% with very few complications (Table 1)[35-46]. It is important to note that in one study reporting on balloon dilation in 72 gastrojejunal strictures after RYGB, late strictures (> 90 d after RYGB) were found to have an inferior rate of response to endoscopic dilation (61% *vs* 98%) and often required revisional surgery[46]. When balloon dilation has failed to succeed, endoscopic incision using a needle knife papillotome prior to balloon dilation can be tried[47]. Suture material at the site of the stenosis can also hinder full balloon expansion and its removal may be necessary before the procedure[48]. In addition, some authors have reported satisfactory results with injection of a saline solution or steroids in the stenosis after balloon dilation. This may prevent restenosis by disrupting the scar tissue; however, the real efficacy and mechanism of action are not well known[40].

The most feared complication is perforation, which occurs in 3%-5% of patients after balloon dilation[37]. Early detection of this complication is crucial. Perforation may be managed by stent insertion or surgical repair. In addition to perforation, another risk of dilation is weight regain related to the loss of volume restriction. Nevertheless, some of the published studies have analyzed the impact of dilation on the decrease in weight-loss rate. The weight loss at baseline and during the follow-up did not differ from that of patients without stricture[41].

Savary-Gilliard bougie dilation (Wilson-Cook Medical Inc, Winston-Salem, NC) is another method to dilate anastomotic strictures. Although few patients with post-bariatric stenoses have undergone this technique, it seems to be highly effective and safe. Two studies have demonstrated a 100% efficacy without serious complications[49,50].

Esophageal FCSEMS have also been used to treat chronic gastrojejunostomy strictures with a 12.5% successful response[51]. In this study, all of the patients had a stricture at the gastrojejunal anastomosis after RYGB but one had a stricture at the duodeno-ileal anastomosis following BPD/DS. The poor response was associated with stent migration.

LS

The prevalence of symptomatic stenosis following laparoscopic sleeve gastrectomy (LSG) is between 0.1%

Table 1 Results of series on post-Gastric Roux-en-Y bypass anastomotic stricture balloon dilation

Ref.	No. patients	Time interval to stricture diagnosis (d)	No. of sessions	Success rate (%)	Balloon diameter	Complication rate (%)	Perforation rate (%)
Barba *et al*[36]	24	28-270	1-3	100	8-13 mm	0	0
Go *et al*[37]	38	53.9 (21-168)	1-6	95	12-16 mm	3	3
						1 pneumothorax and pneumomediastinum	
Rossi *et al*[38]	38	-	1-3	100	-	0	0
Carrodeguas *et al*[39]	94	52.7 (20-154)	1-4	99	-	2.1	2.1
						Perforations	
Catalano *et al*[40]	26	63 (28-63)	1-7	96.2	8-15 mm	3.8	0
						Surgical revision for recurrent stenosis	
Peifer *et al*[41]	43	49.7 (24-197)	1-3	93	9-20 mm	0.5	0
						Surgical revision for recurrent stenosis	
Caro *et al*[42]	111	56 (3-237)	1-4	100	6-18 mm	2.7	1.8
						2 contained perforations	
						1 esophageal hematoma	
Ukleja *et al*[43]	61	60 (30-180)	1-5	100	6-18 mm	4.9	2.2[1]
						3 perforations	
Mathew *et al*[44]	58	66.2 (12-365)	1-7	100	6-20 mm	3.2	3.2
						Perforations	
Da Costa *et al*[45]	105	90 (30-270)	1-4	100	6-20 mm	3.8	1.8[1]
						1 hemorrhage	
						3 perforations	
Espinel *et al*[35]	22	126 (26-768)	1-4	100	12-20 mm	4.5	0
						Small tear	
Yimcharoen *et al*[46]	72	46 < 90	1-15	84.7	8-18 mm	1.3	1.3
		25 > 90		98% < 90 d		1 perforation, pneumoperitoneum and death	
				61% > 90 d			

[1]Perforation rate of the dilations referred to the number of sessions. R: Retrospective; RYGB: Roux-en-Y gastric bypass.

and 3.9%[52]. In patients with LSG, functional stenosis may occur at the angularis incisura or the gastroesophageal junction and endoscopic treatment seems to play a smaller role based on the lower efficacy rates. In a study of 16 patients who underwent TTS balloon dilation under fluoroscopic or endoscopic guidance, the efficacy was only 44% after 1 to 3 sessions[53]. Repeated sessions of endoscopic dilation should be indicated only in patients with some symptomatic relief following the first session because these strictures are more likely due to a fibrotic reaction. In contrast, endoscopic dilation has no efficacy when twisting rotation of the sleeve is the cause of functional stenosis and these patients should be managed surgically[53,54]. There are some reports on the use of 30 mm achalasia balloons to treat SG strictures with 71% to 100% resolution rates[52]. These higher rates of resolution are overshadowed by the higher risk of perforation secondary to the more rigid achalasia balloons.

More recently, new self-expanding metallic stents have been manufactured to treat leaks after SG: Megastents (Taewoong Medical Industries, South Korea) and Hanaro (MITech, Seoul, South Korea). These stents are longer than conventional SEMS positioned from the distal esophagus to the duodenal bulb bypassing the entire gastric sleeve. Although they are intended to reduce the migration rate while sealing a leak after SG, they also confer radial strength useful to dilate a possible stenosis at the same time[55]. Nevertheless, studies using these stents have only reported results of leak closure.

LAGB
Mechanisms of stenosis after gastric banding include fibrotic reaction, band rotation and adhesions with pouch angulation. Dilation is only effective in cases of fibrotic stenosis. If endoscopic dilation is not successful after one session, another endoscopic session should not be performed and surgical options must be considered including conversion to RYGB[56].

ANASTOMOTIC LEAKS AND FISTULAS
Leaks are defined as the exit of luminal contents due to a discontinuity of the tissue apposition at the surgical anastomosis, whereas fistulas are abnormal passageways usually between two hollow viscera or communicating to the skin and they result from chronic healing of local inflammation caused by leaks. The incidence of staple-line or anastomotic leaks varies depending on the type of bariatric surgery, with studies reporting 2% to 5% for laparoscopic RYGB, 1.6% to 2.6% after open RYGB and 0.6% to 7% in patients following a sleeve gastrectomy[29,30,57-59]. Because LAGB does not involve transection of the stomach, the reported incidence of leakage is very low, ranging from 0% to 0.5%[60-62]. Leaks are the most dreadful complication and after pulmonary embolism they represent the second most common complication leading to death after bariatric surgery[63]. Although several patient-

related conditions, such as superobesity, age above 55 years, male sex, and a personal history of diabetes mellitus, sleep apnea, hypertension or previous surgery, are thought to predispose patients to leaks[64], early postoperative leaks within the three first days after surgery are usually due to a technical error, such as anastomotic tension, stapler malfunction and suture or staple-line seepage[65]. However, leaks presenting later in the perioperative setting after RYGB are usually due to ischemia at the staple-line or anastomosis and they appear with decreasing frequency at the gastrojejunostomy, gastric pouch and jejunojejunal anastomosis[66-68]. High pressure in the gastric sleeve due to stenosis at the incisura, pyloric dysfunction and twisted or atonic sleeve is the most common cause of leaks several days after LGS but ischemia may also be responsible following ligation of the short gastric arteries. In this setting, most leaks occur at the angle of His where the highest pressures are present[69-71]. The uncommon cases of leak after LAGB are mainly due to ischemia secondary to band slippage or migration[72]. However, the rate of leaks is increased after revision bariatric procedures for gastric band failures and it has been reported to be as high as 18%[73,74]. This occurs more often when the revision surgery after LAGB is accomplished to treat band complications, such as band erosion, slippage and migration, than after a revision procedure for weigh regain. Factors contributing to this increased risk of leaks are the fibrotic and inflammatory tissue surrounding the band and secondary adhesions to the neighboring structures like the pancreas[73,74]. The incidence of fistulas is not well known although some authors have reported that 14% of patients with anastomotic leaks will develop fistulas[67]. The most common sites are gastrogastric and gastrocutaneous. Gastrogastric fistula is a specific complication of RYGB consisting of an organized communication between the gastric pouch and the gastric remnant. It was one of most common complications in the past but currently, after generalizing the transection of the stomach, the incidence of gastrogastric fistulas has decreased to 1.2%-6%[75-77].

Clinical presentation of leaks is variable, ranging from asymptomatic patients to sepsis-related multiorgan failure. Early suspicion of a leak must be raised in cases of any deviation from the normal postoperative course with tachycardia being the most sensitive indicator of a leak[67,78]. Chronic fistulas show more indolent presentation. Abdominal discomfort and heartburn due to acid flow into the pouch and weight regain are the most common symptoms in patients who present a gastrogastric fistula. The most sensitive method to diagnose leaks is computed tomography with oral, water-soluble contrast[79]. Nevertheless, leaks may be discovered by routine upper gastrointestinal studies performed systematically by some authors during the first three days after surgery, or by oral administration of methylene blue when drains are still in place[80,81].

Endoscopic diagnosis is also feasible, combining a bubble test (drain immersion during endoscopic insufflation) with the administration of contrast with methylene blue into the drain while keeping fluoroscopic and endoscopic view looking for a leak[82].

The treatment strategy depends on the clinical condition of patients and the time of presentation, and relies on the following three mainstays: Medical support, drainage of leaked material and repair of the wall defect. Therapeutic medical measures involve suppression of the oral intake, parenteral nutrition or distal enteral feeding, and broad-spectrum intravenous antibiotics. For hemodynamically unstable patients with generalized peritonitis or sepsis, surgical drainage and cleansing of the peritoneal cavity is mandatory and a feeding jejunostomy should be performed at the same time to allow enteral nutrition. Otherwise, conservative management based on medical therapy and external drainage is a convenient approach that has been reported to achieve leak resolution in 75% of early, asymptomatic and small-volume leaks[83]. However, some authors prefer surgical repair in these early small leaks[84]. In stable patients with larger leaks or leaks presenting late in the postoperative course, where conservative management keeps the patient stable but does not succeed in stopping the leak, further treatment should be considered. Nevertheless, primary surgical repair is associated with high rates of recurrence and other reinterventions, such as gastrectomy, sleeve conversion to gastric bypass or fistulojejunostomy, which have high morbidity; therefore, the management of these patients has shifted from surgery to less invasive endoscopic therapy[67,85].

Endoscopic treatment is used very often as an adjuvant therapy to surgery but the management of post-bariatric leaks may be accomplished entirely by endoscopic means. The endoscopic approach usually involves a stepped and multimodal procedure as has been previously described[86].

Endoscopic internal drainage
Before any attempt to close the wall defect, the first step is to guarantee the appropriate drainage of the leaked content. For early leaks, this is commonly accomplished by surgical drains maintained in the post-operative period but if drains are no longer in place, percutaneous drains should be placed either surgically or by interventional radiology whenever accessible. Nevertheless, in patients with delayed leakage or when surgical cleansing is not required or for those whose collections are not radiologically accessible, the endoscopic internal drainage (EID) into the digestive lumen might be the first option for well-circumscribed collections[87]. In addition when combined with surgical cleansing in patients presenting with severe sepsis, EID allows early removal of surgical drainage preventing chronic fistula tract formation[88]. EID consists of trans-fistulary insertion under fluoroscopy guidance of one
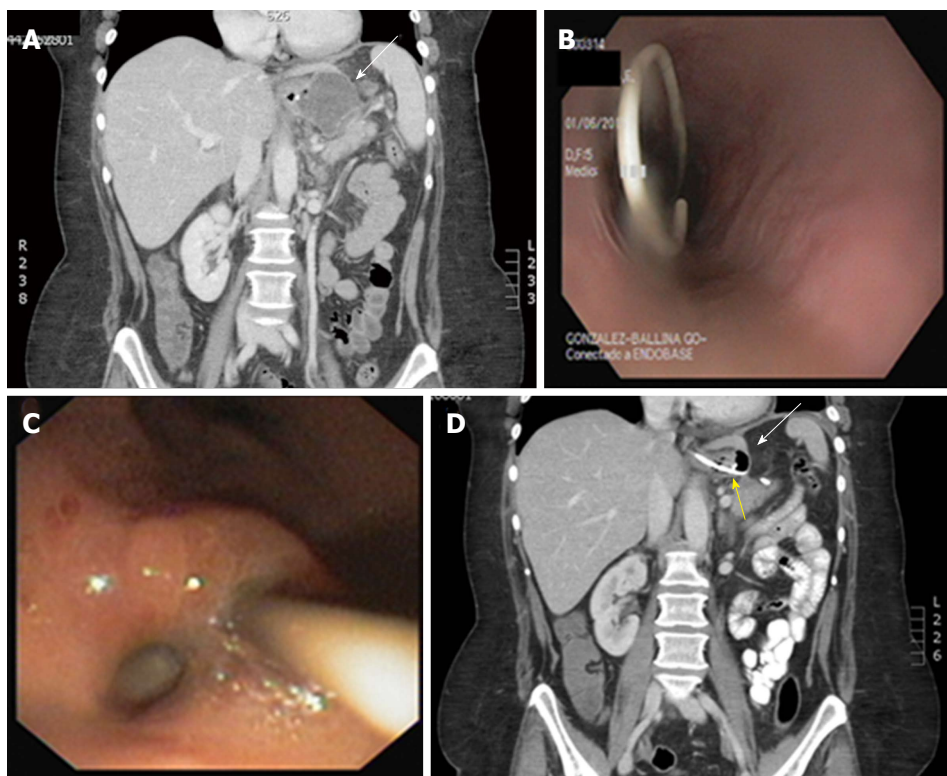
Figure 2 Large collections requiring lavage to eliminate pus and debris. A: Early fluid collection after RYGB; B and C: Transfistulary drainage of the fluid collection. A 10 Fr double pigtail was placed; D: Nine days after stent placement the collection significantly reduced and became a virtual cavity. Yellow arrow: Double pigtail stent; white arrow: Reduced cavity after drainage. RYGB: Roux-en-Y gastric bypass.

or two 7 or 8.5 Fr double-pigtail plastic stents, or one double-pigtail stent and one nasocystic catheter in cases of large collections requiring lavage to eliminate pus and debris[87] (Figure 2). Double-pigtail stents keep the leak orifice open favoring the passage of fluid content into the digestive lumen with progressive reduction in the collection size until it eventually becomes a virtual cavity. Meanwhile, a foreign body reaction in the edges of the leak is triggered by plastic stents promoting the reepithelialization over the stent and the fistula closure, resulting in an all-in-one procedure without the need of further treatment. A residual small cavity like a pseudodiverticulum is common at the end of the process without any clinical repercussion[88]. In some cases, the leak orifice is not clearly identified or the communicating tract between the digestive lumen and the fluid collection is complex, then, internal drainage may be accomplished by EUS-guided drainage, such as for pseudocysts or other postsurgical collections[87-90]. In addition to stenting, debridement may also be needed in cases of infected collections containing necrotic tissue. Endoscopic necrosectomy is also feasible, similar to treatment of organized pancreatic necrosis[86,90,91].

Although EID is now most commonly used as a first-line approach, it has also been reported as a bridge to other endoscopic methods and as a salvage treatment when other endoscopic techniques have failed[87-89]. In the largest series reporting on EID, double pigtails were delivered as a first line approach in 66 patients[88].

Among them, 42 had a surgical drainage placed close to the leak. The 78% of patients were cured by EID after a mean of 58 d. Oral diet was reassumed following the confirmation of collection reduction in a CT performed three days after pigtail insertion. In this study a protocol with systematic endoscopic review every 4-6 wk was followed. At each session stent exchange was performed until fistula healing was achieved to avoid stent obstruction and to stimulate tissue granulation by the traumatism induced by the stent on the fistula edges. In a more recent study on 33 patients with fluid collections after SG or RYGB (in 19 patients after previous unsuccessful endoscopic treatment), internal drainage achieved 78.8% clinical success[87]. After confirming biological and clinical improvement, this approach allowed early oral re-feeding in the first 24-48 h following stent insertion without any negative impact on the final results. No standardized protocol to remove the stents was observed and the decision was left to the discretion of the endoscopist and decided on an individual basis, although the stent retrieval was planned at least 4 mo after complete clinical resolution. However, in most patients successfully treated by internal drainage, no other endoscopic procedures were required because stents often migrated spontaneously. In addition to the high efficacy, EID is burdened with a low complication rate. In the first study 6 stenoses, as well as two stenoses in the second series, were observed, probably related to granulation tissue induced by the

pigtails, and successfully treated either with achalasia balloon dilation or FCSEMS[87,88]. In the second study, two other complications were also reported[87]. One patient presented bleeding from the leak orifice with internal stent migration that was endoscopically treated by endoscopic coagulation and endoscopic retrieval of the migrated stent. The other patient developed a splenic hematoma that required surgical treatment. The authors argued that the proximity of the pigtails to the spleen parenchyma might explain this serious complication. Despite the high efficacy of EID, some patients in both studies did not respond to EID after median stent dwell duration of 58 d (range 10-206) and 115 d (range 23-773) respectively, and other treatments were required. The appropriate time interval for stent exchanging and the optimal timing to consider EID failure in leak healing and to proceed with other surgical or endoscopic treatments remain to be defined.

Methods other than pigtail stenting for internal drainage have been described. To drain the leaked content, stricturotomy, more recently named as septotomy, has been successfully tried in patients with postoperative leaks after SG or DS[92,93]. This procedure derives from the endoscopic treatment for Zencker diverticulum and involves cutting the septum between the perigastric cavity and the gastric pouch using argon plasma coagulation or a needle-knife. In a prospective study, 27 patients were treated with stricturotomy and after 1 to 6 endoscopic sessions, all of the patients had their fistulas closed. More than half of the patients in this study presented stenosis at the angularis incisura, and they were all endoscopically dilated. This result highlights that besides drainage it is of paramount importance to detect and treat predisposing factors that can perpetuate the leak. Therefore, in combination with achalasia balloon dilation of post-LSG stenosis, septotomy has become an appealing alternative to treat chronic leaks connected to a not drained cavity after LSG. This procedure allows decreasing intragastric pressure, rerouting the gastric content and the internal drainage of the cavity by cutting the staple-line interposed between the cavity and the gastric lumen[92,93]. Anecdotal experience with internal drainage using a vacuum-assisted closure system is now available[94,95]. This device consists of a sponge endoscopically placed inside the cavity and connected by a transnasal tube to external continuous vacuum suction[96]. The sponge must be changed every 2-4 d and adapted as the fistula cavity reduces in size until it eventually seals. The sponge results in granulation tissue and the vacuum helps to extract the fluid content, improves blood flow and promotes leak closure. Nine patients in the post-bariatric surgery context have been treated with this device recently. The rescue rate was 89% after an average of 50 d and 10.3 procedures per patient. One patient required surgery and in two others, a complementary over-the-scope clip was placed[95].

Endoscopic treatment of wall defects
Some patients have their leaks closed after conservative

management or internal drainage but in other cases the leak persists. For these patients and for those with larger leaks at presentation who will predictably fail to respond to the above measures, further intervention is required. Therefore, once drainage is ensured, the next step is aimed at treating the wall defect. There are two different endoscopic strategies to proceed, either to primarily close the leak orifice or to exclude it by diverting the enteric content, and the choice mostly depends on the size of the wall defect. Both strategies may be complementary usually in a sequential manner or an adjuvant therapy to surgical drainage.

Wall defect exclusion: The endoscopic technique to divert the gastrointestinal stream is stent placement. Endoscopically placed self-expandable endoscopic stents (SEES) offer several advantages. They decrease the intraluminal pressure, which is one of the pathophysiologic factors of leaks after SG, prevent or decrease peritoneal contamination by excluding the wall defect from esophagogastric secretions and thus, promote healing of the leak and permit oral nutrition to be resumed[51,97]. This is the endoscopic treatment for leaks after bariatric surgery where most evidence is available. Table 2 shows the largest studies in the literature reporting on stent treatment of leaks after bariatric surgery[98-111]. In one meta-analysis on 7 studies published in 2011, fistula closure was achieved in 88%. The rate of successful removal of the stent after leak closure was 92% and stent migration, noted in 17% of cases, was the most common complication[64]. However, the largest studies have been published after this meta-analysis and the rates of leak closure and complications range from 65% to 100% and 14% to 86%, respectively, with migration being the most frequent complication with rates of 5%-67%[98-111]. It is noteworthy that figures of success in most studies have included not only primary success following stenting but also success after combining stenting with other complementary endoscopic techniques. Moreover, these studies have pooled patients with different bariatric surgeries, mostly RYGB and SG. Additionally, the timing of stenting after surgery is heterogeneous, the size of the wall defect has rarely been reported and different stents have been used. All of these issues are important factors influencing rates of success and migration. Due to anatomical reasons, lower rates of leak closure are achieved in SG because the area to cover is larger, it is more difficult to obtain close apposition between the stent and the wall defect and tissue hyperplasia increasing the water tightness is less common[99]. It has also been advised that management of postbariatric surgery leaks must be guided by the size of the wall defect as it has been shown that leaks larger than 1 cm take longer to heal after stenting or even fail to seal with only stent placement[112]. In addition, the time interval between leak development and endoscopic stenting is a proven factor that impacts outcomes. The fibrotic transformation of leaks into chronic fistulas over time

Table 2 Results of endoscopic stenting in anastomotic and staple-line leaks after bariatric surgery

Ref.	N° patients	Bariatric procedure	Time interval to stent	Type of stent	Success rate (%)	Complications rate[1]	Migration rate (%)	N° of procedures	Time to fistula closure
Salinas *et al*[98]	17	RYGB	1-3 wk	PCSEMS	94	41% 1 migration, 2 mucosal tears, 4 stent obstruction by food	6	1.2 (1-2)	3.2 ± 1.2 mo
Eisendrath *et al*[99]	21	RYGB/ LGS/DS	31 d (14-199)	PCSEMS	81	14% 1 migration, 2 dysphagia due to tissue hyperplasia	5	1-6	NA
Eubanks *et al*[100]	13	RYGB/LGS	Acute leaks (11) Chronic leaks (2)	FCSEMS/ FCSEPS	77	70% (not specified)	NA	NA	Acute leaks - 33 d Chronic leaks - 45 d
Blackmon *et al*[101]	10	RYGB/LGS	NA	FCSEMS/ PCSEMS	100	NA	NA	NA	NA
Leenders *et al*[102]	11	RYGB/LSG	8 d (1-33)	FCSEMS	73	50% 3 disintegrated stent, 2 migration	17	2 (1-4)	16 wk (5-63)
El Mourad *et al*[103]	47	RYGB/ LSG/DS	10.5 d (1-74)	PCSEMS	87	30% 1 mucosal stripping, 1 perforation, 1 dysphagia, 1 stricture, 1 bleeding 1 stent angulation, 7 migration	15	NA	44 d (3-90)
Orive-Calzada *et al*[104]	11	LSG	NA	FCSEMS	73	NA	NA	NA	NA
Alazmi *et al*[105]	17	LSG	< 1 wk (10) 1 wk-1 mo (6) > 1 mo (1)	PCSEMS	76	36% 2 bleeding, 3 dysphagia, 1 migration	6	NA	42 d (28-84)
Quezada *et al*[106]	29	RYGB/SG	8 d (0-104)	CSEMS	96.5	41% 10 migration, 1 stent fracture, 1 opening of blind end of alimentary limb	34	NA	82 d (2-352)
Murino *et al*[107]	91	RYGB/LSG	25 d (2-308)	PCSEMS	81	22% 5 bleeding, 2 perforation (1 death), 7 migration, 13 esophageal stricture	8	1 (1-7)	NA
Fishman *et al*[108]	26	LSG	< 1 wk (1) 1-6 wk (17) 7-12 wk (5) > 12 wk (3)	FCSEMS[2]	65	46% 4 severe stent intolerance (stent removal) 1 severe bleeding, 7 migration	27	NA	NA
Southwell *et al*[109]	21	LSG	< 1 wk (6) 1-6 wk (12) 7-12 wk (1) > 12 wk (2)	FCSEMS[2]/ PCSEMS	95	86% 10 migration,, 2 esophageal strictures 1 leak due to erosion by the stent 5 severe intolerance (stent removal)	48	5 (2-13)	75 d (9-187)
Van Wezenbeek *et al*[110]	12	RYGB/LSG	8 d (0-24)	FCSEMS[2]	75	75% 7 migration, 1 perforation 1 perforation secondary to migration	67	2.4 (1-3)	38 d (28-49)
Shehab *et al*[111]	22	RYGB/LSG	11 d (3-30)	FCSEMS[2]	82	41% 1 perforation, 1 esophageal stricture, 4 migrations, 2 bleeding (1 death), 1 stent intolerance (removal)	18	2.8 (2-5)	6.8 wk (2-14)

[1]Including migration. Dysphagia and intolerance were included when required endoscopic dilation and/or stent removal; [2]Sleeve customized stents. R: Retrospective; RYGB: Roux-en-Y gastric bypass; LSG: Laparoscopic sleeve gastrectomy; DS: Duodenal switch; FCSEMS: Fully-covered self-expandable metal stent; PCSEMS: Partially-covered self-expanding metal stent; CSEMS: Covered self-expandable metal stent.

Figure 3 Hanarostent® (MI-tech, Seoul, South Korea). Fully-covered self-expandable stent adapted to the sleeve gastrectomy anatomy.

Figure 4 Over-the-scope clip (Ovesco Endoscopy, Tübingen, Germay). The over-the-scope clip attached to the gastroscope tip and ready to be placed on the wall defect. At the bottom of the figure, different available sizes of over-the-scope clip in the final position once they have been released.

significantly decreases the probability of leak closure after stent placement[51,105,107]. Heterogeneity regarding all of these clinical factors may explain, at least in part, the large differences in rates of success across the studies.

SEES, along with sepsis treatment, have become an attractive alternative due to the high rates of leak closure, its minimally invasive placement, the early restoration of oral nutrition and faster recovery with shorter hospital stays. Although there is no consensus on the optimal timing of stenting, most experts suggest early application after diagnosis[113]. In general, stents are well tolerated. Minor symptoms, such as nausea, vomiting and abdominal discomfort, are common and usually transient, but severe stent intolerance has been reported, leading to early stent removal. The main drawback of SEES is the high rate of migration. Other than migration, most complications are conservatively managed and not severe; however, severe bleeding and perforations have been observed. They are serious complications that have resulted in death in a few cases and in many occasions are associated with stent migration[107,111]. One explanation for the high migration rate is that SEES have been designed to treat benign and malignant esophageal strictures. In the esophagus, close contact between the stent and the mucosa is feasible whereas in a gastric pouch the friction between the stent and the mucosa is not enough to keep the stent in place, predisposing the stent to migrate. This is especially true for stents placed across the gastrojejunal anastomosis in RYGB[100]. Many attempts to decrease the risk of migration and its consequences have been made concerning the type and design of SEES and different methods to anchor the stents. SEES are currently made either of metal (SEMS) or polyester (SEPS). Metal stents are said to have a higher friction coefficient but, in practice, migration rates seem to be similar; however, metal stents are easier to insert due to the small caliber and higher flexibility of the delivery system[100]. There are two types of metal stents used in post-bariatric complications, partially (PCSEMS) and fully covered SEES (FCSEMS), and there is controversy
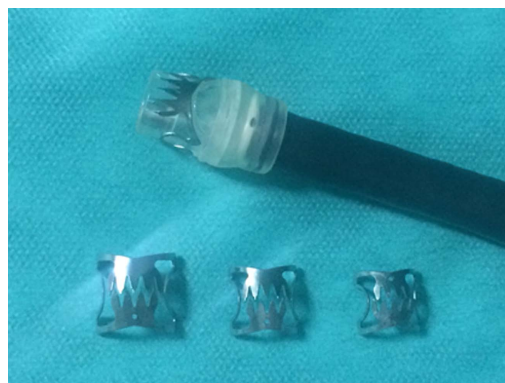
about which is the better option. The silicon coating completely covering the FCSEMS is intended to easily remove the stent but this advantage is overshadowed by the higher trend toward migration. In contrast, the uncovered ends of PCSEMS induce tissue hyperplasia that helps to hold the stent in place and increase the water tightness of the stent, favoring leak closure. Nevertheless, tissue ingrowth into the stent makes stent removal difficult and increases the risk of bleeding, mucosal stripping and perforation. In the absence of randomized prospective trials comparing both stents, the choice relies on the preferences of the endoscopist. To prevent migration, an increasingly expanded practice at present is to use PCSEMS and if significant tissue in growth occurs a second SEPS is inserted to pressure necrosis of the hyperplastic tissue; then, both stents can be safely removed after several days[107]. Ablation of the hyperplastic tissue using argon plasma coagulation is another option and also, anatomic constrictions can improve stent fixation by using overlapping stents (one through another) bridging the esophageal junction and the pylorus.

The following two FCSEMS have been recently designed to be adapted to the sleeve anatomy: ECBB Hanarostent® (MI-tech, Seoul, South Korea) (Figure 3) and Megastent® (Taewoong, Seoul, South Korea). They have a larger diameter to ensure optimal adherence to the sleeve wall and are longer, up to 24 cm, to allow the proximal end to be placed in the distal esophagus and the distal end in the duodenal bulb to decrease migration. Whether these stents reduce the rate of migration is not clear because few cases have been reported and migration has been observed in 18% to 67%[108-111]. However, one highlighted advantage is that these stents are always retrievable endoscopically because their larger sizes prevent them to migrate far distally in contrast with conventional stents[111]. Two problems have been observed with these stents. The first one is the worse tolerability to the stent requiring stent removal in some cases, with common pain,
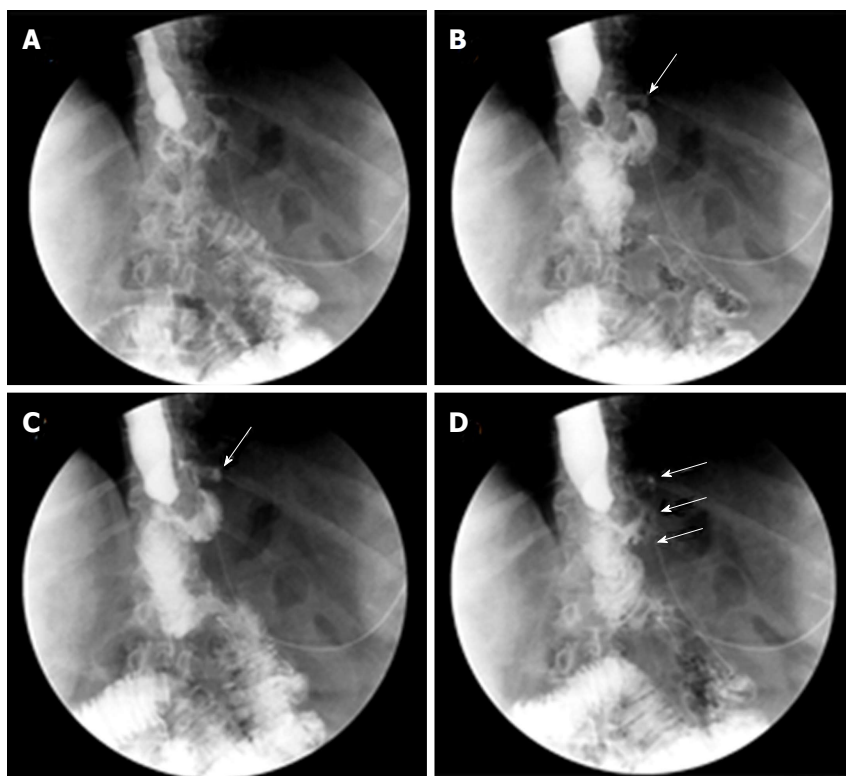
Figure 5 Upper gastrointestinal series displaying a small gastrogastric fistula ten days after Roux-en-Y gastric bypass (arrows).

heartburn and vomiting due to biliary reflux, and the second problem is the decubitus lesion in the duodenal bulb caused by the distal edge[108,114]. Another type of stent is uncovered biodegradable stents. They tend to migrate less than FCSEMS and do not need extraction. However, the severity of tissue hyperplasia and the time to complete degradation cannot currently be accurately predicted[115]. Therefore, degradation before the leak closure is possible. Anecdotal experience with biode-gradable stents has been published in three cases with satisfactory results[116].

A further attempt to prevent stent migration is endos-copic stent fixation. Through-the-endoscope clips are of limited value[86,117,118] and limited experience with the new endoscopic suturing devices to anchor the stents shows variable results[119,120].

Despite the above efforts, stent migration is an unsolved problem and the longer stents remain in place, the higher the probability of migration. For this reason, most experts recommend removing the stent after 6-8 wk, enough time to allow the leak closure and to avoid developing excessive tissue hyperplasia. Until then, weekly scheduled re-evaluations are highly advised because detection of incipient stent dislodgement may allow easy endoscopic stent repositioning or removal. In cases of stent dislodgement or persistent leakage at scheduled controls, additional SEES can be placed, covering the proximal and distal ends, to obtain better anchoring and to seal the leak. In fact, repeated endoscopic procedures are often necessary ranging from 1 to 7 in reported studies[98-111].

Endoscopic closure of wall defects: Several techniques are available to try directly closing leaks instead of covering the leak opening, such as clipping, endoscopic suturing, or obstructing the fistula with fibrin sealants or plugs. Limited data about the use of through-the-scope clips in this indication fail to show any advantage of these clips in post-bariatric leaks. Preliminary experience with a new clipping device made of nitinol and loaded at the tip of the endoscope, over-the-scope clip (OTSC) (Ovesco Endoscopy, Tübingen, Germany) seems promising (Figure 4)[111,121-123]. This clip allows full thickness apposition in wall defects smaller than 3 cm. The OTSC in post-bariatric leaks has been used almost exclusively in SG leaks. Before placing the OTSC, appropriate drainage of leaked material is required as for SEES and it is strongly advised to de-epithelialize the fistula edges either with a cytology brush or with argon plasma coagulation to promote granulation tissue. In two studies reporting on 18 and 26 patients with SG leaks, leak closure was possible in 81% and 89%[122,123]. However, several patients in both studies also received a SEMS, resulting in 61% and 62% of primary success. In one of these studies, most failures occurred in leaks at the level of the antrum, which are well known difficult-to-treat fistulas. The procedure was safe without serious complications; only one patient developed one gastric stricture caused by the OTSC, which was successfully treated with a colonic SEMS and one tearing of the fistula edges occurred in another patient during the procedure[122]. Nevertheless, several endoscopic sessions may be needed ranging
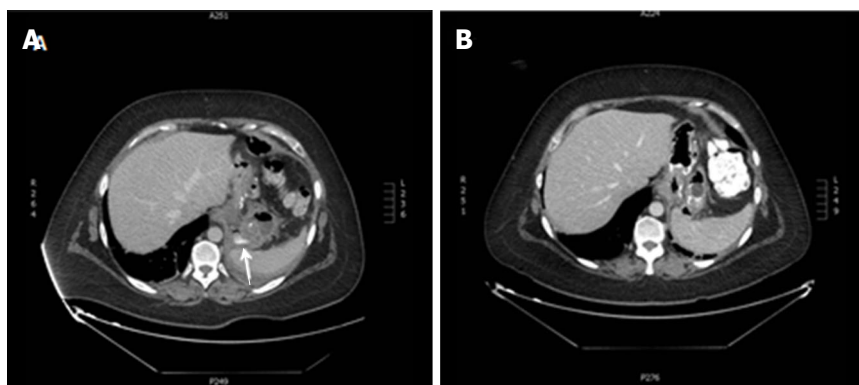
Figure 6 Leak resolution after stent deployement. A: The same gastrogastric fistula (arrow) as in Figure 5 confirmed by CT scan with oral water-soluble contrast. A fully covered self-expandable metal stent was inserted. The stent was removed after forty three days and a complimentary injection of fibrin glue was performed; B: A new CT scan revelaed the fistula closure. CT: Computed tomography.

from 2 to 7 in one study and failures to correctly place the OTSC may be challenging[123].

The endoscopic injection of two sealant materials, fibrin glue and cyanoacrylate, has been used to occlude the leak orifice. The mechanism of action of fibrin glue is two-fold as follows: Mechanical occlusion by rapid formation of a clot and promotion of wound healing by inducing fibroblast proliferation. Cyanocrilate is a synthetic glue that rapidly solidifies when in contact with weak bases, forming a cast[124]. Some cases have reported using glue injection as the sole therapy to occlude post-bariatric leaks, and frequently multiple applications were needed[125-128]. Because these fistulas were occluded early in the postoperative course where the simple watchful waiting strategy could have been enough, the efficacy of glue sealants as the primary treatment has been questioned[121]. More often, this modality of treatment has been used as an adjunct to SEES (Figures 5 and 6). Accordingly, in one study reporting on percutaneous treatment of gastrocutaneous fistula after LSG in 10 patients, glue injection was only effective when performed after endoscopic stent placement[129].

For refractory gastrocutaneous fistulas after bariatric surgery, successful treatment using a biomaterial plug has also been described. First developed to treat anorectal fistulas, cone-shaped plugs manufactured with Surgisis, an acellular matrix extracted from the porcine small intestine submucosa, have been used to heal postsurgical fistulas in different contexts[130,131]. For gastrocutaneous fistulas, these plugs are inserted through the cutaneous orifice up to the gastric lumen by a rendezvous procedure *via* endoscopic and percutaneous approaches. Before inserting the plug, the fistulous tract is abraded using a modified pusher provided with multiple barbs over a guide wire. The Surgisis material stimulates the proliferation of fibroblasts in the wound area without triggering a foreign body response. Two studies have presented the results with fistula plugs in patients with post-bariatric gastrocutaneous fistulas refractory either to at least 4 wk of conservative management or to previous endoscopic or surgical treatments[132,133]. In both studies, fistula closure was achieved in 80% without complications using plugs as the sole endoscopic treatment or as an adjunct to SEMS.

Finally, the use of novel endoscopic suturing systems in post-bariatric leaks is still experimental. The StomaphyX™ system (EndoGastric Solutions, Inc., Redmond, WA, United States) and the OverStitch system (Apollo Endosurgery, Austin, Texas, United States) were reported to be successfully used in two bariatric fistulas each[134,135]. Initial experience with the EndoCinch system (CR Bard, Murray Hill, NJ) showed success but not long-lasting efficacy to close gastrogastric fistulas following RYGB. Among 95 fistulas, 90 closed after suturing but reopening was observed in 65% secondary to absorbable sutures after an average of 177 d[136].

As described above, the management of post-bariatric leaks is challenging and requires a multidisciplinary approach. Frequently, endoscopic treatment is an adjunct to surgery although a complete endoscopic approach is also feasible[86]. In both cases, endoscopic treatment involves not only repeated endoscopic procedures but also a combination of different endoscopic modalities of treatment. As a result, there is an important heterogeneity in the management of these patients through the literature and the individual evaluation of each endoscopic modality is very difficult. Accordingly, one recent study has evaluated the overall efficacy of interventional endoscopy in this setting involving different techniques[137]. Among 110 included patients with post-LSG leaks, 74% healed with endoscopic treatment. In chronic fistulas after 6 mo of management, the success rate decreased to 52.4%. The most common endoscopic techniques were stenting, clip placement and glue application. A mean of 4.7 endoscopic procedures and 2.5 endoscopic techniques per patient were needed. The key role of endoscopic treatment relied on stenting, and morbidity in this study was also related to stent placement, mainly migration, impaction and ulceration, digestive perforation and
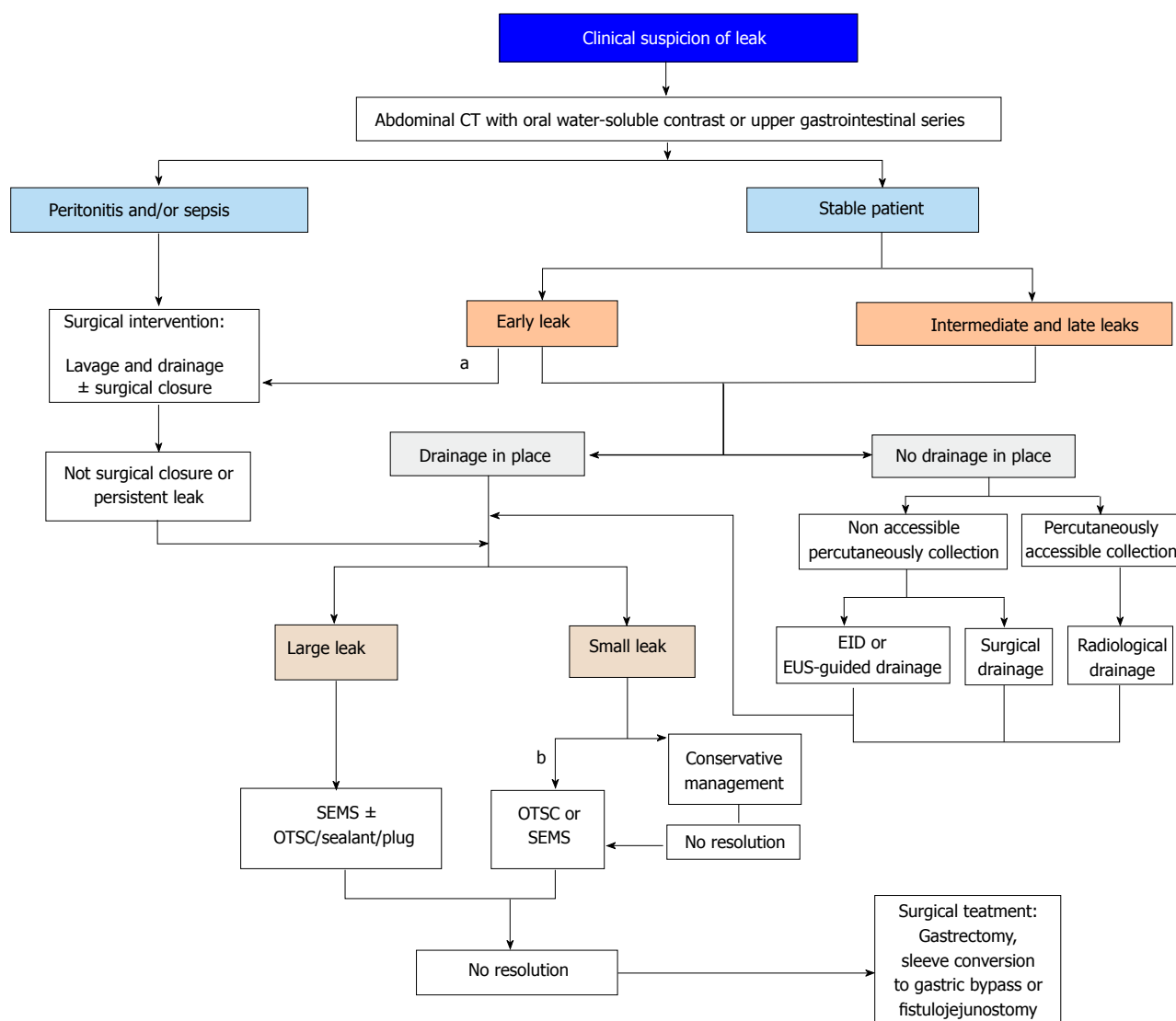
Figure 7 Management algorithm for post-bariatric surgery leaks. Leaks have been classified based on the time period they appear as early, between first and fourth day post-operative, intermediate, between the fifth and ninth day after surgery, and late appearing after day ten. [a]Some authors prefer surgical repair in early small-volume leaks; [b]Except in uncomplicated small early leaks where conservative treatment has 75% of success in leak closure and the potential benefits of SEES are shadowed by the risk of migration and related complications. SEMS: Self-expanding metal stent; OTSC: Over-the-scope clip.

incarceration secondary to tissue hyperplasia. In the multivariate analysis, the authors found the following four predictive factors of healing following endoscopic treatment: The time interval between LSG and fistula diagnosis < 3 d, time interval between fistula diagnosis and first endoscopy < 21 d, no history of gastric banding and a small fistula.

In the last years, EID with double pigtail stents is gaining popularity as a first line endoscopic treatment for early and intermediate leaks after bariatric surgery[87,88]. The abovementioned shortcomings of SEMS have led some experts to carefully reevaluate their place in the treatment of post-bariatric leaks and to consider EID as an attractive alternative with fewer complications and similar success rate[88]. In chronic fistulas the endoscopic treatment should be always offered before considering radical surgery. However, the results of endoluminal therapy, including

SEMS, in chronic leaks after bariatric surgery are far from optimal[51]. Recently, promising results with the septotomy procedure in the management of chronic leaks connected to a not drained cavity have led some experts to favor this technique against SEMS[92,93]. Yet, endoscopic treatment in the field of post-bariatric leaks has not been standardized and there is no consensus about the optimal timing and combination of endoscopic procedures. For this purpose, prospective randomized studies are eagerly awaited. Until then, and based on available evidence at present, we propose an algorithm of treatment for leaks after bariatric surgery (Figure 7).

CHOLEDOCOLITHIASIS

Physiologic changes, such as hypersaturation of bile with cholesterol secondary to rapid weight loss as it occurs after bariatric surgery, induce a lithogenic state[138,139].

Table 3 Results of laparoscopy-assisted trans gastric endoscopic retrograde cholangiography in Roux-en-Y gastric bypass

Ref.	No. ERCP[1]	Success of CBD cannulation (%)	ERCP Findings	Operative time (min)	Complications related to ERCP	Complications related to laparoscopic transgastric access
Ceppa *et al*[144]	5	80 (4/5)	2 BDS/2 CBD stones/1 CBD sludge	NA	None	None
Patel *et al*[145]	6	100	4 BPS/1 CBD stones/1 normal	NA	None	None
Roberts *et al*[146]	5	100	2 BPS/2 SOD/1 CBD stone	64-93	None	None
Gutierrez *et al*[147]	23	100	3 CBC stone/1 PC/2 N/9 SOD/5 BPS/1 cholecystitis/1 BPS + SOD/1BSP+ PS	200 (98-138)	1 postERCP pancreatitis	17% 2 leak after g-tube removal/1 converted to open/1 gastrostomy site infection
Lopes *et al*[148]	9	89 (8/9)	3 BPS/1 CBD stone/2 N/2 SOD	89 (41-245)	2 postERCP pancreatitis	11% 1 pneumotorax
Bertin *et al*[149]	22	100 (20/20)[2]	18 SOD/4 Recurrent pancreatitis	226	1 retroperitoneal perforation	5% 1 hematoma of the abdominal wall
Richardson *et al*[150]	11	100	7 CBD stone/2 BPS/1 SOD/1 CP	NA	None	None
Saleem *et al*[151]	15	100	5 BPS/2 CBD stone/3 CBD sludge/1 PD/1 SOD/1 BPS + SOD/1 BPS + CBD stenosis/1 biliary leak	NA	None	None
Schreiner *et al*[152]	24	100	20 BPS/3 CBD stones/1 PC	172	1 postERCP pancreatitis	8% 1 enterocutaneous fistula
Falcão *et al*[153]	23	100	17 CBD stone/6 BPS 17 CBD stone/1 CBD sludge/1 BSP	93	1 postERCP pancreatitis	None
Snauwaert *et al*[154]	23	100	1 N/1 CBD transection	NA	None	9% 2 converted to open

[1]After excluding laparoscopic trangastric access for gastroduodenoscopy and programmed open procedures; [2]Two patients underwent minor papilla cannulation. R: Retrospective; ERCP: Endoscopic retrograde cholangiopancreatography; CBD: Common bile duct; BPS: Benign papillary stenosis; SOD: Sphincter of Oddi dysfunction; PC: Pancreatic cancer; CP: Chronic pancreatitis; PD: Pancreas divisum; BDS: Bile duct stones.
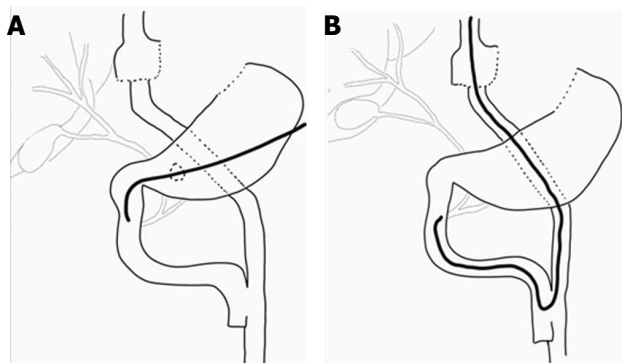

Figure 8 Endoscopic retrograde cholangiopancreatography approaches in Roux-en-Y gastric bypass. A: Laparoscopic-assisted endoscopic retrograde cholangiopancreatography; B: Endoscopically-assisted endoscopic retrograde cholangiopancreatography.

Further complicating the scenario, cholecystectomy is not systematically performed during laparoscopic techniques of bariatric surgery. The decreased gallbladder emptying after RYGB also contributes to gallstone formation[140,141]. Subsequently, cholelithiasis is diagnosed in up to 50% of patients following RYGB and therefore, complications secondary to gallstones, such as choledocolithiasis, are common[141]. Whereas performing endoscopic retrograde cholangiography (ERCP) in patients with LAGB or SG is straightforward because conventional transoral ERCP is feasible, this is not the case for RYGB. Accessing the biliary tree after RYGB is challenging and involves crossing the

gastrojejunostomy, going down the Roux limb to arrive at the jejunojejunal anastomosis and up through the biliopancreatic limb to reach the papilla. The long length of the small bowel that the endoscope must traverse and the sharp angulation at the jejunojejunal anastomosis are the main constraints that render ERCP in patients with RYGB very difficult, even impossible[142].

In the attempt to overcome these limitations, alternative routes have been proposed (Figure 8). The most important one is laparoscopy-assisted ERCP. After the first laparoscopic gastrostomy was created intentionally to perform ERCP in 2002, experience in the procedure has accumulated and it is now a widely accepted technique to perform ERCP in postbariatric RYGB (Table 3)[143-154].

During LA-ERCP, the standard laparoscopy is performed and once the pneumoperitoneum has been established, a gastrostomy is created on the greater curve of the excluded stomach. Then, a 15-mm trocar is placed into the gastrostomy through the abdominal wall at the upper left quadrant. A conventional duodenoscope is finally passed through the trocar into the gastric remnant and progressed through the pylorus into the duodenum. A review of the literature yields a rate of successful ERCP of 80% to 100% although most studies reported a 100% success rate. Complications related to the laparoscopic transgastric access were observed in 0% to 17% of cases. The length of the entire procedure was variable and reported operative times ranged from 41 to 245 min. However, the ERCP time was not

reported in the majority of studies and in many cases, the surgical procedure included cholecystectomy and/or closure of internal hernias found during laparoscopic exploration.

Technological advances in endoscopy have made access of the biliary tree in the conventional transoral route feasible. Endoscopically-assisted ERCP options include double or single balloon assisted ERCP (BEA-ERCP), spiral overtube-assisted ERCP, percutaneous transgastric ERCP and endoscopic ultrasound-directed transgastric ERCP. Double and single balloon enteroscopes, initially conceived for deeper access to the small bowel, are useful for performing ERCP in patients with complex postsurgical anatomy with similar success rates[155-157]. Several studies have evaluated the performance of both enteroscopes in ERCP in patients with Roux-en-Y anatomy. Reaching the blind end was possible in 69%-100% of patients and in these cases ERCP was satisfactorily accomplished in 78%-100%[152,157-166].

However, the majority of patients in these had a non-bariatric RYGB where the Roux limb is usually shorter. One study directly compared the performance of LA-ERCP and BEA-ERCP[152]. In this study, a total of 32 patients with bariatric RYGB underwent BEA-ERCP, either with a single or double balloon, and 24 underwent LA-ERCP. Identification of papilla was possible in 72% and cannulation and therapeutic success was achieved in 59% of patients. The impossibility of reaching the papilla was responsible for the majority of failures; in fact, a limb length (length of the Roux limb plus distance from the Treitz ligament to the jejunojejunal anastomosis) less than 150 cm was the only factor significantly associated with therapeutic success. One case of mild pancreatitis was the only complication observed in this study. Nevertheless, LA-ERCP was found to be superior with rates of papilla identification, cannulation and therapeutic success of 100% each (P = 0.005, P < 0.001, P < 0.001, respectively) without more complications (one mild pancreatitis and one enterocutaneous fistula). Although the mean procedure time was shorter in the BEA-ERCP group (106 min *vs* 172 min, P < 0.001), the endoscopic time was longer (106 min *vs* 75 min, P = 0.006) reflecting the higher complexity of the endoscopic procedure with BEA-ERCP. One reason why BEA-ERCP compares poorly with LA-ERCP is the specific challenges that BEA-ERCP with forward view endoscopes must face. In addition to the long length of the small bowel that must be traversed, it is more difficult to obtain a frontal view of the papilla making the cannulation of a native papilla difficult. Once the papilla is cannulated, the lack of an elevator and the long working channel with limited diameter render therapeutic procedures challenging. Most conventional accessories used in ERCP are shorter than the enteroscope working channel. Although this has been overcome with new short-type enteroscopes with 152 cm length (Fujifilm, Osaka, Japan), the diameter is still limited to allow the insertion of certain devices.

Spiral enteroscopy is a deep enteroscopy technique that uses an overtube with a spiral at the distal end (Endo-Ease Discovery SB overtube, Spirus Medical, Stoughton, MA, United States). While clockwise rotation is applied to the overtube, the spiral transforms the rotational energy into linear force to fold the small bowel on the endoscope allowing for enteroscope advancement[167,168]. Although few series have reported on spiral overtube-assisted ERCP, this technique seems to perform similarly to double or single balloon-assisted ERCP but no specific data are available in patients with bariatric RYGB[157,169-175].

Another route to try ERCP in RYGB is through a gastrostomy approach. In two different studies, 28 and 44 patients respectively underwent ERCP through laparoscopic or open surgical gastrostomy at the gastric remnant[147,171]. In the first study, the ERCP was performed on the same day of the gastrostomy procedure after tacking the stomach to the abdominal wall, whereas in the second study, ERCP was deferred 4-6 wk to allow for gastrostomy tract maturity. After completing ERCP on the same day of gastrostomy creation, a gastrostomy tube was placed to allow for tract maturation before its removal no sooner than 4 wk. In cases of a mature tract, the gastrostomy tube was either completely removed or replaced when further ERCP procedures were thought to be needed. In these two studies, ERCP was successful in 100% and 97% of patients, and complications were observed in 18 and 14.5%, respectively. Most complications were related to the gastrostomy. When compared with BEA-ERCP, ERCP *via* gastrostomy was more successful but its morbidity was also significantly higher[171]. Percutaneous-assisted transprosthetic endoscopy therapy is a new technique that allows for single-session ERCP *via* retrograde percutaneous endoscopic gastrostomy[172,173]. Gastrostomy is created by using a single or double balloon enteroscope to access the excluded stomach, followed by placement of a fully-covered self-expandable metal stent. Conventional ERCP is then performed with a standard side-viewing endoscope through the previously dilated stent. Another alternative is the endoscopic ultrasound directed transgastric ERCP (EDGE)[174]. This technique uses endoscopic ultrasound guidance to perform the gastrostomy, identifying the gastric remnant from the gastric pouch. One week later, transgastric ERCP is performed after dilatation of the gastrostomy tract. To avoid a two stage procedure, a variation of the last technique (internal EDGE) consists of performing a EUS-guided gastrogastric fistula[175]. Then, a fully-covered tissue apposition stent is placed to keep the fistula open and to avoid leakage. The stent is dilated and a conventional duodenoscope is passed through the stent into the gastric remnant and ERCP is performed in an anterograde fashion. All of these innovative techniques have shown promising outcomes in some patients and are appealing due to their minimally

invasive character. However, experience is still very limited.

Despite having several options for accessing the biliary tree in patients with RYGB instead of conventional ERCP, either surgically or endoscopically assisted, if cholecystectomy has not been performed previously, LA-ERCP at the time of laparoscopic cholecystectomy seems to be the most suitable approach. Otherwise, attempting enteroscopy-assisted ERCP (EA-ERCP) first, either with a balloon enteroscope or a spiral overtube, seems reasonable because these techniques are less invasive. In cases of EA-ERCP failure, continuing with LA-ERCP is a cost-saving strategy[152]. There is less experience with other techniques although placing a gastrostomy tube may be practical when repeated ERCP procedures are expected.

CONCLUSION

As obesity becomes more prevalent, weight loss treatment, particularly bariatric surgery, is becoming a more established therapy. Some complications of bariatric surgery, such as leaks, are severe and potentially fatal and their treatment is challenging. Technological enhancements in endoscopy have led to endoscopic management of post-bariatric complications gaining popularity, either as a first-line treatment or as complementary therapy to surgery. In some cases, several endoscopic modalities are available, and, although reported results are promising, evidence in the literature is often weak and is almost entirely from retrospective and small case series. There is a need for standardization and guidelines to assist physicians to address these complications. For this purpose, larger and prospective trials are needed to clearly define the place and optimal timing of endoscopic treatment and determine whether one endoscopic option is superior to surgery or other endoscopic modalities.

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Retrospective Study

Utility of endoscopic retrograde cholangiopancreatography on biliopancreatic diseases in patients with Billroth II-reconstructed stomach

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Abstract

AIM
To examine the utility of endoscopic retrograde cholangiopancreatography (ERCP) on biliopancreatic diseases in the patients with Billroth II-reconstructed stomach.

METHODS
For 26 cases of biliopancreatic diseases in patients with Billroth II-reconstructed stomach, ERCP was conducted using a straight-view scope or a retrograde oblique-viewing endoscope. All the cases were patients aiming at selective insertion into the bile duct. One patient aimed at diagnosis, and 25 patients aimed at treatment. The cases in which the endoscope reached the duodenal papilla and anastomosis, and insertion into the bile duct became possible, were considered successful.

RESULTS
The rate of reaching the duodenal papilla and anastomosis was 84.7% (22/26 patients). Among the cases without reaching the duodenal papilla and anastomosis, there were 2 in which the endoscope did not pass due

to tumor-induced duodenal infiltration. In 1 case, the fiber did not reach the duodenal papilla due to long afferent loop. The success rate of insertion into the bile duct in patients in which the endoscope reached the duodenal papilla and anastomosis was 90.9% (20/22 patients), and the success rate of procedures including treatment was 86.3% (19/22 patients). After treatment, mild cholangitis was observed in 1 patient (4.5%, 1/22 patients) but relieved conservatively. No other accidental symptom was observed.

CONCLUSION

It was considered that the ERCP for biliopancreatic diseases in patients with Billroth II-reconstructed stomach will become a less invasive, safe and useful examination and treatment approach.

Key words: Billroth II-reconstructed stomach; Endoscopic retrograde cholangiopancreatography; Endoscopic papillary balloon dilatation

Core tip: It was considered that the endoscopic retrograde cholangiopancreatography for biliopancreatic diseases in patients with Billroth II-reconstructed stomach will become a less invasive, safe and useful examination and treatment approach.

INTRODUCTION

With the development of endoscopic techniques, equipment and treatment tools in recent years, the endoscopic approach for biliopancreatic diseases is rapidly evolving, and less invasive treatment has become possible. Moreover, it can be said that the necessity for endoscopic retrograde cholangiopancreatography (ERCP)-related procedures is increasing because of improvement of the results of surgical operation and postoperative careful follow-up in patients after gastrectomy. In patients after gastrectomy, however, the difficulty in procedures is high because the methods of approach to the papilla and anastomosis are different according to the anatomy by reconstruction method and because the physical relationship of the papilla is different endoscopically. In the present study, we performed ERCP on cases of biliopancreatic disease in patients with Billroth II-reconstructed stomach to examine its utility and safety.

MATERIALS AND METHODS

The subjects included 26 patients with Billroth II-reconstructed stomach, who have biliopancreatic diseases and have attempted the ERCP 42 times in total from April 1999 to February 2010. There were 21 male and 5 female patients, with the mean age of 70.2-year-old (ranging from 59-year-old to 89-year-old). The diseases were bile duct stone in 20 patients, intrahepatic stone in 1 patient, papilla vater cancer in 1 patient, gallbladder cancer in 1 patient, cholangiocarcinoma in 1 patient, pancreatic cancer in 1 patient and biliary obstruction due to peritoneal metastasis of gastric cancer in 1 patient. One patient underwent diagnostic ERCP, and 25 patients underwent therapeutic ERCP (Table 1).

Among the 42 total procedures, a straight-view scope and a retrograde oblique-viewing endoscope were used 24 and 18 times, respectively (Q200, 230, 240, XQ200, PCF240, JF230 and JF240: Olympus Corp, Tokyo, Japan). For cannulation, catheters PR-104Q, R110Q-1 and PR233Q were used. A 0.025-inch or 0.035-inch guidewire (Jagwire by Microvasive, Boston Scientific Corp, Natick, MA, United States or Revo Wave by Olympus Corp) was used. For endoscopic papillary balloon dilatation (EPBD), the balloon was selected according to the diameter of the bile duct and dilated at 4 atmospheres until the notch disappeared (OLBERT by Maeadox Surgimed Corp, or QUANTUM by Boston Scientific Corp). Endoscopic sphincterotomy (EST) was conducted using a single electrosurgical current generator (PSD-20; Olympus Corp) at a power of 25 W. For incision, the needle-knife (KD10Q-1; Olympus Corp) was used.

When the endoscope reached the duodenal papilla or anastomosis, when insertion into the bile duct or pancreatic duct became possible and when the purposes, including treatment, were achieved, the cases were considered successful. The endoscopic nasobiliary drainage tube (ENBD) of 7 Fr was used (Flexima; Boston Scientific Corp, or SD9 by SILUX). The tube stents of 7 Fr and 8.5 Fr were used (FLEXIMA, SOLOPASS: Boston Scientific Corp). As a metal stent, Flexxus (Kobayashi Medical) uncovered-type was used. Basket catheters (FG-22Q; Olympus Corp) were used for stone quarry, and LBGT-7245S (ZEON Medical) was used for lithotripsy. The rate of reaching the duodenal papilla or anastomosis, the success rate of insertion into bile duct in patients with achievement and the success rate of treatment were examined.

The endoscope and procedures were selected at the discretion of the operating surgeon. All the patients had provided written informed consent before these diagnostic and therapeutic procedures. Iatrogenic morbidity was assessed according to the criteria of Cotton *et al*[1].

Table 1 Patients' background and disease background

Sex		21 males
		5 females
Age		70.2 yr (range: 59-89 yr)
Disease	Bile duct stone	20
	Intrahepatic stone	1
	Papilla vater cancer	1
	Gallbladder cancer	1
	Cholangiocarcinoma	1
	Pancreatic cancer	1
	Metastatic biliary obstruction	1
Target region	Bile duct	25
	Pancreatic duct	1
Purpose	Diagnosis	1
	Treatment	25

RESULTS

The rate of reaching the duodenal papilla or anastomosis was 84.7% (22/26 patients). The Braun anastomosis was observed at a rate of 38.5% (10/26 patients). Among the cases not reaching the papilla or anastomosis, there were 2 in which the endoscope did not pass due to tumor-induced duodenal infiltration. In 1 case, the fiber did not reach the duodenal papilla due to long afferent loop. The success rate of insertion into bile duct in the patients in which the endoscope reached the papilla or anastomosis was 90.9% (20/22 patients). As treatment of papilla, the EPBD and EST were conducted on 18 and 2 patients, respectively. The remaining 1 patient was a patient with intrahepatic stone, who underwent choledochojejunostomy, and since no stenosis of anastomosis was observed, the treatment was started with no procedure for the anastomosis. In the patients with bile duct stone (Figure 1), the mean diameter of stone was 8.6 mm (range of 0 mm to 16 mm), and the number of stones ranged from 0 to 1.5, with 2 patients having spontaneous elimination of stones and showing no stone in cholangiography. All these patients succeeded in collection of stones.

Among the 42 ERCP procedures conducted, drainage was performed 15 times, and the ENBD, placement of tube stent and placement of metallic stent were attempted 9 times, 5 times and 1 time, respectively (Figure 2), all of which were successful. The success rate of treatment was 86.3% (19/22 patients). The one patient who succeeded in cholangiography but failed in treatment was the one with intrahepatic stone who underwent choledochojejunostomy and who failed in lithotripsy because the guidewire passed through stones to the side of liver but the catheter did not pass. On that patient, percutaneous transhepatic cholangioscopic lithotripsy was performed after percutaneous transhepatic biliary drainage (PTBD), and the treatment was successful. In the present treatment, mild cholangitis was observed in 1 patient (4.5%, 1/22 patient) but was relieved conservatively. No other accidental symptom was observed. Among 4 patients in which the endoscope did not reach the duodenal papilla, 3 patients underwent

Figure 1 Endoscopic retrograde cholangiopancreatography on bile duct stone in athe patient with Billroth II-reconstructed stomach. A: Stones, sized 7 mm, were observed by cholangiography; B: Stones were gripped with a basket, and collection of stone was successful.

PTBD. One patient had bile duct stone with no hepatic disorder, and surgery was conducted instead of PTBD. Among 2 patients in which the endoscope reached the papilla but the biliary cannulation was impossible, 1 patient underwent the PTBD and another patient was the one with gallbladder cancer showing no jaundice, and on this patient, the ERCP was conducted for the purpose of diagnosis, which was not successful, so the image of bile duct was substituted with magnetic resonance cholangiopancreatography (MRCP).

DISCUSSION

The patients with biliopancreatic diseases after gastrectomy have experienced open surgery once. In the non-gastrectomized patients, repeated open surgery for the diseases such as bile duct stone, in which the endoscopic treatment becomes the first option, puts a heavy strain on the patients. In recent years, both the rate of reaching the duodenal papilla and the success rate of the procedure have been reported to be relatively good from various institutions for the patients with Billroth II-reconstructed stomach[2-20]. Since the afferent loop is relatively short in the patients with Billroth II-reconstructed stomach, different from the Roux-en-Y-reconstructed stomach, reaching the papilla may frequently be possible even using a straight-view scope or a retrograde oblique-viewing endoscope.

In our present results, the rate of reaching the duodenal papilla and anastomosis was 87.5%, the success rate of cholangiography was 90.5%, and the procedural success rate was 85.7%. Among the patients in which the endoscope did not reach the duodenal papilla and anastomosis, the fiber did not pass due to tumor-induced infiltration in 2 patients. It is shown that, if there is no problem in the passage of fiber and if the fiber can reach the area, the procedure has a high probability of being successful. In the remaining 1 patient of our study, the fiber did not reach the duodenal papilla due to long afferent loop. When the fiber is too short to reach

Figure 2 Endoscopic retrograde cholangiopancreatography on obstructive jaundice in the a patient with Billroth II-reconstructed stomach. A: Intense stenosis was observed from the upper through middle bile duct by cholangiography; B: The endoscopic nasobiliary drainage tube was placed after placement of a metallic stent.

the papilla with a straight-view scope or a retrograde oblique-viewing endoscope, there is a possibility that this problem can be resolved by using a single balloon enteroscopy[18] or a double balloon[19,20] with a long effective length.

Concerning attainment to the duodenal papilla in the patients with the Billroth II-reconstructed stomach, moreover, it is said that the presence or absence of Braun anastomosis may have a large influence on the rate of reaching the papilla. The results in the patients with no Braun anastomosis are good, but those in the patients with Braun anastomosis are bad. Ciçek *et al*[11] reported that the rate of reaching the papilla was 29% in the patients with Braun anastomosis. In the patients with Braun anastomosis, when endoscopy is conducted indefinitely, it may induce repeated round trip of the same route and become a waste of time. It is integral to aim at attainment to the papilla having a clear strategy so as not to neglect to confirm the direction of movement at the anastomosis. Concerning the route into which the endoscope has ever entered, for example, it is considered necessary to mark with clips, *etc*.

As to the fiber, we used a straight-view scope or a retrograde oblique-viewing endoscope. With a straight-view scope, it is easy to secure the field of view of the lumen of the intestinal tract during insertion of the endoscope into the small intestine, which is superior to the retrograde oblique-viewing endoscope from the aspect of prevention of perforation. Since the usual straight view scope has a small inlet of forceps, however, the available devices have some limitations. With the retrograde oblique-viewing endoscope, on the other hand, it is difficult to obtain the field of view of the lumen of the gastrointestinal tract, and insertion of the endoscope into the small intestine is difficult. In the past, there have been a lot of reports of perforation of 0.7% to 18% with a retrograde oblique-viewing endoscope, compared with that of a straight-view endoscope[6-15]. In many cases, the blinded manipulation of endoscope may be associated with this. Since the retrograde oblique-viewing endoscope has a longer effective length than the straight-view endoscope and has a bending forceps

device after reaching the papilla, however, it is effective for selective cannulation. In recent years, very good results have been obtained by an anterograde oblique-viewing endoscope having the same effective length and the same field of view as the straight-view scope and a bending forceps device[21,22]. At present, there is a problem of effective length, but in the case of Billroth II-reconstructed stomach, this fiber can become the first option.

In the patients with Billroth II-reconstructed stomach, however, this method may be difficult because the oppositely-oriented approach should be conducted different from the usual ERCP. In the patients for whom the fiber reached the papilla in this study, the success rate of cannulation was as high as 90.9%. This report does not have inferiority in comparison with the results of an anterograde oblique-viewing endoscope[21,22]. The reason why the success rate was high despite that this patient represented a case with difficulty in cannulation, in which the papilla existed on the opposite side from the usual one, was because the flexible tip catheter[23], *etc*., with which the angle can be changed in cannulation, was used. Since the success rate was not 100%, despite the high success rate, improved techniques of operators and further modification of treatment tools are required.

Concerning the treatment of papilla, the EST and EPBD have been performed. Different from the usual ERCP, it is difficult to perform EST with a needle knife because the oppositely-oriented approach should be performed. If we wish to perform EST because it is advantageous for subsequent treatment of giant bile duct stone, it should be used because there is a papillotome effective for the Billroth II-reconstructed stomach different from usual papillotome[5,10], if EST with a needle knife is technically difficult. Different from the EST, on the other hand, if a guidewire is placed in the bile duct, it may be possible to perform treatment easily with EPBD, even if using usual treatment tools. Therefore, choledocholithiasis in the patients with Billroth II-reconstructed stomach is considered a good indication for EPBD unless otherwise specified.

In the present study, however, we have not experienced cases with pancreatitis as an accidental symptom; but, since EPBD is a risk factor of post-ERCP pancreatitis[24,25], it is considered very important to perform prevention against pancreatitis due to placement of pancreatic stent[26,27] in the patients undergoing erroneous pancreatography or patients in whom a guidewire was erroneously inserted into the pancreatic duct. Considering that stones were spontaneously eliminated in 2 patients among the patients with bile duct stone in the present study, moreover, since attainment to the papilla and subsequent treatment are more difficult in the patients with Billroth Ⅱ-reconstructed stomach than usual patients, it may be better to perform MRCP at first and then to follow-up the patients without conducting the ERCP, as much as possible, if no stone is identified[28-30]. The treatment with endoscope on biliopancreatic disease in the patients with Billroth Ⅱ-reconstructed stomach is less invasive, which is considered the treatment to be tried at first. Since there are some patients who present difficulty in treatment with endoscope, however, we should consider percutaneous approaches and surgical treatment if the percutaneous method is difficult, without sticking to the endoscopic treatment exclusively.

In conclusion, it was considered that ERCP for biliopancreatic diseases in patients with Billroth Ⅱ-reconstructed stomach will become a less invasive, safe and useful examination and treatment approach.

COMMENTS

Background

With the development of endoscopic techniques, equipment and treatment tools in recent years, the endoscopic approach for biliopancreatic diseases has been rapidly evolving and less invasive treatment has become possible. In the present study, the authors performed endoscopic retrograde cholangiopancreatography (ERCP) for biliopancreatic disease in patients with Billroth Ⅱ-reconstructed stomach to examine its utility and safety.

Research frontiers

The subjects were 26 patients with Billroth Ⅱ-reconstructed stomach, who have biliopancreatic diseases and have attempted the ERCP a total of 42 times from April 1999 to February 2010.

Innovations and breakthroughs

The rate of reaching the duodenal papilla or anastomosis was 84.7% (22/26 patients). The success rate of treatment was 86.3% (19/22 patients). In the present treatment, mild cholangitis was observed in 1 patient (4.5%, 1/22 patient) but relieved conservatively.

Applications

Biliopancreatic disease in patients with Billroth Ⅱ-reconstructed stomach.

Terminology

It was considered that ERCP for biliopancreatic diseases in patients with Billroth Ⅱ-reconstructed stomach will become a less invasive, safe and useful examination and treatment approach.

Peer-review

The authors conducted a retrospective study regarding the issue of ERCP in the treatment of biliopancreatic disease in patients with Billroth-Ⅱ gastrectomy. This topic is interesting.

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Clipping prevents perforation in large, flat polyps

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Abstract

AIM
To determine if prophylactic clipping of post-polypectomy endoscopic mucosal resection (EMR) mucosal defects of large, flat, right sided polyps prevents perforations.

METHODS
IRB approved review of all colonoscopies, and prospective data collection of grasp and snare EMR performed by 2 endoscopists between January 1, 2010 and March 31, 2014 in a community ambulatory endoscopy center. The study consisted of two phases. In the first phase, all right-sided, flat polyps greater than or equal to 1.2 cm in size were removed using the grasp and snare technique. Clipping was done at the discretion of the endoscopist. In the second phase, all mucosal defects were closed using resolution clips. Phase 2 of the study was powered to detect a statistically significant difference in perforation rate with 148 EMRs, if less than or equal to 2 perforations occurred.

RESULTS
In phase 1 of the study, 2121 colonoscopies were performed. Seventy-five patients had 95 large polyps removed. There were 4 perforations in 95 polypectomies (4.2%). The perforations occurred in polyps ranging in size from 1.5 cm to 2.5 cm. In phase 2, there were 2464

colonoscopies performed. One hundred and sixteen patients had 151 large polyps removed, and all mucosal defects were clipped. There were no perforations (*P* = 0.0016). There were no post-polypectomy hemorrhages in either phase. An average of 2.15 clips were required to close the mucosal defects. The median time to perform the polypectomy and clipping was 13 min, and the median procedure duration was 40 min. Five percent of all patients undergoing colonoscopy in our community based, ambulatory endoscopy center had flat, right sided polyps greater than or equal to 1.2 cm in size.

CONCLUSION
Prophylactic clipping of the mucosal resection defect of large, right-sided, flat polyps reduces the incidence of perforation.

Key words: Flat polyps; Complications; Perforation; Polypectomy; Prevalence; Clipping; Endoscopic mucosal resection

Core tip: Large, flat, right sided polyps are being recognized with increasing frequency, and have become one of the more technically challenging aspects of colonoscopy. In a prospective study of over 4500 consecutive colonoscopies performed in a community, ambulatory endoscopy center, the prevalence of these polyps was 5%. We showed that it was safe to remove these polyps in the outpatient setting, and that clipping the mucosal defect prevented perforations. An average of 2 clips were required to close the defects, and the average polypectomy time was 13 min. It is not necessary to perform these procedures in a hospital setting.

INTRODUCTION

Colorectal cancer is the second leading cause of cancer mortality in men and women in the United States with about 132700 new cases and 49700 deaths expected in 2015. Screening colonoscopy with polypectomy has contributed to reducing deaths from colon cancer by 47%[1]. While colonoscopy is effective in reducing the incidence of left-sided colon cancer, it is not as effective for right-sided cancers[2]. Flat, right-sided colon polyps are cancer precursors and account for about 50%-55% of interval cancers[3]. Due to the flat morphology, frequent large size, and thin wall of the right colon, these polyps may be difficult to detect, challenging

to remove, and associated with increased procedure-related morbidity, including bleeding and perforation[4].

Endoscopic mucosal resection (EMR) entails injecting a fluid matrix into the submucosal space between the lamina propria and muscularis mucosa to raise the lesion on this bleb of fluid. This allows for snare resection of the mucosal bleb that is safer, more effective and efficient than standard snare resection, particularly in the thin-walled right colon[5]. However, it may be difficult to ensnare the spreading mucosal bleb with conventional snares passed through standard single channel colonoscopes.

The grasp and snare EMR (GSEMR) technique entails using a double channel colonoscope with submucosal injection to raise the lesion on a mucosal bleb. A snare is inserted through one channel which is opened over the polyp and mucosal bleb and a biopsy forceps through the other channel and open snare. The polyp and mucosal bleb are grasped with a forceps and slightly retracted. The snare is closed around the raised polyp and mucosal bleb while applying monopolar energy to excise the lesion[6,7]. Clipping to close the mucosal defect can then be done as required (Figure 1).

The overall management of large flat polyps varies. Due to concerns about prolonged procedures and increased morbidity rates, some endoscopists prefer to not resect these polyps during the initial procedure. The patient is then scheduled to return for an office visit for counseling and/or a subsequent procedure in a hospital setting rather than an ambulatory endoscopy unit, or is referred for surgery[5]. Endoscopic clipping has been used to prevent and treat post-polypectomy bleeding, and close small perforations thereby avoiding surgery[4,8,9]. However, less is known about the safety and efficacy of the GSEMR technique combined with prophylactic clipping of the mucosal defect in a community ambulatory endoscopy unit. The aim of the study was to determine if prophylactic clipping of the GSEMR base prevents perforations.

MATERIALS AND METHODS

This is a prospective cohort study comprised of two phases. Prior to the procedures, all patients were advised to discontinue dipyridamole for 7 d, warfarin for 4 d, and other anticoagulants and antiplatelet agents according to the prescribing provider. Two models of double channel colonoscopes were used throughout the study. The Pentax Medical (Montvale, NJ, United States) EC3890TLK has a 13.2-mm insertion tube diameter and the EC3870TLK has a 12.8-mm insertion tube diameter. Both instruments have working channels of 3.8 mm and 2.8 mm, tip angulation of 180° up/down and 160° right/left, and a 140° angle of view. All procedures were done with white light and no magnification or chromo-endoscopy. I-scan was used at the discretion of the endoscopist.

Polyps that met inclusion criteria were located proximal to the splenic flexure, 1.2 cm or larger in

Figure 1 Images of Flat right polyp removed by the grasp and snare endoscopic mucosal resection technique. A: Flat polyp in proximal colon; B: Polyp lifted with saline and viewed with i-scan; C: Edge of mucosal defect is grasped with a biopsy forceps and then the edges of the defect are approximated and clipped; D: Clip closure of the mucosal defect.

diameter, and had a maximum base width that was larger than the protruding height. Lesions that appeared to be malignant due to size, morphology, and/or infiltration were excluded. Eligible lesions were treated with GSEMR. Post polypectomy hemorrhage was defined as bleeding that occurred after a patient left the endoscopy center, and required evaluation at a medical office or hospital, and required blood transfusion, hospitalization or repeat colonoscopy to evaluate the polypectomy site, or control the bleeding. Perforation was defined as presence of free air on either abdominal radiographs or CT scan of the abdomen and pelvis, in conjunction with abdominal pain.

The study consisted of two phases as shown in Figure 2. During Phase 1 (February 1, 2010-September 30, 2011), the resection sites were clipped at the discretion of the endoscopists to prevent perforation and not as a routine maneuver. A total of 6 polyps were clipped in phase 1. However, 4 of 75 (5.3%) eligible patients with 95 (4.2%) eligible polyps experienced perforations at the resection site. The size of these four polyps were 2, 1.5, 2 and 2.5 cm. No target signs were appreciated. Therefore, Phase 2 (October 1, 2011-March 31, 2014) was initiated with routine endoscopic closure of the post-GSEMR mucosal defect using Resolution clips (Boston Scientific, Natick, MA). The majority of lesions were removed with piecemeal resection and retrieved by suction through the working channels into a specimen trap. Occasionally, larger specimens were retrieved using

an endoscopic net. All resection sites were tattooed with India ink following GSEMR.

Setting
All colonoscopies were done at the Monterey Bay Ambulatory Endoscopy Center, LLC, a Medicare-certified unit with four endoscopy rooms, and 10 board certified gastroenterologists on staff. The study was performed in a practice that serves approximately 215250 people in Monterey County, CA. GSEMR was performed by two gastroenterologists (DGL, JAD), each with over 15 years of experience. The study population consisted of all consecutive adult patients who had colonoscopies performed by these endoscopists during the study period and had GSEMR of large, flat, right colonic polyps. All patients gave standard clinical informed consent, and those who wished to have their data included in the study gave additional research consent as shown in Figure 2.

Pathology
Histopathological evaluation was done by one or more of five experienced pathologists (one with formal advanced gastroenterology pathology training) according to World Health Organization Criteria[10]. Discrepancies were resolved by consensus and/or external referral center consultation. The study was approved by the Institutional Review Board of the Community Hospital of the Monterey Peninsula, Monterey, CA, United States.

Figure 2 Flow chart of eligible and enrolled patients.

Statistical analysis

Phase 2 of the study was powered using a one stage design. The observed perforation rate using the current procedure in Phase 1 was 4.2% (4 perforations in 95 polypectomies). A sample size of $n = 148$ polypectomies was determined to be necessary to provide a one-sided Type I error rate $\alpha = 0.05$ under the null hypothesis that the perforation rate of the new procedure is 4.2% and 80% power to detect a perforation rate of 1% or less. The null hypothesis would be rejected if there were 2 or fewer perforations out of 148 polypectomies.

RESULTS

Figure 2 shows a flow chart of eligible and enrolled patients. Over the 50 mo of the study, a total of 4,585 colonoscopies were performed by the two participating endoscopists. Indications for colonoscopy are shown in Table 1. In both phases, the primary indication was adenomatous polyp surveillance: 69% (Phase 1), 73% (Phase 2).

In Phase 1, the mean procedure duration was 44.70 ± 18.83 min and the mean GSEMR time was 18.69 ± 15.31 min. The overall prevalence of eligible polyps among all patients was 3.8%. Complications included four perforations in 75 (5.3%) patients and 95 (4.2%) polypectomies. There were no post-polypectomy hemorrhages. Table 2 shows histopathology results with 31 (48%) tubular adenomas (TAs), 16 (25%) sessile serrated adenomas (SSAs), and 10 (15%) hyperplastic polyps (HPs).

In Phase 2, 2464 colonoscopies were performed. The prevalence of eligible polyps among all patients was 6.3%. Histopathology revealed SSAs 68 (45%), TAs 47 (31%), HPs 24 (16%) and TVAs 7 (5%). The mean procedure time was 42.90 ± 15.60 min. The mean polypectomy duration was 16.4 ± 10.04 min. A median of 2 clips were used to close the mucosal defects. There were no observed post-polypectomy perforations among the 151 polypectomies. Results of exact binomial test for goodness-of-fit suggests that the findings

were statistically significant ($P = 0.0016$). We are 95% confident that the true polypectomy perforation rate for this new procedure is between 0% and 1.9% - well below the observed perforation rate using the current procedure (4.2%). We reject the null hypothesis that the perforation rate of the new procedure is no different than the current procedure (4.2%). There were no bleeding episodes.

DISCUSSION

The current study supports the hypothesis that prophylactic clipping of the mucosal defect following GSEMR of large, flat, right colonic polyps prevents perforations. The results also demonstrate that these polyps can be safely removed in an ambulatory endoscopy center as opposed to a hospital, and that these procedures do not interfere with overall patient flow in the unit. By using double channel colonoscopes and a biangulated technique, approximation of the mucosal defect can

Table 1 Patient and procedure data for Phases 1 and 2 *n* (%)

	Phase 1 (*n* = 55)	Phase 2 (*n* = 116)
Indications for colonoscopy[1]		
Surveillance	38 (69)	85 (73)
Screening	12 (21.8)	29 (25)
Abdominal pain/diarrhea	8 (14.5)	11 (9.5)
Bleeding	6 (10.9)	7 (6)
Change in bowel habits	2 (3.6)	2 (1.7)
Evaluation/therapy of known lesions	1 (1.8)	2 (1.7)
Anemia	3 (5.5)	2 (1.7)
Abnormal imaging	N/A	2 (1.7)
Other	1 (1.8): Diverticulitis	3 (2.6): Diverticulitis: 1 Rectal prolapse: 1 Rectal pain: 1
Patient characteristics		
Male/female (*n*)	36/19	65/51
Mean age (Range)	69.3 (37-87)	65.5 (29-87)
Family history of colon cancer	12 (21.8)	27 (23.3)
Procedure data and outcomes		
Total colonoscopies	2121	2464
Total polyps	65	151
Polyp size (cm): (Mean ± SD, median, range)	2 ± 0.69, 2, 1.2-4	1.81 ± 0.54, 1.6, 1.2-4
Clips/polyp (Mean ± SD, median)	N/A	2.17 + 0.97, 2
Polypectomy duration (min): Mean (SD), median, range	18.69 (15.31), 18, 2-61	16.4 (10.04), 13, 4-59[2]
Procedure duration (min): Mean (SD), median, range	44.70 (18.83), 41, 14-97	42.90 (15.60), 40, 20-96
Prevalence of large, flat right-sided polyps	3.8% (81/2121 procedures)	6.3% (154/2464 procedures)
Complications	Post-polypectomy bleeds: 0 Perforations: 2 3.6% of patients, 3% of polypectomies	Post-polypectomy bleeds: 0 Perforations: 0

[1]Total indications exceeds number of patients due to patients having multiple indications; [2]Three polypectomies excluded due to incomplete data. N/A: Not available.

Table 2 Polyp histopathology *n* (%)		
	Phase 1[1] (*n* = 65)	Phase 2 (*n* = 151)
Sessile serrated adenoma	16 (25.0)	68 (45.0)
Tubular adenoma	31 (48.0)	47 (31.0)
Hyperplastic	10 (15.0)	24 (16.0)
Tubulovillous	7 (11.0)	7 (5.0)
Normal	1 (1.5)	2 (1.3)
Fibroepithelial	1 (1.5)	N/A
Lipoma	N/A	2 (1.3)
Pneumatosis coli	N/A	1 (0.7)

[1]Phase 1 total exceeds sample size due to 1 mixed polyp. N/A: Not available.

be achieved with a median of two clips per polyp and minimal prolongation of colonoscopy compared to standard EMR[11].

The initial hypothesis was that these polyps could safely be removed without using clips. However, due to the perforation rate of 4.2% in Phase 1, the second phase of the study was powered to determine whether universal clipping of the mucosal defect would decrease the perforation rate. Subsequently, there were no perforations in 151 polypectomies. This is a statistically significant difference that met the primary endpoint for Phase 2 of the study, which was then terminated per protocol. However, prospective randomized studies are required to confirm these results. In addition, there was no post-polypectomy bleeding in either phase of the study.

Two recent studies report that prophylactic clipping does not prevent bleeding or perforations, and is not a cost-effective practice[12,13]. Other studies, including a meta-analysis of eight randomized controlled trials[14], showed that prophylactic clipping reduces bleeding but not perforations[4]. The current study provides prospective data in a community setting to further identify applications for these techniques and justify larger prospective, randomized, controlled studies to validate these results.

A potential criticism of GSEMR combined with pro-phylactic clipping is that it prolongs procedures and interrupts patient flow. In a meta-analysis, three EMR studies reported mean procedure times of 29-30 min[11]. While all lesions in the meta-analysis were large, they were not entirely of flat morphology or right colonic location. The current study demonstrates mean pro-cedure times of 44.7 and 42.9 min in Phase 1 and Phase 2, respectively. However, since the prevalence of these polyps was only 5.1%, we did not find doing these cases disruptive to our schedule.

Over the course of this four-year study, 5.1% of total procedures involved flat, right-sided polyps that were ≥ 1.2 cm. This compares with a 7% prevalence of flat right colonic lesions ranging from 3-40 mm in 1819 patients with 2770 lesions in a Veterans Affairs Hospital[15]. This difference in prevalence is likely due to the larger size range for eligible polyps, and patient demographics consisting of predominantly men over the age of 50 in a Veterans hospital.

The double channel endoscopes that were used had similar angulation ranges and diameters as single channel colonoscopes. Technical advances in colonoscope design are continually being made. However, the emphasis has generally been on image quality and improvement in polyp detection, rather than facilitating therapeutic maneuvers. Double channel colonoscopes allow for biangulated therapeutic maneuvers, which facilitate the removal of large, flat, right colon polyps. Only in rare cases throughout the study period was it necessary to exchange the double channel colonoscope for a pediatric colonoscope, which also occurs with standard colonoscopes. Design enhancements, combined with the development of accessories that facilitate a biangulated or triangulated approach to therapeutic interventions will improve the functional aspects of the currently available instruments.

Large, flat right-sided polyps occurred in 5.1% of patients during the study period. Based on the procedure times and similarities in functionality between double and single channel colonoscopes, removal of these challenging lesions is feasible and safe in a community endoscopy center and does not necessitate performance of the procedure in a hospital setting. Clipping the post-polypectomy defect reduces the perforation rate.

COMMENTS

Background
Large, flat, right sided polyps are cancer precursors, and are increasingly found during colonoscopy. These polyps are challenging to remove, and are frequently either removed in a hospital setting or referred to an expert endoscopist. Removing these polyps during an initial outpatient colonoscopy would decrease the number of procedures performed, and be more cost effective.

Research frontiers
More research should be done with double channel colonoscopes to enable biangulated and triangulated approaches to therapeutic endoscopy.

Innovations and breakthrough
Utilizing a double-channel colonoscope, it is possible to approximate the edges of a mucosal defect with a biopsy forceps, and then close the defect with a clip.

Applications
By utilizing double channel colonoscopes, large, flat polyps can be removed in a safe and cost effective manner in an outpatient setting. Clipping the post-polypectomy defect, reduces the risk of perforation.

Peer-review
Interesting article. As correctly quoted by the authors, multiple studies in the recent past have not shown significant benefit for prophylactic clipping to prevent perforations. It is important to know if there was a difference in size of the polyps resected by GSEMR between the 2 groups rather than just noting the polyps were greater than 1.2 cm for study inclusion.

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CASE REPORT

Langerhans cell histiocytosis masquerading as acute appendicitis: Case report and review

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Abstract

Langerhans cell histiocytosis (LCH) is a rare syndrome characterized by unifocal, multifocal unisystem, or disseminated/multi-system disease that commonly involves the bone, skin, lymph nodes, pituitary, or sometimes lung (almost exclusively in smokers) causing a variety of symptoms from rashes and bone lesions to diabetes insipidus or pulmonary infiltrates. We present a previously unreported case of gastrointestinal LCH as well as a novel characteristic lesion affecting the colon of a young woman who presented with signs and symptoms mimicking acute on chronic appendicitis. Immunohistochemical analysis of appendectomy specimen and nodular specimens on colonoscopy demonstrated S-100, CD1a, and langerin reactivity. The patient underwent systemic chemotherapy with cytarabine and demonstrated excellent response to therapy.

Key words: Langerhans cell histiocytosis; Adult histiocytosis; Appendicitis; Gastrointestinal histiocytosis; Right lower quadrant pain

Core tip: Langerhans cell histiocytosis (LCH) of the adult gastrointestinal tract can affect the appendix and present as mild inflammatory findings on exploratory

laparascopy, or white-yellowish nodularities and polyps on lower endoscopy. Immunohistochemical staining of surgical specimens for CD1a, S-100, and langerin should be considered in gastrointestinal lesions that demonstrate histology concerning for histiocytosis in an attempt to decrease morbidity related to undiagnosed LCH.

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare syndrome characterized by unifocal, multifocal unisystem, or disseminated/multi-system disease that commonly involves the bone, skin, lymph nodes, pituitary, and sometimes lungs (almost exclusively in smokers) causing a variety of symptoms from rashes and bone lesions to diabetes insipidus or pulmonary infiltrates. The liver, spleen, or bone marrow may also be involved and are considered "risk organs" that signify a less favorable prognosis[1,2]. The gastrointestinal tract is rarely involved, and when it is present, it usually affects pediatric patients with severe multisystem disease[3]. LCH typically affects children under 10 years of age with European ancestry. Peak incidence is under 2 years of age with a 2:1 predilection for males[1,2].

There are case reports of patients presenting up to the eight decade of life and some evidence to suggest a higher incidence in patients of Hispanic descent when compared to whites[1,3-5]. An incidence of 1 out of 200000 is commonly cited for the pediatric population compared to 1-2 per 1 million in the adult population. Diagnosis is typically confirmed by CD1a and S-100 reactivity on immunohistochemical staining of biopsied lesions and diagnosis is typically confirmed by the finding of Birbeck granules on electron microscopy or langerin reactivity on histology[1]. Treatment consists of supportive care, surgery, chemotherapy (especially in multisystem involvement), radiotherapy, and sometimes hormone replacement therapy in cases of pituitary dysfunction. Recent research supports the notion that LCH is more align with a neoplastic process rather than a reactive one, with a proportion of lesions presenting with *BRAF* or *MAP2K1* mutations. Such mutations may be of some value for risk stratification and prognostication, and immunotherapy with BRAF inhibitors have shown some promise in treatment[1,6]. Five-year mortality runs up to 20% with a greater risk of mortality in younger patients[2-4].

CASE REPORT

A 20-year-old G1P1 Hispanic female in previously good health with a history of pyelonephritis during pregnancy and eczema presented with 3 d of sharp, intermittent right lower quadrant pain that radiates towards the midline with movement. She vomited non-bloody, non-bilious emesis three times the day before presentation after eating and presented to our emergency department after having acute appendicitis ruled out at an outside hospital three days prior. Her pain responds to ibuprofen. She denies fevers, chills, diarrhea, urinary urgency or hesitancy, vaginal discharge or bleeding, or trauma. She engages in monogamous unprotected sex with a male partner and endorses mild dysuria. She denies alcohol, tobacco, or other drug use. She experienced a similar episode of pain a couple months prior to presentation. Her only medications are intramuscular depo provera for birth control and ibuprofen for her abdominal pain. She is afebrile with vitals within normal limits and body mass index of 19. Abdominal examination revealed present bowel sounds, mild tenderness to the right of midline near the right lower quadrant without guarding, McBurney's point tenderness or Murphy's sign. The remainder of the exam, including a pelvic exam, was unremarkable. Abdominal and pelvic causes of pain including acute appendicitis, nephrolithiasis, pregnancy, tuboovarian abscess, ovarian torsion, small bowel obstruction, functional intestinal obstruction, urinary tract infection, sexually transmitted infection, muscle strain were considered. Transvaginal and limited abdominal ultrasound performed at the outside hospital demonstrated small bilateral follicular cysts and no evidence of appendicitis or other tuboovarian processes. Urine studies were negative for bacteriuria, leukocyte esterase, nitrite, and both gonococcal and chlamydial RNA. Urine cultures acquired at that time were eventually negative for growth. Urine beta-hCG was negative. Wet mount unremarkable. Abdominal X-ray was unremarkable with nonspecific bowel gas pattern. At this point her signs/symptoms and lab testing were unremarkable for acute pathology other than perhaps abdominal pain secondary to follicular cysts. She was discharged in ambulatory, stable condition with instructions to present to pediatric acute follow-up clinic in 2-3 d and pain control with ibuprofen.

The next day she presented to the pediatric acute follow up clinic with severe and constant right lower quadrant pain that was no longer responsive to ibuprofen, and is exacerbated with any ambulation or lifting her child. She is afebrile with normal vitals. Abdominal exam is remarkable for right lower quadrant tenderness to palpation, guarding, and Rovsing's sign with no rebound tenderness. The patient also clarifies that her right lower quadrant pain has been intermittent and ongoing for the last four months. Hemoglobin (13.1 mg/dL), white blood count (7100/μL), platelets (260000/μL), fibrinogen (303 mg/dL) were within normal with a blood differential notable for peripheral eosinophilia (18% eosinophils with 1300/μL absolute count). Inflammatory markers C-reactive protein (< 0.02 mg/dL) and erythrocyte sedimentation rate (8 mm/h) were normal. Amylase

Figure 1 Histology and immunohistochemical stains of appendix confirming diagnosis of Langerhans cell histiocytosis. The appendix shows an overgrowth of histiocytes in the lymphoid aggregates at 10 × (A) and 40 × (B) magnifications of H and E stains; while the electron microscopy images did not show Birbeck bodies due to previous fixation, the Langerin stain (CD207) demonstrates their presence in the areas of concern at 10 × (C) and 40 × (D) magnification. CD1a stains at 10 × (E) and 40 × (F); S-100 stains at 10 × (G) and 40 × (H).

(82 U/L) and lipase (24 U/L) were within normal limits and pelvic as well as right upper quadrant ultrasounds both unremarkable for acute pathology. CT scan of the abdomen and pelvis is unremarkable, particularly demonstrating an air-filled appendix within normal limits and no fat stranding. She is admitted to the pediatrics ward and a gynecology consult determined that a gynecological problem is unlikely. Pediatric surgery was consulted and a diagnostic laparoscopy found normal liver, intestines, uterus, bilateral ovaries and fallopian tubes.

Figure 2 Gross appearance of colonic lesions on endoscopy. Wide (A) and close-up (B) views of approximately 5 mm whitish-yellowish polypoid lesions found throughout the colon. Biopsy and immunohistochemical staining demonstrated CD1a, S-100, and langerin reactivity confirming langerhans cell histiocytosis-related lesions (see Figure 3).

There were anomalous adhesions of the cecum to the anterior abdominal wall and the appendix was mildly injected with some area of thickening and induration suspicious for chronic appendicitis, and thus resected.

Her immediate post-op period was unremarkable and she was discharged with appropriate incisional tenderness on post-op day two. She presented to the emergency department on post-op day five complaining of right lower quadrant pain similar to that prior to surgery. She was readmitted and further imaging and workup including pelvic ultrasound as well as MRI of the brain and spine, and failed to show a cause of her pain. Her pain was managed with non-steroidal anti-inflammatory drugs, intravenous morphine, and Norco while in hospital. Surgical pathology of her appendix was grossly unremarkable, without ulceration or inflammation, yet demonstrated histiocytes in lymphoid aggregates on H and E stain and suspicious for LCH. This was confirmed with S-100, CD1a, and CD207 reactivity (Figure 1). Upper and lower endoscopy demonstrated whitish-yellowish polypoid nodules less than 5 mm in size at the luminal surface of the cecum, transverse, and descending colon (Figure 2). Microscopic evaluation demonstrated similar morphology to the appendix H and E, and immunohistochemical analysis demonstrated S-100, CD1a, CD207 (langerin) reactivity of these nodules (Figure 3) whereas biopsy samples of the esophagus, stomach, duodenum, and rectum failed to show histiocytosis. Bone marrow aspirates, bone scan, and MRI brain were negative for bone marrow, skeletal, and pituitary involvement, respectively.

DISCUSSION

Given the extensive involvement of her colon, she was diagnosed with unisystem, multifocal LCH that solely involves the colon. A port-a-cath was placed and the patient was started on cytarabine chemotherapy at 100 mg/m^2 per day for 5 d. The patient was to undergo 12 cycles, each one month apart, over the course of 12 mo.

At the time of writing this report, the patient is status post six cycles of cytarabine with marked clinical improvement. Follow-up upper and lower endoscopies with biopsy after her third cycle of chemotherapy demonstrated decreased disease burden with residual foci of histiocytosis present in colon biopsies (particularly the ascending colon) and her abdominal pain completely resolved sometime after her fourth cycle of chemotherapy.

In general, gastrointestinal involvement is rare in both child and adult forms of LCH and there are few case reports in the literature documenting gastrointestinal disease in adult patients with LCH. Gastrointestinal involvement in childhood onset LCH typically occurs in systemic LCH and thus forewarns of a poor prognosis. In contrast, adult patients who are diagnosed with unisystem disease such as in this case are thought to have an excellent prognosis upwards of 90% survival at five years[6]. Adult patients who present with enteric-related signs and symptoms seem to have a predilection towards oral lesions such as palatal ulcers, and there is a small case series that demonstrates 12 patients with incidentally found LCH lesions on endoscopy that predominantly affected the colon (with 2 cases of cecal involvement) and described as polyps or ulcerative lesions[3,4,6,7]. There seem to be even fewer case reports of small bowel involvement[8,9]. There are none that report an acute presentation of right lower quadrant pain that presents with features similar to acute appendicitis[3,4,10].

The patient presented with a story concerning for acute on chronic appendicitis. Exploratory laparotomy was performed under this suspicion, and although the appendix was a focus of disease, the gross findings of mild inflammation could have possibly been dismissed as normal variation of anatomy. Additionally, she is a young Hispanic woman in contrast to the stereotypical infant/toddler male of European descent. It is worth mentioning that there is some evidence to suggest this notion may have to be dismissed in favor of one that denotes Hispanics and those who live in crowded counties or areas with a low education level may be at higher risk of LCH[1,3,5,11].

Only after tissue analysis demonstrated histological

Figure 3 Histology of colonic samples consistent with Langerhans cell histiocytosis. Grossly, the colon biopsies were each received as small fragments of tissue, where no tissue defects could be determined due to the size of the specimens received. Microscopically, the cecum (A and B, 10 × and 20 ×, respectively), descending colon (C and D, 10 × and 40 ×, respectively), and transverse colon (E and F, 10 × and 20 ×, respectively) each show nodules that are similar in morphology to the appendix and (although not shown here) share the same staining patterns (CD1a, S-100, and langerin reactivity). Again, electron microscopy was unsuccessful in highlighting the Birbeck bodies due to formalin fixation.

findings suspicious for LCH, was the diagnosis entertained, and further testing performed. It is typical for surgeons to routinely send appendectomy specimens for analysis, and some studies have stressed the importance of routine histological examination of appendectomy specimens in order to identify uncommon etiologies of appendiceal disease such as neoplasms or various infectious processes, however there is some evidence to suggest otherwise[3,4]. In this case, had a surgical specimen not been taken, the time to diagnosis would have likely been prolonged, leading to further patient discomfort, lack of appropriate treatment, and possible loss to follow up due to a combination of these two.

Her persistent right lower quadrant pain was not relieved by the appendectomy, but spontaneously resolved after a considerable amount of chemotherapy. Lacking evidence of musculoskeletal, neurological, or other abdominopelvic pathology, it may be reasonable to suggest that her pain was caused by the histiocytosis of her colon that seems to have affected the entirety of her colon.

Gastrointestinal histiocytosis in the adult may present with an appendicitis-like syndrome that may be harbinger of more extensive colonic involvement. Additionally, whitish-yellowish polypoid lesions on endoscopy should involve a differential diagnosis of gastrointestinal histiocytosis. In total, a combination of surgical specimens and endoscopy are crucial in diagnosing and evaluating the extent of gastrointestinal involvement of LCH in adults.

COMMENTS

Case characteristics
Three days of sharp, intermittent right lower quadrant pain exacerbated by movement accompanied by non-bloody, non-bilious vomiting.

Clinical diagnosis
Mutlifocal gastrointestinal adult langerhans cell histiocytosis (LCH).

Differential diagnosis
Causes of right lower quadrant pain accompanied by nausea in reproductive age women include acute appendicitis, nephrolithiasis, pregnancy, tuboovarian abscess, ovarian torsion, small bowel obstruction, functional intestinal obstruction, urinary tract infection, sexually transmitted infection, muscle strain.

Laboratory diagnosis
Labs notable for peripheral eosinophilia.

Imaging diagnosis
Unremarkable brain, skeletal, abdominal, and pelvic imaging except for subcentimeter polyps found throughout colon on lower endoscopy.

Pathological diagnosis
LCH of the appendix and colon confirmed by S-100, CD1a, and CD207 reactivity.

Treatment
Twelve cycles of cytarabine therapy at 100 mg/m^2 per day for five days with cycles one month apart.

Related reports
Adult LCH is a rare entity, and there are few reports of bowel involvement that are either asymptomatic and found incidentally on endoscopy or a single report of small bowel hemorrhage secondary to the disease; importantly, there are no reports that presented like this case.

Experiences and lessons
Surgical biopsy is an invaluable practice that can identify uncommon etiologies of appendicitis and may be of great value in guiding any further treatment; in the same vein, a practitioner must entertain common and rare diagnoses for a complete differential.

Peer-review
The authors have done a very good job of writing up this fascinating case.

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CASE REPORT

Endoscopic retrograde cholangiopancretography in modified double tracks anastomosis with anastomotic stenosis

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Abstract

A 63-year-old man presented at our hospital with right upper abdomen pain and fever for 4 d. The patient's magnetic resonance cholangiopancreatography revealed dilated common bile duct and choledocholithiasis. In his past history, he received proximal gastrectomy and modified double tracks anastomosis. Endoscopic retrograde cholangiopancretography in modified double tracks anastomosis, especially accompanied with anastomotic stenosis, has been rarely reported. In the present case, the duodenoscope was successfully introduced over the guidewire and the stone taken out using a basket. The patient had good palliation of his symptoms after removal of the stone.

Key words: Endoscopic retrograde cholangiopan-cretography; Proximal gastrectomy; Modified double tracks anastomosis; Surgically altered gastrointestinal anatomy; Choledocholithiasis

Core tip: It has been quite difficult to carry out conventional endoscopic retrograde cholangiopan-cretography (ERCP) for pancreatobiliary diseases in patients with modified double tracks anastomosis after proximal gastrectomy. Thus, this procedure posed a great challenge to the endoscopist. After confirming the long limb, we chose to go back to the cabined anastomosis and switched the gastroscope for the duodenoscope. For

safety, the endoscope that went into the residual stomach across the gastrojejunal anastomosis was introduced by guidewire. Finally, we successfully carried out the ERCP and removed the stone.

Figure 1 Modified double tracks anastomosis. The arrow indicates the long limb.

INTRODUCTION

Endoscopic retrograde cholangiopancretography (ERCP) has been widely applied to pancreatobiliary diseases in recent years. The success rate is 90%-95%[1]. However, it is quite difficult to carry out conventional ERCP for pancreatobiliary diseases in patients with surgically altered gastrointestinal anatomy[2]. Patients with altered anatomy, such as those with a Billroth II gastrojejunostomy or a biliodigestive anastomosis with Roux-en-Y reconstruction, pose serious challenges to the endoscopist when access to the biliary system is required.

With the development of endoscopy, the technology of ERCP has improved greatly. Many modified methods of ERCP, including double-balloon enteroscope (DBE), single-balloon enteroscope (SBE) and spiral enteroscope (SE), have been applied in the clinic. However, deep endoscopic options, including DBE, SBE, SE and any of those modalities, were used mainly according to the preference of the endoscopist. This case with modified double tracks anastomosis after proximal gastrectomy, especially accompanied with anastomotic stenosis, is rarely encountered; thus, it poses a great challenge to the endoscopist. We finally successfully carried out the ERCP and removed the stone in such a challenging case.

CASE REPORT

A 63-year-old man presented at our hospital with right abdomen pain and fever for 4 d. He had radiating pain in his lower back, fever to 38 ℃, nausea without vomiting, icteric sclera, and yellow urine. On admission, his general appearance was acute ill looking and there was tenderness on the right upper quadrant of the abdomen. Cardiac and respiratory examination was unremarkable. Laboratory findings were as follows: white blood cell, 8.600/mm^3 (normal, 4-10/mm^3); neutrophil percentage, 84.9% (normal, 50%-70%); total bilirubin, 21 g/L (normal, 1-10 g/L); direct bilirubin, 12 g/L (normal, 1-4 g/L); aspartate aminotransferase, 54 U/L (normal, 0-37 U/L); alanine aminotransferase, 151 U/L (normal, 0-40 U/L); serum amylase, 779.2 U/L (normal, 40-110 U/L). Magnetic resonance cholangiopancreatography revealed dilated common bile duct

and choledocholithiasis.

The patient's medical history included receipt of proximal gastrectomy due to high grade intraepithelial neoplasia of gastric cardia in 2015. The small intestine was consequently rearranged into a Y-configuration, where one jejunal isoperistaltic limb was anastomosed to the distal esophagus and the other limb connected to the excluded stomach was reattached distally in an end-to-side fashion. Besides, the posterior wall of the gastric remnant had been made into a gastrojejunal anastomosis below the esophagojejunal anastomosis (Figure 1). As a result, there were two ways for food emptying between the esophagus and intestinal anastomosis, with the first including the distal esophagus, partial jejunum, remnant stomach and duodenum, and the second (called the "long limb") including only the distal esophagus and partial jejunum. In addition, the patient had undergone cholecystectomy for gallbladder stones by laparoscopy 1 wk prior to presentation.

The patient was diagnosed with choledocholith, postcholecystectomy and postoperative gastric cancer. ERCP was performed with a cap-assisted forward viewing endoscope (Olympus, Center Valley, PA, United States). When the endoscope passed the distal esophagus some distance, we found an anastomosis, but it was hard to pass the gastroscope (Figure 2). We continued the original way for some distance, until we found another anastomosis. We confirmed that this was the long limb and the stenosed anastomosis is the gastrojejunal anastomosis. Then, we chose to go back to the cabined anastomosis and switched the gastroscope for the duodenoscope (Olympus). For safety, the endoscope that went into the residual stomach across the gastrojejunal anastomosis was introduced by guidewire (Jagwire™, 0.035 in × 450 cm; Boston Scientific, Marlborough, MA, United States) (Figure 3). Then, we successfully arrived at the major papilla (Figure 4) and achieved a cholangiogram (Figure 5). At last, we removed the stone (diameter, 1.1 cm × 1.4 cm) using a stone-removal basket (Boston Scientific) and placed a nasobiliary stent of pig tail type (Boston Scientific) for drainage. Two days later, the patient's symptoms were alleviated and he left

Figure 2 Gastroscopy showing another anastomosis (arrow, gastrojejunal anastomosis) after the esophagojejunal anastomosis.

Figure 4 Duodenoscope introduced by the guide wire and arriving at the major papilla.

Figure 3 Guide-wire (arrow) placed for introducingce the duodenoscope.

Figure 5 Cholangiogram of endoscopic retrograde cholangiopancreatography demonstrating dilated common bile duct with a filling defect.

the hospital to rehabilitation several days later.

DISCUSSION

ERCP is the first choice for the clinical diagnosis and treatment of biliary and pancreatic diseases currently. However, conventional ERCP in patients with surgically altered gastrointestinal anatomy is far more challenging because of the complicated angulation, the inability of the endoscope to reach the blind end (due to the long bowel passage) and the difficulty in identifying the afferent limb[3]. Considering the technical challenges in reaching the papilla and performing therapy in patients with surgically altered gastrointestinal anatomy, modified methods of ERCP were developed. A recent review, including over 945 procedures using DBE, SBE or SE with altered anatomy, found success rates of reaching the papilla were 80% in Roux-en-Y gastric bypass (RYGB) and 96% in Billroth Ⅱ procedures; the rates of desired therapies performed were 70% in RYGB and 90% in Billroth Ⅱ procedures. Moreover, the overall rate of complications of DBE, SBE and SE in patients is only 3.4%[4]. These methods have greatly helped endoscopists complete the operations.

Modified double tracks anastomosis have been used in the surgery of gastric cardia to improve the nutrition and reflux symptoms[5]. It is difficult to study, however, because the overall number of cases is still relatively low.

Cases associated with anastomotic stenosis have been rarely reported, especially. The treatment options for the case presented herein included surgical operation, laparoscopic treatment and ERCP. Surgical operation and laparoscopy may impose an excessive burden on a debilitated patient, resulting in slower rehabilitation and bringing about more complications. In addition, a recent study has demonstrated that ERCP is effective in diagnosing and treating choledocholithiasis[6]. Our patient's general situation was not good because he had undergone surgery for cholecystectomy to address gallbladder stones by laparoscopy 1 wk prior. Duodenoscopic treatment was, therefore, a better choice.

In the endoscopic treatment of the present case, the view of choosing the narrow anastomosis when we had affirmed the long limb was prudential. The way for passing the long limb to the major papilla was too long and had high risk of perforation[7]. However, we would have to try to get to the point of major papilla across the long limb if the anastomosis was too narrow to pass the duodenoscope.

Having reached the gastrojejunal anastomosis, we still faced some difficulties. Firstly, identification of the afferent limb to residual stomach in gastrojejunal anastomosis was very difficult, as it was secluded and an endoscopist could easily miss it. So, we were cautious to slowly move forward and observe the

surrounding tissues carefully to find the gastrojejunal anastomosis. The second challenge was that proximal gastrectomy might result in post-surgical adhesion. Special care needed to be taken, and endoscopists should use discretion in withdrawal because of the high risk of bleeding and perforation. Last, but not least, the gastrojejunal anastomosis is relatively narrow and presents high risks of bleeding and perforation as well as post-surgical adhesion; so, we minimized the operative manipulation of the anastomosis. As such, we decided to directly replace the gastroscope with the duodenoscope. The endoscope was introduced by a guidewire through the anastomotic stenosis. Finally, we overcame the above challenges and successfully removed the stone.

Although a few cases of modified ERCP techniques in surgically altered gastrointestinal anatomy have been reported, this report of ERCP in proximal gastrectomy and modified double tracks anastomosis with anasto-motic stenosis is rather rare. From this case, we learned that endoscopic treatment is feasible for this type of clinical situation. If a similar case is discovered, the above case report may be helpful to solve common challenges.

COMMENTS

Case characteristics
A 63-year-old man presented with right upper abdomen pain and fever that persisted for 4 d before he sought evaluation at the Second Affiliated Hospital of Nanjing Medical University.

Clinical diagnosis
The patient had undergone proximal gastrectomy with modified double tracks anastomosis due to high grade intraepithelial neoplasia of gastric cardia. After admission to the hospital, magnetic resonance cholangiopancreatography revealed dilated common bile duct and choledocholithiasis.

Laboratory diagnosis
White blood cell, $8.600/mm^3$ (normal, $4-10/mm^3$); neutrophil percentage, 84.9% (normal, 50%-70%); total bilirubin, 21 g/L (normal, 1-10 g/L); direct bilirubin, 12 g/L (normal, 1-4 g/L); aspartate aminotransferase, 54 U/L (normal, 0-37 U/L); alanine aminotransferase, 151 U/L (normal, 0-40 U/L); serum amylase, 779.2 U/L (normal, 40-100 U/L).

Imaging diagnosis
Magnetic resonance cholangiopancreatography revealed dilated common bile duct and choledocholithiasis.

Treatment
The duodenoscope was introduced over a guidewire and the stone was removed using a basket. The patient had good palliation of his symptoms several days later.

Related reports
There is no related report about endoscopic retrograde cholangiopancretography in the modified double tracks anastomosis with anastomotic stenosis.

Experiences and lessons
This report emphasizes the importance of understanding surgically altered gastrointestinal anatomy before surgery. Endoscopic treatment is feasible to this case.

Peer-review
This is an interesting case report and eventually needs to be published.

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Laparoscopic surgery for complex and recurrent Crohn's disease

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Abstract

Crohn's disease (CD) is a chronic inflammatory disease of digestive tract. Approximately 70% of patients with CD require surgical intervention within 10 years of their initial diagnosis, despite advanced medical treatment alternatives including biologics, immune suppressive drugs and steroids. Refractory to medical treatment in CD patients is the common indication for surgery. Unfortunately, surgery cannot cure the disease. Minimally invasive treatment modalities can be suitable for CD patients due to the benign nature of the disease especially at the time of index surgery. However, laparoscopic management in fistulizing or recurrent disease is controversial. Intractable fibrotic strictures with obstruction, fistulas with abscess formation and hemorrhage are the surgical indications of recurrent CD, which are also complicating laparoscopic treatments. Nevertheless, laparoscopy can be performed in selected CD patients with safety, and may provide better outcomes compared to open surgery. The common complication after laparoscopic intervention is postoperative ileus seems and this may strongly relate excessive manipulation of the bowel during dissection. But additionally, unsuccessful laparoscopic attempts requiring conversion to open surgery have been a major concern due to presumed risk of worse outcomes. However, recent data show that conversions do not to worsen the outcomes of colorectal surgery

in experienced hands. In conclusion, laparoscopic treatment modalities in recurrent CD patients have promising outcomes when it is used selectively.

Core tip: Despite advanced medical treatment alternatives including biologics, immune suppressive drugs and steroids, approximately 70% of patients with Crohn's disease (CD) require surgical intervention within 10 years of their initial diagnosis. Forty percent to 50% of patients who had an index surgery for CD require a reoperation for recurrent disease in 10 years. Index surgical treatment type and medications used after index surgery appears to be factors related to recurrence risk of CD. In experienced hands, laparoscopic approach has promising outcomes in patients with recurrent CD when it is used selectively.

Crohn's disease (CD) is a chronic inflammatory disease that can develop any part of the digestive tract. CD usually arises at the terminal ileum[1]. Despite advanced medical treatment alternatives including biologics, immune suppressive drugs and steroids, approximately 70% of patients with CD require surgical intervention within 10 years of their initial diagnosis[2,3]. Surgery is warranted for management of medically refractory CD. Surgical treatment overcomes emergent issues, improves symptoms and patient's quality of life. Unfortunately, there is no cure for CD and it tends to recur during the disease course. Recurrent CD is described based on treatment type including medical, endoscopic or surgical.

Endoscopically documented recurrent CD can be up to 93% within one year following intestinal resection[4], while clinically symptomatic recurrence is usually around 30% at first 3 years after surgery[5]. Forty percent to 50% of patients who had an index surgery for CD require a reoperation for recurrent disease in 10 years[6,7]. Index surgical treatment type and medications used after index surgery appears to be factors related to recurrence risk of CD[2,8-10]. CD patients can be good candidates for minimally invasive treatment modalities due to the benign nature of the disease especially at the time of index surgery. However, use of laparoscopy in patients with complex CD such as extensive fistulizing or recurrent disease requiring surgical treatment is

controversial.

Majority of the surgical indications for recurrent CD are also the conditions complicating application of laparoscopic surgery such as intractable fibrotic strictures with obstruction, fistulas with abscess formation and hemorrhage[11,12]. Based on the extension and severity of disease, surgical options including strictureplasty, small bowel resection, ileocolectomy, internal bypass, partial/total colectomy and proctectomy may be performed laparoscopically[11,13]. In selected CD patients, laparoscopic surgery is safe, feasible and provides better outcomes compared to open surgery[14-17]. While operative times have decreased with increased experience, operative mortality is almost none and morbidity rates ranged from 10% to 40% in patients undergoing laparoscopic surgery for recurrent CD[17-19]. Postoperative ileus seems as the most common complication which may strongly relate excessive manipulation of the bowel during dissection[13]. Some surgeons believe that laparoscopic approach may also provide the well-known advantages of minimally invasive surgery such as reduced postoperative pain, lower morbidity, shorter hospital stay, earlier return to daily activity, and improved quality of life in patients with recurrent CD (Table 1).

Unsuccessful laparoscopic attempts requiring conversion to open surgery have been a major concern due to presumed risk of worse outcomes and conversion rates tend to be higher in laparoscopic operations for recurrent CD[20]. Conversion to open surgery rates varies between 6.7% and 42.3% in recurrent CD cases[21,22]. The most common cause of conversion was adhesions[13,23]. Having multiple resections, intraabdominal abscess and phlegmon are the other factors leading conversion in CD patients[22]. This clinical situation raises concerns on conversion related postoperative morbidity[24]. However, recent data show that conversions do not to worsen the outcomes of colorectal surgery in experienced hands[25]. The data regarding to operation type and disease characteristics especially related to index resection for CD are heterogeneous in the previous reports[26,27]. Outcomes after laparoscopic surgery for recurrent CD vary due to selection bias and experience of the surgeon[27,28]. Laparoscopic surgery showed better outcomes with shorter length of hospital stay compared to open surgery in selected cases[28], while laparoscopic approach did not provide expected benefits over open surgery in some series[13,27]. Although wound complications are reduced, the benefits of laparoscopic surgery in patients with a history of previous open intestinal resection through midline laparotomy seem questionable[13]. As an emerging technique, single incision laparoscopy can be performed for recurrent CD[29,30]. Single incision laparoscopy can be promising in complex cases by minimizing overall wound size, decreasing unnecessary adhesiolysis for secondary port placements and it affords the surgeon the opportunity to inspect the density of adhesions through port site and lead the surgeon to convert the operation preemptively if laparoscopic surgery seems unfeasible[31].

Table 1 Perioperative outcomes laparoscopy for complex and recurrent Crohn's disease

Ref.	Year	Patients surgery (*n*)	Conversion to open surgery (*n*)	Operative duration (min)	Hospital stay (d)
Wu *et al*[17]	1997	CL: 14	1	152	4.8
		RL: 10	2	144	3.9
		PL: 22	2	139	4.5
		O: 70	(-)	202[a]	7.9[a]
Hasegawa *et al*[28]	2003	RL: 16	2	210[a]	6.0
		PL: 45	3	180	8.0
Moorthy *et al*[22]	2004	RL: 26	11	118	8.0
		PL: 31	4	127	7.0
Goyer *et al*[32]	2009	Comp: 54[b]	20[a]	214[a]	8.0
		Uncomp: 70	10	191	7.0
Chaudhary *et al*[21]	2010	RL: 30	2	125[a]	3.0
		PL: 29	3	85	3.0
Brouquet *et al*[27]	2010	L: 29	9	215	9.0
		O: 33		226	9.0
Pinto *et al*[18]	2011	RL: 50	16	201	7.4
		PL: 80	15	182	6.7
Aytac *et al*[13]	2012	L: 26	3	169	6.4
		O: 26		158	6.9
Huang *et al*[20]	2012	RL: 48	10	100	ND
		PL: 82	14	106	ND

[a]Bold: Statistically significant; [b]27 of these patients had recurrent disease. CL: Laparoscopic surgery for complicated disease (phlegmon, abscess); PL: Laparoscopic surgery for primary disease; RL: Laparoscopic surgery for recurrent disease; L: Laparoscopic surgery; O: Open surgery; Comp: Complicated; Uncomp: Uncomplicated.

In experienced hands, laparoscopic approach has promising outcomes in patients with recurrent CD when it is used selectively. There is a need for new studies which focus on identification of proper patients who may benefit from laparoscopic surgery for recurrent and complex CD.

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MINIREVIEWS

Non-functioning pancreatic neuroendocrine tumors: Surgery or observation?

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Abstract

Incidentally detected, sporadic, nonfunctional pancreatic neuroendocrine tumors are increasingly diagnosed on imaging studies performed for unrelated purposes. Although their resection is usually recommended, controversy still exists regarding their optimal management, due to their highly variable and difficult to predict biologic behavior. Recently, several studies and guidelines advocated an expectant management approach in small size, low grade, incidentally diagnosed nonfunctional pancreatic neuroendocrine tumors. The aim of this study is to review and summarize the available literature addressing nonfunctional pancreatic neuroendocrine tumors, with an emphasis on surgical management controversies.

Key words: Pancreatic neuroendocrine tumors; Nonfunctional; Incidental; Surgery; Observation

Core tip: Nonfunctional pancreatic neuroendocrine tumors are increasingly diagnosed. Controversy exists regarding their optimal management. Expectant management in small size, low grade, incidentally diagnosed nonfunctional pancreatic neuroendocrine tumors has been suggested as an optional treatment. The aim of this study is to review the available literature addressing nonfunctional pancreatic neuroendocrine tumors, with an emphasis on surgical management controversies.

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INTRODUCTION

Pancreatic neuroendocrine tumors (PNETs) are un-

common neoplasms that arise from the islet cells of the pancreas and represent 1%-2% of all pancreatic cancers[1]. PNETs are clinically classified as functional (F-PNETs) and non-functional (NF-PNETs) based on the existence or non-existence of symptoms caused by hormone hypersecretion[2]. F-PNETs can synthesize and produce hormones such as insulin, gastrin, glucagon, somatostatin, and vasoactive intestinal peptide (VIP) resulting in myriad clinical syndromes. NF-PNETs, on the other hand, may secret some peptides such as chromogranin, pancreatic polypeptide, and others, but without clinical syndromes of hypersecretion[3,4]. Historically, F-PNETs were reported to have increased incidence and earlier diagnosis as compared to NF-PNETs due to their symptoms of hypersecretion, although the later accounts for the majority of PNETs[5-7]. With the widespread use and improvement of cross-sectional imaging techniques, NF-PNETs are increasingly discovered incidentally in asymptomatic patients who undergo evaluation for unrelated conditions[8,9]. This has been accompanied by an increase preoperative histologic diagnosis through endoscopic ultrasonography (EUS) and EUS-guided fine needle aspiration[10]. While there is a unanimity consensus that favors surgical resection in F-PNETs, controversy exists among clinicians regarding the optimal management of asymptomatic, small, incidentally discovered NF-PNETs. This article provides an updated review and aims to address the controversies in the management of sporadic small NF-PNETs. In light of article scope limitations, management and treatment of advanced metastatic disease or familial related diseases will not be addressed in this review.

EPIDEMIOLOGY

PNETs are more common in Caucasian and in males, with an incidence that increases with age, reaching a pick in the fifth-sixth decades. Detection is increasing owing to the widespread use of axial imaging, with one retrospective study demonstrating more than 2-fold increase in the incidence of NF-PNETs compared to 16 years ago and that the increase is related to accidental detection of the tumors[8,11]. NF-PNETs are biologically diverse and account for 65% to 90% of PNETs[1,12,13].

While most of PNETs occur sporadically, 10%-30% of them are associated with various inherited disorders including MEN1, Von Hippel-Lindau syndrome, neurofibromatosis 1, tuberous sclerosis, and Mahvash disease[14,15]. The majority of PNETS related to MEN1 and VHL syndromes are non-functioning tumors[1].

CLINICAL PRESENTATION

Patients with F-PNETs have overt clinical symptoms due to their physiologic response to hormone hypersecretion. In contrast, NF-PNETs can remain asymptomatic before they reach a significant tumor burden. Thus, they often present later during the disease with symptoms

of local compression or metastatic disease in 21% and 60%, respectively[1,6,16]. When symptomatic, the main complaints observed are abdominal pain (35%-78%), weight loss (20%-35%), and anorexia and nausea (45%). Less frequent signs include icterus (17%-50%), intraabdominal hemorrhage (4%-20%), or a palpable mass (7%-40%)[17]. Up to 50% of non-metastatic NF-PNETs will not show any symptoms being diagnosed incidentally on cross-sectional imaging performed for other indications[8,18].

DIAGNOSIS

The diagnostic approach of patients with NF-PNETs should be thorough and starts with detailed past medical and family history followed by complete physical examination. Then biochemical and imaging studies have uttermost importance for treatment strategy and are performed in order to evaluate the degree of local invasion, lymph node involvement, as well as the presence of metastatic disease.

IMAGING

High-resolution computerized tomography (CT) scan is the initial imaging modality at many institutions due to its noninvasiveness and availability. Studies have reported a sensitivity of more than 80%, with a direct correlation to tumor size[19,20].

Compared to CT, magnetic resonance imaging (MRI) has non-ionized radiation advantage and can be used as an alternative imaging modality. Furthermore, studies reported superiority of MRI over CT in detecting smaller pancreatic lesions and liver metastases[21,22]. One study reported a sensitivity and specificity of up to 85% and 100%, respectively[23].

EUS is an additional imaging modality, and has additional benefits in preoperative diagnosis[24]. Somatostatin receptor imaging (SRI) is a functional imaging modality of choice in the evaluation of neuroendocrine tumors. Besides its utility in the staging of these tumors, SRI may help to select the patients with advanced disease that are suitable for systemic somatostatin-based therapies[25,26].

While [111]Indium-DTPA-octreotide (Octreoscan) has been initially used, with the recent availability of the PET imaging technique, somatostatin analogues have been labeled with positron emitting isotopes, including Gallium-68, to image somatostatin receptor (SSR) expressing tumors[27]. The compounds often used in molecular imaging of NETs with PET are ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, and ^{68}Ga-DOTANOC, with a varying affinity to different somatostatin receptors. It has been demonstrated that ^{68}Ga-DOTA-TATE PET CT scan has the highest affinity for SSR2 and can dramatically improve the spatial resolution in parallel with a significantly higher detection rate and accuracy compared to conventional Octreoscan[28,29].

BIOPSY

EUS-guided fine-needle aspiration biopsy can provide preoperative histologic information important for tumor grading. One meta-analysis reported a sensitivity of 87% and a specificity of 98%[30]. The utility of routine preoperative biopsy remains controversial. Some clinicians have argued that the theoretical risk of procedure complications outweighs the benefit, while others, including us, believe in routine biopsy given the importance of characterizing and grading the tumor. Dietrich *et al*[31] demonstrated in a large study the importance of preoperative diagnosis. Among 394 patients with incidental finding of lesions smaller than ⩽ 15 mm, all were diagnosed by imaging-guided biopsy and/or surgery, 156 (about 40%) were diagnosed with neuroendocrine tumors, 146 pancreatic ductal adenocarcinoma, and 92 with various other etiologies. Although retrospective, approximately 60% did not have pancreatic ductal adenocarcinoma and not necessarily require radical surgery that carries significant risks[31].

BIOCHEMICAL STUDIES

Chromogranin A (CgA) can be used as a nonspecific biochemical marker. It has an approximate sensitivity and specificity of 60% and 80%, respectively[32,33]. False positive elevations of CgA can present in many other conditions such as use of anti-acid drugs (*e.g.,* proton pump inhibitors, H2 blockers, *etc.*), atrophic gastritis, renal insufficiency, hepatic insufficiency, *ect*[34].

Pancreatic polypeptide (PP) and neuron specific enolase (NSE) are additional useful NF-PNET markers. As with CgA false positive elevations of pancreatic polypeptide can be postprandial and in renal insufficiency[16,32,35]. Preoperative increased levels of CgA or PP may potentially be helpful in evaluation of response, progression, or recurrence at an early stage[36].

Elevated NSE levels were exclusively associated with poor tumor differentiation[36].

GRADING AND STAGING

From histological point of view, the 2010 World Health Organization (WHO) classification system is the most used grading system. It identifies three categories: Grade 1 tumors (< 2 mitosis/10 HPF and Ki-67 index ⩽ 2%), grade 2 (2-20 mitosis/10 HPF and Ki-67 index 3%-20%), and grade 3 (> 20 mitosis/10 HPF and Ki-67 index of > 20%). This classification forms the basis for evaluating prognosis and predicting malignancy[2,37].

Two TNM based staging systems were developed for PNETs, one from the American Joint Committee on Cancer (AJCC) that covers both pancreatic exocrine and neuroendocrine malignancies and the other proposed by the European Neuroendocrine Tumor Society (ENETS) (Table 1)[38,39]. The difference between them is mainly expressed in the soft tissue involvement criteria. While the AJCC characterize T3-T4 using peripancreatic

invasion of these tumors (sometimes difficult to assess due to the structure of the pancreas), the ENETS staging system relies on more assessable criteria such as tumor size[40,41]. Despite differences, both staging systems are highly prognostic validated and found to be useful for clinical practice[42-44].

One retrospective 11-year period report of 425 patients with PNETs demonstrated that the 5-year overall survival rates using the ENETS classification for patients treated in referral neuroendocrine tumor (NET) center for stages I, II, III and IV disease were 100%, 88%, 85%, and 57%, respectively. The corresponding values using the AJCC classification were 92%, 84%, 81%, and 57%, respectively[44]. Another large cohort study of 1072 post-operative patients suggests the ENETS TNM staging system is superior to the AJCC and WHO 2010 TNM staging system and supports its use in clinical practice[42].

CURRENT GUIDELINES

Several guidelines for the management of PNETs have been established in order to help physicians treating these complex patients. The 2012 and 2016 European Neuroendocrine Tumor Society (ENETS) guidelines, the National Comprehensive Cancer Network 2016 (NCCN), North American Neuroendocrine Tumor Society-2013 (NANETS), and European Society of Medical Oncology-2012 (ESMO) have published diagnostic and therapeutic guidelines[3,12,45-47].

For initial biochemical workup the ENETS, ESMO, and NANETS guidelines all recommend measuring CgA and PP serum levels as a useful tool for reaching a diagnosis in a fraction of NF-PNETs.

The first imaging modality recommended is multi-phasic CT/MRI with contrast agents imaging modality, while octreotide scintigraphy (planar and SPECT) but mainly ^{68}Ga-labeled somatostatin analogues with PET/CT are also recommended, if available.

All four guidelines recommend using the 2010 WHO grading system as the grading of choice and generally advocate surgical resection as the preferred option as long as there are no surgical limiting contraindications, highly diffuse metastatic disease, or selected cases that can be observed discussed in the next sections.

The surgical options for locoregional NF-PNETs mentioned in all guidelines range between simple enucleation, central pancreatectomy, distal pancreatectomy with or without splenectomy, and pancreatoduodenectomy (Whipple's operation). The extent and type of surgery mainly depends on the location of the primary tumor (head, body, or tail). Tumors larger than 2 cm that are locally invasive or have positive lymph node involvement in preoperative evaluation should all include regional lymph node dissection. In patients with smaller than 2 cm NF-PNETs, lymph node sampling is not always mandatory. While both NCCN and ENETS recognize the role of laparoscopic approach in PNETs resections, the EMCO guidelines do not recommend this approach due to the need for thorough intraoperative lymph node

	ENETS	AJCC
Table 1 European Neuroendocrine Tumor Society and American Joint Committee on Cancer TNM grading systems for pancreatic tumors[38,39]		
T Grade (primary tumor)		
Tx	Primary tumor is not assessed	Primary tumor is not assessed
T0	No finding of primary tumor	No finding of a primary tumor
Tis		*In situ* carcinoma
T1	Tumor is limited to the pancreas and < 2 cm	Tumor is limited to the pancreas and ≤ 2 cm
T2	Tumor is limited to the pancreas and 2 to 4 cm	T2 tumor is limited to the pancreas and > 2 cm
T3	Tumor is limited to the pancreas and > 4 cm or with positive duodenum or biliary tract invasion	Tumor has progressed beyond the pancreas but there is no celiac or mesenteric artery involvement
T4	Tumor has invaded the neighboring organs (stomach, spleen, colon, adrenal gland) or walls of the large vessels (celiac artery or superior mesenteric artery)	Tumor shows celiac or superior mesenteric artery involvement
N-lymph node status		
Nx	Regional lymph nodes are not assessed	Regional lymph nodes are not assessed
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	Regional lymph node metastasis is positive	Regional lymph node metastasis is positive
M-distant metastasis		
Mx	Distant metastasis is not assessed	
M0	No distant metastasis	No distant metastasis
M1	Distant metastasis is positive	Distant metastasis is positive
Stage		
0		Tis, N0, M0
I	T1, N0, M0	
IA		T1, N0, M0
IB		T2, N0, M0
IIA	T2, N0, M0	T3, N0, M0; T1, N1, M0
IIB	T3, N0, M0	T2, N1, M0; T3,N1,M0
III		T4, Any N, M0
IIIA	T4, N0, M0	
IIIB	Any T, N1, M0	
IV	Any T, Any N, M1	Any T, Any N, M1

inspection.

Currently, updated ENETS and NCCN guidelines both acknowledge nonoperational options, with different tumor size-cutoff (NCCN < 1 cm, ENETS < 2 cm), as suitable for managing small NF-PNETs while taking into account factors such as incidental discovery, lack of clinical syndromes and radiological signs suspicious for malignancy, as well as patient's characteristics (surgical risk, comorbidities, and personal wishes)[12,45,47]. However, data supporting this non-operational option are controversial and will be reviewed in the next section. Figure 1 offers a suggested algorithm for patient management.

SURGICAL MANAGEMENT CONTROVERSY

In most cases surgery remains the curative modality of choice for NF-PNETs, with preliminary evidence demonstrating improved survival especially with localized disease[48,49]. However, as previously mentioned, during the last recent years there is a significant increase in the detection of small, incidentally discovered, asymptomatic NF-PNETs, that may be managed conservatively by observation. At present there are no RCTs or meta-analyses that can assist to outline the optimal approach for

the management of such small NF-PNETs. Nevertheless, there are 12 retrospective series that may shed some light on this controversy.

Tumor size as criteria for treatment decision
Bettini *et al*[50] demonstrated a distinct correlation between tumor size and lower malignancy potential on 177 patients, who were divided into three groups depending on tumor size (≤ 2 cm, 2-4 cm, > 4 cm), all underwent curative resection. Patients with tumor ≤ 2 cm (*n* = 51) had higher frequency of incidental diagnosis compared with patients with > 4 cm (57% *vs* 32%, *P* = 0.014). Among those who were incidentally discovered, only 6% were malignant and none died from the disease. In addition, a correlation between tumor size and Ki67 was demonstrated. Patients with tumors ≤ 2 cm had lower Ki67 median values compared with patients with tumors > 2 cm ≤ 4 cm and > 4 cm (1% *vs* 2% and 3%, respectively). The authors suggested that nonsurgical management could be advocated in selected cases for low-grade tumors less than 2 cm, due to their indolent course. In an attempt to determine the prognostic value of indicators of malignancy in NF-PNETs ≤ 2 cm, Regenet *et al*[51] demonstrated, by using multivariate analysis, that tumor size is a significant indicator of malignancy, and
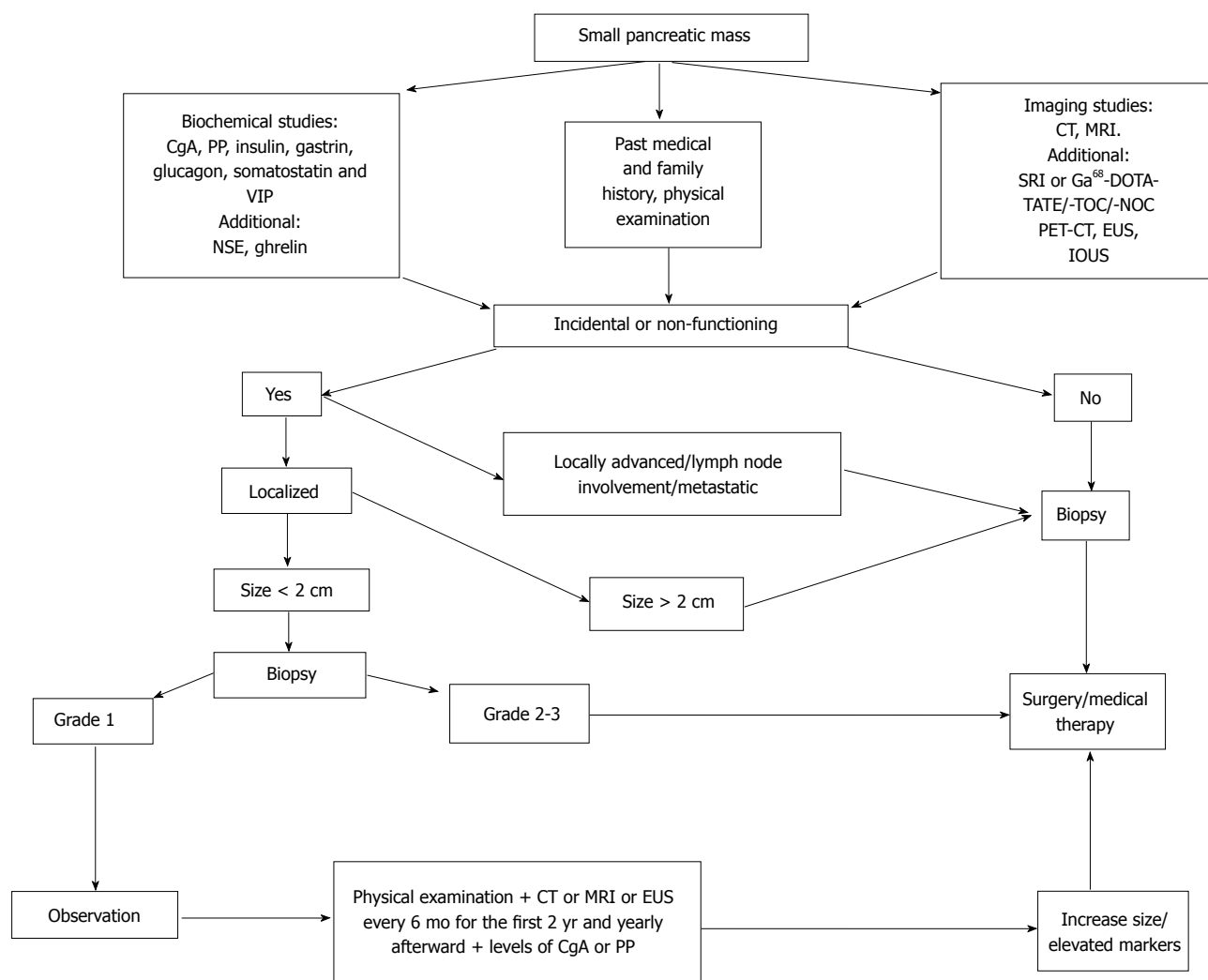
Figure 1 Suggested algorithm for the management of small pancreatic mass. CgA: Chromogranin A; PP: Pancreatic polypeptide; VIP: Vasoactive intestinal peptide; NSE: Neuron-specific enolase; CT: Computed tomography; MRI: Magnetic resonance imaging; SRI: Somatostatin-receptor imaging; EUS: Endoscopic ultrasonography; IOUS: Intraoperatively ultrasonography; PET: Positron emission tomography; Ga68-DOTA-TATE/-TOC/-NOC: 68Gallium-DOTA-TATE, 68Gallium-DOTA-TOC68 and Gallium-DOTA-NOC respectively.

even proposed a new 1.7 cm cutoff as more accurate for prediction of malignancy potential with a sensitivity of 92% and specificity of 75%. Despite these findings, Ki67 was not found to be a significant indicator of malignancy probably due to large number of patients without complete histologic assessment and Ki67 evaluation[51]. In a larger population study by Gratian *et al*[52] among 1854 patients with NF-PNETs ≤ 2 cm, who were identified from the National Cancer Data Base (NCDB), 309 patients (29%) presented with regional lymph node involvement and 180 patients (10%) presented with distant metastases[52]. In contrast to Bettini *et al* findings, they conclude that tumors smaller than 2 cm have a significant risk of malignancy. It is worth mentioning that the study was limited by missing data of several variables, including Ki67.

Incidental vs non-incidental diagnosis as criteria for treatment decision
Different studies have recently tried to distinguish

between incidental and non-incidental NF-PNETs, especially those discovered at early age, in terms of prognosis and treatment approach. Cheema *et al*[18] identified 143 nonmetastatic PNETs, 40% were diagnosed incidentally. They demonstrated that 5-year progression free survival (PFS) was significantly prolonged in patients with incidental diagnosed *vs* symptomatic tumors (86% *vs* 59%, *P* = 0.007).

Tumor grading as criteria for treatment decision
It should be noted that histopathologic grade was another statistically significant factor for progression on multivariate analysis (hazard ratio of 3.0 for Grade 2 *vs* Grade 1, *P* = 0.007), though Ki67 proliferation index was only evaluated in 25% of cases[18]. As opposed to Cheema *et al*[18], Haynes *at el*[53] described 139 patients who all underwent surgery and identified no large difference in tumor size (3.0 cm *vs* 3.5 cm, *P* = 0.48), frequency of malignant histopathologic findings (28% *vs* 30%), or 5-year PFS (83% *vs* 82%, *P* = 0.27)

Table 2 Retrospective studies regarding incidental discovery

Ref.	Study period	Patients (*n*)	Group	Number of patients *n* (%)	5-yr PFS rates (%)	*P* value	Median follow-up time (mo)
Cheema *et al*[18]	1999-2010	143	Incidental	56 (40)	86	0.07	67 (mean)
			Non-incidental	87 (60)	59		
Crippa *et al*[54]	1990-2009	355	Incidental	124 (35)	83	< 0.001	44
			Non-incidental	231 (65)	32		
Haynes *et al*[53]	1997-2009	139	Incidental	109 (82)	82.8	0.27	34.2
			Non-incidental	30 (18)	81.7		
Birnbaum *et al*[55]	1994-2010	108	Incidental	65 (61)	92	0.03	42
			Non-incidental	43 (39)	82		

between incidental and non-incidental groups[18,53]. Of the 39 patients with tumors ≤ 2 cm, 3 patients (7.7%) had late metastases or recurrence. Though problematic due to lack of observational group, they concluded that all patients should undergo tumor resection, even in incidentally discovered NF-PNETs smaller than 2 cm. From a staging point of view Crippa *et al*[54] demonstrated in a larger (*n* = 355) retrospective study that NF-PNETs diagnosed incidentally have greater 5-year PFS rates in all stages than symptomatic tumors: Stage I (97% *vs* 78%, *P* = 0.013), stage II (93% *vs* 74%, *P* = 0.036), stage III (69% *vs* 27%, *P* < 0.0001), and stage IV (60% *vs* 17%, *P* = 0.112). On multivariate analysis Grade 2 NF-PNETs was found to be a predictor of PFS among 124 incidentally diagnosed patients, with a hazard ratio of 3.402 (95%CI: 0.92-12.57, *P* = 0.066). In addition, they reported that 12 excluded patients, who underwent non-operative management of incidental NF-PNETs and had no tumor progression after median follow up of 36 mo. In this small group of patients the median tumor size at diagnosis was 1.4 cm (range 1.0-2.9 cm), and was stable throughout the surveillance period. Similar PFS rates were demonstrated in another retrospective study by Birnbaum *et al*[55] that included 106 patients, 65 discovered incidentally. These patients demonstrated both higher incidence of tumors smaller than 2 cm (65% *vs* 42%, *P* = 0.019) and lower Ki67 proliferation index (1% *vs* 4%, *P* = 0.004) compared to symptomatic patients. The authors concluded that pancreas sparing surgery is recommended as an optional treatment for these incidental NF-PNETs, due to less aggressive characteristics compared with symptomatic tumors (Table 2).

Observation for selected patients

Several retrospectively designed studies tried to answer the question whether observational management is suitable for NF-PNETs smaller than 2 cm and to assess the risk-benefit balance of this approach. Gaujoux *et al*[56] published a series of 46 patients who were followed for at least 18 mo (median 34, range 24-52 mo) with an average of four (range 4-6) serial imaging sessions or followed up after resection[56]. Among the resection group (*n* = 8), all grade 1 and without lymph node involvement, 5 were resected upon initial diagnosis and only 3 were resected due to tumor enlargement

under imaging observations. The remaining 38 patients, who were managed without surgery, did not show any significant characteristics of malignancy such as distant metastases, nodal involvement, or significant increase in tumor size. In this study the overall median tumor growth was 0.12 mm per year. Both Lee *et al*[57] and Rosenberg *et al*[58] published similar results where small NF-PNETs in either the operative or non-operative groups demonstrated no evidence of progression, with lower, though important, operational-morbidity related rates (46% and 35%, respectively)[57,58]. They both conclude that non-operative management may be advocated and safe in selected patients. In the Lee *et al*[57] study, both surgical and nonsurgical group's tumors had low or intermediate grade and Ki67 values smaller than 5%, in all patients with available results[57]. Rosenberg *et al*[58] published a 35 patients series divided into operative and non-operative groups as well: Ki67 proliferation index rates of < 2% and 3%-20% were 65% *vs* 0% and 30% *vs* 27%, respectively. Ki67 data was not available in 1 (5%) patient in the operative group *vs* 11 (73%) in the non-operative group[58].

The observational approach for certain tumors was reinforced by another recently published matched case-control study by Sadot *et al*[59] who demonstrated that 5-year PFS was 95% and 91% (*P* = 0.3) for observational and resection only groups, respectively. A quarter (*n* = 26) of the observation group crossed over to resection group, due to different reasons. After a median follow-up of 7 years, none of these patients developed malignant features (node involvement or metastases). These data imply that initially observational approach and delayed surgical intervention may not compromise long-term outcomes.

Contrary to this claim, Sharpe *et al*[60] performed a population based study and demonstrated that patients who were managed with observation had nearly three times the risk of mortality in comparison to those who underwent resection[60]. Their study was large and based on patients collected from NCDB, all with NF-PNETs smaller than 2 cm. The authors concluded that surgical resection provides a benefit regardless of tumor grade, though it wasn't statistically proven at poorly differentiated/undifferentiated tumor. A summary of the studies regarding surgical *vs* observational approach in NF-PNETs is presented in Table 3.

Table 3 Retrospective studies regarding surgery *vs* observational management

Ref.	Study period	Patients *n*	Group	Number of patients *n* (%)	Median follow-up time (mo)	Surgery morbidity rate (%)
Gaujoux *et al*[56]	2000-2011	46	Observational	38 (83)	> 18	62
			Surgery	8 (17)	27	
Lee *et al*[57]	2000-2011	133	Observational	77 (57)	44 (Mean)	46
			Surgery	56 (43)	52 (Mean)	
Rosenberg *et al*[58]	1999-2014	35	Observational	15 (42)	28	35
			Surgery	20 (58)	34	
Sharpe *et al*[60]	1998-2006	380	Observational	71 (19)	60	N/A
			Surgery	309 (81)	60	
Sadot *et al*[59]	1993-2013	181	Observational	104^2 (57)	44	N/A
			Surgery	77^1 (43)	57	

^{1}Matched group; ^{2}Before cross over; N/A: Not available.

OBSERVATION PROTOCOL

History and physical examination, as well as biochemical markers and conventional trans-sectional high-resolution imaging should be used for both non-operative and postoperative surveillance. Postoperatively in patients with NF-PNETs grade 1 and 2, imaging is indicated every 3-9 mo (CT, MRI, or EUS), while more frequent imaging (up to 2-3 mo intervals periods) is indicated in Grade 3 or recurrent symptomatic patients, during the first year following surgery[12,45,47,61]. Either Octreoscan or PET/CT using ^{68}Ga-DOTA-TOC/-NOC/-TATE should be repeated every 18-24 mo for grades 1-2[61]. In non-surgical patients with less than 2 cm NF-PNETs, Gaujoux *et al*[56] recommend conventional contrast enhanced CT or MRI every 6 mo for the first 2 years and yearly afterward[56]. In patients who underwent surgical resection of the tumor, imaging at 6-12 mo intervals should be performed between one and ten years post resection, although the optimal duration surveillance time for either non-operative nor postoperative patients is unknown[46].

CONCLUSION

In the last two decades the incidence of small NF-PNETs neoplasms has been steadily increasing. Unfortunately, there are still no clear prognostic factors that can enable us to distinguish between tumors suitable for observation and tumors with greater malignant potential that should be treated more aggressively. Several retrospective population based studies were reviewed in this article in an attempt to reduce the uncertainty. However, issues of selection bias, small sampling, and lack of data that are inherent in this type of studies limit our ability to conclude valid recommendations. In our NET center, the decision on treatment approach (follow-up *vs* surgical excision) for incidental NF-PNETs patients is based on tumor size (less or more than 2 cm), tumor grading, intensity of uptake on functional imaging (^{68}GaDOTATATE-PET/CT), on the stage of the disease, as well as on patient's desire. Larger scale, preferably multicenter randomized control trials, are needed in order to clarify the optimal management strategy and treatment for these rare small incidentally discovered tumors.

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ORIGINAL ARTICLE

Case Control Study

Comparative study of outcomes following laparoscopic Roux-en-Y gastric bypass and sleeve gastrectomy in morbidly obese patients: A case control study

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Abstract

AIM

To compare the impact of laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG) on weight loss and obesity related comorbidities over two year follow-up *via* case control study design.

METHODS

Forty patients undergoing LRYGB, who completed their two year follow-up were matched with 40 patients undergoing LSG for age, gender, body mass index and presence of type 2 diabetes mellitus (T2DM). Data of these patients was retrospectively reviewed to compare the outcome in terms of weight loss and improvement in comorbidities, *i.e.*, T2DM, hypertension (HTN), obstructive sleep apnea syndrome (OSAS), hypothyroidism and gastroesophageal reflux disease (GERD).

RESULTS

Percentage excess weight loss (EWL%) was similar in LRYGB and LSG groups at one year follow-up (70.5% *vs* 66.5%, *P* = 0.36) while it was significantly greater for LRYGB group after two years as compared to LSG group (76.5% *vs* 67.9%, *P* = 0.04). The complication rate after LRYGB and LSG was similar (10% *vs* 7.5%,

P = 0.99). The median duration of T2DM and mean number of oral hypoglycemic agents were higher in LRYGB group than LSG group (7 years *vs* 5 years and 2.2 *vs* 1.8 respectively, *P* < 0.05). Both LRYGB and LSG had significant but similar improvement in T2DM, HTN, OSAS and hypothyroidism. However, GERD resolved in all patients undergoing LRYGB while it resolved in only 50% cases with LSG. Eight point three percent patients developed new-onset GERD after LSG.

CONCLUSION

LRYGB has better outcomes in terms of weight loss two years after surgery as compared to LSG. The impact of LRYGB and LSG on T2DM, HTN, OSAS and hypothyroidism is similar. However, LRYGB has significant resolution of GERD as compared to LSG.

Key words: Bariatric surgery; Laparoscopic sleeve gastrectomy; Laparoscopic Roux-en-Y gastric bypass; Weight loss; Comorbidities

Core tip: Laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y gastric bypass (LRYGB) are the most popular bariatric procedures. Few studies have compared the outcomes of LSG *vs* LRYGB in terms of weight loss and comorbidity resolution, especially in India. Using case control design in a well-matched population of 40 patients each undergoing LSG and LRYGB, we found similar weight loss one year after surgery in both the groups but the weight loss was significantly higher in LRYGB group two years after surgery. The complication rate was similar in both groups. Regarding comorbidity resolution, both LRYGB and LSG had significant but similar impact on obesity related comorbidities except gastroesophageal reflux disease where LRYGB showed better improvement. This is also among the first few studies to study the impact of bariatric surgery on hypothyroidism.

INTRODUCTION

Bariatric surgery is an effective tool in the management of obesity and its associated comorbidities[1]. Laparoscopic Roux-en-Y-gastric bypass (LRYGB) is the current gold standard among the various bariatric procedures performed worldwide[2]. Studies have proven its excellent long term outcomes with low rate

of morbidity[3]. Laparoscopic sleeve gastrectomy (LSG) was introduced as a first step procedure to reduce morbidity in high risk patients followed by either LRYGB or bilio-pancreatic diversion with duodenal switch (BPD-DS)[4]. With increasing experience, LSG has proved its efficacy as a stand-alone procedure in the management of morbid obesity. Compared to LRYGB, LSG has several advantages. LSG is relatively easier to perform, preserves pylorus and antrum resulting in less Dumping syndrome, avoids risk of internal hernia and complications due to gastro-jejunostomy or jejuno-jejunostomy, decreases the risk of nutritional deficiencies and provides accessibility of the remnant stomach via endoscopy, which is important especially in Asian population[5]. However, few studies have compared the effect of LRYGB with LSG on weight loss and obesity associated comorbidities, especially in Indian population[5-10].

This study is among the few studies, in the Indian population, to compare the impact of LSG *vs* LRYGB on weight loss and obesity related comorbidities in a matched cohort of morbid obese patients over a period of two years.

MATERIALS AND METHODS

Data of all patients who underwent LSG and LRYGB at our centre, between January 2008 and March 2015 and completed their two year follow up till March 2016, was retrospectively reviewed using a prospectively collected database. All the patients met the National Institute Health criteria for bariatric surgery. These patients include patients with morbid obesity, *i.e.*, body mass index (BMI) > 40 kg/m^2 or patients with BMI > 35 kg/m^2 with obesity associated comorbidities. The patients are counseled about the types of bariatric procedures - LSG and LRYGB and the benefits and complications associated with each of the procedures. The patients having severe gastroesophageal reflux disease (GERD), long-standing type 2 diabetes mellitus (T2DM) and with BMI > 50 kg/m^2 are preferred for LRYGB. The bariatric procedure for a particular patient is decided mutually based on patient's preference and surgeon's viewpoint. The patients undergoing revision surgery or two stage procedure were excluded from the study. Patients undergoing LSG and LRYGB were matched by age, gender, BMI and presence or absence of T2DM. All the procedures were performed by the same surgeon (SA) according to standard surgical protocol. The preoperative workup included blood tests, chest radiography, upper gastrointestinal endoscopy, electrocardiogram, abdominal ultrasound and hormonal and nutritional evaluation. The patients were kept on Very Low Calorie Diet (approximately 800 kcal, 60-70 g protein) for two weeks before surgery. The follow-up data upto 2 years was recorded in a study proforma.

Surgical procedure

LSG: The procedure was performed under general

anesthesia in Reverse Trendelenburg position. The sleeve was performed in a standard way. Four ports were used: Three 12 mm and one 5 mm. A self-retaining liver retractor was introduced through a 5-mm incision in the epigastrium. The greater omentum was detached from a point 4 cm from the pylorus up to the angle of His using either ultrasonic shears or a bipolar sealing device. The left crus was completely exposed up to the medial border. A sleeve was created over a 36F gastric calibration tube with sequential firings of a three-row stapler. Intraoperative leak test using methylene blue was done to check the staple line integrity. The remnant stomach was retrieved using one of the port site and port closure was done. A suction drain was placed as needed.

LRYGB: An antecolic and antigastric Roux-en-Y gastric bypass was done with an alimentary limb ranging 100-150 cm and bilio-pancreatic limb of 70 cm as measured from duodeno-jejunal flexure. The procedure was performed under general anesthesia in Reverse Trendelenburg position. A 30- to 50-cc vertical gastric pouch was created. End to side gastro-jejunostomy and side-to-side jejuno-jejunostomy was done using three row stapler. Mesentric defect was sutured in all cases. Intraoperative leak test using methylene blue was done to check for the staple line integrity. A suction drain was placed as needed.

The data collected included patient demographics, preoperative BMI, presence of medical comorbidities, intra- and postoperative complications, weight loss and status of comorbidities after surgery.

Weight loss
The weight of the patients in preoperative period and at annual follow up till two years was recorded. The yearly absolute weight loss and percentage excess weight loss (EWL%) was calculated as described by Deitel *et al*[11]. Failure of surgery was defined as % EWL < 50% as per Reinhold criteria[12].

Comorbidity outcome
T2DM, hypertension (HTN), obstructive sleep apnea (OSA), hypothyroidism and gastroesophageal reflux disease (GERD) were assessed so as to determine whether it was aggravated, unchanged, improved or resolved compared to preoperative period.

T2DM: Presence of T2DM was defined as glycosylated haemoglobin (HbA1c) level $\geqslant$ 6.5% or fasting blood glucose (FBG) $\geqslant$ 126 mg/dL. Remission was defined as FBG < 100 mg/dL in the absence of anti-diabetic medications, and improvement was defined as decrease in anti-diabetic medications to maintain normal FBG. HbA1c was not available for all the patients in follow up period and hence was not used in the criteria for remission.

HTN: Presence of HTN included both Stage 1 (blood pressure: 120-159/90-99 mmHg) and Stage 2 (> 160/100 mmHg). Remission was defined as normal blood pressure (< 120/80 mmHg) when off antihypertensive medications as reported by the patient. Improvement in HTN was considered if there was decrease in dosage or number of antihypertensive medications to maintain normal blood pressure.

Obstructive sleep apnea syndrome: Obstructive sleep apnea syndrome (OSAS) was defined as apnea hypopnea index (AHI) > 15 events/h or > 5 events/h with typical symptoms[13]. Patients with severe OSAS (AHI > 30 events/h) received night time Continuous Positive Airway Pressure (CPAP) for atleast 2 wk before surgery. Resolution in OSAS was defined as disappearance of symptoms with patient no longer receiving CPAP therapy. Improvement in OSAS was defined as decrease in the symptoms with no longer need of CPAP therapy. Polysomnography could not be done in all patients in post-operative period and hence AHI could not be used as criteria for remission of OSAS.

Hypothyroidism: Presence of hypothyroidism was defined as patients who were on thyroxine therapy for overt hypothyroidism in preoperative period. Remission was considered if patient showed normal thyroid function tests without any thyroxine therapy. Improvement in hypothyroidism was considered if there was decrease in dosage of thyroxine supplement to maintain normal thyroid function tests.

GERD: The presence of GERD symptoms using GERD severity symptom (GERD-SS) questionnaire[14] and proton pump inhibitors (PPI) intake was assessed preoperatively and at follow up visits. A GERD SS Score > 4 or regular intake of PPI was defined as GERD. The resolution of GERD was defined as disappearance of symptoms when patient was no longer taking PPIs, whereas improvement was defined as a decrease in or disappearance of symptoms with a lower PPI dosage. Worsening of GERD was defined as increase in the symptoms or increase in the dosage of PPI after LSG. *De novo* GERD was defined as the postoperative development of reflux symptoms in patients who had not experienced GERD before LSG.

Statistical analysis
Statistical analysis was performed using SPSS software version 20.0 (SPSS Inc., Chicago, IL, United States). Normality of the data was checked using Shapiro-Wilk Test. For continuous variables, results were presented as mean ± standard deviation (SD) or median (Interquartile range) as appropriate. Comparative analysis was performed using Student's *t* test or Mann-Whitney *U* test for continuous variables and χ^2 test for categorical variables. Correlation between data was assessed using Pearson or Spearman Rank Correlation Coefficient

Table 1 Baseline characteristics of study population (*n* = 80)			
Parameter	LRYGB group (*n* = 40)	LSG group (*n* = 40)	*P* value
Age (yr)	44.6 ± 10.2	44.8 ± 10.2	NS
Gender			
Female, *n* (%)	29 (72.5%)	29 (72.5%)	NS
Male, *n* (%)	11 (27.5%)	11 (27.5%)	NS
Weight (kg)	109.9 ± 13.9	113.6 ± 15.2	NS
Body mass index (kg/m²)	43.9 ± 5.5	45.8 ± 4.8	NS
Excess weight (kg)	46.9 ± 12.7	51.3 ± 12.2	NS
Comorbidities			
Type 2 diabetes mellitus, *n* (%)	27 (67.5%)	27 (67.5%)	NS
Patients on insulin	5 (18.5%)	5 (18.5%)	NS
[a]Number of OHA	2.2 ± 0.7	1.8 ± 0.7	
[a,b]Duration (yr)	7 (5-7)	5 (3-7)	
Hypertension, *n* (%)	25 (62.5%)	23 (57.5%)	NS
Number of AHA	1.7 ± 0.7	1.7 ± 0.8	NS
OSAS, *n* (%)	7 (17.5%)	2 (5%)	NS
Hypothyroidism, *n* (%)	11 (27.5%)	7 (17.5%)	NS
Thyroxine dosage (μg/d)	90.9 ± 25.7	89.9 ± 31.8	NS
GERD, *n* (%)	7 (17.5%)	4 (10%)	NS

All *P* values are non-significant except [a]*P* value < 0.05 as assessed by Student's *t* test; All data expressed as mean ± SD except [b]where data is presented as median (Interquartile range). AHA: Anti-hypertensive agents; GERD: Gastroesophageal reflux disease; OHA: Oral hypoglycemic agents; OSAS: Obstructive sleep apnea syndrome; LRYGB: Laparoscopic Roux-en-Y gastric bypass; LSG: Laparoscopic sleeve gastrectomy.

(SRCC) as appropriate. Statistical significance was identified as *P* < 0.05.

RESULTS

Four hundreds and seventy-six patients underwent LSG and 61 patients underwent LRYGB between January 2008 and March 2016 at our centre. Forty patients with primary LRYGB completed their two year follow up and were matched to 40 patients undergoing LSG who also completed this follow up period. Table 1 gives the baseline characteristics of both the groups.

Impact on weight and associated parameters
After one year follow-up, the mean BMI (± SD) decreased from 43.9 (± 3.7) kg/m² to 31.1 (± 4.8) kg/m² in LRYGB group while 45.8 (± 4.8) kg/m² to 32.5 (± 4.5) kg/m² in LSG group (Figure 1). The mean (± SD) %EWL at one year follow-up was 70.5% (± 21.5%) and 66.5% (± 18.6%) in LRYGB and LSG group respectively (Figure 2). Using Student's *t* test, there was no significant difference in mean BMI or %EWL one year after either LRYGB or LSG.

At two year follow up, the mean BMI (± SD) BMI declined to 29.9 (± 4.4) kg/m² and 31.9 (± 4.3) kg/m² in LRYGB and LSG group respectively (Figure 1). The %EWL at 2-year follow up was 76.7% (± 20.2%) and 67.9% (± 17.9%) in LRYGB and LSG group respectively (Figure 2). This difference was statistically significant with LRYGB having better outcome in terms of weight loss after two years. As per Reinhold's criteria of failure of surgery, there was 12.5% failure in LRYGB group compared to 20% failure in LSG group two years after
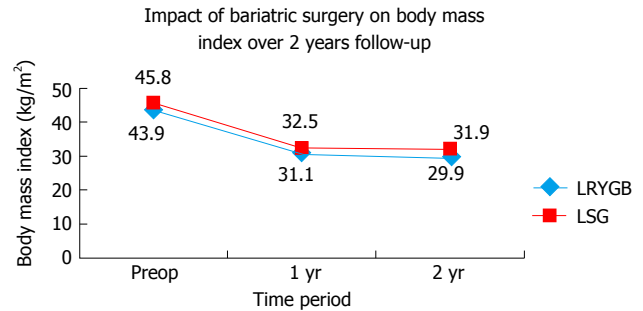

Figure 1 Impact of bariatric surgery on body mass index over two years follow-up: There was no significant difference in body mass index preoperatively (*P* = 0.11) and at 1 year post-op (*P* = 0.175). At 2 years follow-up however, patients who had undergone LSG had significantly higher BMI (*P* = 0.038) compared with those who had undergone LRYGB. Mean BMI were compared using Student's *t* test. LSG: Laparoscopic sleeve gastrectomy; LRYGB: Laparoscopic Roux-en-Y gastric bypass; BMI: Body mass index.
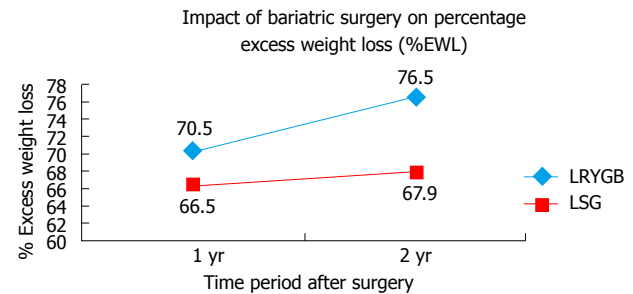

Figure 2 Impact of bariatric surgery on percentage excess weight loss over two years follow-up: There was no significant difference in percentage excess weight loss at 1 year post-op (*P* = 0.36). At 2 years follow-up however, patients who had undergone LRYGB had significantly greater excess weight loss (*P* = 0.044) compared with those who had undergone LSG. %EWL were compared using Student's *t* test. LSG: Laparoscopic sleeve gastrectomy; LRYGB: Laparoscopic Roux-en-Y gastric bypass; %EWL: Percentage excess weight loss.

the surgery. Figure 1 shows the decline in the weight and associated parameters after LSG and LRYGB.

Complication rate
In our experience of 476 LSG and 61 LRYGB, 6 (1.2%) patients in LSG group and no patient in LRYGB group had post-operative staple line leak. However, among the patients in the study cohort, none of the patient had staple line leak. In the LRYGB group, 2 (5%) patients underwent re-diagnostic laparoscopy and repair for internal hernia, one patient underwent laparoscopy adhesive intestinal obstruction eight months after primary surgery and one patient developed gastro-jejunostomy narrowing with edema which responded to conservative management. In the LSG group, 3 (8.3%) patients developed new-onset GERD in post-operative period managed with medical treatment. Overall, the complication rate in two groups was similar (10% in LRYGB *vs* 7.5% in LSG group, *P* = 0.99).

Impact on comorbidities
T2DM: Each of the LRYGB and LSG group had 27 patients with 5 patients each on insulin therapy. The

Table 2 Impact of bariatric surgery on comorbidities (*n* = 80)

Comorbidity	LRYGB			LSG			*P* value[1]
	Preoperative	Resolution	Improvement	Preoperative	Resolution	Improvement	
Type 2 diabetes mellitus	27	18	9	27	21	6	0.36
Hypertension	25	11	12	23	8	14	0.64
OSAS	7	7	0	2	2	0	-
Hypothyroidism	11	3	6	7	1	3	0.58

[1]All *P* values were calculated by applying χ^2 test for every comorbidity comparing LSG and LRYGB. OSAS: Obstructive sleep apnea syndrome; LRYGB: Laparoscopic Roux-en-Y gastric bypass; LSG: Laparoscopic sleeve gastrectomy.

Table 3 Impact of bariatric surgery on medications for various comorbidities (*n* = 80)

Medications	LRYGB		LSG		*P* value[1]
	Preoperative period	Postoperative period	Preoperative	Postoperative period	
Number of OHA	2.17 ± 0.7	0.3 ± 0.5	1.8 ± 0.7	0.3 ± 0.6	0.73
Number of AHA	1.7 ± 0.7	0.5 ± 0.5	1.7 ± 0.8	0.6 ± 0.6	0.78
Dosage of thyroxine (μg/d)	90.9 ± 25.7	45.5 ± 40.1	89.3 ± 31.8	53.6 ± 39.3	0.33

All data expressed as mean ± SD. [1]All *P* values were calculated using Student's *t* test separately for all comorbidities. AHA: Anti-hypertensive agents; OHA: Oral hypoglycemic agents; LRYGB: Laparoscopic Roux-en-Y gastric bypass; LSG: Laparoscopic sleeve gastrectomy.

median duration of T2DM differed significantly between LRYGB and LSG. The median (IQR) duration of T2DM and mean number of Oral Hypoglycemic Agents (OHA) were significantly higher in LRYGB group as compared to LSG group (Table 1).

On follow up, T2DM resolved in 66.7% (18 out of 27) patients while improved in 33.3% (9 out of 27) patients in LRYGB group. In the LSG group, DM resolved in 77.8% (21 out of 27) while improved in 22.2% (6 out of 27) patients. There was no new-onset T2DM noted in any of the groups. Both the procedures had significant impact on T2DM (*P* < 0.001). However, the impact of the two procedures on T2DM was comparable (*P* = 0.544) (Table 2).

In LRYGB group, all 5 patients, who were on insulin therapy pre-operatively, were off insulin therapy in post-operative period (100%) and the mean number (± SD) of OHA declined significantly from 2.17 (± 0.7) to 0.3 (± 0.5) in post-operative period. In LSG group, 3 out of 5 patients (60%), who were on insulin therapy, continued on insulin therapy with decreased dose in post-operative period and the mean number (± SD) of OHA declined from 1.8 (± 0.7) to 0.3 (± 0.6) in post-operative period. The decrease in number of OHA was similar in two groups (*P* = 0.736) (Table 3).

HTN: Twenty-five patients were hypertensive in LRYGB group and 23 patients were hypertensive in LSG group. After surgery, there was remission in 44% (11 out of 25) patients and improvement in 48% (12 out of 25) patients in LRYGB group. Similarly, there was remission in 34.8% (8 out of 23) patients and improvement in 60.8% (14 out of 23) patients in LSG group (Table 2). The mean number (± SD) of anti-hypertensive agents (AHA) declined from 1.7 (± 0.7) to 0.5 (± 0.5) in LRYGB group and 1.70 (± 0.8) to 0.57 (± 0.59) in

LSG group. HTN, thus, improved significantly in both the groups (*P* < 0.001) but there was no significant difference in the outcome of either of the procedures (Table 3).

OSAS: Seventeen point five percent (7 out of 40) patients in LRYGB group and 5% (2 out of 40) patients in LSG group had severe OSA and were on CPAP therapy preoperatively. All the patients were off CPAP in postoperative period (100%) and showed improvement in symptoms of OSAS, irrespective of the procedure performed (Table 2).

Hypothyroidism: Twenty-seven point five percent (11 out of 40) and 17.5% (7 out of 40) patients were on thyroxine therapy for hypothyroidism in LRYGB and LSG group respectively. Twenty-seven point three percent (3 out of 11) patients in LRYGB group and 14.3% (1 out of 7) patients in LSG group maintained normal thyroid function tests without medications, 54.5% (6 out of 11) patients in LRYGB group and 42.8% (3 out of 7) patients in LSG group showed decrease in the dosage of thyroxine while 18.2% (2 out of 11) patients in LRYGB group and 42.8% (3 out of 7) patients in LSG group had no effect on medication for hypothyroidism (Table 2). The mean dosage of thyroxine decreased from 90.9 (± 25.7) μg to 45.5 (± 40.7) μg in LRYGB group and 89.2 (± 31.8) μg to 53.6 (± 39.3) μg in LSG group (Table 3). Both the procedures had significant impact on hypothyroidism but the impact was comparable (*P* > 0.05).

GERD: Based on GERD-SS questionnaire, 17.5% (7 out of 40) patients had GERD preoperatively in LRYGB group which resolved completely after surgery. In LSG group, 10% (4 out of 40) patients had GERD

preoperatively which resolved in 50% (2 out of 4) patients while remained same in rest of them. There was no new onset GERD in LRYGB group but 8.3% (3 out of 36 patients) developed new-onset GERD in LSG group.

DISCUSSION

In this study, we compared the outcomes of the two most commonly performed bariatric procedures- LSG and LRYGB in a well-matched morbidly obese population. We found the weight loss was similar at one year follow-up; however, weight loss was significantly higher in LRYGB group at two year follow-up. The complication rate was similar in both the groups. Regarding the impact on comorbidities, there was similar impact on T2DM, HTN, OSA and hypothyroidism. However, LRYGB led to better outcome in long-standing diabetics on insulin therapy.

The impact of LSG and LRYGB on BMI and weight associated parameters was significant over a follow-up of two years. We found %EWL for LRYGB *vs* LSG at 1-year and 2-year follow-up as 70.5% *vs* 66.5% (*P* = 0.36) and 76.7% *vs* 67.9% (*P* = 0.044) respectively. As per Reinhold's criteria[12], there was 20% failure in LSG group compared to 12.5% in LRYGB group. This suggests LRYGB had better outcome on weight loss over two years as compared to LSG. Similar results were reported by other studies. Lakdawala *et al*[10] reported similar weight loss at one year follow up in 100 patients undergoing LSG and LRYGB. El Chaar *et al*[9] found %EWL of 75% with LRYGB as compared to 60% with LSG over two year follow up period. Boza *et al*[6] also reported significantly higher %EWL with LRYGB (94% *vs* 84%) over two year follow-up in 786 patients undergoing LRYGB and 811 patients undergoing LSG. Such higher %EWL could be explained by lower initial BMI of 38 kg/m^2 in their study population. Nonetheless, there was lesser %EWL in LSG group. Li *et al*[7] in a meta-analysis involving 196 patients undergoing LRYGB and 200 patients undergoing LSG found significantly higher weight loss with LRYGB. The swiss multicentre bypass or sleeve study (SM-BOSS) - a prospective randomised controlled trial published its early results involving 107 patients undergoing LSG and 110 patients undergoing LRYGB[8]. They reported 77% and 73% excess BMI Loss (EBMIL) at one year follow-up and 73% and 63% EBMIL at three year follow-up after LRYGB and LSG respectively (*P* = 0.02)[8]. On the contrary, few studies have reported better outcome in weight loss with LSG at one year follow-up. Karamanakos *et al*[15] found %EWL of 69.7% in LSG group compared to 60.5% in LRYGB group, which they explained due to decreased ghrelin levels which suppressed appetite in initial period after surgery. Boza *et al*[6] also reported 10% and 5.4% failure rate of LSG and LRYGB at follow up of two years. As compared to our study, such lower failure rates could be due to involvement of less obese patients with mean BMI of 38

kg/m^2 in their study.

Both LRYGB and LSG had positive impact on T2DM. We found similar rate of improvement in both the groups. Unlike LSG, all patients on insulin therapy in LRYGB group were off insulin therapy in post-operative period. Buchwald et al reported 83% remission rate of T2DM with LRYGB in a meta-analysis involving more than 22000 patients[16]. Boza *et al*[6] found similar remission rate in LRYGB and LSG group (91% *vs* 87% respectively). Lakdawala *et al*[10] showed 100% and 98% remission rate of T2DM with LRYGB and LSG respectively. Inclusion of lower BMI patients with only 7 and 17 diabetics in LSG and LRYGB groups respectively and shorter duration of diabetes could be the possible reasons for such high rate of remission. They also explained the better results in Asian population could be due to decreased insulin resistance with decrease in central obesity which was more prevalent in Asian population. Other studies by Zhang *et al*[5] and Peterli *et al*[8] also showed similar remission rate of T2DM with LRYGB and LSG. On the contrary, Li *et al*[7] in a meta-analysis reported significantly better remission (Odds ratio = 9.08) of T2DM with LRYGB as compared to LSG. Similar results were reported by Lee *et al*[17].

Multiple mechanisms for remission of T2DM with LRYGB had been proposed. Foregut hypothesis, hindgut hypothesis, decreased ghrelin secretion and starvation followed by weight loss are among the major mechanisms[18]. The mechanism for remission of T2DM post LSG is still not completely understood. The possible mechanism include rise in post-prandial glucagon like peptide-1 due to increase in gastric emptying which lead to increase in insulin secretion. LSG also leads to decrease ghrelin and leptin levels which play role in glucose homeostasis after surgery[19].

The impact of LRYGB and LSG on HTN is variable. Sixty-two point five percent patients and 57.5% patients were hypertensive in LRYGB and LSG group respectively. We found remission rate of 44% and 35% and improvement in 48% and 60.8% in LRYGB and LSG groups respectively. Overall, both the procedures had similar impact on HTN. Similar results were shown by SM-BOSS[8]. Boza *et al*[6] showed 92% and 80% improvement in HTN with LRYGB and LSG respectively. In a study on Indian population, Lakadawala *et al*[10] showed 95% and 91% resolution in HTN. The possible mechanism for resolution of HTN would be decrease in the intra-abdominal pressure and Renin-Angiotension Aldosterone System activity after surgery[20].

Seventeen point five percent patients in LRYGB group and 50% patients in LSG group had severe OSA and were on CPAP therapy preoperatively. All the patients were off CPAP therapy with improvement in symptoms in post-operative period. Similar results were shown by other studies. Zhang *et al*[5] reported 82% and 91% resolution of OSA one year after LRYGB and LSG respectively. They found earlier resolution at 3-6 mo with LRYGB as compared to LSG.

The impact of bariatric surgery on hypothyroidism

is less studied. Both LRYGB and LSG had significant impact on need of thyroxine in post-operative period. Eighty-one point eight percent and 57.2% patients showed improvement in hypothyroidism. The improvement was similar in the two groups. Raftopoulos *et al*[21] reported 48% remission rate with complete resolution in 8% in 23 patients of hypothyroidism undergoing LRYGB. Ruiz-Tovar *et al*[22] found significant decrease in TSH level after LSG. Another study from our centre showed significant decrease in requirement of thyroxine after LSG[23]. Gkotsina *et al*[24] reported significant improvement in pharmacokinetic parameters of levo-T4 absorption after LSG while these remained same after LRYGB. Lips *et al*[25] compared restrictive and malabsorptive procedures and concluded that thyroid hormone regulation is directly proportional to the weight loss irrespective of the bariatric procedure. Hypothyroidism in obese individuals is partially mediated by increased leptin level and peripheral hormonal resistance. Weight loss leads to decrease in the hormone resistance and the need of thyroxine. However, certain subset of patients showed no effect of surgery on hypothyroidism probably because of other factors including autoimmune thyroid disorders[23].

GERD is commonly associated with obesity. While LRYGB led to resolution of GERD in all the patients, LSG led to improvement in GERD in only 50% cases. Importantly, 8.3% developed new onset GERD. Similar results were reported by Lakdawala *et al*[10]. They found 100% remission in GERD post LRYGB while reported rise in incidence in GERD from 5% to 9% after LSG. SM-BOSS trial also showed significantly higher remission in GERD with LRYGB as compared to LSG and reported 12.5% new onset GERD in LSG group[8]. Frezza *et al*[26] reported significant decrease in GERD-related symptoms over the 3-year study after LRYGB. Mechanisms of the anti-reflux effect of RYGB include promoting weight loss, lowering acid production in the gastric pouch, diverting bile from the Roux limb, rapid pouch emptying, and decreasing abdominal pressure over the LES[27]. The impact of LSG on GERD is still an unresolved issue. Multiple mechanisms have been proposed for the impact of LSG on GERD. The mechanisms for improvement of GERD after surgery include faster gastric emptying time, decreased gastric reservoir function, decrease intra-abdominal pressure, decreased acid production and alteration in neuro-hormonal mileu of gastrointestinal tract. Factors which may lead to exacerbation or new onset GERD include increased intraluminal pressure, modification in esophago-gastric junction, partial sectioning of sling fibres and presence of hiatus hernia[28].

Overall both LSG and LRYGB has similar effect on obesity related comorbidities over two year follow-up period, although GERD showed significantly better improvement with LRYGB.

The strengths of the study include well matched groups eliminating bias due to confounding factors and the standardized technique performed by same surgeon in all cases. The outcome of LSG in terms of weight loss and comorbidity resolution has been standardized. Our study is among the first few studies to compare the effect of LSG and LRYGB on thyroid disorder.

There are several limitations of this study. Retrospective nature of the study comes with inherent bias. Small sample size with short-term follow up is another limitation. The duration of T2DM and mean number of OHA were higher in LRYGB group than in LSG group, thereby, leading to a potential bias. The definition of comorbidities and its resolution were not optimally standardized. For T2DM, HbA1c was not available for all patients and hence could not be used in criteria for remission. For HTN, self-reporting of normal blood pressure by the patient was taken as remission or improvement. For OSAS, postoperative polysomnography was not available to objectively document the improvement in OSAS. For GERD, no objective measurement including pH-metry, impedance and high resolution manometry was done. Hyperlipidemia and cardiovascular risk factors could not be studied even knowing that myocardial infarction is the most common cause of mortality in this population.

In conclusion, our results indicate LRYGB has better outcomes in terms of weight loss two years after surgery as compared to LSG. The impact of LRYGB and LSG on T2DM, HTN and OSAS was similar. However, LRYGB had significant resolution of GERD as compared to LSG. Further comparative trials with large sample size and long term follow-up are needed to identify the ideal procedure of bariatric surgery.

COMMENTS

Background
Laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y gastric bypass (LRYGB) are among the most frequently performed bariatric procedures worldwide. Compared to LRYGB, LSG is relatively easier to perform and is associated with less Dumping syndrome, avoids risk of internal hernia and complications due to gastro-jejunostomy or jejuno-jejunostomy, decreases the risk of nutritional deficiencies and provides accessibility of the remnant stomach *via* endoscopy, which is important especially in Asian population. However, few studies have compared the effects of LRYGB and LSG in well-matched Indian population.

Research frontiers
Few studies have compared the outcomes of LRYGB and LSG in a well matched Indian obese population undergoing bariatric surgery.

Innovations and breakthroughs
This study compared 40 patients undergoing LRYGB, who completed their 2-year follow-up with 40 patients undergoing LSG matched for age, gender, body mass index and presence of type 2 diabetes mellitus (T2DM). Data of these patients was retrospectively reviewed to compare the outcome in terms of weight loss and improvement in comorbidities, *i.e.*, T2DM, hypertension (HTN), obstructive sleep apnea syndrome (OSAS), hypothyroidism and gastroesophageal reflux disease. Using case control design , this study found similar weight loss one year after surgery in both the groups but the weight loss was significantly higher in LRYGB group two years after surgery. The complication rate was similar in both groups. Regarding comorbidity resolution, both LRYGB and LSG had significant but similar impact on obesity related comorbidities except gastroesophageal reflux disease where LRYGB showed better improvement. This is also among

the first few studies to study the impact of bariatric surgery on hypothyroidism, which improved significantly in both LSG and LRYGB groups.

Applications

This study compares the outcomes of LRYGB with LSG in a well-matched population over a period of two years follow-up. This is important in clinical practice as the impact of LRYGB and LSG on weight loss and obesity associated comorbidities is a casue of concern while selecting a particular bariatric procedure for a patient.

Terminology

Percentage excess weight loss (%EWL) is defined as [(Preoperative weight-current weight/preoperative weight-ideal weight] × 100%.

Peer-review

This is a retrospective study to compare the impact of LRYGB and LSG on weight loss and obesity related comorbidities. This is an important issue in clinics.

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Retrospective Cohort Study

Does serotonin reuptake inhibitor therapy increase the risk of post-sphincterotomy bleeding in patients undergoing endoscopic retrograde cholangio-pancreatography?

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Abstract

AIM
To evaluate the risk of immediate and delayed bleeding following sphincterotomy procedure.

METHODS
This retrospective cohort study was conducted with all patients who underwent endoscopic sphincterotomy during January 2006 to September 2015 at a tertiary academic center. Patients were grouped according to pre procedural usage of serotonin reuptake inhibitors (SRIs). Both groups were matched for demographic and clinical characteristics. Patients with thrombocytopenia, increased international normalized ratio, or a history of bleeding or coagulation disorders, concurrent use of other antiplatelet/anticoagulants were excluded from the study.

RESULTS
A total of 447 patients were included, of which 219 (45.9%) used SRIs and 228 (54.1%) cases did not. There was no significant difference in acute or delayed bleeding during endoscopic sphincterotomy between the two groups. (8.2% *vs* 12.3%, *P* = 0.16).

CONCLUSION

The use of SRIs was not associated with an increased risk of post-sphincterotomy bleeding. To our best knowledge, this is the first study to explore this association.

Key words: Serotonin reuptake inhibitors; Post-sphincterotomy bleeding; Endoscopy; Endoscopic retrograde cholangiopancreatography; Gastrointestinal bleeding

Core tip: Serotonin reuptake inhibitors (SRIs) are a very commonly prescribed medication. The use of SRIs is reportedly associated with an increased risk for gastrointestinal bleeding in few studies. In this retrospective cohort study we analyzed the association between use of SRI and risk of post sphincterotomy bleeding with meticulous exclusion of all the confounders associated with increased risk of sphincterotomy bleeding. To our knowledge, this is a first study to assess the SRIs impact on post sphincterotomy bleeding.

INTRODUCTION

Since its earliest description in 1974, endoscopic sphincterotomy has become a commonly performed procedure for a variety of therapeutic indications during endoscopic retrograde cholangiopancreatography (ERCP)[1]. Including choledocholithiasis, placement of stents through malignant and benign strictures, as well as to treat dysfunction of the sphincter of Oddi. It is a technically difficult endoscopic procedure performed under visual and fluoroscopic guidance. It involves deep insertion of the cannula into the bile duct through the ampulla of Vater and the subsequent use of electrocautery to incise the sphincter of Oddi. Sphincterotomy has been associated with pancreatitis, hemorrhage, perforation and other complications most of which occur within the initial 24 h of procedure[2,3]. Hemorrhage is a well-known complication occurring in up to 2%-7% of all cases[1].

Serotonin reuptake inhibitors (SRIs) are considered to be a first-line pharmacologic therapy for depression, and are among the most commonly prescribed medications in the United States. The safety and side effect

Table 1 Complications of sphincterotomy and risk factors for hemorrhage

Complications of sphincterotomy	Risk factors for hemorrhage
Pancreatitis - 1.0%-15.7% (Most common complication)	Presence of coagulopathy
Hemorrhage - 2%-7%	Use of anti-coagulation
Cholangitis - 1% - (Fever, chills, elevated liver enzymes, and/or positive blood culture within 48 h after the procedure)	Cholangitis
Cholecystitis - (Clinical and radiographic evidence of an inflamed gallbladder)	Low endoscopist case volume

profile of these drugs have been well-described in the existing literature. In numerous studies, SRI therapy has been associated with an increased risk of gastrointestinal bleeding. Similarly, the use of non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulants and aspirin has been associated with an increased risk of bleeding during sphincterotomy procedures[4]. These drugs are typically discontinued a week prior to the procedure date. Our aim was to evaluate the risk of immediate and delayed bleeding following sphincterotomy procedure. Our hypothesis was that SRIs medications increase the risk of post sphincterotomy bleeding.

MATERIALS AND METHODS

Definitions

Immediate post endoscopic sphincterotomy (post-ES) bleeding is considered to be oozing of blood during ERCP. Delayed post ES bleeding occurs within 10 d after ERCP and manifested as melena, hematemesis or hematochezia (Table 1). Classification of bleeding according to Cotton *et al*[3] states mild bleeding is defined as hemoglobin drop of less than 3 g/dL without the need of transfusion, moderate bleeding is considered when blood transfusion of 4 units or less is required without any surgical intervention, severe bleeding is defined as blood transfusion of 5 units or more and surgical intervention is required (Table 2).

Patient selection

This retrospective cohort study was conducted after obtaining necessary approval from the Institution Review Board and patients consent. Patients who underwent ERCP with sphincterotomy at a tertiary referral center by a group of ten therapeutic endoscopists with a minimum of 5 years of experience during the study period of January 2006 - September 2015 were reviewed. One of the confounding factor of bleeding is low endoscopist case volume (Table 1). This study was conducted at a tertiary referral center with an average 2500 ERCP are performed in a year, in total 22500 during 2006-2015. SRI is a commonly prescribed drug in United States. Patients using either selective SRIs or serotonin-nor-epinephrine reuptake inhibitors (SNRIs) at the time of

Table 2   Bleeding grading system

Mild	Moderate	Severe
Transfusion is not required, with evidence of bleeding	Transfusion of 4 units or less is required	Transfusion of 5 units or more is required
Hemoglobin drop of less than 3 g/dL	No surgical intervention	Angiographic or surgical intervention
Immediate bleeding - seen in 30% patients (8) - endoscopic venous oozing which stopped with epinephrine		
Delayed bleeding - occur up to 2 wk after the procedure - hematemesis, melena, haematochezia		
Severe bleeding - 0.1%-0.5%		

Adapt from Cotton *et al*[3].

Table 3   Serotonin reuptake inhibitors medications included in the study

Serotonin reuptake inhibitors	Serotonin-norepinephrine reuptake inhibitors
Citalopram (Celexa)	Desvenlafaxine (Pristiq)
Escitalopram (Lexapro, Cipralex)	Duloxetine (Cymbalta)
Paroxetine (Paxil, Seroxat)	Levomilnacipran (Fetzima)
Fluoxetine (Prozac)	Milnacipran (Ixel, savella)
Fluvoxamine (Luvox)	Tofenacin (Elamol, tofacine)
Sertraline (Zoloft, lustral)	Venlafaxine (Effexor)

the procedure were included (Table 3). The patients were grouped according to whether they continued to take SRIs until the day of the procedure and patients who never had been on SRI's or SNRI's. Patients SRI dose wasn't included as the purpose of study was to analysis bleeding risk with SRI therapy. Patients with following risk factors that could independently increase the risk of bleeding (such as coagulopathies, liver disorders, and cholangitis), patients taking aspirin and NSAIDs, patients with abnormal lab values for PT-INR > 1.5, platelet count < 150000, and PTT > 25 s were excluded from the study (Figure 1). Data pertaining to the patient demographics (Tables 4 and 5), technical aspects of the procedure (Tables 6 and 7), medical co-morbidities including renal, cardiac, hepatic issues, coagulation disorder, bleeding disorder, history of alcohol intake, drug history, coagulation profile, platelet levels, recent antiplatelet or NSAID use was abstracted.

Statistical analysis

Continuous variables are presented as mean ± SD or median (25th, 75th percentiles) and categorical factors as frequency (percentage). A univariable analysis was performed to assess differences between subjects who used SRIs at the time of ERCP and those who did not. Analysis of variance or the non-parametric Kruskal-Wallis tests were used for continuous or ordinal variables and Pearson's χ^2 tests were used for categorical factors. In addition, univariable and multivariable logistic regression analyses were performed to assess factors associated with occurrence of post-sphincterotomy

bleeding; factors seen in < 5 patients were not considered for this part of the analysis. An automated stepwise variable selection method performed on 1000 samples was used to choose the final model. The use of SRI was forced into the models and the additional three variables with highest inclusion rates were included in the final models. A *P* value < 0.05 was considered statistically significant. SAS version 9.4 (The SAS Institute, Cary, NC) was used to perform all analyses.

RESULTS

Out of 22500 who had undergone endoscopy, 447 subjects who underwent sphincterotomy were included in the study (Tables 5-7). At the time of the procedure, 219 patients were taking SRI therapy and 228 patients had never been on SRI therapy.

There was no evidence of a significant difference in the incidence of post-sphincterotomy bleeding between the groups 8.2% *vs* 12.3% (Table 8 and Figure 2). The absence of alcohol intake, depression, and lower PTT were significantly more common in subjects taking SRIs.

On univariable analysis, there was no evidence of an association between any of the assessed factors and post-sphincterotomy bleeding. The use of SRIs, demographic, BMI, clinical comorbidities including cardiovascular disorders, renal disease, indication of ERCP, and number of ERCPs were included in the final model but these did not reach statistical significance. None of the patients who experienced immediate post-sphincterotomy bleeding required blood transfusion therapy. Only two patients < 1% of the study group experienced delayed bleeding and did not require any transfusion. Patients who oozed blood were managed by injecting epinephrine.

DISCUSSION

It is a widely perceived, yet never before tested in patients undergoing sphincterotomy, theory that the use of SRI therapy is associated with an increased risk of gastrointestinal bleeding. In this retrospective cohort study, we found no significant association between the use of SRI and post-sphincterotomy bleeding. Moreover, no difference in estimated blood loss was observed in these two group. Association between percutaneous endoscopic gastrostomy and SRI's bleeding has been reported[5]; however, unlike our study, none of these studies excluded other confounding potential risk factors for bleeding. Our findings contradict the other studies that have found SRI to increase bleeding. The exact mechanism is unknown but the purported mechanism of SRI's on bleeding states that SRI's inhibits the serotonin transport protein and by blocking the uptake of synaptic serotonin into presynaptic neurons, it impairs the hemostasis function. SRI's act as a blocker and inhibit entry of serotonin from blood into platelets. Release of serotonin from platelets into the bloodstream during an injury is an important step platelet aggregation[9,11-13]. This

Table 4 Patient demographics *n* (%)

Factor	Overall (*n* = 447)		SRI (*n* = 219)		No SRI (*n* = 228)		*P* value
	n	Summary	*n*	Summary	*n*	Summary	
Age (yr)	445	64.4 ± 17.9	219	64.0 ± 16.8	226	64.7 ± 19.0	0.68[1]
Male	447	112 (25.1)	219	47 (21.5)	228	65 (28.5)	0.086[3]
BMI	442	29.5 ± 7.5	218	29.7 ± 7.6	224	29.3 ± 7.4	0.59[1]
Smoking	435	216 (49.7)	216	114 (52.8)	219	102 (46.6)	0.20[3]
Alcohol use	432	161 (37.3)	215	69 (32.1)	217	92 (42.4)	0.027[3]
Cardiovascular disorder	447	111 (24.8)	219	53 (24.2)	228	58 (25.4)	0.76[3]
Depression	445	160 (36.0)	219	99 (45.2)	226	61 (27.0)	< 0.001[3]
Renal disease	447	55 (12.3)	219	30 (13.7)	228	25 (11.0)	0.38[3]
Intestinal disease	447	66 (14.8)	219	29 (13.2)	228	37 (16.2)	0.37[3]
History of UGI bleed	389	1 (0.26)	207	0 (0.0)	182	1 (0.55)	0.47[4]

[1]ANOVA; [3]Pearson's χ^2 test; [4]Fisher's exact test. Intestinal diseases: Peptic ulcer, inflammatory bowel disease. Values presented as Mean ± SD or *n* (%). SRI: Serotonin reuptake inhibitor.

Figure 1 Exclusion criteria.

Table 5 Patients lab values

Factor	Overall (*n* = 447)		SRI (*n* = 219)		No SRI (*n* = 228)		*P* value
	n	Summary	*n*	Summary	*n*	Summary	
PPI	447	111 (24.8)	219	51 (23.3)	228	60 (26.3)	0.46[2]
Platelets	435		213		222		0.59[1]
140-400		432 (99.3)		212 (99.5)		220 (99.1)	
> 400		3 (0.69)		1 (0.47)		2 (0.90)	
INR	391		190		201		-
0.9-1.2		391 (100.0)		190 (100.0)		201 (100.0)	
PTT	361		171		190		-
24.7-32.7 s		361 (100.0)		171 (100.0)		190 (100.0)	

[1]Kruskal-Wallis test; [2]Pearson's χ^2 test. Values presented as Mean ± SD or *n* (%). SRI: Serotonin reuptake inhibitor.

Table 6 Number of endoscopic retrograde cholangiopancreatography

Number of ERCPs	Overall (*n* = 447)	SRI (*n* = 219)	No SRI (*n* = 228)	*P* value
1	432 (96.6)	214 (97.7)	218 (95.6)	0.23[1]
2	13 (2.9)	3 (1.4)	10 (4.4)	
3	2 (0.45)	2 (0.91)	0 (0.0)	

[1]Kruskal-Wallis test. Values presented as *n* (%). SRI: Serotonin reuptake inhibitor; ERCP: Endoscopic retrograde cholangiopancreatography.

Table 7 Indications for endoscopic retrograde cholangiopancreatography

	Overall (*n* = 447)	SRI (*n* = 219)	No SRI (*n* = 228)	*P* value
	Summary	*n* (%)	*n* (%)	
Abnormal CT	16 (3.8)	9 (4.3)	7 (3.3)	0.57[1]
Abdominal pain	90 (21.2)	43 (20.6)	47 (21.9)	0.75[1]
Abnormal LFT	62 (14.6)	32 (15.3)	30 (14.0)	0.69[1]
Biliary dilation	8 (1.9)	6 (2.9)	2 (0.93)	0.17[2]
Bile duct stones	187 (44.1)	96 (45.9)	91 (42.3)	0.45[1]
Complications of prior biliary surgery	6 (1.4)	4 (1.9)	2 (0.93)	0.44[2]
Jaundice	49 (11.6)	16 (7.7)	33 (15.3)	0.013[1]
Cholangitis	9 (2.1)	209	4 (1.9)	5 (2.3)	0.99[2]

[1]Pearson's χ^2 test; [2]Fisher's exact test. Values presented as *n* (%). CT: Computed tomography; LFT: Lung function testing; SRI: Serotonin reuptake inhibitor.

Table 8 Bleeding and management

	Overall (*n* = 447)	SRI (*n* = 219)		No SRI (*n* = 228)		*P* value
	n (%)	*n*	Summary	*n*	Summary	
Post-sphincterotomy bleeding	46 (10.3)	219	18 (8.2)	228	28 (12.3)	0.16[1]
Injected with epinephrine	25 (54.3)	18	7 (38.9)	28	18 (64.3)	0.091[1]

[1]Pearson's χ^2 test;. Values presented *n* (%); SRI: Serotonin reuptake inhibitor..

Figure 2 Post-sphincterotomy bleeding.

presumed mechanism can further predispose to bleeding disturbances. However, our finding did not show any evidence indicating SRI to increase bleeding.

Many studies suggest an association between SRI's and upper gastrointestinal bleeding. It's suggested that SRIs increase gastric acidity by targeting gastric mucosa which potentiates the risk of upper GI bleeding[9,11]. In a recent meta-analysis on risk for GI bleeds, it was noticed that patients on combined therapy such as NSAIDs, aspirin, SRIs were at higher risk for bleeding[8]. To our knowledge, only two studies have studied risk of post sphincterotomy bleeding with patients using NSAIDS and aspirin. The finding of the studies were equivocal:

Both found different results suggesting the safety of aspirin use during procedure[4,6] one study results showed that use of aspirin resulted in increased risk of bleeding[6], and the other study results showed aspirin and NSAIDs not associated with the risk bleeding[4].

Drugs that cause prolonged bleeding, such as aspirin and NSAIDS are advised to discontinue a week prior to surgery. Patients who experience bleeding during the procedure are injected with epinephrine around the sphincterotomy site. This is considered to be the most commonly used method to manage immediate bleeding.

Our usual approach is local therapy in the form of 1:10000 diluted epinephrine injection, either alone or in combination with cautery, hemoclips. Covered metal stents are placed in patients who are expected to resume therapeutic anticoagulation or have underlying coagulopathy.

While recognizing that no definite guidelines can be derived from this retrospective study, our result presented here provides novel knowledge about complex question of management of SRI's prior to therapeutic ERCP. We conclude if the confounding variables for bleeding are excluded, SRI's alone do not increase the risk of post-sphincterotomy bleeding. According to our knowledge, this is the first study to assess the SRI's impact on post sphincterotomy bleeding.

COMMENTS

Background

Since its earliest description in 1974, endoscopic sphincterotomy has become a commonly performed procedure for a variety of therapeutic indications during endoscopic retrograde cholangio-pancreatography. Including choledocholithiasis, placement of stents through malignant and benign strictures, as well as to treat dysfunction of the sphincter of Oddi.

Research frontiers

The authors hypothesis was that serotonin reuptake inhibitors (SRIs) medications increase the risk of post sphincterotomy bleeding.

Innovations and breakthroughs

The authors conclude if the confounding variables for bleeding are excluded, SRI's alone do not increase the risk of post-sphincterotomy bleeding. According to our knowledge, this is the first study to assess the SRI's impact on post sphincterotomy bleeding.

Peer-review

The paper of Yadav *et al* is original and well written. The interest to know there is no bleeding risk with SRI therapy is not so high but important to know.

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ORIGINAL ARTICLE

Retrospective Study

Does deep sedation with propofol affect adenoma detection rates in average risk screening colonoscopy exams?

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Abstract

AIM
To determine the effect of sedation with propofol on adenoma detection rate (ADR) and cecal intubation rates (CIR) in average risk screening colonoscopies compared to moderate sedation.

METHODS
We conducted a retrospective chart review of 2604 first-time average risk screening colonoscopies performed at MD Anderson Cancer Center from 2010-2013. ADR and CIR were calculated in each sedation group. Multivariable regression analysis was performed to adjust for potential confounders of age and body mass index (BMI).

RESULTS
One-third of the exams were done with propofol ($n = 874$). Overall ADR in the propofol group was significantly higher than moderate sedation (46.3% *vs* 41.2%, $P =$

0.01). After adjustment for age and BMI differences, ADR was similar between the groups. CIR was 99% for all exams. The mean cecal insertion time was shorter among propofol patients (6.9 min *vs* 8.2 min; *P* < 0.0001).

CONCLUSION
Deep sedation with propofol for screening colonoscopy did not significantly improve ADR or CIR in our population of average risk patients. While propofol may allow for safer sedation in certain patients (*e.g.*, with sleep apnea), the overall effect on colonoscopy quality metrics is not significant. Given its increased cost, propofol should be used judiciously and without the implicit expectation of a higher quality screening exam.

Key words: Sedation; Propofol; Adenoma detection rate; Cecal intubation rate; Colonoscopy; Quality metrics

Core tip: This is a retrospective study to evaluate the effect of propofol deep sedation *vs* opioid/benzodiazepine moderate sedation on adenoma detection rate (ADR) and cecal intubation rate (CIR) colonoscopy quality metrics. After adjusting for confounding variables of age, gender and body mass index, there was no difference seen in ADR or CIR between the two groups.

INTRODUCTION

In the United States endoscopic procedures routinely utilize sedation to minimize patient discomfort. Today, moderate sedation is widely used, with a combination of opioid and benzodiazepine for amnestic and analgesic effects[1]. In recent years endoscopists have increasingly turned to deep sedation provided by anesthesiologists using propofol although significant regional differences in utilization exist[2]. Between 2008 and 2011, one third of colonoscopies were performed using anesthesia services[3]. Propofol provides sedative, amnestic and hypnotic effects but does not have analgesic properties.

Propofol is gaining popularity among United States endoscopists in part due to its rapid onset of action and faster patient recovery[4]. In a nationwide survey, physicians under age 65 used propofol in their practice more frequently and were more satisfied with propofol over moderate sedation compared to older physicians[5]. Half of the physicians in this survey favored propofol sedation for their own endoscopy as they felt that this would improve the quality of the exam[5]. However, the data on patient satisfaction compared with conscious sedation are mixed with a recent meta-analysis showing no difference[6].

Adenoma detection rate (ADR) is the premier quality indicator in screening colonoscopy and is inversely related to the risk of interval colorectal cancer development and death[7,8]. Since some gastroenterologists perceive that propofol sedation improves the quality of the exam, investigators have evaluated the effect of sedation on ADR. While multiple studies have compared varying levels of sedation to no sedation and found conflicting results in terms of exam quality[9,10] other studies have compared different levels of sedation to each other. However, these studies either did not utilize propofol[11], did not describe the level sedation achieved with various agents[12], or gave conflicting results[13]. Thus the question of whether deep sedation with propofol improves ADR when compared to moderate sedation with benzodiazepines/opioids remains unresolved.

Adenoma detection depends on the entire colon being examined, therefore cecal intubation rate (CIR) is another quality parameter in screening colonoscopy. The more comfortable the patient is, the higher likelihood that the cecum will be reached especially in technically difficult cases. In general, the use of any level of sedation has improved the rates of cecal intubation over unsedated exams[9,10]. In one study using propofol for sedation, CIR was 98% and incomplete exams were associated with patient history of constipation and poor bowel prep[14].

Given the recent trend toward increased anesthesia involvement in endoscopy and the added cost, the current emphasis on value in health care services makes it worthwhile to evaluate the relationship between deep sedation and colonoscopy quality metrics. Our primary outcome was to determine the effect of deep sedation with propofol (total intravenous anesthesia, TIVA) compared to moderate sedation on ADR in a population of average-risk patients presenting for their index screening colonoscopy. Our secondary aim was to determine any differences in cecal intubation rates between these two sedation groups.

MATERIALS AND METHODS

We performed a retrospective chart review of all average risk patients aged 50 to 75 undergoing initial screening colonoscopy between July 2010 and May 2013 at the University of Texas MD Anderson Cancer Center. Patients who have had prior exams often cannot recall the pertinent details (whether adenomas were removed, if the exam was complete, preparation quality, *etc.*) in addition the risk of adenomas increases with patient age. Therefore based on chart review, we excluded patients who had undergone a prior colonoscopy to get a homogenous group of patients to determine ADR. High-risk patients (*i.e.*, with a family history of colon cancer or genetic syndromes), diagnostic exams (done

for evaluation of symptoms) and patients who had undergone prior colon resection were excluded. Patients with a personal history of non-gastrointestinal cancers were included. In our group practice, the endoscopy time assigned to TIVA or moderate sedation use can vary between physicians. Endoscopists who performed less than 20 exams in either sedation group during the study period were excluded from analysis. This was done to evaluate a group of physicians who had contributed to both sedation groups to minimize bias and obtain accurate ADRs[15]. Full time faculty with endoscopic experience ranging from one year to 25 years post fellowship training performed all exams. All patients received a standard split dose bowel to optimize the quality of bowel prep[16]. Our Institutional Review Board approved this study. Informed consent was not required for this retrospective study, data was collected in a de-identified manner and in the course of usual patient management.

Patients are referred to our endoscopy unit for screening exams after being evaluated in a cancer pre-vention center, gastroenterology clinic, or by other MD Anderson clinics. These referrals are reviewed within our department and the patients are scheduled with moderate sedation or TIVA based on uniform criteria. Our criteria for TIVA mirror those of the American Society for Gastrointestinal Endoscopy and fall into three categories: (1) pulmonary (*e.g.,* increased risk of airway obstruction or aspiration, documented sleep apnea with use of continuous positive airway pressure device); (2) co-morbid conditions (*e.g.,* BMI ≥ 35, cardiac disease such as arrhythmia, pacemaker, decompensated heart failure, myocardial infarction within 6 mo*, etc*.); or (3) anticipated intolerance of moderate sedation (*e.g.,* scheduled use of narcotics or benzodiazepines or patient preference)[4]. Moderate sedation consisted of intravenous midazolam and either meperidine or fentanyl under the direction of the endoscopist with routine monitoring. Deep sedation was the target for TIVA patients. In addition to routine monitoring of blood pressure, EKG, and use of nasal cannula oxygen, TIVA patients were also monitored with end-tidal capnography.

Two investigators (WR and ST) performed data collection from the electronic medical record to identify patients for inclusion. Demographic information including age, gender, race and BMI were recorded for each patient. Transcribed clinic notes were reviewed to determine family history, presence of symptoms at the time of colonoscopy and reports of prior colonoscopy exams. Procedure notes and the endoscopy reporting software database (Endoworks Olympus Inc. Center Valley, PA, United States) were examined to determine method of sedation, insertion time to the cecum and scope withdrawal time (which are marked by the endoscopy technician during the procedure) as well as the number of polyps removed. The software system default for bowel prep quality is set to good/adequate and the physician must make the effort to change it.

Since there is variability among our endoscopists in doing this, we did not specifically collect this data point. We used CIR as a surrogate marker for adequacy of bowel prep. Pathology reports were reviewed to record polyp histology (hyperplastic, adenoma, sessile serrated adenoma, or adenocarcinoma).

ADR was calculated for male and female patients by method of sedation. Statistical analysis was performed using the chi-square test for categorical variables and *t* test for continuous variables. Multivariable logistic regression analysis was performed to determine the effect of TIVA *vs* moderate sedation on ADR for male and female patients. The analyses were adjusted for potential confounders, namely BMI and age[17,18]. The relationship between the depths of sedation and CIR, as well as scope insertion times was evaluated. Pearson's correlation coefficient was calculated to assess for any relationship between ADR and the proportion of TIVA procedures performed by each endoscopist. We did not perform any additional provider-level analyses (such as ADR by years in clinical practice) because of unequal sub-group distribution of physicians in our practice.

RESULTS

A total of 2604 first-time screening colonoscopies were performed during the study period. The majority were done under moderate sedation (*n* = 1730, 66.4%; TIVA: *n* = 874, 33.6%). Female patients outnumbered male patients (*n* = 1681 and *n* = 926 respectively) and most patients were non-Hispanic whites (Table 1). Patients in the TIVA group had a significantly higher BMI and were older than the moderate sedation group as expected based on our allocation criteria. Adenomas were detected in 1118 exams while 1486 patients had negative exams. Of these, approximately 9% of patients had advanced adenomas and 6% had sessile serrated adenomas.

The overall ADR was higher in the TIVA group than the moderate sedation group (46.3% *vs* 41.2% *P* = 0.01). The ADR was significantly higher among female patients undergoing exams with TIVA compared to moderate sedation (42.4% *vs* 36.4% *P* = 0.03). There was no significant difference in ADR in male patients between the TIVA and moderate sedation groups (53.7% *vs* 50.4% *P* = NS). Detection of sessile serrated adenomas and advanced adenomas was similar be-tween the two groups. Multivariate analysis was per-formed to adjust for potential confounders (*i.e.*, age and BMI)[17]. There was no significant difference in ADR in either male or female patients between the study groups after multivariable analysis (Table 2).

Cecal intubation rates were evaluated for the study group. CIR was 99.0% overall and similar between sedation groups (98.8% moderate sedation, 99.4% TIVA, *P* = 0.15). Failure to reach the cecum was more common among female patients (*n* = 15 of 19 incomplete exams). The most common reason for an incomplete colonoscopy was poor bowel prep,

Table 1 Patient characteristics by type of sedation

	Moderate sedation, *n* (%)	Propofol sedation, *n* (%)	*P* value
Total	1730 (66.4)	874 (33.6)	
Gender			0.16
Female	1133 (67.4)	548 (32.6)	
Male	597 (64.7)	326 (35.3)	
Race			< 0.0001
Non-Hispanic White	1190 (66.2)	607 (33.8)	
African American	166 (55.7)	132 (44.3)	
Hispanic	186 (65.5)	98 (34.5)	
Asian	172 (83.9)	33 (16.1)	
Unknown	16 (80.0)	4 (20.0)	
BMI			< 0.0001
< 25	617 (81.8)	137 (18.2)	
25-30	645 (76.0)	204 (24.0)	
> 30	451 (45.8)	533 (54.2)	
Missing	17 (100)	0 (0)	
Mean age (SD)	55.4 (5.3)	56.7 (5.9)	< 0.0001
Adenoma			0.01
No	1017 (58.8)	469 (53.7)	
Yes	713 (41.2)	405 (46.3)	
Mean insertion time, min (SD)	8.2 (6.5)	6.9 (4.7)	< 0.0001
Mean scope withdrawal time, min (SD)	12.8 (6.3)	12.6 (6.6)	0.75
Advanced adenoma detection rate (SD)	134 (7.8)	95 (10.4)	0.065
Sessile serrated adenoma detection rate (SD)	106 (6.1)	54 (5.9)	0.52

followed by technical difficulty (adhesions, fixed angulations, redundant colon). Three patients in the moderate sedation group had an incomplete exam due to inadequate sedation (pain during the procedure, paradoxical reaction to medication). In these cases, examination of the colon was completed by CT colonography or repeat colonoscopy with TIVA.

The mean scope insertion time to the cecum was calculated for complete exams and was significantly shorter among patients in the TIVA group compared to moderate sedation (6.9 min *vs* 8.2 min; *P* < 0.0001). Within the TIVA group, mean insertion times were longer for female patients compared to male patients (7.3 min *vs* 6.3 min; *P* = 0.003). Use of TIVA was associated with a significantly shorter scope insertion time to cecum among both females (OR = 0.96, 95%CI: 0.94-0.97, *P* < 0.001) and males (OR = 0.96, 95%CI: 0.60-0.99, *P* = 0.02) and remained significant even after adjusting for age and BMI (Table 2). Scope withdrawal times were similar for the TIVA and moderate sedation groups for exams done without polypectomy (*P* = 919, mean 12.6 min *vs* 12.8 min respectively, *P* = 0.75). The proportion of TIVA procedures performed by each endoscopist had no correlation with the ADR the physician achieved (R = 0.11).

DISCUSSION

Our group aimed to evaluate the effect of deep sedation with propofol compared to moderate sedation on ADR and CIR in our clinical setting. The overall ADR for our

group was 40.9% for moderate sedation and 46.1% for TIVA cases, higher than commonly reported rates and higher than the recently modified national society performance targets of 20% ADR for women and 30% for men[8]. Although our reported ADR is higher than generally expected, comparable rates are seen in high performers[19]. Our initial analysis found a significantly higher ADR among female patients having exams with TIVA but no difference among male patients. After adjusting for age and BMI, there was no difference in ADR among male or female patients regardless of the type of sedation. CIR was 99% in both sedation groups.

Although previous investigators have studied the effect of sedation on colonoscopy quality metrics, there are several important distinctions in our study[9-11]. One of our strengths is that we specifically compare propofol for deep sedation *vs* an opioid/benzodiazepine combination to achieve moderate sedation and is reflective of clinical practice. The depth of sedation achieved with this cocktail can be variable while propofol reliably induces deep sedation. Another strength is our homogenous patient population best suited to evaluate ADR among average-risk patients undergoing their first screening colonoscopy. Other studies were performed among higher risk patients presenting for colonoscopy by virtue of positive symptoms, prior adenoma, older age, positive family history, *etc.* which influence adenoma prevalence[10-12]. Our group had more female than male patients presenting for screening colonoscopy which supports existing literature[20].

The decision to perform colonoscopy with moderate *vs* deep sedation is often left to a practitioner's clinical judgment and this variability can affect study outcomes. We consistently applied our department's criteria in selecting patients for exams with TIVA, to ensure uniform patient selection for the sedation groups. While we recognize that our specific criteria are not used universally, we feel that they are fairly generalizable (age, comorbidity, BMI) and done with the patients' safety in mind. While random assignment is ideal, it does not reflect clinical practice.

We realize that our study has limitations. This was a retrospective study with the limitations inherent in that design. While we are a tertiary care center, MD Anderson has a Cancer Prevention and Screening clinic. As a result, over half of our colon cancer screening practice consists of patients without a prior cancer history. While we included patients with a prior history of cancer, we excluded those with a prior gastrointestinal malignancy in order to reduce bias. We feel that survivors of non-gastrointestinal malignancies and are representative of the patients seen in general clinical practice. In addition, we have previously demonstrated that there was no difference in the ADR between patients without a cancer history and those with a history of non-gastrointestinal malignancy[21]. There may be additional unmeasured confounders or selection bias present. Sedation may have an effect on detection of right sided *vs* left sided lesions but our database did not allow us to investigate

	Variable	Propofol, *n* (%)	Crude odds ratio (95%CI)	*P* value	Adjusted odds ratio[1] (95%CI)	*P* value
Table 2 Multivariable analysis: Association of type of sedation (propofol *vs* moderate) with adenoma detection rate and scope insertion time						
Adenoma detection						
Gender	Female	548 (32.6)	1.27 (1.03-1.56)	0.03	1.07 (0.84-1.35)	0.60
	Male	326 (35.3)	1.14 (0.87-1.49)	0.34	1.16 (0.87-1.55)	0.32
Scope insertion time, mean (SD)						
Gender	Female	7.3 (5.0)	0.96 (0.94-0.97)	< 0.001	0.97 (0.95-0.99)	0.02
	Male	6.3 (4.2)	0.96 (0.60-0.99)	0.02	0.97 (0.93-1.00)	0.05

[1]Adjusted for patient age and body mass index.

this further.

Ease of scope insertion to the cecum and performing a deliberate exam during scope withdrawal are important factors for a quality exam[22]. In addition to overall CIR, we also evaluated mean scope insertion times and scope withdrawal times. The mean insertion time to the cecum was significantly shorter in our TIVA group. Investigators have shown that scope insertion to the cecum takes longer for female patients than male patients and this was confirmed in our study[23-26]. Increasing patient age and BMI are other well-recognized factors that independently prolong scope insertion time[23-26]. When adjusted for these factors, the scope insertion times were shorter with deep sedation compared to moderate sedation only in females. Our scope withdrawal times were similar between the two sedation groups for normal exams. One limitation is that polyp removal time was not separately recorded from insertion or withdrawal time. We assume that the endoscopist's preference of polypectomy during insertion or withdrawal would be performed consistently regardless of the method of sedation. Reaching the cecum more quickly could allow for additional time for inspection and increased polyp detection in the deep sedation group, but this was not seen. Apart from patient and procedure-related factors that affect ADR, the endoscopist themselves may have a greater impact on ADR than patient age or gender[27]. Therefore we wanted to determine if there was a correlation between the proportion of TIVA procedures performed by an individual endoscopist and their ADR. No such correlation was seen in our study.

Although the majority of propofol sedation is done safely, some have reported increased complications with deep sedation[3,28]. This may be a reflection of patient selection as regions of the country with more selective use of propofol show the highest complication rates compared to moderate sedation[3]. In areas where propofol is used indiscriminantly, the complication rates are more modest. While the participation of anesthesiologists can expand the population that can undergo endoscopy safely, the use of propofol for routine procedures and, in some centers, without specific medical justification, contributes to escalating healthcare costs[2]. We were not able to demonstrate an improvement in screening colonoscopy quality metrics with the use of propofol sedation. The additional expense of propofol may not be fully mitigated by enhanced

efficiency[29]. In these times of heightened concern for value in health care expenditures, the effect of propofol use for endoscopic sedation on patient outcomes deserves further study.

COMMENTS

Background
Screening colonoscopy exams are being performed with deep sedation using propofol with increasing frequency in the United States. The authors aimed to determine if there was any effect of deep sedation (compared to moderate sedation) on colonoscopy quality metrics, specifically adenoma detection rates and cecal intubation rates.

Research frontiers
Although previous investigators have studied the effect of sedation on colonoscopy quality metrics, there are several important distinctions in this study. One of the strengths of this study is that we specifically compare propofol for deep sedation to opioid/benzodiazepine combination for moderate sedation which is reflective of clinical practice. This study inclusion criteria allowed us to identify average risk patients undergoing first-time screening colonoscopy, a homogenous group to evaluate adenoma detection rate.

Applications
Physicians using anesthesia services for propofol administration during elective screening colonoscopy should not have the expectation that this will improve the quality of their exam. Deep sedation with propofol did not affect adenoma detection rate in this retrospective study.

Peer-review
This is a retrospective study looking at a single institution's experience with colonoscopy using deep sedation with propofol or moderate sedation, and its impact on adenoma detection rate and other colonoscopy metrics such as completion rate, insertion time, and withdrawal time.

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ORIGINAL ARTICLE

Retrospective Study

Endoscopic balloon catheter dilatation *via* retrograde or static technique is safe and effective for cricopharyngeal dysfunction

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Abstract

AIM
To evaluate the safety and efficacy of upper esophageal sphincter (UES) dilatation for cricopharyngeal (CP) dysfunction. To determine if: (1) indication for dilatation; or (2) technique of dilatation correlated with symptom improvement.

METHODS
All balloon dilatations performed at our institution from over a 3-year period were retrospectively analyzed for demographics, indication and dilatation site. All dilatations involving the UES underwent further review to determine efficacy, complications, and factors that predict success. Dilatation technique was separated

into static (stationary balloon distention) and retrograde (brusque pull-back of a fully distended balloon across the UES).

RESULTS

Four hundred and eighty-eight dilatations were reviewed. Thirty-one patients were identified who underwent UES dilatation. Median age was 63 years (range 27-81) and 55% of patients were male. Indications included dysphagia (28 patients), globus sensation with evidence of UES dysfunction (2 patients) and obstruction to echocardiography probe with cricopharyngeal (CP) bar (1 patient). There was evidence of concurrent oropharyngeal dysfunction in 16 patients (52%) and a small Zenker's diverticula ($\leq$ 2 cm) in 7 patients (23%). Dilator size ranged from 15 mm to 20 mm. Of the 31 patients, 11 had dilatation of other esophageal segments concurrently with UES dilatation and 20 had UES dilatation alone. Follow-up was available for 24 patients for a median of 2.5 mo (interquartile range 1-10 mo), of whom 19 reported symptomatic improvement (79%). For patients undergoing UES dilatation alone, follow-up was available for 15 patients, 12 of whom reported improvement (80%). Nineteen patients underwent retrograde dilatation (84% response) while 5 patients had static dilatation (60% response); however, there was no significant difference in symptom improvement between the techniques (P = 0.5). Successful symptom resolution was also not significantly affected by dilator size, oropharyngeal dysfunction, Zenker's diverticulum, age or gender (P > 0.05). The only complication noted was uvular edema and a shallow ulcer after static dilatation in one patient, which resolved spontaneously and did not require hospital admission.

CONCLUSION

UES dilatation with a through-the-scope balloon by either static or retrograde technique is safe and effective for the treatment of dysphagia due to CP dysfunction. To our knowledge, this is the first study evaluating retrograde balloon dilatation of the UES.

Key words: Cricopharygeal dysfunction; Cricopharyngeal bar; Dysphagia; Esophageal dilatation; Endoscopic balloon dilation

Core tip: Cricopharyngeal dysphagia can be treated with endoscopic balloon dilatation. In this series, a novel dilatation technique of pulling a fully inflated 15-20 mm balloon dilator in a retrograde manner across the upper esophageal sphincter was safe and effective for the treatment of cricopharyngeal dysphagia.

INTRODUCTION

The upper esophageal sphincter, comprised of the cricopharyngeus, or the cricopharyngeal (CP) muscle, inferior pharyngeal constrictor, and proximal cervical esophagus serves a pivotal role in the act of deglutition. The CP muscle normally remains in a contracted state and relaxes during swallowing prior to penetration of a food bolus into the cricopharyngeal region. Cricopharyngeal dysfunction (CPD) refers to incoordination of the cricophyngeal muscle either due to a primary functional disorder or as a result of an underlying neurological or medical condition[1]. Symptoms of CPD can range from a globus sensation to oropharyngeal dysphagia manifested by regurgitation, coughing, choking and recurrent aspiration.

The diagnosis of CPD can be difficult to make and often requires a meticulous history and physical examination. Videofluoroscopy is often helpful for the diagnosis of CPD with the typical appearance of a shelf in the posterior column of barium at the level of the cricoid cartilage, more commonly described as a cricopharyngeal bar[2]. The incidence of CP bars is variable in the reported literature, ranging from 5% to 22% in patients who undergo videofluoroscopic swallow studies for dysphagia[2-4]. CP bars are frequently detected in asymptomatic individuals and therefore other modalities such as esophageal manometry and upper endoscopy must be performed to exclude other etiologies of dysphagia.

Endoscopic treatment for CPD has not been well studied and remains controversial. Historically, management has relied upon surgical CP myotomy[5-7]. Endoscopic dilatation poses an attractive option, given the risks associated with myotomy; however, published case series to date have included very small numbers of patients with varying dilatation techniques[8-13]. The aim of our study was to determine the efficacy and safety of through-the-scope (TTS) balloon dilatation of the upper esophageal sphincter (UES) in patients with CPD and to compare the traditional static technique of sequential distention of the balloon with a brusque "pull-back" retrograde approach across the UES.

MATERIALS AND METHODS

The study was approved by the Johns Hopkins Medicine institutional review board. The medical records of all patients that underwent esophageal dilatation with a through-the-scope balloon dilator at the Johns Hopkins Hospital over a consecutive 3-year period were reviewed. Patients were included in the study cohort if they had CPD that was treated with TTS balloon dilatation of the UES, including those with a Zenker's diverticulum. Patients were excluded if they were under the age of 18 years old and if balloon dilatation of the UES was not performed. Patient demographics, prior radiographic data, procedural indications, test results, complications and follow-up clinical outcomes were recorded.

Data was analyzed using Stata version 9 (StataCorp,

Table 1 Patient demographics *n* (%)	
Patients undergoing UES dilation	*n* = 31
Age, yr, median (range)	63 (27-81)
Sex	
Male	17 (55)
Female	14 (45)
Indications	
Radiographic CP hypertrophy with dysphagia	22 (71)
Endoscopic UES tightness with dysphagia	3 (10)
Inclusion body myositis with dysphagia and prominent cricopharyngeus	3 (10)
Globus sensation with evidence of UES dysfunction	2 (6)
Obstruction to echocardiography probe with CP bar, but otherwise asymptomatic	1 (3)
Presence of oropharyngeal dysfunction	16 (52)
Presence of Zenker's diverticulum	7 (23)

UES: Upper esophageal sphincter; CP: Cricopharyngeal.

Table 2 Balloon dilatation procedural details *n* (%)	
	Enrolled (*n* = 31)
Number of procedures per patient, median (range)	1 (1-3)
Type of initial dilatation	
Retrograde (brusque pull-back)	24 (77)
Static (sequential distention)	7 (23)
UES dilatation alone	20 (65)
Concurrent dilatation of the UES and other portions of the esophagus	11 (35)
Maximal diameter size, median (range)	20 mm (15-20 mm)
Total Number of complications	1 (3)
Serious complications requiring hospitalization	0

UES: Upper esophageal sphincter.

College Station, TX) on a per-patient basis. Descriptive statistics were calculated for all covariates and outcomes including *t* test, χ^2 test, and Fisher's exact test, where appropriate.

Procedural technique

Balloon dilatation of the upper esophageal sphincter was performed using two different techniques: Static and retrograde. With the traditional "static" technique, a through-the scope balloon dilation catheter (Boston Scientific Corporation, Natick, MA) is positioned across the upper esophageal sphincter under visual guidance without the use of a guidewire or fluoroscopy. The balloon is then sequentially inflated, holding the balloon in position for 30 to 60 s with each distention to a maximum diameter of 15 mm to 20 mm at the discretion of the endoscopist.

The retrograde approach across the UES is a newly described technique for the management of CPD. The actual technique has been used for mucosal disruption and treatment of esophageal rings, but has not been described in the management of CPD[14]. In this approach, the TTS balloon is inflated to the maximal desired diameter under visual guidance in the proximal esophagus, distal to the UES. The fully distended balloon is then brought back to the tip of the endoscope. Both the endoscope and distended balloon are then withdrawn across the UES into the oropharynx as one unit, usually with moderate resistance.

In all cases, individuals were sedated for the procedure. After dilatation was performed, the UES and the surrounding structures were closely inspected for evidence of mucosal damage.

RESULTS

Over a consecutive three-year period 488 esophageal TTS balloon dilatations were performed at our institution, of which 31 patients had dilatation of the UES for CPD. The median age at time of UES dilatation was 63 years and 55% of the patients were male (Table 1). Indications for UES dilatation are summarized in Table 1. Twenty-eight patients (90%) were experiencing dysphagia symptoms. In addition to CPD, 16 patients (52%) had evidence of concurrent oropharyngeal dysfunction and 7 patients (23%) were also found to have a Zenker's diverticulum.

Each individual underwent a median of 1 dilatation (range, 1-3), with 24 individuals (77%) receiving a retrograde approach (Table 2). The majority of individuals (26) underwent only 1 dilatation session. Four individuals underwent two dilatation sessions and one patient had three dilatation sessions. Eleven individuals had dilatation of other esophageal segments concurrently with UES dilatation and 20 patients had UES dilatation alone. Of those with multiple sites of esophageal dilatation, nine were for a Schatzki ring, one was for a peptic stricture and one was for subjective stenosis at the esophagogastric junction. The median maximal diameter for UES balloon dilatation was 20 mm, ranging from 15 to 20 mm. Three individuals were dilated with a 15 mm balloon, nine individuals were dilated with an 18 mm balloon, and nineteen individuals were dilated with a 20 mm balloon.

Follow-up was available for 24 of the 31 patients, 19 of whom underwent retrograde brusque technique. The median duration of follow-up was 2.5 mo (interquartile range: 1-10 mo), of whom 19 (79%) reported symptomatic improvement. Sixteen patients (84%) patients with the retrograde approach responded to dilatation, whereas 3 patients (60%) with the static dilatation approach responded to treatment. However, there was no statistically significant difference in symptom improvement between the two techniques ($P = 0.5$). Successful symptom resolution was also not significantly affected by dilator size, presence of oropharyngeal dysfunction, presence of a Zenker's diverticulum, age or gender (Table 3). Of those patients undergoing UES dilatation alone, follow-up was available for 15 patients, 12 of whom (80%) reported symptom improvement.

One patient developed uvular edema and a shallow ulcer after static dilatation of the UES that spontaneously resolved in the recovery room and did not require hospitalization. A second patient initially underwent dilatation of the GE junction that resulted in a

Characteristic	Clinical response		*P* value
	Y (19)	N (5)	
Age, mean ± SD	61.9 ± 11.9	66.4 ± 22.4	0.48
Sex, Male	10 (53)	2 (40)	0.68
Technique			
Retrograde	16	3	0.49
Static	3	2	
Maximal dilator size	19.2 ± 1.4	19.6 ± 0.9	0.25
(mean ± SD, mm)			
Oropharyngeal dysfunction	11 (58)	2 (40)	0.68
Zenker's diverticulum	4 (21)	2 (40)	0.45

Table 3 Predictors of clinical response *n* (%)

small mucosal tear that was adequately treated with placement of a single endoclip. During the same endoscopy, subsequent to endoclip placement, the patient underwent retrograde dilatation of the UES without complication. There were no adverse events associated with the retrograde brusque technique of the UES.

DISCUSSION

Oropharyngeal dysphagia can be associated with significant morbidity and treatments to date are imperfect and limited. Since first used for treatment of post-poliomyelitis dysphagia in 1951[15], surgical myotomy has been the traditional approach for dysphagia related to cricopharyngeal prominence or dysfunction[16-18]. However, efficacy remains controversial and this procedure is not without risk - particularly in elderly patients in whom cricopharyngeal bars are more common[18-20]. Botulinum toxin injection has also been studied as a potential therapy and has been shown to be of benefit in several series[21-23]. Reported complications have stemmed from diffusion of Botox to adjacent muscles leading to aspiration, worsened dysphagia, vocal cord paralysis and at least one recorded death[24-26]. Moreover, the average duration of effect appears to be approximately 4 mo and waning efficacy may be observed with repeated therapy[25].

Endoscopic dilatation of the upper esophageal sphincter poses an attractive therapeutic alternative for dysphagia related to CPD. Data, however, is limited to small case series - most of which contained less than 10 patients. The published data suggest that endoscopic dilatation may be a safe and effective option for carefully selected patients. A small series reported clinical improvement in 7 of 12 patients (58%) after dilatation with a Savary dilator (17 mm)[8]. Another limited series reported higher rates of symptomatic improvement in 9 of 10 patients (90%) with similar dilatation techniques (18-20 mm)[9]. Patel *et al*[13] recently reported a larger experience with 31 patients undergoing Savary dilation with 45 French to 60 French size dilators. In this study, 65% of patients had significant improvement for at least 6 mo using a functional outcome swallow score.

One study of 5 patients undergoing static balloon dilation of the UES to a maximal diameter of 20 mm achieved 100% success rate[10]. Another study reported complete success in 6 patients undergoing dilatation of CP bars, but this study only included one patient with balloon dilation to 20 mm and the five others underwent Savary dilation[12]. In these series and reports, there have been no recorded major complications. There has been one report of superficial mucosal injury after dilatation that was self-limited and did not require treatment or hospitalization[10]. The recent systematic review on management of CPD reported comparable success rates of endoscopic dilation and myotomy; however, the authors comment that there were significantly fewer studies investigating endoscopic dilatation (6 studies involving 113 patients) and therefore the data were insufficient to make a strong recommendation on the role of endoscopic dilatation for CPD[1].

Our series represents the largest published series to date looking at endoscopic balloon dilatation of the upper esophageal sphincter for dysphagia related to CPD. When compared to reported success rates for cricopharyngeal myotomy[18,20], the results for endoscopic dilatation appear equivalent. Moreover, the safety profile of this approach appears to be excellent. In our series, the only reported complication was uvular edema and a shallow ulcer after balloon dilatation using a static technique in 1 patient that did not require admission and spontaneously improved over time. To our knowledge, there have been no perforations reported in the literature with this approach and certainly no fatalities.

At our institution, the preference has been to utilize endoscopic balloon dilatation via either a static or retrograde technique for CPD. The idea behind the static approach is to maximize radial forces while avoiding any sheering movements, whereas the concept for the retrograde approach is to combine radial and sheering forces with directed attention to the upper esophageal sphincter. As opposed to a Savary dilatation, the retrograde balloon technique may allow a more rapid increase in diameter and, with experience, a better subjective gauge of sphincter resistance. To our knowledge, this technique has not been previously reported in the literature for the management of CPD but has been used frequently at our institution for disruption of Schatzki rings, mucosal webs and upper esophageal sphincter dysfunction. While the safety of this approach has not been directly compared to conventional static dilatation, it has been our subjective opinion that the safety of these two approaches is equivalent. The one patient who developed a shallow ulcer in our series did so in the context of a static dilatation.

Traditionally, the presence of a Zenker's diverticulum has often been felt to represent a relative contraindication to endoscopic dilatation; however, mechanistically, these diverticula often arise in the context of elevated intrabolus pressure and/or upper esophageal sphincter dysfunction and for this reason may actually portend a better prognosis[27]. Certainly in our series, response rates seemed equivalent between patients with and without a diverticulum and there did not appear to be any safety concerns. Likewise, oropharyngeal

dysfunction has been hypothesized to be a potential issue that may limit efficacy. However, this group may actually be more sensitive to minor mechanical alterations in outflow resistance and the presence of oropharyngeal dysfunction in our series did not affect or predict response.

Our study does have several limitations worth noting. To begin with, it is a retrospective evaluation and clinical response was determined subjectively through review of medical records. A prospective study with validated dysphagia questionnaires would have been ideal and this certainly is worth future consideration. Second, 11 of our patients had dilatation of other esophageal segments other than the upper esophageal sphincter and it is unclear if the symptom response was due to dilatation of the cricopharyngeus or the other segment of the esophagus. However, even without including these patients, this remains the largest published experience with endoscopic balloon dilatation for CPD. Third, the indications for dilatation in our series were heterogeneous and it is possible (and indeed likely) that certain subsets have significantly varied responses. For example, it is our subjective opinion that patients with inclusion body myositis likely have a greater response to dilatation; however, given the total number of patients in our study there is no way to statistically address that question. Finally, our median follow-up was 2.5 mo and given the underlying mechanisms of upper esophageal sphincter dysfunction a longer evaluation period would have been ideal.

In summary, UES dilatation with a TTS balloon by either static or retrograde technique is safe and effective for the treatment of dysphagia in the context of CP dysfunction. As suggested in prior smaller series, this appears to be a safe and effective approach. Our series, however, is the first to describe retrograde balloon dilatation of the UES. Given this data is tandem with the reported complications of surgical myotomy and Botulinum toxin injection, we suggest that endoscopic dilatation of the upper esophageal sphincter should be the first therapy offered for patients with oropharyngeal dysphagia in the context of upper esophageal sphincter dysfunction. In addition, our experience would suggest that balloon dilatation *via* a retrograde technique is at least as safe and effective as conventional methods with either Savary or static balloon dilatation.

COMMENTS

Background
Cricopharyngeal dysfunction (CPD) is associated with a variety of symptoms including globus sensation, oropharyngeal dysphagia, regurgitation, coughing, choking and recurrent aspiration. While a variety of treatment options have been proposed, endoscopic dilatation by pulling a fully inflated 15-20 mm balloon dilator in a retrograde manner across the upper esophageal sphincter appears to be safe and effective for the treatment of cricopharyngeal dysphagia.

Research frontiers
Optimal management of cricopharyngeal dysphagia is not clear. Endoscopic dilatation appears to be safe with immediate relief of symptoms. Several small series have demonstrated benefit with endoscopic dilatation using a variety of techniques. Additional research into the durability of the procedure and objective parameters of relief are needed.

Innovations and breakthroughs
This represents the largest endoscopic experience for managing CPD. In this series, a novel dilatation technique of pulling a fully inflated 15-20 mm balloon dilator in a retrograde manner across the upper esophageal sphincter was safe and effective for the treatment of cricopharyngeal dysphagia.

Applications
The retrograde dilatation technique provides another method for effective dilatation and disruption of the upper esophageal sphincter complex to relieve symptoms associated with cricopharyngeal dysphagia. Many endoscopists are more comfortable with balloon dilatation and this technique may allow them to better treat CPD using this technique.

Terminology
CPD - refers to incoordination of the cricophyngeal muscle either due to a primary functional disorder or as a result of an underlying neurological or medical condition.

Peer-review
This is a study assessing the efficacy of endoscopic balloon catheter dilatation for treatment of criocopharyngeal dysfunction. The authors retrospectively reviewed all UES dilatations performed during a three year period. Thirty-one patients were included although follow-up was only available for 24. A symptomatic improvement was confirmed for 80% of patients. The manuscript is well written and describes a large series of cases.

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Retrospective Study

Analysis of the risk factors for severity in post endoscopic retrograde cholangiopancreatography pancreatitis: The indication of prophylactic treatments

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Abstract

AIM

To determine the risk factors of severe post endoscopic retrograde cholangiopancreatography pancreatitis (sPEP) and clarify the indication of prophylactic treatments.

METHODS

At our hospital, endoscopic retrograde cholangiopancreatography (ERCP) was performed on 1507 patients from May 2012 to December 2015. Of these patients, we enrolled all 121 patients that were diagnosed with post endoscopic retrograde PEP. Fourteen of 121 patients diagnosed as sPEP were analyzed.

RESULTS

Forty-one patients had contrast media remaining in the pancreatic duct after completion of ERCP. Seventy-

one patients had abdominal pain within three hours after ERCP. These were significant differences for sPEP ($P < 0.05$). The median of Body mass index, the median time for ERCP, the median serum amylase level of the next day, past histories including drinking and smoking, past history of pancreatitis, sphincter of Oddi dysfunction, whether emergency or not, expertise of ERCP procedure, diverticulum nearby Vater papilla, whether there was sphincterotomy or papillary balloon dilation, pancreatic duct cannulation, use of intra-ductal ultrasonography enforcement, and transpapillary biopsies had no significant differences with sPEP.

CONCLUSION
Contrast media remaining in the pancreatic duct and the appearance of abdominal pain within three hours after ERCP were risk factors of sPEP.

Key words: Pancreatic duct stent; Post endoscopic retrograde cholangiopancreatography pancreatitis; Prophylactic treatment; Risk factor; Severe acute pancreatitis

Core tip: Post endoscopic retrograde cholangiopan-creatography pancreatitis (PEP) is a typical endoscopy-related accident in the biliopancreatic field. Since PEP is a predictable pathology, and if discovered and appropriately treated early many patients rapidly recover. However, some cases aggravate to a severe state and become fatal. Therefore, it is important to identify factors leading PEP to a severe state. In our study, significant differences were noted in residual enhancement of the pancreatic duct and development of abdominal pain showing that these were independent risk factors of severe PEP. The presence of these findings is an indication of therapeutic intervention for severe PEP.

INTRODUCTION

Post endoscopic retrograde cholangiopancreatography pancreatitis (PEP) is a typical endoscopy-related accident in the biliopancreatic field, and there are many reports on its risk factors[1-4]. Many researchers reported methods to prevent PEP[5-17]. However, treat-ment to prevent PEP in all endoscopic retrograde cholangiopancreatography (ERCP) patients is not recommended in consideration of accidents caused by the addition of preventive techniques, adverse reactions of preventive drug administration, and cost[13]. Since PEP is a predictable pathology, and if discovered and appropriately treated early many patients rapidly recover. However, some cases aggravate to a severe state and become fatal. Therefore, it is important to identify factors leading PEP to a severe state, and when such risk factors are observed, therapeutic intervention, such as the addition of preventive techniques and preventive drug administration, should be performed. The objective of this study was to retrospectively clarify risk factors aggravating PEP to a severe state and determine the indications to prevent and treat PEP.

MATERIALS AND METHODS

Patients
Between May 2012 and October 2015, 1507 patients were examined by ERCP at our hospital. PEP was diagnosed in 121 of them (8.02%), and 14 of them were diagnosed with severe PEP (sPEP) and analyzed. Patients accompanied by acute pancreatitis at the time of undergoing ERCP were excluded (Figure 1). The study was performed in conformity with the Declaration of Helsinki and registered at UMIN-CTR (000022086).

ERCP procedure
For ERCP, a side-view duodenoscope was used. The endoscope used was JF260V (Olympus Medical, Tokyo, Japan). For the cannula, for contrast medium, a 0.035-inch V system (Olympus Medical, Tokyo, Japan) was used. For the guide wire, Jagwire (0.035inch; Boston scientific Corporation, Tokyo, Japan) or Visigride (0.025 inch; Olympus Medical, Tokyo, Japan) was used. Replacement fluid (2000 mL) was intravenously administered within 24 h before and after ERCP. Patients received protease inhibitor (nafamostat mesilate, 20 mg/d) and prophylactic antibiotic administration (sulbactam/cefoperazone, 2 g/d) for 2 d. Vitals were checked 3 h after completion of ERCP. For patients in whom abdominal pain developed before this, 25 or 50 mg of indomethacin suppositories were administered. When PEP was diagnosed, sufficient fluid replacement including protease inhibitor and antibiotics was continued so as to maintain the urinary volume at 1 mL/min under monitoring of circulatory dynamics.

Diagnoses and grading of PEP
PEP was diagnosed following the Cotton's criteria[16]: When abdominal pain developed on the day following ERCP and the serum amylase level was 3 times or higher than the normal upper limit, the patient was diagnosed with PEP. sPEP was defined as PEP with 10 d or longer prolongation of inpatient treatment, hemorrhagic pancreatitis, phlegmon, and pseudocyst.

Risk factors for sPEP
Clinical data of PEP patients were retrospectively

Figure 1 Patients' flow chart. ERCP: Endoscopic retrograde cholangiopancreatography; PEP: Post endoscopic retrograde cholangiopancreatography pancreatitis.

extracted from their clinical records. As sPEP risk factors, age, gender, Body mass index (BMI), past medial history including cigarette smoking and alcohol drinking and acute pancreatitis, the presence or absence of the sphincter of Oddi dysfunction (SOD), diverticulum nearby Vater papilla and common bile duct (CBD) diameter of patient with CBD stones, whether or not it was emergency ERCP, whether or not EST or EPBD was performed, pancreatography, the presence or absence of residual contrast medium in the pancreatic duct after completion of ERCP, the use of IDUS and transpapillary biopsy, treatment time, experience of operators, development of abdominal pain within 3 h after completion of ERCP, and serum amylase level, white blood cell count, and C-reactive protein on the day following ERCP were surveyed (Tables 1 and 2). The time from insertion to removal of a scope was defined as the ERCP treatment time. Experience of operators was defined based on the total and recent numbers of ERCP performed. Operators with a total number of ERCP performed of 200 or fewer and/or a recent number of ERCP performed of 40 or fewer per year were regarded as non-expert. Unfortunately, no study has examined role of sphincterotomy and number of pancreatic cannulation except our following conference paper.

Statistical analysis

In the univariate analysis, the difference between the two groups of categorical parameters were analyzed using Pearson's χ^2 test. The Kruskal-Wallis test was used for continuous parameters. The stepwise logistic regression model (forward selection) was used to calculate the odds ratio (OR) with 95%CI. Significant predictors in the univariate analysis were then included in a forward stepwise multiple logistic regression model. All tests were two-sided and P values of < 0.05 were considered significant. Analyses were performed using IBM SPSS statistical software (version 21; SPSS Japan Inc., Tokyo, Japan).

Table 1 Characterization of patients with post endoscopic retrograde cholangiopancreatography pancreatitis		
Variables	**Mild-moderate PEP**	**Severe PEP**
Age (yr) ($n = 121$)		
Median	73.7	76.5
(range)	(18-93)	(32-88)
Gender ($n = 121$)		
Male/female	57/50	7/7
BMI (kg/m^2) ($n = 121$)		
Median	21.6	23.2
(range)	(13.97-35.20)	(14.79-29.5)
Smoking status ($n = 121$)		
Non-smoker/Ex- or current smoker	83/24	7/7
Drinking status ($n = 121$)		
Absent/present	67/40	12/2
Past history ($n = 121$)		
Absent/present	31/76	4/10
Malignant disease ($n = 121$)		
Absent/present	84/23	10/4
History of pancreatitis ($n = 121$)		
Absent/present	106/1	1/13
SOD ($n = 121$)		
Absent/present	101/6	1/13
Diverticulum nearby vater papilla ($n = 121$)		
Absent/present	70/37	11/3
CBD diameter of patient with CBD stones ($n = 41$)		
$\geqslant$ 10 mm/< 10 mm	21/16	2/2

PEP: Post endoscopic retrograde cholangiopancreatography pancreatitis; BMI: Body mass index; SOD: Sphincter of Oddi dysfunction; CBD: Common bile duct.

RESULTS

Patient characteristics in the PEP

The median age of the 121 PEP patients was 76 (18-91) years old, and there were 64 male (52.9%) and 57 female (47.1%) patients. The median BMI was 21.2 (14.0-35.2) kg/m^2. Thirty-one and 42 patients were cigarette smokers and habitual alcohol drinkers, respectively. The past medical history was heart disease in 21 patients, diabetes in 24, chronic kidney disease in 41, malignant disease in 27, and acute pancreatitis in 2. SOD was suspected in 7. Diverticulum nearby Vater papilla was noted in 40. Forty-one patients had CBD stones (Table 3).

Clinical data and ERCP intervention in the PEP

ERCP was performed urgently in 17 patients. EST and EPBD were performed in 31 and 14 patients, respectively. Pancreatography was performed in 74 patients, and residual enhancement of the pancreatic duct was noted at completion of ERCP in 41 patients. IDUS and transpalillary biopsy were performed in 26 and 35 patients, respectively. The median treatment time was 50 (12-170) min. Experts and non-experts performed ERCP in 50 and 71 patients, respectively. Abdominal pain developed within 3 h after completion of ERCP in 71 patients. The median serum amylase level, WBC count, and serum CRP on the day following ERCP

Table 2 Clinical data and endoscopic retrograde cholangiopancreatography intervention of patients with post endoscopic retrograde cholangiopancreatography pancreatitis

Variables	Mild-moderate PEP (n = 107)	Severe PEP (n = 14)
ERCP procedure		
Not emergency/emergency	91/16	13/1
EST	29	2
EPBD	12	2
Pancreatography		
No/yes	38/69	9/5
Contrast media remained in the pancreatic duct		
No/yes	75/32	5/9
IDUS		
No/yes	86/21	9/5
Transpapillary biopsies		
No/yes	76/31	10/4
Time for ERCP procedure (min)		
Median	50	56
(range)	(12-170)	(26-150)
Expertise of ERCP procedure		
Not expert/expert	62/45	9/5
Abdominal pain within three hours after ERCP		
No/yes	49/58	1/13
Serum amylase level of the next day (IU/mL)		
Median	1001	1543
(range)	(83-3604)	(258-2969)
White blood cell of the next day (/μL)		
median	8040	8790
(range)	(3240-26320)	(6270-13410)
C-reactive protein of the next day (mg/dL)		
Median	2.08	3.1
(range)	(0.04-32.55)	(0.20-38.31)

ERCP: Endoscopic retrograde cholangiopancreatography; PEP: Post endoscopic retrograde cholangiopancreatography pancreatitis; EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; IDUS: Intraductal ultrasonography.

were 1065 (83-3604) IU/mL, 8050 (3240-26320)/μL, and 2.1 (0.04-38.31) mg/dL, respectively (Table 4). No patients died during the study.

Risk factors of sPEP

On univariate analysis, residual enhancement of the pancreatic duct at completion of ERCP and development of abdominal pain within 3 h after completion of ERCP were significant risk factors of sPEP (Tables 3 and 4). On multivariate analysis, significant differences were noted in residual enhancement of the pancreatic duct (OR = 4.254, 95%CI: 1.238-14.616) and development of abdominal pain (OR = 11.881, 95%CI: 1.400-100.784), showing that these were independent risk factors of sPEP (Table 5).

DISCUSSION

It has been reported that the incidence of PEP in all patients examined by ERCP was about 3.5%, and

PEP aggravated to a severe state (sPEP) in 0.4%[17]. Therefore, the indication of ERCP should be carefully judged. It has become possible to refrain from performing diagnostic ERCP as low-invasive examination techniques, such as MDCT, MRI, and EUS, have improved. However, ERCP is still essential as a therapeutic measure to diagnose the advancement of biliary tract malignancy and obstructive disease of the pacreaticobiliary duct, and ERCP has to be inevitably performed although there is a risk of causing PEP. There are many previous reports on risk factors of PEP, but risk factors of sPEP are unclear. Generally admitted risk factors of PEP include female gender, pancreatic sphincterotomy, difficulty in cannulation, 3 times or more applications of ERP, ERP reaching the tail of the pancreas even if it was performed once, excess contrast pressure, contrast imaging of the pancreatic acinus, brushing pancreatic juice cytology, and SOD[1-4]. These were risk factors of PEP, but not risk factors of sPEP in our study.

In our study, the residual contrast medium in the pancreatic duct at completion of ERCP was an independent risk factor of sPEP, suggesting that reduction of intraductal pressure of the pancreas at completion of ERCP may prevent sPEP, which may lead to a method to effectively avoid sPEP. Akashi *et al*[5] compared groups with and without the addition of EST and observed that the incidence of sPEP was lower in the group with EST. They hypothesized that reduction of intraductal pressure of the pancreas by the addition of EST reduced the incidence of sPEP. However, EST may accidentally perforate the digestive tract and it is contraindicated for patients treated with oral antithrombin. Thus, not all patients should be treated with EST. On the other hand, Nakahara *et al*[6] reported that when the pancreatic duct guide wire method is employed for a patient with difficult bile duct cannulation, pancreatic duct stenting should be performed even though EST was added. In addition, Ito *et al*[7] reported that preventive pancreatic duct stenting contributes to reducing the incidence of PEP, excluding IPMN patients not accompanied by pancreatic duct dilatation in the pancreatic head. The European Society of Gastrointestinal Endoscopy Guideline[18] and the American Society for Gastrointestinal Endoscopy Guideline[19] recommend pancreatic duct stenting in patients with a risk factor, and Sofuni *et al*[8] reported that the use of a spontaneous dislodgment pancreatic duct stent prevented PEP regardless of the presence or absence of a risk factor. However, the frequency of cannulation for stenting increases as a problem with preventive pancreatic duct stenting. We also consider that pancreatic duct stenting reported by many researchers[6-12,15], is an effective method to prevent PEP including sPEP, but no patients with pancreatic duct stenting were included in our study. The appropriate conditions for pancreatic duct stenting in ERCP patients have not been established, but, based on the results of our study, conduct of a large-scale clinical study on the addition of preventive EST and pancreatic duct

Table 3 Univariate analyses of characterization for severe post-endoscopic retrograde cholangiopancreatography pancreatitis

Variables	No. of patients	Median of patients (range)	Univariate analysis *P* value
Age (yr) (*n* = 121)		76 (18-91)	0.874
Gender (*n* = 121)			0.818
Male/female	64/57		
BMI (kg/m²) (*n* = 121)		21.2 (14.0-35.2)	0.379
Smoking status (*n* = 121)			0.201
Non-smoker/Ex- or current smoker	90/31		
Drinking status (*n* = 121)			0.302
Absent/present	79/42		
Past history (*n* = 121)			0.967
Absent/present	35/86		
Malignant disease (*n* = 121)			0.550
Absent/present	94/27		
History of pancreatitis (*n* = 121)			0.606
Absent/present	119/7		
SOD (*n* = 121)			0.644
Absent/present	114/7		
Diverticulum nearby vater papilla (*n* = 121)			0.325
Absent/present	81/40		
CBD diameter of patient with CBD stones (*n* = 41)			0.796
≥ 10 mm/< 10 mm	23/18		

BMI: Body mass index; SOD: Sphincter of Oddi dysfunction; CBD: Common bile duct.

Table 4 Univariate analyses of clinical data and endoscopic retrograde cholangiopancreatography intervention for post-endoscopic retrograde cholangiopancreatography pancreatitis

Variables	No. of patients (*n* = 121)	Median of patients (range)	Univariate analysis *P* value
ERCP procedure			0.429
Not emergency/emergency	104/17		
EST	31		0.302
EPBD	14		0.736
Pancreatography			0.798
No/yes	47/74		
Contrast media remained in the pancreatic duct			0.011
No/yes	80/41		
IDUS			0.168
No/yes	95/26		
Transpapillary biopsies			0.975
No/yes	86/35		
Time for ERCP procedure (min)		50 (12-170)	0.343
Expertise of ERCP procedure			0.65
Not expert/expert	71/50		
Abdominal pain within three hours after ERCP			0.006
No/yes	50/51		
Serum amylase level of the next day (IU/mL)		1065 (83-3604)	0.184
White blood cell of the next day (/μL)		8050 (3240-26320)	0.668
C-reactive protein of the next day (mg/dL)		2.1 (0.04-38.31)	0.601

ERCP: Endoscopic retrograde cholangiopancreatography; EST: Endoscopic Sphincterotomy; EPBD: Endoscopic papillary balloon dilation; IDUS: Intraductal ultrasonography.

Table 5 Multivariate analyses of risk factors for severe post-Endoscopic retrograde cholangiopancreatography pancreatitis

Variables	Multivariate analysis	
	Odds ratio (95%CI)	*P* value
Contrast media remained in the pancreatic duct		
No	1	
Yes	4.254 (1.238-14.616)	0.021
Abdominal pain within three hours after ERCP		
No	1	
Yes	11.881 (1.400-100.784)	0.023

ERCP: Endoscopic retrograde cholangiopancreatography.

stenting in patients with residual contrast medium in the pancreatic duct at completion of ERCP is expected.

In addition, development of abdominal pain within 3 h after completion of ERCP was a strong risk factor of sPEP. In our facility, cannulation is intended to be followed by 25-50 mg dose of rectal indomethacin only when abdominal pain exceeded restraining pain. Elmunzer *et al*[14] reported that rectal indomethacin significantly reduced the incidence of PEP in patients with a PEP risk factor. On the other hand, Levenick *et al*[13] reported that the preventive rectal indomethacin does not always inhibit PEP in all ERCP-applied cases. They mentioned that the rectal indomethacin can prevent PEP only in patients with a risk factor of PEP, and its indication should be reconsidered. Moreover, 100 mg of indomethacin is excessive for Japanese with a relatively small physique, and not all ERCP cases are treated with rectal indomethacin at our facility. Furthermore, this treatment inhibited some cases of PEP, but it did not prevent the progression to sPEP in our study. This might have been due to differences in the indication of the rectal indomethacin.

There are several limitations in this study. No diagnosis by exclusion based on the indication and intervention was established. Since it was a retrospective study performed at a single institution, the sample size was small. However, risk factors of sPEP were clarified and these may contribute to demonstrate appropriate conditions and methods to prevent sPEP. As discussed with many PEP-inhibitory methods, the addition of preventive techniques, such as EST and pancreatic duct stenting, and preventive drug administration, such as rectal indomethacin, should be performed after clarifying risk factors of sPEP.

Residual contrast medium in the pancreatic duct at completion of ERCP and development of abdominal pain within 3 h after completion of ERCP are risk factors of sPEP. The presence of these findings is an indication of therapeutic intervention for sPEP, and a method to avoid it should be considered.

COMMENTS

Background

Cholangiopancreatography pancreatitis (PEP) is an unavoidable endoscopic complication for pancreatobiliary systems. Since PEP is a predictable pathology, and if discovered and appropriately treated early many patients rapidly recover. However, some cases aggravate to a severe state and become fatal. Therefore, it is important to identify factors leading PEP to a severe state.

Research frontiers

There are many reports about risk factors of PEP; however, there are few reports to assess the risk factors of severe PEP (sPEP).

Innovations and breakthrough

Significant differences were noted in residual enhancement of the pancreatic duct and development of abdominal pain showing that these were independent risk factors of sPEP.

Applications

The presence of residual contrast medium in the pancreatic duct at completion of endoscopic retrograde cholangiopancreatography (ERCP) and development of abdominal pain within 3 h after completion of ERCP is an indication of therapeutic intervention for sPEP, and a method to avoid it should be considered.

Terminology

PEP is one of the major adverse events of ERCP. Some PEP aggravate to severe state as sPEP. sPEP sometimes results in the death, so that it has been the most concern still now.

Peer-review

This is a unique single center retrospective study with a significant number of patients investigating an important topic, the risk factors of severe PEP and clarify the indication of prophylactic treatments. The results have a clinical impact on detecting the patients in need for therapeutic intervention for preventing severe PEP; patients with residual contrast medium in the pancreatic duct at completion of ERCP and development of abdominal pain within 3 h after completion of ERCP. This is a well-written article; the manuscript is concise, clear, comprehensive, and convincing.

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ORIGINAL ARTICLE

Observational Study

Endoscopic assessment and management of sporadic duodenal adenomas: The results of single centre multidisciplinary management

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Abstract

AIM

To review the role of multidisciplinary management in treating sporadic duodenal adenomas (SDA).

METHODS

SDA managed at North Shore Hospital between 2009-2014 were entered into a prospective database. Pathology, endoscopic and surgical management as well as follow up were reviewed.

RESULTS

Twenty-eight patients (14 male: Median age 68 years) presented with SDA [18 were classified as non ampullary location (NA), 10 as ampullary location (A)]. All SDA were diagnosed on upper gastrointestinal endoscopy and were imaged with a contrast enhanced CT scan of the chest, abdomen and pelvis. Of the NA adenomas 14 were located in the second part, 2 in the first part and 2 in the third part of the duodenum. Two patients declined treatment, 3 patients underwent surgical resection (2 transduodenal resections and 1 pancreaticoduodenectomy), and 23 patients were treated with endoscopic mucosal resection (EMR). The only complication with endoscopic resection was mild pancreatitis post procedure. Patients were followed with gastroduodenoscopy for a median of 22 mo (range: 2-69 mo). There were 8 recurrences treated with EMR with one

patient proceeding to pancreaticodeuodenectomy because of high grade dysplasia in the resected specimen and 2 NA recurrences were managed with surgical resection (distal gastrectomy for a lesion in the first part of the duodenum and a transduodenal resection of a lesion in the third part of the duodenum).

CONCLUSION
SDA can be treated endoscopically with minimal morbidity and piecemeal resection results in eradication in nearly three quarters of patients. Recurrent SDA can be treated with endoscopic reresection with surgical resection indicated when the lesions are large (> 4 cm in diameter) or demonstrate severe dysplasia or invasive cancer.

Key words: Duodenal adenoma; Endoscopic resection; Surgical resection; Pancreaticoduodenectomy; Endoscopic surveillance; Dysplasia

Core tip: Sporadic duodenal adenomas can be treated endoscopically with minimal morbidity and even piecemeal resection results in eradication in nearly three quarters of patients. Optimal surveillance strategies include re-endoscopy 6 mo after the initial resection is a satisfactory starting point. Recurrent sporadic adenomas can be treated with endoscopic re-resection with surgical resection indicated when the lesions are large (> 3 cm in diameter) or demonstrate severe dysplasia or invasive cancer.

INTRODUCTION

Sporadic duodenal adenomas (SDA) are rare lesions with a prevalence of 0.3%-1.5%[1]. Due to this rarity, the natural history of SDA is not well understood although it is known to follow an adenoma to carcinoma sequence similar to colorectal cancer[2]. The reported rate of malignant transformation of SDA ranges from 25% to 85% and this provides a rationale for preventative intervention and surveillance[2-4]. The majority of sporadic adenomas are sessile and occur in the second part of the duodenum[5,6] and can be divided into those with an ampullary location (A) or non ampullary location (NA)[1,2].

Currently there is no consensus on the optimal management of SDA and, in particular, the choice of surgical or endoscopic resection remains controversial since surgical resection involves either local resection by the transduodenal approach or by pancreaticoduodenectomy with the risk of significant morbidity and mortality. In contrast endoscopic mucosal resection (EMR) was first described in 1992 and has become increasingly favoured as the first line treatment modality[6-8].

This investigation describes the multidisciplinary management strategy for SDA as used at a single unit and involves contributions from surgery, endoscopy and gastroenterology. The specific aims of this study were to: (1) define the role of EMR of SDA; (2) define the role of whole *vs* piece meal endoscopic resection; (3) define an optimal surveillance strategy following endoscopic resection; and (4) define the optimal treatment for recurrence SDA following endoscopic resection.

MATERIALS AND METHODS

Consecutive cases of duodenal adenoma diagnosed at North Shore Hospital (NSH) between 2009 and 2014 were reviewed. The pathology findings from all patients was entered into a prospective database. Demographic, diagnostic, biopsy, treatment and follow up information was then reviewed as well as details pertaining to local recurrence rate and salvage treatments.

This project was logged with the Awhina Research and Knowledge Centre at NSH and ethics approval was obtained from the Regional Ethics Committee.

RESULTS

Thirty-four patients were diagnosed with duodenal adenomas between 2009 and 2014 of which six patients were excluded because of an underlying diagnosis of familial adenomatous polyposis. Data from 28 patients was analysed for the investigation of whom 18 were classified as NA and 10 as A.

Demographics, presentation and investigation

A summary of patient demographics, polyp morphology and investigations utilized in the management of the reported patients with SDA are presented in Table 1. All patients were New Zealand European with no Maori or Pacific Island patients presenting with SDA. Five patients (50%) with ampullary lesions presented with adenoma specific symptoms (iron deficiency anaemia 3, obstructive jaundice 2), while five (28%) of the NA patients presented with iron deficiency anaemia. The remaining patients with ampullary lesions underwent investigation for non-specific abdominal pain or following an incidental finding on ERCP for choledocolithiasis. In patients with NA upper gastrointestinal endoscopy was also undertaken for non-specific pain (4 patients), peptic ulcer disease or reflux (4 patients), and one patient each for globus, dysphagia, incidental finding during ERCP and investigation of Crohn's disease and incidentally noted raised carcino-embryonic antigen. All SDA were diagnosed on upper gastrointestinal endoscopy and were biopsied (Table 1). All patients

Table 1 Summary of patient demographics, adenoma morphology and investigations utilized *n* (%)

	Non-ampullary (*n* = 18)	Ampullary (*n* = 10)
Demographics		
Median age, yr (range)	69 (47-88)	67 (48-80)
Male: female	9:9	5:5
Morphology		
Pedunculated	3 (17)	1 (10)
Sessile	15 (83)	9 (90)
Median size, mm (range)	15 (9-24)	20 (10-35)
Number ≥ 20 mm	7 (39)	6 (60)
Investigations		
Biopsy	7 (39)	8 (80)
EUS	3 (17)	0
ERCP	0	10 (100)

ERCP: Endoscopic retrograde cholangiopancreatography; EUS: Endoscopic ultrasound.

Table 2 Summary of treatment, biopsy and final pathology and recurrence

	Non-ampullary (*n* = 18)	Ampullary (*n* = 10)
Endoscopic treatment	15	8
Stenting		
Biliary	0	2
Pancreatic	0	5
Specimen removal		
Piecemeal	11	6
En bloc	4	2
Complications	0	1
Surgical resection	2	1
No treatment	1	1
Histology		
	1 no dysplasia	7 low grade dysplasia
	13 low grade dysplasia	1 high grade dysplasia
	3 high grade dysplasia	1 adenocarcinoma
Concordance with biopsy	4/7	7/8
Recurrence	5	5

were imaged with a contrast enhanced CT scan of the abdomen to define signs of invasion or metastases. Of the non-ampullary adenomas 14 were located in the second part of the duodenum, two in the first part and two in the third part of the duodenum. Endoscopic ultrasound (EUS) was used selectively to locoregionally stage lesions that were large, ulcerated or had high grade dysplasia on biopsy (5 of 8 ampullary adenomas and 8 of 15 non-ampullary adenomas). EUS permitted detailed assessment of lesional size and depth and location of further biopsy specimens[4,5,7].

Treatment

Patient management is summarised in Figure 1 and Table 2. All endoscopically treated patients had an EMR. All endoscopic procedures were undertaken in a specialist endoscopy suite with conscious sedation administered intravenously followed by recovery and same day discharge. Endoscopic resection was undertaken after submucosal injection of saline, epinephrine or methylene blue depending on the endoscopist's preference. The median number of endoresections per patient was 1 and was higher for ampullary (median 2.5) than non-ampullary adenomas (median 1). Endoscopic *en bloc* resection was aimed for in all cases but, due to the size of the lesions, 11 NA and 6 A underwent piecemeal resection (Table 2). The only complication of endoscopic resection was one episode of mild pancreatitis post-procedure which was self-limiting.

Once removed specimens were orientated and sent for pathological examination. Overall biopsies were concordant with final pathology in 4 of 7 NA and 7 of 8 A (Table 2).

Two non-ampullary adenomas underwent surgical resection: Two patients underwent transduodenal resection of lesions in the second and third parts of the duodenum and one patient with a large ampullary adenoma, was treated with a pancreaticoduodenectomy. In addition, two elderly patients declined any treatment.

Surveillance

All patients had follow up gastroscopies although five patients declined follow up and one patient had undergone a pancreaticoduodenectomy (*n* = 1). The average time taken for the first endoscopic surveillance post resection was 7.9 mo for NA and 5.9 mo for A. The median follow up period was 22 mo (range 2-69 mo).

Recurrence

Details on recurrence rate in the 20 cases actively followed up are presented in Table 3 in addition to salvage therapy employed. EMR was used to treat 8 recurrences. Endoscopic ultrasound was used in two ampullary recurrences to rule out transmural invasion. One of eight patients treated with endoscopic resection was shown to be a high grade dysplastic lesion and was subsequently treated with a pancreaticoduodenectomy (final pathology T_1N_0 adenocarcinoma). Two non-ampullary recurrences were managed with surgical resection (distal gastrectomy for a lesion in the first part of the duodenum and a transduodenal resection of a lesion in the third part of the duodenum).

DISCUSSION

This investigation was undertaken to review multidisciplinary management of SDA and confirms that the majority of SDA are not symptomatic and are found incidentally[6-9]. Endoscopically SDA tend to be large, sessile and located in the second part of the duodenum[6,10-13] and this series also confirms that most SDA harbour dysplasia[14-19]. Kim *et al*[13] found that all of their 17 non ampullary adenomas were dysplastic while a larger series from Japan[14] demonstrated that dysplasia was presented in all 233 non-ampullary adenomas assessed. The rate of low grade dysplasia

Figure 1 Summary of treatment of ampullary and non-ampullary adenomas. EMR: Endoscopic mucosal resection.

Table 3 Comparison of characteristics of recurrences (*n* = 10) *vs* no recurrence (*n* = 10)

	Recurrence (*n* = 10)	No recurrence (*n* = 10)
Non-ampullary/ ampullary	5:5	7:3
Median size (mm)	20 mm	10 mm
Treatment		
Endoscopic resection	10	8
Surgical resection	0	2
Specimen retrieval		
Piecemeal	8	6
En bloc	2	4
Margin positivity	9 (90%)	6 (60%)
Salvage therapy		
Endoscopic resection	8	
Surgical resection	2	

in non-ampullary adenomas in our series was 73.3%, which was within range (52%-84%) of recently published series[13-15,19], while the rate of low grade dysplasia in our ampullary adenomas (78%) was higher than 53%-66% previously reported[16-18]. The processes responsible for the high rates of dysplasia in SDA are not clear however Rubio[19] suggested that the duodenum of those patients may exhibit gastric duodenal metaplasia and bile acids and pancreatic juices may provide a milieu that encourages the metaplasia to proceed onto the adenoma-carcinoma sequence. It is possible that SDA progress to dysplasia faster than other adenomas in the gastrointestinal tract[19].

Strategy for investigations
The variable investigations performed during patient workup is a reflection of the lack of guidelines available in managing this rare entity.

Role of biopsy: There are no clear guidelines regarding the absolute need to biopsy all lesions and therefore the decision is often left to the discretion of the endoscopist. However a pre resection biopsy for SDAs may compromise a subsequent safe "lift off" technique of EMR and may increase the risk of perforation especially in the setting of a thin duodenal wall or a large duodenal

tumour. Moreover morphological changes after biopsy may give the false impression of submucosal infiltration of a superficial lesion[20,21]. The American Society for Gastrointestinal Endoscopy (ASGE) guidelines suggests that all suspicious lesions should be biopsied[22]. Although biopsy concordance with final pathology is commonly around 75%, as in this investigation[23-25], and the non-concordant biopsies usually fail to sample a small focus of malignancy within the SDA particularly ampullary adenomas[26]. Elek suggests taking large, multiple biopsies (up to 6) or doing papillectomies to improve the diagnostic yield[27].

Role of EUS: We pursued a selective policy of EUS prior to resection to define invasion or pancreatic ductal involvement in large SDA that were suspicious (large size, ulceration or the presence of high grade dysplasia on biopsy)[8,27-29]. However SDA size is a variable determinant of high grade dysplasia or malignant change with authors quoting a size > 10 mm[30], > 20 mm[8,27,28,31], and > 30 mm[29]. ASGE guidelines suggest the use of EUS in lesions > 2 cm in non-ampullary and > 1 cm in ampullary adenoma[22]. Currently the role of intraductal ultrasound is not well defined. Menzel *et al*[32] suggested it was more useful than EUS in tumour diagnosis but a recent prospective study suggested that it could overstage tumours[33].

Role of ERCP: This is the least controversial investigational tool for ampullary adenomas and was performed in all our patients since it provides an accurate means of assessing ductal involvement[34-36].

Treatment
Most of the SDAs were resected endoscopically, which is in line with contemporary management[37].

Role for EMR: The factors affecting the suitability for a lesion to undergo endoscopic resection include size, presence of malignant signs, extension along the wall

Figure 2 Management of ampullary adenomas. ERCP: Endoscopic retrograde cholangiopancreatography; EUS: Endoscopic ultrasound.

Figure 3 Management of non-ampullary adenomas. EUS: Endoscopic ultrasound.

of the duodenum and extension into biliary/pancreatic ducts[37]. There is no consensus regarding the absolute size that would make a lesion suitable for endoscopic resection although a maximum size of 4-5 cm for an endoscopic ampullectomy has been suggested, due to the increased risk of malignancy. Large adenomas can be challenging to resect *en bloc* although Irani had a success rate of 84%, with a mean lesion size of 2.4 cm[38].

There has been a significant shift with respect to size criteria for non ampullary lesions. In 2003 Perez *et al*[8] suggested that lesions more than 2 cm ought to be resected surgically. In 2009 Alexander *et al*[7] showed that lesions with mean size of 27.6 mm could be resected endoscopically. Apart from size, the physical appearance of the lesion is important. If the depressed segment is < 10 mm and non-depressed segment < 50 mm then it will be suitable for endoscopic resection and the non-lift sign is a strong sign of malignancy[39].

Role for endoscopic submucosal dissection: In our institution we have favoured EMR as a method of endoscopic resection. In general it has a success rate of 79%-100% with ability to deal with any lesion in only one session in 80%. The complication rate been quoted as 0.6% for perforation and up to 9% for non-fatal bleeding. Endoscopic submucosal dissection has recently been trialled in duodenal adenomas and electrosurgical dissection with an endoscopic knife achieves a better *en bloc* resection of the lesion[11]. However the complication rate is higher with perforation rates of 31%, 15% for post-procedural bleeding and a longer procedural duration.

***En bloc vs* piecemeal resection:** We have more commonly resorted to piecemeal resection for both types of adenoma. Ideally *en bloc* resection would

allow an oncologically better resection of the tumour but this can be challenging for lesions > 2 cm[7,40]. Piecemeal resection allows tumours of larger size to be resected endoscopically with reduced risk of perforation, reduces resection time and uses less electrocautery. Unfortunately it does predispose to repeated subsequent resections[22] as there is increased risk of recurrence[7] especially when the lesion is > 20 mm[7,22].

Role of pancreatic stenting following ampullectomy: Pancreatic duct stenting has been shown to reduce the risk of post procedural pancreatitis in a prospective randomised trial[41], although the study only included 19 patients. A meta-analysis of five studies involving 481 patients showed that patients in the no stent group had a 3-fold increased risk of post-ERCP pancreatitis[42]. Our pancreatic stenting rate is only 62.5%, without however any trend towards significant pancreatitis post resection. There is no strong evidence regarding prophylactic biliary stenting, although it has a role should biliary drainage post procedure be a concern[33].

Complications

We reported a 4.3% complication rate. This was a single patient with self-limiting mild pancreatitis after a papillectomy. The rate of specific complications associated with endoscopic resections include pancreatitis (8%-15%), perforation (up to 4%), cholangitis (up to 2%), papillary stenosis (0%-8%)[22]. A recent prospective study showed a risk of minor bleeding of 18% and 6.5% for major bleeding[43]. The low rate of bleeding at our institution could be due to meticulous hemostasis being achieved once resection is completed.

Surveillance and recurrence

In our series of cases, recurrences in ampullary

adenomas occurred earlier and more often than in non ampullary SDA. The inherent risk of recurrence after endoscopic resection has been investigated separately in both subgroups of adenomas. Two series on ampullary adenomas showed a recurrence rate of 19% on follow-up[43,44] while a published case series of endoscopic resection of non-ampullary adenomas showed an average recurrence rate of 19.9%[31]. However subset analysis shows that the recurrence rate of 37% can go up to 63% if lesion of > 2 cm diameter are analysed separately[6]. Currently there is no accepted standardized follow up regime. Most commonly it is suggested that patients should have annual endoscopic follow up for first 2 years after complete resection[6], while Apel *et al*[10] suggests 3 monthly endoscopy for 1 year, increasing to 6 monthly for 2 years followed by annual endoscopy.

Best salvage therapy

A treatment plan for recurrences should be devised by all units offering endoscopic therapy of duodenal adenomas as recurrences are common, especially if there has been more than one endoresection, the lesion was large or the resection was incomplete. Unfortunately there is no consensus on the optimal salvage therapy. As more experience is being gathered with endoresection it is increasingly becoming an attractive tool to treat recurrences, often coupled with ablative therapy such as argon beam coagulation (APC). Alexander *et al*[7] noted 5 recurrences after treating 23 patients with NA by EMR, with median size of 20 mm. Those were cleared with a further session of APC ± EMR with a mean follow up of 13 mo. Similarly a series of 54 patients with non-ampullary adenomas (mean size 15 mm)[45] had 16 recurrences of which 15 were eradicated with a further session of EMR ± APC. However, the median follow up period was only 10.8 mo.

Very few series have assessed ablation therapy in isolation. Lienert *et al*[46] assessed 16 cases of NA treated with APC ± polypectomy where 3 of the 4 recurrences were successfully treated with ablative therapy. Apel *et al*[10] had assessed 18 cases of non-ampullary adenoma, with a median size of 27.5 mm, treated with a combination of serial sessions of polypectomy and APC (33 sessions) carried out over 3 wk to achieve a 55% success rate although 6 cases could not be eradicated despite multimodal endoscopic therapy.

Recently Schneider *et al*[47] addressed the role of surgery to treat recurrences after failed endoscopic treatment of ampullary adenomas. Forty-four cases were referred for transduodenal surgical ampullectomy following a median of 3 endoscopic treatments before referral. The surgical cure rate was 84% with a postoperative morbidity of 24%, the majority being mild (Clavien-Dindo grade I/II). This was comparable to morbidity associated with endoresection (8%-27%).

Proposed management algorithm

Based on this information a management algorithm for sporadic non-ampullary and ampullary adenomas is summarised in Figures 2 and 3 respectively. However, management does depend on the experience of the endoscopist (*e.g.*, with respect to size of polyp), the availability of investigative tools (*e.g.*, EUS) and the fitness of the patient to tolerate the treatment offered.

In conclusion, this investigation has confirmed that SDA can be treated endoscopically with minimal morbidity and that piecemeal resection results in eradication in nearly three quarters of patients. Optimal surveillance strategies following resection are not clearly established but re-endoscopy 6 mo after the initial resection is a satisfactory starting point. Recurrent SDA can be treated with endoscopic reresection with surgical resection indicated when the lesions are large (> 3 cm in diameter) or demonstrate severe dysplasia or invasive cancer.

COMMENTS

Background

The optimal treatment strategy for sporadic duodenal adenomas (SDA) is not yet established although it is clear that this involves contributions from both advanced endoscopy and upper gastrointestinal surgery.

Research frontiers

Developing algorithms to accurately predict the optimal treatment (endoscopic or surgical resection) based on morphology and pathology of both primary and recurrent SDA will assist in their multidisciplinary management.

Innovations and breakthrough

Most SDA can be treated endoscopically with even piecemeal resection resulting in eradication in three quarters of patients. Surgical resection can be reserved for lesions > 4 cm in diameter or with malignant change.

Applications

With multidisciplinary review, endoscopic resection can be the primary treatment modality for SDA.

Terminology

SDA is a management challenge due to their anatomical position and the often comorbid status of patients.

Peer-review

This manuscript is interesting due to the paucity of precise international guidelines regarding the topic.

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FLYLEAF

EDITORS FOR THIS ISSUE

Retrospective Study

Association of trainee participation with adenoma and polyp detection rates

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Abstract

AIM

To investigate whether adenoma and polyp detection rates (ADR and PDR, respectively) in screening colonoscopies performed in the presence of fellows differ from those performed by attending physicians alone.

METHODS

We performed a retrospective review of all patients who underwent a screening colonoscopy at Grady Memorial Hospital between July 1, 2009 and June 30, 2015. Patients with a history of colon polyps or cancer and those with poor colon preparation or failed cecal intubation were excluded from the analysis. Associations of fellowship training level with the ADR and PDR relative to attendings alone were assessed using unconditional multivariable logistic regression. Models were adjusted for sex, age, race, and colon preparation

quality.

RESULTS
A total of 7503 colonoscopies met the inclusion criteria and were included in the analysis. The mean age of the study patients was 58.2 years; 63.1% were women and 88.2% were African American. The ADR was higher in the fellow participation group overall compared to that in the attending group: 34.5% *vs* 30.7% (P = 0.001), and for third year fellows it was 35.4% *vs* 30.7% (aOR = 1.23, 95%CI: 1.09-1.39). The higher ADR in the fellow participation group was evident for both the right and left side of the colon. For the PDR the corresponding figures were 44.5% *vs* 40.1% (P = 0.0003) and 45.7% *vs* 40.1% (aOR = 1.25, 95%CI: 1.12-1.41). The ADR and PDR increased with increasing fellow training level (P for trend < 0.05).

CONCLUSION
There is a stepwise increase in ADR and PDR across the years of gastroenterology training. Fellow participation is associated with higher adenoma and polyp detection.

Key words: Screening colonoscopy; Adenoma detection rate; Polyp detection rate; Gastroenterology training; Colorectal cancer

Core tip: In this large sample of screening colonoscopies, we found that fellow participation has an overall favorable effect on adenoma and polyp detection rates, especially for fellows after their first year of training. The higher detection rate was evident in both the right and left colon. There were no differences overall regarding adenoma per colon or polyp per colon, between the fellow participation and attending groups. In summary, performance of screening colonoscopies by fellows under the strict supervision of attendings does not negatively affect the quality of the procedure, but rather increases adenoma and polyp detection.

INTRODUCTION
Colorectal cancer (CRC) is the third most common cancer and second leading cause of cancer death in the United States. In 2016, it is estimated that 134490 individuals will be diagnosed with CRC, and approximately 49190 will die from this disease (26020 males and 23170 females)[1]. While these numbers are substantial, there has been an overall steady decline in the incidence of CRC, which represents a 40% decrease since 1975. More recently, between 2008 and 2012, CRC incidence decreased annually by about 3.6% in men and 3.8% in women[1]. An increase in screening for CRC with colonoscopy and other modalities is the most likely cause of those declines in CRC incidence. Colonoscopy is an important screening modality for CRC. The advantages of colonoscopy compared to the other modalities are the ability to directly examine the colonic mucosa and remove precancerous polyps during one session. The American College of Gastroenterology recommends colonoscopy as the preferred screening modality[2]. The results from several studies support that colonoscopy and polypectomy decrease mortality from colon cancer[3-5]. However, it has been consistently shown that the quality of colonoscopy varies among providers, and is dependent on several factors such as colon preparation quality, skills of the endoscopist, and length of withdrawal (examination) time. Furthermore, some studies found that colonoscopy decreases the risk of distal, but not proximal, colon cancer[6,7]. Given the importance of providing a quality colonoscopy, there is great interest in studying the effects of different procedural factors on the Adenoma and Polyp Detection Rates (ADR and PDR). Central to this discussion is the skill of the provider performing the colonoscopy. Colonoscopy quality differs widely among providers, and studies have reported a wide range of ADR (15%-50%) among endoscopists[8,9]. There is also some evidence that colonoscopies performed by gastroenterologists are associated with higher protection against colon cancer than are those performed by other providers[5].

Fellows are gastroenterology trainees who enroll in a three-year gastroenterology fellowship. Throughout their training, gastroenterology trainees acquire several procedural and non-procedural skills. They are supervised by attending gastroenterologists during procedures. First-year fellows rapidly acquire procedural skills; however, it is unclear whether their skill level changes substantially enough within the first year of training to affect their screening colonoscopy ADR and PDR. Most fellows in their third year of training have acquired adequate endoscopic skills, are ready for unsupervised practice, and are considered more skillful than first and second year fellows. Given that there is a known learning curve for colonoscopy, it is unclear whether the participation of fellows in screening colonoscopy affects the quality of the procedure, and whether their skill level at different stages of their training contributes to any changes in the quality of colonoscopy. There are relatively few reported studies that addressed this subject. In a small retrospective study of 309 patients, colonoscopies performed by fellows under the supervision of an attending had a higher ADR compared to those performed by attendings alone (37.2% *vs* 23%, P < 0.01)[10]. Another retrospective study found that ADRs increased as fellows advanced throughout their fellowship, with third year

fellows having a higher ADR than did attendings (39.5% *vs* 27.7%), OR = 1.7 (1.33-2.17)[11]. Another study found that colonoscopies performed by fellows under the supervision of attendings were associated with a higher detection of small adenomas (< 5 mm), compared to procedures performed without a fellow (25% *vs* 17%, *P* = 0.001)[12]. There are several limitations to these studies, including the small sample sizes, the small number of procedures performed by fellows, inclusion of non-screening colonoscopies, and no stratification of fellows by year of training.

Herein we provide further clarification on the effect of fellow participation at different stages of training on the quality of screening colonoscopies. The primary aim of our study was to investigate whether GI fellows at various stages of training performing screening colonoscopies have different ADR and PDR compared to attendings. This was done by examining a large database of screening colonoscopies performed in patients aged 40 or older at a large teaching hospital.

MATERIALS AND METHODS

This was a retrospective study using the endoscopic procedure database at Grady Memorial Hospital in Atlanta, GA. This database includes prospectively collected information about all endoscopic procedures performed in the Grady Memorial Hospital gastroen-terology endoscopy unit, and includes procedure type, patient's medical record number, age, race, procedure indication, endoscopist, fellow participation in the procedure, and fellow training level. The study included all outpatients who were at least 40 years old who underwent a screening colonoscopy between July 1, 2009 and June 30, 2015. Excluded patients included those who underwent colonoscopy for diagnostic purposes (*e.g.,* abdominal pain, diarrhea, bleeding), surveillance for colorectal polyps, personal history of CRC, colorectal surgery, or inflammatory bowel disease. We also excluded patients whose procedures were aborted due to complications, severe pain and discomfort, failed cecal intubation, and those with poor bowel cleansing preparation ("prep"). The study was approved by the Institutional Review Board.

The computerized medical record was used to confirm the age and race of the patient, endoscopic findings, prep quality, cecal intubation, and polyp size, number, location, and histology. Race was categorized as white, black, and other. Bowel prep quality was categorized as good, fair-adequate, fair-inadequate, and poor. Colonoscopies with fair-adequate prep were those in which the prep quality was judged to allow for detection of all polyps ≥ 5 mm in size. Colonoscopies with poor prep had solid stool and generally required a repeat procedure within 3 mo. Polyp location was divided into right sided (cecum, ascending colon, hepatic flexure, and transverse colon), and left sided (descending colon, sigmoid, and rectum). Polyps were categorized into adenomatous and non-adenomatous

polyps. Adenomatous polyps were categorized into advanced and non-advanced adenomas. Advanced adenomas included polyps with size ≥ 10 mm, villous or tubulovillous histology, high-grade dysplasia, or adenocarcinoma. Colonoscopies were categorized according to fellow participation as follows: Attending alone (procedure performed solely by attending) *vs* fellow present (fellow participated in any part of the procedure). Given that fellows start their fellowship training without endoscopic experience and rapidly accumulate endoscopic skills during their first year of training, fellow participation was also categorized as follows: Attending alone, fellow in first six months of training, fellow in second six months of training, fellow in second year, and fellow in third year.

Colonoscopy information

Patients who were candidates for CRC screening were referred to the endoscopy unit from their primary care or gastroenterology clinic. Patients were given a standard 4 L of polyethylene glycol solution as a standard bowel preparation regimen. During the study period, there were 10 attendings and 34 fellows who performed the colonoscopies. In the endoscopy unit, patients were randomly assigned to endoscopy rooms during the course of the day. Attendings staffed the endoscopy rooms, with or without a fellow. All procedures were performed under moderate sedation. In colonoscopies performed with fellows, the fellow started the procedure and attempted insertion of the colonoscope to the cecum. In general, attendings intervened when there was difficulty passing a specific part of the colon, or if there was significant patient discomfort. Once the attending traversed the problematic area of the colon or the patient was better sedated, the scope was usually given back to the fellow to complete the insertion to the cecum and subsequent withdrawal of the scope. However, this was left to the discretion of the attending. Second and third year fellows are usually able to complete the colonoscopy without participation of the attending. The attending physicians strictly monitored all fellows during insertion and withdrawal of the scope.

Statistical analysis

Descriptive statistics, including mean, standard devia-tion, and frequencies, were used to characterize the study population. Characteristics of patients undergoing screening colonoscopy according to whether their colonoscopy was performed by an attending physician alone or with a fellow were compared using the student *t* test for continuous variables and the chi square test for categorical variables. Differences in the ADR, PDR, and advanced ADR across those for attendings alone and fellows at different points in training duration were assessed using the Mantel-Haenszel χ^2 test to calculate the *P* for trend (non zero correlation). Associations of fellowship training level with the ADR, PDR, and advanced ADR (AADR) relative to attendings alone were assessed using unconditional multivariable logistic
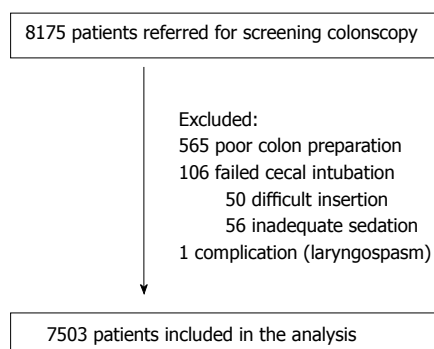
8175 patients referred for screening colonscopy

Excluded:
565 poor colon preparation
106 failed cecal intubation
50 difficult insertion
56 inadequate sedation
1 complication (laryngospasm)

7503 patients included in the analysis

Figure 1 Study flow diagram.

regression to calculate the adjusted odds ratios (ORs) and 95%CIs. Models were adjusted for sex, age, race, and colon preparation quality. Statistical significance was defined as a two-sided *P* value of ⩽ 0.05% or a 95%CI that excluded 1.0. Analysis was performed using SAS version 9.4.

RESULTS

Patient population

Between July 1, 2009 and July 1, 2015, 8175 col-onoscopies were performed for the sole indication of screening for colon cancer. All procedures were performed under moderate sedation. Of these, 672 colonoscopies were excluded for the following reasons: 565 for poor colon preparation quality, 106 for failed cecal intubation, and 1 complication (laryngospasm). A total of 7503 screening colonoscopies were included in the analysis. Figure 1 shows the study flow diagram leading to the study population. Selected characteristics of the study patients according to whether their colonoscopy was performed by an attending physician alone or with a fellow are summarized in Table 1. The mean age of the study patients was 58.2 years, and 63.1% were women, 88.2% were African American, and 88.9% had a good colon preparation quality. A total of 67.2% of colonoscopies were performed with a training fellow, and an attending alone performed the rest.

Adenoma, advanced adenoma, and polyp detection rates

Differences in the ADR, PDR, and advanced ADR across those for attendings alone and fellows at different points in training duration are summarized in Tables 1 and 2. The ADR in the fellow participation group (all levels of training combined) was higher than that in the attending group (34.5% *vs* 30.7%, *P* = 0.001). The higher ADR in the fellow group was mainly related to second and third year fellows, but not first year fellows. Fellows in their third year of training had a higher ADR than did attendings alone (35.4% *vs* 30.7%; aOR = 1.23, 95%CI: 1.09-1.39). The higher ADR was evident in both the right and left colon. Similarly, the PDR was

Table 1 Characteristics of patients undergoing screening colonoscopy (*n* = 7503), by gastroenterology fellow participation; Grady Memorial Hospital, Atlanta, Georgia, July 1, 2009 – July 1, 2015

Characteristic	Attending alone (*n* = 2464, 32.8%)	Attending with fellow (*n* = 5039, 67.2%)	*P* value[1]
Age in years (mean ± SD)	57.9 ± 7.1	58.3 ± 7.1	0.02
Female sex, *n* (%)	1572 (63.8)	3161 (62.7)	0.37
Race, *n* (%)			
White	120 (4.9)	261 (5.2)	0.15
Black	2198 (89.2)	4423 (87.8)	
Other	146 (5.9)	355 (7.1)	
Preparation quality, *n* (%)			
Good	2199 (89.3)	4469 (88.7)	0.02
Fair-adequate	152 (6.2)	382 (7.6)	
Fair-inadequate	113 (4.6)	188 (3.7)	
Fellow training level, *n* (%)			
1st 6 mo	N/A	627 (12.4)	
2nd 6 mo	N/A	651 (12.9)	
2nd year	N/A	1413 (28.0)	
3rd year	N/A	2348 (46.6)	
⩾ 1 adenoma (ADR), *n* (%)	756 (30.7)	1736 (34.5)	0.001
⩾ 1 advanced adenoma (AADR), *n* (%)	215 (8.7)	416 (8.3)	0.49
⩾ 1 polyp (PDR), *n* (%)	988 (40.1)	2244 (44.5)	0.0003
⩾ 1 adenoma in right colon (RT-ADR), *n* (%)	521 (21.1)	1212 (24.1)	0.005
⩾ 1 adenoma in left colon (LT-ADR), *n* (%)	365 (14.8)	862 (17.1)	0.01
Mean number of APC	0.61	0.68	0.03
Mean number of PPC	0.86	0.96	0.01

[1]*P* value from χ^2 test for categorical variables, and student *t* test for continuous variables. ADR: Adenoma detection rate; PDR: Polyp detection rate; AADR: Advanced adenoma detection rate; APC: Adenomas per colon; PPC: Polyps per colon.

higher in procedures performed with fellows compared to those performed by attendings alone (44.5% *vs* 40.1%, *P* = 0.0003). Fellows in their third year of training had a higher PDR than did attendings alone (45.7% *vs* 40.1%, aOR = 1.25, 95%CI: 1.12-1.41). The ADR and PDR statistically significantly increased with increasing fellow training level (trend *P* value < 0.05). Fellows also detected more adenomas and polyps than did attendings. The mean number of adenoma per colon (APC) was higher in the fellows' group than in the attendings alone group (0.68 *vs* 0.61, *P* = 0.03). Similarly, the mean number of polyps per colon (PPC) was higher in the fellows' group than in the attendings alone group (0.96 *vs* 0.86, *P* = 0.01).

There was no difference in the AADR between the fellows group and the attending group (8.3% *vs* 8.7%, *P* = 0.49). However, fellows in their first six months of training had a lower AADR than did attendings alone (4.8% *vs* 8.7%, aOR = 0.52, 95%CI: 0.35-0.76). We further analyzed this finding by examining the pro-portion of procedures that had a large adenoma (⩾ 1 cm), villous histology, or high-grade dysplasia (HGD) and/or cancer (Table 3). The lower AADR in the fellows

Table 2 Associations of gastroenterology fellow training level with adenoma detection rate, polyp detection rate, and advanced adenoma detection rate; Grady Memorial Hospital, Atlanta, Georgia, July 1, 2009 – July 1, 2015

Outcome	Fellowship training level	Detection rate	Trend *P* value[1]	aOR[2]	95%CI	*P* value
≥ 1 adenoma (ADR)	Attending alone (reference)	30.7%	0.0003	1.00	-	
	Fellow in 1st 6 mo	32.4%		1.07	0.89-1.3	0.47
	Fellow in 2nd 6 mo	33.3%		1.16	0.96-1.39	0.13
	Fellow in 2nd year	34.4%		1.15	1.00-1.32	0.06
	Fellow in 3rd year	35.4%		1.23	1.09-1.39	0.001
≥ 1 polyp (PDR)	Attending alone (reference)	40.1%	< 0.0001	1.00	-	
	Fellow in 1st 6 mo	42.4%		1.10	0.92-1.32	0.28
	Fellow in 2nd 6 mo	42.7%		1.14	0.96-1.36	0.14
	Fellow in 2nd year	44.4%		1.17	1.02-1.33	0.02
	Fellow in 3rd year	45.7%		1.25	1.12-1.41	0.0001
≥ 1 advanced adenoma (AADR)	Attending alone (reference)	8.7%	0.7	1.00	-	
	Fellow in 1st 6 mo	4.8%		0.52	0.35-0.76	0.001
	Fellow in 2nd 6 mo	9.1%		1.06	0.78-1.44	0.71
	Fellow in 2nd year	9.3%		1.05	0.83-1.31	0.7
	Fellow in 3rd year	8.3%		0.93	0.76-1.15	0.51
≥ 1 adenoma in right colon (RT-ADR)	Attending alone (reference)	21.1%		1.00	-	
	Fellow in 1st 6 mo	22.3%	0.002	1.05	0.85-1.3	0.64
	Fellow in 2nd 6 mo	23.4%		1.16	0.94-1.42	0.17
	Fellow in 2nd year	23.9%		1.14	0.98-1.34	0.1
	Fellow in 3rd year	24.8%		1.22	1.06-1.39	0.005
≥ 1 adenoma in left colon (LT-ADR)	Attending alone (reference)	14.8%	0.01	1.00	-	
	Fellow in 1st 6 mo	16.1%		1.16	0.87-1.41	0.42
	Fellow in 2nd 6 mo	16.4%		1.15	0.91-1.46	0.24
	Fellow in 2nd year	16.8%		1.13	0.94-1.35	0.18
	Fellow in 3rd year	17.7%		1.23	1.06-1.44	0.01

[1]Mantel-Haenszel χ^2 (non zero correlation); [2]From unconditional logistic regression model controlling for age, sex, race, and colon-cleansing preparation quality. ADR: Adenoma detection rate; PDR: Polyp detection rate; AADR: Advanced adenoma detection rate; RT-ADR: Right sided ADR; LT-ADR: Left sided ADR; aOR: Adjusted odds ratio.

in their first six months of training was mainly related to lower detection of large adenomas (3.4% *vs* 7.9%, *P* < 0.0001). There were no differences in the detection of adenomas with villous histology or those with HGD and/or cancer. In addition, there was no difference in the detection of right or left sided adenomas. On average, fellows in their first six months of training and attendings detected a similar number of adenomas per colon (0.64 *vs* 0.61, *P* = 0.54).

DISCUSSION

Our results suggest that the participation of gastroenterology fellows overall in screening colonoscopy may be associated with higher adenoma and polyp detection. In our study, a higher level of detection was manifested both as the number of colonoscopies with at least one adenoma or polyp (ADR and PDR), and the mean number of adenomas and polyps per colon. Furthermore, our findings suggest that fellow's level of training and experience is directly associated with polyp detection. There was a stepwise increase in adenoma and polyp detection with higher levels of fellow training. Fellows in the first year of training and attendings had similar ADRs and PDRs, while fellows in their second and third year of training had higher values. The higher ADR in the fellows group was seen in both the right and left colon. These findings have clinical significance. Performance of colonoscopies by gastroenterology

fellows, who have less experience than attendings, does not appear to negatively affect adenoma and polyp detection in colonoscopy, provided that they are adequately supervised, and may be associated with somewhat greater adenoma and polyp detection. The higher detection of polyps in procedures in which fellows participate could be related to the presence of an additional observer who monitors the screen with the primary endoscopist, and can lead to an increased recognition of small polyps. Previous studies found that endoscopy nurse participation leads to increased polyp detection[13,14]. In addition, participation of fellows could lead to a more focused withdrawal of the colonoscope in which the attending physician actively instructs the fellow to examine behind each colonic fold, thereby increasing the chances of detecting polyps. Our findings also suggest that detection of polyps is a learned skill that continues to improve during fellowship training, highlighting the importance of gaining adequate experience during training to maximize polyp detection.

Our study had several strengths. Unlike previous studies that included non-screening colonoscopies, we focused our analysis on outpatients presenting for the sole indication of colorectal cancer screening. The goal of colonoscopy in patients presenting with clinical indications, such as acute overt bleeding, abdominal pain or constipation, is often to diagnose the etiology of symptoms and not to detect and resect polyps. Polypectomy is often deferred in these patients with acute

Table 3 Advanced adenomas and total adenomas per colon found during screening colonoscopies by gastroenterology attendings alone and fellows in their first 6 mo of training; Grady Memorial Hospital, Atlanta, Georgia, July 1, 2009 – July 1, 2015

	Attending alone n = 2464 n (%)	Fellows 1st 6 mo n = 627 n (%)	P value[1]
⩾ 1 advanced adenoma (AADR)	215 (8.7)	30 (4.8)	0.001
⩾ 1 adenoma ⩾ 1 cm	194 (7.9)	21 (3.4)	< 0.0001
⩾ 1 adenoma with villous histology	83 (3.4)	14 (2.2)	0.15
⩾ 1 adenoma with HGD and/or cancer	26 (1.1)	4 (0.6)	0.34
Mean number of APC	0.61	0.64	0.54

[1]P value from χ^2 test for categorical variables, and student t test for continuous variables. AADR: Advanced adenoma detection rate; HGD: High-grade dysplasia. APC: Adenomas per colon.

indications until their symptoms resolve. In addition, our study included a large number of colonoscopies performed by trainees at different levels of training. Finally, comparisons of colonoscopy quality between attendings alone and fellows are more meaningful when the level of fellow training is considered. We categorized the level of fellow training in a way that reflects their learning curve, as fellows rapidly gain endoscopic skills in the first 6 mo of training, and progress to become more independent endoscopists in their second and third year. Finally, the retrospective nature of this study eliminated the possibility of the "Hawthorne effect", in which endoscopists alter their behavior as they know that detection rates are being recorded and compared, which is more likely to occur in a prospective study design. One study found that when endoscopists know that their procedures are being recorded for review, they improve the quality of their exam (luminal distension, cleaning of the colon, and length of inspection time), resulting in an increased ADR[15].

Our study had several limitations. It was a retrospective study and it was not possible to accurately describe the degree of fellow participation in colonoscopy. It is possible that attendings performed the withdrawal part of some procedures, and therefore we cannot directly attribute the differences in adenoma and polyp detection to the fellow's technical skills. We had no data on the colonoscopy insertion and withdrawal times. This would have provided insight about the observed increased polyp detection in second and third year fellows. Longer withdrawal times have been linked to higher adenoma detection rates in screening colonoscopy[16]. It is unclear whether the higher detection rate in second and third year fellows was related to longer withdrawal times or to the technical skill of the fellow combined with the guidance and supervision from the attending, or both. In addition, we did not account for several factors that affect polyp and adenoma prevalence, such as family history of colon cancer, smoking, and aspirin use, the data for which were unavailable. However, we accounted for several important confounders such as age, race, sex, and colonoscopy preparation quality. Given the nature of patient flow through the endoscopy unit where patients are shared between attendings, it is unlikely that there was significant difference in the proportion of patients with a family history of CRC, aspirin use, or other unmeasured confounders between the attending alone and the fellows group. Finally, our study was limited to one training program, and thus may not be generalizable to others.

The finding of a lower AADR in fellows in their first six months of training than in attendings alone was unexpected. This difference was likely primarily attributable to there having been a higher percentage of colonoscopies in which one adenoma ⩾ 1 cm was detected in procedures performed by attendings alone. It is unlikely that this was related to fellows underestimating polyp size while they were documenting their procedures early in their training. In general, attendings and fellows discuss findings and write down the sizes and locations of polyps during the procedure, and a final report is entered in the medical record system after the procedure is completed. In addition, attendings sign off on the colonoscopy report and make the necessary changes as they see appropriate. It is reassuring that the ADR itself was not different between fellows in the first six month of training and attendings alone (32.4% *vs* 30.7%, P = 0.47). Furthermore, there was no difference in the average number of adenomas per colon between these two groups (0.61 *vs* 0.64, P = 0.54), nor was there a difference in adenoma detection in the right *vs* the left colon. This suggests that fellows are finding the same number of polyps, though the size of these polyps may be smaller than those found by attendings.

In summary, we found that gastroenterology fellow involvement overall in screening colonoscopy is associated with overall higher ADR and PDR. These higher detection rates were mainly seen in procedures performed by second and third year fellows. Since the AADR was lower in procedures performed with fellows in their first six month of training, increased vigilance in these procedures and an attending joining the fellow in performing a careful withdrawal of the scope, with adequate withdrawal time and careful documentation of polyp size, are indicated. Further studies that document the exact involvement of fellows in the procedure, withdrawal time, and location of polyps would help identify factors related to higher polyp detection rates in more experienced fellows. This would ultimately

allow us to optimize fellow involvement and training in screening colonoscopy, while maintaining a high quality examination.

COMMENTS

Background
Colonoscopy is an important screening modality for colorectal cancer. Participation of gastroenterology fellows in screening colonoscopies has been shown to have a positive effect on the quality of the procedure. However, it is unclear how participation of fellows in their early stages of training (*e.g.,* first six months) affects the quality of colonoscopy. Furthermore, it is unclear if the effects are the same in the right and left side of the colon.

Research frontiers
The adenoma detection rate (ADR) is an important measure of colonoscopy quality and it has been linked to the development of interval colon cancer. In addition to patient-related factors that affect ADR, it is important to study the endoscopist-related factors ADR, such as participation of fellows and their stage of training.

Innovations and breakthroughs
Similar to previous studies, they found that participation of fellows in screening colonoscopy increases ADR and polyp detection rate (PDR) compared to attendings alone. This is the first study to examine the effect of fellows in the very early stage of training (first 6 mo) on colonoscopy findings. The authors found that fellows in their first six months of training have similar ADR compared to attendings, but have lower advanced ADR. The lower ADR was mainly related to lower percentage of polyps ⩾ 1 cm.

Applications
This study suggests that participation of fellows in their second and third year of training increases ADR and PDR in both the right and left side of the colon. Gastroenterology attendings should continue to adequately supervise fellows performing colonoscopy, and patients can be reassured that participation of fellows, even in their early stages of training, does not negatively affect the quality of their procedure.

Peer-review
Qayed and colleagues conducted a large retrospective study examined the association of trainee participation with adenoma and polyp detection rate. This is a retrospective study with all the potential limitation of that but it is very well written.

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ORIGINAL ARTICLE

Retrospective Study

Nerve preserving *vs* standard laparoscopic sacropexy: Postoperative bowel function

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Abstract

AIM

To compare our developed nerve preserving technique with the non-nerve preserving one in terms of *de novo* bowel symptoms.

METHODS

Patients affected by symptomatic apical prolapse, admitted to our department and treated by nerve preserving laparoscopic sacropexy (LSP) between October, 2010 and April, 2013 (Group A or "interventional group") were compared to those treated with the standard LSP, between September, 2007 and December, 2009 (Group B or "control group"). Functional and anatomical data were recorded prospectively at the first clinical review, at 1, 6 mo, and every postsurgical year. Questionnaires were filled in by the patients at each follow-up clinical evaluation.

RESULTS

Forty-three women were enrolled, 25/43 were treated by our nerve preserving technique and 18/43 by the standard one. The data from the interventional group were collected at a similar follow-up (> 18 mo) as those collected for the control group. No cases of de novo

bowel dysfunction were observed in group A against 4 cases in group B (*P* = 0.02). Obstructed defecation syndrome (ODS) was highlighted by an increase in specific questionnaires scores and documented by the anorectal manometry. There were no cases of de novo constipation in the two groups. No major intraoperative complications were reported for our technique and it took no longer than the standard procedure. Apical recurrence and late complications were comparable in the two groups.

CONCLUSION

Our nerve preserving technique seems superior in terms of prevention of *de novo* bowel dysfunction compared to the standard one and had no major intraoperative complications.

Key words: Apical prolapse; Bowel dysfunction; Laparoscopic sacrocolpopexy; Nerve sparing; Vaginal vault prolapse

Core tip: Laparoscopic sacropexy is associated with postoperative bowel dysfunction (constipation, obstructed defecation syndrome) in 10%-50% of cases, with significant worsening in the quality of life. Iatrogenic denervation of the autonomic pelvic nerves was reported as a relevant cause of this kind of dysfunction. The aim of this observational study was to evaluate the safety and efficacy of our nerve preserving technique.

INTRODUCTION

Abdominal sacropexy was first described in 1957[1] and the first formal abdominal technique was defined by Lane[2] in 1962. A study reported the first laparoscopic sacropexy (LSP) in 1993[3], which led to its adoption and further development by different schools[4-6]. Since then various adaptations have been described in literature with different indications, techniques, meshes and associated procedures. It has been reported that the laparoscopic approach is as effective as the abdominal approach[7], with the advantages of less blood loss, a shorter hospitalization and a more rapid post-surgical recovery.

Although sacropexy does remain the "gold standard" procedure for apical prolapse[8], the subjective outcome of the procedure has been reported to be not so satisfactory as its anatomic outcome[9]. Literature has reported a 10% to 50% new onset of bowel symptoms after abdominal and laparoscopic surgery, 18% of voiding problems and 8% of women with sexual dysfunctions[10].

Although there is abundant literature of the underlying causes of urinary dysfunctions and the procedures that might be adopted to avoid them[11], there is little on the underlying causes of bowel dysfunctions.

Our recently published anatomoclinical data revealed a correlation between the occurrence of iatrogenic denervation during LSP and the postoperative onset of the obstructed defecation syndrome (ODS), identifying the source of this kind of post-LPS bowel dysfunction in the superior hypogastric plexus (SHP) iatrogenic lesion, during sacral dissection[12]. Consequently, we adopted the use of a modified dissection technique with the aim of preserving nervous pelvic autonomic pathways.

The main aim of this study was to compare the outcomes of our nerve preserving technique to those of the standard one in terms of incidence of *de novo* ODS and constipation. The secondary endpoints were to compare the other functional outcomes, the anatomical results and complications.

MATERIALS AND METHODS

A retrospective study was carried out on patients affected by symptomatic apical prolapse, admitted to the Department of Surgical Sciences of the University of Torino between October 2010 to April 2013 and treated with nerve preserving LSP (Group A or "interventional group"). The postoperative ODS and complications of these patients were compared to those of the patients treated by the standard LSP (Group B or "control group") between September 2007 and December 2009, the study population of our preliminary anatomoclinical research[12].

All women who presented with genital apical prolapse (vaginal or utero-vaginal), stages ⩾ 2, according to the Pelvic Organ Prolapse Quantification (POP-Q) System[13], with clinical indication for LSP, were eligible. Patients were excluded if they were not candidates for general anaesthesia, had a history of sacropexy and/or previous rectal prolapse surgery or presacral surgery.

The data on patient age, parity, body mass index, previous abdominopelvic surgery, operating time, amount of blood loss, length of hospital stay, intraoperative, early and late postoperative complications were prospectively recorded in a computerized database. Subjective data on bladder, bowel, sexual functions and POP-Q examination were recorded prospectively at the first clinical review, then at 1 and 6 mo, followed by every postsurgical year. Questionnaires were filled in by the patients at baseline, 6 mo and then at the end of each follow-up clinical evaluation. An Italian translation of the Pelvic Floor Distress Inventory Short Form 20 (PFDI-20)[14], the Agachan-Wexner constipation scoring system[15] and the Prolapse/Incontinence Sexual Questionnaire Short Form (PISQ-12)[16], were used. Each patient had preoperative urodynamic tests; if stress
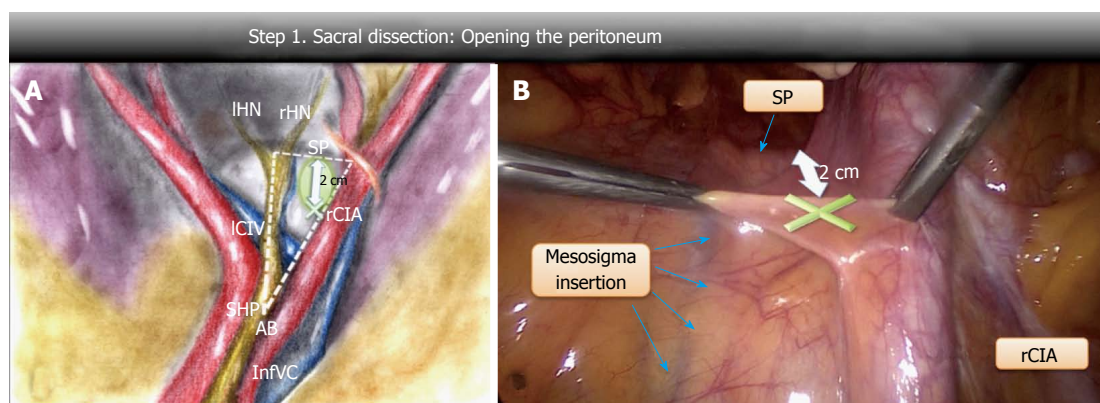
Figure 1 Step 1: Opening the peritoneum. A: Schematic drawing of the "dissection triangle" on the right lumbosacral spine with the safe area (X) for opening the peritoneum; B: Laparoscopic view of the peritoneal opening point (X). rCIA: Right common iliac artery; SP: Sacral promontory; AB: Aortic bifurcation; SHP: Superior hypogastric plexus; rHN: Right hypogastric nerve; lHN: Left hypogastric nerve; InfVC: Inferior vena cava; lCIV: Left common iliac vein.

urinary incontinence (SUI) was present, transobturator tension-free vaginal tape procedure (TVT) (Gynecare TVT-O, Ethicon Inc., Somerville, NJ) was used. The symptomatic postoperative findings, early and late complications of our two groups were then compared. Constipation was defined as ≤ 2 defecations/week for at least 3 mo; ODS was evidenced by the association of the following symptoms: Difficulty in evacuation, excessive straining during defecation, a sensation of incomplete evacuation, prolonged time to defecate and anal pain[17] and evidenced by an increase in the Agachan-Wexner score and the PFDI-20 (CRADI-8) score in answer to the questions: "Do you feel you need to strain too hard to have a bowel movement?"; "Do you usually have pain when you pass your stools?"; "Do you feel you have not completely emptied your bowel at the end of a bowel movement?".

To avoid bias we collected the data from the interventional group at a similar follow-up as those collected in the previous review for the control group. The application of the experimental procedure was approved by the local Institutional Review Board and written informed consent was obtained from all patients before surgery.

All surgical procedures were performed by two senior gynaecologists. One 10-mm umbilical trocar, two 5-mm ancillary lateral ports and a 10-mm suprapubic ancillary trocar were used. The sigmoid colon was temporarily fixed to the abdominal wall with straight needles to improve the exposure of the promontorium and the right lumbosacral spine. A standard laparoscopic approach was used in group B patients[4,18]. Whilst group A patients were treated by our nerve preserving technique, which preserved the SHP, right hypogastric nerve (rHN), lumbosacral sympathetic trunk and inferior hypogastric plexus.

This technique can be summarized in two steps.

Step 1: Sacral dissection and preservation of the SHP
Opening of the peritoneum: Four anatomical landmarks were considered on the right lumbosacral spine: The aortic bifurcation, the mesosigma insertion on the sacral promontory, the sacral promontory and the right common iliac artery. An imaginary outline of a right-angled triangle, that we called "the dissection triangle", was drawn by the intersection of three straight lines: One lying along the aortic axis from the aortic bifurcation to the sacral promontory (longer cathetus), the other along the sacral promontory from the mesosigma insertion to the right common iliac artery (shorter cathetus) and the last one along the right common iliac artery (hypotenuse) (Figure 1A). After being raised, the peritoneum was opened medially to the right common iliac artery about 20 mm above the sacral promontory, a safe area far from the nervous and vascular structures (Figure 1B). Infact, the SHP and the rHN run close to the major cathetus of the dissection triangle, the left common iliac vein along its 30 degree angle, the iliac bifurcation along its 60 degree angle and the middle sacral vein crosses longitudinally the central area of the triangle[12] (Figure 1A).

Presacral fascia medialization: The peritoneal incision was extended towards the promontory (Figure 2A). The underlying presacral fascia, containing the SHP and the rHN, was incised and pushed medially to expose the longitudinal anterior vertebral ligament. No further medial dissection was attempted once the middle sacral vein had been detected (Figure 2B).

Prevertebral fascia opening: After a small longitudinal incision, the prevertebral fascia was opened and medially pushed with a gauze until the periosteum between the lower side of L5 and the cranial portion of L5-S1 discs was visible (Figure 2C and D). The cranial aspect of the mesh was secured by tacks at this level.

Step 2: Opening of the peritoneum on the right pelvic sidewall and preservation of the rHN
The peritoneum was opened up along the right pelvic wall; the dissection line started half way between the rHN and the ureter, then, with a lateral-medial course
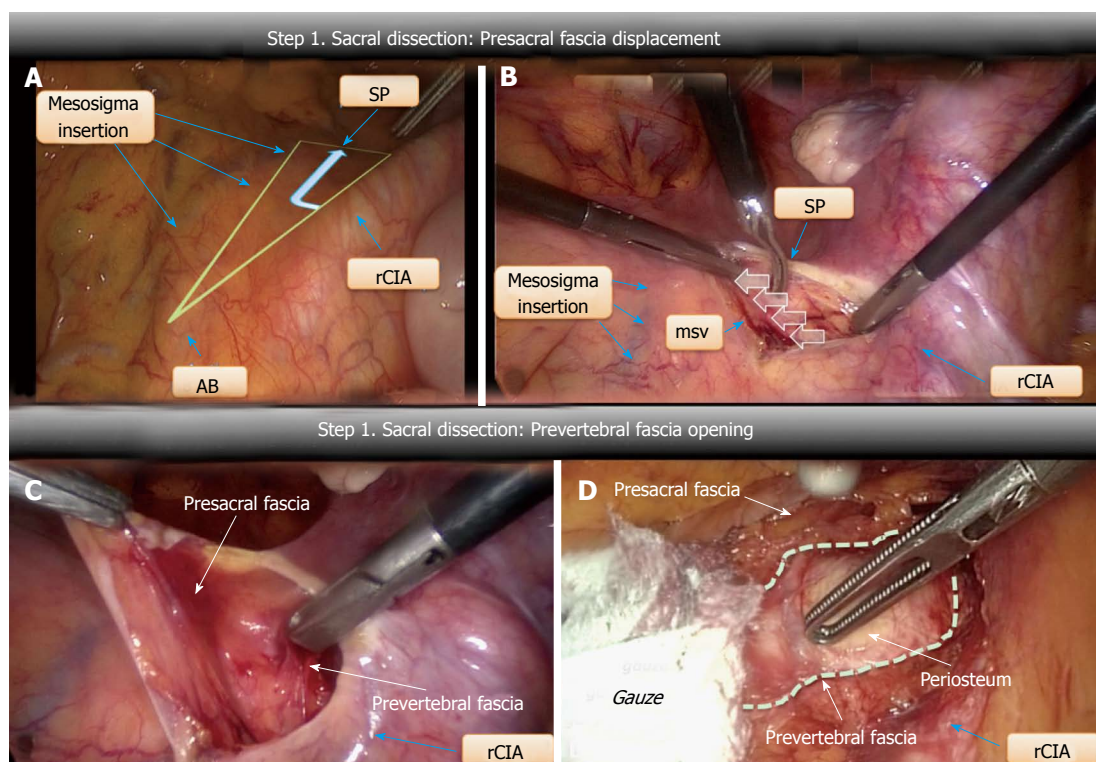
Figure 2 Step 1: Presacral fascia displacement, prevertebral fascia opening. A: The imaginary outline of the "dissection triangle" on the right lumbosacral spine between the four anatomical landmarks; B: Presacral fascia displacement not beyond the middle sacral vein (msv); C: Presacral fascia and prevertebral fascia; D: Denuded periosteum after prevertebral fascia opening. rCIA: Right common iliac artery; SP: Sacral promontory; AB: Aortic bifurcation.

towards the uterosacral ligament insertion, it crossed the upper edge of the ligament at its proximal third. At this level, blunt, careful and superficial dissection was used to avoid iatrogenic damage of the rHN or pelvic plexus, close to the dissection line. The peritoneum was then opened up to the cervix or vaginal stump (Figure 3).

The procedure was then continued in the same manner for both groups, according to the steps recommended by the main schools[4,18] with adaptations. Our technique provided a recto and vesicovaginal dissection limited to the upper third of the vagina and subsequent fixation of two polypropylene rectangular mesh pieces to the anterior and posterior vaginal walls, using 3 interrupted stitches. Peritonization of the mesh through a continuous suture then followed.

Fisher's exact test was used to determine any statistically significant differences in the distribution of outcomes in the nerve preserving LSP and non-nerve preserving LSP groups. Any two-sided *P*-values below 5% of the conventional threshold were considered to be statistically significant. Elaborations were made using SPSS 17.0 software (SPSS Inc., Chicago, IL, United States).

RESULTS

A total of 43 women were evaluable for analysis and no patient required laparotomic conversion. The standard technique was used in 18 consecutive patients and our nerve sparing technique in 25. No statistically significant differences were observed in the stage of the prolapse, or associated procedures, or personal characteristics, in the two groups under study (Table 1).

The group B follow-up followed the same time frame as the one we had previous used in the anatomoclinical study[12]. So as to make the two groups as comparable as possible, we analyzed group A at similar follow-up times as those used for group B, as this time was considered adequate enough to evidence any early post-surgical dysfunctional complications, which were the object of our study. No significant differences were observed in either group at similar follow-ups as to the symptomatic postoperative findings, anatomical outcome, late complications, prolapse and urinary related quality of life. Bowel function and related quality of life was the exception, as there were no cases of ODS in the nerve sparing LSP group, against 4 cases (4/18; 22%) in the standard LSP group (*P* = 0.02), equally distributed between the two surgeons (Table 2).

The quality of life of the patients who were suffering from post LSP ODS worsened as they could not evacuate spontaneously, meaning the use of daily micro-enemas for at least 3 post-surgical months. Bowel dysfunction was clinically characterized by difficult, incomplete and painful defecation as evidenced by an increase in the quality of life and symptomatic questionnaire scores. Anorectal manometry evidenced that patients with bowel dysfunction had an objective
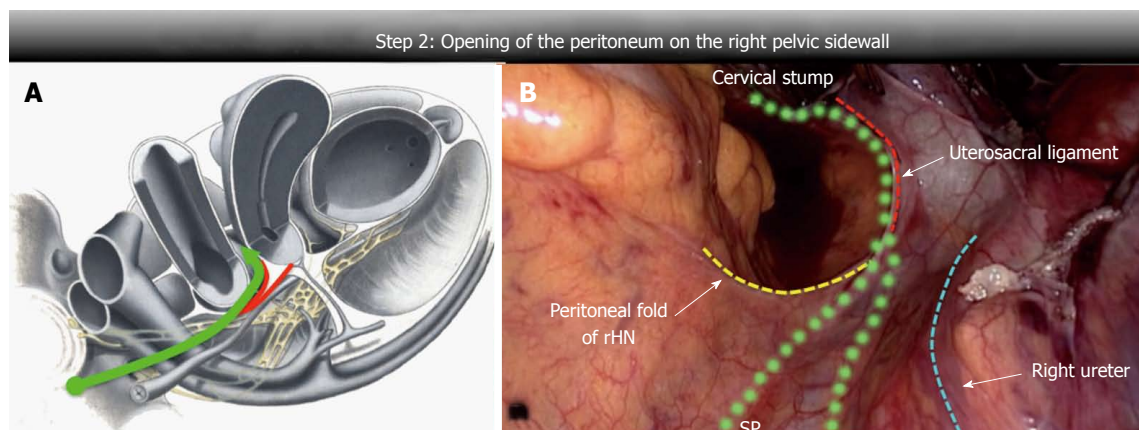
Figure 3 Step 2: Opening of the peritoneum on the right pelvic sidewall. A: Schematic drawing of the dissection line (green arrow) and the autonomic pelvic nerves; B: Dissection line (dotted green line) at the cross of the caudal proximal third of the uterosacral ligament. Modified from Ceccaroni M, Fanfani F, Ercoli A, Scambia G (2006). Innervazione viscerale e somatica della pelvi femminile. CIC Edizioni Internazionali, Roma. rHN: Right hypogastric nerve.

basal spasticity of the anal sphincter with poor relaxation under strain, along with a slightly endorectal sensitivity reduced. There was a gradual improvement of ODS over time and, although it did not disappear altogether, the average CRADI-8 and Agachan-Wexner scores were lower at 2 years (47.5 → 14 and 13.2 → 7, respectively). Indeed, only 2/4 patients had values comparable to those of controls at the two-year follow-up. Although there were no cases of *de novo* constipation in any of the patients, all those present preoperatively persisted.

One patient in both groups required reoperation for anterior mesh detachment, whereas 1 patient in Group B had second surgery for mesh erosion, without any total reoperation rate difference. No interventional procedure was switched to the classical one.

DISCUSSION

Bowel dysfunction after LSP has been poorly investigated and when it has been reported it has been defined in different ways, such as constipation, ODS and dyschezia. Moreover, it has often been evaluated with the use of non-validated questionnaires, without preoperative data and sometimes even in the presence of concomitant confounding procedures. We reviewed the current literature on LSP, pooling studies that accurately reported functional outcomes, procedural steps, associated procedures, mesh types and placement, in order to accurately quantify this issue (Table 3).

Although SUI *de novo* was invariably reported to have similar rates in all studies, the rate of bowel dysfunction varied greatly (SUI range: 0%-23.7%/ODS range: 0%-65.7%). This surprising variability cannot be explained by the associated procedures alone. In fact, though the post LSP bowel dysfunction rate correlates with the positioning of the single posterior mesh[33] and rises after deep posterior dissection, this variability is also found in homogeneous studies with the same associated procedures, *e.g.*, levator ani mesh anchorage (Table 3).

On the other hand, although studies without confounding associated procedures, like our case series, have a lower incidence of dysfunction, it does not reach zero[5]. This might indicate that other pathologic conditions influence bowel functions and that this complication, unlike urinary dysfunction, cannot be attributed solely to the anatomic postoperative aspects. Therefore, the hypothesis of iatrogenic denervation might well provide an explanation for this variability and justify the postoperative bowel dysfunction rate, which would otherwise be unexplainable.

Group B was the same target population as our previous anatomoclinical study[12], where a correlation between an iatrogenic nerve lesion during dissection of the sacral promontory and bowel postoperative dysfunction was demonstrated, with the identification of the involved nerves in the caudal part of the SHP. An objective gynecological and proctological clinical evaluation excluded any secondary functional and organic underlying causes of ODS. As our technique involves anchorage to the upper third of the vaginal stump, post LSP bowel dysfunction could not be attributed to the depth of posterior mesh placement in our series. Furthermore, bowel dysfunction was found both after sacrocervicopexy (3 patients) and sacrocolpopexy (1 patient) without any significant difference.

To date, the rates of iatrogenic pelvic nerve damage after surgery for pelvic prolapse have not yet been quantified, therefore, it is most likely that they have been widely underestimated. Possover analyzed 93 patients who had referred to his centre complaining of symptoms related to probable pelvic nerve damage secondary to surgery for pelvic prolapse[34]. The most frequently observed injury was damage to the sacral nerve roots secondary to laparoscopic rectopexy. He used the term "primary nerve injuries" to describe any nerve lesions caused by coagulation, suturing, ischemia or cutting. Whilst the term "secondary nerve entrapments" was used for lesions caused by fibrotic

Table 1 Demographic and personal characteristics, pre-operative findings, prolapse stage and associated procedures in Group A and B patients

No. of patients	Group A 25	Group B 18	P
Demographic and personal details, mean (SD)			
Mean age	55.8 (± 10.2)	56.1 (± 8.6)	0.9
Parity	2 (± 0.9)	1.5 (± 0.6)	0.14
BMI	25.2 (± 4.7)	23.9 (± 2.7)	0.41
Symptomatic preoperative findings			
Vaginal bulge, *n* (%)	25 (100)	18 (100)	> 0.99
Stress urinary incontinence, *n* (%)	4 (16)	2 (11.1)	> 0.99
ODS, *n* (%)	0	0	> 0.99
Constipation, *n* (%)	3 (12)	3 (16.6)	0.68
POPDI-6 (PFDI)[a], mean (SD)	53.9 (± 13.8)	51.6 (± 1.5)	0.52
UDI-6 (PFDI)[b], mean (SD)	12.3 (± 19.4)	21.2 (± 2.4)	0.21
CRADI-8 (PFDI)[c], mean (SD)	9.0 (± 12.2)	11.1 (± 1.2)	0.58
Agachan-Wexner score[d], mean (SD)	3.9 (± 4.2)	6.4 (± 9.1)	0.08
PISQ-12[e], mean (SD)	10.1 (± 3.9)	9.11 (± 3.8)	0.38
POP-Q stage at baseline, *n* (%)			
Utero-vaginal prolapse	13 (52)	14 (77.8)	0.11
Vaginal cuff prolapse	6 (24)	4 (28.6)	> 0.99
Anterior stage 2	12 (48)	8 (44.4)	> 0.99
Anterior stage 3	5 (20)	7 (38.8)	0.3
Anterior stage 4	0	0	> 0.99
Apical stage 2	12 (48)	7 (38.8)	0.75
Apical stage 3	10 (40)	9 (50)	0.54
Apical stage 4	3 (12)	2 (11.1)	> 0.99
Posterior stage 2	3 (12)	5 (27.7)	0.24
Posterior stage 3	2 (8)	0	0.5
Posterior stage 4	0	0	> 0.99
Intraoperative data			
Concomitant subtotal hysterectomy, *n* (%)	13 (52)	13 (72.2)	0.21
Concomitant total hysterectomy, *n* (%)	0	1 (5.5)	0.41
Concomitant sub-urethral sling placement, *n* (%)	4 (16)	2 (11.1)	> 0.99
Cervical stump fixation, *n* (%)	13 (52)	13 (72.2)	0.21
Vaginal cuff fixation, *n* (%)	6 (24)	5 (27.8)	> 0.99
Uterine preservation, *n* (%)	6 (24)	0	0.03
Operating time (min), mean (SD)	132 (± 27)	141 (± 21)	0.11
Hb decrease (g/dL), mean (SD)	1.1 (± 0.6)	1.2 (± 0.5)	0.48
Hospital stay, mean (SD)	2.2 (± 1.1)	2.9 (± 1.1)	0.06

[a]Pelvic Organ Prolapse Distress Inventory-6 scores ranges from 0 to 100 with lower scores indicating a better quality of life; [b]Urinary Distress Inventory-6 scores ranges from 0 to 30 with lower scores indicating a better quality of life; [c]Colo-rectal-anal Distress Inventory-8 scores rangefrom 0-48, with a higher score indicating a better sexual function; [d]The Agachan-Wexner score ranges from 0 to 30 with the lower scores indicating a lower bowel dysfunction; [e]The PISQ-12 score ranges from 0-48 with a higher score indicating a more satisfactory sexual function. SD: Standard deviation; Hb: Hemoglobin.

Table 2 Symptomatic postoperative findings, anatomical results and late complications in Group A and B patients

No. of patients	Group A 25	Group B 18	P
Follow-up, mo (SD)	19.5 (± 8.4)	17.3 (± 9.8)	0.33
Symptomatic post-operative findings			
Persistent vaginal bulge, *n* (%)	2 (8)	1 (5.5)	> 0.99
De novo stress urinary incontinence, *n* (%)	0	3 (16.6)	0.07
De novo ODS, *n* (%)	0	4 (22.2)	0.021
De novo constipation, *n* (%)	0	0	> 0.99
POPDI-6 (PFDI)[a], mean (SD)	4 (± 11.6)	6.8 (± 1.5)	0.5
UDI-6 (PFDI)[b], mean (SD)	3.2 (± 5.4)	7.1 (± 1.0)	0.11
CRADI-8 (PFDI)[c], mean (SD)	8.3 (± 12.2)	16.9 (± 21.6)	0.1
Agachan-Wexner score[d], mean (SD)	3.0 (± 3.0)	6.8 (± 5.2)	0.00
PISQ-12[e], mean (SD)	7.6 (3.3)	5.7 (± 2.9)	0.06
Anatomical results, *n* (%)			
Recurrence of vault prolapse	0	1 (5.5)	0.41
Cystocele recurrence/*de novo*	1 (4)	1 (5.5)	> 0.99
Rectocele recurrence/*de novo*	0	0	> 0.99
Late complications, *n* (%)			
Erosion	0	1 (5.5)	0.41
Reintervention[f]	1 (4)	2 (11.1)	0.56

[a]Pelvic Organ Prolapse Distress Inventory-6 scores ranged from 0 to 100 with lower scores indicating a better quality of life; [b]Urinary Distress Inventory-6 scores ranged from 0 to 30 with the lower scores indicating a better quality of life; [c]Colo-rectal-anal Distress Inventory-8 scores ranged from 0-48, with a higher score indicating a better sexual function; [d]The Agachan-Wexner score ranges from 0 to 30 with the lower scores indicating a lower bowel dysfunction; [e]The PISQ-12 score ranges from 0-48 with a higher score indicating a more satisfactory sexual function; [f]Anterior recurrence and mesh erosion; [1]Statistically significant. SD: Standard deviation.

tissue or vascular compression. Nerve injury after LSP may be associated with both kinds of nerve damage. The ODS observed in Group B onset soon after surgery and gradually improved over time, even if it did persist in 2/4 patients. Early onset is typical of a primary nerve injury, whilst the presence of a temporary functional deficit, that partially resolves in variable time lapses, is a common finding in partial nerve damage. The basal internal anal sphincter tone is under the modulation of the sympathetic autonomic system[35]. Conversely, the parasympathetic nervous system is responsible for internal anal sphincter relaxation[36]. Mechanoreceptors transmit signals *via* the SHP promoting sphincter constriction until distention signaling overcomes the sympathetic tonic firing and defecation occurs. Extrinsic compression or lesions to only a few nerve fibres most commonly induces irritative symptoms that are connected to either a hypersensitivity or hyperactivity of the pelvic visceral organs, which accounts for the anal sphincter hypertonia we observed.

Some kind of underlying neurological cause for the bowel complications observed after LSP has been invoked, but without further elaboration. However, Shiozawa *et al*[37]'s 2010 study was in agreement with ours and suggested that dysfunctional consequences post laparotomic sacropexy were due to lesions of the autonomic fibers, advocating their preservation. In their recently published overview on surgery involving the presacral space, Huber *et al*[38] included sacropexy amongst the procedures at risk of postoperative bladder and bowel dysfunctions due to iatrogenic nerve injury.

Three *de novo* SUI were observed in Group B and 2/3 of these patients had ODS and negative pre-surgical urodynamic testing. Undoubtedly, the preservation of autonomic fibres is able to prevent the onset of urinary dysfunctions[39]. However, on the basis of the data obtained in our study, we cannot definitely conclude that there are no other underlying causes of the SUI observed in the ODS patients. Likewise, the data obtained from

Table 3 Laparoscopic sacropexy functional outcomes, associated procedures, mesh type and placement: Literature review

Ref.	N° pz	FU (mo)	Bowel dysfunction (n)	Bowel dysfunction (%)	SUI (n)	SUI (%)	Associated procedures									Mesh characteristics			
							SLH	TLH	Uterus pres.	TOT/TVT	Burch	PVR	ACR	PCR	LM	Type	N°	Anterior placement	Posterior placement
[5]	77	11.4	0	0	0	0	60	0	10	0	74	0	0	0	55	Polyest.	2	Vagina	Vagina
[19]	41	24	1 (ODS)	2.4	1	2.4	0	0		13	15	0	0	0	0	Polyest.	2	Below the trigone	Perineal body
[20]	71	27.5	48 (C)	65.7	0	0	13	0		55	24	0	0	0	0	Polyest.	1 or 2	Vagina	Levator ani
[21]	325	14.6	20 (C)	6	19	5.8	0	15		163	0	0	0	0	0	Polyest.	2	Vagina	Levator ani
[18]	43	60	2 (ODS)	4.6	1	2.3	0	0		0	46	28	0	19	0	Polyprop.	2	Vagina	Perineal body/vagina
[22]	101	12	18 (C)	17.8	24	23.7	55	0		30	0	0	0	0	0	Polyprop.	2	Below the trigone	Levator ani
[23]	83	21	19 (C)	22.8	4	4.8	12	29		38	0	0	0	0	0	Polyprop.	2	Vagina	Levator ani
[24]	138	43	26 (C;ODS)	13.4 (C) 5.8 (ODS)	7	5	0	0		0	63	63	24	77	0	Polyest.	2	Vagina	Levator ani/vagina
[25]	47	33.5	8 (C)	17	6	12.7	/	0		/	0	0	0	0	0	Xenograft	2	Vagina	Levator ani
[26]	132	12.5	5 (C)	3.7	8	6	12	0		5	0	0	0	0	0	Polyprop.	2	Vagina	Levator ani
[27]	84	30.7	23 (C;ODS)	15.4 (C) 11.9 (ODS)	18	21.4	9	83	9	13	0	0	0	0	0	Polyest.	2	Vagina	Levator ani
[28]	176	60	47 (C)	26.3	7	3.9	0	13		100	25	0	0	0	0	polyprop.	2	Vagina (before the trigone)	Levator ani
[29]	116	34	2 (C;D)	1.7 (C) 0 (D)	6	5.1	56	0		28	1	0	0	0	0	Polyest.	2	Vagina	Levator ani
[30]	501	20.7	28 (C)	5.5	18	3.5	nr	nr		nr	0	0	0	0	0	Polyest./ polyprop.	2	Vagina (before the trigone)	Levator ani
[31]	80	12	13 (ODS)	16.2	10	12.5	47	0		37	0	0	0	0	0	Polyest.	2	Vagina (3° superior)	Levator ani
[32]	150	2	8 (C;ODS)	3.3 (C) 2 (ODS)	10	6.6	26	0		35	0	0	0	0	0	Polyest./ polyprop.	1 or 2	nr	Levator ani
	2165 (total)	26.5 (mean)	268 (total)	12.3 (mean)	139 (total)	6.4 (mean)													

ACR: Anterior colporrhaphy; C: Constipation; D: Dischezia; FU: Follow up; LM: Levator miorrhaphy; nr: Not reported; PCR: Posterior colporrhaphy; PVR: Paravaginal repair; SLH: Subtotal laparoscopic hysterectomy; TLH: Total laparoscopic hysterectomy; TOT/TVT: Transobturator tape/tension-free vaginal tape; Uterus pres.: Uterus preservation.

our review did not show a linear relationship between the urinary and bowel dysfunction (Pearl index -0.04) (Table 3). Furthermore, the dysfunctional patients reported a slight worsening in their sexuality, even if this was not statistically significant.

We are well aware that this study does have limitations, *i.e.*, its retrospective design and the relatively small sample size. However, the comparable follow-up period and population sample, the absence of concomitant surgical procedures and the administration of validated questionnaires, allowed us to mitigate confounders and make an adequate assessment of the dysfunctional symptoms.

The nerve preserving technique we developed has shown to be both effective and safe. Moreover, it took no longer than did the standard technique to perform and there were no major intraoperative complications. The curve of nerve preserving procedure time demonstrated no specific learning effect.

Furthermore, we are of the opinion that our technique should be studied in a systematic fashion and cannot be generalized due to the heterogeneity in the suspension techniques and anchoring sites used by other authors. However, our personal experience and the data we have obtained, lead us to conclude that a midline, medial dissection, over the sacral promontory, close to the mesosigma insertion, is to be avoided and that the location of neural pathways must be borne in mind throughout the steps involved in this urogynecological procedure.

linguistic advice.

COMMENTS

Background

The authors recently carried out an anatomoclinical study on the laparoscopic sacropexy (LSP) which demonstrated the correlation between the iatrogenic lesion of the autonomic nerves during sacral promontory dissection and postoperative obstructed defecation syndrome (ODS), identifying the fibers involved in the caudal part of the superior hypogastric plexus (SHP). The aim of this current observational study was to evaluate the efficacy and safety of a modified sacral dissection technique that the authors later adopted and called "nerve preserving".

Research frontiers

Results from this study may encourage surgeons to develop and systematically adopt pelvic nerve sparing techniques also for other kinds of benign reconstructive surgery with the aim of improving the patients' quality of life. Although nerve preserving technique does seem to be effective, the interesting data the authors obtained, require further confirmatory study and research.

Innovations and breakthroughs

Patient quality of life is the goal of every surgical procedure which approaches a benign pathology. However there is a risk of invalidating the good results due to the iatrogenic morbidity that follows many surgical procedures. The nervous origin of the bowel complications after LSP has sometimes been invoked, but without any further elaboration. "Borrowing" a concept from oncological surgery, the authors developed and applied a nerve sparing technique in this benign pathology. To the best of our knowledge, to date, there are no published data on the clinical outcomes of a nerve preserving technique in a benign gynaecological procedure.

Applications

The research attempted to reduce the relevant iatrogenic morbidity of a procedure considered the "anatomical gold standard" in the correction of the central segment prolapse. This retrospective study supports the hypothesis that a nerve preserving technique produces better clinical outcomes. The results from future randomized controlled trials could well provide a higher level of evidence as to the potential benefits of this procedure.

Terminology

In this study, "nerve preserving" technique during LSP referred to a surgical procedure that aims at sparing the autonomic component of the female pelvis, specifically the orthosympathetic fibers of the SHP and the right hypogastric nerve.

Peer-review

It is a well written manuscript concerning the outcome of nerve preserving procedure in laparoscopic sacropexy focusing on the outcome of bowel function. It is very helpful for the readers.

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ORIGINAL ARTICLE

Observational Study

Adult intussusception: A case series and review

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Abstract

AIM

To identify factors differentiating pathologic adult intussusception (AI) from benign causes and the need for an operative intervention. Current evidence available from the literature is discussed.

METHODS

This is a case series of eleven patients over the age of 18 and a surgical consultation for "Intussusception" at a single veteran's hospital over a five-year period (2011-2016). AI was diagnosed on computed tomography (CT) scan and or flexible endoscopy (colonoscopy). Surgical referrals were from the emergency room, endoscopy suites and the radiologists.

RESULTS

A total of 11 cases, 9 males and 2 females were diagnosed with AI. Median age was 58 years. Abdominal pain and change in bowel habits were most common symptoms. CT scan and or colonoscopy diagnosed AI, in ten/eleven (90%) patients. There were 6 small bowel-small bowel, 4 ileocecal, and 1 sigmoid-rectal AI. 8 patients (72%) needed an operation. Bowel resection was required and definitive pathology was diagnosed in 7 patients (63%). Five patients had malignant and 2 patients had benign etiology. Small bowel enteroscopy excluded pathology in 4 cases (37%) with AI. Younger patients tend to have a benign diagnosis.

CONCLUSION

Majority of AI have malignant etiology however idiopathic intussusception is being seen more frequently. Operative intervention remains the mainstay however, certain small bowel intussusception especially in younger patients may be a benign, physiological, transient phenomenon and laparoscopy with reduction

or watchful waiting may be an acceptable strategy. These patients should undergo endoscopic or capsule endoscopy to exclude intrinsic luminal lesions.

Core tip: In the current era with advances in diagnostic imaging techniques and overutilization of computed tomography, idiopathic or asymptomatic intussusception is being seen more commonly. The majority of adult intussusceptions however, have pathologic etiology. Patients with palpable mass, obstruction, gastrointestinal bleeding, or a lead point on computed tomography should undergo operative exploration. Certain small bowel intussusception may have a benign, physiological cause and laparoscopy with reduction may be an acceptable strategy. However these patients should undergo small bowel enteroscopy or capsule endoscopy if not obstructed to exclude luminal lesions. All colonic intussusceptions should be resected *en-bloc* without reduction, whereas a more selective approach may be applied for entero-enteric intussusceptions.

INTRODUCTION

Intussusception is an infrequent cause of bowel obstruction in adults compared to pediatric age group[1]. Any focus of an intraluminal irritant such as inflamed mucosa or a mass lesion may act as a lead point and the resulting hyperperistaltic activity causes a segment of bowel (intussusceptum) possibly along with its mesentery to telescope into the adjacent distal bowel lumen (intussuscipiens). Adult intussusception is classified according the location of the lead point as entero-enteric, ileocolic, ileocecal, and colo-colic.

Ninety percent of adult intussusception (AI) patients harbor a pathological process. In contrast majority of pediatric patients have a benign or physiologic diagnosis[2]. In the pediatric population non-surgical therapies such as pneumatic or hydrostatic reductions is sufficient to treat this condition in 80% of patients. Surgical management remains the mainstay treatment modality for a majority of patients with AI.

The frequent use of abdominal computed tomography (CT) scans for abdominal imaging has led to increased detection of small bowel intussusception which may be a benign, physiological, transient phenomenon with no apparent underlying disease[3]. With the advances made in three dimensional CT scans, flexible endoscopy, enteroscopy and capsule endoscopy, surgical exploration and bowel resection may not be necessary in all AI and surgical treatment should be tailored to individual patients. The present study reviews our experience of this clinical entity.

MATERIALS AND METHODS

This is a case series of eleven patients over the age of 18 with a surgical consultation for "Intussusception" at a single veteran's hospital over a five year period (2011-2016). These patients were diagnosed with AI on various modes of investigation such as CT scan and or flexible endoscopy (colonoscopy). These surgical referrals were from the emergency room, endoscopy suites and the radiologists. There were no exclusion criteria. We specifically aimed to identify factors which will differentiate pathological from benign causes, such as age, sex, prior operations, and malignancy. The clinical features, diagnostic studies, surgical findings, surgical techniques, final pathology and surgical follow up were reviewed from the medical charts and are discussed. An electronic search of PubMed, Medline was performed; the search terms used were intussusception, adults, bowel obstruction. The references from the retrieved literature were further searched for relevant studies.

RESULTS

Age, gender and clinical presentation

A total of 11 patients with a diagnosis of AI were identified from surgical consultation database with a diagnosis of intussusception (Table 1, Figures 1-5). There were 9 males and 2 females. The median age at diagnosis was 58 years. with a range of 26-74 years. Coincidently none of these 11 patients had prior abdominal operations. A single patient had a prior history of malignancy (lung). Abdominal pain was the most common presenting symptom (80%). Changes in the bowel pattern (constipation/diarrhea) were other symptoms (50%). Three patients (27%) presented with acute small bowel obstruction. Acute gastrointestinal tract bleeding was present in two patients (18%) and one patient (9%) was asymptomatic with jejunal intussusception as an incidental finding diagnosed on the CT scan. None of the patients had anemia, or familial syndromes such as familial adenomatosis polyposis (FAP), juvenile polyposis syndrome, Peutz-Jeghers syndrome, or Lynch syndrome to suggest increased risk for small and large bowel malignancy.

Diagnostic studies

CT scan was the most frequently used diagnostic imaging test and identified AI in nine/eleven (81%) patients. It confirmed a mass lesion in seven/eleven (63%) patients, and diagnosed obstruction in three/eleven (27%) patients. Colonoscopy was performed on

Table 1 Case series adult intussusception

Case sex/age (yr)	Presentation	Classification	Diagnostic modality	Operation	Pathology	Follow up months	Lead point
Case 1 F/65	Chronic abdominal pain	Ileocecal	Colonoscopy	Right hemicolectomy	Lipoma	65	Ileocecal valve (Figure 1)
Case 2 M/54	Chronic abdominal pain	Ileocecal	Colonoscopy	Right hemicolectomy	Terminal ileal carcinoid	25	Terminal ileum (Figure 2)
Case 3 M/65	Acute small bowel obstruction	Jejunal-Jejunal	CT scan	Small bowel resection	Metastatic lung cancer	27	Jejunal
Case 4 M/50	Incidental finding	Jejunal- Jejunal	CT scan, small bowel enteroscopy	None	Idiopathic	14	None
Case 5 M/58	GI bleeding	Ileocecal	Colonoscopy	Right hemicolectomy	Tubulo-villous adenoma	16	Ileocecal valve (Figure 3)
Case 6 M/74	Partial small bowel obstruction	Ileocecal	CT scan and colonoscopy	Right hemicolectomy	GIST	6	Terminal ileum (Figure 4)
Case 7 M/63	Acute small bowel obstruction	Ileal-ileal	Laparotomy	Small bowel resection	Poorly differentiated adenocarcinoma	6	Mid ileum
Case 8 M/26	Acute small bowel obstruction	Jejunal-jejunal	CT scan and laparoscopy	Laparoscopy and reduction	Idiopathic/*H. pylori* duodenitis	5	None (Figure 5)
Case 9 F/38	Chronic abdominal pain	Jejuno-jenunal	CT scan, small bowel enteroscopy	None	Idiopathic/*H. pylori* duodenitis	4	None
Case 10 M/66	GI bleeding	Sigmoid-rectal	Colonoscopy	Low anterior resection	Adenocarcinoma	3	Sigmoid
Case 11 M/58	Abdominal pain	Jejunal-jejunal	CT scan, small bowel enteroscopy	None	Idiopathic	2	None

CT: Computed tomography; GIST: Gastrointestinal stromal tumor; GI: Gastrointestinal.

Figure 1 Cecal mass (black arrow, lead point) pulling the terminal ileum (blue arrow) causing intermittent intussusception, appendix is depicted by yellow arrow.

five/eleven patients and diagnosed AI in one patient. It however confirmed a mass in all five patients and permitted a biopsy which assisted with a definitive operative planning. The diagnosis of AI was made preoperatively in ten/eleven (90%) patients with the above modalities.

Small bowel enteroscopy (SBE) was performed on four/eleven patients. It was primarily chosen in three patients for patients who had a non-operative conservative care with resolution of symptoms and one patient after diagnostic laparoscopy. These patients were in a younger age group and had a low index of suspicion for a pathological diagnosis. SBE was performed to exclude any intraluminal small bowel pathology and to confirm the transient, physiological cause for AI in these patients. All four patients had a normal SBE exam and therefore these patients were

diagnosed as idiopathic AI.

Treatment, pathology and follow up

Six (54%) patients had a lead point of the intussusception (one in the small bowel, four at the ileocecal region, and one sigmoid-rectal). Total of eight patients (72%) needed an operation. Three of the operated eight patients presented with acute intestinal obstruction and underwent emergency operation (37.5%). The rest five patients were operated on an elective basis.

Laparotomy in seven/eight (87.5%) and a diagnostic laparoscopy in one/eight (12.5%) were performed. Multiple jejunal-jejunal AI was observed in this last patient (case 8; Table 1) and laparoscopic reduction was performed without bowel resection. A subsequent small bowel enteroscopy ruled out an intrinsic lesion. In the laparotomy group four/eight patients had a right hemicolectomy due to ileocecal mass, two patients had small bowel resection and one had a low anterior resection for a malignant mass.

In three/eleven patients with subacute presentation, pathologic AI and intraluminal pathology was excluded with a small bowel enteroscopy thus avoiding an operation. There were six entero-enteric, four ileocecal, and one sigmoid-rectal AI. Ileocecal and colo-colic AI had a definitive pathology, while most jejuno-jejunal AI was transient and physiologic. The location, pathology, extent of surgery and follow up are presented in Table 1.

A definitive pathologic diagnosis was seen in seven/eleven (64%) patients. Of these cases five (46%) had malignant etiology and two (18%) had benign etiology. Four patients had no abnormality and were idiopathic (36%). Two of these four patients tested positive for *H. pylori* duodenitis on small bowel enteroscopy. This was
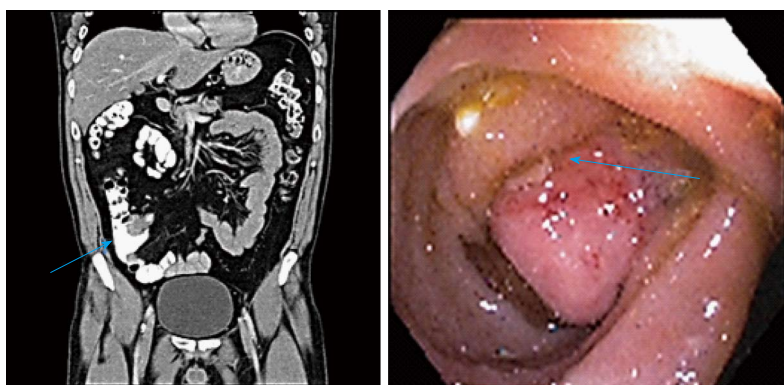
Figure 2 Terminal ileal mass intussusception into the cecum. Computed tomography (CT) scan shows the mass, colonoscopy view confirms the CT finding. Both depicted with a blue arrow.
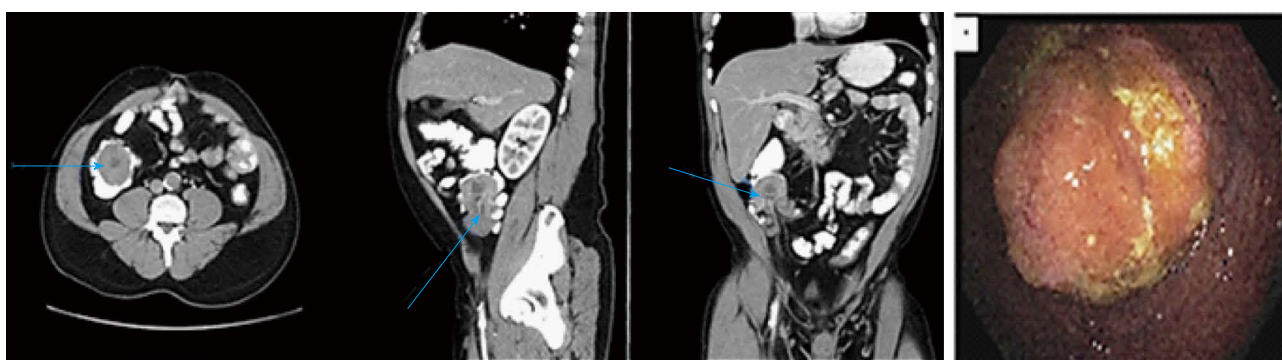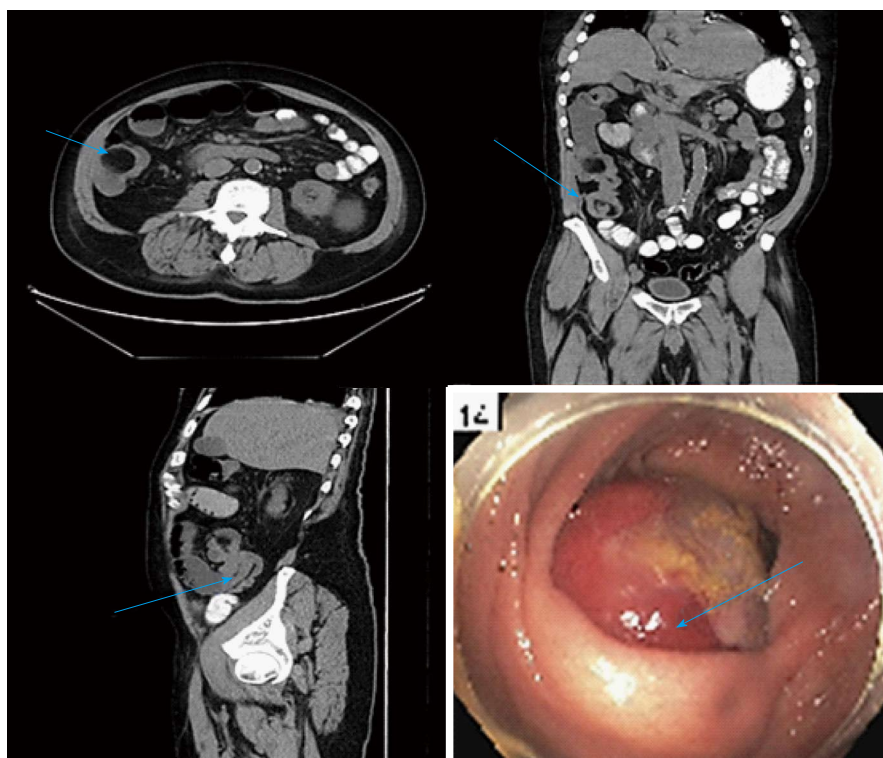

Figure 3 Ileocecal Intussusception. Computed tomography scans (axial, sagittal, coronal) shows the terminal ileum intussusception in the cecum. Colonoscopy confirms the mass protruding into the cecum.
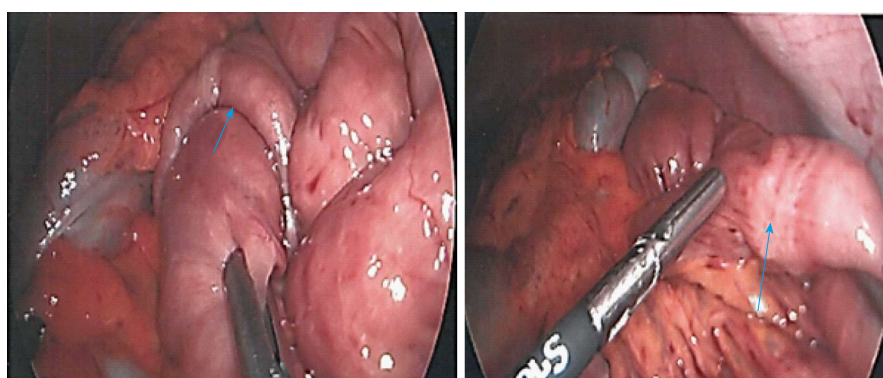
probably an incidental finding. There were no significant post-operative morbidities or thirty day mortality.

The mean follow up was 15 mo, range 2-65 mo. Ninety percent of the patients were alive and only one patient with poorly differentiated adenocarcinoma of ileum succumbed to his disease.

DISCUSSION

AI is a rare finding and an unusual cause of bowel obstruction. They are an infrequent cause in adult patients although common in pediatric population. It represents 1% of all bowel obstructions in adults and 5% of all intussusceptions[1].

Although pathologic in most instances, 20% of patients have no apparent etiology and are labelled as primary or idiopathic. Idiopathic AI is more likely to occur in the small intestine[1,2,4]. The majority of secondary AI have a lead point (Table 2). Most lead points in the small intestines are of benign etiology and comprises of inflammatory polyps, lipomas, leiomyoma, Meckel's diverticulum and post-operative adhesions[5-7]. Patient with Crohn's disease and celiac disease are known to present with transient AI of small bowel and generally manifest as a non-lead point intussusception[3,8]. Malignant lesions include primary

Table 2 Lesions associated with intussusception		
Benign	**Malignant**	
	Primary	Metastatic
Crohns disease	Adenocarcinoma	Melanoma
Celiac disease	Gastrointestinal stromal tumor	Lung
Lipoma	Carcinoids	Renal cell cancer
Leiomyoma	Leiomyosarcomas	Breast
Neurofibromatosis	Lymphoma	
Fibro-epithelial polyps		
Henoch-Schonlein purpura		
Human immunodeficiency virus		
Post-operative adhesions		
Endometriosis		
Meckel's diverticulum		

tumors such as carcinoids, adenocarcinoma, malignant polyps, gist's, leiomyosarcomas, lymphoma and metastatic tumors, most commonly melanoma[2,9-11]. Majority of AI involving the ileocecal region and large bowel have a malignant etiology[1,12,13]. In a large multicenter study of forty four patients with AI, 37% with small bowel and 58% with colonic AI were malignant[14]. Abdominal pain is the most common symptom of AI, followed by change in bowel habits, nausea and vomiting, gastrointestinal bleeding. The majority of adult patients have chronic abdominal symptoms

Figure 4 Ileocecal intussusception. Computed tomography scans (axial, sagittal, coronal) shows the mass intussusception in the cecum. Colonoscopy confirms the mass protruding through the ileocecal valve.

Figure 5 Laparoscopic view of jejunal-jejunal intussusception which was reduced. Physiologic peristalsis, idiopathic finding.

consistent with chronic partial small bowel obstruction.

Diagnostic tests

A contrasted CT scan of the abdomen and pelvis is the most sensitive imaging modality to detect intussusception. Characteristic features include a soft tissue mass, target or sausage shaped, enveloped with an eccentrically located area of low density. Findings of a bowel within bowel configuration with or without mesenteric fat and mesenteric vessels are pathognomonic for intussusception[3]. CT scans also provides other critical information such as length and diameter of the intussusception, three dimensional views of the bowel and surrounding viscera, possible lead point, type of and location of intussusception, the mesenteric vasculature, possibility of strangulation,

and the likelihood of partial or complete bowel obstruction[15,16]. In general AI without a lead point is transient and may resolve spontaneously. Further if there is no associated bowel obstruction, these patients may not require an operation[3]. Our series had four patients with a CT diagnosis of intussusception without a lead point and a subsequent negative small bowel enteroscopy examination.

In a retrospective analysis of a large number of patients (170/380999, 0.04%) diagnosed with AI on the CT scan, demonstrated differences in length, diameter, lead point and bowel obstruction amongst the three categories of patients: (1) observed without operation; (2) without intussusception on exploration; and (3) with confirmed intussusception. In these study patients with CT scan findings of intussusception

length less than 4 cm were more likely to respond to conservative management and have transient AI compared to patients with intussusception length of 9.6 cm. Similarly patients with an intussusception diameter of less than 3.2 cm were more likely to have transient AI compared to a diameter of greater than 4.8 cm in pathological AI. Finally patients with presence of a lead point AI and bowel obstruction had a fifty percent likelihood of pathologic AI.

The authors concluded that AI discovered by CT scanning does not always mandate exploration. Most cases can be treated expectantly despite the presence of gastrointestinal symptoms. Close follow up was recommended with imaging and endoscopic surveillance[17].

Another retrospective study of CT scan in diagnosing pathologic intussusception suggested length of intussusception shorter than 3.5 cm as likely to be transient, self-limiting. However there was a lack of pathological correlation in this study[18].

Abdominal ultrasonography has been a useful technique in the diagnosis of AI[19]. The features described include a target and doughnut signs on the transverse view and a pseudo kidney sign on a longitudinal view[20,21]. Ultrasonography carries no radiation risks and is readily available; however in our opinion the test is operator dependent and requires an experienced examiner. Further limitations include obesity and bowel gas which may obscure the typical findings and information on mesenteric vasculature, location and surrounding viscera is not clearly defined. It may however play a role in self-limiting, transient AI as seen in celiac disease and Crohn's disease to monitor resolution of intussusception and thus avoiding repeated CT scans and exposure to radiation[19].

Flexible endoscopy including colonoscopy and small bowel enteroscopy may be a useful diagnostic tool in patients with subacute or chronic intermittent bowel obstruction[22,23]. It permits the confirmation of the intussusception, location and biopsy to aid with the diagnosis and plan surgery[24]. Colonoscopy is most useful for AI involving the colon and the terminal ileum and cecum[25]. Small lesions can be snared endoscopically if the surrounding bowel appears normal without signs of inflammation or ischemia, however lesions larger than 2 cm with a wide base should not excised due to increased risk of perforation of the bowel[6]. In our series colonoscopy was performed in five patients and confirmed a mass in all five cases. Small bowel enteroscopy was used in four patients and was able to rule out an intrinsic lesion, thus preventing an operation in three patients and bowel resection in the third. Flexible endoscopy should be avoided in patients with acute obstruction as it may increase the risk for perforation[26].

Management
Ninety percent of AI patients harbor a pathological process[1,14]. Surgical management remains the main-

stay treatment modality for a majority of patients with AI. Surgical decision making and the extent of resection depends upon factors such as presence of acute bowel obstruction with jeopardized mesentery, the probability of a malignant etiology, the location of the intussusception[27]. Before the advent of diagnostic modalities, immediate laparotomy and bowel resection without reduction was the standard of care and advocated by most surgeons[1,12,28]. The current controversy remains on the extent of surgical resection *vs* reduction of the intussusception. The initial favor to resect *en-bloc* the intussuscepted segment of bowel was based on the theoretical risks of venous embolization of the tumor cells on bowel manipulation and also the risks of perforating the ischemic, friable, edematous bowel which may lead to seeding of tumor cells and microorganisms into the peritoneal cavity[1,29]. However it lacks supportive evidence as most of the literature is based on case reports, series and anecdotal evidence. Certain authors have questioned these hypothesis and selective criteria for reduction and resection have been proposed[27,30].

Our experience suggests a more conservative approach to AI. Only three patients in our series presented with acute bowel obstruction, confirmed on the CT scan and required an immediate operation. Two of these patients required small bowel resection and one patient had intussusception reduced. This last patient subsequently had a small bowel enteroscopy followed by a capsule endoscopy and no intraluminal lesion was discovered labelling it as idiopathic. Five patients with intermittent chronic partial small bowel obstruction and GI tract bleeding had further diagnostic tests such as colonoscopy, small bowel enteroscopy and a CT scan. This provided us with an opportunity to complete workup, stage the patients and administer bowel preparation for a planned definitive surgical resection. Small bowel enteroscopy in three patients with jejunal-jejunal intussusception excluded intraluminal lesions and no operation was performed in these patients. The AI resolved in the subsequent scans in these three patients and they remain symptom free.

Small bowel intussusception may be reduced intraoperatively only in patients in whom a benign diagnosis or medically treatable diseases such as inflammatory bowel disease is strongly suggested preoperatively, and in patients in whom resection may result in short gut syndrome[4,13,31-33]. In addition we recommend a follow up small bowel enteroscopy and or a capsule endoscopy in these idiopathic, non-obstructed patients to exclude any intrinsic luminal lesions which may lead to recurrent intussusception.

We agree with other authors that colonic lesions should be resected without reduction as most of these could harbor a pathologic etiology and may not respond to conservative management[14,25,34,35].

Any AI with signs of mesenteric vasculature compromise, strangulation, severe bowel edema, complete bowel obstruction and elevated white blood cell counts

should undergo segmental resection as the risks for perforation with contamination of the peritoneal cavity remains high[36,37].

Diagnostic laparoscopy and resection has been used successfully in selected patients with AI. In patients with chronic and subacute presentation with partial small bowel obstruction, laparoscopy offers the benefit of a conservative approach with possible reduction of the bowel and provides clues to the etiology[38]. In a series of 12 patients with AI, laparoscopic diagnosis and resection was accomplished safely without significant morbidity or mortality[39]. Another series reported eight patients with AI where laparoscopy with reduction and resection was performed without any complications or conversions. The laparoscopic approach thus offers both a diagnostic, and a therapeutic option for intussusception in adults[40]. However we urge caution in using laparoscopy in acutely obstructed patients with bowel distension where visualization may be poor, and bowel manipulation may further risk perforation and increase the morbidity of an operation.

In general, preoperative probability of harboring a malignancy is higher in patients older than sixty years, previous history of malignancy such as melanoma, lung cancers, and patients with genetic risks for small bowel malignancy such as FAP, Lynch syndrome, chronic long standing history of Crohn's disease and celiac disease[41]. Reduction should not be attempted in these patients as malignancy may be difficult to confirm or exclude intraoperatively. Bowel resection is recommended for this subset of patients. Patients with Peutz-Jeghers syndrome are predisposed to multiple small bowel polyps which may frequently cause intussusception. A combined surgical and endoscopic approach can assess the extent of the polyposis, and small polyps can be removed by snare polypectomy. This may prevent multiple laparotomies and resections reducing the risk of short bowel syndrome[42].

In the current era with advances in diagnostic imaging techniques and overutilization of computed tomography, idiopathic or asymptomatic intussusception is being seen more commonly. The majority of adult intussusceptions however, have pathologic etiology. Patients with palpable mass, obstruction, gastrointestinal bleeding, or a lead point on computed tomography should undergo operative exploration. Certain small bowel intussusception especially in younger patients may have a benign, physiological cause and laparoscopy with reduction may be an acceptable strategy. However these patients should undergo small bowel enteroscopy or capsule endoscopy if not obstructed to exclude intraluminal lesions. All colonic intussusceptions should be resected *en-bloc* without reduction, whereas a more selective approach may be applied for entero-enteric intussusceptions.

Our series has limitations for being a retrospective study and with small volume. There is a potential for selection and referral bias. Because of rarity of the outcome, the study may be underpowered. However as mentioned AI is a rare finding and clinical presentation and acuity should determine the operative decision making *vs* conservative care with a close follow up.

COMMENTS

Background
In the current era with advances in diagnostic imaging techniques and overutilization of computed tomography, idiopathic or asymptomatic intussusception is being seen more commonly. The majority of adult intussusceptions however, have pathologic etiology. Certain small bowel intussusception especially in younger patients may have a benign, physiological cause and laparoscopy with reduction may be an acceptable strategy.

Research frontiers
Small bowel enteroscopy or capsule endoscopy are important diagnostic tools in evaluating patients with small bowel intussusceptions which in many younger patients may be a physiologic, normal peristalsis. This is especially useful if patients do not present with obstruction, to exclude intraluminal lesions. Further research is needed to elucidate the role of these diagnostic modalities.

Innovations and breakthroughs
Small bowel adult intussusception (AI) discovered by computed tomography scanning does not always mandate exploration. Most cases can be treated expectantly despite the presence of gastrointestinal symptoms. Close follow is recommended with imaging and endoscopic surveillance. However patients with palpable mass, obstruction, gastrointestinal bleeding, or a lead point on computed tomography should undergo operative exploration.

Applications
Flexible endoscopy including colonoscopy and small bowel enteroscopy may be a useful diagnostic tool in patients with subacute or chronic intermittent bowel obstruction. It permits the confirmation of the intussusception, location and biopsy to aid with the diagnosis and plan surgery. Colonoscopy is most useful for AI involving the colon and the terminal ileum and cecum. Small lesions can be snared endoscopically if the surrounding bowel appears normal without signs of inflammation or ischemia, however lesions larger than 2 cm with a wide base should not excised due to increased risk of perforation of the bowel.

Peer-review
The author presents an interesting study and review on a less frequent but certainly relevant and important entity to gastrointestinal disease, surgery, and endoscopy.

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META-ANALYSIS

Does music reduce anxiety and discomfort during flexible sigmoidoscopy? A systematic review and meta-analysis

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Abstract

AIM

To investigate the role of music in reducing anxiety and discomfort during flexible sigmoidoscopy.

METHODS

A systematic review of all comparative studies up to November 2016, without language restriction that were identified from MEDLINE and the Cochrane Controlled Trials Register (1960-2016), and EMBASE (1991-2016). Further searches were performed using the bibliographies of articles and abstracts from major conferences such as the ESCP, NCRI, ASGBI and ASCRS. MeSH and text word terms used included "sigmoidoscopy", "music" and "endoscopy" and "anxiety". All comparative studies reporting on the effect of music on anxiety or pain during flexible sigmoidoscopy, in adults, were included. Outcome data was extracted by 2 authors independently using outcome measures defined a priori. Quality assessment was performed.

RESULTS

A total of 4 articles published between 1994 and 2010, fulfilled the selection criteria. Data were extracted and analysed using OpenMetaAnalyst. Patients who listened to music during their flexible sigmoidoscopy had less anxiety compared to control groups [Random effects; SMD: 0.851 (0.467, 1.235), S.E = 0.196, $P < 0.001$]. There was no statistically significant heterogeneity ($Q = 0.085$, df = 1, $P = 0.77$, $I^2 = 0$). Patients who listened to music during their flexible sigmoidoscopy had less pain compared to those who did not, but this difference did not reach statistical significance [Random

effects; SMD: 0.345 (-0.014, 0.705), S.E = 0.183, P = 0.06]. Patients who listened to music during their flexible sigmoidoscopy felt it was a useful intervention, compared to those who did not ($P < 0.001$). There was no statistically significant heterogeneity ($P = 0.528$, $I^2 = 0$).

CONCLUSION
Music appeared to benefit patients undergoing flexible sigmoidoscopies in relation to anxiety and was deemed a helpful intervention. Pain may also be reduced however further investigation is required to ascertain this.

Key words: Music; Flexible sigmoidoscopy; Anxiety; Discomfort; Screening

Core tip: The use of flexible sigmoidoscopy is becoming more prevalent particularly in the context of bowel cancer screening; however uptake remains low and patients are often anxious when attending about discomfort and embarrassment. We conduct a systematic review and meta-analysis of studies investigating the role of music in reducing anxiety and discomfort in patients undergoing screening flexible sigmoidoscopy. In our review, music reduced anxiety and was deemed a helpful intervention by the patients. It may also reduce discomfort but further studies are required to confirm this. Music may potentially improve patient experience and have a positive effect on the test uptake.

INTRODUCTION

Rationale
Colorectal cancer is the third most common cancer diagnosed amongst men, and second amongst women. It is the fourth common cause of cancer deaths[1]. The United Kingdom Flexible Sigmoidoscopy Trial demonstrated that a once only flexible sigmoidoscopy screening between ages 55 and 64[2], significantly reduced the incidence of colorectal cancers and cancer-related mortality from the disease. Following this study, screening using flexible sigmoidoscopy was piloted across six centers in England, inviting anyone aged 55 years to undergo screening. The uptake was 43% (45% in men and 42% in women, 33% in low socioeconomic areas)[3]. A Study on patient attitudes towards screening

flexible sigmoidoscopy (FS) showed as possible reasons for poor uptake to be embarrassment and concern regarding pain during the procedure[4]. Anxiety is also thought to be an important factor that may deter patients undergoing screening FS[5].

Given the benefit of FS screening, techniques designed to improve patient tolerance without increasing costs may lead to an increase in uptake. Methods such as distraction have previously been used as cost-effective and noninvasive interventions to alleviate acute and chronic pain[6]. It would therefore be useful to see if distraction techniques such as music can be used to reduce anxiety and pain in patients undergoing flexible sigmoidoscopy.

Music has been shown to modulate activity in parts of the brain that control emotions[7,8], and modulate the dopaminergic systems of the brain[9,10]. The association between music and emotions is complex and can be explained by a series of mechanisms including brain stem reflexes, musical expectancy and contagion[11]. A meta-analysis by Lee found music to be an effective complimentary adjunct, for pain and discomfort in different scenarios like acute or chronic pain, during procedures and cancer[12]. Cepeda *et al*[13] agreed that music can reduce pain intensity and requirements for analgesia, but suggested that the size of these effects was small.

Music has been shown to reduce anxiety levels in patients who have had acute myocardial infarction[14]. In promoting relaxation and diverting attention from anxiety or painful stimuli[5] music has been utilized as a tool to improve user experience in sectors like hospitality, through a positive perceptual experience. Music as a therapy is regarded as one of the most effective distraction techniques with high level of patient compliance[15], because it introduces a competing sensory stimulus, which alters the cognitive perception of pain.

Objective
This article focuses on the role of music on anxiety, pain scores and helpfulness during flexible sigmoidoscopy. Our primary hypothesis was that music results in lower post-procedural anxiety compared to those who do not listen to music in the endoscopy room. Secondary hypotheses were: (1) that there is less pain in the music group; and (2) patients find music helpful during their procedure. Anxiety and pain were assessed using a continuous scale whilst helpfulness was a binary outcome.

MATERIALS AND METHODS

The title, methods and outcome measures were stipulated in advance and the protocol is available in the PROSPERO database[16].

We searched the MEDLINE, EMBASE and CINAHL databases available through the NHS National Library

Figure 1 Flow diagram of search strategy.

Table 1 Inclusion criteria

All studies reporting on music therapy during flexible sigmoidoscopy
All comparative studies using any control
All study designs, adults of any sex and any languages

of Health website, the Cochrane library and PubMed available online, up to November 2016. There was no language restriction. Text words "music", "melody", "opera", "classical music", "distraction", "flexible sigmoidoscopy", "anxiety", "screening" and "endoscopy" were used in combination with the medical subject heading "sigmoidoscopy" and "music". Relevant articles referenced in these publications were obtained and the references of identified studies were searched to identify any further studies. A flow chart of the literature search according to PRISMA guidelines is shown in Figure 1[17].

We identified and selected all comparative studies reporting the use of any type of music in adult patients of any age or gender undergoing flexible sigmoidos-copy. No regional restriction was placed. No language or publication date restriction was used. Studies that reported on anxiety, pain or usefulness of music during procedure irrespective of assessment methods used were included (Table 1). Studies, which used post-procedure questionnaires assessing whether

patients found music helpful, were also included. Each included article was reviewed by two researchers (MRSS and APS). This was performed independently and where more specific data or missing data was required the authors of manuscripts were contacted. Data was entered onto an Excel worksheet and compared between authors. Any disagreements that arose between the reviewers were resolved through discussion and if no consensus could be reached, a third senior author would decide.

Patient demographics and study characteristics were extracted from the relevant studies. The study characteristics included were country of origin, year, music selection and study type. Patient demographics included total number of patients, age and gender (Tables 2 and 3).

Statistical analyses were performed using OpenMeta-Analyst (http://www.cebm.brown.edu/openmeta)[18]. Conventional comparative meta-analytical techniques were used. For comparative outcomes, a value of $P <$ 0.05 was chosen as the significance level for outcome measures. Binary data was summarized using risk ratios (RR) and combined using the Mantel-Haenszel method for fixed effects and the DerSimonian and Laird method in the random effects model[19]. For continuous data (anxiety and pain scores), Hedges g statistic was used for the calculation of standardized mean differences

A

B

Figure 2 Authors performed assessment independently. A: Risk of Bias Graph review authors' judgements about each risk of bias item presented as percentages across all included studies; B: Risk of bias summary; review authors' judgements about each risk of bias item for each included study.

(SMD). The SMDs were combined using inverse variance weights in the fixed effects model and the DerSimonian and Laird method in the random effects model[19]. Heterogeneity of the studies was assessed according to Q and I^2. A random effects method was used due to presence of clinical heterogeneity. In a sensitivity analysis, 0.5 was added to each cell frequency for trials in which no event occurred, according to the method recommended by Deeks *et al*[20]. Forest plots were used for the graphical display. The statistical methods used were reviewed by MRS Siddiqui, PhD Research Fellow at The Royal Marsden Hospital NHS Trust and Croydon University Hospital, London, United Kingdom.

The methodological quality of the trials included for meta-analysis was assessed using the risk of bias tool available from Revman Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014)[21]. Authors performed assessment independently (Muhammed R S Siddiqui and Arun P Shanmuganandan) (Figure 2). There were insufficient studies to perform a meta-regression according to music type, patient age and gender. Furthermore, we could not formally assess for publication bias due to the

Table 2 Study characteristics

Ref.	Year	From	Types of music used	Control population			Study population		
				n	Age (mean)	Sex (m/f)	*n*	Age (mean)	Sex (m/f)
Palakanis *et al*[5]	1994	United States	Pt selected from classical, country western, popular, gospel music, blues	25	49	20/5	25	55	17/8
Lembo *et al*[6]	1998	United States	Ocean shore sounds	12	59	12/0	12	60	12/0
Chlan *et al*[15]	1999	United States	Pt selected from classical, country-western, new-age, pop, rock, religious, soundtracks, jazz	34	ND	ND	30	ND	ND
Meeuse *et al*[22]	2010	Europe	Pt selected from classical, English/dutch popular, jazz	154	51	72/82	153	53	75/78

ND: No data; Pt: Patients; m/f: Male/female.

Table 3 Study outcomes

Ref.	Year	Group	*n*	State anxiety score STAI (post procedure)		Anxiety score after SSR		Pain score		Helpful (*n*)
				Score	SD/SEM	Score	SD/SEM	Score	SD/SEM	
Palakanis *et al*[5]	1994	Control	25	31.48	6.7	-	-	-	-	11
		Music	25	25.24	6.7	-	-	-	-	22
Lembo *et al*[6]	1998	Control	12	-	-	4.4	0.6	10.8	1.6	-
		Music	12	-	-	2.8	0.4	9.5	1.3	-
Chlan *et al*[15]	1999	Control	34	41.8	9	-	-	5.2	1.7	19
		Music	30	34.5	9	-	-	4.3	2.1	25
Meeuse *et al*[22]	2010	Control	154	-	-	-	-	40	29	-
		Music	153	-	-	-	-	36	27	-

ND: No data; STAI: State-Trait Anxiety Inventory; SSR: Stress symptom ratings.

low number of studies although this may imply inherent bias highlighting the need for further studies.

RESULTS

Study selection

Three hundred and six articles were screened for relevance (Figure 1). The electronic databases searched (Medline, Cochrane, EmBase) yielded 177 records and in addition 129 citations were identified through bibliographies and conference proceedings. After removal of duplicates 297 unique records were left. Records were excluded if they were deemed irrelevant or not related to the study. On further scrutiny, 4 studies[5,6,15,22] reported on outcomes after music during flexible sigmoidoscopy in respect to anxiety, pain scores and whether it was deemed helpful. These studies were chosen based on our inclusion criteria (Table 1). There was no data from any unpublished or grey literature.

Study characteristics and types

The characteristics of the 4 studies included are summarised in Table 2. All 4 studies[5,6,15,22] were published in English. Three studies were carried out in the United States[5,6,15] and one[22] in Europe. All studies were comparative, 3 used randomized allocation, but no blinding. None of the patients received sedation. 3 studies offered patients a choice of music from collections of a variety of styles of music like jazz, classical, country-western, blues, gospel music, pop and rock, while in the fourth study[6], patients listened to ocean shore sounds.

Participants

A total of 445 patients were included in this review. Of the studies that reported sex there were 208 men (55%) and 173 women (45%). Of the studies that reported age the mean was 53.5 years (range = 20-76 years).

Assessment methods

Anxiety was measured using the State-Trait Anxiety Inventory (STAI) and the Stress symptom ratings (SSR). STAI is a widely used tool to measure subject anxiety in two dimensions; State and Trait anxiety. State anxiety is a transitory emotional condition usually as a response to external stimuli, and Trait anxiety is the subject's baseline emotional status. STAI scoring scales consists of 20 statements to which subjects respond as to how they generally feel (Trait) and how they feel currently (State). Scores range from 1-4 for each statement[23,24]. In our meta-analysis the STAI was used by 2 studies. SSR anxiety scoring includes 12 visual analogue scale ratings based on mood-related adjectives and grouped into 6 sub-scales (arousal, stress, anxiety, anger, fatigue, attention). In our meta-analysis the SSR was used by one study[6].

Patient discomfort was measured using either a numeric rating scale or a visual analog scale, which was

Figure 3 Comparison of patient. A: Anxiety with or without music; B: Pain with or without music; C: Comparison of whether patients found music helpful.

quantified using a standardized scale[25,26].

Quality assessment

The methodological quality and risk of bias in the trials included is shown in Figure 2.

Qualitative synthesis of effect on anxiety

Three studies reported on anxiety during or after flexible sigmoidoscopy[5,6,15]. Two studies used the STAI[5,15] score and 1 study used the SSR score[6].

In the studies that used STAI scores, there was no significant difference between the baseline pre-procedure STAI scores: Chlan *et al*[15] , the mean scores were 40.2 ± 11.9 and 36.9 ± 12.5 in the control and music arms, with a *P* = 0.28; in Palakanis *et al*[5], the respective scores were 35.68 and 36.92, with no statistically significant difference.

However, both studies showed post-procedure STAI were statistically different and that patients who listened to music had better scores compared to the control group: In Chlan *et al*[15], the scores were 41.8 ± 13.5 and 34.5 ± 10, with a *P* = 0.002; in Palakanis *et al*[5],

the scores were 31.48 and 25.24, with a *P* < 0.002.

In the study by Lembo *et al*[6], that used SSR scoring system to measure the anxiety, the scores were 4.4 ± 0.6 and 2.8 ± 0.4 in the control and music groups respectively (*P* < 0.05).

Quantitative synthesis of effect on anxiety

Two studies[5,15] contributed to a summative quantitative outcome and used the STAI anxiety scores. Patients who listened to music during their flexible sigmoidoscopy had less anxiety compared to those who did not [Random effects; SMD: 0.851 (0.467, 1.235), S.E = 0.196, *P* < 0.001] (Figure 3A). Statistical heterogeneity between studies was not significant (*Q* = 0.085, df = 1, *P* = 0.77, I^2 = 0).

Qualitative synthesis of pain

Three studies reported on pain during or after the flexible sigmoidoscopy[6,15,22]. In study by Chlan *et al*[15], there was a statistically significant difference between the control and music arms (*P* = 0.026). Subjects in the control group reported mean discomfort ratings of 5.2

± 1.7, while those in the music group, reported lower discomfort ratings of 4.3 ± 2.1.

In the study by Lembo *et al*[6], the subjects in the music group reported a lower discomfort score of 9.5 ± 1.3, when compared to the score in the control group of 10.8 ± 1.6.

In the study by Meeuse *et al*[22], there was no statistically significant difference between the mean pain intensity scores in the control and intervention groups 40 ± 29 and 36 ± 27, *P* = 0.27).

Quantitative synthesis of pain
Three studies[6,15,22] contributed to a summative quantitative outcome. Patients who listened to music during their flexible sigmoidoscopy had lower mean pain scores than those who did not, however this reduction did not reach statistical significance in the random effects model. [Random effects; SMD: 0.345 (-0.014, 0.705), S.E = 0.183, *P* = 0.06] (Figure 3B). Statistical heterogeneity between studies was not significant (*Q* = 3.65, df = 2, *P* = 0.161, I^2 = 45).

Qualitative synthesis of helpfulness
Two studies reported on whether music was helpful during a flexible sigmoidoscopy[15]. In the study by Chlan *et al*[15], 25 of the 30 patients (83%) found the intervention helpful. Nineteen of the 34 (56%) subjects in the control group, did not feel music would have been helpful during the procedure.

In the study by Palakanis *et al*[5], 22 of 25 the subjects (88%) in the music group, deemed the intervention as helpful, while 14 of the 25 subjects (56%) felt music would not have helped or were unsure of its role.

Quantitative synthesis of helpfulness
Two studies[5,15] contributed to a summative quantitative outcome. Patients who listened to music during their flexible sigmoidoscopy found it was a useful intervention and this was statistically significant compared with patients who did not listen to music [Random effects; RR = 0.61 (0.46, 0.80), *P* < 0.001] (Figure 3C). Statistical heterogeneity between studies was not significant (*Q* = 0.999, df = 1, *P* = 0.318, I^2 = 0).

Risk of bias
Three[5,6,15] studies selected patients by randomization; in two of these[5,15] it was by the flip of a coin, while in the other the technique of randomization has not been described[6]. The study by Meeuse *et al*[22], chose control and intervention groups from consecutive patients referred for flexible sigmoidoscopy, during different periods of time. None of the studies describe concealed allocation post randomization. This does lead to an element of selection bias.

Both the subjects and the person carrying out the tests, along with the investigators collecting the data, were not blinded. This theoretically implies a high risk of performance/observer bias, but it is unavoidable

considering the nature of the procedure and intervention being studied.

Publication bias
Publication bias was not formally assessed due to low number of studies. This may indicate there is potential for publication bias and therefore conclusions should be taken with caution. In addition, exclusion of unpublished data is a source of publication bias.

DISCUSSION
Our study has shown that music reduced anxiety during flexible sigmoidoscopy (*P* < 0.001). This is in keeping with other studies[27], which in a similar population to ours showed that music decreased the anxiety levels in patients undergoing awake colonoscopy, without sedation. In a study by Ovayolu *et al*[28], listening to Turkish classical music reduced levels of anxiety and sedative medication. This was further confirmed in a meta-analysis by Rudin *et al*[29]. A subsequent Randomized controlled trial by El-Hassan *et al*[30], demonstrated that music reduced anxiety levels in patients undergoing any type of endoscopic procedure, which was maintained across all age groups. This again is in keeping with our study findings. Music has also shown to reduce the physiological signs of stress like heart rate and blood pressure during colonoscopy, and analgesia requirements[31]. In another study by Uedo *et al*[32] music during colonoscopy reduced salivary cortisol levels, which was a sign of reduced stress levels.

The complex effects of music on emotions through its action on certain parts of the brain and its neurotransmitters can be an explanation for this observation. This may also explain why music reduced anxiety in women significantly when compared to men, during colonoscopy, as they were found to have a significantly higher anxiety scores before the procedure[33]. There were no reviews on effect of music on anxiety in patients undergoing flexible sigmoidoscopy alone.

Our study has also showed that patients who listened to music during flexible sigmoidoscopy deemed it more helpful compared to those who did not [Random effects; RR = 0.61 (0.46, 0.80), *P* < 0.001] (Figure 3C). Statistical heterogeneity between studies was not significant (*Q* = 0.999, df = 1, *P* = 0.318, I^2 = 0). This is in keeping with most other studies involving music during colonoscopy, where the patients felt listening to music was helpful and improved their satisfaction scores[28,34-36].

As for the effect of music on pain and discomfort during flexible sigmoidoscopy, this is less certain. In our study, patients who listened to music had less pain and discomfort compared to those who did not listen to music, but this difference was not statistically significant [Random effects; SMD: 0.345 (-0.014, 0.705), SE = 0.183, *P* = 0.06] (Figure 3B). Statistical heterogeneity between studies was not significant (*Q* = 3.65, df =

2, $P = 0.161$, $I^2 = 45$). One of the studies, by Meeuse *et al*[22], did not reveal any reduction in pain with music, even though the choice of music and method of intervention were not different from the other two studies. It is difficult to explain this dichotomy and lack of uniform response of pain and discomfort to music but interestingly this is replicated in similar studies involving colonoscopy[29,37]. More evidence is needed to study this variable and until then, the potential benefit of music to reduce pain should not be discounted.

The main strength of this study is the comprehensive nature of methodology and hypothesis testing. We employed traditional meta-analytical techniques to answer our hypotheses and highlight the areas that need further investigation and work. The advantage of looking into the utilization of music as an adjunct in flexible sigmoidoscopy means that there is potential for application during any medical procedure that can potentially cause distress, during which patients are awake.

The main limitation in our study pertains to the low number of studies involved in investigating the role of music specific to flexible sigmoidoscopy. Much larger, prospective, better-designed randomized controlled trials with some degree of blinding would have given much more definitive answers to this question. Even though the studies did not exhibit any statistically significant heterogeneity there was some clinical heterogeneity and results should be interpreted with caution.

Assessment of pain and its scoring were not adequately described in the studies, making interpretation difficult. Also, the techniques of patient selection, with particular attention to different subgroups like age, sex, previous surgery, previous sigmoidoscopy, could have been more thorough to make results clinically more relevant. The studies could also have described the length of the intervention, when the intervention started in relation to procedure and the type of music used and choice offered to patient, to make the methodology more comprehensive. The types of music offered to patients could have been described in detail and this may yield itself to a sub-group analysis to study the effects of different types of music.

In summary, this study has effectively documented the potential use of music as a non-pharmacological, almost cost-free intervention for allaying anxiety and potentially reducing discomfort in patients undergoing flexible sigmoidoscopy. The study also showed that music was deemed helpful intervention by patients who listened to it. In the context of relatively low uptake of screening FS, this intervention has the potential to improve patient experience and may facilitate increasing the uptake. However, we feel that further randomized studies with blinding, and involving larger sample sizes may help consolidate our findings. Sub-group analysis, with respect to age, gender, types of music, timing of intervention, duration of the intervention, previous surgery or endoscopy, baseline pain and anxiety scores, experience of the endoscopist, biopsy and therapeutic procedure during sigmoidoscopy, may help clarify further, the benefits of such relaxation and distraction techniques in improving patient experience during flexible sigmoidoscopy.

CONCLUSION

Music appears to reduce anxiety and was deemed a helpful adjunct in patients undergoing flexible sigmoidoscopy. It may also reduce pain during procedure but further studies are required to confirm this finding. This intervention may potentially improve patient experience and have a positive effect on the uptake of the screening test. There is a paucity of trials focusing only on flexible sigmoidoscopy and more work is required to consolidate our findings.

COMMENTS

Background
Flexible sigmoidoscopy is being increasingly used in the early detection of colorectal pathology, especially as a screening tool in asymptomatic patients. The United Kingdom Flexible Sigmoidoscopy Trial showed a once-only flexible sigmoidoscopy screening between ages 55 and 64, significantly reduced the incidence of and cancer related mortality from colorectal cancer. Despite this, the uptake of flexible sigmoidoscopy remains low, due to patients' anxiety and concerns about discomfort and embarrassment during the procedure. So this study aims to evaluate the role of music as an adjunct during flexible sigmoidoscopy in improving patient experience.

Research frontiers
In this study, the authors have assessed the role of music in reducing patients' anxiety and discomfort and if this intervention was found by patients to be helpful during the test. They have reviewed comparative studies that used music as an intervention during flexible sigmoidoscopy and have performed both qualitative assessment and quantitative synthesis of outcomes. This is the first such study to systematically review and meta-analyse the use of music during flexible sigmoidoscopy in improving patient satisfaction. This is significant because unlike other endoscopic procedures like colonoscopy and oesophagogastroduodenoscopy, where intravenous sedation is widely used, flexible sigmoidoscopy is mostly performed with no sedation and hence any non-pharmacological relaxation or distraction technique will greatly improve patient experience.

Innovations and breakthroughs
This study appears to conclude that music reduced patient anxiety during the procedure and patients deemed it to be a helpful adjunct. Discomfort was also apparently improved, but a larger study may be needed to confirm this observation.

Applications
This study will encourage endoscopists to actively use music as a non-pharmacological, practically cost and risk free adjunct to improve patient experience and this may potentially help increase uptake of this very important screening test. This has helped consolidate a long-held and widely considered speculation that music can act as an effective distraction and relaxation technique during flexible sigmoidoscopy. This study was however limited by the small number of comparative studies addressing this clinical question; hence results should be interpreted with caution. However, as the intervention is completely risk and adverse effects free, this can still be applied in practice, pending further larger, better constructed randomized comparative studies.

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CASE REPORT

Successful endoscopic treatment of an intraductal papillary neoplasm of the bile duct

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Abstract

We present a case of a 76-year-old man with right upper quadrant abdominal pain and weight loss, who was found to have an intraductal papillary neoplasm of the bile duct (IPNB) of the pancreaticobiliary subtype, deemed curatively resectable. The patient declined surgery and opted for endoscopic therapy. He underwent two sessions of endoscopic retrograde cholangiopancreatography (ERCP)-guided radiofrequency ablation (RFA). Ten months later, no evidence of recurrence was identified on repeat ERCP. To our knowledge, this is the first reported case of successful use of RFA as a primary treatment modality for resectable IPNB.

Key words: Bile duct neoplasms; Ablation technique; Common bile duct diseases; Extrahepatic bile duct; Advanced endoscopy

Core tip: Intraductal neoplasms of the bile duct (IPNB) classically present with jaundice and/or pruritus, but nonspecific symptoms such as right upper quadrant discomfort and weight loss may also develop. The first-line treatment for these tumors is surgical resection. Endoscopic retrograde cholangiopancreatography-guided radiofrequency ablation (RFA) has historically been used as adjunctive treatment; self-expanding metal stents may be used for palliation. We report a case of successful primary treatment of an IPNB with RFA alone.

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treatment of an intraductal papillary neoplasm of the bile duct. *World J Gastrointest Endosc* 2017; 9(5): 238-242 Available from: URL: http://www.wjgnet.com/1948-5190/full/v9/i5/238. htm DOI: http://dx.doi.org/10.4253/wjge.v9.i5.238

INTRODUCTION

Intraductal papillary neoplasms of the bile duct were first recognized as a distinct entity by the World Health Organization in 2010[1]. These tumors may harbor varying degrees of dysplasia and even invasive malignancy[1,2]. Surgical resection is therefore recommended in patients who are operative candidates[1]. Non-surgical cases are managed with palliative biliary stenting using self-expandable metal stents (SEMSs), and radiofrequency ablation (RFA) has been employed as an adjunctive therapy for malignant biliary obstruction of several different etiologies[3-6]. RFA is safe, produces good 90-d stent luminal patency rates, and has been associated with an improvement in clinical outcomes[5,7,8]. However, its utility as a primary treatment modality has not been studied.

CASE REPORT

A 76-year-old man with a history of coronary artery disease and tobacco abuse was referred to our institution for evaluation of a common bile duct (CBD) stricture. Several months prior, he had presented to his primary care physician with right upper quadrant abdominal pain associated with an unintentional weight loss of 13 kg. Liver function tests (LFTs) revealed an AST of 46 IU/L (10-42), ALT of 37 IU/L (0-54), ALP of 197 IU/L (40-130), and a TB of 0.4 mg/dL (0.2-1.1). Mild intrahepatic ductal dilatation and a CBD of 10 mm were seen on right upper quadrant ultrasound. There was no choledocholithiasis. Subsequent magnetic resonance cholangiopancreatography revealed intra- and extrahepatic biliary ductal dilatation and a filling defect in the distal CBD. The pancreatic duct was not dilated. The patient was referred for endoscopic retrograde cholangiopancreatography (ERCP) at a different facility. Inspection of the ampulla of Vater was normal. The CBD was cannulated using a 0.35 inch sphincterotome and guidewire, and initial contrast injection showed dilatation of the CBD to approximately 15 mm and a saccular collection of contrast distally. A 10 mm biliary sphincterotomy was performed, and no choledocholithiasis or sludge was found after sweeping of the CBD. Cholangiogram showed a distal CBD stricture 10 mm proximal to the ampulla. Brushings for cytology were obtained, and a 10 Fr × 5 cm plastic stent was deployed across the stricture to facilitate biliary drainage. Cytology revealed atypical cells but was otherwise non-diagnostic. Due to the intraductal location of the lesion, ERCP was considered the best modality through which to obtain a tissue diagnosis, and endoscopic ultrasound was thus not performed.

Figure 1 Distal common bile duct stricture on initial cholangiogram.

Figure 2 Polypoid lesion seen with SpyGlass™ cholangioscopy.

The patient was brought back for repeat ERCP six weeks later. Following removal of the plastic stent and balloon sphincteroplasty to 10 mm, the CBD was cannulated using a pediatric gastroscope to allow for direct visualization of the intraductal mucosa. Catheter-based cholangioscopy was not available at the outside hospital. The area of the stricture appeared nodular and erythematous. The procedure was aborted due to hypotension and hypoxemia before biopsies could be obtained. The patient was then transferred to our institution for ERCP with SpyGlass™ cholangioscopy (Boston Scientific, Natick, MA). Initial cholangiogram confirmed a distal CBD stricture (Figure 1). A 10 mm polypoid lesion was seen with SpyGlass™ cholangioscopy (Figure 2), and targeted intraductal biopsies were performed using SpyBite™ forceps (Boston Scientific, Natick, MA). Pathological findings of atypical cells, papillary configuration, and bile duct epithelium with mucinous metaplasia were consistent with intraductal papillary neoplasm of the bile duct (IPNB) without malignant transformation (Figure 3). Immunohistochemical staining was positive for MUC1 and negative for CDX2, highlighting pancreaticobiliary and lack of intestinal epithelium, respectively. The normal appearance of the ampulla, intraductal location of the neoplasm, and histology excluded an ampullary lesion. Furthermore, the most distal aspect of the CBD was normal. He was referred to hepatobiliary surgery

Figure 3 Biliary epithelium with papillary configuration and atypical cells.

Figure 5 Repeat SpyGlass™ cholangioscopy showing no residual polypoid lesion.

Figure 4 Occlusion cholangiogram performed four months after last radiofrequency ablation treatment, revealing no polypoid lesion or stricture in the distal common bile duct.

Figure 6 Repeat endoscopic retrograde cholangiopancreatography demonstrating a 10 mm distal common bile duct stricture without evidence of a mass lesion.

for consideration of pancreaticoduodenectomy with curative intent, but surgical intervention was deferred due to patient preference. The decision was made to proceed with ERCP-guided RFA as primary therapy. Two sessions of RFA using an 8 Fr Habib™ EndoHPB probe were performed at 10 W for 90 s (EMcision, Montreal, Canada). A 10 mm × 4 cm WallFlex™ fully covered SEMS was deployed following the first round of RFA and exchanged at the completion of the second RFA session, three months later (Boston Scientific, Natick, MA). The procedures were uncomplicated. Four months after the second RFA session, ERCP with SpyGlass™ was repeated, the biliary stent was removed, and no residual polypoid tissue or stricture was observed on occlusion cholangiogram (Figure 4) or with Spyglass™ choledochoscopy (Figure 5). The stent was not replaced. Cytology of distal CBD brushings revealed no malignant cells. Repeat ERCP six months later (nine months after the last RFA session) demonstrated a 10 mm distal CBD stricture but no mass lesion (Figure 6). Spyglass™ choledochoscopy revealed only erythematous mucosa in the distal CBD; targeted intraductal biopsies of this area were performed using SpyBite™ forceps and revealed reactive epithelium. Cytology was negative for malignant cells, and fluorescence *in situ* hybridization (FISH) analysis of the distal CBD brushings showed no

abnormalities. The patient underwent his last ERCP six months later, and no residual stricture or CBD lesion was seen on cholangiogram. He remained asymptomatic, and his LFTs and weight normalized.

DISCUSSION

In 2010, the World Health Organization first categorized rare bile duct tumors characterized by papillary growth as intraductal papillary neoplasms of the bile duct[1]. IPNBs are associated with mucobilia due to excessive mucin secretion, and are more commonly found in the hepatic biliary system[1]. However, mucobilia may be absent, and extrahepatic growth patterns have been described[1,9]. Four histological subtypes exist including pancreaticobiliary, oncocytic, gastric, and intestinal[10,11]. Differentiation between subtypes is made according to morphology seen on hematoxylin and eosin staining and immunohistochemical features of mucin glycoproteins[10]. Pancreaticobiliary IPNB is more frequently associated with an invasive phenotype and harbors a worse prognosis[10,11]. IPNB tumors are graded based on degree of dysplasia, from low- to high-grade and finally to invasive carcinoma, which was seen in 74% of IPNBs in one study[1,2]. Pancreatic IPMNs are

classified similarly and are thought to follow the same sequence from benign to malignant[2]. The incidence of IPNBs is highest in Far Eastern countries, and particularly in patients between 50 and 70 years of age, with a slight male predominance[1]. Patients may be asymptomatic, or may present with abdominal pain, jaundice, elevated LFTs, or cholangitis[1,2]. Biliary ductal dilatation and an intraductal mass may be seen on computed tomography or magnetic resonance imaging[1]. Duodenoscopy may reveal a prominent ampulla with mucinous secretion[1]. Diagnosis is often difficult; sensitivity of brush cytology and fluoroscopically-guided biliary biopsies is low, and mixed pathologic findings may be present within a single lesion[1,12]. The majority of IPNBs contain high-grade epithelial neoplasia or carcinoma; low- or intermediate grade neoplasia is infrequent[1]. Excessive mucin secretion may impede identification of IPNB *via* cholangiography; cholangioscopy, however, can allow direct visualization of IPNBs[1]. Regardless of the level of dysplasia or presence of malignancy, treatment of IPNBs is warranted due to the heterogeneity of pathology within a single lesion, and to prevent complications such as obstructive jaundice and cholangitis[1]. Preoperative assessment of disease extent should be performed, and surgical resection is recommended for patients who are candidates without distant metastasis[1]. The surgical approach depends on tumor location, with pancreaticoduodenectomy being the procedure of choice for distal biliary lesions[1]. Palliative biliary stenting with SEMSs is employed in non-operative cases[12]. Over the last decade, much effort has been devoted to studying RFA as an adjunct therapy to stent placement. Using thermal energy, RFA induces coagulative necrosis of tumor tissue[13]. The procedure is safe and produces good 90-d stent luminal patency rates in patients with unresectable pancreatic carcinoma with obstructive jaundice[7,8]. RFA has also been used in the treatment of cholangiocarcinoma and biliary obstruction as a result of metastatic disease from distant primary malignancies[3-6]. These studies included only one patient with IPNB[4]. Use of RFA may result in benefits beyond local tumor ablation, and may induce secondary anti-tumor effects in patients with hepatocellular carcinoma and metastatic colorectal cancer[14]. RFA has also been associated with improved clinical outcomes, including prolonged survival[5,7]. The mechanism behind this positive effect on survival is not known but could be due to improved stent patency resulting in less infectious complications and superior biliary drainage which subsequently allows patients to receive oncologic treatment. Complications of RFA are rare but include biliary tract perforation, stricture formation, post-procedural pain, pancreatitis, cholecystitis, and bleeding[5,15]. Further investigation is needed to elucidate the effect of RFA on outcomes in patients with IPNB. This case demonstrates that, in patients who defer surgery, RFA, in combination with biliary stenting, may be used as a primary therapy for intraductal malignancies.

COMMENTS

Case characteristics
A 76-year-old man presenting with right upper quadrant abdominal pain and weight loss.

Clinical diagnosis
He had dilatation of the common bile duct (CBD), a 10 mm polypoid lesion visualized on cholangioscopy, and pathology consistent with intraductal papillary neoplasm of the bile duct.

Differential diagnosis
The differential diagnosis includes a biliary stricture, choledocholithiasis, pancreatic adenocarcinoma, cholangiocarcinoma, and choledochal cyst.

Laboratory diagnosis
Aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase were mildly elevated.

Imaging diagnosis
Right upper quadrant ultrasound was notable for mild intrahepatic and CBD dilatation. Magnetic resonance cholangiopancreatography showed intra- and extra-hepatic biliary ductal dilatation and a filling defect in the distal CBD. Serial endoscopic retrograde cholangiopancreatography revealed CBD dilatation and a nodular and erythematous distal CBD stricture. SpyGlass™ choledochoscopy showed a polypoid mass within the CBD.

Pathological diagnosis
Initial cytology from brushings showed atypical cells. Intraductal biopsies of the CBD mass revealed atypical cells, papillary configuration, and bile duct epithelium with mucinous metaplasia; immunohistochemistry was positive for MUC1 and negative for CDX2. Intraductal biopsies after treatment were negative for malignant cells.

Treatment
Two sessions of radiofrequency ablation were performed.

Related reports
Radiofrequency ablation (RFA) has not been previously studied as the primary treatment modality for Intraductal neoplasms of the bile duct (IPNB).

Experiences and lessons
In patients who choose to defer or forego surgery, RFA may be an acceptable option for primary treatment of intraductal malignancies.

Peer-review
Authors describe a case of successful treatment of intraductal papillary tumor of the bile duct with endoscopic retrograde cholangiopancreatography guided RFA. The case is interesting.

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FLYLEAF

EDITORS FOR THIS ISSUE

Endoscopic ultrasound in oncology: An update of clinical applications in the gastrointestinal tract

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Abstract

An accurate staging is necessary to select the best treatment and evaluate prognosis in oncology. Staging usually begins with noninvasive imaging such as computed tomography, magnetic resonance imaging or positron emission tomography. In the absence of distant metastases, endoscopic ultrasound plays an important role in the diagnosis and staging of gastrointestinal tumors, being the most accurate modality for local-regional staging. Its use for tumor and nodal involvement in pre-surgical evaluation has proven to reduce unnecessary surgeries. The aim of this article is to review the current role of endoscopic ultrasound in the diagnosis and staging of esophageal, gastric and colorectal cancer.

Key words: Endoscopic ultrasound; Staging; Esophageal cancer; Gastrointestinal cancer; Gastric cancer; Colorectal cancer

Core tip: Endoscopic ultrasound (EUS) has an important role in staging, establishing prognosis and optimizing therapeutic decisions. Also, it has proved to be a useful alternative therapeutic modality in surgery. In terms of cost-benefit, it reduces the number of unnecessary diagnostic or therapeutic procedures, leading to lower morbidity and mortality rates and reduced cost in cancer treatment. This review summarizes the current role of EUS in the diagnosis and staging of esophageal, gastric and colorectal cancer.

INTRODUCTION

Endoscopic ultrasound (EUS) was first used in 1980

as a technology prototype for pancreatic cancer evaluation[1]. It was designed as a combination of two techniques, endoscopy and ultrasound, allowing the visualization of the gastrointestinal mucosa as well as the tract wall in deep and surrounding structures. In 1989 its standardized indications in clinical practice were described[2]. Due to the constant evolution of this technology, it is now considered an important diagnostic and therapeutic method in the oncology field. EUS has an important role in staging, establishing prognosis and optimizing therapeutic decisions[3]. Also, it has proved to be a useful alternative therapeutic modality in surgery. In terms of cost-benefit, it reduces the number of unnecessary diagnostic or therapeutic procedures, leading to lower morbidity and mortality rates and reduced cost in cancer treatment[4,5]. The TNM classification (American Joint Committee on Cancer, AJCC) is the most accepted staging classification and is based on the analysis of local tumor invasion (T), lymph node involvement (N) and distant metastasis (M). Staging usually begins using noninvasive imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET), which are generally better than EUS for excluding M. In the absence of metastasis, EUS has proved to be an accurate modality for assessing T and N[2]. Moreover, the development of EUS-related technology such as fine needle aspiration (FNA), high frequency catheter probe, elastography and contrast enhancement has helped to improve EUS staging accuracy. EUS indications in oncology is therefore increasing[6]. The aim of this review is to summarize the current role of EUS in the staging of esophageal, gastric and colorectal cancer.

ESOPHAGEAL CANCER

Characteristics of esophageal cancer and clinical implications

The prognosis of esophageal cancer (EC) is poor because these tumors are usually detected in an advanced stage. Surgery is not possible in most cases and has a high rate of morbidity and mortality. The level of tumor invasion and lymph node metastasis will determine treatment and prognosis. Therefore, EUS plays a vital role by providing an accurate T and N staging, which allows deciding on the best treatment[7]. The use of EUS evaluation in preoperative staging has led to a mortality reduction of 42.1% and a better recurrence-free survival rate, compared to patients with no EUS evaluation[8]. According to the TNM classification (Table 1), superficial EC includes mucosal and submucosal involvement (Tis, T1a or T1b)[9]. Patients with any nodal involvement (N$^+$) or advance tumors (T2-T4a) (Figure 1) need preoperative neoadjuvant chemoradiotherapy, whereas T1 patients with no nodal metastasis can benefit from endoscopic (Tis, T1a N0) or surgical resection (T1bN0)[10-12]. When different staging methods were compared, CT, MRI and PET-scan showed themselves

to be better than EUS in evaluating distant metastasis (M), however EUS proved superiority in the detection of tumor stage (T) and lymph nodes (N)[13-16]. One method does not have to exclude the other. The incorporation of CT, PET and EUS in preoperative staging reduces the number of unnecessary surgical procedures from 44% to 21%[17].

The role of EUS in T staging

EC limited to the mucosa (Tis, T1a) can be treated effectively with minimally invasive endoscopic therapy, whereas submucosal (T1b) EC carries relatively high risk of lymph node metastasis and requires surgical resection. According to a meta-analysis by Puli *et al*[18] (49 articles), EUS sensitivity and specificity for T stage was 81.6% and 99.4%, for T1, 81.4% and 96.3%, for T2, 91.4% and 94.4%, for T3, and 92.4% and 97.4% for T4 staging, respectively. The accuracy was higher for T3-T4 lesions (> 90%) than T1-T2 (65%). However, a study by Thosani *et al*[19] reported, on the analysis of 1019 patients with only superficial EC, that EUS sensitivity and specificity was 85% and 87% for T1a and 86% and 86% for T1b respectively, with an overall EUS accuracy for superficial EC staging of > 93%.

The role of EUS in N staging

The lymph node (LN) metastasis in EC is considered the main fact that influences prognosis and it depends on the number of nodes involved. This pathology has a high rate of LN involvement at an early stage. T1sm (T1b) disease has a 15% to 30% rate of LN dissemination. The 7th edition of the AJCC (Table 1) classifies the N stage according to the number of metastasized lymph nodes in N1 (1 to 2), N2 (3 to 6), and N3 ($\geq$ 7). The use of EUS evaluation in preoperative staging has led to a mortality reduction of 42.1% and a better recurrence-free survival rate, compared to patients with no EUS evaluation[8]. According to the TNM classification (Table 1)[9], the presence of node metastasis indicates the need of neoadjuvant therapy. Therefore, identification of the N stage is mandatory. PET and CT have a low accuracy (51%) compared to EUS[20]. The evaluation of the LN features using EUS have shown that malignant nodes tend to be larger than 1 cm, round, sharply demarcated, and hypoechoic. When all these features are present there is an 85% chance of malignancy. However, only 25% of malignant LN have all four features[21]. A systematic review found that EUS has a sensitivity range of 59.5% to 100% and a specificity range of 40% to 100% for N staging[22]. Puli *et al*[18] described a EUS sensitivity for N stage of 85% and showed that the use of FNA substantially improves the sensitivity and specificity of EUS nodal staging from 85% to 97% and 85% to 96% respectively, with a low rate of complications, ranging from 0% to 2.3%. Chen *et al*[23] found an accuracy rate of 99.4% using EUS-FNA. In patients with EC, the identification of a celiac lymph node is synonymous to LN metastasis in 90% of the cases regardless of echo features and size and

Table 1 TNM in esophageal cancer

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable tumor invading pleura, pericardium, or diaphragm
T4b	Unresectable tumor invading other adjacent structures, such as the aorta, vertebral body, and trachea
Regional lymph nodes (N)	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-2 regional lymph nodes
N2	Metastasis in 3-6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Figure 1 Esophageal carcinoma staging by endoscopic ultrasound T2 N1. The tumor is being measure (13.3 mm × 20.2 mm). It invades up to the muscularis propria (white arrow). A round, sharply demarcated and hypoechoic lymph node can be seen next to the tumor. EUS images were obtained using a Hitachi-Avius console with a radial scope EG-3630URK (from Pentax Medical). EUS: Endoscopic ultrasound.

therefore indicates a poor prognosis[24]. EUS-FNA for celiac lymph node diagnosis has shown a sensitivity of 72% to 83%, a specificity of 85% to 98%, and an accuracy of 94%[25].

Limitations

The role of EUS has some limitations. It may be less accurate for assessing the T1-T2 stage compared with T3-T4. According to some authors there is a trend to overstaging the depth of the submucosal invasion, with a low accuracy rate in early T staging (64%)[26]. The use of high frequency catheter probes may improve the diagnostic accuracy in early lesions from 83% to 92%, but the results are heterogeneous[27,28]. EUS criteria are not accurate after neoadjuvant radio-chemotherapy because EUS poorly differentiates tumor from necrosis or inflammatory reaction[29]. The presence of esophageal malignant stenosis that cannot be overcome can make TNM evaluation more difficult. A recent multi-center study suggested that routine EUS examinations may not be required in all patients with EC as the inability to advance a diagnostic gastroscope through a malignant stricture correlates 100% with locally advanced disease, so that performing a EUS does not change the treatment decision[30].

Role of EUS in Barrett's esophagus

EUS has long been used to evaluate Barrett's eso-phagus (BE)[6]. In the case of BE associated with high-grade dysplasia (HGD) or early (T1m) esophageal adenocarcinoma (EAC), the patient may benefit from endoscopy resection, but if EUS shows an advanced disease with tumor invading the submucosal, or beyond, or lymph node involvement, endoscopic therapy may

not be warranted. Qumseya *et al*[31] showed in a recent meta-analysis that 14% of patients referred to EUS for BE associated with HGD or EAC will have advanced cancer (> T1sm or > N1) detected by EUS that is not amenable to endoscopic treatment and which therefore changes the therapeutic approach. With EUS it was found that 4% of these patients have advanced disease in the absence of nodules. The sensitivity and specificity for T stage was 56% and 89% and for N stage was 71% and 94 % respectively[31]. However, even the data mentioned, the American College of Gastroenterology has stated that EUS routine staging of patients with BE before EMR is unwarranted as clinical decision making will rest with the EMR findings and given the possibility of over- and under-staging in patients with superficial EAC[32-35]. In case of T1a lesions the rate of lymph node (LN) involvement is low, making these lesions optimally treated by EMR[36,37]. In patients with known T1b sm1 disease, there is conflicting data with respect to the likelihood of LN invasion[38,39]. The evidence of LN involvement, especially if substantiated by FNA, means that any attempt at endoscopic therapy would be palliative and therefore EUS may have a role in assessing and sampling regional LN, given the increased prevalence of lymph node involvement in these patients compared with less advanced disease[19].

GASTRIC CANCER

Characteristics of gastric cancer and clinical implications

Gastric cancer (GC) is the fourth most common cancer and the second cause of cancer-related deaths (10%)[40]. An accurate staging (Table 2) can be extremely useful in providing patients with the best therapeutic option. Patients with early gastric cancer, in the presence of favorable prognosis features (well-differentiated carcinoma, limited to the mucosa, diameter < 2 cm, absence of ulceration) and no lymph node involvement

Table 2 TNM in gastric cancer	
Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*: Intraepithelial tumor without invasion of the lamina propria
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures
T4	Tumor invades serosa (visceral peritoneum) or adjacent structures
T4a	Tumor invades serosa (visceral peritoneum)
T4b	Tumor invades adjacent structures
Regional lymph nodes (N)	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-2 regional lymph nodes
N2	Metastasis in 3-6 regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes
N3a	Metastasis in 7-15 regional lymph nodes
N3b	Metastasis in 16 or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Figure 2 Gastric adenocarcinoma staging by endoscopic ultrasound T3 N0. The tumor overcomes the muscularis propria (blue arrow) and penetrates the subserosal connective tissue (white arrow). EUS images were obtained using a Hitachi-Avius console with a radial scope EG-3630URK (from Pentax Medical). EUS: Endoscopic ultrasound.

(N0) can benefit from endoscopic resection rather than surgical resection[41,42]. On the other hand, patients with advanced gastric cancer (T3-T4 tumors or N$^+$) need to be treated with neoadjuvant therapy (chemotherapy, radiotherapy or both)[43,44].

CT is a frequent imaging method for the preoperative staging of GC[45]. It has a high accuracy for distant metastasis (M), however its overall accuracy for loco-regional staging (T and N stages) is low, ranging from 65% to 85%[46,47]. The CT sensitivity and specificity for N stage is 77% and 78%, respectively[48]. No better results appear to be achievable with MRI or PET[48-50].

Thus, these imaging devices are mostly used to diagnose locally advanced lesions (T3-T4 or N$^+$) or distant metastasis than early stages of GC. On the contrary, EUS is an accurate device for the loco-regional staging[51,52] (Figure 2). The employment of EUS in the preoperative stage of GC has shown to change the therapeutic management in 30% of cases, resulting in more limited surgical resections, especially in stages T1 and T3[53].

The role of EUS in T staging

A recent meta-analysis by Mocellin *et al*[54] and the Cochrane Collaboration Group (2015) evaluated 66 articles (n = 7747) about GC staged with EUS. The aim was to evaluate EUS ability to separate patients with GC who would best benefit from surgery without preoperative radio-chemotherapy (T1-T2) from those with advanced tumors (T3-T4) who are likely to benefit from neoadjuvant therapy. They found EUS sensitivity and specificity to discriminate T1-T2 from T3-T4 lesions to be 86% and 90% respectively. A second analysis

was made to evaluate EUS ability to discriminate between patients with superficial cancers (T1 from T2 and T1a from T1b), with the intention of identifying patients who would benefit from endoscopic resection rather than surgery. The sensitivity and specificity of EUS to distinguish T1 (early GC) from T2 (muscle-infiltrating) was 85% and 90% respectively. As for the capacity of EUS to distinguish between T1a (mucosal) *vs* T1b (submucosal), they showed that the sensitivity and specificity was 87% and 75% respectively. They concluded that EUS can distinguish between superficial (T1-T2) and advanced (T3-T4) primary tumors with a sensitivity and specificity greater than 85%. This performance is maintained for the discrimination between T1 and T2 superficial tumors. However, EUS diagnostic accuracy is lower when it comes to distinguishing between the different types of early tumors (T1a *vs* T1b)[54]. This conclusion correlates with Mocellin *et al*[55] previous results (2011) when they described that EUS can differentiate T1-2 from T3-4 GC with high accuracy (sensitivity of 86% and specificity of 91%). Cardoso *et al*[56] (2012) also showed that EUS seems to identify advanced T stage (T3 and T4) better than it identifies less advanced T stage or N stage, with a combined accuracy for T staging of 75%. Puli *et al*[57] (2008) evaluated 22 studies (n = 1896) and described the usefulness of EUS in GC. The sensitivity and specificity by stage were, 88.1% and 100% for T1, 82.3% and 95.6% for T2, 89.7% and 94.7% for T3, and 99.2% and 96.7% for T4. Incidentally, EUS for T stage detection was more accurate in advanced cancer than in early cancer. Kwee *et al*[58] (2008) showed in a systematic review (18 studies), the accuracy of EUS in differentiating mucosal (T1m) from deeper GC (> T1sm) and found that sensitivity and specificity of EUS in detecting cancerous extension beyond the mucosa ranged from 18.2% to 100% (median 87.8%) and from 34.7% to 100% (median 80.2%) respectively. They concluded that the studies showed too much heterogeneity and it is still unclear whether EUS can

Table 3 TNM in rectal cancer	
Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*: Intraepithelial or invasion of lamina propria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum
T4b	Tumor directly invades or is adherent to other organs or structures
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-3 regional lymph nodes
N1a	Metastasis in 1 regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in 4 or more regional lymph nodes
N2a	Metastasis in 4-6 regional lymph nodes
N2b	Metastasis in 7 or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site (for example, liver, lung, ovary, nonregional node)
M1b	Metastases in more than one organ/site or the peritoneum

accurately differentiate between mucosal and deeper GC[58].

The role of EUS in N staging

The accuracy of EUS for N staging has shown remarkable heterogeneity of results. Mocellin *et al*[54] described after the evaluation of 44 studies (*n* = 3573) an overall sensitivity and specificity of 83% and 67% respectively[54]. Cardoso *et al*[56] reported accuracy for N stage of 64%, sensitivity of 74%, and specificity of 80%. These results were due to the low possibility of detecting metastasized lymph nodes that are distant from the lesion[56]. Kwee *et al*[59] found that sensitivity and specificity of EUS varied from 16.7% to 95.3% (median 70.8%) and 48.4% to 100% (median, 84.6%). Puli *et al*[57] after the analysis of 22 studies (*n* = 1896) reported a sensitivity for N1 of 58.2% and N2 of 64.9%. The pooled sensitivity to diagnose distant metastasis was 73.2%.

Limitations

There is a remarkable heterogeneity of the evidence currently available about the ability of EUS to differentiate T1a *vs* T1b tumors and to diagnose lymph node metastasis (N0 *vs* N+). Therefore, physicians should be cautious at the time of interpreting these results. Tumor features like size and location may affect diagnostic performance of EUS. A tumor size greater than 3 cm is associated with overstaging by EUS and decreases the diagnostic accuracy to 50%[60]. The cardia, the greater

curve of upper body, the lesser curve at the incisura and the pyloric channel are the most challenging areas to examine[61].

Gastric lymphoma

Even though CT has proved useful for evaluating an abnormal gastric wall thickening, EUS, on the other hand, has shown itself to be superior for examining nodal involvement, extension and depth of tumor invasion[62]. The EUS diagnostic accuracy in gastric lymphoma is 91%-95% for T stage and 77%-83% for N stage[63,64]. The use of EUS-FNA combined with flow cytometry and immunohistochemistry can improve N staging accuracy substantially[65].

EUS has also shown a significant impact on treatment decisions. Gastric lymphoma confined to the mucosal and submucosal (T1) can simply be treated with *H. pylori* eradication therapy. However, if EUS shows deeper invasion, chemotherapy, radiation or surgical treatment may be necessary[66]. Moreover, EUS has proven to be useful for surveillance of recurrences at an early stage[62].

RECTAL, COLON AND ANAL CANCER

Characteristics of rectal cancer and clinical implications

Accurate staging in rectal cancer (RC) is crucial for choosing the best multimodal therapy. Treatment decisions and prognosis depends on both T and N stage of the disease at the time of diagnosis[67]. In the absence of distant metastasis (M), EUS is the most accurate imaging modality for loco-regional staging (T and N stages) of rectal tumors[68]. Stage Ⅰ disease includes early rectal lesions (T1-T2 N0 M0) (Table 3). While T1 lesions can benefit from endoscopic mucosal resection or transanal endoscopic microsurgery, T2 lesions need surgery[69,70]. Stage Ⅱ disease with locally advanced cancer (T3-T4 N0 M0), or stage Ⅲ with lymph node metastasis (T1-4 N1-2 M0) will benefit maximally and improve recurrence-free survival when neoadjuvant radio-chemotherapy is given[71-74]. Preoperative biopsies of rectal tumors may fail to diagnose an invasive carcinoma, with up to 24% false negative results. The preoperative use of EUS reduces the rate of missed carcinomas from 21% to 3%[75]. EUS compared to other imaging modalities (CT, PET/CT, MRI) is superior and more accurate in determining T stage (EUS: 87%, CT: 76% and MRI: 77%)[70,76-77]. In N stage situations, it is also superior, but the difference is less obvious and accuracy varies between studies (EUS 63%-85%, CT 56%-79% and MRI 57%-85%)[78-82]. Usually CT and PET/CT are used for distant metastasis diagnosis[82]. It is also reported that when CT was the original mode of investigation but a further EUS was done, in 31% of the cases the mode of treatment was changed because of the result[70]. The combination of CT and EUS seems to be the most cost-effective diagnostic strategy[83]. MRI has less accuracy in the T stage than EUS does,

but provides a good definition of the circumferential resection margin (CRM). While EUS is more useful for staging early RC, MRI is indicated for staging advanced disease and defines CRM. Also, it can be used in the case of stenotic tumors, when EUS is less accurate. Thus, EUS and MRI are complementary and should be both used for preoperative staging[81,84].

RC recurrence rates range from 20% to 50%, depending on how advanced the cancer is and if neoadjuvant therapy has been administered before surgery[85,86]. It has been proven that there is a significant reduction in tumor recurrence when patients undergo EUS staging compared to those who do not[87]. In addition to this, EUS can be used to evaluate the colorectal anastomosis during follow-up of patients operated for RC and confirm or rule out recurrence with 97% sensitivity, 100% specificity, 100% positive predictive value (PPV), 94% negative predictive value (NPV), and an overall accuracy of 98%[88,89]. One limitation that has been attributed to EUS is its difficulty in differentiating between post-operative benign lesions and recurring cancer in post-operative lesions. However, the use of EUS-guided FNA increases the specificity from 57% to 97%[85,86]. Thus, EUS has a key role in both preoperative staging and follow-up after surgery.

The role of EUS in T staging

Over- or under-staging leads to changes in a patient's treatment. Surgery instead of endoscopic resection and the use of chemoradiotherapy could be wrongly indicated when there is over-staging. On the other hand, under-staging with the lack of neoadjuvant indication could lead to an insufficient treatment. According to a recent review performed by Marone *et al*[90] (33 articles, n = 4976), EUS assesses the tumor penetration depth into the rectal wall with an overall accuracy for T stage of about 84%, ranging from 63% to 96%, while the reported accuracy of CT and MRI are 65%-75% and 75%-85%, respectively. They showed also that EUS accuracy for T stage is strictly related to the depth of infiltration, being lower for T2 stage than for early (T1) or advanced (T3-4) RC (T1: 88%, T2: 78.4%, T3: 85.4% and T4: 80.2%)[90]. Similarly, a meta-analysis (42 studies, n = 5039 patients) showed that EUS has an overall RC staging sensitivity of 81%-96% and specificity of 91%-98%, showing higher sensitivity for advanced RC (95%) than early cancer (88%). The pooled sensitivity and specificity by stage was for T1: 88% and 98%, T2: 81% and 96%, T3: 96% and 91% and T4: 95% and 98%, respectively. The authors concluded that EUS should be the imaging method of choice for the T staging of RC[91] (Figure 3). Superficial RC limited to the mucosa can be resected endoscopically. EUS has a high accuracy rate in differentiating T1 from T2 lesions, ranging from 81% to 95%, with an overstaging or understaging rate of 9%[92]. Puli *et al*[93] evaluated, in a meta-analysis (11 studies, n = 1791), the efficacy of preoperative EUS in staging patients with RC confined to the mucosa (T0) and found that sensitivity was 97% and specificity 96%.

They concluded that EUS should be strongly considered for staging of early RCs[93].

The role of EUS in N staging

EUS role in the determination of lymph node (LN) metastasis is less precise than T staging, with a mean accuracy of 74% (range 63%-85%)[90]. However, the accuracy is still better than others imaging modalities like CT (56%-79%) or MRI (57%-85%)[78-82]. Similarly, a meta-analysis including 35 articles showed that EUS has a sensitivity of 73% and specificity of 76% for N staging. This low EUS performance is related to the difficulty in evaluating distant metastatic LN that are out of EUS scanning, discriminating between inflammatory and metastatic LN and the tendency to overlook small metastatic LN compared to larger LN[94-98]. The presence of all malignant features (enlarged node $\geqslant$ 1 cm, hypoechoic appearance, round shape, and smooth border) is related to 100% of PPV for malignancy, however this situation is seen in less than 25% of cases[21]. It is known that there is a correlation between T stage and risk of LN involvement in patients with RC. The risk varies from 6%-11% for T1, 10%-35% for T2 and 26%-65% for T3-T4 RC[99]. Similarly, the EUS accuracy for N staging also depends on T staging and seems to be better for advanced disease (84% in T3 compared to 48% in T1). This is explained by the fact that in T1 lesions metastatic nodes are possibly small[98]. On the other hand, beside EUS limitations in N staging, EUS guided FNA can be used to balance and improve the accuracy from 75% to 87%[100]. EUS-FNA has a sensitivity, specificity, PPV and NPV of 89%, 79%, 89% and 79% respectively[97,101]. The fact that EUS-FNA has a moderate NPV (77%) for N staging means that LN metastases cannot be ruled out by a negative FNA[102]. Even though most perirectal nodes detected by EUS in patients with RC are metastatic, it is important to confirm this. EUS-FNA should be indicated when results change the therapeutic strategy. The presence or absence of LN metastasis in T1-T2 lesions change the stage of the patient from I to III and indicates the chemoradiotherapy strategy. EUS-FNA changes patient management in 19% of the cases[70,103].

Limitations

EUS performance is operator-dependent and accuracy improves with experience. This fact explains the wide range of overall accuracy for T and N staging between studies (63% to 95%)[104,105]. A high inter-observer variability (61%-77%) has been described according to the experience of the operator, with overstaging values of 19% and understaging of 12%[104]. Also, EUS seems to be less accurate in restaging RC after neoadjuvant therapy (NAT), due to the limitations in differentiating inflammation, edema, necrosis and fibrosis from neoplastic infiltration, with the risk of overstaging and overtreatment[68,106,107]. EUS correctly predicts complete response to chemoradiation in 50%-63% of the cases. It has an overall accuracy for T stage of 48%, with 38%

Figure 3 Rectal adenocarcinoma staging by endoscopic ultrasound T4 N0. The tumor invasion overcomes the rectal wall and penetrates the prostate. There is a lack of separation plane between the tumor and the prostate (white arrow).
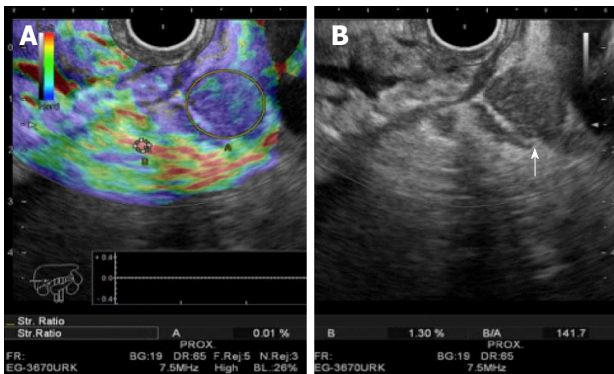

Figure 4 A lymph node being evaluated by elastography, for a gastric tumor staging. A: Qualitative elastography (color tones red-green-blue) shows the lesion with a blue-predominant color tone, which represents a hard tissue and suggest malignancy. The Strain Ratio (quantitative elastography) is being calculated by compering two different areas (A and B). Area A includes as much of the target lesion as possible. Area B is selected within a soft (red) reference area outside the target lesion. The result (B/A = 141.7) suggests malignancy; B: Shows the round, sharply demarcated and hypoechoic lymph node (white arrow). The endoscopic ultrasound-elastography was done using a Hitachi-Avius console with a radial scope EG-3630URK (from Pentax Medical).

Figure 5 The same lesion presented in Figure 3 being evaluated by contrast enhanced ultrasonography. The white arrow shows the lymph node with no enhancement after the contrast application, which suggests malignancy. The endoscopic ultrasound-contrast enhancement was done using a Hitachi-Avius console with a radial scope EG-3630URK (from Pentax Medical) and a Sonovue contrast agent (from Bracco).

Figure 6 Rectal adenocarcinoma staging by 3D endoscopic ultrasound T1 N1. The yellow arrows on the left show the muscularis propria. The tumor invades up to the submucosa. A white submucosa plane can be seen between the tumor (TU) and the muscularis propria. The yellow arrow on the right shows a round lymph node. The 3D image was obtained using a transanal rigid probe with an ultrasound from bk medical.

of overstaging and 14% of understaging[108,109]. Another limitation is that in 14% of RC there is a stricture that cannot be traversed by the echoendoscope, leading to an inaccurate T and N staging. The presence of a stricture decreases the EUS accuracy rate for T stage from 93% to 56%. When the T stages were analyzed separately, the accuracy was 76% for T1, 72% for T2, 91% for T3 and 67% for T4 stage. Moreover, there was an 11% of over-staging and 5% of under-staging errors[110]. Ultrasound catheter probes can be used to compensate this limitation. A meta-analysis (10 studies, *n* = 642) showed a high performance using ultrasound catheter probes for T and N staging. The pooled sensitivity and specificity were for T1: 91% and 98%, T2: 78% and 94%, T3-T4: 97% and 90%, respectively. The sensitivity and specificity for N staging were 63% and 82%, respectively[111]. Finally, the circumferential resection margin (CRM) is an important factor in predicting local recurrence. MRI has been described to

have a better overall accuracy compared to EUS (92% *vs* 84%) with similar NPV (97%), especially in mid-rectum[112]. However, in low RC the accuracy in both modalities is similar (87%) with a NPV of 96%[113].

New technologies
EUS elastography is a software application that can analyze the elastic properties of tissues (Figure 4). Harder tissue (usually malignant) appears blue which allows one to distinguish between adenocarcinomas and adenomas with high accuracy (94%)[114]. It seems that EUS elastography is better in RC staging than EUS alone especially for early cancers[115]. Contrast enhanced ultrasonography (CE-US) can be used to evaluate tumor

vascularity and response to antiangiogenic treatment[116] (Figure 5). Computed parameters can be used to quantify tumor angiogenesis and measure vascularity changes after therapy[117]. Finally, 3D-EUS development allows spatial display of rectal and perirectal anatomy[112] (Figure 6). It improves accuracy for both T and N staging, better than EUS alone, especially in the middle third of the rectum[118]. Published data shows that its accuracy for N stage improves from 65% to 85% and for T stage is 97.1% for T1, 94.3% for T2, 95.7% for T3 and 98.5% for T4[119-121].

COLON CANCER

Despite improvements in EUS technology that allows a forward viewing, the EUS examination of the colon has proved to be less accurate for T and N staging (81% and 52.4% respectively)[122]. This decrease is due to the difficulty in evaluating the proximal colon segments and bowel movement[123]. Mini-probe EUS can be passed through the working channel of regular colonoscopes and can be used to evaluate lesions of the entire colon compensating for some of these limitations[124].

ANAL CANCER

EUS is useful for assessing the involvement of anal sphincters in low rectal tumors and in the staging of anal squamous-cell carcinomas. Treatment decisions in anal cancer depends on sphincter invasion and EUS has an accuracy of 96%, sensitivity of 100%, specificity of 87% and NPV of 100% in evaluating it[125,126]. Clinical staging of anal cancer tends to under-diagnose sphincter invasion[127-129]. Most clinically classified T1-T2 patients will have T3 lesions under EUS evaluation[129]. Giovannini *et al*[130] confirm this in a prospective multicenter study and recommend that in T1-T2 N0 tumors, a transrectal EUS should be performed. EUS can be used also to determine multimodality therapy response[131]. A greater proportion of T1-T2 N0 lesions classified by EUS had a complete response to treatment than those classified by conventional clinical staging (94.5% *vs* 80%, respectively)[130]. The use of 3D-EUS in anal carcinoma seems to add some benefits in perirectal lymph node and tumor invasion detection, when compared to standard EUS, but further studies are needed[132].

CONCLUSION

Prognosis of patients with gastrointestinal cancer is strictly related to the stage of the disease at the time of diagnosis. Therefore, an accurate staging is crucial to decide the best treatment in each patient, because of the possibility of under-staging or over-staging, with subsequent mistreatments. CT scan, MRI, PET are the imaging methods that can give better information on distant disease. EUS has proven to be essential for loco-regional staging in pre-surgical evaluation. It reduces

the number of unnecessary surgeries, reduces local recurrences, improves survival outcomes and guides physicians in the development of the most appropriate therapeutic strategy. It has excellent sensitivity and specificity in accurately diagnosing T and N cancer stages. FNA substantially improves EUS outcomes by enabling tissue sampling, especially for N staging. New technologies, like elastography, contrast-enhancement EUS, high-frequency probes and 3D technology are also improving EUS accuracy. On the other hand, physicians should be warned that EUS has some limitations. EUS has low accuracy in restaging RC after treatment due to the difficulty in differentiating inflammation and tissue fibrosis from residual cancer. There is also some heterogeneity in the evidence currently available about EUS results in diagnosing superficial tumors (T1a) and LN in some situations.

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Endoscopic recommendations for colorectal cancer screening and surveillance in patients with inflammatory bowel disease: Review of general recommendations

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Abstract

Screening for colorectal cancer (CRC) in patients with inflammatory bowel disease (IBD) is recommended by all scientific societies. However, there are differences in the recommendations they make regarding screening and surveillance. We address a series of questions that come up in the daily clinical practice of a physician. The first two questions that are raised are: (1) Who should be offered screening for CRC? and (2) When should the first colonoscopy be performed? The next step is to decide who should undergo endoscopic surveillance and at what intervals they should be performed. Chromoendoscopy is emerging as the recommended endoscopic technique for screening and surveillance. The terminology for describing lesions detected with endoscopy is also changing. The management of visible lesions or non-visible dysplasia is also a motive for the review. We end the review by addressing the follow-up for endoscopically resected lesions. These questions often cannot be answered easily due to the varying degrees of evidence available; therefore, we have made some general recommendations based on those made by the various guidelines and consensuses. The first screening colonoscopy should be offered 8 years after a IBD diagnosis and we recommend that patients be stratified according to the individual risk for each for endoscopic surveillance intervals.

Key words: Colitis surveillance; Colitis screening; Chromoendoscopy; Colorectal cancer; Inflammatory bowel disease

Core tip: There is a worldwide consensus among all scientific societies regarding the recommendation

of screening for colorectal cancer in patients with inflammatory bowel disease (IBD). However, there are differences between the various recommendations that they make regarding the screening and surveillance that must be performed with these patients. We have reviewed the guidelines and consensuses from around the world on this subject and extracted some simple, general recommendations that can be used by all physicians who treat patients of this type. The first screening colonoscopy should be offered 8 years after a IBD diagnosis and we recommend that patients be stratified according to the individual risk for each for endoscopic surveillance intervals.

INTRODUCTION

There is a worldwide consensus among all scientific societies regarding the recommendation of screening for colorectal cancer (CRC) in patients with inflammatory bowel disease (IBD)[1-19]. This should be carried out by means of colonoscopy. The optimal timing for the performance of the colonoscopy, as far as possible, is during the remission phase and with appropriate colonic cleansing. The objective is to detect potentially resectable premalignant lesions (dysplasia) and CRC in the early stages, which gives a better prognosis. Since the introduction of endoscopic screening techniques, the risk of CRC in IBD does not appear to have decreased, but CRC-related mortality has[20].

However, there are differences among the various recommendations of the scientific societies about the screening and surveillance which must be performed with these patients. The reasons for this are the different dates of publication of these consensuses and the fact that, in some aspects, there is no clear evidence that can be applied. In addition, adherence to the guidelines is not always optimal, and this was demonstrated in a recent Japanese study in which only 63% of the respondents stated that they started screening between seven to ten years after onset of ulcerative colitis (UC), while up to 20% initiated it at three years or less[21], thus not conforming to the Guidelines for the management of UC in Japan[19].

The objective of this review is to address all the recommendations of the scientific societies regarding the screening and surveillance of CRC in IBD, so that the opportunity to formulate recommendations based on the guidelines and consensuses of the various scientific societies can be made available throughout the world. For

Table 1 Consensus of reviewed scientific societies

Abbreviations	Scientific society
ECCO	European Crohn's and Colitis Organisation
NZGG	New Zealand Guidelines Group
BSG	The British Society of Gastroenterology
ACPGBI	The Association of Coloproctology for Great Britain and Ireland
CCA	Cancer Council Australia
ASGE	American Society for Gastrointestinal Endoscopy
ESGE	European Society of Gastrointestinal Endoscopy
ACG	American College of Gastroenterology
NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition
CCFA	Crohn's and Colitis Foundation of America
NICE	National Institute for Health and Clinical Excellence
WGO	World Gastroenterology Organisation
AGA	American Gastroenterological Association
CAG	Canadian Association of Gastroenterology
Asia-Pacific	Asia Pacific Association of Gastroenterology
ACOG	Asociación Colombiana de Gastroenterología
SVG	Sociedad Venezolana de Gastroenterología
JPN	Research Group of Intractable Inflammatory Bowel Disease. Japan

our revision, we selected every scientific society whether local, national or international who ever published one or several papers with recommendations about the screening and surveillance process of the CRC in patients with IBD (Table 1). To make our recommendations we followed these criteria: (1) publishing date of the guide (stronger as more recent the date was); (2) number of scientific societies that supported the recommendations; and (3) agreement of at least 70% of the authors (5 out of 7) to add a recommendation to the list. The present review is structured as a series of questions which the physician poses in his or her daily clinical practice, followed by our recommendation with a subsequent review of the evidence available in the published guidelines and consensuses.

TO WHOM SHOULD CRC SCREENING BE OFFERED?

Our recommendation: Screening for CRC should be offered to the following patients with IBD: Patients with UC regardless of its extent; Patients with Crohn's disease (CD) which affects at least 1/3 of the colon or with complex perianal disease; Patients with an ileo-anal pouch; Patients with indeterminate or unclassified colitis (IC). The endoscopy should preferably be performed in clinical-biological remission situations and should allow an estimation of the individual risk of CRC, as well as the extent of the disease.

All scientific societies agree on this point[1-19] without exception, in offering screening to patients with IBD. NZGG (New Zealand Guidelines Group) recommends a risk-benefit assessment for patients with significant associated comorbidities and for patients over 75 years of age for whom screening risks may outweigh the

benefits[4]. These issues are also taken into account by European Crohn's and Colitis Organisation (ECCO)[22] and NICE (National Institute for Health and Clinical Excellence)[13]. The ECCO guidelines[1-2] mention that the ileo-anal pouch should be examined, but given the low evidence available, that decision is left to the discretion of the clinician. Its assessment is also recommended by BSG (The British Society of Gastroenterology) and ACPGBI (The Association of Coloproctology for Great Britain and Ireland)[5], CCA (Cancer Council Australia)[6] and SVG (Sociedad Venezolana de Gastroenterología)[18].

WHEN SHOULD THE FIRST SCREENING COLONOSCOPY BE PERFORMED?

Our recommendation: The first screening colonoscopy should be offered 8 years after a CD or UC diagnosis. For a diagnosis of primary sclerosing cholangitis (PSC), colonoscopy should be performed as soon as possible. With an ileo-anal pouch, it should be performed one year after the surgical intervention. Patients with first-degree relatives who have been diagnosed with CRC at an age of less than 50 should be offered the first endoscopy ten years before the age of the family member when affected by CRC or eight years after diagnosis of IBD (whichever occurs earlier).

Most scientific societies recommend performing the first endoscopy between eight and ten years after the diagnosis or onset of symptoms. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) recommends starting screening 1 year earlier than other protocols. The 2013 ECCO guidelines for UC[3] management bring this first colonoscopy forward to six to eight years from the onset of symptoms. However, ECCO recommends starting the screening at eight years in its 2013 endoscopy guideline[1], as do CCA[6], American Society for Gastrointestinal Endoscopy (ASGE)[7], American Gastroenterological Association (AGA)[15] and Asia-Pacific in its CD guideline[23]. However, BSG[5], Asociación Colombiana de Gastroenterología (ACOG)[17] and NICE[13] recommend initiating the first screening endoscopy ten years after the diagnosis. Yet other scientific societies delay the initiation of screening depending on whether it is a left-side colitis or pancolitis[12]. The rest recommend the first screening at between eight and ten years after diagnosis or the onset of symptoms[4,9,11]. For a PSC diagnosis, there is a consensus that the first endoscopy should be performed when the disease is detected and, as we will see later, there is no doubt that there should be annual colonoscopy[1,3-7,9-11,13,15-18]. None of the guidelines or consensuses specify when the first endoscopy should be performed for an ileo-anal pouch, although there is more consensus regarding the subsequent follow-up. There is a consensus that there is an added risk factor for CRC in patients with IBD who have a family history of CRC. However, CCA is the only society that makes

a specific recommendation, indicating that if there is a family history of CRC, screening should begin before eight years after the diagnosis of the disease[6]. It also indicates that, in those young patients whose only additional risk factor is having a first-degree relative with CRC at less than 50 years of age, the screening should be performed ten years before the age of the affected family member at the time of diagnosis[6].

WHO SHOULD BE OFFERED ENDOSCOPIC SURVEILLANCE?

Our recommendation: After endoscopic screening, endoscopic follow-up should be performed for all patients except for those with ulcerative proctitis, CD with involvement of less than 1/3 of the colon, and those in which the risks outweigh the possible benefits.

This aspect is addressed by the majority of the guidelines, and there is a general consensus about not performing endoscopic surveillance for CRC screening in patients with proctitis or with CD of minimal extent[3,6,7,9,11,12,13,18,23], as their risk of developing neoplasia is very low. AGA also excludes patients with procotosigmoiditis from follow-up[15]. Only the ECCO-Elderly[22], NICE[13] and NZGG[4] guidelines refer to the need for balancing the risks and benefits of performing endoscopic surveillance for elderly patients and those with significant comorbidities or with a short life expectancy.

SHOULD THE SAME ENDOSCOPIC SURVEILLANCE INTERVALS BE FOLLOWED FOR ALL PATIENTS?

Our recommendation: No. We recommend that patients be stratified according to the individual risk for each.

The most recently published guidelines and consensuses recommend stratifying patients with IBD who will be included in an endoscopic surveillance programme according to individual risk[1,3-7,11,13-15,17,18]. In this way, we will be able to offer a more individualised endoscopic follow-up to each patient.

ARE THERE INDIVIDUAL RISK FACTORS THAT ALLOW US TO STRATIFY ENDOSCOPIC SURVEILLANCE?

Our recommendation: Yes.

In patients with left-sided UC or pancolitis and CD which affects at least 1/3 of the colon, having any of the following must be considered high risk factors: PSC, extensive involvement, moderate-severe active inflammation sustained over time (endoscopic or histological), first-degree relative with CRC at an age of less than 50, stenosis or dysplasia detected during the previous five years. Any of the following should also be

	High risk	Intermediate risk	Low risk
Table 2 Risk factors for the development of colorectal cancer in patients with inflammatory bowel disease and recommended surveillance[1-7,9,11,13-15,17,18,24]			
Risk factors	PSC Extensive involvement Moderate-severe active inflammation sustained over time (endoscopic or histological) First-degree relative with CRC at an age of less than 50 Stenosis or dysplasia detected during the previous five years Appearance of IBD at a young age[1] If ileo-anal pouch: Dysplasia Previous CRC PSC Type C mucosa in the pouch	Extensive colitis with mild or moderate sustained inflammatory activity (endoscopic or histological) Inflammatory polyps First-degree relative with CRC at an age of above 50	Other factors different from high and intermediate risk
Surveillance	Annual	Every three years	Every five years

[1]BSG[5], CCFA[11], WGO[14] and SVG[18]. CRC: Colorectal cancer; IBD: Inflammatory bowel disease; PSC: Primary sclerosing cholangitis.

considered as intermediate risk factors: Extensive colitis with mild or moderate sustained active inflammation (endoscopic or histological), the occurrence of inflammatory polyps or having a first-degree relative with CRC at an age of greater than 50. A diagnosis of IBD at a young age should be taken into account as a relative risk factor (due to the long duration of the disease).

The following should be considered high-risk factors in cases where there is an ileo-anal pouch: Dysplasia or previous CRC, PSC, type C mucosa in the pouch (persistent atrophy and severe inflammation).

The most recent recommendations coincide in establishing some risk factors for the development of CRC in patients with IBD. The following are risk factors according to ECCO, NZGG, BSG and ACPGBI, CCA, ASGE, American College of Gastroenterology (ACG), Crohn's and Colitis Foundation of America (CCFA), NICE, AGA, World Gastroenterology Organization (WGO), ACOG and SVG: PSC, extensive involvement, moderate-severe active inflammation sustained over time (endoscopic or histological), first-degree relative with CRC at an age of less than 50, and stenosis or dysplasia detected during the previous five years[1-4,6,7,9,11,13-15,17,18,24]. They also agree that a liver transplant for PSC does not eliminate the risk of CRC. There is no consensus in the guidelines regarding whether the onset of IBD at a very young age should be considered a risk factor. In relation to this, AGA considers that the screening should be performed on these patients more for the duration of the disease than for its appearance at a young age[24]. However, according to BSG[5], CCFA[11], WGO[14] and SVG[18], the appearance of IBD at a young age should be considered a high risk factor. The following are considered intermediate risk factors according to ECCO, NZGG, BSG and ACPGBI, NICE, and ACOG: Extensive colitis with mild or moderate sustained inflammatory activity (endoscopic or histological), the occurrence of inflammatory polyps, and a first-degree relative with CRC at an age of above 50[1,4,5,13,17] (Table 2).

On the other hand, ECCO, BSG and ACPGBI, CCA and SVG consider the following to be high risk factors for

patients with an ileo-anal pouch: Dysplasia or previous CRC, PSC, type C mucosa in the pouch (persistent atrophy and severe inflammation)[1,5,6,18].

HOW LONG SHOULD THE ENDOSCOPIC FOLLOW-UP INTERVALS BE?

Our recommendation: Patients with IBD: According to the presence of risk factors for each patient. High risk factors: Annual colonoscopy. Intermediate risk factors: Colonoscopy every three years. Low risk factors or without other risk factors: Colonoscopy every five years. Patients with an ileo-anal pouch: According to the presence of risk factors: With risk factors: Annual colonoscopy. Without risk factors. Colonoscopy every five years.

There is some consensus in clinical practice guidelines which stratify patients according to risk for deciding on the follow-up intervals according to the risk presented. Patients with high risk factors should have an annual colonoscopy. Patients with intermediate risk factors should have a colonoscopy every two to three years. And for those patients with low risk factors or with no other risk factors, surveillance can be spaced at one colonoscopy every five years[1,4-6,13,17]. ASGE agrees about which patients require annual monitoring; however, for the rest, it states that colonoscopy should be performed every one to three years[7]. According to NASPGHAN, ACG, CCFA, Asia-Pacific and AGA, surveillance should be conducted annually or biennially[9-12,15,23].

The absence of endoscopic activity in two consecutive examinations allows the follow-up to be spaced according to some scientific societies[3,4,6,7,11,15]; even in the NICE guideline, surveillance could be stopped for those low-risk patients for whom no adenomas are detected[13].

On the other hand, scientific societies that make recommendations regarding patients with an ileo-anal pouch (ECCO, BSG and ACPGBI, CCA and SVG) are of the opinion that, when risk factors are present, an annual colonoscopy should be performed, and when

there are no risk factors, a colonoscopy should be performed every five years[1,5,6,18].

WHAT IS THE RECOMMENDED ENDOSCOPIC TECHNIQUE FOR SCREENING AND SURVEILLANCE?

Our recommendation: Chromoendoscopy with endoscopic resection or taking biopsies directed at visible lesions is the technique of choice. If this is not possible, high-definition video-colonoscope should be used and four biopsies taken for every ten cm of the colon.

The consensuses published in recent years coincide in pointing out that chromoendoscopy with endoscopic resection or taking biopsies directed at visible lesions is the preferred surveillance technique, as it increases the number of dysplastic lesions that can be detected[1,5-7,9,25]. Although it is true that this technique increases the time required for the exploration, the analysed studies conclude that it is more cost-effective than white-light colonoscopy. The principal disadvantages to its performance are that it requires thorough intestinal preparation and more time to complete the exploration, and the endoscopist must be specifically trained[25]. The guidelines of AGA[24], BSG[5], NICE[13], ECCO[1] and CCFA[11] support this technique if done properly by expert endoscopists. This technique may improve the detection of flat dysplasia and help ensure the complete resection of polypoid or minimally elevated lesions. Therefore, it could be of value in the follow-up of high risk patients[7,9,12,24].

When chromoendoscopy is not available, or a suitable expert is not available, or if its performance is hindered due to significant inflammation, pseudopolyps, poor preparation or poorly visualised mucosal areas, then the taking of random biopsies in addition to biopsies targeting any suspected lesions appears to be a reasonable alternative[1,3,5-7], but it must be taken into account that the detection of neoplasias is inferior to that of chromoendoscopy[1]. For cases in which white-light colonoscopy are used, the high-definition colonoscope are preferred to the standard colonoscope, as the visualisation is better. When using a standard endoscope, the use of chromoendoscopy is preferred over white-light[25]. Although there is no evidence regarding the quantity of biopsies to be taken, some guidelines recommend taking at least four biopsies from each segment of the colon every ten cm[1,4]. In the recently published SCENIC Consensus (Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in IBD Patients: International Consensus Recommendations)[25], there is no clear agreement among experts regarding the quantity of biopsies to take or the manner in which they should be taken.

Narrow-band imaging has not been shown to increase the detectability of dysplasia during endoscopy[1,7,25]. More studies are needed to evaluate the effectiveness of Narrow-band imaging as well as other techniques such as the use of autofluorescence or microscopic confocal endoscopy[1,5,8,24,25].

HOW IS CHROMENDOSCOPY PERFORMED?

Our recommendation: Use 0.04% to 0.1% methylene blue or between 0.1% to 0.03% indigo carmine. Perform cecal intubation and apply a dye to the colon mucosa as the endoscope is removed, if possible using a catheter spray. Examine one segment before apply colorant in the next.

Normally 0.1% methylene blue or 0.03% to 0.1% indigo carmine is used. Cecal intubation should be performed using a white-light endoscope. The colonic mucosa should then be stained by spray aspirating the excess fluids and carefully evaluating the mucosa. Once the lesion is localised, chromoendoscopy helps to delimit it, assess its size and borders and perform techniques that help rule out submucosal invasion[1,7,8,25].

DOES THE OCCURRENCE OF DYSPLASIA REQUIRE CONFIRMATION?

Our recommendation: The occurrence of dysplasia must be confirmed by a second pathologist.

Histopathological analysis is qualitative and consequently has a high inter-observer variability, especially in low grade dysplasia and in inflamed mucosa. Therefore, there is a general consensus that the occurrence of dysplasia should be confirmed by an independent expert gastrointestinal pathologist[1,4-7,9,11,15,18,23,25].

WHAT TERMINOLOGY SHOULD WE USE TO DESCRIBE LESIONS DETECTED WITH ENDOSCOPY?

Our recommendation: The terms "dysplasia-associated lesion or mass" (DALM) and "flat lesions" should be discontinued. We should be using the modified Paris Classification in which lesions are divided into visible dysplasia and invisible dysplasia depending on whether the biopsy has been taken from a lesion visualised in the colonoscopy or not. Visible dysplasia is divided into polypoid and non-polypoid depending on whether or not the lesion protrudes from the lumen $\geqslant$ 2.5 mm. The descriptions of visible lesions should also include mention of whether they are ulcerated and whether the borders are easily distinguished from the surrounding mucosa.

The ECCO guideline[1] insists on discontinuing the terms "DALM" and "flat lesions" and using the Paris Classification[26]. It also differentiates between endoscopically visible and non-visible lesions. The ASGE[7] guideline adds to the above the importance of distinguishing whether the lesions are located in an area affected by colitis, whether or not the borders

Table 3 SCENIC international consensus	
Term	**Definition**
1 Visible dysplasia	Dysplasia identified on targeted biopsies from a lesion visualised at colonoscopy
Polypoid	Lesion protruding from the mucosa into the lumen ≥ 2.5 mm
Pedunculated	Lesion attached to the mucosa by a stalk
Sessile	Lesion not attached to the mucosa by a stalk: Entire base is contiguous with the mucosa
Nonpolypoid	Lesion with little (< 2.5 mm) or no protrusion above the mucosa
Superficially elevated	Lesion with protrusion but < 2.5 mm above the lumen (less than the height of the closed cup of a biopsy forceps)
Flat	Lesion without protrusion above the mucosa
Depressed	Lesion with at least a portion depressed below the level of the mucosa
General descriptors	
Ulcerated	Ulceration (fibrinous-appearing base with depth) within the lesion
Border	
Distinct border	Lesion's border is discrete and can be distinguished from surrounding mucosa
Indistinct border	Lesion's border is not discrete and cannot be distinguished from surrounding mucosa
2 Invisible dysplasia	Dysplasia identified on random (non-targeted) biopsies of colon mucosa without a visible lesion

Terminology for reporting findings[23].

are well delimited, and assessing indirect signs of submucosal invasion. The SCENIC Consensus[25] agrees with regard to recommending the discontinuation of the terms "DALM" and "flat lesion" as well as separating the dysplasia into visible and non-visible. Among visible lesions, it distinguishes between those that are endoscopically resectable and those that are not. They also recommend a modification of the Paris classification, adding descriptive phrases about the delimitation of the borders of the lesions and whether or not they are ulcerated (Table 3). The detection of non-polypoid lesions is recent, thanks to advances in endoscopic imaging techniques; therefore the risk of developing CRC is still unknown. Likewise, resection of these types of lesions is more complex, and there may be doubts about whether the resection has been complete. However, there are still scientific societies that continue to use the terms "sporadic adenomas" and "DALM"s[4,6,9,15,18]. The AGA guideline distinguishes between prevalent dysplasia (that which is detected in the first screening colonoscopy), which presents an increased risk of developing CRC, and incident dysplasia (detected during follow-up). In addition, low-grade dysplasia emphasises discernment between unifocal or multifocal dysplasia[15].

HOW SHOULD A VISIBLE LESION BE MANAGED?

Our recommendation: Visible lesions which are well delimited, with no evidence of dysplasia in the mucosa adjacent to the lesion and without synchronous dysplasia, should be resected endoscopically regardless of the degree of dysplasia.

Lesions that are endoscopically visible and well-defined, irrespective of their location and degree of dysplasia or whether or not there is involvement by colitis, should be endoscopically resected by an expert endoscopist, and biopsies should be taken of the adjacent mucosa[1,5,7,11,15,25]. The ASGE guideline also recommends preparing tattoo and photo-documentation of the resected lesions. They also suggest colectomy as a possibility to discuss with the patient, if the completely excised lesion exhibits high-grade dysplasia (HGD)[7]. If complete resection is anatomopathologically confirmed, and there is no dysplasia in the adjacent mucosa or elsewhere in the colon, the indication is close endoscopic follow-up. If the described conditions are not met, the treatment would be total colectomy.

HOW SHOULD NON-VISIBLE DYSPLASIA BE INITIALLY MANAGED?

Our recommendation: Dysplasia which is not endoscopically visible but found in serial biopsies of the colon must be confirmed by an independent pathologist after the performance of a chromoendoscopy by an expert endoscopist. If confirmed, management will depend on the degree of dysplasia.

As for the management of invisible dysplasia, that which is detected in random colon biopsies, the quality of the evidence in the recommendations is very low[27]. The ECCO[1] and ASGE guidelines[7] and the SCENIC Consensus[25] indicate repeating colonoscopy with chromoendoscopy, regardless of the degree of dysplasia, by an expert endoscopist to confirm that there is no endoscopically visible lesion, and taking random biopsies to rule out the occurrence of synchronous dysplasia. If an endoscopically visible lesion is detected after this examination, and there is no more dysplasia elsewhere, they recommend endoscopic resection.

HOW SHOULD NON-VISIBLE DYSPLASIA BE MANAGED IN RELATION TO THE DEGREE OF DYSPLASIA?

Our recommendation: Endoscopically non-visible HGD is an indication for colectomy. The management of low-grade, invisible dysplasia should be agreed upon in a multidisciplinary committee and with the patient, with colectomy or endoscopic follow-up being the two possible options.

In the event that HGD or adenocarcinoma is detected without a visible lesion, surgery is the recommended option[1,5,7,15]. If low-grade dysplasia without a visible lesion is detected in the second chromoendoscopy performed by an expert, the degree of agreement among the guidelines is lower. It must be a multidisciplinary decision and discussed with the

patient[1,4,5,7,11,15,25]. Colectomy is recommended if low-grade dysplasia is mutifocal, but the recommendations are more conservative for low-grade, unifocal dysplasia, and a closer annual endoscopic follow-up may be offered[1,5,7,11,15,25].

The New Zealand Guidelines Group[4] advocates offering colectomy to all patients who are found to have dysplasia, and performing close endoscopic follow-up only in those who refuse or are unfit for surgical treatment.

HOW SHOULD ENDOSCOPICALLY RESECTED LESIONS BE FOLLOWED?

Our recommendation: The follow-up for resected lesions in healthy mucosa which is not affected by colitis should be the same as that for sporadic adenomas. Lesions which are endoscopically resected in areas affected by colitis should be examined endoscopically at three months, and annually thereafter.

There is a strong consensus that the management of lesions detected in mucosal areas not affected by colitis should be the same as that of sporadic adenomas[1,3,7,11,15,25]. As for lesions located in areas where there is or has been active inflammation, which have been endoscopically resected and in which there is no dysplasia of the surrounding mucosa, the follow up should be close. The ECCO guideline[1] recommends performing an endoscopy at three months, and if there is no dysplasia, to change to annual endoscopic follow-up, preferably with chromoendoscopy. ASGE[7] recommends an initial examination at between one to six months and then changing to annual monitoring. The SCENIC Consensus[25] distinguishes between polypoid and non-polypoid lesions. For polypoid lesions, it advises follow up at three to six months and then annually if they are sessile, large and excised in a fragmented manner. However, for those smaller polyps excised en bloc, it advises immediate annual follow-up. As for non-polypoid dysplastic lesions, they recommend monitoring at three to six months (the risk of CRC is greater, and it is more difficult to ensure that the polypectomy has been complete).

SUMMARY OF OUR RECOMMENDATIONS

CRC screening should be offered to patients with IBD (UC, IC, CD affecting at least 1/3 of the colon or with complex perianal disease and to patients with an ileo-anal pouch). The first screening colonoscopy should be offered eight years after a diagnosis of CD or UC; at one year after the surgical construction of an ileo-anal pouch, or at the time of the diagnosis of PSC. It should be kept in mind that subsequent endoscopic surveillance should be performed on all patients except for those with ulcerative proctitis, CD with involvement of less than 1/3 of the colon and those for which the risks far

outweigh the possible benefits. We recommend patient stratification according to the individual risk of each patient in order to determine more individualised follow-up intervals. The technique of choice for endoscopic surveillance is chromoendoscopy with endoscopic resection or biopsy of visible lesions. Regarding the terminology to be used, we should use the modified Paris Classification and abandon terms such as "DALM" and "flat lesions". Regarding the management of lesions, we should differentiate between visible and invisible lesions. Visible lesions which are well delimited, with no evidence of dysplasia in the mucosa adjacent to the lesion and without synchronous dysplasia, should be resected endoscopically regardless of the degree of dysplasia. Dysplasia which is not endoscopically visible but found in serial biopsies of the colon must be confirmed by an independent anatomical pathologist after the performance of a chromoendoscopy by an expert endoscopist. If this is confirmed, management will depend on the degree of dysplasia. Endoscopically non-visible HGD is an indication for colectomy. The management of low-grade invisible dysplasia should be agreed upon in a multidisciplinary committee and with the patient, with colectomy or endoscopic follow-up being the two possible options. The follow-up for resected lesions in healthy mucosa which is not affected by colitis should be the same as that for sporadic adenomas. However, lesions which are endoscopically resected in areas affected by colitis should be examined endoscopically at three months, and annually thereafter.

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Retrospective Cohort Study

Endoscopic resolution and recurrence of gastric antral vascular ectasia after serial treatment with argon plasma coagulation

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Abstract

AIM
To evaluate long-term endoscopic resolution and recurrence rate of gastric antral vascular ectasia (GAVE) after argon plasma coagulation (APC) treatment.

METHODS
This was an IRB-approved retrospective single center study that included patients endoscopically treated for GAVE between 1/1/2008 to 12/31/2014. The primary and secondary end points of the study were rate of endoscopic resolution of GAVE after APC treatment and recurrence rate of GAVE after endoscopic resolution, respectively. Endoscopic resolution of GAVE was defined as no endoscopic evidence of GAVE after treatment with APC. Recurrence of GAVE was defined as endoscopic reappearance of GAVE after prior resolution.

RESULTS
Twenty patients met the study criteria. Median age (range) of the patients was 59.5 years (42-74 years). GAVE was associated with underlying cirrhosis in 16 (80%) patients. Indications for initial esophagogastroduodenoscopy (EGD) included hematemesis and/or melena (9/20, 45%), iron deficiency anemia (6/20, 30%), screening or surveillance of varices (4/20, 20%), and occult gastrointestinal bleeding (1/20, 5%). The patients were treated with a total of 55 APC sessions (range 1-7 sessions). Successful endoscopic resolution of GAVE was

achieved in 8 out of 20 patients (40%). There was no correlation between number of treatment sessions and GAVE treatment success (P = NS). Recurrence of GAVE was noted on a subsequent EGD in 2 out of 8 patients (25%) with prior endoscopic resolution of GAVE. Median follow-up period for the study population was 627 d (range 63-1953 d).

CONCLUSION
Endoscopic resolution rate of GAVE was low (40%) with a 25% recurrence rate after treatment with APC. These rates suggest that APC treatment of GAVE may not be optimal in many circumstances.

Key words: Gastric antral vascular ectasia; Argon plasma coagulation

Core tip: Argon plasma coagulation (APC) has a good short-term success rate (> 80%) in improving symptoms related to gastric antral vascular ectasia (GAVE). However, GAVE related symptoms can recur in up to 50% of patients. This is the first study to evaluate resolution of GAVE after treatment with APC and its recurrence after successful treatment. The study showed a 40% resolution rate of GAVE after serial treatment with APC. The resolution of GAVE was not associated with number of APC sessions. GAVE was noted to recur in 25% of cases after successful resolution. These results suggest that APC may not be the best modality for treatment of symptomatic GAVE.

INTRODUCTION

Gastric antral vascular ectasia (GAVE) is a well-defined clinical entity characterized endoscopically by prominent flat or erythematous streaks radiating in a spoke-like fashion from the pylorus to the antrum and pathologically by spindle cell proliferation in the mucosal blood vessels, intravascular fibrin thrombi and fibrinohyalinosis[1]. It is associated with portal hypertension or other systemic diseases like systemic sclerosis, and typically presents clinically as iron deficiency anemia and/or overt gastro-intestinal (GI) bleeding[2]. In various case series, argon plasma coagulation (APC) has been shown to have > 80% success for treatment of GAVE related anemia or GI bleeding[1-6]. However, these results have not been uniformly confirmed; Boltin *et al*[7], for example,

reported a lower success rate (25.8%) of APC in treating GAVE related anemia or GI bleeding at a mean follow up period of 46.8 mo. Similarly in a recent systemic review, Swanson *et al*[8] reported a 44%-50% failure rate of APC in the treatment of anemia or GI bleeding related to GAVE. They concluded that there is very low quality evidence for the use of APC in the treatment of GAVE. A possible reason for this observation is that APC is used for controlling GAVE related symptoms but not for complete eradication of GAVE itself. None of the prior studies have evaluated endoscopic resolution of GAVE after APC therapy. This study was undertaken to evaluate endoscopic resolution and recurrence rate of GAVE after therapy with APC.

MATERIALS AND METHODS

This was an IRB-approved retrospective study. Cases were identified by reviewing billing data for the period January 1, 2008 - December 31, 2014 to identify all patients who had an EGD (CPT codes 43200 - 43259 excluding 6 codes for EUS) at University of Kentucky Medical Center and with a billing diagnosis of GAVE (ICD-9 code 537.82). The diagnosis of GAVE was made endoscopically in each case.

The primary end point of the study was rate of endoscopic resolution of GAVE after APC treatment as seen on additional endoscopic exams subsequent to the index (first) exam which included treatment. The secondary end point of the study was GAVE recurrence rate after endoscopic resolution. Endoscopic resolution of GAVE was defined as no endoscopic evidence of GAVE after at least 1 treatment session with APC. Recurrence of GAVE was defined as endoscopic reappearance of GAVE on a subsequent EGD after successful resolution. Patients who did not undergo an APC session and at least one follow-up endoscopy, or had treatment of GAVE by a method other than APC were excluded from further analysis. The following information was collected from each patient's medical record: Demographics, etiology of GAVE, indication and date of endoscopy(s), endoscopic findings, adverse effects during endoscopy, follow-up period and death.

Treatment for GAVE at this institution did not follow a standardized protocol, but was instead directed by individual physician and patient preference according to the clinical circumstances. GAVE was treated with APC during the initial endoscopy when it was assessed to be the cause of patient's symptoms. Treatment of GAVE was repeated according to physician preference, generally every 4-8 wk; but not all patients underwent subsequent treatments. Procedures were done under appropriate sedation or anesthesia. APC treatment was performed using a high-frequency electrosurgical ERBE generator coupled to an argon gas delivery unit. The settings used for APC treatment were 20-60 Watts of power and 0.3 to 2 L/min of argon gas flow rate. In each APC session, affected areas were coagulated as much as

Table 1 Demographic features of patients with symptomatic gastric antral vascular ectasia *n* (%)

	Patients with cirrhosis (*n* = 16)	Patients without cirrhosis (*n* = 4)	*P* value
Median age (range) in years	59.5 (42-74)	62.5 (53-73)	0.51
Males	9 (56.3)	1 (25)	0.58
Caucasians	16 (100)	4 (100)	-
Indication for initial EGD			-
Upper gastrointestinal tract bleeding	7 (43.7)	2 (50)	
Iron deficiency anemia	5 (31.3)	1 (25)	
Esophageal varices screening or surveillance	4 (25)	-	
Follow up of arteriovascular malformations	-	1 (25)	
Median number of APC sessions (range)	2 (1-7)	2.5 (1-6)	0.66
Endoscopic resolution of GAVE	8 (50)	0	0.12
Recurrence of GAVE	2/8 (25%)	-	-

APC: Argon plasma coagulation; EGD: Esophagogastroduodenoscopy; GAVE: Gastric antral vascular ectasia.

Table 2 Eradication success rate by number of argon plasma coagulation treatment sessions

No. of APC sessions	No. of total patients	Patients with GAVE resolution (%)	*P* value
1	7	2 (29)	0.33
2	5	2 (40)	
3	3	1 (33)	
4-7	5	3 (60)	
Total	20	8 (40)	

APC: Argon plasma coagulation; GAVE: Gastric antral vascular ectasia.

Statistical analysis

Categorical data were described in fractions or percentages, and analyzed using Fischer's exact or χ^2 test depending on sample size. Continuous data were described as mean or median, and analyzed using *t* test or Wilcoxon rank-sum test depending on the distribution. Multivariate logistic regression was used to analyze the relationship between number of APC sessions and resolution of GAVE with APC. Two-sided *P* value of $\leq$ 0.05 was considered significant. The data were analyzed using STATA 13.1 (Statacorp® Texas).

RESULTS

A total of 45 patients with GAVE were identified by the initial screen for review. Twenty five patients were excluded from the final analysis: 8 patients did not get any treatment, 14 patients did not have a follow up EGD, and 3 patients had treatment of GAVE by other modalities. Twenty patients were included in the final analysis (Table 1). Median age (range) at the time of first EGD was 59.5 years (42-74 years). Ten patients were males (50%) and all the patients were Caucasians. GAVE was associated with underlying cirrhosis in 16 (80%) patients.

Indications for initial EGD were hematemesis and/or melena (9/20, 45%), iron deficiency anemia (6/20, 30%), screening or surveillance of varices (4/20, 20%), and occult gastrointestinal bleeding (1/20, 5%). A total of 55 APC sessions were done for the treatment of GAVE (2.75 sessions per patient, range 1-7 sessions). Successful endoscopic resolution of GAVE was achieved in 8 out of 20 patients (40%, 95%CI: 19%-64%). In all these 8 patients, GAVE was associated with underlying

cirrhosis whereas none of the patients without cirrhosis had endoscopic resolution of GAVE. However, this difference was not statistically significant (*P* = 0.12). There was no correlation between number of treatment sessions and GAVE treatment success (*P* = 0.33, Table 2). In 2 out of 8 patients (25%, 95%CI: 3%-65%) who had endoscopic resolution of GAVE, it was noted again on a subsequent EGD that was performed for a different indication. Median follow-up period for the study population was 627 d (range 63-1953 d).

Portal hypertensive gastropathy (PHG) was noted in 3 out of 16 (18.75%) patients with GAVE and cirrhosis. GAVE resolution with APC treatment was noted in 2 of these 3 patients with PHG. PHG was not noted in patients with recurrence of GAVE after initial resolution. No endoscopy related adverse events were found during the study period. Three patients (15%) died during the follow-up period. Time to death ranged from 123-986 d. None of the deaths were related to the endoscopy or symptoms related to GAVE.

DISCUSSION

This is the first study to evaluate endoscopic resolution of GAVE and its recurrence rate after APC therapy. In this study, APC had a low success rate (40%) for endoscopic resolution of GAVE, with recurrence of GAVE seen in 25% of patients after documented endoscopic resolution on a subsequent EGD. Historically, APC has been reported to have > 80% success rate for treatment of anemia or GI bleeding related to GAVE. However, most of these case series did not evaluate endoscopic resolution or recurrence of GAVE[1-7].

Findings in this study support the low success rate of APC in the treatment of GAVE related anemia or GI bleeding as reported by Boltin *et al*[7] and Swanson *et al*[8]. It would be empirically expected that endoscopic appearance of GAVE would correlate with improvement in GAVE-related anemia or GI bleeding. Therefore, if the 70% rate of combined endoscopic non-resolution and recurrence seen in this series is correct, then APC would be expected to show suboptimal rates of improvement in GAVE-related symptoms.

There are several possible reasons for the low success rate of APC in endoscopic resolution of GAVE. GAVE varies significantly in morphology (flat *vs* nodular)

and severity (striped distribution in the antrum *vs* diffuse involvement of antral mucosa) between patients. APC may not work with similar effectiveness in all these situations. Additionally, the abnormal dilated capillaries and fibromuscular hyperplasia in GAVE extend to the lamina propria[9]. However, the coagulation effect of APC rarely (4.8%) ablates the entire thickness of lamina propria. Moreover, coagulation of the entire thickness of the lamina propria needs power of 90-Watts or more which is significantly higher than the usual power settings (30-80 W) used to treat GAVE [4,7,10].

There are some limitations of this study. The study has a small sample size. It is retrospective in nature and does not have a control group or a second intervention group to compare the outcomes with APC treatment. The study did not follow a defined program of consecutive APC sessions to achieve GAVE eradication, nor was there a defined surveillance protocol to search for recurrence. However, the lack of correlation between number of APC sessions and treatment success in this study suggests that this might not be an effective modality even in principle, or might require an excessive number of APC sessions. A prospective, protocol-driven study will be needed to resolve these questions.

In summary, APC may not be an effective therapy in long term for the treatment of symptomatic GAVE. Alternate therapies including radiofrequency ablation and/or banding should be evaluated in a prospective, randomized fashion against APC in order to determine the appropriate endoscopic approach for the treatment of symptomatic GAVE.

COMMENTS

Background
Argon plasma coagulation (APC) is the most widely used treatment method for gastric antral vascular ectasia (GAVE). However, a recent systematic review reported 44%-50% recurrence rate of symptoms related to GAVE after treatment with APC. None of the prior studies have evaluated endoscopic resolution of GAVE after therapy with APC.

Research frontiers
This is the first study to evaluate endoscopic resolution of GAVE after treatment with APC and its recurrence rate after successful treatment with APC therapy.

Innovations and breakthrough
The results of this study showed that serial treatment with APC was associated with only 40% resolution of GAVE as evaluated by endoscopy. Out of these 40% cases, GAVE was noted to recur during a subsequent esophagogastroduodenoscopy (EGD) in 25% of cases. The resolution of GAVE was not associated with number of APC sessions performed to treat GAVE.

Applications
The results of this study suggest that APC may not be an effective therapy in long term for the treatment of symptomatic GAVE. Alternate therapies including radiofrequency ablation and/or banding should be evaluated in a prospective, randomized fashion against APC in order to determine the appropriate endoscopic approach for the treatment of symptomatic GAVE.

Terminology
GAVE is a distinct clinical entity characterized endoscopically by prominent flat or erythematous streaks radiating in a spoke-like fashion from the pylorus to the antrum and pathologically by spindle cell proliferation in the mucosal blood vessels, intravascular fibrin thrombi and fibrohyalinosis. EGD is a procedure used to examine the upper gastrointestinal tract (from esophagus to forth part of duodenum) using a flexible video endoscope. APC is a type of non-contact thermal therapy used during EGD to obtain hemostasis or tissue destruction. It involves infusion of argon gas through a catheter into the lumen of gastrointestinal tract. The gas is converted into plasma by passing electricity through the catheter. The plasma then conducts the electricity to the tissue to achieve hemostasis or tissue destruction. The catheter does not come into direct contact with the tissue.

Peer-review
The authors have looked into the outcomes of 20 patients with GAVE who underwent endoscopic APC treatment and concluded that endoscopic resolution rate of GAVE was low (40%) with a 25% recurrence rate after treatment with APC. The manuscript is interesting and provided some insight on the treatment of GAVE using APC.

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Observational Study

Utility of the balloon-overtube-assisted modified over-the-wire stenting technique to treat post-sleeve gastrectomy complications

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Abstract

AIM

To describe a modified technique of deployment of stents using the overtube developed for balloon-assisted enteroscopy in post-sleeve gastrectomy (SG) complications.

METHODS

Between January 2010 and December 2015, all patients submitted to an endoscopic stenting procedure to treat a post-SG stenosis or leakage were retrospectively collected. Procedures from patients in which the stent was deployed using the balloon-overtube-assisted modified over-the-wire (OTW) stenting technique were described. The technical success, corresponding to proper placement of the stent in the stomach resulting in exclusion of the SG leak or the stenosis, was evaluated. Complications related to stenting were also reported.

RESULTS

Five procedures were included to treat 2 staple line leaks and 3 stenoses. Two types of stents were used, including a fully covered self-expandable metal stent designed for the SG anatomy (Hanarostent, ECBB-30-240-090; M.I. Tech, Co., Ltd, Seoul, South

Korea) in 4 procedures and a biodegradable stent (BD stent 019-10A-25/20/25-080, SX-ELLA, Hradec Kralove, Czech Republic) in the remaining procedure. In all cases, an overtube was advanced with the endoscope through the SG to the duodenum. After placement of the guidewire and removal of the endoscope, the stent was easily advanced through the overtube. The overtube was pulled back and the stent was successfully deployed under fluoroscopic guidance. Technical success was achieved in all patients.

CONCLUSION
The adoption of a modified technique of deployment of OTW stents using an overtube may represent an effective option in the approach of SG complications.

Key words: Bariatric surgery; Sleeve gastrectomy; Stenosis; Anastomotic leaks; Balloon-overtube; Stent

Core tip: Sleeve gastrectomy (SG) represents a type of bariatric surgery, whose postoperative complications include anastomotic leaks and strictures. Endoscopic treatment may encompass stenting, which may be technically challenging in angulated and tortuous SG anatomies. Furthermore, the delivery systems of some stents used in this indication are larger and less flexible. These aspects may result in recurrent kinking of the delivery system of the stent preventing its correct progression in the altered gastric cavity. Therefore, the adoption of a modified technique of deployment of stents using the overtube developed for balloon-assisted enteroscopy may represent an effective option to overcome those technical difficulties.

INTRODUCTION
Sleeve gastrectomy (SG) represents one of the most commonly performed type of bariatric surgeries[1,2]. The increased number of SG has also lead to an increased prevalence of postoperative complications, namely anastomotic and staple line leaks and strictures[2]. The management of post-SG complications has also evolved and endoscopic treatment may currently play an important role in these patients[2]. Endoscopic treatment of staple line leaks and stenoses includes stenting, which may be technically challenging in angulated and tortuous SG anatomies. Furthermore, the delivery systems of some stents used in this indication are larger and less flexible. In some patients these difficulties may result in recurrent kinking of the delivery system of the stent preventing its correct progression in the stomach. Therefore, the adoption of a modified technique of deployment of stents using the overtube developed for balloon-assisted enteroscopy may represent an effective option to overcome those technical difficulties[3].

This study aims to describe a case series of patients with post-SG complications submitted to endoscopic stenting, in whom a conventional over-the-wire (OTW) technique failed and a modified OTW technique with the adaptation of an overtube was adopted.

MATERIALS AND METHODS
Between January 2010 and December 2015, all patients submitted to an endoscopic stenting procedure to treat a post-SG stenosis or leakage were retrospectively collected. Procedures from patients in which the stent was deployed using the balloon-overtube-assisted (STSB1, Olympus) modified OTW stenting technique, after failure of the standard OTW stenting deployment, were described.

SG leaks were diagnosed based on clinical symptoms including fever and radiological evidence of fistula or abdominal abscesses. Patients were referred for stent placement only after resolution of sepsis and drainage of the abdominal collections. SG stenoses were diagnosed based on clinical symptoms including vomiting and endoscopic or barium studies revealing a narrowing of the stomach.

All procedures using the balloon-overtube assisted technique were performed under deep propofol sedation by two experienced endoscopists (RP and LP) with endoscopic and fluoroscopic guidance. Two types of stents were used, including a fully covered self-expandable metal stent (SEMS) designed for the SG anatomy (Hanarostent, ECBB-30-240-090; M.I. Tech, Co., Ltd, Seoul, South Korea) in four procedures and a biodegradable stent (BD stent 019-10A-25/20/25-080, SX-ELLA, Hradec Kralove, Czech Republic) in the remaining procedure. Informed consent was provided by all patients for this technique. The technical success, corresponding to proper placement of the stent in the stomach resulting in exclusion of the SG leak or the stenosis, was evaluated. Complications related to stenting were also reported.

RESULTS
During this period, 13 stents were placed to treat complications of SG, including anastomotic leaks (*n* = 6), stenoses (*n* = 4) and leaks associated with stenoses (*n* = 3). In 3 procedures, standard esophageal covered SEMS were used; in 1 procedure a biodegradable self-expandable stent was used and in the remaining 10 patients a covered SEMS specifically designed to the SG anatomy was used (Hanarostent, ECBB; M.I. Tech,

Table 1 Characteristics of the procedures

Procedure	SG complication	Reasons for failure of conventional OTW stenting	Type of stent	Technical success
1	Dehiscence	Angulation in the antrum	Bariatric SEMS	Yes
2	Dehiscence	Angulation in the antrum	Bariatric SEMS	Yes
3	Stenosis	Long and angulated stenosis in the antrum	Biodegradable stent	Yes
4	Stenosis	Angulated stenosis in the antrum	Bariatric SEMS	Yes
5	Stenosis	Angulated stenosis in the antrum	Bariatric SEMS	Yes

SG: Sleeve gastrectomy; OTW: Over the wire; SEMS: Self-expandable metal stent.

Co., Ltd, Seoul, South Korea). These later 2 stents have a larger and stiffer delivery device that adds difficulty in the passage of angulations and stenosis, resulting in kinking and subsequent damage to the stent. In five (38%) of all procedures, representing 50% of patients (5/10) with these larger delivery devices, the presence of angulations and/or stenosis prevented the advancement of the stent delivery system (4 bariatric surgery stents and 1 biodegradable stent), precluding the standard OTW technique. In these 5 cases, the balloon-overtube-assisted modified OTW stenting technique was used to overcome these angulated stenoses. In Table 1 the characteristics of the five procedures are summarized.

Procedure 1

This patient was referred for our department to treat a large early leak post-SG in the proximal antrum. Endoscopy revealed a 30-mm dehiscence in the proximal antrum and a marked angulation in the distal antrum. This angulation caused persistent kinking of the delivery device, preventing the technical success of stenting using the standard OTW approach. Hence, an overtube was used to overcome the initial difficulties. The overtube and endoscope were advanced through the SG to the duodenum (Figure 1A). After placement of the guidewire and removal of the endoscope leaving the overtube in place (Figure 1B), a fully covered SEMS (Hanarostent, ECBB-30-240-090; M.I. Tech, Co., Ltd, Seoul, South Korea) was easily advanced through the overtube (Figure 1C). The overtube was then pulled back and the stent was successfully deployed under fluoroscopic guidance (Figure 1D). Correct placement of the stent was confirmed by injection of contrast revealing no extravasation of contrast through the leak. No immediate or late complications related to the stent were reported.

Procedure 2

This procedure was performed to treat early dehiscences post-SG. Endoscopy revealed 3 small leaks, one located in the proximal body and two located in the proximal antrum. The angulated configuration of the SG caused repeated kinking preventing the advancement of the stent using the standard OTW technique. Therefore, an overtube was used and was advanced with the endoscope through the SG to the duodenum. After placement of the guidewire up to the duodenum and removal of the endoscope leaving the

overtube in place, a fully covered SEMS (Hanarostent, ECBB-30-240-090; M.I. Tech, Co., Ltd, Seoul, South Korea) was easily advanced through the overtube that was left *in situ*. The overtube was then pulled back and the stent was successfully deployed under fluoroscopic guidance. Correct placement of the stent was confirmed endoscopically and with fluoroscopy that showed no extravasation of contrast through the leak.

Procedure 3

This patient was referred to our department to stent a chronic fibrotic stenosis post-SG in the distal antrum refractory to balloon dilation. The stenosis was 4-cm long and angulated, which prevented the advancement of the stent's delivery system using the standard OTW technique. Before stenting, the fibrotic stenosis was dilated using a controlled radial expansion balloon with a diameter up to 15 mm. Then, the limits of the stenosis were marked using submucosal contrast injection and the endoscope mounted with the overtube was advanced to the duodenum. The guidewire was then inserted to the jejunum and the endoscope was removed, leaving the overtube through the stenosis. A biodegradable stent (BD stent 019-10A-25/20/25-080, SX-ELLA, Hradec Kralove, Czech Republic) was used, which was advanced through the overtube under fluoroscopic guidance. Then the overtube was split and removed, and the stent was successfully deployed under fluoroscopic guidance. The luminal patency was confirmed with injection of contrast which progressed easily to the jejunum.

Procedure 4

This patient was submitted to a SG which complicated with a stenosis. Firstly, serial balloon dilations were attempted with no clinical success. Therefore, the patient underwent endoscopy to place a stent. The stenosis was dilated with a balloon up to 15 mm. The angulation of the stenosis in the antrum resulted in recurrent kinking of thedelivery system, preventing the advancement of the stent using the standard OTW technique. The overtube-assisted modified OTW stenting technique previously described was then used enabling the advancement of the endoscope and overtube to the duodenum, after delimitation of the limits of the stenosis. The guidewire was subsequently advanced, the endoscope was removed and the overtube was left through the angulation. A fully covered SEMS (Hanarostent, ECBB-30-240-090; M.I. Tech, Co., Ltd,
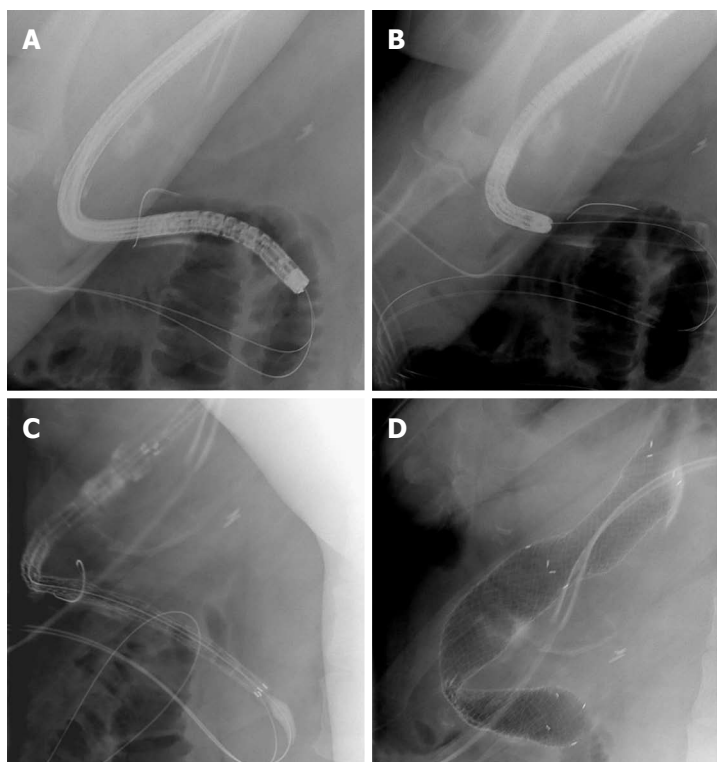
Figure 1 Deployement of the bariatric stent. A: Fluoroscopic image showing advancement of the overtube and endoscope through the sleeve gastrectomy; B: Fluoroscopic image depicting removal of the endoscope after placement of the guidewire and the overtube; C: Fluoroscopic image revealing the progression of the stent over-the-wire and through the overtube; D: Fluoroscopic image showing the release of the stent after the overtube was slightly pulled back. A marked angulation of the stent is seen.
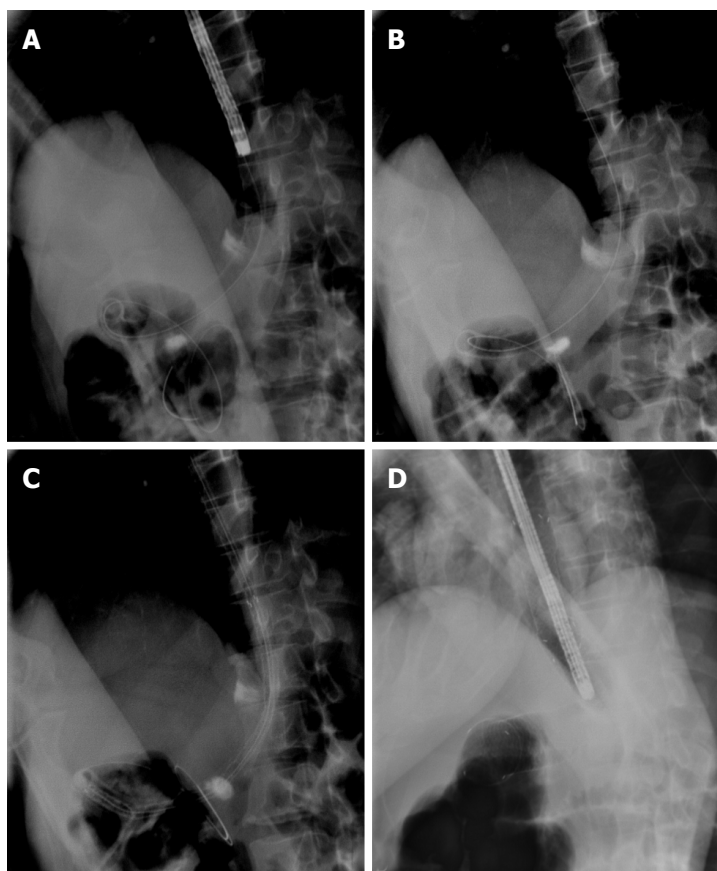

Figure 2 Deployement of the bariatric stent. A: Fluoroscopic image showing the overtube correctly placed in the sleeve gastrectomy while the endoscope is being removed; B: Fluoroscopic image depicting the overtube and the guidewire in place; C: Fluoroscopic image revealing the advancement of the stent over-the-wire and through the overtube; D: Fluoroscopic image showing the deployed stent with a marked angulation.

Seoul, South Korea) was then advanced through the overtube, under fluoroscopic guidance. The overtube was slightly pulled back to prevent the release of the stent in its interior, and finally the stent was deployed under fluoroscopic guidance. Luminal patency was confirmed with administration of oral contrast. Three weeks later, stent migration occurred due to dilation of the stenosis caused by the stent, requiring endoscopic

retrieval of the stent.

Procedure 5

This patient underwent an overtube-assisted modified OTW stenting technique to treat a chronic and angulated stenosis post-SG refractory to balloon dilation. The configuration and angulation of the stenosis prevented the technical success of the standard OTW technique and the modified technique described above using the overtube was adopted. As in procedure 4, after delimitation of the limits of the stenosis with submucosal contrast injection, the overtube and endoscope were advanced through the stenosis to the duodenum. After placement of the guidewire and removal of the endoscope (Figure 2A and B), the fully covered SEMS (Hanarostent, ECBB-30-240-090; M.I. Tech, Co., Ltd, Seoul, South Korea) was easily advanced through the overtube (Figure 2C). The overtube was then pulled back and the stent was successfully deployed under fluoroscopic guidance (Figure 2D). No immediate or late complications related to the stent were reported.

DISCUSSION

Laparoscopic SG is a new surgical procedure for morbid obesity that has gained wide acceptance due to its simplicity and efficacy compared to the gastric bypass technique[4]. Nevertheless, its long staple line and altered intragastric pressures may lead to postoperative complications, including staple line leaks and stenoses[5].

The main early postoperative complication after SG is staple line leak, which affects 0.5%-5% of the patients and typically occurs in the proximal third of the stomach, near the gastroesophageal junction[1,4,6]. Clinical suspicion and imaging are the cornerstone in the diagnosis[1]. Patients may present with fever, tachycardia, abdominal pain, peritonitis, septic shock and multiorgan failure or may be asymptomatic[1,7,8]. Tachycardia is the earliest sign of a possible leak[8]. Management mainly depends on the timing and clinical presentation of the leak, being a new surgical approach indicated in septic or hemodynamically unstable patients[1,6-9]. After controlling the septic state, efforts must be focused on healing the gastric leak and various endoscopic techniques have been successfully applied, namely endoclips, fibrin glue, over-the-scope clips, septotomy combined with balloon dilation and covered stents[2,4,6,8,10-13]. Covered stents are a novel treatment approach for leaks after bariatric surgery, being minimally invasive, relatively safe and successful in 88% of cases[4,7,9]. Post-SG stenoses range from 0.26% to 4% and may result from a prior leak or anastomotic ulceration, unintentional narrow gastric tubularization, a twisted or spiral suture and segmental imbrication[2,5]. Segmental imbrication usually results in stenoses at the level of the incisura due to the retraction of tissues[5]. The diagnosis is based on clinical symptoms including vomiting and endoscopic or barium studies revealing a narrowing of the stomach[6]. Endoscopic therapy may encompass balloon dilation and stenting to

prevent restenosis[2].

Endoluminal stents provide a physical barrier between the gastric lumen and the leak, preventing further peritoneal contamination and allowing its healing while affording enteral nutrition[2,8]. The main limitations of stent employment are distal migration and mucosal hypertrophy[7-9]. The SEMS used in 4 procedures of our series may obviate these complications as it was specifically designed for bariatric surgery allowing better adjustment to the anatomy of the SG and it is fully covered preventing mucosal hypertrophy.

The placement of self-expanding stents is usually easily accomplished, using either the through-the-scope (TTS) or the OTW technique. The TTS technique is easier to perform in stenoses that are angulated or located after sharp angulations. Nevertheless, some stents as the models used in our case series have a larger delivery system, which prevents the use of the TTS technique. Furthermore, this stent is larger and stiffer than usual SEMS, turning its advancement over angulated stenoses challenging. Conversely, as occurred with these stents in 50% of patients (5/10) in our case series, the conventional OTW procedure may not be technically successful due to recurrent kinking or looping of the delivery system in an angulated stenosis. To overcome these limitations, the adaptation of an overtube to the OTW technique may prevent kinking of the delivery system as the overtube will have a role similar to a working channel[3,14,15]. In our case series, this technical modification of the OTW procedure resulted in technical success in all cases.

In conclusion, this modified overtube-assisted OTW technique represents a safe and easy method for stent insertion in challenging SG anatomies, allowing the placement of different models of stents and the technical success in all 5 procedures.

COMMENTS

Background

Sleeve gastrectomy (SG) represents a type of bariatric surgery, whose postoperative complications include anastomotic leaks and strictures. Endoscopic treatment of staple line leaks and stenoses includes stenting, which may be technically challenging in angulated and tortuous SG anatomies. Furthermore, the delivery systems of some stents used in this indication are larger and less flexible preventing the through-the-scope stenting technique. In some patients these difficulties may result in recurrent kinking of the delivery system of the stent preventing its correct progression over-the-wire (OTW) in the stomach.

Research frontiers

The adoption of a modified technique of deployment of stents OTW using the overtube developed for balloon-assisted enteroscopy may represent an effective option to overcome technical difficulties of stenting deployment.

Innovations and breakthroughs

The adaptation of an overtube to the OTW technique may prevent kinking of the delivery system as the overtube will have a role similar to a working channel. The overtube-assisted modified OTW stenting technique enables the advancement of the endoscope and overtube through the SG to the duodenum. The guidewire is subsequently advanced, the endoscope removed and the overtube is left in place. The stent is then advanced through the overtube, under fluoroscopic guidance. The overtube is slightly pulled back to prevent the release of the stent

in its interior, and finally the stent is deployed under fluoroscopic guidance.

Applications
The modified overtube-assisted OTW technique represents a safe and easy method for stent insertion in challenging SG anatomies and a good option in cases of conventional OTW stenting failure.

Terminology
SG is a type of bariatric surgery resulting in tubulization of the gastric cavity.

Peer-review
The most interesting topic of the paper is the novelty of the technique described. This technique seems easy to perform, in expert hand, and can impact positively on the resolution of serious complications due to laparoscopic SG.

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ORIGINAL ARTICLE

Randomized Controlled Trial

Multicenter randomised controlled trial comparing the high definition white light endoscopy and the bright narrow band imaging for colon polyps

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Author contributions: Singh R and Lau JYW conceptualized and designed this study; Singh R, Cheong KL, Mangira D, Koay DSC, Ng SC, Rerknimitr R, Aniwan S, Ang TL, Goh LK, Ho SH and Lau JYW recruited the patients involved in this study; Singh R, Cheong KL, Zorron Cheng Tao Pu L, Kee C and Lau JYW interpreted the data, performed statistical analyses, and edited the manuscript into its final version to be published.

Institutional review board statement: Institutional medical and ethics committees of each participating hospital approved the study protocol.

Clinical trial registration statement: This study is registered at https://clinicaltrials.gov. The registration identification number is NCT01422577.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors declared no conflicting interests (including, but not limited to, commercial, personal, political, intellectual, or religious interests) related to the manuscript submitted for consideration of publication.

Data sharing statement: Technical appendix and dataset available from the corresponding author at rajvinder.singh@sa.gov.au. Participants gave informed consent for data sharing.

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Abstract

AIM
To compare high definition white light endoscopy and bright narrow band imaging for colon polyps' detection rates.

METHODS
Patients were randomised to high definition white light endoscopy (HD-WLE) or the bright narrow band imaging (bNBI) during withdrawal of the colonoscope. Polyps identified in either mode were characterised using bNBI with dual focus (bNBI-DF) according to the Sano's classification. The primary outcome was to compare adenoma detection rates (ADRs) between the two arms. The secondary outcome was to assess the negative predictive value (NPV) in differentiating adenomas from hyperplastic polyps for diminutive rectosigmoid lesions.

RESULTS
A total of 1006 patients were randomised to HD-WLE ($n = 511$) or bNBI ($n = 495$). The mean of adenoma per patient was 1.62 and 1.84, respectively. The ADRs in bNBI and HD-WLE group were 37.4% and 39.3%, respectively. When adjusted for withdrawal time (OR = 1.19, 95%CI: 1.15-1.24, $P < 0.001$), the use of bNBI was associated with a reduced ADR (OR = 0.69, 95%CI: 0.52-0.92). Nine hundred and thirty three polyps (86%) in both arms were predicted with high confidence. The sensitivity (Sn), specificity (Sp), positive predictive value and NPV in differentiating adenomatous from non-adenomatous polyps of all sizes were 95.9%, 87.2%, 94.0% and 91.1% respectively. The NPV in differentiating an adenoma from hyperplastic polyp using bNBI-DF for diminutive rectal polyps was 91.0%.

CONCLUSION
ADRs did not differ between bNBI and HD-WLE, however HD-WLE had higher ADR after adjustment of withdrawal time. bNBI surpassed the PIVI threshold for diminutive polyps.

Key words: Narrow band imaging; Dual focus; High definition; White light endoscopy; Colon; Polyps; Randomised controlled trial

Core tip: Adenoma detection rate (ADR) is one of the most important quality measures in colonoscopy and bright narrow band imaging (bNBI) can theoretically improve imaging and thus reconnaissance of colorectal polyps. In addition, the magnification using bNBI with dual focus (bNBI-DF) allows the prediction of the polyp's histology. This multicenter randomised controlled trial was conceived to compare the ADR of high definition white light endoscopy (HD-WLE) *vs* bNBI during withdrawal of screening colonoscopies. No difference was found in ADR between HD-WLE and bNBI. The

prediction of diminutive distal polyps with bNBI-DF was satisfactory according to the American Society for Gastrointestinal Endoscopy's threshold.

INTRODUCTION

Colorectal cancer is a leading cause of morbidity and mortality worldwide[1]. Its incidence in Asia-Pacific region has been rising at an alarming rate[2,3]. Screening colonoscopy and polypectomy have been shown to reduce the mortality related to colorectal cancer[4]. Despite its effectiveness, the potential to miss polyps can range between 15% to 30% with screening colonoscopy[5]. Current guidelines recommend removal of all visible polyps (except benign diminutive distal polyps) and subjection to histological assessment, irrespective of their endoscopic morphological features. This could make colonoscopy a less cost effective screening strategy[6]. Novel image enhanced endoscopic technologies have the potential to overcome some of the limitations of standard while light endoscopy (WLE) by increasing the detection rate of polyps/neoplasms and providing real-time histological diagnosis.

Narrow band imaging (NBI) is one of the most widely available and convenient to use technologies developed. Narrowed bandwidth light is used to visualize superficial vasculature and mucosal pit patterns in real-time[7,8]. The light penetrates the mucosa and submucosa and is absorbed by hemoglobin in surface microvessels, which appear as linear darker structures[9]. This enables the endoscopist to differentiate thicker and more irregular vascular landmarks. Multiple classification systems based on surface pit-pattern and vascular pattern have been developed and validated to differentiate hyperplastic polyps from adenomatous polyps[10,11]. This real-time differentiation has been proposed as a part of "resect and discard" strategy in which diminutive polyps (measuring < 5 mm) are resected without histological assessment and hyperplastic polyps in rectosigmoid region are left *in situ*[12]. This approach could confer substantial cost savings by avoiding unwarranted histological evaluation[13] and may avoid complications related to polypectomy[14]. Few published studies showed no significant difference in adenoma detection rates (ADRs) between NBI and WLE[15-18]. Only one meta-analysis demonstrated an increased accuracy of NBI over WLE in characterising colonic polyps with hierarchical summary receiver-operating characteristic

curves exceeding 0.90[19]. Dimmer images compared to WLE[20], type of endoscopes and monitors used (high *vs* low resolution), inconsistent color enhancement settings and endoscopists' experience have been proposed as potential reasons for the unimpressive performance of NBI.

Recently, a newer generation NBI system has been introduced. The system appears to provide brighter NBI (bNBI) images (by 2 fold) in a high-definition (HD) mode and has the option of further magnifying a particular target with the dual focus (DF) magnification function, up to 65 times. These provide an in-depth view of desired areas of the mucosa with clear and crisp images, which potentially may improve polyp detection as well as characterisation.

In this study we hypothesized that, when compared to high definition white light endoscopy (HD-WLE), the newer generation colonoscopes with the brighter NBI capability and the bNBI with dual focus (bNBI-DF) magnification mode could improve ADR and accurately predict polyp histology.

MATERIALS AND METHODS

Study design
We performed a prospective multicenter randomised controlled trial across four centers in the Asia Pacific region (The Prince of Wales Hospital, Hong Kong; The King Chulalongkorn Memorial Hospital, Thailand; Changi General Hospital, Singapore and The Lyell McEwin Hospital, Australia) from October 2010 to April 2012. Institutional medical and ethics committees of each participating hospital approved the study protocol. The study was registered with clinicaltrials.gov (NCT 01422577).

Study population
We recruited subjects who were referred for outpatient screening colonoscopy across four centers during the study period. All patients were 40 years and older with no significant medical comorbidities and met the criteria for average risk for the colorectal cancer with no previous colonoscopies in the last five years. Patients were excluded if they were on anti-platelets or anticoagulants, had any colorectal surgical resection, inflammatory bowel disease, familial colorectal cancer syndromes (familial adenomatous polyposis and hereditary non-polyposis colorectal cancer), were unable to provide written informed consent or had poor bowel preparation.

All participating subjects were informed about the study and written informed consent was obtained before initiation of the procedure. Participants were allowed to have clear fluids on the day before the procedure and were given four liters of polyethyleneglycol as bowel preparation followed by a 6-h fast (previous day preparation). Appropriate doses of conscious sedation (Fentanyl and Midazolam ± Propofol) were given prior to and during the procedure.

Eleven endoscopists participated in the study. Each of the endoscopists had extensive experience with the use of NBI in colonoscopy having performed more than 2000 procedures each using the earlier generation colonoscopes with NBI. The CF-HQ 190 or 290 series colonoscopes with the DF mode for magnification (Olympus, Tokyo Co. Ltd) were used for all patients. The colonoscope was connected to a CLV video processor with images transmitted to HD monitors (1280 × 1024 pixels). All participating endoscopists were consultants who had experience with an earlier generation of NBI scopes.

Randomisation
Subjects were randomised to receive the examination during withdrawal either in the HD-WLE or in the bNBI mode, followed by bNBI-DF to characterise each polyp that was identified in both arms (Figure 1). The colonoscope was inserted using HD-WLE until caecum was reached, in all subjects. Randomisation took place once the caecum or appendiceal orifice was identified and adequacy of bowel preparation was established as per the modified Aronchick scale[21]. Subjects with suboptimal bowel preparation were excluded. Patients were randomised according to a computer-generated randomisation scheme in blocks of twenty. Allocation to HD-WLE or bNBI mode of withdrawal was kept in a concealed envelope and revealed by a research assistant to the endoscopist just before withdrawal was initiated. A dedicated nurse assistant monitored both insertion (time to reach caecum from insertion) and withdrawal (time of scope removal from initiation of withdrawal) times with a stopwatch. During insertion, the stopwatch was paused during patient position change or while exerting abdominal pressure to facilitate colonoscope advancement. Similarly, the stopwatch was paused during withdrawal when biopsies or polypectomies were performed. The withdrawal time was set to a minimum of 6 min in both bNBI and HD-WLE arms and endoscopists were deliberately reminded of the time during the withdrawal phase.

Data collection
Colonoscope withdrawal commenced from the caecum with the patient in the left lateral position and was carried out according to randomisation. Location of each polyp was identified using anatomical landmarks and categorised into either the right or left side of the colon. The size of each polyp was assessed using diameter of the opened biopsy forceps (7.5 mm) or the diameter of the snare used. Identified polyps were characterised by using bNBI-DF mode in both arms.

Characterisation of polyps was made by bNBI-DF using Sano's classification, which has been found to be valid tool for predicting polyp histology[11]. The classification was based on vascular pattern on the surface of the polyp. Characterisation of polyps was made with high confidence if the polyp demonstrated endoscopic features, which were strongly suggestive of
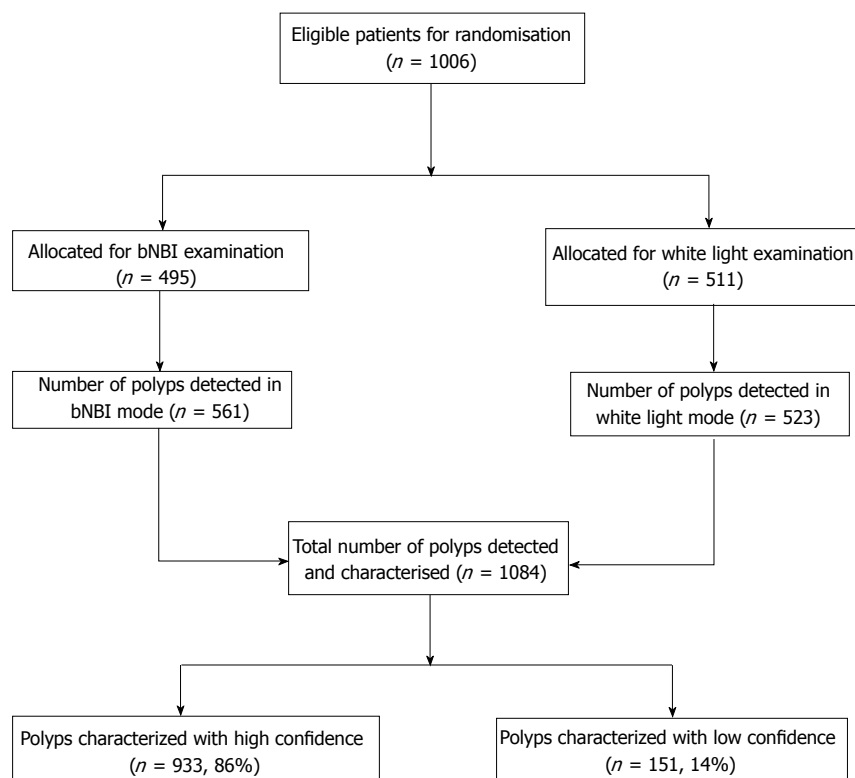
Figure 1 Study flow chart. bNBI: Bright narrow band imaging.

its pathology according to Sano's classification. Polyps were characterised with low confidence if exposure was limited secondary to non-removable debris, inadequate focus or if the polyp demonstrated features of more than one Sano's class.

The preferred mode of polypectomy was left to the endoscopists' discretion. Once the polypectomy was performed, mucosal viewing was switched back to respective mode as per randomisation. Each identified polyp was resected and retrieved into an individual container for pathologic examination. Pathologists with experience in gastrointestinal tract, who were blinded for the endoscopic mode of the examination, evaluated all resected polyps.

Outcomes
The primary outcome of the study was to compare the ADR, defined as percentage of patients with one or more adenomatous polyp detected, between the two arms (HD-WLE *vs* bNBI). The secondary outcome was to assess if bNBI-DF could meet the American Society for Gastrointestinal Endoscopy (ASGE)'s Preservation and Incorporation of Valuable Endoscopic Innovation (PIVI) threshold in predicting histopathology of colon polyps[22]. We only assessed the second criteria from the PIVI guideline [where the technology, when used with high confidence, should provide > 90% negative predictive value (NPV) for adenomatous histology in diminutive rectosigmoid polyps] as we believed that this strategy would be more practical and generalizable.

Sample size
We previously conducted a colonoscopy screening study amongst average risk Hong Kong Chinese subjects older than 50 years of age and found an ADR of 30%[23]. The prevalence of colon adenomas in asymptomatic subjects in Asia is unknown and is likely to vary across different ethnic groups. The sample size evaluation was based on assumption that improved optics and bNBI is superior to the HD-WLE mode in detection of colon polyps. We thus hypothesized that bNBI would be able to detect more adenomas than HD-WLE. A sample size of 500 per group was required to detect a relative risk of 1.28 (*i.e.,* a difference of 38.4% *vs* 30%) with a power of 80% and a type 1 two-sided error of 0.05.

Statistical analysis
Continuous variables were compared using the *t*-test if normally distributed. Categorical variables were compared using the χ^2 test or Fisher's exact test when appropriate. The Mann-Whitney's *U* test was used for skewed variables. To compare the detection of all adenomas and hyperplastic polyps (per-polyp analysis), the Poisson regression model or negative binomial regression model was used. The accuracy of bNBI-DF in examining early colorectal lesions was evaluated using Sano's classification compared to the final histopathology and measures of sensitivity (Sn), specificity (Sp), positive predictive value (PPV), and NPV; and their correspondent 95%CIs were performed. These diagnostic tests were calculated by means of

Table 1 Characteristics of patients and colonoscopy performance in both groups *n* (%)

Parameters	bNBI (*n* = 495)	WLE (*n* = 511)	*P* value
Patients			
Men	210 (42.43)	237 (46.38)	0.207
Age, mean ± SD	58.31 ± 6.17	58.36 ± 6.13	0.904
BMI, mean ± SD	23.75 ± 3.29	23.74 ± 2.99	0.942
Current smoker	24 (4.9)	29 (5.7)	0.536
Current drinker	38 (7.7)	44 (8.7)	0.815
Current use of NSAID	6 (1.2)	9 (1.8)	0.705
Current use of aspirin	13 (2.6)	22 (4.3)	0.345
Current use of warfarin	0	2 (0.4)	0.232
Comorbidities			
Hypertension	123 (24.8)	131 (25.6)	0.774
Diabetes	56 (11.3)	32 (6.3)	0.005
Ischemic heart disease	10 (2.0)	10 (2.0)	0.943
Chronic obstructive airway disease	2 (0.4)	0	0.15
Previous stroke	1 (0.2)	2 (0.4)	0.582
Cirrhosis	1 (0.2)	1 (0.2)	0.982
Gastro-esophageal reflux	10 (2)	8 (1.6)	0.587
Dyslipidemia	31 (6.3)	29 (5.7)	0.694
History of cancer	19 (3.8)	12 (2.3)	0.172
Examination time (min), mean ± SD			
Time to cecum	6.66 ± 4.56	7.06 ± 4.94	0.183
Time for withdrawal	11.23 ± 6.36	9.84 ± 5.03	< 0.0001

bNBI: Bright narrow band imaging; WLE: White light endoscopy.

the generalized estimating equations to account for the clustering of polyps within patients.

In addition, we performed statistical analysis to examine the effect of the withdrawal time, entered as a covariate, on the ADR on a per-patient level. Specifically, a multiple logistic regression was used to estimate adjusted odds ratio (OR) and its 95%CI with all variables (see Table 1) excluding time taken to reach cecum, entered as covariates. The presence or absence of one or more adenomas was considered a response variable. Mode of withdrawal (HD-WLE or bNBI) was forced to remain into all regression models. Two-tailed *P* value lower than 0.05 was considered statistically significant. Multiple outcomes were tested without adjusting for the type I error rate. Statistical tests were performed with the use of SPSS software (version 19.0, SPSS, Chicago, IL, United States).

RESULTS

A total of 1006 patients were enrolled during the 17-mo study period (October 2010 to April 2012), of which 44.4% were men and the mean age was 58 years. Four hundred and ninety-five participants were randomised to the bNBI arm and 511 participants to the HD-WLE arm. Table 1 demonstrates the demographics of the study population in the two arms by age, gender, body mass index (BMI), social habits, medical comorbidities and mean insertion and withdrawal times. There were no significant differences in baseline characteristics in both arms except for the prevalence of diabetes, which was seen more frequently in bNBI arm (bNBI, *n* = 56

Table 2 Pathologic diagnosis in both bright narrow band imaging and high definition white light endoscopy *n* (%)

	bNBI (*n* = 495)	HD-WLE (*n* = 511)	*P* value
Adenomas	341	326	0.425
Subjects with adenomas[2] (ADR)	185 (37.4)	201 (39.3)	0.523
Adenomas per adenoma carrier[1]	1.84	1.62	0.129
Size			
Subjects with 0-5 mm adenomas[2]	149 (30.1)	162 (31.2)	0.583
Subjects with 6-9 mm adenomas[2]	52 (10.5)	52 (10.2)	0.864
Subjects with ≥ 10 mm adenomas[2]	31 (6.3)	31 (6.1)	0.897
Adenomas < 10 mm	306	290	0.283
Adenomas 0-5 mm	241	229	0.334
Adenomas 6-9 mm	65	61	0.896
Adenomas ≥ 10 mm	35	36	0.837
Location			
Right-sided adenomas	157	155	0.400
Left-sided adenomas	168	159	0.797
Histopathology			
Carcinomas	3	5	0.418
Tubular	315	304	0.343
Tubulovillious	10	12	0.689
Villious	2	0	NA
Adenomas with high grade dysplasia	6	7	0.992
Hyperplastic polyps	178	136	0.020
Hyperplastic polyps < 10 mm	176	135	0.020
SSA/Ps	13	7	0.257
Subjects with SSA/P, *n* (SSA/P-detection rate in %)	13 (2.6)	6 (1.2)	0.091
Inflammatory polyps	12	14	0.572
Indeterminate or non-significant	16	15	0.987
Not submitted for histologic examinations	13	31	0.010
Xanthoma	1	1	0.961

[1]Mann-Whitney's *U* test used; [2]χ^2 test or Fisher's exact test used as appropriate. HD-WLE: High definition white light endoscopy; bNBI: Bright narrow band imaging.

(11.3%) *vs* HD-WLE, *n* = 32 (5.3%). The mean time to reach caecum was similar in both arms; however, the mean withdrawal time was 1.39 min longer in the bNBI arm (*P* < 0.05).

Adenoma detection rates

A total of 1084 polyps were detected in both arms. The overall mean polyp detection rate per colonoscopy in the bNBI arm was 1.13 and in the HD-WLE arm was 1.02 (*P* = 0.093). Two hundred and sixty subjects in the bNBI arm (52.53%) and 257 in the HD-WLE group (50.29%) had one or more polyp (*P* = 0.479). About two thirds (*n* = 638) of polyps were identified on left side of the colon and 92.8 % (*n* = 1005) of polyps were less than 10mm in size.

The ADR in the bNBI group and HD-WLE group was 37.4% and 39.3% respectively (185 of 495 subjects and 201 of 511 subjects had at least one adenoma) (Table 2). Table 2 demonstrates the pathological diagnosis of polyps detected in both arms. Sixty one percent (341/561) of polyps in bNBI arm and 62% (326/523) in HD-WLE arm were adenomatous (*P* = 0.425) in nature. ADRs were directly related to withdrawal time in both arms, as shown in Figure 2, ADR progressively

Table 3 Polyp categorization according to Sano's classification - Hyperplastic/SSA/P *vs* adenoma/cancer

	Pathology		Total
	Hyperplastic/ SSA/P	Adenoma/ cancer	
Sano's classification			
I	245	24	269
II, IIIa, IIIb	36	555	591
Total	281	579	

Sensitivity of predicting adenoma = 95.7% (93.4% to 97.2%); Specificity of predicting adenoma = 86.5% (81.7% to 90.2%); PPV of predicting adenoma = 93.9% (91.7% to 95.6%); NPV of predicting adenoma = 91.0% (86.4% to 94.0%).

Table 4 Polyp characterisation according to Sano's classification - Adenoma *vs* cancer

	Pathology		Total
	Adenoma	Cancer	
Sano's classification			
II, IIIa	547	1	548
IIIb	0	7	7
Total	547	8	

Sensitivity of predicting cancer = 87.5% (47.4% to 99.7%); Specificity of predicting cancer = 100% (99.3% to 100%); PPV of predicting cancer = 100% (59.0% to 100%); NPV of predicting cancer = 99.8% (98.7% to 100%).

Table 5 Polyp characterisation based on Sano's classification for polyps in the rectosigmoid region (5 mm or less in size)

	Pathology		Total
	Hyperplastic	Adenoma/cancer	
Sano's classification			
I	146	10	156
II, IIIa, IIIb	7	130	137
Total	153	140	

Sensitivity of predicting adenoma = 94.5% (89.1% to 97.3%); Specificity of predicting adenoma = 95.4% (90.6% to 97.8%); PPV of predicting adenoma = 94.8% (89.5% to 97.5%); NPV of predicting adenoma = 93.7% (87.7% to 96.9%).

increased with increasing withdrawal time. A higher number of hyperplastic polyps were identified in bNBI arm than in HD-WLE arm (bNBI, n = 178 *vs* HD-WLE, n = 136), which was statistically significant (P = 0.021). According to logistic regression analysis, withdrawal time (OR = 1.19, 95%CI: 1.15-1.24, P < 0.001), age (OR = 1.03, 95%CI: 1.00-1.05, P = 0.032) and male sex (OR = 1.49, 95%CI: 1.11-2.00, P = 0.008) were independently associated with an improved ADR when adjusted for differences in baseline variables. When we adjusted for withdrawal time (OR = 1.19, 95%CI: 1.15-1.24, P < 0.001), the use of bNBI was associated with a reduced ADR (OR = 0.69, 95%CI: 0.52-0.92).

Polyp characterisation

Nine hundred and thirty-three polyps (86%) from both arms were categorized into various classes with high confidence according to Sano's classification. The other 13.9% (n = 151) were classified with low confidence. Among the high confidence polyps, 308 (33%) polyps were Sano type I; 598 (64%) were type II; 20 (2.1%) were type IIIA and 7 (0.75%) were type IIIB.

The Sn, Sp, PPV and NPV in differentiating adenomatous from non-adenomatous polyps of all sizes were 95.7%, 86.5%, 93.9% and 91.0% respectively (Table 3). The Sn, Sp, PPV and NPV in differentiating an adenoma from cancer were 87.5%, 100%, 100%, and 99.8% respectively (Table 4). The Sn, Sp, PPV and NPV of bNBI-DF in the characterisation of polyps with 5mm or less in the rectosigmoid region were 94.5%, 95.4%, 94.8% and 93.7% respectively (Table 5).

DISCUSSION

This prospective multicenter randomised study compared two different modalities: HD-WLE and bNBI to assess if there was a difference in ADRs. In addition, bNBI-DF was used to characterise polyps using the Sano's classification. We did not find a statistically significant improvement in ADR with bNBI when compared to HD-WLE. Polyp characterisation was effective with bNBI-DF in differentiating adenomas from hyperplastic polyps in diminutive distal polyps, meeting the second PIVI standard.

The study design was similar to that of Rex and Helbig, who evaluated an earlier version of NBI[24]. Their study represented a single operator experience, in contrast to this study, which involved several academic centers. In a recent tandem study, Leung *et al*[25] compared bNBI to HD-WLE in colonoscopy. Subjects were submitted to bNBI first and followed by HD-WLE or *vice versa*. The use of bNBI was associated with a higher ADR with a higher number of polyps detected per subject. However, for the HD-WLE group, the older generation 260 series colonoscopes were used. Illumination with 260 series colonoscopes is considerably less sharp when compared to the 190/290 series colonoscopes. Hence, one cannot be certain if the superiority of bNBI in finding adenomas was not a result of a "brighter processor". In another study by Wallace *et al*[26], average risk subjects presenting for screening were randomised to receive the examination by a standard colonoscope (H180) or a dual focus colonoscope (HQ-190). ADR were similar between both groups (52% *vs* 50%). The NPV for diminutive rectosigmoid polyps were 96 and 97% respectively, which was not too dissimilar to our study.

Multiple randomised studies and a meta-analysis compared ADRs of NBI with conventional colonoscopy. The results have thus far been mixed with very few studies[27,28] demonstrating improved ADRs with NBI. Despite having endoscopists with considerable experience in using NBI and a large sample size, we were unable to demonstrate a statistically significant improvement in ADR. Actually, this study suggests that NBI could actually decrease the ADR if used exclusively for

bNBI, N(n) 20 (3) 69 (19) 74 (18) 67 (11) 44 (16) 32 (13) 32 (11) 23 (9) 20 (10) 18 (10) 15 (11) 11 (8) 4 (1) 8 (3) 8 (5) 36 (29)

HD-WLEE, N(n) 46 (0) 117 (29) 70 (18) 60 (26) 45 (19) 37 (18) 22 (13) 23 (14) 12 (7) 7 (3) 11 (8) 9 (6) 8 (7) 6 (5) 6 (5) 24 (21)

N = Number of procedures

n = Number of procedures detected adenoma

The figure represents the adenoma detection rate (%) and error bard indicate 95%CI

Figure 2 Adenoma detection rate *vs* withdrawal time. HD-WLE: High definition white light endoscopy; bNBI: Bright narrow band imaging.

overview of the whole colon during withdrawal. The similar ADRs achieved in this study may be attributed to the fact that improved resolution could be achieved using the same high definition processor for both bNBI and HD-WLE. These findings are not too dissimilar to studies conducted in the past with older generation systems[29-31].

Previous studies conducted using bNBI to differentiate adenomatous from non-adenomatous lesions demonstrated accuracies ranging from 77% to 93%[8,32-36]. Sessile serrated adenomas/polyps (SSA/Ps), which endoscopically may resemble hyperplastic polyps but have malignant potential, were detected in 1.8% of all polyps. Previous studies have shown the prevalence of SSAs ranging from 1% to 7%[37], but a more recent study shows that the reported prevalence of SSA/Ps is raising with the years and it can get up to 15.8%[38]. This difference may be due in part to the different prevalence rate in the studied population, which included predominantly a younger Asian cohort. These polyps unfortunately do not fit into any of the available classifications at the time the study was performed.

This study adds strength to the usefulness of bNBI in characterising colonic lesions in real-time. This "endopathology" concept supports the "resect and discard" approach that carries many practical advantages. In a simulation model by Hassan *et al*[6], this strategy resulted in a substantial economic benefit without any impact on efficacy. Kessler *et al*[13] demonstrated that endoscopic diagnosis of polyp histology during colonoscopy and forgoing pathologic examination would result in substantial up-front cost savings whilst the downstream consequences of the resulting incorrect surveillance intervals appear to be negligible. bNBI-DF used in this study not only successfully met the second PIVI threshold established by the ASGE but also demonstrated the highest accuracy so far in differentiating adenomas from hyperplastic polyps[6]. More than 85% of polyps were characterised with high confidence and the overall sensitivity and specificity demonstrated was significantly higher than in other studies[18].

This study has some limitations. First, the mean withdrawal time was prolonged in both arms, but particularly in the bNBI's arm (11.23 min *vs* 9.84 min). In a multiple regression model, examination of the colon in the HD-WLE mode was associated with a better ADR. Similar to this study, longer withdrawal times with bNBI were also noted in a meta-analysis by Jin *et al*[39] as well as by Rex *et al*[24]. This could be potentially explained by the lack of confidence in assessing the mucosa in an overview mode with bNBI, although endoscopists were

experienced with previous versions of the modality. The ADRs in both arms of the study were higher than the target ADR set by the United States Multi-Society Task Force (men > 25% and women > 15%)[40]. Longer withdrawal times and high-definition imaging are the possible reasons for the overall higher adenoma detection rates.

In conclusion, ADR was not different between bNBI and HD-WLE. Male sex, larger withdrawal time and older age where positively correlated with ADR. When adjusted for withdrawal time, HD-WLE had higher ADR. With bNBI-DF, 85% of the polyps could be characterised with high confidence, of which more than 95% of them were predicted accurately. The most worthwhile strategy to reduce the risks associated with unwarranted polypectomies and save costs incurred with pathological assessment of polyps could be a "combination strategy" where withdrawal is performed using HD-WLE and polyp characterisation with bNBI-DF.

COMMENTS

Background
Colorectal polyps are the precursors of colorectal cancer and their removal through colonoscopy is effective in preventing colorectal cancer. New technologies continuously improve the imaging ability of the colonoscopes. Whether these new technologies effectively differ from each other for detection of polyps is debatable.

Research frontiers
The development of state-of-the-art endoscopes are not always associated with better results. Technologies that enhance imaging supposedly could improve the detection of polyps. So far, the use of light filters to improve adenoma detection rate (ADR) is not recommended.

Innovations and breakthrough
Improvement in ADR is important as it is inversely correlated with colorectal cancer risk. The improvement of old technologies has been shown beneficial for detection of polyps (*i.e.,* HD *vs* non-HD imaging). However, comparison between new technologies is less studied. The authors therefore evaluated the use of two cutting-edge technologies [high definition white light endoscopy (HD-WLE) and bright narrow band imaging (bNBI)] to detect colorectal polyps.

Applications
Although virtual chromoendoscopy is useful for characterising polyps, its use for detecting them did not differ from HD-WLE in this study. Therefore, even though there is improvement in the brightness with the new light filter, it is still not recommended as standard of care for screening purposes.

Terminology
Adenoma detection rate is defined as the percentage of patients that were submitted to colonoscopy and had at least one adenomatous polyp. Narrow band imaging is an optical image-enhanced technology based on specific light wavelengths, which allows enhanced visualisation of vasculature and superficial mucosal surface.

Peer-review
The authors compared ADR of two different modalities. They found that HD-WLE had higher ADR after adjustment of withdrawal time. bNBI had satisfactory negative predictive value in differentiating adenomatous from non-adenomatous histology in dimunitive polyps, which was above the preservation and incorporation of valuable endoscopic innovation threshold. The paper is well written.

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Bladder urothelial carcinoma extending to rectal mucosa and presenting with rectal bleeding

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Abstract

An 87-year-old-man with prostate-cancer-stage-T1c-Gleason-6 treated with radiotherapy in 1996, recurrent prostate cancer treated with leuprolide hormonal therapy in 2009, and bladder-urothelial-carcinoma *in situ* treated with Bacillus-Calmette-Guerin and adriamycin in 2010, presented in 2015 with painless, bright red blood per rectum coating stools daily for 5 mo. Rectal examination revealed bright red blood per rectum; and a hard, fixed, 2.5 cm × 2.5 cm mass at the normal prostate location. The hemoglobin was 7.6 g/dL (iron saturation = 8.4%,

indicating iron-deficiency-anemia). Abdominopelvic-CT-angiography revealed focal wall thickening at the bladder neck; a mass containing an air cavity replacing the normal prostate; and adjacent rectal invasion. Colonoscopy demonstrated an ulcerated, oozing, multinodular, friable, 2.5 cm × 2.5 cm mass in anterior rectal wall, at the usual prostate location. Histologic and immunohistochemical analysis of colonoscopic biopsies of the mass revealed poorly-differentiated-carcinoma of urothelial origin. At visceral angiography, the right-superior-rectal-artery was embolized to achieve hemostasis. The patient subsequently developed multiple new metastases and expired 13 mo post-embolization. Comprehensive literature review revealed 16 previously reported cases of rectal involvement from bladder urothelial carcinoma, including 11 cases from direct extension and 5 cases from metastases. Patient age averaged 63.7 ± 9.6 years (all patients male). Rectal involvement was diagnosed on average 13.5 ± 11.8 mo after initial diagnosis of bladder urothelial carcinoma. Symptoms included constipation/gastrointestinal obstruction-6, weight loss-5, diarrhea-3, anorexia-3, pencil thin stools-3, tenesmus-2, anorectal pain-2, and other-5. Rectal examination in 9 patients revealed annular rectal constriction-6, and rectal mass-3. The current patient had the novel presentation of daily bright red blood per rectum coating the stools simulating hemorrhoidal bleeding; the novel mechanism of direct bladder urothelial carcinoma extension into rectal mucosa *via* the prostate; and the novel aforementioned colonoscopic findings underlying the clinical presentation.

Core tip: Comprehensive literature review revealed 16 reported cases of bladder-urothelial-carcinoma involving rectum. None of these cases presented with daily rectal bleeding. Among 11 cases with direct extension, none had pathologically-proven rectal mucosal involvement. A case is reported of recurrent bladder-urothelial-carcinoma presenting with daily bright red blood per rectum coating stools from bladder-urothelial-carcinoma involving rectal mucosa. A hemorrhagic, multinodular, rectal mass, identified by colonoscopy, from direct extension of Bladder-Urothelial-Carcinoma *via* prostate to rectal mucosa underlies the presentation with daily bright red blood per rectum. This report shows that bladder-urothelial-carcinoma can cause rectal bleeding by directly extending to rectal mucosa.

INTRODUCTION

Bladder urothelial carcinoma rarely spreads to the gastrointestinal (GI) tract, with comprehensive literature review revealing only 33 previously reported cases; even more rarely surrounds or extends into the rectum with only 16 previously reported cases; and has not been previously reported to appear at colonoscopy as a rectal mucosal nodular mass from direct cancer extension from the bladder *via* the prostate (3 prior patients had rectal mucosal metastases without direct extension) (Tables 1-3)[1-21]. A novel case is reported in which bladder urothelial carcinoma directly extended to rectal mucosa, *via* the prostate; mimicked hemorrhoidal bleeding in presenting with chronic, daily, painless, bright red blood per rectum coating the stools; and demonstrated novel, colonoscopic findings underlying the clinical presentation.

The literature was systematically reviewed using PubMed with the following medical subject heading (MeSH) or keywords: {"rectum" or "rectal" or "sigmoid" or "descending colon" or "transverse colon" or "ascending colon" or "cecum" or "large intestine" or "large bowel" or "colon" or "duodenum" or "jejunum" or "ileum" or "jejunoileum" or "small intestine" or "small bowel" or "stomach" or "gastric" or "esophageal" or "esophagus"} and {"bladder cancer" or "bladder carcinoma" or "urothelial carcinoma" or "transitional cell carcinoma"}. Two authors independently reviewed the literature, and decided by consensus which articles to incorporate in this study. Patients with bladder adenocarcinoma; renal cell carcinoma, even with bladder involvement; or urothelial (transitional cell) carcinoma solely extrinsic to the bladder were excluded. One article written in French was professionally translated[15]. Data about 2 cases in one article, written in Japanese, were obtained from the abstract written in English[20]. Data regarding 4 cases were derived from a table present in one reference[20]. This case report received exemption/approval by the IRB at William Beaumont Hospital, Royal Oak, on August 27, 2015. Informed consent for publication was unobtainable from the patient because he had expired prior to writing this case report.

CASE REPORT

An 87-year-old, severely debilitated man with a 20-year-long oncologic history presented in 2015 with daily, painless, bright red blood per rectum coating the stool for five months. He had been treated in 1996 for prostate adenocarcinoma stage-T1c-Gleason-6 with external beam radiotherapy; retreated in 2009 for recurrent prostate adenocarcinoma with leuprolide hormonal therapy every 3 mo; and treated in 2010 for bladder urothelial carcinoma *in situ* stage-TCC-Ta-G1-2

Table 1 Direct extension of bladder urothelial carcinoma to rectum

Patient No., age and sex	Prior oncologic history	Clinical presentation with GI involvement	Radiologic imaging subsequent endoscopy/ surgery	Metastatic location: Pathologic diagnosis	Treatment	Outcome	Ref.
1. 87-year-old man	Nineteen years PTA underwent external beam radiotherapy and leuprolide hormonal therapy for prostate cancer stage T1c Gleason 6. Five years PTA underwent Bacillus Calmette-Guérin immunotherapy and adriamycin chemotherapy for bladder urothelial carcinoma *in situ* stage Ta G1-2	Painless, bright red blood coating stools for 5 mo. Rectal exam: Bright red blood per rectum and large, hard, fixed, multinodular, "prostate" mass. Hemoglobin = 7.6 g/dL	CT angiography: Mass containing air-fluid cavity replacing prostate, with rectal invasion. Colonoscopy: Ulcerated, friable, oozing, multinodular, hemorrhagic, 2.5 cm × 2.5 cm mass on anterior rectal wall, just proximal to dentate line	Rectum: Poorly differentiated carcinoma of urothelial origin	Abdominopelvic angiography: Successful right-superior-rectal-artery embolization using embolospheres	Stopped bleeding for 3 mo. Subsequently rebled. Underwent palliative colostomy for the rebleeding. Died 13 mo after diagnosis of rectal lesion	Current report
2. 64-year-old man	Sixteen month PTA, underwent radical cystectomy, left nephroureterectomy, and right ureterocutaneostomy for Grade 3 urothelial carcinoma Stage pT3aN0. 11 mo PTA, received 3 courses of MVAC chemotherapy for lymph node metastases	Anorexia, tenesmus	Abdominopelvic CT: Focal, annular thickening of rectal wall	Rectum: Urothelial carcinoma	Fecal diversion	Died 2 mo later	Katayama *et al*[1]
3. 60-year-old man	Prior high grade bladder urothelial carcinoma	Anal pain, fatigue, weight loss, and anorexia. Rectal exam: Hard, fixed, annular, constrictive mass, 6 cm from anal verge. Hemoglobin = 11.6 g/dL	Pelvic CT: Mass posterior to bladder. Perirectal wall thickening	Rectum: Grade 4 urothelial carcinoma	Chemotherapy with VP-16 and cisplatin in 3 mo cycles and external beam RT	Died 9 mo after initiating RT	Stillwell *et al*[2]
4. 58-year-old man	Two year PTA underwent partial cystectomy for grade 3 N0 bladder urothelial carcinoma	Anorexia, weight loss, fatigue, straining with bowel movements, narrow-caliber stools, rectal pain, and tenesmus for several months. Rectal exam: hard, annular, constricting lesion with a narrowed lumen, at 8 cm from anal verge	Pelvic CT: Large mass encircling rectum, lytic lesion in third lumbar vertebra, and bilateral hydronephrosis. Proctoscopy: Constricting lesion with normal overlying mucosa, suggestive of extrinsic compression. Exploratory laparotomy: Hard mass extending from posterior bladder wall, obliterating rectovesical pouch, and encompassing rectum	Rectum: Biopsy during proctoscopy showed normal mucosal tissue. Transrectal (deep) and transperineal biopsy: Poorly differentiated grade 3 urothelial cancer	Sigmoid loop colostomy, RT to pelvis and lumbar spine, followed by single dose of cisplatin	Died 3 mo later from liver metastasis	Stillwell *et al*[2]
5. 73-year-old man	Three years PTA underwent radical cystoprostatectomy, with clear margins, and ileal loop urinary diversion for Stage pT3a N0 bladder urothelial carcinoma. At that time, biopsy also demonstrated areas of adenocarcinoma and signet ring cell carcinoma	Diarrhea, rectal pain, fatigue, weight loss, and fecal incontinence for 1 mo. Physical exam: Thin elderly male, bilateral lower extremity edema. Rectal exam: rectal stenosis 1 cm from anal verge. Guaiac negative stool	Abdominopelvic CT: annular rectal mass. Exploratory laparoscopy: Solid pelvic tumor adherent to sacrum	Rectum: Urothelial cancer invading muscularis propria of rectal wall	Diverting loop colostomy	Chemotherapy planned, but patient developed lower extremity ischemia, requiring leg amputation. Died shortly thereafter	Langenstroer *et al*[3]

6. 76-year-old man	Underwent left nephroureter-ectomy. 1 mo PTA underwent right ureteral diverting cutaneostomy for grade 3 bladder urothelial carcinoma. Bladder mass firmly attached to pelvic wall and to thickened lateral pedicles	Symptoms of rectal obstruction. Rectal exam: Stenosis with intact rectal mucosa	Pelvic CT: Annular thickening of rectal wall and thickened lateral pedicles, bilaterally	Rectum: Urothelial carcinoma	Diverting colostomy and unspecified immunotherapy	Died 5 mo later	Kobayashi *et al*[4]
7. 66-year-old man	No prior oncologic history	Rectal exam: Severe rectal stenosis with intact rectal mucosa	Abdominopelvic CT: Thickened bladder and rectal walls, bilateral hydronephrosis. Colonoscopy: Narrow rectal lumen with edematous mucosa, suggesting extrinsic compression	Rectum: Grade 3 urothelial carcinoma	Ileal-conduit and colostomy	Died 3 mo after surgery	Kobayashi *et al*[4]
8. 51-year-old man	1 mo PTA underwent ureterocutaneostomy for unresectable grade 3 bladder urothelial carcinoma attached to pelvic wall, causing bilateral hydronephrosis	Thin stools. Rectal exam: Narrow rectal lumen	Pelvic CT: Annular constriction of rectum	Rectum: Grade 3 urothelial carcinoma	Diverting colostomy and one course of M-VAC chemotherapy	Died 10 mo after surgery	Kobayashi *et al*[4]
9. 74-year-old man	Eleven months PTA underwent radical cystectomy for grade 3 urothelial carcinoma of bladder	Continuous watery rectal discharge and thin stools	Barium enema: Stenosis of lower rectum Pelvic MRI: Thickened rectal mucosa and muscle layer without evident tumor	Rectum: Grade 3 pT3a urothelial carcinoma	Colostomy, MVAC chemotherapy, and radiation	Died 7 mo after presentation	Ito *et al*[5]
10. 54-year-old man	Underwent radical cystoprostatectomy with neobladder for grade 3 bladder urothelial carcinoma	Presumed refractory ulcerative proctitis	Pelvic MRI: Circumferential thickening of rectum. Endoscopy: Circumferential rectal wall thickening 11 cm from anal verge. EUS: Circumferential hypoechoic infiltrate extending through all rectal wall layers	Rectum: Urothelial carcinoma	Chemotherapy	NR	Gleeson *et al*[6]
11. 55-year-old man	Underwent radical cystoprostatectomy with neobladder for grade 3 bladder urothelial carcinoma	Constipation	Abdominopelvic CT: No evident metastasis Endoscopy: Circumferential rectal wall thickening with stricture 16 cm from anal sphincter EUS: Diffuse circumferential thickening of rectal wall	Rectum: urothelial carcinoma	Chemotherapy	NR	Gleeson *et al*[6]
12. 60-year-old man	Underwent radical cystoprostatectomy with neobladder, for grade 3 urothelial cancer of bladder	Constipation	Abdominopelvic CT: Abnormal perirectal lymph nodes. Endoscopy: Circumferential rectal wall thickening. EUS: Diffuse circumferential thickening of all layers of rectal wall with several hypoechoic lymph nodes in extraluminal space	Rectum: Urothelial carcinoma	Chemotherapy	NR	Gleeson *et al*[6]

CT: Computed tomography; GI: Gastrointestinal; M-VAC: Methotrexate, vinblastine, Adriamycin; NR: Not reported; PTA: Prior to admission; RT: Radiation therapy; MRI: Magnetic resonance imaging.

Table 2 Metastases of urothelial bladder carcinoma to the colorectum

Patient age, sex	Prior oncologic history	Clinical presentation with GI involvement	Radiologic imaging, endoscopy, surgery	Metastasis location: Pathologic diagnosis	Treatment	Outcome	Ref.
1. 63-year-old man	Ten months PTA underwent radical cystectomy and MVAC chemotherapy for bladder urothelial carcinoma	Painless jaundice, 5-kg weight loss, and constipation for 2 wk. Physical exam: mild right upper quadrant tenderness. Laboratory: Elevated liver function tests	Abdominopelvic CT: Concentric thickening of rectal wall; bile duct hilar stricture with diffuse intrahepatic ductal dilation. MRI: Diffusely thickened common hepatic duct with extension into secondary branch ducts suspicious for cholangiocarcinoma. Colonoscopy: Concentric rectal constriction blocking colonoscopic intubation. ERCP: Strictures of common hepatic and right intrahepatic ducts; obstructed left intrahepatic duct	Rectum and hepatic duct: Micropapillary variant of transitional cell (urothelial) carcinoma	Rectal tumor: RT with external beam and brachy-therapy. Hepatic tumor: Polyethylene stent placed in intrahepatic bile duct. RT is planned	Alive at 4 mo	Hong *et al*[7]
2. 55-year-old man	Fifteen months PTA underwent TURBT and 6 wk of mitomycin C, followed by 4 rounds of gemcitabine and cisplatin chemotherapy for high grade urothelial carcinoma of bladder with iliac lymph node chain involvement. Six months PTA underwent radical cystoprostatectomy with neobladder creation and pelvic lymphadenectomy	Worsening constipation, abdominal distention, anorexia, and dyschezia. Rectal exam: palpable mass 3 cm from anal verge	Abdominopelvic CT: Pelvic and omental nodules. PET: Increased uptake at these nodules. Flexible sigmoidoscopy: 3 cm wide rectal lesion near anal verge	Rectum, omentum, other pelvic structures: Urothelial carcinoma	Diverting loop colostomy	Brain and lung metastases	Asfour *et al*[8]
3. 77-year-old man	Eleven years PTA underwent resection of papillary bladder urothelial carcinoma. Eight years PTA underwent TURBT and RT for recurrence. Underwent periodic cystoscopies and bladder biopsies thereafter	Progressive constipation, weight loss, and malaise	Barium enema: barium could not pass beyond sigmoid colon. Laparotomy: Sigmoid colon obstructed due to adherent tumor of terminal ileum and cecum	Sigmoid, right-transverse colon, cecum, ileum, appendix, omentum: Urothelial carcinoma	Ileotransverse colostomy and loop colostomy of descending colon	NR	Aigen *et al*[9]
4. 60-year-old man	Five months PTA underwent radical cystectomy with ileal conduit for invasive bladder urothelial carcinoma	Painless hematochezia. Rectal exam: Red blood in rectal vault. No externally visible or palpable hemorrhoids. Hemoglobin declined from 11.6 g/dL to 8.7 g/dL	Necrotic pelvic lesions suspicious for metastases *vs* abscess. Colonoscopy: Irregular, friable, partially obstructing mass at splenic flexure	Splenic flexure: Urothelial carcinoma	None	Refused treatment. Transferred to hospice	Kumar *et al*[10]

5. 57-year-old man	Five years PTA underwent total cystectomy for bladder urothelial carcinoma. One year PTA underwent lymph node resection, RFA, bone cement injection, and chemotherapy for left obturator lymph node and several pulmonary and left pelvic bone metastasis. Five months PTA underwent RT for regrowth of left obturator lymph node metastasis	Massive melena, HR = 120 beats/min, BP = 76/39 mmHg, Hemoglobin = 9.2 g/dL	Abdominopelvic CT: Malignant lymph node invading sigmoid colon, with pseudoaneurysm of mesenteric artery supplying sigmoid Colonoscopy: Large, oozing, ulcerated colonic tumor	Sigmoid colon: NA	Pelvic angiogram: 10 mm × 8 mm pseudoaneurysm of left inferior gluteal artery successfully embolized using microcoils and vasopressin	Alive at 5 mo	Kakizawa *et al*[11]
6. 83-year-old man	No prior oncologic history	Diarrhea and weight loss during prior 6 mo. Rectal exam: Mass 3 cm from anal verge	Abdominopelvic CT: Thickened right posterior wall of bladder, circumferential rectal wall thickening, and infiltrative lesions in multiple skeletal muscles Proctoscopy: Mass 3 cm from rectal verge	Rectum and skeletal muscles: Poorly differentiated urothelial carcinoma	Chemotherapy (regimen not specified)	NR	Ying-Yue *et al*[12]
7. 54-year-old man	Two years PTA underwent radical cystectomy and ileal neobladder reconstruction for grade 3 bladder urothelial carcinoma	Change in bowel habits	Abdominopelvic MRI: Circumferential thickening and high-grade stenosis of rectal wall. Sigmoidoscopy: Luminal narrowing with erythematous and edematous folds. EUS: Hypoechoic, circumferential, rectal wall thickening, mimicking primary rectal cancer. No evident direct cancer extension from bladder	Rectum: Urothelial carcinoma	Chemotherapy (regimen not specified)	NR	Yusuf *et al*[13]
8. 73-year old man	Two years PTA underwent resection of grade 2 bladder urothelial carcinoma	Severe constipation	Sigmoidoscopy: Friable, erythematous, and thickened distal rectal wall, with nearly obstructed lumen. EUS: Hypoechoic, symmetric, circumferential wall thickening, with loss of deep wall layers, and pseudopodia-like extensions into perirectal tissues. No evident direct tumor extension from bladder	Rectum: Poorly differentiated urothelial carcinoma	Total pelvic exenteration and chemotherapy (regimen not specified)	NR	Yusuf *et al*[13]

Patient age and sex	Prior oncologic history	Clinical presentation with GI involvement	Radiologic imaging, endoscopy, surgery	Metastasis location: Pathologic diagnosis	Treatment	Outcome	Ref.
9. 67-year-old man	Eighteen months PTA underwent transurethral excisional biopsy of bladder cancer. Ten months PTA underwent partial cystectomy, chemotherapy with gemcitabine, and RT. 1 mo PTA, nephrostomy tubes inserted for bilateral hydronephrosis	Massive rectal bleeding and altered mental status for one day. HR = 106 beats/min, BP = 65 mmHg/palpable. Rectal exam: Rectal mass and large amount of bright red blood and clots. Hemoglobin = 8.0 g/dL	Selective angiography of celiac trunk, superior mesenteric artery and inferior mesenteric artery: No bleeding source identified. Colonoscopy: Large amount of bright red blood in colon. Emergency laparotomy: Indurated, fixed, mass involving cecum, right lower retroperitoneum, and right pelvic side wall. Dilated colon. Active bleeding from fistula between iliac artery and cecum	Cecum: Urothelial carcinoma	Resection of cecum and terminal ileum, ligation of right external iliac artery, end-ileostomy	Alive at 6 mo	Chin et al[14]

BP: Blood pressure; CT: Computed tomography; ERCP: Endoscopic retrograde cholangiopancreatography; GI: Gastrointestinal; HR: Heart rate; M-VAC: Methotrexate, vinblastine, Adriamycin; NR: Not reported; PET: Positive electron tomography; PTA: Prior to admission; RFA: Radiofrequency ablation; RT: Radiation therapy; TURBT: Transurethral resection of bladder tumor; EUS: Endoscopic ultrasound; NA: Not available.

Table 3 Metastases of urothelial bladder carcinoma to the esophagus, stomach, and small intestine

Patient age and sex	Prior oncologic history	Clinical presentation with GI involvement	Radiologic imaging, endoscopy, surgery	Metastasis location: Pathologic diagnosis	Treatment	Outcome	Ref.
1. 55-year-old man	1 mo PTA underwent total cystoprostatectomy, bilateral ilio-obturator lymphadenectomy, and bladder reconstruction for bladder urothelial carcinoma pT3-GIII, N0	Hematemesis 8 d after surgery	Chest and abdominopelvic CT: Esophageal mass. EGD: 2-cm-wide mass in proximal esophagus. EUS: No lymphadenopathy	Esophagus: Urothelial carcinoma infiltrating submucosa	Chemotherapy with M-VAC, and RT of metastasis	Developed radiation pericarditis but recovered. Alive at 2 yr	Jung et al[15]
2. 66-year-old man	No prior oncologic history	Dysphagia, anorexia, weight loss, headaches, and lightheadedness for 6 wk. Palpable, tender, 2 cm mass on left neck	Neck and thoracic CT: 3 cm × 2 cm soft tissue mass with dilation and thickening of proximal esophagus. EGD: Focal stricture at 25 cm from incisors with a 2 cm × 1 cm ulcer with irregular margins	Esophagus: Poorly differentiated urothelial carcinoma	None	Died 10 d after discharge from hospital	Dy et al[16]
3. 80-year-old man	Four years PTA underwent RT and chemotherapy (after declining radical cystectomy) for bladder urothelial carcinoma. Three years PTA underwent lung lobe wedge resection for solitary lung metastasis. 1 mo PTA had a normal EGD and colonoscopy in evaluation of anemia	Malaise, dizziness, dyspnea, melena. Rectal exam: Positive occult blood in stool. Hemoglobin = 5.4 g/dL	Small bowel enteroscopy: 3 cm, ulcerated, infiltrating tumor in distal duodenum. Tumor has an adherent, friable, clot	Duodenum: High-grade urothelial carcinoma	Duodenectomy and duodenomy jejunostomy	PET scan 2 mo later: Metastases to liver and lungs. Patient expired soon thereafter from cardiac arrhythmia	Girotra et al[17]

4. 62-year-old man	Two years PTA underwent partial cystectomy with lymph node dissection and adjuvant chemotherapy for stage IIIb bladder urothelial carcinoma	Hematemesis, hemoglobin = 7.0 g/dL	EGD: Large bleeding mass in descending duodenum. Treated with proton pump inhibitor therapy. Repeat EGD 4 d later: large partly obstructing, 7-cm-long mass in descending duodenum	Duodenum: Poorly differentiated urothelial carcinoma	Palliative radiation	Died 6 wk later	Chan *et al*[18]
5. 74-year-old man	Four years PTA underwent exploratory laparotomy which demonstrated nodal metastasis. Completed preoperative chemotherapy, but declined surgical resection	Abdominal pain, bloating, distention, nausea, and vomiting	Serial pelvic CT (to monitor cancer progression): Stable bladder wall thickening Small bowel barium contrast radiography: Narrowing of third portion of duodenum Gastroscopy: Fluid-filled, dilated, stomach without obstruction. EGD: Luminal narrowing with overlying normal mucosa in third portion of duodenum. EUS: Circumferential wall thickening	Duodenum: urothelial carcinoma	Enteral stent and palliative chemotherapy	Died 9 mo later	Yusuf *et al*[13]
6. 42-year-old woman	No prior oncologic history	Nausea, vomiting, abdominal discomfort, and 6-kg weight loss for 2 mo	Barium meal: Abrupt stricture at junction between second and third portion of duodenum. Abdominopelvic CT: Infiltrative soft tissue mass around duodenum, calcified bladder wall. No pelvic lymphadenopathy. EGD: Gastric outlet obstruction with distorted and erythematous duodenum without ulceration, or mucosal tumor	Duodenum: Micropapillary variant of poorly differentiated urothelial carcinoma	Duodenal stent and RT to periduode-nal lesion. Administered palliative gemcitabine and carboplatin	Died 15 mo after diagnosis	Hawtin *et al*[19]
7. 87-year-old man	Sixteen months PTA underwent TURBT for grade 3, pT2bN0M0, bladder urothelial carcinoma	Ileus	Abdominopelvic CT: Pneumoperitoneum due to GI perforation Laparotomy: Elastic hard tumor at site of ileal perforation	Ileum: Metastatic urothelial carcinoma	Partial resection of ileum	NA	Hoshi *et al*[20] (in Ja-panese)
8. 53-year-old man	No prior oncologic history	Gross hematuria	Abdominopelvic CT: Bladder tumor invading prostate. Cystoscopy: Non-papillary, broad based, tumor in right wall of bladder	Ileum and prostate: Urothelial carcinoma pT4aN1M0	Total cystec--tomy and creation of ileal conduit. Neoadjuvant chemotherapy	NA	Hoshi *et al*[20] (article in Japanese)
9. 56-year-old man	Fifty-nine months PTA underwent TURBT for bladder urothelial carcinoma	Abdominal pain and GI perforation	NA	Small intestine, lymph nodes, lung, and liver: Urothelial carcinoma	NA	NA	Hoshi *et al*[20] (Case from table 2)

10. 63-year-old woman	Seven months PTA underwent total cystectomy for pT3b bladder urothelial carcinoma	Abdominal pain	NR	Small intestine: Urothelial carcinoma	NR	NR	Hoshi et al[20] (Case from table 2)
11. 46-year-old man	Thirty-eight months PTA underwent RT and chemotherapy for pT3b bladder urothelial carcinoma	Ileus	NR	Small intestine: Urothelial carcinoma	NR	NR	Hoshi et al[20] (Case from table 2)
12. 71-year-old man	Thirty-six months PTA underwent total cystectomy for bladder urothelial carcinoma	Melena and anemia	NR	Small intestine: Urothelial carcinoma	NR	NR	Hoshi et al[20] (Case from table 2)
13. 55-year-old man	Seven years PTA underwent total cystectomy, pelvic lymphadenectomy, and neobladder reconstruction. Underwent two cycles of adjuvant chemotherapy for pT3apN0 G2 bladder urothelial carcinoma	Massive melena, HR = 120 beats/min, BP = 72/36 mmHg. Hemoglobin = 7.9 g/dL	Abdominopelvic CT: Right hydronephrosis from external iliac lymph node metastasis invading ileum. Angiography: Right external iliac artery successfully embolized using microcoils and n-butyl cyanoacrylate. Then developed ischemic colitis, treated with iliac artery bypass grafting, and right common and internal iliac artery embolization	Ileum: NR	Three cycles of unspecified chemotherapy	Died 4 mo after embolization	Honda et al[21]

BC: Bladder cancer; BP: Blood pressure; CT: Computed tomography; EGD: Esophagogastroduodenoscopy; GI: Gastrointestinal, HR: Heart rate; M-VAC: Methotrexate, vinblastine, Adriamycin; NR: Not reported; PTA: Prior to admission; RT: Radiation therapy; TURBT: Transurethral resection of bladder tumor; EUS: Endoscopic ultrasound.

with bacillus-Calmette-Guerin and adriamycin. In 2014 the patient underwent suprapubic catheter placement for severe urinary frequency, urinary incontinence, recurrent urethral stricture, and hematuria. Four months prior to admission the patient underwent cystoscopy for refractory, severe hematuria, which demonstrated a small, contracted bladder, chronic urethral stricture, and friable, hemorrhagic tissue at the bladder neck felt most likely secondary to recurrent (invasive) urothelial carcinoma, but radiation cystitis could not be excluded. The hemorrhagic area was treated with electrocautery during cystoscopy, and by continuous bladder irrigation administered for 24 h. No biopsies were obtained during cystoscopy because the patient refused aggressive therapy of chemotherapy or surgery based on his old age, severe chronic debilitation, and multiple prior cancers.

Physical examination revealed normal vital signs; a soft, nontender, abdomen; and no palpable abdominal mass. Rectal examination revealed a hard, fixed, multinodular, 2.5 cm × 2.5 cm mass, at the normal prostate location; gross bright red blood on the examining finger; and no visible or palpable hemor-hoids. The hemoglobin = 7.6 gm/dL, with iron deficiency anemia (iron = 26 mcg/dL, total iron binding capacity = 301 mcg/dL, iron-saturation = 8.4%). Hemoglobin increased to 9.7 gm/dL after transfusing 2 units of packed erythrocytes. The prostate specific antigen (PSA) = 43.3 ng/mL (normal < 2.5 ng/mL). Urinalysis revealed significant hematuria, trace proteinuria, nitrite positivity, and bacteriuria with 26-50 leukocytes/high power field (hpf). There were 10000-50000 colony forming units/mL of Enterobacter cloacae isolated from a urine culture. The patient was administered ceftriaxone 1 g/24 h for the bacteriuria.

Abdominopelvic CT angiography revealed focal thickening of the bladder wall at its neck; a mass containing an air cavity replacing most of the prostate; and adjacent rectal invasion (Figure 1). Colonoscopy, with rectal retroflexion, demonstrated an ulcerated, friable, multinodular, 2.5 cm × 2.5 cm mass in the anterior rectal wall, just proximal to the dentate line, at the usual prostate location (Figure 2), no internal hemorrhoids, and no mucosal telangiectasia or other signs of radiation proctitis despite prior prostate radiotherapy. Histologic examination of rectal mucosal

Figure 1 Abdominopelvic computed tomography angiography demonstrating thickened bladder wall (red arrowhead), with adjacent prostate margin (dashed arrow). Air-filled cavity within the prostate gland (white arrowhead), is consistent with the known bladder urothelial carcinoma penetrating, *via* the prostate, into the rectum (horizontal solid arrows). The colonoscopic findings (Figure 2) strongly support this mechanism of cancer spread.

Figure 2 Colonoscopy reveals, just above the anorectal margin (line between pale skin and red mucosa), a multinodular, friable, 2.5-cm-wide, hemorrhagic, mass that replaces the normal prostate and overlying rectum (A, B). Tissue surrounding the lesion appears to be normal. Biopsy of this mass revealed bladder urothelial carcinoma. The finding of bladder urothelial carcinoma in the normal location of the prostate and overlying rectum, just inferior to the bladder cancer, is consistent with direct extension of bladder urothelial carcinoma into the immediately adjacent prostate and its overlying rectal mucosa. This cancer location is highly consistent with the abdominopelvic computed tomography findings (Figure 1).

biopsies revealed poorly differentiated carcinoma (Figure 3A). Immunohistochemical analysis demonstrated the tumor cells stained positively with cytokeratin 20, indicating either a colonic or bladder (urothelial) primary (Figure 3B). Additional diffuse positivity for cytokeratin 7, 34bE12, and GATA-3 (Figure 3B); and focal positivity for CK5/6 strongly supported urothelial origin. Negative immunohistochemical staining for CDX2 (Caudal Type Homeobox 2) confirmed that this tumor did not arise from colonic adenocarcinoma (Figure 3C). The diffuse positivity for cytokeratin 20 and only focal positivity for CK5/6 (< 20% of cells positive) excluded anorectal squamous carcinoma. Immunohistochemical markers for prostate carcinoma, including PSA, PAP and P501S, were all negative. The history of non-invasive urothelial carcinoma in bladder biopsies in 2010, further supported the link between the cancers located in the bladder and rectum. The pathologic diagnosis was therefore poorly-differentiated carcinoma of urothelial origin.

At visceral angiography, the right-superior-rectal-artery was successfully embolized using 900-1200-micron embolospheres to achieve rectal hemostasis. However, the patient experienced recurrent rectal bleeding three months later requiring periodic packed erythrocyte transfusions and eventually requiring palliative colostomy. CT scans of chest, abdomen, and pelvis ten months post-embolization identified new hepatic and pulmonary metastases. At this time the patient also had progression of the bladder urothelial carcinoma with bilateral ureteral obstruction, prominent rectovesical fistula, and bilateral hydronephrosis that required bilateral nephrostomy tube placement. The patient expired 3 mo thereafter.

DISCUSSION

Bladder urothelial carcinoma, the most common urinary tract cancer, constitutes the fourth leading cause of cancer mortality in males, and the ninth leading cause of cancer mortality in females[10]. Urothelial carcinoma is the predominant histologic type in the United States and Europe, accounting for 90% of bladder cancers, but non-urothelial carcinomas are relatively more common in other countries[17].

GI involvement

This cancer most commonly metastasizes to lungs, liver, and bone, *via* lymphogenous or hematogenous routes. It rarely extends or metastasizes to the GI tract[10]. Comprehensive literature review revealed only 33 previously reported cases (or 34 cases including the present case) of GI involvement including: Direct extension to rectum-12 (Table 1); metastases to rectum-5, cecum-1, splenic flexure-1, sigmoid colon-1, and multiple colonic segments-1 (Table 2); and metastases to duodenum-4, ileum-3, esophagus-2, appendix-1, and unspecified-3 (Table 3). No metastases occurred in the stomach. The mean patient age was 64.0 ± 11.3 years (SD). Thirty-two patients were male, and only 2 patients were female. Patients developed GI extension/metastases on average, 28.5 ± 30.3 mo after the initial diagnosis of bladder urothelial carcinoma.

Figure 3 Histologic examination and immunohistochemical analysis. A: Low power photomicrograph shows segments of detached poorly differentiated cancer (arrows), amidst segments of normal rectal mucosa (arrowhead). Right inset shows high power photomicrograph of polygonal tumor cells (HE stain) that have a histologic appearance characteristic for urothelial carcinoma. Immunohistochemistry confirmed the urothelial histology of the cancer (Figure 3B and C); B: Left: Immunohistochemistry for cytokeratin-20 demonstrates positive staining of tumor cytoplasm. Right: Immunohistochemistry for GATA-3 demonstrates positive staining of tumor cell nuclei. This immunohistochemical profile indicates that the rectal mass is of urothelial origin; C: Immunohistochemistry for CDX-2 shows negative staining of tumor cell nuclei, indicating that this tumor is not colonic adenocarcinoma. Right inset is a control of normal colonic glands set on the same slide which demonstrates positive nuclear staining for CDX-2.

Therapies for the primary bladder urothelial carcinoma prior to GI extension/metastases included radical or partial cystectomy-19, adjuvant chemotherapy-11, and radiotherapy-6 (including patients receiving multiple

therapies). Presenting symptoms with GI involvement included: (1) systemic/extraintestinal symptoms of weight-loss-8, malaise/fatigue-5, anorexia-5, dizziness-2, dyspnea-2, and encephalopathy-1; (2) generalized abdominal symptoms of abdominal pain-4, abdominal distention-2, ileus-2, and GI obstruction-1; (3) GI bleeding including hematemesis-4, melena-4, and hematochezia-3; (4) upper GI symptoms of nausea/vomiting-2, and dysphagia-1; and (5) lower GI symptoms of constipation-7, diarrhea-4, anal pain-3, tenesmus-2, and fecal incontinence-1. Rectal examination, performed in 12 patients, revealed rectal stenosis-6, rectal mass-4, bright red blood per rectum-2, and fecal occult blood-1. The average hemoglobin on presentation was 8.8 ± 2.2 g/dL. Three patients presented with profound hypovolemia, manifesting as severe tachycardia or hypotension.

Colonoscopy, performed in 9 patients, revealed extrinsic colorectal constriction-5, ulcerated/friable mass-3, and profuse bright red blood per rectum-1 (Tables 1 and 2). Flexible sigmoidoscopy, performed in 5 patients, revealed extrinsic constriction-4, and rectal mass-1 (Table 2). Esophagogastroduodenoscopy, performed in 6 patients, revealed stricture of esophagus or duodenum-2; a moderately large, non-obstructive, mass in esophagus or duodenum-2; gastric outlet obstruction-1, and normal findings-1 (Table 3). Enteroscopy revealed a large, ulcerated, duodenal mass in one patient (Table 3). Endoscopic ultrasound performed in 7 patients, revealed hypoechoic, circumferential, rectal wall thickening in 6 patients (Tables 1 and 2).

On presentation with GI metastases, three patients had pathologically-proven extra-intestinal metastases, including one patient with common hepatic duct and intrahepatic duct strictures, identified by endoscopic retrograde cholangiopancreatography. Three other patients had suspected extraintestinal metastases identified by radiologic imaging.

Thirteen patients underwent surgery, including, diverting surgery (such as colostomy and ileostomy)-8, and local bowel resection-5. Seven patients underwent radiotherapy with external beam or brachytherapy. Sixteen patients underwent chemotherapy with carboplatin, cisplatin, etoposide, and gemcitabine; or with methotrexate, vinblastine, adriamycin and cisplatin. The prognosis remains poor for metastatic bladder urothelial carcinoma. Six patients expired from the cancer at a mean of 6.0 ± 4.5 mo. Four patients were reported alive at a mean of 9.8 ± 9.5 mo of follow-up. Most patients, however, had limited follow-up.

Rectal involvement

Bladder urothelial carcinoma has been previously reported to involve the rectum in 16 cases, including 11 cases by direct extension, as demonstrated by abdominopelvic CT-8, rectal endoscopic ultrasound (EUS)-3, and abdominopelvic magnetic resonance imaging (MRI)-2; and including 5 cases by metastases as demonstrated by abdominopelvic CT-2, EUS-2, MRI-1, and positron emission tomography (PET) scan-1 (1 patient had 2 diagnostic tests) (Tables 1 and 2). Rectal involvement was pathologically proven at surgery-6, by fine needle aspiration during EUS-5, colonoscopic biopsies-3, and transrectal needle biopsy-2. None of the 11 patients with direct bladder extension to rectum had pathologically-proven involvement of rectal mucosa; three of the 5 patients with rectal metastases had pathologically-proven mucosal involvement. Three patients had proven extraintestinal metastases at the time of diagnosis of rectal involvement, including hepatic duct-1, omentum and pelvic organs-1, and skeletal muscles-1. The average patient age at diagnosis of rectal involvement was 63.7 ± 9.6 years. All 16 patients were male. Rectal involvement was diagnosed on average 13.5 ± 11.8 mo after the bladder urothelial carcinoma was first diagnosed (includes 2 patients with simultaneous diagnosis of primary bladder urothelial carcinoma and rectal involvement, excludes 4 cases in which time interval between the two diagnoses was not reported). Patient symptoms included constipation or GI obstruction-6, weight loss-5, diarrhea-3, anorexia-3, pencil thin stools-3, tenesmus-2, anorectal pain-2, fatigue-1, straining with bowel movements-1, fecal incontinence-1, abdominal distention-1, and change in bowel habits-1. Rectal examination, performed in 9 patients, revealed annular rectal stenosis in 6, and rectal mass in 3. One patient presented with mild anemia.

This case report describes the novel colonoscopic appearance of bladder urothelial carcinoma extension, *via* the prostate, into the rectum, forming a multinodular, oval, ulcerated, friable mass. Bladder carcinoma extension *via* the prostate underlies the colonoscopic detection of rectal invasion only over the prostate location, just as the colonoscopic finding of a friable, multinodular, hemorrhagic rectal mass underlies the clinical presentation with daily bright red blood covering the stools. Invasion *via* the prostate may have been facilitated by prior radiotherapy and hormonal therapy for prostate cancer, or perhaps by prostate tissue being receptive to urothelial metastases. Bladder (and prostate) cancer have been reported to cause annular rectal constriction, presenting as constipation or GI obstruction, *via* contiguous spread to the rectal submucosal or muscular layers, but the current report of extension to rectal mucosa is novel. Bladder urothelial carcinoma is believed to break through the bladder wall, and follow along, the fascia of Denonvillier[2], or spread locally along the lateral pedicles of the bladder to reach the posterior rectal wall, to cause rectal constriction[4]. The current case, like all the prior 16 cases of rectal involvement, occurred in men. Female internal reproductive organs and their corresponding ligaments and fascia might serve as barriers that protect the rectum from local invasion by bladder urothelial carcinoma, whereas the prostate might be a weak

barrier to protect the rectum from local invasion because of susceptibility to urothelial invasion. Metastasis, to other GI regions, have, likewise, been reported much more frequently in men than women, partly explained by bladder urothelial carcinoma being four times as common in men than women[22], but other potential contributing factors require further investigation.

The currently reported patient had two reported risk factors for bladder urothelial carcinoma: Prior prostate cancer[23], and prior radiotherapy for prostate cancer[24]. The current case demonstrates that the clinical symptoms of rectal mucosal invasion can mimic that of hemorrhoids: chronic, daily, bright red blood per rectum coating the stools. However, the currently reported patient also had an enlarged, hard, fixed, "prostate" on rectal examination, and had prior prostate and bladder cancers, findings suggesting recurrent bladder or prostate cancer.

This study is limited by reporting a single case and by reporting it retrospectively. This study is also somewhat limited by not entirely excluding prostate cancer as contributing to the pelvic mass. However, the cystoscopic findings of friable, hemorrhagic tissue at the bladder neck identified 4 mo prior to admission; the colonoscopic findings of a friable, multinodular rectal mass; the histologic and immunohistochemical findings of multiple rectal biopsies revealing bladder urothelial carcinoma; the CT demonstration of a mass extending from the bladder neck through the prostate into the rectum; and the absence of immunohistochemical markers for prostate cancer in the rectal biopsies all favor the diagnosis of bladder urothelial carcinoma over prostate cancer. In conclusion, a case of bladder urothelial carcinoma penetrating into the rectum *via* the prostate is reported, with apparently previously unreported, but likely characteristic colonoscopic findings. In the previously reported cases, rectal lesions were metastatic, presumably *via* lymphogenous or hematogenous routes, or caused rectal constriction from direct rectal wall extension without rectal mucosal involvement.

COMMENTS

Case characteristics
An 87-year-old man was treated in 1996 for prostate adenocarcinoma stage-T1c-Gleason-6 with external beam radiotherapy recurrent prostate cancer treated with leuprolide hormonal therapy in 2009, and bladder-urothelial-carcinoma *in-situ* treated with Bacillus-Calmette-Guerin and adriamycin in 2010, presented in 2015 with painless, bright red blood per rectum coating stools daily for 5 mo. Rectal examination revealed bright red blood per rectum; and a hard, fixed, 2.5 cm × 2.5 cm mass at the normal prostate location.

Clinical diagnosis
The symptom of daily, painless, bright red blood per rectum for 5 mo without other symptoms suggests hemorrhoidal bleeding. First, hemorrhoidal bleeding is very common and is typically unassociated with other symptoms. Second, hemorrhoids generally cause bright red blood because hemorrhoidal blood, despite being venous, is relatively well oxygenated. Third, hemorrhoidal bleeding is generally painless in the absence of hemorrhoidal thrombosis. Rectal examination did not, however, support this diagnosis. No external hemorrhoids were identified by anal inspection, and no internal hemorrhoids were palpated on

digital rectal examination. Moreover, rectal examination revealed a hard, fixed, multinodular, mass, at the normal location of the prostate, and gross red blood on the examining finger, findings suspicious for rectal bleeding from prostate cancer. This diagnosis is further suggested by the prior history of prostate cancer in 1996, prostate cancer recurrence in 2009 six years before the current clinical presentation, and palliative hormonal therapy for the cancer recurrence in 2009. The diagnosis of recurrent bladder urothelial cancer is also possible given the prior diagnosis of bladder urothelial carcinoma *in situ* in 2010; recurrent bladder urothelial carcinoma could cause rectal bleeding from metastases or direct extension to the rectum. Radiation proctitis must be included in the differential diagnosis because the patient had undergone external beam radiotherapy for prostate cancer in 1966, 19 years before the clinical presentation. Chronic radiation proctitis can cause rectal bleeding from telangiectasias caused by radiation-induced endothelial injury. Anal fissure must also be included in the differential diagnosis of bright red blood per rectum, but is unlikely in this case because anal fissure is typically very painful and this patient had no anorectal pain. Also the patient did not have the classic symptoms of anorectal bleeding commencing after passing a large, hard stool, the patient had daily rectal bleeding for 5 mo which is atypical for rectal fissure, and anal fissure is relatively uncommon.

Laboratory diagnosis
The key finding in the blood tests is a hemoglobin level of 7.6 gm/dL, with iron saturation of 9%, indicating iron deficiency anemia. Hemorrhoidal bleeding tends to produce minimal-to-mild anemia because of minimal daily bleeding, whereas prostate or bladder cancer invading rectal mucosa can cause much more significant blood loss and more severe anemia.

Imaging diagnosis
Abdominopelvic computed tomography (CT) angiography revealed focal thickening of the bladder wall at its neck; a mass containing an air cavity replacing most of the prostate; and adjacent rectal invasion. These imaging findings strongly support the diagnosis of recurrent bladder urothelial carcinoma penetrating rectal mucosa *via* the prostate, or less likely support the diagnosis of recurrent prostate cancer penetrating rectal mucosa. These CT findings do not support the diagnosis of hemorrhoids. Either of these malignancies would be more likely to produce iron deficiency anemia from chronic blood loss than hemorrhoidal bleeding. Colonoscopy demonstrated an ulcerated, friable, multinodular, oval, hemorrhagic, 2.5 cm × 2.5 cm mass in the anterior rectal wall, just proximal to the dentate line, at the usual anatomic location of the prostate, no hemorrhoids, and no signs of radiation proctitis, such as mucosal telangiectasia despite the prior prostate radiotherapy. These colonoscopic findings are highly consistent with cancer invading rectal mucosa. These CT findings are most compatible with bladder urothelial carcinoma invading rectal mucosa by direct extension.

Pathological diagnosis
Histologic examination of colonoscopic biopsies of rectal tissue biopsies revealed poorly differentiated carcinoma. Immunohistochemical analysis demonstrated the tumor cells stained positively with cytokeratin 20, indicating either a colonic or bladder (urothelial) primary. Additional diffuse positivity for cytokeratin 7, 34bE12, and GATA-3; and focal positivity for CK5/6 strongly support urothelial origin. Negative immunohistochemical staining for CDX2 (Caudal Type Homeobox 2) confirms that this tumor does not arise from colonic adenocarcinoma. The diffuse positivity for cytokeratin 20 and only focal positivity for CK5/6 (< 20% of cells positive) excludes anorectal squamous carcinoma. Immunohistochemical markers for prostate carcinoma, including PSA, PAP and P501S, were all negative. The pathologic diagnosis was therefore poorly-differentiated carcinoma of urothelial origin. This pathology explains all the findings: Clinical presentation of painless, daily bright red blood per rectum from friable rectal mucosa from malignant invasion; iron deficiency anemia from chronic GI bleeding from rectal metastases; CT findings of direct cancer extension to rectal mucosa; and colonoscopic findings of an ulcerated, friable, multinodular, mass in the anterior rectal wall.

Treatment
The patient received palliative therapy for the daily rectal bleeding. The right-superior-rectal-artery was successfully embolized during visceral angiography

using embolospheres to achieve hemostasis. The patient did not undergo curative therapy in accordance with the patient's wishes, because of the minimal likelihood of cure given that the patient presented with recurrent urothelial carcinoma spreading beyond the bladder, previously had recurrent prostate cancer, and was very elderly. The patient experienced recurrent rectal bleeding requiring periodic packed erythrocyte transfusions three months after embolectomy that required palliative colostomy. The patient expired 13 mo after embolization from widespread metastases from the advanced cancer with rectal penetration treated with palliative therapy.

Related reports

Comprehensive literature review revealed 16 previously reported cases of rectal involvement of bladder urothelial carcinoma, including 11 cases of direct cancer extension and 5 cases of metastases. The current case is novel in that the bladder urothelial carcinoma directly penetrated into rectal mucosa; in that rectal involvement caused daily bright red blood per rectum and iron-deficiency anemia; and in the colonoscopic findings that were in accord with the clinical presentation of daily bright red blood per rectum and the CT findings.

Experiences and lessons

This work demonstrates the novel findings that bladder urothelial carcinoma can directly extend to rectal mucosa *via* the prostate, can cause daily, painless, bright red blood per rectum mimicking hemorrhoidal bleeding; and produce colonoscopic findings of a multinodular rectal mucosal mass from cancer extension.

Peer-review

The authors reported on a single case of urothelial bladder cancer extending to rectal mucosa *via* the prostate and mimicking hemorrhoidal bleeding, and reviewed the literature on this subject. The case is well described and of clinical interest. The background literature review is comprehensive and well done.

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World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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INDEXING/ABSTRACTING

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ORIGINAL ARTICLE

Retrospective Cohort Study

Assessment of the July effect in post-endoscopic retrograde cholangiopancreatography pancreatitis: Nationwide Inpatient Sample

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Abstract

AIM

To assess incidence of post-endoscopic retrograde cholangiopancreatography (post-ERCP) pancreatitis in the early (July/August/September) *vs* the late (April/May/June) academic year and evaluate in-hospital mortality, length of stay (LOS), and total hospitalization charge between these time periods.

METHODS

This was a retrospective cohort study using the 2012 Nationwide Inpatient Sample (NIS). Patients with International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9 CM) procedure codes for ERCP were included. Patients were excluded from the study if they had an ICD-9 CM code for a principal diagnosis of acute pancreatitis, if the ERCP was performed before or on the day of admission or if they were admitted to non-teaching hospitals. Post-ERCP pancreatitis was defined as an ICD-9 CM code for a secondary diagnosis of acute pancreatitis in patients who received an ERCP as delineated above. ERCPs performed during the months of July, August and September was compared to those performed in April, May and June in academic hospitals. ERCPs performed at academic hospitals during the early *vs* late year were compared. Primary outcome was incidence of post-ERCP

pancreatitis. Secondary outcomes included in-hospital mortality, length LOS, and total hospitalization charge. Proportions were compared using fisher's exact test and continuous variables using student *t*-test. Multivariable regression was performed.

RESULTS
From the 36480032 hospitalizations in 2012 in the United States, 6248 were included in the study (3065 in July/August/September and 3183 in April/May/June) in the 2012 academic year. Compared with patients admitted in July/August/September, patients admitted in April/May/June had no statistical difference in all variables including mean age, percent female, Charleston comorbidity index, race, median income, and hospital characteristics including region, bed size, and location. Incidence of post-ERCP pancreatitis in early *vs* late academic year were not statistically significant (OR = 1.03, 95%CI: 0.71-1.51, *P* = 0.415). Similarly, the adjusted odds ratio of mortality, LOS, and total hospitalization charge in early compared to late academic year were not statistically significant.

CONCLUSION
Incidence of post-ERCP pancreatitis does not differ at academic institutions depending on the time of year. Similarly, mortality, LOS, and total hospital charge do not demonstrate the existence of a temporal effect, suggesting that trainee level of experience does not impact clinical outcomes in patients undergoing ERCP.

Key words: Pancreatitis; Academic training; Endoscopic retrograde cholangiopancreatography; Endoscopy; July effect

Core tip: The changeover of medical trainees has been shown to negatively impact patient care. At academic institutions, endoscopic retrograde cholangio-pancreatography (ERCP) involves advanced endoscopy fellows, and outcomes may vary based on the time of year. We assessed the incidence of post-ERCP pancreatitis in the early *vs* the late academic year and evaluated in-hospital mortality, length of stay (LOS), and total hospitalization charge between these time periods. We found that the incidence of post-ERCP pancreatitis in early *vs* late academic year were not statistically significant. Furthermore, mortality, LOS, and total hospitalization charge in early compared to late academic year were not statistically significant.

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is frequently used for the diagnosis and management of many biliary and pancreatic diseases. Pancreatitis is the most common and serious complication of ERCP, accounting for more than half of all complications following this procedure[1-3]. The estimated incidence of post-ERCP pancreatitis (PEP) varies substantially and is reported to be between 1% to 15%, with select studies reporting incidences as high as 30% in some populations[4,5]. While the majority of PEP is mild, up to 20% of reported cases are moderate or severe[6], and in some instances even fatal[4]. In a small number of patients, it can lead to prolonged hospitalizations, anatomical complications such as bile duct or duodenal obstruction, pseudoaneurysms, and psuedocysts, as well as a significant financial burden to hospitals[7].

The changeover of medical trainees at the beginning of the academic year has been shown in a variety of settings to negatively impact the quality of patient care, an observation referred to as the "July effect"[8-10]. Although results have been substantially variable across studies addressing the July effect, most large and high-quality studies find a relatively small but statistically significant increase in mortality at the start of the academic year across multiple medical conditions[10-14]. Furthermore, numerous studies have demonstrated decreased efficiency in healthcare delivery during turnover months in teaching hospitals as demonstrated by increased length of hospital stay (LOS) and increased mean total hospitalization charges[15-19].

At teaching institutions, ERCP involves the participation of advanced endoscopy fellows who are trainees with minimal experience with this procedure, especially at the commencement of the academic year. These fellows are expected to gradually gain mastery and independence in performing ERCP. This learning curve is particularly relevant since several studies have shown that a number of endoscopic technique-related factors predict the occurrence of PEP. For example, papillary trauma induced by multiple attempts at cannulation was reported to be an independent risk factor for development of this complication in a large, prospective, multicenter study[20]. Furthermore, multiple pancreatic injections and pancreatic duct instrumentation have also been identified as factors that independently increase the risk of PEP[21].

These findings support the fact that physician technique, expertise, and experience may play a role in the occurrence of PEP. Consequently, outcomes may vary based on the time of year during which the procedure is performed. Specifically, the incidence of PEP may decrease at the end of the academic year when the advanced endoscopy fellows are more seasoned and possess enhanced procedural skills.

Large national databases are ideal resources for

addressing such clinical questions because they contain sufficient data to overcome participation and reporting biases, and the results are readily generalizable. We used the National Inpatient Sample (NIS), the largest publically available all-payer inpatient database in the United States. The primary aim of the current study is to assess incidence of PEP among hospitalized patients in the early (July/August/September) *vs* the late (April/May/June) academic year. Secondary aims assess in-hospital mortality, length of stay (LOS), and total hospitalization charges between these time periods.

MATERIALS AND METHODS

Data source

This was a retrospective cohort study using the 2012 National Inpatient Sample (NIS) database. This database was created and is maintained by the Agency for Healthcare Research and Quality. It is the largest publically available all-payer inpatient database in the United States. The NIS is designed as a stratified probability sample to be representative of all non-federal acute care inpatient hospitalizations in the United States. Briefly, hospitals are stratified according to ownership/control, bed size, teaching status, urban/rural location, and geographic region. A random 20% sample of all discharges from all participating hospitals within each stratum is then collected and information about patients' demographics, diagnoses, resource utilization including length of hospital stay, procedures and total hospitalization charges are entered into the NIS. Each discharge is then weighted (weight is equal to the total number of discharges from all acute care hospital in the United States divided by the number of discharges included in the 20% sample) to make the NIS nationally representative. In 2012, the NIS included 7296968 discharges from 4378 hospitals in 44 states.

The NIS contains both patient and hospital level information. Up to 25 discharge diagnoses and 15 procedures are collected on each patient using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9 CM) coding system. The NIS has been used to provide reliable estimates of the burden of gastrointestinal diseases[22,23].

Study sample

Patients were included in the study if they had an ICD-9 CM procedure codes for ERCP. Patients were excluded from the study if they had an ICD-9 CM code for a principal diagnosis of acute pancreatitis, if the ERCP was performed before or on the day of admission or if they were admitted to non-teaching hospitals. Post-ERCP pancreatitis was defined as an ICD-9 CM code for a secondary diagnosis of acute pancreatitis in patients who received an ERCP as delineated above. ERCPs performed during the months of July, August and September was compared to those performed in April, May and June in academic hospitals.

Study variables

Admission month, vital status at discharge, length of hospital stay and total hospitalization charges are directly provided in the NIS for each hospitalization. Patient demographics collected are: Age (assessed as a continuous variable), sex, race (Caucasian, African American, Hispanic, Asian or Pacific Islander, native American and other), median income in the patient's zip code (Quartile 1: $1-$38999; Quartile 2: $39000-$47999; Quartile 3: $48000-$63999; quartile 4: $64000+), primary insurance (Medicare, Medicaid, private insurance and uninsured), comorbidities measured by Charlson comorbidity index (categorized as 0, 1 to 2, or greater than 2), hospital location (rural *vs* urban), region (Northeast, Midwest, West, or South), teaching status, and size (small, medium or large). Patients' demographics were directly provided in the NIS except for Charlson comorbidity index which was calculated for each patient using the Deyo adaptation of the Charlson comorbidity Index for administrative data[24].

Outcomes

The primary outcome was incidence of post-ERCP pancreatitis. Secondary outcomes were: All cause in-hospital mortality, length of hospital stay (LOS) and total hospitalization charges for patients who developed PEP.

Statistical analysis

Proportions were compared using Fisher's exact test and continuous variables were compared using Student's *t*-test (under the assumption of the Central Limit Theorem). Confounders were adjusted for using multivariable regression models. Linear regression was used for continuous outcomes and logistic regression was used for binary outcomes. Each model was constructed by including all variables that were statistically significantly associated with the outcome on univariate analysis with a cutoff *P*-value of 0.2. In addition, variables that were considered clinically important predictors of the outcome based on prior studies' findings were included in the models irrespective of the *P*-value on univariate analysis. Patients with missing information on any of the variables included in the regression analyses were excluded.

All analyses were performed using STATA version 13 (STATACorpLP, College Station, TX, United States). Survey (svy) commands were used to account for the stratified sampling design of the NIS. A two tailed *P*-value of 0.05 was chosen as the threshold for significance for all tests.

The statistical methods of this study were reviewed by Marwan Abougergi from Catalyst Medical Consulting.

RESULTS

Patient characteristics

Figure 1 shows the flow diagram for study inclusion. From the 36480032 hospitalizations in 2012 in the
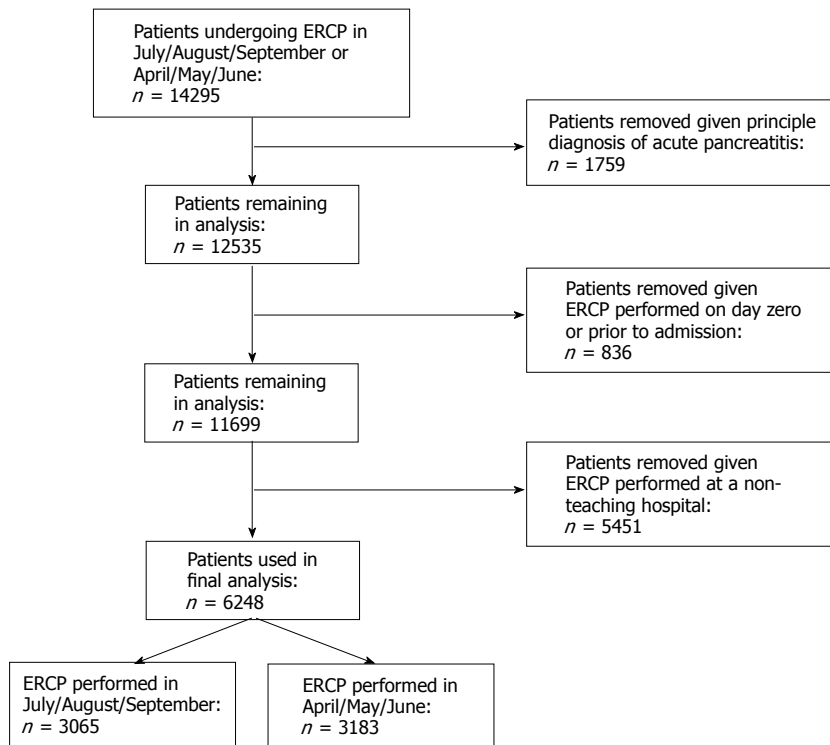
Figure 1 Flow diagram demonstrating selection of patients. ERCP: Endoscopic retrograde cholangio-pancreatography.

United States, 6248 were included in the study (3065 in July/August/September and 3183 in April/May/June) in the 2012 academic year. Patient's characteristics are presented in Table 1. Compared with patients admitted in July/August/September, patients admitted in April/May/June had no statistical difference in all variables including mean age, percent female, Charleston co-morbidity index, race, median income, and hospital characteristics including region, bed size, and location.

Incidence of post-ERCP pancreatitis based on time during academic year
The overall post-ERCP pancreatitis incidence was 12.9%. Table 2 shows the post-ERCP pancreatitis incidence based on time of the academic year, as well as the adjusted odds ratio of PEP. Compared with patients admitted in July/August/September, patients admitted in April/May/June had similar odds of developing PEP after adjusting for confounders (adjusted OR = 1.03, 95%CI: 0.71-1.51; *P* = 0.41).

Mortality following post-ERCP pancreatitis based on time during academic year
The overall mortality rate following PEP was 19/801 = 2.37%. Table 3 shows the mortality rate following post-ERCP pancreatitis based on time of the academic year along with the mortality adjusted odds ratio. The adjusted odds of mortality following PEP was similar in in April/May/June compared with July/August/September (adjusted OR = 33.2, 95%CI: 0.55-1980.7; *P* = 0.09).

Length of hospital stay following post-ERCP pancreatitis based on time during academic year
Following PEP, the overall LOS was 10.48 d. The mean adjusted LOS following post-ERCP pancreatitis based on time of the academic year along with the mean additional LOS for patients admitted in July/August/September compared with April/May/June are shown in Table 4. The adjusted mean LOS following PEP was similar in July/August/September compared with April/May/June, with an adjusted mean difference of 2.04 d, 95%CI: -0.76 to 4.84; *P* = 0.15.

Total hospitalization charges for post-ERCP pancreatitis based on time of time academic year
The mean adjusted total hospitalization charges for patients who developed PEP was $101218. The mean total hospitalization charges among patients who developed PEP in July/August/September and April/May/June are shown in Table 4. The adjusted mean total hospitalization charges were similar in July/August/September compared with April/May/June: $20990, 95%CI: -563210 to 1434; *P* = 0.24.

DISCUSSION
This large nationwide study found no difference in incidence of post-ERCP pancreatitis following in-hospital ERCP at academic institutions over the course of the academic year. To our knowledge, this study is the first to address the presence, or lack thereof, of a July effect in the incidence and treatment of post-ERCP pancreatitis following in-hospital ERCP. It is also among the few studies that measures the PEP incidence rate after in-hospital ERCP. Our findings suggest that close supervision by attending endoscopists in the academic inpatient setting mitigates potential risks incurred by novice advanced endoscopy fellows, as evidenced by

Table 1 Baseline characteristics of patients included *n* (%)		
Variable	**July/August/ September**	**April/May/ June**
Total number of ERCPs	3065	3183
Post-ERCP pancreatitis	404 (13.2)	402 (12.6)
Age (mean ± SD)	58.9 ± 0.8	59.5 ± 0.9
Female	1672 (54.6)	1617 (50.8)
Charleston Comorbidity Score		
0	190 (6)	131 (4)
1-2	490 (16)	550 (17)
> 2	2385 (78)	2503 (79)
Race		
Caucasian	1834 (64)	1967 (66)
African American	395 (14)	441 (15)
Hispanic	411 (14)	311 (11)
Asian or Pacific Islander	123 (4)	96 (3)
Native American	15 (1)	23 (1)
Other	98 (3)	130 (4)
Median income ($) in zip code		
1-38999	836 (28)	865 (28)
39000-47999	636 (22)	688 (22)
48000-63999	726 (24)	845 (27)
64000+	819 (27)	732 (23)
Hospital region		
Northeast	791.8 (26)	819.5 (26)
Midwest	679.2 (22)	918.1 (29)
South	997.6 (33)	925.5 (29)
West	596.9 (19)	520.4 (16)
Hospital bed size		
Small	293.2 (10)	343.3 (10)
Medium	680.2 (22)	728 (23)
Large	2092 (68)	2112 (67)
Hospital location		
Rural	43.2 (1)	20.4 (1)
Urban	3022 (99)	3163 (99)

ERCP: Endoscopic retrograde cholangiopancreatography.

Table 2 Incidence and incidence rates of patients who develop post-endoscopic retrograde cholangiopancreatography pancreatitis in the early *vs* late academic year				
		Incidence *n* (%)	**Adjusted OR (95%CI)**	**P value**
July/August/ September	ERCPs performed	3065	1.03 (0.71-1.51)	0.415
	Post-ERCP Pancreatitis rates	404 (13.2)		
April/May/ June	ERCPs performed	3183		
	Post-ERCP Pancreatitis rates	402 (12.6)		

ERCP: Endoscopic retrograde cholangiopancreatography.

Table 3 Mortality rate in patients who develop post-endoscopic retrograde cholangiopancreatography pancreatitis in the early academic year compared to the late academic year				
	Mortality		**Adjusted OR (95%CI)**	**P value**
	n/total	**%**		
July/August/September	5/404	1.24	33.2	0.092
April/May/June	14/402	3.48	(0.55-1980.7)	

Table 4 Length of stay and total hospitalization charges in patients who develop post-endoscopic retrograde cholangiopancreatography pancreatitis in the early academic year compared to the late academic year				
	Length of stay		**Total charges**	
	Mean (95%CI) (d)	**P value**	**Mean (95%CI) ($)**	**P value**
July/August/ September	10.6 (8.5-12.7)	0.91	101904 (78785-125023)	0.938
April/May/ June	10.4 (8.2-12.6)		100519 (70214-130824)	

similar PEP adjusted incidence across the academic year.

Whether these results are also true for PEP following outpatient ERCP is still controversial. Several smaller previous studies have sought to determine whether a difference in outcomes exists between ERCP that involves trainees and those that do not, and results have been inconsistent. The study by Freeman et al was among the first prospective studies investigating trainee participation in ERCP. Specifically, the authors measured the complications that occurred within 30 d of endoscopic biliary sphincterotomy in consecutive patients treated at 17 institutions over a two year period[20]. The study failed to show an increased risk of adverse events including pancreatitis due the presence of a trainee. Subsequently, Rabenstein *et al*[25] sought to analyze the risk factors associated with complications of endoscopic sphincterotomy in a series of 436 consecutive patients. While several independent risk factors for the development of PEP were identified, trainee involvement did not significantly affect the outcome. However, more recently, Cheng *et al*[26] found that trainee involvement did increase the risk of PEP, and was attributed to a variety of procedural-related factors

including traumatic cannulation, prolonging a difficult cannulation, and delivering excess electrosurgical current during sphincterotomy.

Our data suggest that the overall efficiency of the hospital, similar to mortality rate, does not seem to exhibit a temporal effect. LOS and total hospital charge were not significantly increased at the beginning of the academic year, suggesting no effect on adeptness during turnover months at teaching hospitals. It is important to note that, since the number of patients who died following PEP was very low, the lack of difference in mortality at the beginning and the end of the academic year could be either due to a beta error or a true lack of difference. Case-control studies or cohort studies combining patients from the NIS over several years could help distinguish between these two possibilities. However, combining patients over several years has its own limitations, including the inherent necessity to adopt the assumption that time is not a

significant confounder in the relationship between PEP and mortality.

Several previous studies have examined length of hospital stay and hospitalization charge for a broad range of admission diagnosis as a marker for the July effect, and conflicting conclusions have been reached. In one multicenter retrospective study, LOS in the intensive care unit was examined and, after adjusting for illness severity, no differences in LOS were found between early and late academic year[15]. Similarly, a single center study analyzing hospital LOS and ancillary charges in over 2700 patients admitted for any condition over a two year period found no evidence of a temporal effect[27]. In contrast, a study in a single institution over seven years demonstrated a significant and steady decline in both total hospital charge and LOS for a variety of diagnoses over the academic year[16]. For each additional month of house staff experience, total charges declined by approximately 0.94% in total charges, or about 11% during a one-year period. Furthermore, for each additional month of house staff experience, there was a 0.036-d decline in length of hospital stay, leading to a 0.43-d reduction during a one-year period.

Inexperienced fellow involvement in ERCP proce-dures has clear implications for patient outcomes, with the potential to lead to increased complications and higher medical expenditures. Our results, however, do not suggest that this is the case. We have demonstrated the lack of existence of a July effect. Novice fellow participation in these procedures at the beginning of the academic year does not seem to be associated with worse patient outcomes or increased charges compared to late academic year, when trainees have substantially more procedural experience. To clarify, these results do not suggest that novice endoscopists can safely perform ERCP in an unsupervised setting. However, the results of this study show that our current training method allows for the safe development of ERCP skills in a clinical setting, with close supervision from expert endoscopists.

Our study has several strengths. NIS is one of the largest medical databases in the United States, which allows for the analysis of health care practice patterns at the national level. Selection and participation biases, as well as regional variations in healthcare delivery and medical practice which commonly limit smaller studies, are minimized given that the sample is taken from a broad range of patient demographics and hospital characteristics from almost every state. Furthermore, the generalizability of the results to different hospitals and regions of the United States is tremendously en-hanced for the same reason.

There are also several limitations of our study. First, some academic institutions may not have gastro-enterology and/or advanced endoscopy fellowships, possibly diluting any effect that may be attributable to the involvement of a trainee. However, since caring for patients with PEP is a multi-disciplinary approach,

this fact should not have had a major impact on our outcomes, with the possible exception being PEP incidence. Second, there is no ICD-9 CM code specific for PEP pancreatitis. The definition we adopted (secondary diagnosis of pancreatitis for admissions during which ERCP was performed) could potentially include patients who had ERCP because of acute pancreatitis. However, we minimized this possibility by excluding patients who had a principal diagnosis of acute pancreatitis and limiting the inclusion to patients who had ERCP on day 1 of admission. Third, the severity of PEP is difficult to ascertain using ICD-9 codes, which lead us to restrict treatment outcomes to mortality only. Fourth, despite controlling for confounders and hospital characteristics, residual confounding is an inherent limitations to all retrospective studies where randomization is impossible. Fifth, while these results are compelling given the number of patients included in this database, we are unable to assess whether differences in technique affected PEP rates in this study. The NIS database does not allow the ability to control for factors that may affect the incidence of PEP but do not have a discrete ICD-9 code including inadvertent cannulation of the pancreatic duct, time until successful cannulation, use of sphincterotomy, degree of supervision by attending physician, and so on. Additionally, the database does not reveal the number of ERCPs performed for biliary *vs* pancreatic indications. Finally, coding errors have been shown to exist in the NIS data[28]. However, such errors are theoretically randomly distributed among patients who had PEP early *vs* late in the academic year and therefore should not be a source of bias.

In conclusion, the safety of ERCP at academic ins-titutions is consistent over the course of the year, with no difference in incidence or mortality following post-ERCP pancreatitis. Similarly, outcomes of healthcare delivery in the treatment of PEP are also steady across the academic year, as evidenced by similar LOS and total hospital charges. Our results suggest that trainee level of experience does not impact clinical outcomes in patients undergoing ERCP. As we train the next generation of endoscopic proceduralists, efforts to continue graduated responsibility, while maintaining optimal patient outcomes, will remain a top priority in the field of therapeutic endoscopy.

COMMENTS

Background
Endoscopic retrograde cholangiopancreatography (ERCP) is frequently used for the diagnosis and management of many biliary and pancreatic diseases. Pancreatitis is the most common and serious complication of ERCP. At teaching institutions, ERCP involves the participation of advanced endoscopy fellows who are trainees with minimal experience with this procedure, especially at the commencement of the academic year. As the changeover of medical trainees at the beginning of the academic year has been shown in a variety of settings to negatively impact the quality of patient care, an observation referred to as the July effect, they sought to determine whether a July effect existed with ERCP.

Research frontiers
The authors sought to determine whether a "July effect" existed with ERCP in

academic hospitals.

Innovations and breakthroughs

This large nationwide study found no difference in incidence of post-ERCP pancreatitis following in-hospital ERCP at academic institutions over the course of the academic year. To the knowledge, this study is the first to address the presence, or lack thereof, of a July effect in the incidence and treatment of post-ERCP pancreatitis following in-hospital ERCP.

Applications

These findings suggest that close supervision by attending endoscopists in the academic inpatient setting mitigates potential risks incurred by novice advanced endoscopy fellows, as evidenced by similar PEP adjusted incidence across the academic year. These results do not suggest that novice endoscopists can safely perform ERCP in an unsupervised setting. However, the results of this study show that the current training method allows for the safe development of ERCP skills in a clinical setting, with close supervision from expert endoscopists.

Terminology

ERCP is frequently used for the diagnosis and management of many biliary and pancreatic diseases. Pancreatitis is the most common and serious complication of ERCP, accounting for more than half of all complications following this procedure. This is referred to as post-ERCP pancreatitis (PEP).

Peer-review

This is a valuable paper, objectively reflects the incidence of PEP, and reveals no relationship with the beginner.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Efficacy of a newly developed dilator for endoscopic ultrasound-guided biliary drainage

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Abstract

AIM

To evaluate the efficacy of a newly developed dilator for endoscopic ultrasound (EUS)-guided drainage (ES Dilator).

METHODS

Fourteen consecutive patients who had undergone EUS-guided choledochoduodenostomy (EUS-CDS) with the ES Dilator were identified from a prospectively maintained database and enrolled in the study group. Fourteen other patients who had undergone EUS-CDS without the dilator just prior to its introduction were analyzed as the control group. A historical cohort study was carried out comparing the two groups. The main outcome measurement was the procedure time. The technical success rate and early AE rate were also compared between the two groups.

RESULTS

There were no significant differences in age, sex and etiology of biliary obstruction. The utilization rate of a plastic stent was higher in the control group (36% *vs* 0%). The technical success rate was 100% in both groups. The mean procedure time was significantly shorter in the study group than in the control group (27 ± 7 min *vs* 44 ± 26 min, $P = 0.026$). Additionally, there were no patients who required more than 40 min for the procedure in the study group. Early adverse events occurred in 29% (4/14) of the control group whereas none in the study group. The adverse events in all 4 patients was bile peritonitis, including pan-peritonitis in one patient. All patients

recovered with conservative treatment by medication.

CONCLUSION
The newly developed dilator was found to be useful for shortening procedure time and would prevent adverse events related to bile leakage in EUS-CDS.

Key words: Endoscopic ultrasound; Dilation; Adverse event; ES Dilator; Cautery

Core tip: The newly developed dilator (ES Dilator®) was useful for shortening procedure time and would prevent adverse events related to bile leakage in endoscopic ultrasound-guided choledochoduodenostomy.

INTRODUCTION

Endoscopic ultrasound (EUS)-guided biliary drainage (EUS-BD) is a challenging palliative treatment for biliary obstruction in patients who have unsuccessfully undergone transpapillary stenting[1]. Despite its difficulty, the technical success rate of this procedure is over 90% according to reports from high volume centers, which seems sufficiently high and acceptable[2-4]. When EUS-BD has been successfully accomplished, biliary decompression is achieved in most patients[2,5,6]. Moreover, the patency of the deployed stent is expected to be reasonably long[2,5,6].

EUS-BD can cause some adverse events (AEs) induced by bile leakage. Although bile always leaks in varying degrees in EUS-BD, a lesser amount of bile leakage may result in fewer AEs, including peritonitis and biloma formation.

Bile leakage occurs between puncture of the bile duct and stent deployment at the puncture tract, and thus shortening of the procedure time between puncture and stenting would contribute to less bile leakage. One of the most important factors resulting in longer procedure time is the difficulty of dilation of the puncture tract. When the dilation is unimpededly achieved, EUS-BD would be smoothly performed in many cases.

Recently, a new dilator for smooth dilation of the puncture tract has been developed. In this study, the efficacy of this dilator in EUS-guided choledochoduodenostomy (EUS-CDS) was evaluated.

MATERIALS AND METHODS

Patients
Fourteen consecutive patients who had undergone EUS-CDS utilizing the new dilator for malignant biliary obstruction at Sendai City Medical Center (Sendai, Japan) between November 2012 and January 2016 were identified from a prospectively maintained database and enrolled in the study group. Fourteen other consecutive patients who had undergone EUS-CDS without the dilator just prior to its introduction between February 2010 and October 2012 were analyzed as a control group. This retrospective study was conducted after approval by the Sendai City Medical Center Institutional Review Board. The ID issued by UMIN was 000020772.

Dilator
The newly developed dilator, ES Dilator® (Zeon Medical Co., Tokyo, Japan), 7 French (Fr) in diameter, is characterized by high pushability and a lesser difference in diameters of the inner lumen and the guidewire (Figure 1). It has two types of internal diameter tailored to accommodate 0.025-inch and 0.035-inch guidewires. The ES Dilator was utilized in all patients after its use was commenced in November 2012. It is commercially available in Japan.

Procedures
With a linear echoendoscope (UC240P or UCT260, Olympus Medical Systems Co., Tokyo, Japan), the extrahepatic bile duct was punctured from the duodenum by a 19-gauge needle for endosonography-guided fine needle aspiration (EUS-FNA) (EchoTip, Cook Co. Bloomington, Indiana; or Expect, Boston Scientific, Natick, Massachusetts). After contrast medium had been injected into the bile duct, a guidewire was advanced to the hilar side. After the puncture tract was dilated along the guidewire, a stent was finally placed at the puncture site (Figure 2).

Prior to the availability of the ES Dilator in November 2012, dilation was performed with a 5- to 7-French tapered catheter, including a Soehendra dilator (Boston Scientific), and a 4-mm balloon dilator. After November 2012, insertion of the ES Dilator was initially attempted in all patients in the study group. When dilation was not achieved with these catheters, a cautery dilator was utilized.

Procedures were performed by one of 6 expert endoscopists who had experience performing 10 or more EUS-guided drainage procedures as an operator or assistant. All of them had also experienced more than 1000 endoscopic retrograde cholangiopancreatography (ERCP) procedures and 1000 EUS examinations as an operator.

Study design
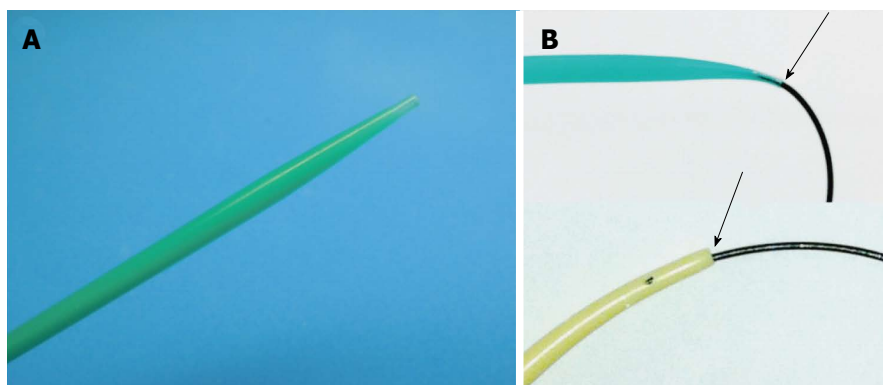A historical cohort study was carried out, the population

Figure 1 Newly developed dilator, ES Dilator® (Zeon Medical Co., Tokyo, Japan), characterized by high pushability and lesser difference in diameters of the inner lumen and the guidewire. A: Tip of the ES Dilator; B: The ES Dilator has a lesser difference between the diameter of the inner lumen and that of the guidewire (upper figure), compared with traditional tapered catheters for ERCP (lower figure). ES Dilator: Endoscopic ultrasound-guided drainage; ERCP: Endoscopic retrograde cholangiopancreatography.

Figure 2 Technique of endoscopic ultrasound-guided choledochoduodenostomy. A: The extrahepatic bile duct is punctured by a 19-gauge needle under EUS guidance; B: After contrast medium is injected, a guidewire is inserted; C: The puncture tract is dilated with a tapered catheter, a balloon dilator, and/or ES Dilator; D and E; A plastic stent (D) or a metal stent is deployed at the puncture site (E). EUS: Endoscopic ultrasound.

being divided into a control group consisting of 14 patients who received the intervention without use of the ES Dilator and a study group of 14 patients in whom the dilator was used.

Procedure time was defined as the main outcome measure. The technical success rate and early AE rate were also compared between the two groups.

Early AEs investigated included bile peritonitis, biloma formation, hemorrhage requiring endoscopic/radiological/surgical intervention or blood transfusion, stent dislocation within 7 d, and procedure-related death. Bile peritonitis was defined as a state with abdominal tenderness accompanied by peritoneal symptoms which

appeared within 24 h after the intervention.

Statistical analysis

Student's *t*-test was used for continuous data comparison. Fisher's exact probability test and χ^2 test were used for comparison of categorical data. A *P*-value of < 0.05 was considered to be significant. For analyses, SPSS software (ver.11, SPSS, Chicago, IL, United States) was used.

RESULTS

The patient characteristics of the two groups are shown

Table 1 Patient characteristics and deployed stents

	Study group (*n* = 14)	Control group (*n* = 14)	*P* value
Age (yr), mean ± SD	74.6 ± 16.1	73.5 ± 9.3	0.82
Sex (male:female)	9:5	8:6	1.00
Etiology			0.28
Pancreatic cancer	8	12	
Biliary cancer	3	1	
Duodenal cancer	2	0	
Metastatic lymph nodes	1	1	
Deployed stent			0.041
Plastic stent	0	5	
Metal stent	14	9	

Table 2 Procedure time

	Study group (*n* = 14)	Control group (*n* = 14)	*P* value
Procedure time (min), mean ± SD	44 ± 26	27 ± 7	0.026
≤ 20	3	1	
20-40	11	8	
40-60	0	2	
> 60	0	3	

Table 3 Procedure-related complications

	Study group (*n* = 14)	Control group (*n* = 14)	*P* value
Overall	0	4 (29%)	NA
Localized peritonitis	0	3	
Pan-peritonitis	0	1	
Hemorrhage	0	0	
Death	0	0	

NA: Not applicable.

group whereas no AEs occurred in the study group (Table 3). The AE in all 4 patients was bile peritonitis, including pan-peritonitis in one patient. All patients recovered with conservative treatment by medication. The procedure time in the 4 patients who developed peritonitis was 39, 45, 67, and 95 min. Among these 4 patients, a metal stent was deployed in 2 and a plastic stent in 2. The patients whose intervention required a longer procedure time (95 min) with a metal stent had severe pan-peritonitis although it did not progress to death.

DISCUSSION

Many reports on EUS-guided drainage have been published at an accelerated pace in the past decade[1-4,7], and this procedure has rapidly superseded percutaneous biliary drainage as an alternative technique after failed ERCP[4,8]. Some studies have reported that EUS-BD has a similar level of efficacy and results in fewer adverse events in comparison with percutaneous drainage[9,10]. EUS-BD seems to be the palliative intervention of choice after failed ERCP in cases with malignant distal biliary obstruction[9,10].

Due to a lack of dedicated devices for EUS-guided drainage, various devices developed for other endoscopic interventions, including EUS-FNA and ERCP, have been applied. Dilation of the puncture tract in EUS-CDS has been performed with tapered catheters and balloon catheters developed for the purpose of aspiration of bile or pancreatic juice, dilation of a biliary stricture, or endoscopic papillary balloon dilation in ERCP. However, they are inadequate for advancement into the narrow tract made by a fine needle because of their deficiency of stiffness and the difference of diameter between the inner lumen of the device and the guidewire. The ES Dilator seems to have resolved these problems.

Cautery devices would also be better in dilation of the puncture tract. It remains unknown whether physical dilation or electric dilation is more appropriate because there have been no studies comparing them. Cautery devices have not been initially used at our institution because an unexpected huge hole might be formed by electric ablation[9]. However, such a device has been used initially in some institutions with a high success rate and low AE rate[3,10]. Although there is a retrospective study reporting that electric dilation by a needle knife was the risk factor for postprocedural AEs, it is doubtful that mere needle-knife utilization was

in Table 1. There were no significant differences in age, sex and etiology of biliary obstruction. The utilization rate of a plastic stent was higher in the control group. Plastic stents used in the control group were 7-Fr Flexima (Boston Scientific, Natick, Mass, United States). Metal stents, 10-mm covered Zeostents (a delivery system 8 Fr in diameter, Zeon Medical Co.) were used in all 9 patients of the control group and in 9 patients of the study group; 10-mm X-SuiteNIR stents (a delivery system approximately 7.5 Fr in diameter, Olympus Medical Systems Co.) were used in 3 patients of the study group; and 10-mm partially covered Niti-S stents (a delivery system approximately 8.5 Fr in diameter, TaeWoong Medical Co., Wolgot-myeon, South Korea) were used in 2 patients of the study group.

The technical success rate was 100% in both groups.

The procedure time was significantly shorter in the study group than in the control group (27 ± 7 min *vs* 44 ± 26 min, *P* = 0.026, Table 2). Additionally, there were no patients who required more than 40 min for the procedure in the study group.

Because neither a 5-French tapered catheter nor a balloon catheter could pass through the puncture tract, a cautery catheter was used in only one patient (7%) in the control group. In the study group, the ES Dilator passed through the puncture site on the first attempt and a cautery dilator was not used in any of the patients.

The mean procedure time in the patients who received metal stent placement in the control group was 38 ± 23 min. In comparison with the study group, it was also found to be shorter although the difference was not statistically significant (*P* = 0.18).

Early AEs occurred in 29% (4/14) in the control

actually related to AEs because it was used only when insertion of a 6-Fr tapered catheter failed[2].

Whereas the ES Dilator shortens procedure time in EUS-CDS, such shortening would be uncertain in EUS-guided hepaticogastrostomy (EUS-HGS). EUS-HGS is considered to include other various factors relevant to longer procedure time, *i.e.*, difficulty in puncture of an appropriate hepatic duct, difficulty in guidewire insertion into the hilar side, and an inexpedient increase of the distance between the liver and the gastric wall which move apart from each other when a metal stent is advanced. Moreover, dilation of the puncture tract is often easier because of less mobility of the intrahepatic bile duct in EUS-HGS, whereas the extrahepatic bile duct can move and separate from the gastrointestinal wall in EUS-CDS. In addition, although the liver parenchyma always intervenes in the puncture tract and prevents bile leakage in EUS-HGS as in the case of percutaneous transhepatic gallbladder/biliary drainage, there is little intervening tissue in EUS-CDS, resulting in the likelihood of bile leakage. Thus, prevention of bile leakage is considered to be more essentially important in EUS-CDS than in EUS-HGS. Therefore, especially in EUS-CDS, the ES Dilator is considered to have a favorable effect, and thus this study was limited to EUS-CDS.

The ES Dilator, unfortunately, has an extremely low visibility of the fluoroscopic image. Although it did not seem to affect the procedural success rate and the adverse events rate, it would need to be improved.

The type of deployed stent can affect the procedural outcomes. Although covered metal stents are more difficult to advance through the narrow tract than plastic stents, the procedure time was significantly shorter in the study group in which all the patients underwent intervention with a covered metal stent. Additional dilation after dilation with the 7-Fr ES Dilator was unnecessary in all patients of the study group, indicating that the most important factor related to successful EUS-CDS is dilation just up to 7-Fr, not up to the diameter of the stent which is to be inserted. On the other hand, covered metal stents could limit bile leakage after stent deployment. It is also worth noting that the 2 patients among 4 who had peritonitis in the control group received intervention with a metal stent. Metal stents are not always advantageous in preventing bile peritonitis.

This study has some limitations, namely, it was a retrospective investigation with a small population. Additionally, the proficiency level of the endoscopist may have been associated with the shorter procedure time. Despite these limitations, the present data appear to be of value because this study was carried out at a referral center which had experienced more than 30 cases of successful EUS-guided drainage before the study period. It seems to be less valuable to prospectively carry out large population studies for evaluation of a mere dilator in a field which has been rapidly evolving regardless of the low number of such patients.

In conclusion, the newly developed ES Dilator which was dedicated to EUS-BD was found to be useful for shortening procedure time and may prevent AEs relevant to bile leakage in EUS-CDS.

ACKNOWLEDGMENTS

COMMENTS

Background
Endoscopic ultrasound (EUS)-guided biliary drainage is now an alternative option when transpapillary drainage has failed. Due to the lack of dedicated devices for use in such cases, dilation of the punctured tract is often difficult, resulting in longer procedure time and adverse events.

Research frontiers
Many new devices have been developing for EUS-guided drainage.

Innovations and breakthroughs
The newly developed dilator characterized by high pushability and a lesser difference in diameter tailored to accommodate 0.025-inch and 0.035-inch guidewires has become available.

Applications
The dilator was found to be useful.

Peer-review
The authors reported a novel dilator for the use of EUS-guided choledochoduodenostomy (EUS-CDS). In this paper the authors retrospectively compare the incidence of complications in patients who palliatively underwent EUS-CDS with/without ES Dilator.

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ORIGINAL ARTICLE

Retrospective Study

Use of shape-from-shading to characterize mucosal topography in celiac disease videocapsule images

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Abstract

AIM

To use a computerized shape-from-shading technique to characterize the topography of the small intestinal mucosa.

METHODS

Videoclips comprised of 100-200 images each were obtained from the distal duodenum in 8 celiac and 8 control patients. Images with high texture were selected from each videoclip and projected from two to three dimensions by using grayscale pixel brightness as the Z-axis spatial variable. The resulting images for celiac patients were then ordered using the Marsh score to estimate the degree of villous atrophy, and compared with control data.

RESULTS

Topographic changes in celiac patient three-dimensional constructs were often more variable as compared to controls. The mean absolute derivative in elevation was 2.34 ± 0.35 brightness units for celiacs *vs* 1.95 ± 0.28 for controls ($P = 0.014$). The standard deviation of the derivative in elevation was 4.87 ± 0.35 brightness units for celiacs *vs* 4.47 ± 0.36 for controls ($P = 0.023$). Celiac patients with Marsh ⅢC villous atrophy tended to have the largest topographic changes. Plotted in two dimensions, celiac data could be separated from controls with 80% sensitivity and specificity.

CONCLUSION

Use of shape-from-shading to construct three-dimensional projections approximating the actual spatial geometry of the small intestinal substrate is useful to observe features not readily apparent in two-dimensional videocapsule images. This method represents a potentially helpful

adjunct to detect areas of pathology during videocapsule analysis.

Key words: Celiac disease; Duodenum; Shape-from-shading; Small intestine; Videocapsule

Core tip: Videocapsule images can assist in determining the presence and status of celiac disease; however, pathology is not always apparent by visual inspection. A computerized shape-from-shading technique was used to characterize the topography of the small intestinal mucosa. It was hypothesized that the automated measure would be helpful to distinguish celiac from control images and to gauge the degree of villous atrophy in the celiac patient data.

INTRODUCTION

Celiac disease is prevalent throughout the world and affects approximately 1% of the population[1]. Patients with celiac disease are reactive to the protein gluten, which is present in wheat, rye, and barley grains[2]. Currently, the only treatment is a lifelong gluten-free diet[3]. It is a disease with often occult symptoms that differ from one individual to the next[4]. Diagnosis of celiac disease is difficult owing to the fact that symptoms are highly varied from one individual to another, both in their type and severity. In some patients with celiac disease, no symptoms may be evident[5]. Diagnosis is made by a positive antibody test, which is followed by biopsy of the abnormal appearing mucosa and confirmation of atrophy by light microscopy[6]. Utilizing light microscopy, the small intestinal mucosa is evaluated for presence and degree of villous atrophy and an increase in intraepithelial lymphocytes. Mucosal alterations in celiac disease are assigned a Marsh score, which varies from 1 (normal villous architecture but increased intraepithelial lymphocytes) to ⅢA-C (severe degrees of villous atrophy accompanied by crypt hyperplasia and increased intraepithelial lymphocytes)[7].

Recent advances in imaging technology have enabled visualization of the small intestinal mucosa *via* a videocapsule to assess areas of villous atrophy[8]. This is convenient to use and is minimally invasive. Images are obtained at a rate of 2 per second or more. A light source within the capsule illuminates the mucosal surface. The videocapsule is swallowed, sends information by radio control, and then passes harmlessly through the gastrointestinal system[9]. Analysis of two-dimensional videocapsule endoscopy images by quantitative means can assist in determining areas of pathology in these patients.

A difficulty with the use of videocapsule technology, is that areas of pathology are not always clearly identifiable on review of the images[10]. The two-dimensional images provide a very limited perspective of the actual three-dimensional structure of the substrate when viewed retrospectively by the data analyst. The endoscopist who is performing the procedure, views these same images *via* an endoscopic system, and is similarly at a disadvantage for understanding the three-dimensional mucosal architecture. Hence, it can be difficult for both endoscopist and data analyst to determine the precise regions and boundaries of any abnormality that is present in the images. This renders the detection of regions of patchy villous atrophy, which are important to biopsy for confirmation that there is pathology, and therefore for diagnosis of the disease and to monitor treatment, difficult at best.

For improved analysis, it would be useful to provide additional information regarding the mucosal substrate throughout the small intestine[11,12]. If it were possible to estimate the three-dimensional architecture of this substrate, and render it visually, it could be useful for improved detection of the presence and severity of villous atrophy, to detect any changes in architecture that occur after onset of a gluten-free diet, as well as to understand the mechanisms by which the structure of the small intestinal mucosa is altered during untreated *vs* treated celiac disease. In prior quantitative studies, a method was introduced to estimate three-dimensional structure from two-dimensional endoscopic images[13,14]. This technique uses the principle of shape-from-shading. In the shape-from-shading process, as a first approximation, image brightness is linearly related to image depth. Thus a third spatial axis, the Z-axis, is obtained so that a map of the three-dimensional structure of the substrate can be constructed. In this study, the visual manifestations of three-dimensional image projection are shown for celiac patients with various levels of villous atrophy, *vs* controls. Special attention is paid to the types of structures that are evident in the projections, and their variation from one patient to the next, which can be helpful to detect the presence and severity of villous atrophy during the diagnosis of celiac disease, and to evaluate treatment efficacy. The purpose of the study is to show that visualization of the three-dimensional architecture can be useful to detect pathology in the small intestinal mucosa when the presence of patchy villous atrophy is suspected.

MATERIALS AND METHODS

A retrospective data series from 8 celiac patients and 8 controls were used for analysis. All patients were evaluated at the Columbia University Medical Center,

New York, NY using both standard and videocapsule endoscopy. Suspected celiac patients were diagnosed by the presence of villous atrophy in standard endoscopy images and improvement on follow-up endoscopy after onset of the gluten free diet. The indication for endoscopy in control patients included obscure bleeding, suspected Crohn's disease, and diarrhea. The study exclusion criteria were patients less than 18 years of age, pregnancy, history of intestinal obstruction, presence of a pacemaker, and chronic use of non-steroidal anti-inflammatory drugs. Only studies in which the videocapsule reached the cecum were included for analysis. All included patients, except one celiac patient with hemophilia, first underwent a standard endoscopic procedure with biopsy to determine the presence and severity of any villous atrophy in the proximal duodenum. The patients then underwent videocapsule endoscopy.

Videocapsule endoscopy images were acquired using the PillCam SB2 videocapsule (Given Imaging, Yoqneam, Israel). The device included a recorder unit and its container, battery pack, antenna, harness for the recorder unit, and a battery charger. The capsule dimensions were 26 mm × 11 mm, and the frame rate for acquisiton was two digital images per second (2/s). After a 12 h overnight fast, all subjects swallowed the PillCam SB2 videocapsule with 200 cc water and 80 mg of simethicone. Subjects were permitted to drink water at 2 h following ingestion of the capsule, and to eat a small meal after 4 h. The data recorder was affixed to a belt worn by the patient, and received radio image signals transmitted by the videocapsule *via* an array sensor as it passed through the gastrointestinal tract. The videocapsule endoscopy images were recorded over an eight hours period. At the end of eight hours, the images were offloaded to a PC-type computer workstation. The videos were subsequently interpreted using Rapid5 software (Given Imaging, Yoqneam, Israel) by gastroenterologists, each with experience in reading many videocapsule endoscopies.

Videoclips of length 100-200 images (50-100 s at 2/s frame rate) were obtained from the distal duodenum in each patient and were deidentified prior to analysis. The use of patient data and the analysis protocols were approved by the Institutional Review Board of Columbia University Medical Center. The quantitative biopsy results obtained during standard endoscopy were used as a reference as to the presence and severity of villous atrophy.

An algorithm was developed to convert the two-dimensional endoscopic images from color to grayscale, and then to project to three dimensions using the shape-from-shading technique. The algorithm used in this study can be described as follows[13,14]: (1) at each pixel (x, y) location, extract the grayscale brightness level; (2) write brightness level b, which ranges from 0-255 (black to white), to file along with (x, y) location; (3) the format of the stored information is trivariate (x, y, b); (4) all (x, y, b) information for all image pixels (x, y), with the dimensions of the image being 576 × 576, are written to file; (5) display the file in map3d, a program which enables viewing of three-dimensional data objects from any perspective[15]; (6) separately, store the trivariate information along with the brightness value, *i.e.*, as (x, y, b, b) where the fourth variable is used as a false color for enhanced display; and (7) organize the original two-dimensional endoscopic image, the three-dimensional projection, and the false-color three-dimensional image according to Marsh score pathology for the celiac patients, *vs* the control patients.

Once the data were displayed, special attention was given to the presence of certain three-dimensional structures that had been quantitatively modeled by syntactic means in prior work[13]. Specifically, the ch-aracteristics of mucosal protrusions present in the mucosa were assessed, highlighting differences in celiac patients with villous atrophy (Marsh ⅢA, ⅢB, or ⅢC score) and celiac patients with little or no evident villous atrophy (Marsh Ⅱ score) *vs* control patients lacking villous atrophy. The Marsh score was determined by the pathologist, who evaluated biopsy specimens for the presence of villous atrophy under light microscopy.

From the three-dimensional constructs, topographic variation was calculated using a computerized method. The first derivative of the elevation level of each image pixel, done row-by-row in an automated raster scan fashion, was determined. The mean absolute value of this derivative was used as one measure of topographic variation. The standard deviation of the absolute derivative was used as a second measure of topographic alteration. The mean and standard deviation of these parameters were calculated for celiac *vs* control image data, and the statistical significance of the difference was determined using the two-tailed *t*-test (SigmaPlot ver. 13, 2016, Systat Software Inc., San Jose, California). The parameter values were plotted, with celiac data labeled according to the Marsh score. The best linear discriminant function to separate celiac *vs* control data was determined, and the sensitivity and specificity for detecting pathology in celiacs, *vs* the lack of pathology in control patient images, were calculated.

RESULTS

The patient data used in the study are depicted in Tables 1 and 2. Information regarding the age, gender and Marsh score of small intestinal biopsies of celiac patients is shown in Table 1. Six of eight patients (75%) were female. The average age of all celiac patients was 45.8 ± 14.8. The Marsh score of patient 1, who had hemophilia, could not be determined precisely as a biopsy could not be obtained, but significant pathology was apparent from visual inspection of the endoscopic images. This patient was estimated to have Marsh Ⅲ C pathology. Analysis of biopsy results revealed there were two additional patients with Marsh score pathology of ⅢC, one with ⅢB, two with ⅢA, and two with a Marsh score of Ⅱ. The control patient data is shown in

Table 1	Patient data - celiac		
Number	**Age**	**Gender**	**Marsh score**
1	19	M	NA
2	44	M	ⅢC
3	44	F	ⅢC
4	40	F	ⅢB
5	63	F	ⅢA
6	38	F	ⅢA
7	53	F	Ⅱ
8	65	F	Ⅱ

Patient 1 had hemophilia and had no biopsy, but was suspected to have a Marsh ⅢC level of villous atrophy. NA: Not applicable, *i.e.*, no biopsy was performed; M: Male; F: Female.

Table 2	Patient data-control		
Number	**Age**	**Gender**	**Marsh score**
1	31	F	Suspected Crohn's disease
2	36	M	Severe esophagitis
3	36	F	Peptic duodenitis
4	86	F	Obscure bleeding
5	26	F	Peptic duodenitis
6	87	M	Peptic duodenitis
7	55	M	Esophageal inflammation due to reflux
8	28	M	Suspected Crohn's disease

NA: Not applicable, *i.e.*, no biopsy was performed; M: Male; F: Female.

Table 2. There were four male and four female control patients, with an average age of 48.1 ± 25.3, similar to the average age of the celiac patients. Three of the control patients received the videocapsule because of abdominal pain presumed to be due to peptic duodenitis, two for suspected Crohn's disease, and one each for inflammation of the esophagus due to reflux, severe esophagitis, and obscure bleeding. None of the control patients had any evidence of villous atrophy on biopsy.

Examples of image processing results are shown in Figures 1 and 2 for celiac patient images (Patients 1 and 2), each from a region of the distal duodenum with high apparent texture and pathology. The data from two patients is shown in each image. In Figure 1 are shown images from a patient with Marsh ⅢC pathology score, and from the patient with hemophilia, who has similar apparent severe pathology and likely Marsh ⅢC score. The two-dimensional endoscopic image is to the left for each patient data. There are similar appearances in rough texture, and the images are thought to have been acquired from regions with villous atrophy. Some scalloping of the mucosal folds is apparent in the celiac patient with Marsh ⅢC score at lower left in the image, for example at the fold noted by the asterisk. The three-dimensional projection using shape-from-shading is provided at center. Large protrusions are evident throughout each three-dimensional construction. For perspective, the same location noted by an asterisk in the left panel is shown in the center panel for patient 2.

Depicted in the right-hand panel are smoothed three-dimensional projections with false color used to show depth. Again for perspective, the location of the scalloped area with asterisk is shown. The highest area in the false color three-dimensional image at right corresponds to the brightest area in the two-dimensional endoscopic image at left (triangular shaped ridge at upper center). Mucosal folds in the two-dimensional endoscopic images of both patients are readily identifiable as three-dimensional structures in the projection panels at center and right. The large fold at top in the two-dimensional endoscopic image of patient 1 is evident as a large mass of three-dimensional tissue structure in the projection image in the center and right-hand panels. Also evident in the three-dimensional images are some artifacts at the edges, which are due to the white lettering in the original endoscopic image prior to framing. These are left in the images to show orientation.

In Figure 2, data from celiac patients 3 and 4 are shown, with Marsh scores ⅢC and ⅢB, respectively. The distal duodenum of patient 3 has folds with marked scalloping, which are the curved structures at the edge of each mucosal fold (top panels). These folds are evident as very large and prominent three-dimensional structures in the projection images in the center and right panels. The bright horizontally-oriented ridge at center in the patient 3 endoscopic image at left is converted to a very prominent three-dimensional ridge in the center and right-hand panels. In the patient 4 data (Marsh ⅢB score) there is marked folding, with many large protrusions on each fold (center panel), similar to the visual appearance of patient 3 data (center panel).

Examples of control patient data are shown in Figures 3 and 4. For the control patients, protrusion features appear in the three-dimensional projection images in the center panels. However, the protrusions appear to be diminished and less connected to meandering ripples, as compared with the celiac patients with Marsh Ⅲ scores whose data are shown in Figures 1 and 2. The three-dimensional protrusion structures are sometimes markedly diminished or even completely absent over some areas of the projections for the control patient data (Figures 3 and 4).

Summary data for all patients are shown in Figure 5. On the abscissa is noted the standard deviation from the mean of the first derivative, while the ordinate axis gives the mean absolute first derivative. Celiac points (black) are labeled according to Marsh score. The patient data can be mostly separated based on the linear discriminant function (straight black line). Thus the sensitivity and specificity for classification are both 80%. The control patient data are mostly clustered together and the celiac patient data are mostly clustered together. Celiac patient data with Marsh ⅢC scores as labeled, are all clustered toward the top right in the graph, *i.e.*, they possess larger topographic variation

Figure 1 Celiac patient images. A-C: Patient 1; D-F: Patient 2; A, D: The grayscale endoscopic images; B, E: The three-dimensional projections; C, F: Projections in false color. Colors from blue to yellow, orange, and red represent areas with progressively greater amplitude along the Z-axis (vertical axis). Patient 1 did not have a biopsy obtained due to hemophilia but was thought to have a Marsh score ⅢC. Patient 2 also had a Marsh score ⅢC. Note the prominent protrusions evident in the three-dimensional projections of both patients, and the similar appearance of texture in the original two-dimensional endoscopic images.

Figure 2 Celiac patient images. A-C: Patient 3 (Marsh ⅢC score); D-F: Patient 4 (Marsh ⅢB pathology); A, D: The grayscale endoscopic images; B, E: The three-dimensional projections; C, F: Projections in false color. Colors from blue to yellow, orange, and red represent areas with progressively greater amplitude along the Z-axis (vertical axis). Again note the prominent protrusions evident in the three-dimensional projections of both patients, even though the appearance of texture is somewhat dissimilar in the original two-dimensional endoscopic images.

Figure 3 Control patient images. A-C: Patient 1 (no villous atrophy); D-F: Patient 2 (no villous atrophy); A, D: The grayscale endoscopic images; B, E: The three-dimensional projections; C, F: Projections in false color. Note the lack of prominent protrusions evident in the three-dimensional projections of both patients, even though there is a dissimilar appearance of texture in the original two-dimensional endoscopic images.

Figure 4 Control patient images. A-C: Patient 3 (no villous atrophy); D-F: Patient 4 (no villous atrophy); A, D: The grayscale endoscopic images; B, E: The three-dimensional projections; C, F: Projections in false color. Note the lack of prominent protrusions evident in the three-dimensional projections of both patients, even though there is a dissimilar appearance of texture in the original two-dimensional endoscopic images.

Figure 5 Scatterplot of celiac (black circles) *vs* control (open circles) patient topographic data. The ordinate scale gives the standard deviation of the derivative in elevation. The abscissa shows the absolute value of the derivative in elevation. A linear discriminant function mostly separates celiac *vs* control patient parameter values (black line). Based on the scatterplot, the topography of celiac three-dimensional constructs is typically greater than for controls.

based on both the absolute derivative and the standard deviation from the mean. The mean absolute derivative in elevation was 2.34 ± 0.35 brightness units for celiac images *vs* 1.95 ± 0.28 for controls ($P = 0.014$). The standard deviation of the derivative in elevation was 4.87 ± 0.35 brightness units for celiac images *vs* 4.47 ± 0.36 for controls ($P = 0.023$).

DISCUSSION

Comparison with prior work

The study findings and observations are in accord with prior scanning electron microscopy studies conducted by Michael Marsh[16], and our prior work showing that the protrusions, when modeled syntactically, tend to be taller in height for celiac patients as compared with controls[13,14]. The mean height of protrusions was previously found to be 3.10 ± 2.34 grayscale levels in celiac patients with villous atrophy *vs* 2.70 ± 0.43 grayscale levels for controls ($P < 0.001$). The prominence of the mucosal protrusions in celiac patients, particularly ⅢC patients, is evident in the three-dimensional constructs of Figures 1 and 2, and the resulting large variation in topography as measured *via* automated computerized means is evident in Figure 5. Large mucosal protrusions, when villous atrophy is present in celiacs, which likely corresponds to clumping of villi[13,14], translates to greater topographic variation (Figure 5). By comparison, control patient biopsies with normal villi tend to possess narrowed, smaller topographic structures (Figures 3 and 4) corresponding to individual villi, which reduces the overall degree of topographic change as compared with celiac patients with villous atrophy. In the false-color celiac images of Figures 1 and 2C, topographic structure often appears to include more high-elevation areas (combined red-orange false-color regions) as compared to controls (Figures 3 and 4), in agreement with the quantitative topographic results

presented in Figure 5 and in the summary statistics. The mechanism by which the prominent three-dimensional architectural alterations occur in the celiac patient small intestinal mucosa is an interesting topic for further research.

Three-dimensional printing

The three-dimensional projections shown in the center panels of Figures 1-4 only provide a single snapshot of the tissue structure. A 3D printer would be useful in this regard to provide additional perspective. By printing the structure in three dimensions, the observer could view it from any perspective. Three-dimensional tissue reconstruction of intestinal villi has been demonstrated previously[17]. This could potentially be helpful for improved understanding concerning the relationship of small intestinal architecture with other disease features in celiacs. It would also be useful to improve syntactic modeling of structure. Protrusions can be modeled as square objects[13,14]. Although not a strictly correct interpretation of structure, the syntax utilized is sufficiently accurate to detect most or all mucosal protrusions automatically, and to estimate the height and width of each. Using a 3D printer for guidance, it would be possible to improve modeling of the projection features, as well as the syntactic modeling of any other pathologic structures embedded in the mucosa. Structural characteristics could be incorporated into the algorithm for improved, automated detection and measurement of the quantitative tissue structural characteristics in suspected and actual celiac patients.

Other rendering methods

Use of endoscopy for patient diagnosis and intervention is based on image sequences that are acquired *via* a video-camera. Yet, the sequence of images lacks depth information. Recognition and evaluation of pathology therefore becomes more difficult. In this study, a straightforward method was described for rendering three-dimensional surfaces, which can be useful in real time during endoscopic procedures, as well as for retrospective analysis. More complex procedures for three-dimensional rendering of the mucosa include one that solves the structure-from-motion problem using parallax, *i.e.*, camera motion is estimated, and it is used to reconstruct the three-dimensional scene[18]. Another method is to use an optical fiber to act as a probe to transmit three-dimensional information regarding the internal landscape[19]. Volumetric images are obtained by using a spectrally encoded endoscopy system. The resulting images provide depth information, although the process would be slow to complete for all areas where villous atrophy is suspected, due to the need to direct the probe across small areas at a time. An advantage of syntactic and textural-based methods for videocapsule analysis is the speed of computation, which would be useful for real-time analysis[20,21]. These methods, like the calculation done in this study to generate Figure 5, are entirely automated, thus

eliminating observer bias.

Limitations

The method uses shape-from-shading as a linear function. Thus depth was as a first approximation, linearly dependent on brightness. However, this is not precisely correct, as the actual function will be nonlinear. Construction and update of the three-dimensional projections in real-time by computerized means could be done during the endoscopic procedure, but was not included in this study. Small intestinal pathology is patchy in celiac patients, thus the results obtained from analysis of selected videocapsule images may differ from histopathologic findings, as the sites chosen for biopsy do not correspond to the images and they only represent limited sampling of the mucosa. The series of patients used for celiac *vs* control cohorts, *n* = 8 each, should be increased for confirmation of the results. Use of a larger sample size in subsequent studies may assist in clarifying the specific clinical settings in which this methodology will be useful. The Marsh scoring of celiac patient data shown in Figure 5 is not entirely aligned with the magnitude of the x and y variables, perhaps suggesting that there is a lag between cellular-level phenomena and gross architectural structure.

COMMENTS

Background

Celiac disease is prevalent throughout the world and affects approximately 1% of the population. Patients with celiac disease are reactive to the protein gluten, which is present in wheat, rye, and barley grains. Currently, the only treatment is a lifelong gluten-free diet. It is a disease with often occult symptoms that differ from one individual to the next. Diagnosis of celiac disease is difficult owing to the fact that symptoms are highly varied from one individual to another, both in their type and severity. In some patients with celiac disease, no symptoms may be evident. Diagnosis is made by a positive antibody test, which is followed by biopsy of the abnormal appearing mucosa and confirmation of atrophy by light microscopy. Utilizing light microscopy, the small intestinal mucosa is evaluated for presence and degree of villous atrophy and an increase in intraepithelial lymphocytes. Mucosal alterations in celiac disease are assigned a Marsh score, which varies from 1 (normal villous architecture but increased intraepithelial lymphocytes) to ⅢA-C (severe degrees of villous atrophy accompanied by crypt hyperplasia and increased intraepithelial lymphocytes).

Research frontiers

Recent advances in imaging technology have enabled visualization of the small intestinal mucosa *via* a videocapsule to assess areas of villous atrophy, which is convenient to use and is minimally invasive. Analysis of two-dimensional videocapsule endoscopy images by quantitative means can assist in determining areas of pathology in these patients. A difficulty with the use of videocapsule technology, is that areas of pathology are not always clearly identifiable on review of the images. The two-dimensional images provide a very limited perspective of the actual three-dimensional structure of the substrate. It's difficult to determine the precise regions and boundaries of any abnormality that is present in the images. In prior quantitative studies, a method was introduced to estimate three-dimensional structure from two-dimensional endoscopic images, which uses the principle of shape-from-shading. As a first approximation, image brightness is linearly related to image depth. Thus a third spatial axis, the Z-axis, is obtained so that a map of the three-dimensional structure of the substrate can be constructed. The purpose of this study is to show that visualization of the three-dimensional architecture can be useful to detect pathology in the small intestinal mucosa when the presence of patchy villous atrophy is suspected.

Innovations and breakthroughs

In this study, the visual manifestations of three-dimensional image projection are shown for celiac patients with various levels of villous atrophy, *vs* controls. Special attention is paid to the types of structures that are evident in the projections, and their variation from one patient to the next, which can be helpful to detect the presence and severity of villous atrophy during the diagnosis of celiac disease, and to evaluate treatment efficacy.

Applications

This study showed that visualization of the three-dimensional architecture can be useful to detect pathology in the small intestinal mucosa when the presence of patchy villous atrophy is suspected.

Peer-review

This study shows an interesting new approach to be validated in a prospective way and bigger sample size in order to clarify the potential use in specific clinical situations of celiac patients.

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Retrospective Study

Use of volumetric laser endomicroscopy for dysplasia detection at the gastroesophageal junction and gastric cardia

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Abstract

AIM

To determine specific volumetric laser endomicroscopy (VLE) imaging features associated with neoplasia at the gastroesophageal junction (GEJ) and gastric cardia.

METHODS

During esophagogastroduodenoscopy for patients with known or suspected Barrett's esophagus, VLE was performed before biopsies were taken at endoscopists' discretion. The gastric cardia was examined on VLE scan from the GEJ (marked by top of gastric folds) to 1 cm distal from the GEJ. The NinePoints VLE console was used to analyze scan segments for characteristics previously found to correlate with normal or abnormal mucosa. Glands were counted individually. Imaging features identified on VLE scan were correlated with biopsy results from the GEJ and cardia region.

RESULTS

This study included 34 cases. Features characteristic of the gastric cardia (gastric rugae, gastric pit architecture, poor penetration) were observed in all (100%) scans. Loss of classic gastric pit architecture was common and there was no difference between those with neoplasia and without (100% *vs* 74%, *P* = NS). The abnormal VLE feature of irregular surface was more often seen in patients with neoplasia than those without (100% *vs* 18%, *P* < 0.0001), as was heterogeneous scattering (86% *vs* 41%, *P* < 0.005) and presence of anomalous glands (100% *vs* 59%, *P* < 0.05). The number of anomalous glands did not differ between individual histologic subgroups (ANOVA, *P* = NS).

CONCLUSION

The transition from esophagus to gastric cardia is reliably identified on VLE. Histologically abnormal cardia mucosa produces abnormal VLE features. Optical coherence tomography algorithms can be expanded for use at the GEJ/cardia.

Key words: Volumetric laser endomicroscopy; Cardia; Gastroesophageal junction; Barrett's; Optical coherence tomography; Neoplasia

Core tip: This is a retrospective study to explore volumetric laser endomicroscopy (VLE) imaging features associated with neoplasia at the gastroesophageal junction (GEJ) and gastric cardia. Histologically abnormal mucosa due to inflammation or neoplasia more often produces abnormal VLE imaging. Specifically, VLE imaging features of irregular surface, heterogeneous scattering and presence of anomalous glands were more often seen in cases of neoplasia than those without. The GEJ and gastric cardia can be difficult to assess endoscopically for dysplasia, and VLE imaging in this area can aid in a "red-flag" biopsy technique.

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INTRODUCTION

Barrett's esophagus (BE) has been well established as a precursor to esophageal adenocarcinoma (EAC)[1,2]. Management of patients diagnosed with BE includes surveillance endoscopy[3]. Using the Seattle protocol, targeted biopsies of visible lesions should be taken followed by 4-quadrant biopsies at 2 cm intervals along the length of the BE segment[4]. In cases of known dysplasia, the random 4-quadrant biopsies should be taken every 1 cm[3].

Though currently the standard of care, these techniques are subject to sampling error since random biopsies may miss areas of high-grade dysplasia (HGD) or intramucosal carcinoma (IMC)[5,6]. There has been increasing interest in evaluating advanced imaging modalities which may allow for better visualization of the entire upper GI mucosal surface and subsurface in order to increase diagnostic yield with targeted biopsies[7,8].

Optical coherence tomography (OCT) is an imaging technique that utilizes low-coherence interferometry to produce high resolution images of biologic tissue by measuring back-scatter light intensity from a near-infrared light source[9]. Recently, an OCT based technology called Fourier-domain OCT or volumetric laser endomicroscopy (VLE) is now commercially available and offers higher imaging speed and improved sensitivity as compared to traditional OCT[10]. The system allows for real time cross-sectional imaging of the esophagus and proximal stomach as an adjuvant to esophagogastroduodenoscopy (EGD). Surface and subsurface architecture such as mucosal layers, gastric pits, and gland morphology can be identified[11]. Several studies have analyzed the correlation between OCT images and histology from biopsy specimens. Specifically, a blinded prospective study found OCT to have an 81% specificity for diagnosing squamous intestinal metaplasia (SIM) at the squamocolumnar junction (SCJ)[12].

Due to the limited knowledge about VLE findings at the gastroesophageal junction (GEJ) and gastric cardia, the purpose of this study is to correlate VLE imaging characteristics with histology in this area in order to determine specific features associated with neoplasia.

MATERIALS AND METHODS

Study design

This was a retrospective study conducted at a tertiary care center with a referral BE practice. Patients with known or suspected Barrett's esophagus presented for EGD and VLE. During EGD, biopsies were taken with cold forceps in a targeted and random fashion. Using the NinePoints VLE console, a segment of the VLE scan was delineated from the GEJ (marked by top of gastric folds) to 1 cm distal from the GEJ in order to approximate the gastric cardia. These segments were analyzed frame-by-frame to determine the presence of various imaging features. This analysis was done by a trained reviewer who was initially blinded to the corresponding pathology. Once the image analysis was completed, biopsy results from the GEJ to 1 cm distal to the GEJ were reviewed in order to determine the highest level of pathology found in the segment. Patients were then grouped according to the highest level of pathology indicted on biopsy

4 cases excluded due to technical problem with VLE image file

52 available VLE cases

2 cases excluded because VLE scan did not include GEJ/gastric cardia

50 available VLE scans with region of interest

15 cases excluded because biopsy report corresponding to VLE scan was not available

35 available VLE scans with corresponding histology

1 cases excluded because no biopsies were taken at the GEJ/cardia

34 available VLE scans with corresponding histology at the GEJ/cardia

Figure 1 Inclusion and exclusion criteria flowchart. VLE: Volumetric laser endomicroscopy; GEJ: Gastroesophageal junction.

report: neoplasia, Barrett's with no dysplasia, inflamed cardia, and normal mucosa. Within these histologic subgroups, the frequency of each imaging characteristic was calculated based on the VLE scan analysis that had been done.

Cases (Figure 1)

From July 2014 to September 2015, forty-six patients underwent a total of fifty-six procedures with VLE scan at a tertiary care center with referral Barrett's practice. These patients were undergoing screening or had known BE and were undergoing endoscopic follow-up. Cases were included in the study of they had a VLE scan available for review and had biopsies taken specifically at the GEJ/gastric cardia.

Cases were excluded if the VLE scan did not include imaging of the GEJ/gastric cardia, biopsies were not taken in this region, or if there was a technical problem with the VLE scan.

Of the fifty-six cases, thirty-four met criteria for inclusion in the study. This study was approved by the Institutional Review Board.

Endoscopy

All endoscopic procedures were performed by 3 expert endoscopists with experience in detection and management of BE. EGD procedures were performed using the high resolution Olympus GIF-HQ190 gastro-

scope. After insertion of the gastroscope, the esophagus, GEJ and gastric cardia were first examined by WLE for gross evidence of BE. Narrow band imaging features with near focus was also used. Following this, VLE ODFI imaging was performed using the NinePoints system described below. Lastly, biopsies were taken with cold forceps and/or endoscopic mucosal resection at the endoscopist's discretion.

VLE system

The NinePoints Medical VLE optical frequency domain imaging (ODFI) system was used in this study. Technical specifications of ODFI imaging are described in detail in previous publications[12]. Briefly, the NinePoints VLE system includes a balloon centered probe and user console with monitor. The probe consists of a transparent balloon surrounding a laser light source and optical system. Commercially available probe sizes range from 14-25 mm. These are compatible with endoscope channels 2.8 mm and lager. After the balloon is placed into the esophagus and inflated, the central component helically scans while simultaneously retracting throughout the length of the balloon (6 cm). A data set is generated using interferometry and measurement of optical reflection delay from the laser light source. The scan takes 90 s to complete and produces circumferential cross-sectional images of the tissue abutting the edge of the inflated balloon probe. In total, 1200 cross sectional images are obtained from the mucosa to a depth of 3 mm. These images have a resolution of 7 μm making it comparable to low-power microscopy.

VLE images were analyzed on a console that allows for simultaneous cross-sectional and longitudinal views. Additionally, a zoom view was available for both dimensions.

VLE image assessment

All VLE scans were viewed using the NinePoints VLE console. For each scan included in the study, the corresponding endoscopy report was reviewed to determine the centimeter marking at which the top of gastric folds was seen. The corresponding centimeter marking was found on the VLE scan and this was designated as the GEJ. Each scan was assessed frame by frame from the GEJ to 1 cm below the GEJ. Each frame was viewed circumferentially for presence of the specified features which have been found in previous studies to correlate with normal or abnormal mucosa (Table 1). The features or interest were based on OCT criteria set forth by Evans *et al*[12] and included gastric rugae, gastric pit architecture, image penetration, homogenous or heterogeneous scattering, surface to subsurface intensity, and surface irregularity. Following this, another review was done during which the number of typical, atypical, and septated glands were counted individually. Glands were deemed to be atypical if they were dilated or had irregular morphology, similar to the definition used in previous publications[13].

Figure 2 Correlating histology. A: Normal gastric cardia with regular gastric pit architecture; B: Inflamed gastric cardia with chronic inflammatory infiltrate and loss of structured gastric pits; C: Low grade dysplasia in Barrett's mucosa with a prominent atypical septated gland; D: High grade dysplasia with cytologic and architectural atypia extending to the surface.

Table 1 Validated criteria for interpretation of volumetric laser endomicroscopy Images of gastroesophageal tissue[12]

Diagnosis	Imaging criteria on volumetric laser endomicroscopy
Squamous epithelium	Layered horizontal architecture
	Absence of glands
Gastric cardia	Vertical pit architecture
	Regular glandular architecture
	Poor image penetration
	Homogeneous scattering
	Regular, broad gastric rugae
Metaplasia	Lack of layered or vertical pit architecture
	Heterogeneous scattering
	Irregular surface
	Atypical glandular structure

Statistical analysis

Statistical analysis was performed using Microsoft Excel software for Windows. χ^2 test was used when comparing the proportion of each group that exhibited a particular imaging feature. The *t*-test was used when determining if the number of typical and atypical glands differed between two groups. Analysis of variance (ANOVA) analysis was performed comparing the number of atypical glands between all histologic subgroups. A *P*-value of < 0.05 was considered statistically significant in this study. The statistical methods of this study were reviewed by a biostatistician through the University of Chicago Biostatistics Laboratory which is part of the Department of Public Health Sciences.

RESULTS

Patients

Thirty-four patients with VLE imaging and cardia level biopsies were included in the study and had an average age of 63 years (SD 9). Twenty-two patients had undergone prior therapy while twelve had not. Of the 22 patients who had undergone prior treatment, 4 patients had undergone endoscopic mucosal resection (EMR), 6 radiofrequency ablation (RFA), 12 hybrid therapy.

Endoscopy review

Hiatal hernias were present in 20 cases. In two cases, the patient was status post a fundoplication and in one case the patient was status post a duodenal switch surgery. Visible BE was seen during EGD in 22 cases of which 14 had short segment BE and 8 had long segment BE. Visible lesions at the GEJ/gastric cardia such as nodularity or abnormal vascularity were seen in 4 cases.

Pathology review (Figure 2)

In patients who had no prior treatment for BE, the highest pathology identified from the GEJ and cardia region was intramucosal carcinoma (IMC)/high grade dysplasia (HGD) in one case, Barrett's with low grade dysplasia (LGD) in four cases, Barrett's without no dysplasia (NDBE) in four cases, and normal mucosa (NL) in three cases.

Among the 22 patients who had previously under-

Figure 3 Volumetric laser endomicroscopy imaging snapshots. A: Normal gastric cardia with gastric rugae and gastric pit architecture; B: Inflamed gastric cardia with loss of gastric pit architecture and anomalous glands; C: Low grade dysplasia with loss of gastric pit architecture, heterogeneous scattering, anomalous septated gland; D: High grade dysplasia with irregular surface and anomalous glands.

gone treatment, the pre-treatment pathology was IMC in 1 case, HGD in 11 cases, LGD in 8 cases and NDBE in 2 cases and study procedure pathology was LGD in 2 cases, NDBE in 2 cases, inflamed gastric cardia (IGC) in 9 cases, and NL in 9 cases.

VLE findings (Table 2 and Figure 3)

Of the fifty-six VLE cases available for this study, twelve cases were excluded due to inadequate VLE imaging of the GEJ/cardia or because corresponding biopsies were not taken in that region.

Features characteristic of the gastric cardia (gastric rugae, gastric pit architecture, and poor penetration) were observed in all (100%) scans. A focal area with loss of normal gastric pit architecture was also a prevalent finding, seen in 79.4% of total patients. Heterogeneous scattering was found in exactly half (50%) of patients. Irregular surface was less common, seen in 35% of patients. Similarly, subsurface intensity greater than surface intensity was a rare finding, also occurring only in 6 of 34 patients (17.6%).

All 34 cases showed some typical epithelial glands with a range of 3-56 glands in the GE junction and cardia region examined. Anomalous glands were found in 25 of 34 scans (73.5%) and the number of anomalous glands ranged from 2 to 39.

Focal loss of normal gastric pit architecture was a prevalent finding, notably in patients with neoplasia, non-dysplastic Barrett's, and inflamed cardia. There was no difference of this feature between those with neoplasia and those without (100% *vs* 74%, P = NS). However, patients with all types of abnormal cardia (IMC/HGD, LGD, NDBE, IGC) more frequently had loss of normal gastric pit architecture than patients with no mucosal abnormality (90.0% *vs* 58.3%, $P < 0.05$).

Irregular surface was more often seen in patients with neoplasia than those without neoplasia (100% *vs* 18.5%, $P < 0.0001$). Irregular surface was also more often seen in those patients with neoplasia compared to those with IGC (100% *vs* 11.1%, $P < 0.001$).

A greater proportion of patients with neoplasia had heterogeneous scattering as compared to patients without neoplasia (85.7% *vs* 40.7%, $P < 0.005$). Additionally, patients with neoplasia or non-dysplastic BE analyzed together more often had heterogeneous scattering compared to those with inflamed cardia or normal mucosa (84.6% *vs* 28.5%, $P < 0.005$).

Anomalous glands were more commonly found in patients with neoplasia as opposed to those without (100% *vs* 59.2%, $P < 0.05$). When analyzed together, patients with either neoplasia or non-dysplastic BE were found to have anomalous glands more often that those with inflammation or normal mucosa (92.3% *vs* 52.4%, $P < 0.05$).

In terms of the number of anomalous glands found, ANOVA analysis did not reveal a difference between individual histologic subgroups (P = NS). When grouped, patients with neoplasia did not have a significantly higher number of anomalous glands than all patients without neoplasia (*t*-test P = NS). However, patients

Table 2 Frequency of volumetric laser endomicroscopy imaging features in histologic subgroups *n* (%)

	IMC/HGD (*n* = 1)	LGD (*n* = 6)	NDBE (*n* = 6)	Inflamed cardia (*n* = 9)	No diagnostic abnormality (*n* = 12)	Neoplastic[1] (*n* = 7)	Non-neoplastic[2] (*n* = 27)	*P*-value[3]
Gastric rugae	1 (100)	6 (100)	6 (100)	9 (100)	12 (100)	7 (100)	27 (100)	NS
Gastric pit architecture	1 (100)	6 (100)	6 (100)	9 (100)	12 (100)	7 (100)	27 (100)	NS
Poor penetration	1 (100)	6 (100)	6 (100)	9 (100)	12 (100)	7 (100)	27 (100)	NS
Loss of normal gastric pit architecture	1 (100)	6 (100)	5 (83)	8 (89)	7 (58)	7 (100)	20 (74)	NS
Irregular surface	1 (100)	6 (100)	2 (33)	1 (11)	2 (20)	7 (100)	5 (19)	< 0.0001
Heterogeneous scattering	1 (100)	5 (83)	5 (83)	6 (67)	3 (25)	6 (86)	14 (52)	< 0.005
Epithelial glands	1 (100)	6 (100)	6 (100)	9 (100)	12 (100)	7 (100)	27 (100)	NS
Anomalous glands	1 (100)	6 (100)	5 (83)	6 (67)	5 (42)	7 (100)	16 (59)	< 0.05

[1]Neoplastic: HGD + IMC; [2]Non-neoplastic: NDBE + IGC + NL; [3]*P* value: Neoplastic *vs* non-neoplastic. IMC: Intramucosal carcinoma; HGD: High-grade dysplasia; LGD: Low grade dysplasia; NDBE: Barrett's without no dysplasia; IGC: Inflamed gastric cardia; NL: Normal mucosa; NS: Not significant.

with neoplasia did have significantly more anomalous glands than the subgroup of patients with no mucosal abnormality (*t*-test *P* < 0.05). Septated glands were seen in 8 patients across histology subtypes and did not appear to be associated with higher levels of pathology.

Notably, WLE or narrow band imaging (NBI) failed to detect suspicious lesions within BE at the GEJ or cardia in 3 cases of LGD.

DISCUSSION

This is the first study to analyze the correlation between imaging features and histology specifically in the GEJ and gastric cardia region. Our first main finding was that all scans exhibited features such as broad based rugae, gastric pits, and poor penetration. These features have been previously described in the gastric cardia, and our findings confirm that these are reliable markers for identifying the transition from tubular esophagus to gastric cardia.

We found that patients with neoplasia at the GEJ and gastric cardia more frequently have abnormal features on VLE imaging. In fact, the loss of normal gastric pit architecture was the only abnormal feature that did not differ significantly between those with neoplasia and those without. This is likely because this feature was loosely defined, and any deviation from the normal gastric pit architecture was counted. In the tubular esophagus, loss of layering is found in cases of NDBE. Thus, it was already known that NDBE can appear with an irregular architecture. In addition, gastric pit architecture appears as subtle alternation of vertical dark and light bands at the mucosal surface and this imaging feature could have been easily disturbed by artifact.

Other studies of VLE have similarly shown this imaging modality to be a safe and useful adjuvant to endoscopy. The safety and feasibility of VLE imaging was evaluated by Wolfson *et al*[14] who were able to successfully perform VLE imaging in 87% of a 100 patient cohort. Probe and console issues were the reason for unsuccessful VLE imaging in 13 patients.

Two minor mucosal lacerations occurred in the study and neither required therapy. The diagnostic utility of VLE has been explored by several groups. Trindade *et al*[15] presented a small case series which found that targeted biopsy by VLE upstaged or diagnosed dysplasia in several patients who then became candidates for ablation or resection. VLE has even been found to detect dysplasia missed by other advanced imaging techniques such as NBI[16] and missed on random biopsy[17]. Currently, two validated OCT image assessment algorithms exist. The OCT-scoring index (OCT-SI) created in 2005 by Evans *et al*[13] focuses on signal intensity and glandular architecture whereas the newer VLE diagnostic algorithm (VLE-DA) from Leggett *et al*[18] is based on degree of mucosal effacement, surface intensity, and atypical glands. The OCT scoring index (score > 2) was found to have an 83% sensitivity and 75% specificity for dysplasia detection when tested *in-vivo*[13]. The VLE-DA performed slightly better with 86% sensitivity, 88% specificity, and 87% diagnostic accuracy, thought this is based on an *ex-vivo* study[18]. Based on our results, we propose adding "red-flag" features of irregular surface and heterogeneous scattering in the GEJ region to the current protocols in order to capture areas of dysplasia which may otherwise be missed.

These interpretation systems are focused on the tubular esophagus. However, there is a role for expanding the applicability of these criteria to the GEJ/cardia region since this is a difficult place to assess endoscopically and can harbor SIM or dysplasia[19]. Cardia tissue may be present at the anatomical region of the cardia but may also be present in a mosaic pattern in Barrett's esophagus amidst intestinal type mucosa and fundic type mucosa. The appearance of cardia type tissue within this mosaic pattern in the tubular esophagus is a potential confounder and may be a cause for false positives in VLE interpretation.

One limitation of this study is that exact correlation of biopsy location to VLE scan location was unable to be performed in this retrospective study. Rather, a circumferential area scanning 1 cm in length was

designated as the GEJ/gastric cardia region and biopsy and imaging features from this area were compared. Currently, general location correlation can be done by matching a registration line on the probe to one of the cross-sectional image. This allows for clock-face orientation. However, to allow for even more precise targeting Suter *et al*[20] validated the recently developed method for using a cautery marking laser coupled into the VLE balloon catheter's optical fiber to mark areas of interest with simultaneously acquiring a VLE image.

The results of this study show a promising role for VLE as an adjuvant for endoscopic assessment of the GEJ and gastric cardia region. The current OCT-scoring algorithms may be expanded to include GEJ/cardia assessment in order to target areas that exhibit irregular surface, heterogeneous scattering, or anomalous glands. A prospective study validating these features utilizing 1:1 histologic correlation will be required. With *in-vivo* laser marking soon to be commercially available, we anticipate with this be a feasible study in the near future. Ultimately, the clinical comparison of yield of VLE targeted biopsy protocol compared with a standard Seattle protocol biopsy protocol will be needed to assess clinical impact.

COMMENTS

Background
Barrett's esophagus can lead to the development of esophageal adenocarcinoma. Because of this, patients with known Barrett's esophagus are recommended to have surveillance upper endoscopies. Biopsies are taken of visible lesions as well as in a random fashion according to the Seattle Protocol. However, this technique is suboptimal because occult dysplasia may still be missed. Several adjuvant modalities have been explored to help identify potentially dysplastic areas and allow for more targeted biopsies. Targeted biopsies improve dysplasia detection rates. volumetric laser endomicroscopy (VLE) is a type of OCT imaging modality that produces cross sectional images of the esophagus and proximal stomach. It is currently used for Barrett's surveillance and biopsy targeting in the tubular esophagus. This study explores the use of VLE specifically at the gastroesophageal junction (GEJ) and gastric cardia to determine the correlation of imaging features with neoplasia in this region.

Research frontiers
In Barrett's esophagus, there is increasing interest in a moving toward targeted biopsies by identifying abnormal "red-flag" areas. The correlation of VLE imaging with histology is increasingly being studied, however many of these studies are *ex-vivo* and their applicability may be limited. Additionally, most studies of VLE are limited to the tubular esophagus even though VLE scans also image the GEJ and gastric cardia. The results of this *in-vivo* study contribute to understanding the applicability of VLE imaging at the GEJ/cardia, as well as contributing to knowledge of correct VLE image interpretation.

Innovations and breakthroughs
This is the only study known to date which focus on VLE imaging characteristics specifically at the GEJ and gastric cardia. This is important because dysplasia can occur in this region just as it can in the tubular esophagus. Similar to prior VLE studies, this study found that VLE features of abnormal surface architecture and atypical glands are associated with dysplasia. However, this study also found that the scattering pattern of the VLE image (heterogeneous *vs* homogeneous) was correlated with dysplasia and should be considered in the image assessment.

Applications
This study suggests that VLE imaging is useful for assessing the GEJ and gastric cardia. Current OCT scoring systems can be expanded for use in this region.

Terminology
Barrett's esophagus: A pre-cancerous cellular change in the esophagus that is often the result of longstanding acid reflux. Optical coherence tomography (OCT): An imaging technique that produces high resolution images of biologic tissue by measuring back-scatter light intensity from a near-infrared light source. Volumetric laser endomicroscopy (VLE): A specific type of OCT that is probe-based and produces cross sectional images of the esophagus and gastric cardia.

Peer-review
This retrospective study correlates VLE imaging characteristics with histology at the GEJ and gastric cardia, which is helpful to determine specific features associated with neoplasia. The authors investigated a new area of invasive gastroenterology field. Their findings have some novel findings and also lead new investigations as a prospective designed.

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Observational Study

All ileo-cecal ulcers are not Crohn's: Changing perspectives of symptomatic ileocecal ulcers

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Abstract

AIM

To investigated clinical, endoscopic and histopathological parameters of the patients presenting with ileocecal ulcers on colonoscopy.

METHODS

Consecutive symptomatic patients undergoing colonoscopy, and diagnosed to have ulcerations in the ileocecal (I/C) region, were enrolled. Biopsy was obtained and their

clinical presentation and outcome were recorded.

RESULTS
Out of 1632 colonoscopies, 104 patients had ulcerations in the I/C region and were included in the study. Their median age was 44.5 years and 59% were males. The predominant presentation was lower GI bleed (55, 53%), pain abdomen ± diarrhea (36, 35%), fever (32, 31%), and diarrhea alone (9, 9%). On colonoscopy, terminal ileum was entered in 96 (92%) cases. The distribution of ulcers was as follows: Ileum alone 40% (38/96), cecum alone 33% (32/96), and both ileum plus cecum 27% (26/96). The ulcers were multiple in 98% and in 34% there were additional ulcers elsewhere in colon. Based on clinical presentation and investigations, the etiology of ulcers was classified into infective causes (43%) and non-infective causes (57%). Fourteen patients (13%) were diagnosed to have Crohn's disease (CD).

CONCLUSION
Non-specific ileocecal ulcers are most common ulcers seen in ileo-cecal region. And if all infections are clubbed together then infection is the most common (> 40%) cause of ulcerations of the I/C region. Cecal involvement and fever are important clues to infective cause. On the contrary CD account for only 13% cases as a cause of ileo-cecalulcers. So all symptomatic patients with I/C ulcers on colonoscopy are not Crohn's.

Key words: Ileocecal; Crohn's disease; Diffuse large B-cell non-hodgkin's lymphoma

Core tip: This is one of the largest studies till date defining etiology, endoscopic and histological features of ileocecal (I/C) ulcers. Non-specific ileocecal ulcers are most common ulcers seen in ileo-cecal region. And if all infections are clubbed together then infection is the the most common (> 40%) cause of ulcerations of the IC region. On the contrary Crohn's disease (CD) account for only 13% cases as a cause of ileo-cecal ulcers. So all symptomatic patients with I/C ulcers on colonoscopy are not CD. Also, we conclude that with increasing use of Colonoscope in diagnosis and treatment, majority of the patients with ileo-cecal ulcers can be managed conservatively without surgery.

INTRODUCTION
Term ileocecum pertains to the cecum and the terminal filament of ileum including the region where they are connected by the ileocecal (I/C) valve[1]. Due to distinct anatomy and physiology this region is affected by various diseases like ulcerative colitis, Crohn's disease (CD), non-specific ulcers, Malignancies, Amoebiasis, Enteric fever and Tuberculosis (TB)[2-6]. CD in particular affect Ileum alone or ileo-colonic region in about 60%-70% cases[7]. But whether 60%-70% of I/C ulcers are CD needs evaluation. I/C ulcers may manifest as small bowel obstruction, abdominal pain, perforation, acute or chronic gastrointestinal blood loss, cachexia, fever or malabsorption syndrome[8]. There is paucity of data on etiology, clinical profile and histo-pathological correlation of patient with I/C ulcerations. To evaluate the etiology of ileocecal ulcers is challenging for Clinician, Endoscopist and Histopathologistalike[9-13]. In the present study, clinical, endoscopic and histo-pathological parameters of the patients presenting with ileocecal ulcers on colonoscopy, were summarized, and investigated.

MATERIALS AND METHODS
This study was conducted at Sir Ganga Ram Hospital, New Delhi. This was an observational study conducted over a period of 18 mo from May 2010 to October 2011. Colonoscopy was done with fibro-optic colonoscope (Olympus, Japan 180 cf or 160 cf). Colonic preparation was done using a polyethylene glycol-electrolyte-based solution (Peglec, Tablets India Ltd, Chennai). The procedure was performed under conscious sedation with intravenous diazepam (5-10 mg) and pentazocine (25-50 mg). During colonoscopy a careful search was made for the presence of ulcers in cecum,ileocecal valve or terminal ileum. If any ulcer was present then multiple biopsies were obtained from the lesion and the margins for histopathological examination. Exclusion criteria included patients < 18 years of age and asymptomatic patients undergoing screening colonoscopy. The data was prospectively collected. This study was conducted in accordance with the principles of the Declaration of Helsinki, and written informed consent for the treatment and colonoscopy was obtained from all patients. We did not seek individual ethical approval by the Committee because this was an observational study without inter-positions and with the medical practice necessary for therapeutic purposes. Descriptive statistics was used for data analysis. Continuous variables were presented as mean or median (range). Categorical variables were expressed as frequencies and percentages. SPSS 17 for windows statistics package (Microsoft corp. Richmond, VA) was used for analysis. One hundred and four patients with ileo-cecal ulcerations and biopsy specimen

Table 1 Etiology of ileo-cecal ulcers *n* (%)		
Infective causes *n* = 45 (43%)	Amoebic	13 (12)
	Tubercular	11 (11)
	Typhoid	4 (4)
	Pseudomembranous colitis	2 (2)
	Unspecified bacterial infections	15 (14)
Non-infectious causes *n* = 59 (57%)	CD	14 (13)
	NSAID induced	6 (6)
	Malignant	6 (6)
	Miscellaneous	4 (4)
	Non-specific	29 (28)

CD: Crohn's disease; NSAID: Nonsteroidal antiinflammatory drug.

Figure 1   Amoebic ulcer in cecum.

subjected to histopathological examination were included in the study.

Definitions

(1) Amoebic ulcers were diagnosed if the biopsy specimen demonstrated trophozoites of E. histolytica or test for amoebic serology was positive in blood sample; (2) enteric or typhoid ulcers were diagnosed either on histology or if widal titer was positive or blood culture was positive for Salmonella typhi; (3) unspecified infective ulcers were diagnosed if patient presented with acute onset diarrhea or dysentery with febrile illness and tests for other infections like amoebiasis; enteric fever were negative; or by histopathological evidence; (4) tubercular ulcers were diagnosed if tubercle bacilli was demonstrated in biopsy specimen or by presence of caseating granuloma in biopsy specimen or if there was evidence of extra-intestinal tuberculosis; or past history of tuberculosis; (5) Crohn's ileocecal disease was diagnosed by presence of skip lesions, pseudopolyps or fistulas on endoscopic or radiological examination with presence of cryptitis or cryptic abscesses or non-caseating granulomas on biopsy. Use of data and criterias from past studies was made to differentiate between TB and CD[9-11,13]; (6) NSAID induced ileocecal ulcers were diagnosed either on histology or if patient had history of NSAID intake; (7) malignant ileocecal ulcers were diagnosed if malignancy was demonstrated on biopsy from ulcers or biopsy/fine needle aspiration cytology from surrounding lymphnode; (8) psedomembranous colitis was diagnosed if stool examination demonstrated the presence of *C. difficle* toxin A and B; (9) eosinophilic enteritis was diagnosed as per standard criteria[14]; (10) non-specific ileocecal ulcer was diagnosis of exclusion; where other causes were ruled out and biopsy demonstrated the same; (11) small ulcers were ulcers with maximum diameter < 1.5 cm; and (12) large ulcers were ulcers with maximum diameter of > 1.5 cm.

RESULTS

Total 1632 colonoscopies were performed during the study period. One hundred and four (7%) patients with ulcer in cecum, ileo-cecal valve or terminal ileum

and biopsy specimen subjected for histopathological examination formed the study group. The median age was 44.5 years with a range of 18-85 years. Sixty-one (59%) patients were males. The predominant presentation was lower Gastro-intestinal (GI) bleed (*n* = 55), Pain abdomen with or without diarrhoea (*n* = 36), weight loss (*n* = 20), constipation (*n* = 10), diarrhoea alone (*n* = 9). Associated fever was present in 33 patients. On colonoscopy, terminal ileum could be entered in 96 (92%) cases. The distribution of ulcers was as follows: Ileum alone 38 (40%), cecum alone 32 (33%), and both ileum plus cecum 26 (27%). In the 8 patients in whom ileum could not be entered ulcerations were present on the cecum and the IC valve. The ulcers were multiple in 99 (98%). In 35 (34%) there were additional ulcers elsewhere in colon. One patient left the hospital against medical advice. Three patients expired. Eight patients required surgical treatment. Remaining 92 patients had uneventful recovery. Various causes of Ileo-cecal ulcers are summerised in Table 1.

Amoebic ulcers (*n* = 13) predominantly affected males. Most common presentation was lower gastro-intestinal (GI) bleeding. Twelve patients had multiple ulcers. Ileum was affected in only one case but cecum (Figure 1) was involved in twelve cases. Ulcers were large, multiple, necrotic, with inflammatory edges. Amoebic serology was positive in all patients. Amoebic trophozoites (Figure 2) were seen on biopsy in 1 patient. Six patients had active ooze from ulcers. Two patients required surgery in form of right hemicolectomy to control the bleed. Rest were managed with conservative treatment including antibiotics.

Eleven patients had I/C ulcers due to tuberculosis (Figure 3). Presenting complaints were weight loss and pain abdomen. Cecum was cicatrised in 8 patients and I/C valve was deformed in four. Ulcers were small and multiple. Biopsy (Figure 4) was diagnostic in 7. In view of persistant obstruction 1 patient required surgery while the remaining 10 patients were managed with anti-tubercular treatment.

Fifteen patients were diagnosed as unspecified infective ulcers. GI bleed and fever were most common presentation. Ileum was involved in 10 and cecum in 8 patients. Ulcers were small, large, multiple and with

Figure 2 Amoebic trophozoites on histopathology.

Figure 5 Pseudopolyps in Crohn's disease.

Figure 3 Tubercular ulcers in ileum.

Figure 6 Ulcer on ileo-cecal valve ileocecal-lymphoma.

Figure 4 Tubercular granuloma.

Figure 7 Ileal ulcer-lymphoma.

various morphologies. Ten patients had active ooze or stigmata of recent bleed,on colonoscopy. Biopsy was diagnostic in 9 patients. One patient expired due to sepsis and renal failure. One patient left the hospital against medical advice.

Fourteen patients were diagnosed as ileocecal Crohn's. Eleven were females. Most common presenting complaints were pain abdomen or gastrointestinal bleed. Ileum was involved in 12, ceacum in 6 and I/C valve in only one. Ulcers were small or large. Skip lesion were present in 3 cases. Pseudopolyps (Figure 5) were present in two cases. Biopsy was diagnostic in 6 patients. No patient required surgical intervention.

Six patients had non-steroidal anti-inflammatory drugs (NSAID) induced I/C ulcers. All had history of NSAID intake ranging for 5 d to 24 mo prior to presentation. Presenting complaints were gastrointestinal bleed, diarrhea, pain abdomen. No patient had fever. Ileum was involved in 5 patients and cecum in 3. Biopsy was diagnostic in 1 patient. All patients recovered without the need for surgery.

Six patients were diagnosed to have malignancies-3 adenocarcinoma cecum and 3 ileocecal diffuse large B-cell non-hodgkin's lymphoma (DLBCL) (Figures 6 and 7). Colonic biopsy (Figure 8) was diagnostic in 4 cases. Two patients of adenocarcinoma were operated, while

Figure 8 Biopsy demonstrating lymphoma.

Figure 9 Non-specific ileal ulcer.

1 was treated with chemotherapy. The later expired. Of the 3 DLBCLall were treated with chemotherapy.

Four patients had I/C ulcers secondary to enteric fever. Presenting complaints were fever, pain abdomen, GI bleed. Ileum was involved in 3 cases and cecum in 2 cases. Ulcers were large (> 1.5 cm) with necrotic slough; associated with active ooze in 2 cases. Biopsy was diagnostic in one.Haemostasis by endoscopic therapy was achieved in one patient while one patient underwent right hemicolectomy.

Two patients were diagnosed with eosinophilic enteritis with ileal ulcers on colonoscopy. Both presented with pain abdomen.

Two patients were diagnosed as pseudomembranous colitis with I/C involvement. Biopsy was diagnostic in one patient whereas stool for Clostridium difficle toxin A and B was positive for both. On endoscopy Ulcers were multiple with necrotic slough.

Twenty-nine patients were diagnosed with non-specificileocecalulcers (Figure 9). Presenting complaints were GI bleed in 14, pain abdomen in 11 and diarrhea in 7 patients. No patient had fever. Ileum was involved in 21 patients. Ulcers were small or large and with various morphologies. Active ooze was noted in eight patients of whom six were managed by Endoscopic therapy. Two required surgery. One expired due to massive bleeding.

With infective cause, fever was significantly more common (47% *vs* 19%, $P < 0.01$) and cecum was preferentially involved (82% *vs* 45%, $P < 0.01$).

DISCUSSION

This is one of the largest study till date defining eti-ology,colonoscopic and histo-pathological features of ileo-cecal ulcers.This study is interesting for several reasons.

First, Crohn's disease in particular affect ileum or ileum along with colon in about 60%-70% patients[7]. However, the converse is not true, *i.e.,* 80% of ileo-cecal ulcers are not Crohn's. In our study CD was cause for ileo-cecal ulcers in 13% of patients.Ileum was affected in 90% cases. Pain abdomen and GI bleed were common presentations. Absence of fever and sparing of ileo-cecal valve were helpful in diagnosing Crohn's.

Second, in our study most common etiology of ileo-ceal ulcers was non- specific ulcers. Clinically these ulcers manifest without fever. They are pleomorphic in nature on colonoscopy and predominantly involve the ileum. They can cause massive GI bleed and result in mortality. However, if treated promptly hemostasis can be achieved by endoscopic treatment. These results were comparable to studies by Boydstun *et al*[6] and Thomas *et al*[15] in terms of, presenting complaints and site of ulcers. However, as they conducted studies when endoscopic methods of hemostasis were not practiced. So surgery was the only curative treatment for their patients.

Third, Infections,if clubbed together, was most common cause of ulcerations in Ileo-cecal region. Findings were comparable with a Chinese study[8]. Both these studies demonstrated that most common cause of ileocecal ulcers is infection especially in tropics. We also hypothesize that infection can be most common etiology of ulcers in other parts of world. Though, Amoeba and Tuberculosis are uncommon in Europe and America, bacterial infections are common worldwide.

Amoebic serology was useful diagnostic tool to differentiate amoebic ileocecal ulcers from other causes of ileocecal ulcers. Male sex, fever, gastrointestinal bleed, and large necrotic ulcers involving the cecum with ileal sparing favored amoebic ulcers. Findings were comparable to other studies[16].

Multiple ulcers with cicatrisation of Cecum and de-formed I/C valve suggest tubercular etiology. Biopsy is always not diagnostic. Abdominal pain, weight loss, fever, and a lump in the abdomen are common presentations. Clinical features combined with colonoscopy need to be considered to start treatment. Cai *et al*[8] even suggested that based on these findings anti-tubercular treatment can be started and response to treatment can be evaluated after 6-8 wk of treatment.

In enteric fever, patients are febrile with widal test or blood culture positive for *S. typhi*. Large ieal ulcers with necrotic slough; associated with active ooze is common colonoscopic findings. Majority of them can be treated

by conservative treatment including antibiotic therapy.

Unspecified bacterial infections was most common cause of infective ileocecal ulcers. Febrile patients with multiple ileal ulcers and associated oozing of blood are common findings. Tests for other infective causes are negative. These findings were comparable to other studies but in these studies causative bacteria were defined[17,18].

And lastly, NSAIDs, Eosinophilic enteritis and malignancies have been described in literature as cause of ulcerations in ileo-cecal region[3,14,19]. These causes were also noted in our study. But, they were cause of ulcerations in minor group of patients. Findings of our study were comparable with literature.

To conclude, non-specific ileocecal ulcers are most common ulcers seen in ileo-cecal region. And if all infections are clubbed together then infection is the the most common (> 40%) cause of ulcerations of the IC region. Cecal involvement and fever are important clues to infective cause. On the contrary CD account for only 13% cases as a cause of ileo-cecalulcers. So all symptomatic patients with I/C ulcers on colonoscopy are not Crohn's. And with increasing use of Colonoscope in diagnosis and treatment, majority of the patients with ileo-cecal ulcers can be managed conservatively without need for surgery.

COMMENTS

Background

Evaluation of ileocecal ulcers is challenging for Clinician, Endoscopist and Histopathologist. Data on ileocecal ulcers, from Asian countries, differ from western world. In this study, all these parameters of the patients presenting with ileocecal ulcers on colonoscopy, were summarized, and investigated.

Research frontiers

Colonoscope is a novel tool that allows evaluation as well as treatment of ileocecal ulcers in majority of cases. It has largely replaced surgery for evaluation and treatment of these ulcers. The present study confirmed this hypothesis in Indian patients.

Innovations and breakthroughs

The present study showed that symptomatic ileo-cecal ulcers, are mainly caused by infections; specially in tropical Asian countries. Non-specific ulcers also predominate the list and are cause of significant morbidity and mortality. Fortunately, with the use of colonoscope for achieving hemostasis majority of these patients can be managed conservatively.

Applications

This study suggests that Crohn's disease is cause of ulcers in ileo-cecal region in a very small subset of patients. Majority of ulcers are caused by infections. Involvement of cecum and fever are important clues to diagnoses these infective ulcers.

Terminology

Ileo-cecal (I/C) ulcers are ulcers located in terminal ileum, cecum or on ileocecal valve noted during colonoscopic examination.

Peer-review

I/C ulcers were evaluated in this study. Jay Toshniwal *et al* evaluated their patients undergoing colonoscopy. It was detected that 104 patients (of 1632 colonoscopies) had ulcerations in the I/C region and non-specific ileocecal

ulcers are most common ulcers seen in ileo-cecal region. The results may be meaningful for interested specialists.

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Prospective Study

Endoscopic submucosal dissection of gastric adenomas using the clutch cutter

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Abstract

AIM
To evaluate the efficacy and safety of endoscopic submucosal dissection (ESD) using the clutch cutter (CC) (ESD-CC) for gastric adenoma (GA).

METHODS
From June 2007 to August 2015, 122 consecutive patients with histological diagnoses of GA from specimens resected by ESD-CC were enrolled in this prospective study. The CC was used for all ESD steps (marking, mucosal incision, submucosal dissection, and hemostatic treatment), and its

therapeutic efficacy and safety were assessed.

RESULTS
Both the *en-bloc* resection rate and the R0 resection rate were 100% (122/122). The mean surgical time was 77.4 min, but the time varied significantly according to tumor size and location. No patients suffered perforation. Post-ESD-CC bleeding occurred in six cases (4.9%) that were successfully resolved by endoscopic hemostatic treatment.

CONCLUSION
ESD-CC is a technically efficient, safe, and easy method for resecting GA.

Key words: Endoscopic submucosal dissection; Clutch cutter; Gastric adenoma

Core tip: The clutch cutter (CC) was developed to reduce risk of complications related to endoscopic submucosal dissection (ESD) using conventional knives. The CC can grasp, pull, coagulate and/or incise targeted tissue using electrosurgical current, as with a bite biopsy. The CC can be used in all ESD steps (marking, mucosal incision, submucosal dissection, and hemostatic treatment). ESD using the CC (ESD-CC) for gastric adenoma (GA) gave a 100% R0 resection rate in this study, with no perforation. ESD-CC is a technically efficient, safe, and easy method for resecting GA.

INTRODUCTION
Endoscopic submucosal dissection (ESD) has considerable advantages regarding rates for local recurrence, and *en-bloc* and R0 resections, compared with conventional endoscopic mucosal resection (EMR)[1,2]. Worldwide, ESD gradually increases in its indication share instead of EMR. However, the major disadvantages of ESD with conventional knives is its technical difficulty; Therefore, it has a high complication incidence and protracted procedural time, requiring advanced endoscopic skills and many devices[3-5]. Conventional devices (such as IT and needle knives) are gently pushed to the targeted tissue; then, these tissues are cut using electrosurgical current. Because these cutting mechanisms cannot grasp or pull at the targeted tissue, accurate targeting, compressive hemostasis and the ability to draw the targeted tissue away from the muscle layer are lacking, causing the risk of serious adverse events including gastric perforation and hemorrhage[6,7]. In order to resolve the hazards of ESD using conventional knives, the Clutch Cutter (CC) was developed and can precisely grasp, pull, coagulate, and/or resect the targeted tissue using high frequency current[5-9]. In our previous prospective study of early gastric cancers (EGCs), we were able to remove cancers safely and easily without unexpected electrical tissue damage by using ESD with the CC (ESD-CC)[5]. However, until now clinical performance in many patients with GA treated by this new method of ESD-CC has not been sufficiently investigated. In this study, we evaluated the clinical performance of ESD-CC for GA in larger number of patients.

MATERIALS AND METHODS

Inclusion criteria/curability criteria and ethical considerations
We enrolled 122 consecutive patients (78 men, 44 women; mean age: 71.8 years, range: 52-91 years) who were histologically diagnosed with GA using specimens resected by ESD-CC at Aso Iizuka Hospital from June 2007 to December 2015 (Table 1) in this study. R0 resection (*en-bloc* resection with negative horizontal and vertical margins) is considered to be curative. To evaluate the learning curve for ESD-CC, 122 cases were grouped chronologically into four periods: (1) cases 1-30; (2) cases 31-60; (3) cases 61-90; and (4) cases 91-122. This study was carried out at Aso Iizuka Hospital and was approved by its ethics committee. Written informed consent was obtained from all patients in accordance with the Declaration of Helsinki.

Clutch cutter
The clutch cutter (CC) (DP2618DT, FUJIFILM Corporation, Tokyo, Japan; Video 1) has serrated jaws that allow the endoscopist to grasp the targeted tissue securely. The width and length of the jaws is 0.4-mm and 5-mm respectively[5-9]. The jaws can be rotated 360 degrees and the outer edges are insulated to minimize the electrical risk. The diameter of the insertion portion is 2.7 mm. The CC can manage all steps of ESD. The high-frequency electrosurgical unit is the VIO 300D (Erbe, Tübingen, Germany). The forced coagulation mode (30 W, effect 3) was used for marking. The Endocut-Q mode (effect 2, duration 3, interval 1) was used for mucosal incision and submucosal dissection, whereas the soft coagulation mode (effect 5, 100 W) was used for hemostasis and preventive coagulation (pre-cut and post-ESD).

ESD-CC
The ESD-CC procedures were performed by two endoscopists; one maneuvered the video-endoscope, and the other one operated the CC. The ESD-CC procedure

Table 1 Clinicopathological characteristics (*n* = 122)	
Sex, male/female	78/44
mean ± SD (range) age years	71.9 ± 8.4 (52-91)
Locatio	
Lower	44 (36)
Middle	54 (44)
Upper	24 (20)
Macroscopic type	
Ⅰ (protruded)	10 (8)
Ⅱa (flat elevated)	65 (53)
Ⅱa + Ⅱc	16 (13)
Ⅰc + Ⅱa	5 (4)
Ⅱa + Ⅰ	2 (2)
Ⅱc (shallow depressed)	24 (20)

Table 2 Technical outcomes of endoscopic submucosal dissection procedures using the clutch cutter (*n* = 122)	
mean ± SD size of the lesion, mm (range)	15.3 ± 8.8 (2-43)
mean ± SD size of resected specimen, mm (range)	41.4 ± 14.3 (8-90)
En-bloc resection rate (%)	122/122 (100)
R0 resection rate (%)	122/122 (100)
mean ± SD surgical time, min (range)	77.4 ± 52.8 (13-325)
Complication rate	6/122 (4.9)
Intra-ESD perforation rate	0/122 (0)
Intra-ESD uncontrollable bleeding rate	0/122 (0)
Post-ESD bleeding rate	6/122 (4.9)
Post-ESD perforation rate	0/122 (0)

ESD: Endoscopic submucosal dissection.

used a one-channel endoscope with water jet function (EG-450RD5, EG-530RD5, Fujifilm, Tokyo, Japan) or a two-channel multi-bending endoscope with water jet function (GIF-2T240M; Olympus, Tokyo, Japan). A transparent attachment (F-01, Top Co. Ltd., Tokyo, Japan) was fitted onto the tip of the endoscope to obtain an adequate endoscopic view and to create tension on the targeted submucosal tissue during ESD-CC.

The ESD-CC technique

Using the CC in closed mode, dots placed approximately 5 mm outside the lesion margin were made to mark the circumference of the target lesion. Next, 1-2 mL of hyaluronic acid solution (MucoUp: Johnson and Johnson Co., Tokyo, Japan) mixed with small volumes of epinephrine and indigo carmine dye were injected into the submucosal layer; this injection was repeated a few times to obtain sufficient elevation of the mucosa (Videos 2 and 3).

A mucosal incision and subsequent submucosal excision using the CC were repeated to remove the lesion *en-bloc*. The bleeding artery or vein was grasped, pulled or lifted, and coagulated with the CC to stop the bleeding. Finally, the *en-bloc* resection of the lesion was completed. All incisions and excisions consisted of four basic procedures: (1) grasping; (2) pulling or lifting up; (3) initiating precut-coagulation with soft coagulation (if a blood vessel is observed); and (4) cutting with the Endo-cut Q.

Histopathological evaluation

All resected specimens were sectioned into 2-mm wide slices. Histological diagnosis, tumor diameter, infiltration depth, presence of ulcer, and tumor involvement of horizontal and vertical margins were evaluated.

Assessment of the clinical outcomes

Surgical time was calculated as the time from the beginning of the submucosal injection to the end of the submucosal dissection. *En-bloc* resection was defined as the lesion being removed in one piece with macroscopically intact resection margins.

Involvement of the tumor to the resected margins was determined as R0 (*en-bloc* resection with histologically lateral and basal tumor-free resection margins), R1 (incomplete resection with histologically tumor-positive lateral or basal margins), or Rx (resection with unevaluable histological tumor margins resulting from burning effects or multiple-piece resection). All patients stayed in the hospital for 7 d following the procedure, after which follow-up endoscopic examinations were conducted at 2 d, then at 2 (or 3) mo, and annually thereafter. All patients took proton pump inhibitors for a minimum of 8 wk.

Statistical analysis

All data analysis was conducted with a statistical software package (SAS version 9.2 and JMP version 8.0.1, SAS Institute Inc, NC, United States). The Kruskal-Wallis test was used to evaluate differences with respect to tumor size and location, and ESD-CC surgical time. *P* < 0.05 was considered significant.

RESULTS

Table 1 shows the patients' clinical findings. The ratio between males and females was 1.8: 1 (78/44), and the average age was 71.9 years (52-91 years of age). Table 2 shows technical outcomes. The step of grasping and lifting or pulling before cutting the target tissue facilitated the confirmation of the distance between the grasped tissue and the proper muscle layer and enabled the use of sufficient pre-cut coagulation. All tumors could be removed easily and safely without unexpected incision. The mean diameters of GAs were 15.3 ± 8.8 mm. The mean size of resected specimens were 41.4 ± 14.3 mm. Rates for both *en-bloc* resections and R0 resections were 100%. Mean surgical time was 77.4 ± 52.8 min.

During ESD-CC, we encountered no uncontrollable bleeding. Post-ESD bleeding was observed in 4.9% (6/122) of cases. All postoperative bleeding was successfully treated by endoscopic hemostasis using mechanical clip or electrical hemostatic forceps. No patients suffered perforation. Tumor size and location significantly affected the mean surgical time (Table 3).

Learning curves showed changes in proficiency over

Table 3 Surgical time of endoscopic submucosal dissection using the clutch cutter by tumor size and location (*n* = 122)	
Tumor size	
0-20 mm	65.2 ± 41.6 (13-260)
21-mm	116.3 ± 65.6 (29-325)
P value	*P* < 0.001
Location	
Lower	57.5 ± 32.4 (13-192)
Middle	85.7 ± 58.5 (21-325)
Upper	94.8 ± 60.1 (32-264)
P value	*P* < 0.005

Figure 1 Learning curves. Video 1: The clutch cutter mechanism; Video 2: The basic ESD technique, using the clutch cutter; Video 3: Endoscopic view of ESD using the clutch cutter on gastric adenoma on the greater curvature of the lower gastric body. ESD: Endoscopic submucosal dissection.

time (Figure 1). Proficiency was expressed as surgical time only; because we had a 100% R0 resection rate and a 0% perforation rate, these parameters were not used to assess proficiency. The surgical time in the introduction stage of ESD-CC was significantly longer than in later stages (*P* < 0.01).

DISCUSSION

Gastric adenoma is usually a benign localized protruding neoplastic lesion, and is a histopathologically, proliferation of mildly atypical epithelium and tubular and/or papillary structures[10,11]. Since the prevalence of cancerous change of gastric adenoma is relatively low, it is generally considered that follow-up observation is sufficient if the biopsy result during periodic endoscopic examination is Group III and there is no increase in size or change in morphology of the lesion[12]. However, non-invasive carcinomas sometimes coexist within GAs and can progress to invasive carcinomas[12,13]. Generally, if a GA is diagnosed through an endoscopic forceps biopsy, the possibility that the lesion has not been diagnosed correctly or that the presence of cancer lesions is overlooked should be carefully considered[13]. Therefore, a total biopsy, such as endoscopic resection, is often used to obtain a conclusive diagnosis. Although most GAs are removed by conventional EMR, ESD has a high R0 resection rate regardless of the size of the tumor, it allows for more accurate and detailed histopathological examination compared with the EMR, and the recurrence rate can also be reduced[2-5]. However, ESD is a more difficult and meticulous procedure than EMR, and occasionally causes serious complications. GA is basically a benign disease, and the aim of ESD for this disease is total biopsy. Therefore, safety is vital for performing ESD, and a new and safer device is wanted in this situation.

To resolve the adverse events associated with conventional ESD using a knife devices, Akahoshi and FujiFilm developed the Clutch Cutter (CC) which can accurately grasp, pull, coagulate, and/or cut targeted tissue using high frequency current[5,8,9]. The CC has four main mechanical functions: (1) fixation (precise targeting); (2) pulling or lifting up (away from the proper muscle layer); (3) compression (high hemostatic capability); and (4) outside insulation (minimization

of outside electric damage)[5-9]. In this investigation and in our previous studies[5-9,14-17], no unintentional incisions were made, and we were able to stop intra-ESD bleeding promptly and without difficulty using the CC without changing devices (Video 2). ESD-CC is performed only by grasping, pulling (or lifting up), and cutting or coagulating procedures; most endoscopists may accept it without difficulty, because ESD-CC is similar to a forceps biopsy (Videos 2 and 3). Moreover, the CC is available for all ESD sub-procedures. These benefits of ESD-CC seem to be effective for reducing the difficulty level of ESD procedures, the frequency of adverse events, and cost[5-7].

Reported performance ranges for the use of knife devices in EGCs were *en-bloc* resection rate: 94.9%-97.7%; R0 resection rate: 82%-95.5%; and surgical time: 47.8-108.1 min[2,4,5,18-20]. In our previous study, these rates were *en-bloc* resection rate: 99.7%; R0 resection rate: 95.3%; and mean procedure time using the CC for EGC: 97.2 min[5], and in this study, these variables were 100%, 100%, and 77.4 min, respectively, using the CC for GA. Thus, rates for *en-bloc* and R0 resection and surgical time of ESD-CC for GAs appears to be slightly better than those of ESD for EGC using a conventional knife. We hypothesize that these better results are because of the CC's fixation mechanism (improving target accuracy), and the fact that GA does not cause ulcerative changes.

Perforation by ESD procedures is of two types, depending on time of onset. The first type is intra-ESD perforation, which is mainly the result of an electrical incision of the proper muscle layer by knife devices. The second fashion is post-ESD perforation that ordinarily shows 1-2 d after the ESD procedure because of deep coagulation. Intra-ESD perforation reportedly occurs in 1.2%-8.2% of gastric ESDs[3,5,21,22]. Avoiding electric damage to the proper muscle layer is important to avoid unintended incisions. The CC's mechanisms, such as the grasping function (allowing accurate targeting),

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pulling function and external insulation are very effective in preventing intra-ESD perforation, and we had none in this ESD-CC study for GAs (0%). Although post-ESD perforation is a rare complication (0.45%), it can lead to serious conditions that often require emergency surgery[23,24]. Deep thermal damage to the proper muscle layer is considered to be the main cause of perforation after ESD. A gentle push of the knife to the visible vessel using adequate power and duration of electrosurgical coagulation for hemostatic treatment is vital to avoid delayed perforation, a maneuver that requires considerable skill. In addition, there are currently no hemostatic devices with external insulation. These mechanical problems of currently available ESD devices can be associated with Post-ESD perforation. The mechanical advantages of the CC including the pull effect and external insulation are effective to prevent deep thermal tissue damage; we had no post-ESD perforations in this ESD-CC study for GAs.

Bleeding from ESD procedures is also of two types, depending on the time of onset. The first type is intra-ESD bleeding that usually occurs during mucosal incision and submucosal excision. The second type is post-ESD bleeding that occurs after the ESD procedure. Although intra-ESD bleeding occurs frequently, measuring its severity is difficult. Reportedly, significant intra-ESD bleeding occurs in 7% of procedures[25]. Its prevention and quick hemostasis are crucial because bleeding can lead to a poor endoscopic view, resulting in increased surgical time and the likelihood of perforation. Prophylactic electrosurgical coagulation of visible blood vessels and quickly stopping any bleeding are critical to safe ESDs. The CC can fix (accurately target), pull or lift-up (decreased deep thermal tissue damage), and compress (high hemostatic capability) the target tissue[5-7]. Therefore, the CC can perform effective precut coagulation and stop intra-ESD hemorrhage quickly without changing the device. We encountered no uncontrollable intra-ESD bleeding in this study. Reportedly, post-ESD gastric bleeding occurs in 5.3%-15.6% of procedures[3,21,25-28], usually within a week after ESD. Therefore, patients are hospitalized for seven days after ESDs in our institute. The CC can perform precut coagulation or coagulation for exposed blood vessels of a bottom of ESD ulcer. In our research of GAs, the post-ESD bleeding incidence was 4.9%. We must focus on post-ESD bleeding as well as conventional ESD bleeding.

In the introduction stage of ESD, endoscopist has to overcome its technical difficulties and high rates of complication including perforation and bleeding[29,30]. Previous studies[30-32] of learning curves for ESD using knife devices show decreased surgical durations and complication rates and increased rates of successful R0 resections, over time. However, ESD-CC is a simple method that consists of (1) grasping; (2) pulling; and (3) cutting or coagulating, as with a standard bite biopsy. Therefore, we obtained a 100% R0 resection rate and a 0% perforation rate, even at the beginning of the learning curve, because of the ease of learning the ESD-CC procedure, although we were beginners of conventional ESD method using knives. Based on the results of the learning curve analysis, about 30 cases of experience are needed to master the skills to perform ESD-CC for GAs safely and effectively.

In conventional ESD procedures, several specific knives and devices are needed to accomplish the ESD[5-7], whereas ESD-CC was carried out using only the CC. Before introducing ESD-CC into our institute, we performed conventional ESD procedures that required a needle knife for marking and creating the starting hole, an insulation-tipped electrosurgical knife for mucosal incision and submucosal dissection and an electric hemostat for intra-ESD hemorrhage[5-7]. The total number of devices for a single ESD was at least three. In our research, we used only one device, the CC, throughout the ESD. Thus, the ESD-CC significantly reduces the number of devices and the cost of ESD[5,7].

In conclusion, because of its safety, effectiveness of use, technical ease of operation, and low cost of performance, the ESD-CC represents a promising option in the treatment of GAs.

COMMENTS

Background
Compared with endoscopic mucosal resection (EMR) for early gastric tumors, endoscopic submucosal dissection (ESD) has considerable advantages with regard to the rates for *en-bloc* resection, R0 resection and local recurrence. The main shortcoming of ESD using conventional knives is its technical difficulty. Therefore, it has a high rate of complications, and requires advanced endoscopic skills and many devices.

Research frontiers
Conventional knife devices gently push the knife to the tissue and cut using electrosurgical current. As these cutting methods lack a grasping function (which would allow more accurate targeting and hemostatic effect) and pulling function (to lift tissues away from the proper muscle layer), they carry a risk of major complications such as perforation and bleeding.

Innovations and breakthroughs
To reduce the risk of complications related to ESD using a conventional knife, Akahoshi and FujiFilm developed a new grasping type of scissor/forceps, the clutch cutter (CC), which can accurately grasp, pull (or lift), coagulate, and/or incise targeted tissue using electrosurgical current. The CC can safely perform four characteristic mechanical procedures: (1) fixation for accurate targeting; (2) pulling or lifting tissue away from the proper muscle layer; (3) compressing tissue through high hemostatic capability; and (4) external insulation, which minimizes risk of unintended electric damage.

Applications
The authors performed ESD-CC for 122 patients with gastric adenoma. The *en-bloc* resection rate was 100% and the R0 resection rate was 100%. No patients in this study suffered perforation. Post-ESD-CC bleeding occurred in 6 cases (4.9%), which were successfully treated by endoscopic hemostatic treatment.

Terminology
The CC (DP2618DT, FujiFilm Corporation, Tokyo, Japan) is a grasping type of scissor/forceps (VTR. 1), which can grasp and cut or coagulate a piece of tissue with electrosurgical current. It has a 0.4-mm width and a 3.5-mm or 5-mm long serrated cutting edge to facilitate grasping the tissue. The outer side of the forceps is insulated so that electrosurgical current energy is concentrated at the enclosed blade, to avoid unintentional incision. Furthermore, the forceps can be

rotated to the desired orientation. The diameter of the forceps is 2.7 mm. The CC is disposable and not reusable. The CC is available for all steps of ESD.

Peer-review

This manuscript "Endoscopic submucosal dissection of gastric adenomas using the clutch cutter" is the nice paper and good results with the CC.

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CASE REPORT

Management of hyperplastic gastric polyp following upper gastrointestinal bleeding in infant with Menkes' disease

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Abstract

We report a case of an infant with Menkes' disease (MD) presented at the age of five months, with coffee ground vomiting, melaena with a significant drop of haemoglobin. Urgent endoscopic assessment revealed a friable bleeding trans-pyloric multi-lobulated sessile polyp. Due to further significant upper gastrointestinal bleeding, polypectomy occurred. Endoscopic mucosal resection was performed with a grasp-and-snare technique using a dual channel operating gastroscope. Haemostasis was achieved by application of argon plasma coagulation where required. No perforation occurred. Repeated debridement was required 6 wk after which the growth was excised completely with no further blood transfusion required after that procedure. Histological examination confirmed ulcerated and inflamed hyperplastic polyp. We discuss our endoscopic technique and discuss the reported gastrointestinal manifestation of MD in the literature.

Key words: Menkes' disease; Gastrointestinal bleeding; Grasp and snare technique; Polypectomy; Gastric polyp

Core tip: Infant with Menkes' disease can present with a potentially life threatening bleeding from hyperplastic gastric polyp. Removing hyperplastic polyp in those infants using grasp and snare technique is feasible and can avoid unnecessary surgical excision in those children.

INTRODUCTION

Menkes' disease (MD) is a rare metabolic disease secondary to copper deficiency. It usually presents within the first year of life. Failure to thrive, neurological deficits, and seizures, along with subdural haematomas, connective tissue abnormalities and bony changes are classical features of MD[1]. Gastrointestinal disorder had been reported in MD including gastrointestinal bleeding. Surgical intervention is the only described treatment in the management due to the challenges of endoscopic management in the first year of life.

CASE REPORT

A Caucasian boy was born of an unrelated couple after an uncomplicated pregnancy. He was vaginally delivered at 39-wk gestation with a birth weight of 2880 g. At birth, no abnormal physical findings were recorded. At one month of age, he was referred because of two cephalohaematoma. Further examination revealed mild dysmorphic features including bilateral adducted thumbs, pectus excavatus, lax skin, moderate hypotonia and bilateral inguinal herniae. In view of mild respiratory distress a chest X-ray was performed and revealed two posterior rib fractures. Following that a skeletal survey was performed and revealed a Wormian bone raising the suspicion of MD. Further physical examination showed bronze and steely hair. The diagnosis of MD was made based on a serum copper level of 0.6 (reference range 5.9-16.3 mg/dL), and confirmed by positive genetic testing for the ATP7A gene. He developed epilepsy which was treated with anti-convulsants. In addition, an echocardiogram revealed aortic stenosis and abdominal US showed bladder diverticuli.

Subcutaneous copper histidinate therapy was introduced at around 8 wk of life. He was nasogastrically fed due to concerns regarding safe swallowing. At the age of five months, he presented with multiple coffee ground vomiting episodes and evidence of aspiration. Initially this was assumed to be secondary to gastro-oesophageal reflux disease (GORD). He was managed conservatively with proton pump inhibitors and naso-jejunal feeding. At the age of six months and after a significant drop of haemoglobin from 10 mg/dL to 7.6 mg/dL associated with melaena, urgent endoscopic assessment revealed a friable bleeding trans-pyloric multi-lobulated sessile polyp of around 4 cm in diameter (Figure 1). The lesion was partially obstructing the pylorus but pyloric intubation was easily performed. Histological examination of the biopsied sample was suggestive of hyperplastic polyp.

Due to further significant upper gastrointestinal (GI) bleeding polypectomy occurred. Tissue lifting was

Figure 1 Endoscopic appearance of the hyperplastic polyp.

Figure 2 Piecemeal polypectomy.

achieved with plasma expander mixed with adrenaline and methylene blue. Piecemeal polypectomy was the procedure of choice (Figure 2). Due to the difficulty in lifting up such a folded and small area, endoscopic mucosal resection was performed with a grasp-and-snare technique (20 mm eccentric snare and crocodile grasping forceps) using a dual channel operating gastroscope (Erbe Endocut level 1 and 2); the snare was connected to the ERBE and placed down channel one of the dual scope whereas the grasping forceps was down channel two (Figure 3). Table 1 describes the required equipment for the procedure.

Haemostasis was achieved by application of argon plasma coagulation where required (Figure 4). No perforation occurred. Repeated endoscopic debridement was required 6 wk after which finally excised the growth (Figure 5) with no further blood transfusion required after that procedure. Histological examination of the polyp revealed granulation tissue with fibrosis and neovascularisation of the submucosa with evidence of an ulcerated surface and hence the histological confirmation of ulcerated and inflamed hyperplastic polyp.

DISCUSSION

Connective tissue abnormalities in MD are caused by decreased lysyl oxidase (LO) activity. LO is the

Figure 3 The use of grasp-and-snare technique.

Figure 4 The use of argon plasma coagulation to achieve hemostasis.

Figure 5 Appearance post procedure.

Table 1 The equipments during the procedure
GIF-XQ 260; Olympus Optical Co. , Ltd
Dual channel operating scope (2TQ260M), Olympus Optical Co., Ltd
Argon plasma coagulator and ERBE electraucatery
Argon catheter. 1500 A, 1.5 mm, ERBE electraucautery.
Polyloop (2.8 mm channel); Olympus®
25 mm eccentric snare(1.8 mm channel); Quick Clip®
Clip applicators (single use rotatable clip fixing devise), Olympus®
Resolution clip, Boston Scientific®
Rat toothed grasper, Olympus®
Roth net, 2.5 mm, 3 cm, US endoscopy®
Injection needle, 2.8 mm, 155 cm, Olympus®
50 mL syringe
Succinylated Gelatin, Volplex®
Methelionum blue
Adrenaline 1 in 10000

mittent obstruction to the gastric outlet. Exposure of the functional mucosa of this polyp in the alkaline media of the duodenum possibly resulted in continuous gastrin secretion and in turn hypergastrinaemia and erosion of the polyp leading to haematemesis[3].

Review of the literature reveals 4 similar cases of hypertrophic gastric polyps in MD: EMBASE, PubMed, and google scholar databases were searched from 1970 till now using the keywords "Menkes", "gastrointestinal bleeding", and or "polyp".

First case presented at 3 and a half months with coffee ground emesis, upper GI endoscopy revealed an irregular growth around the posterior wall of the gastric antrum there which was managed conservatively as per his parental wishes. At seven months he had massive GI bleeding with melaena leading to hypovolemic shock and death. Post-mortem revealed an ulcerated polypoid mass obstructing the pyloric opening[4].

The second case presented at the age of 10 mo with haematemesis managed conservatively followed by large haematemesis eight months lated. Endoscopy revealed a large solitary ulcerated polypoid mass, again partially obstructing the pylorus. Surgical excision of the mass was performed successfully[4].

The third case was discovered at a post mortem examination of an 11-mo-old infant with MD and revealed an isolated hyperplastic gastric polyp located around the pyloric antrum[5].

The fourth was a Japanese boy with MD who developed multiple gastrointestinal polypoid masses on the palate, the posterior wall of the oropharynx, the gastric body, and pyloric antrum despite normal serum copper levels following copper therapy[6].

Hyperplastic polyps in infancy of such a large size with extensive involvement of the antrum and pylorus of the stomach are extremely rare[7]. Two previous report in non MD has been described in infancy period and required surgical resection secondary to hematemesis and obstructive symptoms[7,8]. Gastric polyps have been described in children receiving long term proton pump inhibitor (PPI) therapy as in our patient[9]; however, the majority of PPI-associated polyps are small (2-8 mm), with a partly translucent surface and usually located in

copper dependent enzyme responsible for oxidative deamination of lysine and hydroxylysine as the first step in collagen cross-link formation and is low in this condition[2,3].

It has been hypothesized that the connective tissue weakness caused by LO deficiency creates a predisposition toward mucosal redundancy and hypertrophic polyp formation at the pyloric outlet, a site exposed to chronic localized pressure during gastric peristalsis[4].

Haematemesis in our patient can be explained by the presence of a polyp found in the pyloric region which acted as a ball-valve mechanism, causing inter-

the fundus or proximal in the gastric corpus. In most cases, these polyps appear to be fundic gland polyps, although in a minority hyperplastic and inflammatory polyps occur[10,11].

In Western countries, adults hyperplastic polyps constitute 20% of all gastric polyps and are sessile or pedunculated polyps of usually less than 2 cm in diameter. They can occur as single polyps usually in the antrum or as multiple polyps throughout the stomach[12]. Hyperplastic polyps of the gastric antrum are a rare but significant cause of gastrointestinal blood loss in older patients. Removal of the polyps using endoscopic or surgical methods may be required for resolution of the blood loss along with iron supplementation[13].

Though bleeding from hyperplastic gastric polyps is not well documented in adult series, a review by Al-Hadad *et al*[14] of all gastric polyps encountered in their centre revealed 1.4% to be hyperplastic polyps in the gastric antrum, of whom 35% presented with melaena and significant iron deficiency anaemia.

The British Society of Gastroenterology (BSG) recommends the removal of hyperplastic polyps > 1 cm whenever possible whilst multiple, or smaller ones can be biopsied and monitored annually. Biopsies should be taken of the intervening or surrounding mucosa and *Helicobacter pylori* eradicated when present[15].

Endoscopic treatment

To the best of our knowledge our case is the first reported in a child with MD to undergo endoscopic treatment of such a hyperplastic gastric polyp. In addition, and allowed by recent advances in endotherapeutic techniques, this is the first reported case of an infant of a weight of less than 6 kg that has undergone extended endoscopic submucosal dissection (ESD) using the grasp-and-snare technique.

In an adult series of 11 patients: The grasp-and-snare technique was used to perform EMR with good outcomes where sub-mucosal lifting and accessibility were problematic[16]. Complication rates are known to be higher after EMR and ESD relative to other basic endoscopic interventions[17]. In an adult series gastric lesions treated with EMR and ESD demonstrated complete resection in 73.9% and a combined complication rate of 1.9% (1.4% bleeding, 0.5% perforation)[18].

Of note our case also had significant GORD, which is noted to be more frequent in MD and in one case during open Nissen fundoplication, loose connective tissues were noted around the GOJ, especially the crura of the diaphragm[19]. GOR is probably one of the connective tissue manifestations od MD and may reflect a failure in elastin and collagen crosslinking caused by a decrease in the functional activity of copper-dependent LO. Defective elastic fibres within the internal elastic lamina, tunica media, and intimal layers of arteries and arterioles result in vascular tortuosity and ectasia with greater predisposition to mucosal haemorrhage[20].

This case identifies an unusual gastrointestinal complication of MD and for the first time shows the possibility of successful and uncomplicated EEMR even in very small infants.

COMMENTS

Case characteristics
Upper gastrointestinal bleeding in infants with Menkes' disease (MD).

Clinical diagnosis
Hyperplastic gastric polyp.

Differential diagnosis
Upper gastrointestinal endoscopy ruled out other diagnosis of gastrointestinal bleeding like gastric/ duodenal ulcers /erosive oesophagitis/erosive gastritis.

Laboratory diagnosis
Low serum Copper level was documented. Patient had recurrent low haemoglobin level after bleeding episodes necessitating blood transfusions. The diagnosis was confirmed with upper gastroesophageal endoscopy.

Pathological diagnosis
Bleeding from ulcerated hyperplastic gastric polyp in the gastric antrum was the diagnosis as per endoscopic finding and the histological examinations.

Treatment
The patient was treated endoscopically. Piecemeal polypectomy was the procedure of choice. Due to the difficulty in lifting up such a folded and small area, endoscopic mucosal resection was performed with a grasp-and-snare technique. Repeated debridement was required 6 wk after which the growth was excised completely with no further blood transfusion required after that procedure. Histological examination confirmed ulcerated and inflamed hyperplastic polyp.

Related reports
Four similar cases of hypertrophic pyloric gastric polyps in MD were all presented in infancy period, two patients had fatal extensive bleeding and two managed with surgical excision of the pylorus.

Experiences and lessons
Infants with MD can present with a potentially life threatening bleeding from hyperplastic gastric polyp. Endoscopic removal of the polyp infants using grasp and snare technique is feasible and can avoid unnecessary surgical excision in those children.

Peer-review
Nice case. Good literature review.

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FLYLEAF

EDITORS FOR THIS ISSUE

Terahertz endoscopic imaging for colorectal cancer detection: Current status and future perspectives

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Abstract

Terahertz (THz) imaging is progressing as a robust platform for myriad applications in the field of security, health, and material science. The THz regime, which comprises wavelengths spanning from microns to millimeters, is non-ionizing and has very low photon energy: Making it inherently safe for biological imaging. Colorectal cancer is one of the most common causes of death in the world, while the conventional screening and standard of care yet relies exclusively on the physician's experience. Researchers have been working on the development of a flexible THz endoscope, as a potential tool to aid in colorectal cancer screening. This involves building a single-channel THz endoscope, and profiling the THz response from colorectal tissue, and demonstrating endogenous contrast levels between normal and diseased tissue when imaging in reflection modality. The current level of contrast provided by the prototype THz endoscopic system represents a significant step towards clinical endoscopic application of THz technology for in-vivo colorectal cancer screening. The aim of this paper is to provide a short review of the recent advances in THz endoscopic technology and cancer imaging. In particular, the potential of single-channel THz endoscopic imaging for colonic cancer screening will be highlighted.

Key words: Endoscopy; Terahertz imaging; Colonoscopy; Colon; Cancer detection; Flexible waveguides; Metal-coated; Polarization-sensitive; Polarization; Cross-pol

Core tip: Terahertz (THz) imaging is progressing as a robust platform for a myriad of applications in the field of medicine. The non-ionizing THz radiation associated with safe energy levels has the potential to achieve high-resolution images of an organ or tissue, effectively combining both macroscopic and microscopic information. THz reflection imaging provides an intrinsic contrast between normal and diseased tissues, in real-time. This review describes the design, development, and practical implication of flexible THz endoscopic system, while simultaneously obtaining an overview of the existing

technology. In addition to the state-of-art THz endoscopy, the feasibility study of a single-channel THz endoscopic system for colorectal cancer screening will be highlighted.

INTRODUCTION

Colorectal cancer

Cancers represents the most common reason for death worldwide causing 8.2 million deaths each year with more than 14 million new diagnosed cases. Colorectal cancer (CRC) is the third most commonly diagnosed cancer in the world causing 0.7 million deaths per year (WHO Data and Statistics). The most effective method of bringing down the cancer risk is the early diagnosis. The current staging and treatment of CRC relies on the traditional imaging technologies; such as conventional colonoscopy[1,2], optical coherence tomography (OCT)[3,4], computed tomography (CT)[5,6], magnetic resonance imaging (MRI)[7,8], and positron emission tomography (PET)[9,10]. The present method for CRC screening is colonoscopy, which relies exclusively on the physician's experience and judgment. During colonoscopy, the obtained abnormal tissue will be sent for pathological examination for diagnosis.

Besides colonoscopy, the aforementioned CT, MRI and PET are the conventional diagnostic imaging modalities for the detection of CRC. Optical coherence tomography offers micrometer resolution and is proved to be ideal for cancer imaging. However, it has the limitation due to unwanted high optical scattering in the tissue[11]. Computed tomography is a noninvasive technique and provides 3D tomographic images of the entire colon. CT is better at detecting small lesions (less than 1 cm size) as compared with MRI. Despite of that CT cannot detect most common tumors, especially the lesions smaller than 0.5 cm diameter[12]. Furthermore, CT uses harmful ionizing X-rays[13] and cannot be used in renal failure patients[14]. In contrast, magnetic resonance imaging relies on liquid enema for contrast and hence is expensive[12]. On the other hand, positron emission tomography provides good sensitivity and specificity of 80%-90% and can differentiate tumors from scar tissue created by surgery. However, MRI provides very low resolution if the tumor is not metabolically active and also has less sensitivity for lymph node staging[15].

Macroscopic information of the tissue can be attained using conventional CT and MRI techniques, but they provide low-resolution images with less specificity. The microscopic (structural and functional) information can be extracted only from the biopsied samples. It is still not plausible to achieve *in-vivo* high-resolution images of an organ or tissue with microscopic information in real-time using conventional imaging methods. One can potentially bridge this gap between macroscopic and microscopic imaging using the terahertz (THz) wavelengths spanning from microns to millimeters. In addition, to ascertain the presence of cancer during conventional colonoscopy, a biopsy will be performed from the suspected regions or polyps[16]. Since most of the CRCs, above 80%, are difficult to detect in the early stage; clinicians often schedule regular patient visits and perform biopsy excisions for pathological examination. If an imaging modality provides the ability of delineating the diseased or abnormal region of fresh tissue in real-time, without staining the tissue, it's not only time effective but also improves the screening capability of endoscopy. Since, THz is nonionizing and provide endogenous contrast within the tissue based on the abnormalities[17], alternative to the conventional colonoscopy, a THz endoscope can potentially be used for the *in-vivo* cancer screening.

Tissue abnormality and cell disorder

Figure 1 displays the histology slides[18-20] of hyperplastic, normal, and various stages of colon cancer tissues. Usually, a tumorous tissue contains larger size nuclei with irregular shapes. The structures are disorganized and crowded. Figure 1 (N) shows the enface section of normal mucosa with an inset showing normal mucus-secreting colon cell. In the enface direction, Figure 1 (HP) shows both normal and hyperplastic mucosa structures for comparison. Crypts are the columnar structures in the mucosa layer of the colon tissue, made up of goblet cells, with approximately 100 μm diameter. The hyperplastic crypts tend to be order of magnitude larger and elliptical in shape. The hyperplastic crypts shown in the Figure 1 (HP) are 4 times larger than normal crypts and oblong in shape. Figure 1 (P) shows an enface cut of a sporadic juvenile polyp (benign). The smooth eroded surface with numerous mucus retention cysts is typical of these polyps. Figure 1 (S1) shows a benign neoplasm of mucus-secreting colon cell. The Mu denoted in the figure is the mucin contained inside goblet cells. The benign tumor is characterized by crowded nuclei and shortage of mucin production in goblet cells. Figure 1 (S2) exhibits neoplasm of mucus-secreting colon cell. The characteristics shown are larger nuclei, nuclei that are no longer arranged at the bottom of goblet cells, and almost no mucin production.

The typical size of the nucleus is around 1 micron, whereas in neoplastic cells the nuclei tend to be larger and around 3 to 5 μm. Figure 1 (S3) shows a malignant neoplasm of mucus-secreting colon cell, which is characterized by the disorganization of cellular components such that it no longer resembles the normal colon tissue. The aggressive tumor cells are randomly arranged and contain large nuclei that vary

Figure 1 Enface histology[19,20] sections of hyperplastic mucosa (HP), normal (inset: Mucus secreting colon cell) (N), sporadic juvenile benign polyp (P), low grade stage Ⅰ (S1), intermediate stage Ⅱ (S2), and high grade stage Ⅲ colon (S3). Mu: Mucin; E: Epithelium; M: Mitoses.

in size and shape, dominating most of the cell volume. Therefore, the normal tissue is very homogenous at THz wavelengths while cancerous and dysplastic tissue has structures approaching the size of the wavelength. In addition, the dense structure of abnormal region can lead to higher refractive indices and can result in greater reflectance values. As a result, both of these mechanisms can engender an intrinsic contrast between normal and cancerous regions.

Screening techniques

CRC is one of the most common cancers across the world. The disease is slow to develop, but the early diagnosis and removal of abnormal growths is an effective method of reducing cancer risk. Expert groups recommend that people at average risk for CRC should start regular screening at the age of 50. Several tests can be used to screen CRCs[21] and these tests were classified into two types; tests that can detect both polyps as well as cancer and tests that detect mainly cancer. The first kind looks at the structural information to recognize abnormal regions, which can be achieved with the insertion of scope into the rectum or by using a special X-ray imaging method. This test can prevent CRC, since the polyps found in the benign stage will be removed during the test. The second type diagnostics involve testing stools for the presence of cancer. These tests are less invasive and can be easily performed but are less likely to detect polyps. Although most expert groups generally recommend high sensitivity fecal occult blood test, sigmoidoscopy, and colonoscopy for cancer screening; several other tests such as virtual colonoscopy and barium enema are also used. Table 1 describes the merits and demerits of the techniques used for CRC screening.

THz endoscopy

The THz frequency region is situated between microwave and infrared regions of the electromagnetic spectrum with frequencies ranging from 10^{11} to 5×10^{12} Hz. THz imaging has shown a great potential for *in-vivo* and *ex-vivo* identification of tissue abnormalities, hydration and sub-layer probing[22]. Since THz frequencies are sensitive to water content and they can penetrate deep into the tissue, THz was proven to be ideal for cancer[23,24] imaging. Researchers have affirmed the use of THz wavelengths and in turn the potential of THz colonoscopic imaging by demonstrating positive results with dental[25,26], skin[17,27], breast[28], liver[29], oral[30] and especially gastric cancer studies[31].

Endoscopy is a less invasive medical procedure to diagnose the interior surfaces of an organ or cavity of body without the need for surgery. To address the physician's requirement in accessing different areas of the body[32], endoscopes were traditionally designed in "rigid" and "flexible" configurations. Rigid endoscopes relay images from the tip of the scope to eyepieces with the help of arranged stack of lenses and provide high-quality images. These rigid endoscopes are surgical devices and have to be inserted through temporary access ports created by the physician. Unlike the rigid endoscope, flexible endoscope is more versatile and can be directly inserted through natural body cavities. Usually flexible endoscopes provide low quality images and typically contain either a fiber-optic or miniature video camera at the tip[33]. Using conventional endoscopes, the cancer screening and decision to remove abnormal region solely depends on the visual inspection and experience of a physician. In contrast, a THz endoscope integrated into a conventional endoscopic system will suffice the *in-vivo* CRC screening requirement in real

Table 1 Merits and demerits of current conventional techniques used in colorectal cancer screening

Test	Advantages	Disadvantages
Flexible sigmoidoscopy	Quick and safe method	Bowel cleansing is required
	Biopsy or polypectomy can be done	Can miss small polyps
	Usually doesn't require full bowel preparation	Views only the lower third of the colon
	Sedation is not required	Can't remove all polyps
	Done every 5 yr	If an abnormality is found, colonoscopy will be required
Standard colonoscopy	Very sensitive	Full bowel preparation needed
	Can view entire colon	Can miss small polyps
	Can do biopsy and remove polyps	More expensive
	Can diagnose other diseases	Minor sedation is required
	Done every 10 yr	Small risk of bleeding, bowel tears, or infection
Virtual colonoscopy	Quick and noninvasive	Need full bowel preparation
	Can view entire colon	Cannot detect polyps < 5 mm
	No sedation is needed	Possibility of false positive test results
	Done every 5 yr	Cannot remove polyps
		If an abnormality is found, colonoscopy will be required
Fecal occult blood test	Non-invasive	May miss polyps and cancers that doesn't cause bleeding
	No bowel preparation is required	Some false positive results
	No sedation is required	Pre-test dietary limitations
	Inexpensive	Should be done every year
	Sampling done at home	If an abnormality is found, colonoscopy will be required

time. The THz endoscope is a medical device consisting of a flexible THz waveguide instead of an optical fiber and uses a THz laser as light source and a THz detector in place of a video camera for examining the interior surface of an organ or cavity and detects abnormal regions.

THz endoscopic imaging has the potential to offer a safe, minimally invasive medical imaging modality for screening and detecting CRCs. To test this hypothesis, the experimental measurements have to be performed in four steps: Obtaining ideal system-imaging frequency, evaluating base contrast, testing flexible THz waveguides for use as an endoscope, and demonstrating THz waveguide based imaging of colorectal tissue. To confirm system-imaging frequency, the frequency dependent absorption coefficient and refractive index of colorectal tissues must be acquired using a traditional time domain pulsed THz system with frequency bandwidth of 0.1 to 5 THz. To evaluate the base contrast, THz reflectance images of human colonic tissues need to be obtained on *ex vivo* specimens and compared with the tissue histology. To test the flexible THz waveguides for use as an endoscope, waveguides should be characterized at the desired imaging frequency prior to the determination of waveguide operational parameters. Finally to demonstrate THz endoscopic imaging, the requirement is to integrate flexible waveguide with the transceiver system, implement waveguide based reflection modality imaging, and obtain sensitivity and specificity of the device from colorectal specimens.

Previously proposed THz endoscopes fall into two categories. The first category uses an uncoated polymer tube to transmit THz radiation and works in transmission modality. This study based on anti-resonant hollow core waveguides used a Teflon pipe to transmit THz radiation. However, the guiding capability is compromised due to the radiation not confining inside the bent tube and results in high bending losses[34]. Also, for endoscopic applications that require extensive bending, the guided field easily escapes into the air and interacts with the surrounding and ultimately contaminates the resultant image. In addition, a recent study that relied on a polymer tube to propagate the THz beam with an attached bull's-eye structure, works in transmission modality, to obtain near-field enhancement[35]. However, in general, the high absorption associated with THz demands reflection based imaging for *in vivo* applications. The second category uses a mode locked femtosecond laser and relies on optical fibers for pulse propagation. It contains the THz source at the end of the optical fiber and is inserted into the patient[36]. Consequently, electrical connections to drive the THz source must be inserted into the patient. Also it requires two channels, including a first channel for guiding radiation to the sample and a second channel for guiding the reflected light to a detector. In addition, the photoconductive antenna connected with the optical fiber necessitates high input voltage that is inadmissible for in-vivo imaging.

A recent study by Doradla *et al*[37] demonstrated a bendable prototype endoscopic system that relies on metal-coated THz waveguides for cancer imaging. The endoscopic system uses a single flexible waveguide channel to transmit the THz and collect the reflected signal from the tissue. The system is able to operate in both transmission and reflection configurations. Using a metal-coated THz waveguide provides 99% inner surface reflectivity at all THz wavelengths and confines the THz radiation. It preserves the linearly polarized launched mode and exhibits low bending loss even at larger bending angles. The hyper hemi spherical lens attached to the waveguide output end provides diffraction limited, approximately half the wavelength ($\lambda/2$) sized beam waist, which is free from lens aberrations. The resulting THz intensity images, attained

Figure 2 Terahertz spectroscopic results for the absorption coefficient (A) and refractive index (B) of fresh excisions of normal (blue) and cancerous (red) colon tissues[38] (Printed with permission). THz: Terahertz.

using polarization sensitive detection, exhibited an endogenous natural contrast between normal and abnormal (cancer) regions of both formalin fixed and fresh tissues. Henceforth, this study shows the potential of THz endoscopic imaging for cancer screening and detection.

OVERVIEW OF EXPERIMENTAL WORK

THz spectroscopy of colorectal tissue

Intrinsic contrast observed in THz images of human colonic tissues is indicative of a change in the complex refractive index between cancer and normal tissue at THz frequencies. Thus the first step to develop an imaging system is to measure the THz spectroscopic response of colorectal tissues and determine frequency regimes for the contrast. Reid *et al*[38] and Faustino *et al*[39] performed THz time domain spectroscopy on cancerous and normal colon tissues, in this section we summarize their results.

Reid *et al*[38] used a conventional THz-TDS system to image cancer, dysplastic and healthy colon tissues from 30 patients. Their study was carried out in reflection mode and histopathological sections of the imaged tissues were used as the gold standard to classify tissue regions as cancer/dysplastic/normal and the corresponding optical properties were determined and averaged over different specimens. Their results for the frequency dependent absorption coefficient and refractive index are shown in Figure 2. As expected, the absorption increases with increasing frequency (this mimics how liquid water responds in this frequency region) and the refractive index (real part) is fairly steady in the region of interest. What is of interest for imaging applications, however, is the variation of these parameters between healthy and diseased tissue.

Faustino *et al*[39] investigated the THz reflectance and transmittance of specimens of paraffin embedded colon cancer and normal tissues. The samples investigated were cut to 2 mm thicknesses and the results are displayed in Figure 3.

As seen in Figure 3, there is a difference in the absorption coefficient of normal and cancerous colon in dehydrated formalin fixed samples. This result is extremely interesting as it indicates that water is not the sole contributor to THz contrast. Other studies[40], have shown that while water does contribute to the observed contrast in fresh tissues, it is not the sole mechanism. Other factors such as tissue morphology leading to scattering might also measurably affect the tissue response. We discuss possible contrast mechanisms later in this review, however, at this point the complete mechanism for the intrinsic contrast seen in THz images of colon tissue is not completely understood.

When determining the exposure frequency for THz imaging of colon cancers, it is the difference in the complex refractive index that ultimately determines contrast. Transmission images rely primarily on differences in the absorption coefficient while sample reflectance is dominated by changes to the real part of the refractive index. As seen in Reid *et al*[38]'s data (Figure 3) while the absorption increases with increasing frequency, the difference in absorption decreases- thus frequencies above approximately 0.7 THz are not suited for transmittance based images. For reflection based imaging, however, the frequency region of interest spans 0.2-1 THz, as the difference in refractive index is equitably constant.

Different imaging approaches are discussed in later sections; however, there are other factors that also influence modality and frequency selection that we discuss below. *In vivo* applications require reflection based imaging-THz radiation is strongly absorbed by tissue, thus transmission through thick sections is not feasible. Lower frequencies correspond to longer wavelengths and thus lower resolution in the far field. However, higher frequencies experience stronger absorption, thus exhibit less penetration into tissue. Most single frequency systems used for imaging colon tissue thus far work at around 0.6 THz (500 μm) as a compromise between these two factors. A notable exception is the work done by Chen *et al*[41]

Figure 3 Absorption (A) and reflectance (B) measurements of paraffin embedded dehydrated fixed specimens of normal and cancerous colon tissue[39] (printed with permission). THz: Terahertz.

Figure 4 Photographs, absorption (transmittance) and reflection images of formalin fixed dehydrated colon tissue[39] (printed with permission).

in transmission imaging at 0.3 THz (approximately 1 mm); they compensate for the lower far-field resolution by using a specially designed aperture which allows for significantly higher resolution in the near field.

THz imaging of human colorectal tissues

Continuous-Wave (CW), or single frequency imaging of *ex vivo* samples of normal and cancerous colon tissues has been demonstrated. Faustino *et al*[39] have imaged paraffin embedded, formalin fixed specimens of normal and cancerous colon in both transmission and reflection modalities. They used a solid-state multiplier/amplifier chain as their source (VDI systems) and a microbolometer array for detection. The frequency of the imaging system was 0.6 THz (500 μm). As can be seen in Figure 4, the transmittance images of dehydrated fixed tissue still show contrast between

normal and cancer, while the reflection images do not show any appreciable difference. This is expected based on the spectroscopy results for these tissues, which are discussed in prior section. The change in absorption persists in the imaging while the lack of difference in the real part of the refractive index shows up as no observable contrast in the reflectance images.

Reid *et al*[38] have imaged excised healthy, dysplastic, and cancerous colonic tissues obtained from 30 patients in reflection modality. They used a stand-alone portable THz imaging system TIP imaga1000. The frequency of the imaging system was 0.03-1 THz. The difference in the reflected waveforms and the ultimate contrast between normal, dysplastic, and cancerous tissue regions were depicted in Figure 5.

Doradla *et al*[42] measured the THz reflectance of thick, fresh excisions of cancerous and normal colon tissue using a CW THz imaging system operating at 0.584 THz (513 μm). They used far-infrared laser based on CO_2 gas and a silicon bolometer that runs with liquid helium as a detector. Figure 6, below shows a schematic of the imaging system. The beam is incident normal to the sample and the reflectance is measured using a beam-splitter. Wire-grid polarizers allow for the selection of specific polarizations and both images comprised of the co-polarized and cross-polarized remittance of the samples can be measured. The samples used in this study were thick fresh excisions of normal and cancerous colon tissues. The samples were measured the same day as the surgical procedure and were backed with saline soaked gauze during the measurement process to make sure that they did not dry out. Figure 7 shows some of the images collected alongside digital photographs of the sample.

As shown in Figure 7, the cross-polarized reflectance of normal colon is lower than the cross-polarized reflectance of cancerous colon. This result was found for all 4 sample sets (each sample set consisted of one normal and one cancerous tissue) measured in this study. The authors also computed the percent reflectivity difference between normal and cancerous

Figure 5 An example terahertz image of excised cancerous, dysplastic and healthy colonic tissues. A: Example terahertz (THz) image of tissue containing healthy regions, dysplasia and cancerous tissue; B: The histology results (drawn onto a photographic image of the tissue samples); C: The histology results are overlaid on the THz image. In this example, regions a and b are normal tissue, c is dysplastic tissue and d is cancerous tissue[38] (printed with permission).

Figure 6 Schematic of continuous-wave terahertz reflection imaging system[42].

colon tissue for both the cross-polarized and co-polarized data for each sample set while accounting for background.

As can be seen in Table 2, the cross-polarization channel exhibits a significantly larger reflectivity difference than the co-polarized channel. Moreover, the difference observed in cross-polarization is consistent across different sample sets (*i.e.*, it is consistent across samples from different patients), thus it presents a potential quantitative screening tool for cancer detection.

Waveguide based imaging
Biomedical imaging of organs or hollow cavities of human body often demands endoscopic access. Highly bendable waveguides with low transmission loss are inevitable for endoscopic applications. Therefore, flexible THz waveguides with good mode preservation

characteristics and low propagation and bending losses are essential for *in-vivo* THz imaging of CRC. Previously, THz waveguides were fabricated from various materials[43-45] with multifarious cross sectional designs[46-48]. Most of these waveguides are either rigid or not flexible at larger bore diameters[49,50]. In addition the flexible THz waveguides suffered from excessive propagation losses[51,52]. On the other hand, the fabrication technique used for the fabrication of the cylindrical waveguides is not applicable for waveguides with < 3 mm diameter[53]. Doradla *et al*[54,55] reported the characteristics of hollow, flexible, cylindrical THz waveguides that were fabricated with inner metal and metal/dielectric coatings. They provide low loss (less than 1 dB/m) and are small enough in diameter and satisfy the criteria for endoscopic applications.

The three operational parameters of waveguides

Figure 7 Digital photograph (A) and corresponding terahertz reflectance images (B) of normal (N) and cancerous (C) colon tissue[42].

Figure 8 Experimental setup for the transmission loss measurement in metal and metal dielectric. Inset: A: 4 mm Ag (top), 3 mm Ag, 2 mm Au, and 2 mm Ag; B: 3 mm Ag/PS (top), 2 mm Au/PS, and 4 mm Ag/PS) coated terahertz waveguides[54].

Table 2 The relative reflectance difference between normal and cancerous colonic tissue[42]

Sample #	Co-pol ($\times$ 10^{-1} %)	Cross-pol (%)
Set 1	1.53	7.74
Set 2	3.03	7.74
Set 3	1.56	7.75
Set 4	2.44	7.30

that are crucial in determining the transmission losses and modal characteristics are waveguide inner diameter, coating material, and material thickness. Selection of coating materials such as silver and polystyrene were described in the preliminary investigation[56]. Also, the optimal coating thicknesses and requisite fabrication processes were detailed[55]. In order to choose a suitable candidate waveguide for THz endoscopic imaging, the characterization was done in three steps: Measuring propagation loss of the waveguide as a function of its

inner diameter and coating material, obtaining bending loss as a function of bend radius and bending angle, and acquiring modal characteristics as a function of bending angle, bend radius, waveguide inner diameter, and coating material. The transmission losses and modal characteristics for flexible waveguides can be obtained using the optical layout shown in Figure 8. Harrington *et al*[49] showed that when the waveguide bore size is about 17 times wavelength the guide is multimode, but when it is 12 times the wavelength or less then the waveguide becomes essentially single mode[54]. The characterization of flexible waveguides at the selected frequency[56], suitable for THz endoscopic system, is described in Ref 56.

Two groups so far have demonstrated waveguide based THz imaging. Chen *et al*[41] used a polymethyl-methacrylate waveguide to demonstrate THz transmission imaging of human colon tissue and Doradla *et al*[37] demonstrated reflection modality imaging using a single channel THz waveguide.

Figure 9 Schematic of waveguide based terahertz near-field transmission imaging system[41] (printed with permission). PMMA: Polymethyl methacrylate.

The work by Chen *et al*[41] utilized a continuous-wave source (Gunn diode) centered at 0.3 THz. Figure 9 shows a schematic of their system. As mentioned in Section 2, while 0.3 THz offers contrast in absorption, the resolution is limited in the far-field by the relatively long wavelength (1 mm). Chen *et al*[41] overcome the resolution restriction by using a bull's eye structure with a sub-wavelength aperture to get a near field resolution of 0.2 mm.

Figure 10 shows THz transmission images at 0.3 THz of specimens of fresh normal and cancerous colon that have been sectioned into 30 μm thick slices. As expected, the cancerous specimens exhibit significantly higher absorption than normal tissue. Chen *et al*[41] investigated the response of 30 specimens and were able to demonstrate 100% sensitivity and specificity.

The work by Doradla *et al*[42,57,58] utilized a far-infrared gas laser operating at 513 μm wavelength (0.58 THz). The THz endoscopic system contains THz transceiver system, system optics and a low-loss flexible THz waveguide. The transceiver system is used for the generation and detection of the THz signal. System optics control and guide the THz beam based on the coupling requirements. Hollow metal-coated waveguide confines and transport the THz beam. Ultimately, to achieve the maximal coupling efficiency and transmission through the waveguide, off axis parabolic mirror (OAP1 of Figure 11) has been adjusted to maintain the ratio of beam size and waveguide diameter as 0.77. This prototype endoscopic system utilized a single-channel for the THz signal transmission, collection from the specimen and works in both transmission and reflection configurations to overcome the higher THz absorption associated with the tissue and satisfy the *in-vivo* imaging criteria. It uses a highly reflective flexible waveguide lens assembly to propagate THz beam.

Metal-coated waveguides provide 99% inner surface reflectivity at all THz wavelengths and confine the radiation inside the tube. Metal-coated waveguides preserve the linearly polarized launched mode and exhibits low bending loss even at larger bending angles. The hyper hemispherical lens attached to the waveguide output end provides an aberration free diffraction limited beam waist. The technique in accordance with the present work acquires both co- and cross-polarized THz images using polarization sensitive detection. The data analysis indicates utilizing the cross-polarized component not only helps in obtaining Fresnel reflection free volume sampling but also in achieving a reflectance parameter that doesn't vary with patient/individual[42,58]. The THz endoscopic system doesn't need any conventional contrast agents to detect abnormal tissue as an intrinsic contrast was observed between normal and diseased tissue in fresh colonic specimens. Also, the device uses just one channel and hence can be easily integrated with the conventional optical endoscope. Moreover, the prototype THz endoscope is integrated with the flexible THz waveguides, which are small enough in diameter (2 mm to 100 μm). Therefore, based on the application and requirement, the dimensions of the THz probe can be reduced further.

This study[37,58] demonstrated the first prototype continuous-wave THz endoscopic system for cancer detection. The 2D THz intensity images attained using polarization based detection scheme exhibited an endogenous natural contrast between normal and abnormal (cancerous) regions of both formalin fixed and fresh colorectal tissue (Figure 12). The imaging system demonstrated the capability of identifying cancerous colonic tissue based on the intrinsic reflectance difference. The optical layout evident the potential and the experimental manifestation confirms the feasibility

Figure 10 Terahertz transmittance images and stained histology sections showing cancerous and normal colon tissue[41] (printed with permission).

Figure 11 Schematic of single-channel prototype terahertz endoscopic imaging setup. Inset: Terahertz (A) transmission imaging of a small 10 mm leaf, and (B) reflection imaging of a 25-cent coin. THz: Terahertz.

of using THz endoscopic device in accessing data from previously inaccessible organs[59]. Furthermore, this study significantly increased and prevail the overall impact of THz imaging for biomedical detection/

Figure 12 Digital photograph, cross-polarized terahertz reflection images of normal N *vs* cancerous C human colonic formalin fixed (A and B) and fresh (C and D) tissue sets[58].

screening applications[60].

CONCLUSION

CRC is the third most commonly diagnosed cancer in the world. Early detection and treatment of CRC can significantly reduce the number of deaths. Current standard of care for CRC screening is an optical endoscopy, which relies on physician's visual inspection and experience followed by histological analysis of biopsied specimens. Thus, an *in vivo* imaging modality capable of measuring quantitative differences between diseased (cancerous) and normal colon can significantly improve the screening of CRCs. THz imaging, which is non-ionizing and highly sensitive to tissue water content can potentially fill this niche.

This review article has outlined the steps required for clinical application of THz imaging of CRC and provided an update on the current status of the technology. The first step was to measure the refractive indices and absorption coefficients of normal and diseased colon tissue in the THz region. This has been accomplished by several groups using both fresh and formalin fixed dehydrated colon tissue. The results indicate a measurable difference in specific frequency ranges for both fresh and fixed tissue. The second step was to image normal and cancerous colon at desired frequencies to confirm the contrast can be imaged. This has also been accomplished for both fresh and fixed tissue in both transmission and reflection imaging modalities using THz imaging systems. In order to

proceed to clinical systems, the next step was to develop thin, flexible waveguides capable of endoscopic applications. This step has also been accomplished by multiple groups postulating a variety of endoscopic setups. The fourth step was to integrate the waveguide with a THz imaging system and test if waveguide enabled image acquisition was feasible. This was also demonstrated by different groups in both transmission and reflection modalities on fresh colon tissues. There is considerable evidence that THz imaging can potentially screen for colon cancers. A lot of the technological barriers have been overcome and the next step for the field is the development and testing of an *in vivo* THz endoscopy system capable of providing sensitivity and specificity numbers for the technique in identifying multiple stages of colon cancer.

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Use and barriers to chromoendoscopy for dysplasia surveillance in inflammatory bowel disease

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Abstract

Traditionally, patients with inflammatory bowel disease (IBD) have been thought to be at increased risk of developing colitis-associated colorectal cancer. Although there are recent data suggesting that rates of colitis-associated cancer in IBD patients is declining, current guidelines still recommend regular dysplasia surveillance for early detection and prevention of neoplasia in patients with IBD. White-light endoscopy with random biopsies has been the traditional approach for dysplasia detection; however, newer technologies and approaches have emerged. One method, dye-based chromoendoscopy, has the potential to detect more dysplasia. However, longitudinal data to showing a benefit in morbidity or mortality from the use of chromoendoscopy are still lacking. Many societies have included recommendation on the use of chromoendoscopy with targeted biopsies as a method of surveillance for colitis - associated colorectal cancer. This narrative review seeks to outline data on dysplasia detection as well as barriers to the implementation of dye-based chromoendoscopy for the prevention and early detection of colitis-associated colorectal cancer.

Key words: Chromoendoscopy; Inflammatory bowel disease; Dysplasia surveillance

Core tip: Patients with inflammatory bowel disease (IBD) are at an increased risk of developing colorectal cancer. Current guidelines recommend surveillance for early of neoplasia in patients with IBD. White-light endoscopy with random biopsies has been the traditional approach for dysplasia detection. Dye-based chromoendoscopy has the potential to detect more dysplasia. Many societies have endorsed the use of chromoendoscopy with targeted biopsies as a method of surveillance for colitis associated colorectal cancer. This review seeks to outline

data on dysplasia detection as well as barriers to the implementation of chromoendoscopy for the prevention and early detection of colitis associated colorectal cancer.

INTRODUCTION

Inflammatory bowel disease (IBD), which includes ulcerative colitis (UC) and Crohn's disease (CD), is a chronic inflammatory disease of the GI tract. Both ulcerative colitis and Crohn's colitis have historically been thought to be associated with an increased risk of developing colorectal cancer (CRC)[1-3]. Current guidelines provide various permutations of surveillance colonoscopy to detect and remove precursor lesions at an early stage[4-7]. Over the last several years, dye-based chromoendoscopy (CE) with targeted biopsies has emerged as an option to improve the ability to detect these early, subtle lesions. CE is a technique using absorptive stains or contrast stains dye such as methylene blue and indigo carmine that can aid in the early detection of malignant changes in the gastrointestinal tract. In this technique, 0.4% indigo carmine or 0.1% methylene blue is sprayed directly onto the colonic mucosa to help detect subtle mucosal irregularities that aid in the detection of changes indicative of dysplasia as well as help in differentiation of neoplastic and non-neoplastic lesions by assessing crypt architecture and modified pit patterns[8]. The technique of colonic CE was first described by Tada in 1976 with work two decades later indicating a role for CE with high resolution video endoscopy in increasing the detection of small flat neoplastic lesions in UC patients[9,10]. In this review, we will review current guidelines for the surveillance of colitis-associated colorectal cancer (CAC), barriers to implementation, and areas that require further study.

CRC RISK AMONG PATIENTS WITH IBD

The concept of carcinoma arising as a complication of chronic inflammation from IBD was first described by Crohn and Rosenberg in 1925, with later reports expanding on this observation[1-3]. A review of the literature in 1961 by Goldgraber and Kirsner[2] made the observation of increased risk of carcinoma of the colon in patients with UC with pancolonic disease and in those with disease duration greater than 10 years. The presence of dysplastic lesions in the colon of patients with UC was recognized as early as 1949 with the recommendation to search for precancerous lesions which often were flat (non-polypoid) with rectal biopsies annually as an aid to the detection of early colon cancer being made in 1969[11,12]. It was not until 1983 that a standardized terminology and grading system were established to help guide surveillance protocols. In the landmark paper by Riddell et al[13] in 1983, dysplasia was defined as an unequivocal neoplastic alteration of the colonic epithelium that may represent a precursor of carcinoma or itself be malignant and associated with direct invasion into the underlying tissue. The classification for dysplasia was further categorized into either negative, indefinite or positive for dysplasia.

In a landmark meta-analysis conducted by Eaden et al[14] in 2001, the authors assessed 116 studies and found that the cumulative risk of developing CAC was 2% by 10 years of disease, 8% by 20 years, and 18% by 30 years. Subsequent studies investigating the CAC risk in IBD patients have shown considerable variability, depending on the population studied, with cumulative risk ranging between 2.1% to 33.2%[15-18]. Remarkably, more recent studies have actually shown that the risk of CAC in IBD patients may actually be declining and nearing the risk of the general population[19]. In a meta-analysis by Jess et al[20] assessing 47374 Danish patients with IBD over 30 years, the authors found that the relative risk of developing CAC in UC patients was comparable to non-IBD controls (RR = 1.07, 95%CI: 0.95-1.21) as was the risk of CAC in patients with Crohn's colitis (RR = 0.80, 95%CI: 0.43-1.49). This study also found that the overall risk of CAC was declining in UC patients where the overall RR for CAC decreased from 1.34 (95%CI: 1.13-1.58) in 1979-1988 to 0.57 (95%CI: 0.41-0.80) in 1999-2008. This decline potentially may be attributed to improvement in therapies to reduce intestinal inflammation in IBD or to improved surveillance programs to promote early detection of neoplastic lesions.

Despite the decline in overall risk, there is still consistent information across many studies that there is a particularly higher risk of developing CAC in a subset of patients - those with extensive and long standing UC or CD[20-22]. Rutter et al[23] evaluated 68 patients in a case-control study at St. Mark's Hospital in England and found that severity of colonic inflammation is also an important predictor for development of neoplasia. Moreover, in the aforementioned study by Jess et al[20], despite an overall decline in incidence of CAC in IBD patients, there are particular subsets of patients- those with a diagnosis of UC in childhood or adolescence, those with long standing UC and those with concurrent primary sclerosing cholangitis (PSC)-who were at a notably increased risk of developing CAC during the study period.

CURRENT GUIDELINES FOR CAC SURVEILLANCE

While CAC may only represent a small proportion of

Table 1 Colorectal cancer surveillance guidelines for inflammatory bowel disease patients

Guideline (year of publication)	Timing of initiating surveillance	Surveillance interval	Biopsy protocol
AGA (2003)[4]	After 8 yr of disease (pancolitis) After 15 yr of disease (left-sided colitis)	1-2 yr	Random biopsy
BSG (2010)[46]	10 yr after onset of colitic symptoms	5 yr (lower risk)[1] 2-3 yr (intermediate risk) 1 yr (higher risk)	Targeted biopsy with CE (preferred) otherwise random biopsy
ECCO (2013)[6]	8 yr after onset of colitic symptoms	5 yr (lower risk)[2] 2-3 yr (intermediate risk) 1 yr (higher risk)	Targeted biopsy with CE (preferred), random biopsies if CE expertise unavailable
ASGE (2015)[7]	8 yr after symptom onset	1-3 yr (1 yr if any risk factor)[3]	Targeted biopsy with CE recommended with SD-WLE (preferred with HD-WLE as well); random biopsies with targeted biopsies of suspicious lesions is alternative

[1]Higher risk group: Dysplasia in the past 5 years declining surgery, PSC/liver transplantation for PSC, family history of CRC in a first degree relative < 50 years, or extensive colitis with moderate/severe active endoscopic/histological inflammation; intermediate risk group: Post-inflammatory polyps, family history of CRC in a first degree relative > 50 years, extensive colitis with mild active endoscopic/histologic inflammation; lower risk group: Left sided colitis, Crohn's colitis with less than 50% of the colonic mucosal surface affected by the disease, or extensive colitis with no active endoscopic/histologic inflammation; [2]Higher risk group: Stricture or dysplasia in the past 5 years, PSC, extensive colitis with severe active inflammation, or family history of CRC in a first degree relative < 50 years; intermediate risk group: extensive colitis with mild or moderate active inflammation post-inflammatory polyps, or family history of CRC in a first degree relative > 50 years; lower risk group: Patients with neither intermediate nor higher risk features; [3]Risk factors: Active inflammation, anatomic abnormality (stricture or multiple pseudopolyps), history of dysplasia, family history of CRC in a first degree relative, PSC. AGA: American gastroenterological association; BSG: British society of gastroenterology; ECCO: European crohn's and colitis organisation; ASGE: American society of gastrointestinal endoscopy; PSC: Primary sclerosing cholangitis; CRC: Colorectal cancer; CE: Chromoendoscopy; SD-WLE: Standard definition white light endoscopy; HD-WLE: High definition white light endoscopy.

all CRC cases (1%-2%), CRC is responsible for one in six deaths of IBD patients[24]. As such, colonoscopy has been the test of choice for early detection and prevention of CAC in IBD patients. The major United States gastroenterology societies have endorsed colonoscopy for prevention of early CAC[25-27]. There are limited data on the benefit of the recommended surveillance programs. Some studies have found that patients with IBD undergoing surveillance colonoscopies may have reduced rates of CAC or detection of CAC at an earlier stage[28].

Choi *et al*[29] examined 41 UC patients who developed CAC. The authors found that CAC was detected at a significantly earlier Dukes' stage in patients taking part in an endoscopic surveillance program (*P* = 0.039). Furthermore, the 5-year survival rate was 77.2% for the surveillance group and 36.3% for the no-surveillance group (*P* = 0.026). Though this study is promising evidence in favor of CRC surveillance, other studies have not shown a similar benefit. Lynch *et al*[30] prospectively examined 160 UC patients and found no mortality benefit in patients undergoing CRC surveillance. More recently, Ananthakrishnan *et al*[31] studied 6823 established patients (following for at least 3 years) with IBD of which 2764 had undergone recent colonoscopy. They found that the incidence of CAC among patients without a recent colonoscopy (2.7%) was significantly higher than among patients with a recent colonoscopy (1.6%) (OR = 0.56, 95%CI: 0.39-0.80). This was one of the few studies which specifically addressed the risk of CAC in IBD patients undergoing surveillance.

Current society guidelines recommend regular dysplasia surveillance in patients with long-standing colitis. Several major GI societies guidelines, including those published by the American Gastroenterological Association in 2003, recommend initiating a surveillance program to evaluate for dysplasia in patients who have had colitis for at least 8 years[4,5]. After starting a surveillance program, colonoscopy should continue every 1-2 years. The consensus of the expert panel formulating these guidelines is that random biopsy specimens should be taken every 10 cm in all 4 quadrants and that additional biopsies should be taken of any endoscopically abnormal appearing lesions (strictures, mass lesions, *etc*.). This results in a minimum of 33 biopsies to meet the threshold for neoplasia detection - a process that can be quite cumbersome and time consuming. Newer society guidelines, such as those issued by the American Society for Gastrointestinal Endoscopy (ASGE) and the European Crohn's and Colitis Organization (ECCO)[6,7], have now updated their guidelines to incorporate the use of chromoendoscopy for dysplasia surveillance. A summary of the current guidelines from the major GI societies is outlined in Table 1.

There have been many criticisms of the random biopsy strategy as less than 1% of the entire mucosal surface was sampled and low dysplasia detection rates as well as high sampling-error[32]. There are also no prospective studies that have determined the optimal number of biopsies that should be taken to detect dysplasia reliably though one study has recommended a minimum of 33 biopsy specimens to be taken in patients with pancolitis[33]. It has also been estimated that this surveillance method provides only 80% confidence that dysplasia involving ≥ 5% of the colon can be detected[34]. There have also been several studies showing poor adherence of gastroenterologists

in taking the recommended number of biopsies along with practice variability in surveillance[35-37]. These initial recommendations were made at time prior to high-definition colonoscopy and lesions previously considered "invisible" or flat may be visualized with modern day high-definition equipment. It is now understood that most dysplasia can be visualized endoscopically and have led some to question the added value of random biopsies[26]. Recent studies have supported the strategy of targeted biopsies of abnormal lesions without random biopsies only when high definition white light endoscopy (HD-WLE) is used. A clinical practice cohort of 454 IBD patients undergoing surveillance colonoscopy between 2011-2014 using standard definition white light endoscopy (SD-WLE), HD-WLE, virtual electronic CE, or CE found that most lesions were visible and of the four dysplastic lesions and one adenocarcinoma identified all were visible with HD-WLE and biopsied in a targeted manner. No dysplasia was identified on random biopsies[38]. A recent randomized controlled trial of 256 of patients with UC performed in Japan comparing surveillance with either a targeted biopsy protocol *vs* a random biopsy protocol with white light endoscopy found neoplasia was detected in 11.4% of patients in the targeted biopsy group *vs* 9.3% in the random biopsy group (*P* = 0.617) with less biopsies specimens being required per neoplasia diagnosis, suggesting a targeted biopsy approach as being more cost-effective and more efficient without missing dysplasia[39].

SCENIC CONSENSUS STATEMENT

In March of 2015, the SCENIC (Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations) consensus statement[40] regarding use of chromoendoscopy for dysplasia surveillance was released. In this statement, the authors made several updates regarding the approach to dysplasia surveillance among which they suggested that endoscopists consider the use of CE, when utilizing high definition colonoscopy, to enhance dysplasia detection. A commentary by Marion and Sands[41] accompanying the publication of the SCENIC statement propounded an important argument: The lack of longitudinal data regarding CE limits the ability to accept this as the standard of care in dysplasia surveillance. More specifically, while there is certainly evidence that CE increases dysplasia detection, it remains unclear what the long-term management of these patients should be. While pursuing the goal of cancer prevention, the accompanying risk profile of increased dysplasia detection including onerous surveillance schedules, possibly unnecessary colectomies or post-surgical complications also increases. This risk/benefit profile, along with the limited evidence to support use of CE, must all be considered when deciding to employ this technique.

EVIDENCE FOR CHROMOENDOSCOPY

Two studies increased the attention on CE as a means to more efficiently detect dysplasia in IBD compared to random biopsies. In one study of 100 patients with long-standing UC using a tandem colonoscopy design, random biopsies along with targeted biopsies using standard white light was compared to CE with targeted biopsies only using indigo carmine. This study demonstrated a 3.5-fold increase in diagnostic yield of dysplasia along with a 4.5-fold increase in dysplasia detection, with no dysplasia being detected on random biopsies[42]. In the first randomized prospective trial using CE for IBD-associated colonic dysplasia, methylene blue was compared to conventional colonoscopy in patients with long-standing UC. Chromoendoscopy was associated with an increased diagnostic yield for total number of detected intraepithelial neoplasia compared to conventional colonoscopy (32 *vs* 10, *P* = 0.003). The CE group also required less biopsies and using the modified pit pattern demonstrated a sensitivity and specificity for differentiation between neoplastic and non-neoplastic lesions of 93%[43]. Subsequent studies also have shown an increased detection yield of CE over standard white light endoscopy (WLE), which was highlighted by a meta-analysis evaluating prospective studies comparing CE to WLE. Six prospective studies were included in the analysis and concluded that CE resulted in a 7% higher yield in detection of neoplasia as well as a pooled increase in targeted dysplastic (low or high grade) lesion detection of CE over standard definition WLE of 44% (95%CI: 28.6-59.1)[44]. Mounting data of the effectiveness in dysplasia detection with CE lead to the 2010 position statement from the American Gastroenterological Association recommending CE as an alternative to analyses of random biopsies for endoscopists experienced with the technique[45]. The British Society of Gastroenterology also recommended CE with targeted biopsies with a grade A recommendation as the preferred method of surveillance[46].

Though clinical trials demonstrated a benefit of CE over WLE for dysplasia detection, a large retrospective study covering 13 years did not confirm this conclusion in the clinical practice setting. This multicenter study from the Netherlands including 401 patients undergoing CE and 772 patients undergoing WLE found no difference in the detection of dysplasia between the two groups (11% *vs* 10%, *P* = 0.80)[47]. This conclusion was in accordance with a previous study using narrow-band imaging showing no difference in dysplasia yield between CE and HD WLE[48]. Of note, the authors of this study highlighted that prior studies assessing outcomes in chromoendoscopy had a "back-to-back" design where WLE was performed first followed by CE (as WLE cannot be performed after dye spraying). They postulated that such a design may have overestimated the yield of CE in detecting neoplasia and generated potential bias. To try and fill the discrepancy in the

data, Carballal *et al*[49] conducted the first randomized prospective trial evaluating the real-life experience of CE for dysplasia detection in long-standing IBD. In this prospective, multicenter cohort study from Spain, 350 patients with long-standing IBD underwent surveillance using a tandem colonoscopy method with each colonic segment being evaluated with WLE followed by CE using 0.4% indigo carmine with targeted biopsies of suspicious lesions. This study found a 57.4% incremental yield in dysplasia detection with CE *vs* WLE which was comparable in standard WLE *vs* HD WLE. The dysplasia miss rate was 40 of 94 lesions for white-light examination. Overall dysplasia detection rate was 15.7% in this real-life setting which is in line with previous estimates[50]. This study also demonstrated no significant difference in dysplasia detection between CE-expert and non-expert endoscopists with no significant learning curve being observed. Though it has been concluded that CE improves dysplasia detection and is the most effective modality for surveillance, data regarding the effect on patient outcomes and cancer-related morbidity and mortality are still lacking.

BARRIERS TO PERFORMING CHROMOENDOSCOPY

While CE may provide some benefit with regards to increased dysplasia detection, there are several barriers to performing CE that must be considered when deciding whether to implement this technique.

Does expertise affect outcomes?

Much of the existing data, especially data demonstrating positive results, on CE arises from centers where gastroenterologists have particular expertise in performing CE[42,43,50-53]. In the article by Mooiweer *et al*[47], the neoplasia detection rate for CE-based surveillance procedures was 11% compared with an average rate of 14% over several prior randomized trials examining neoplasia detection using CE. The authors of the study postulated that the lower neoplasia detection rate could be due to the inexperience of the endoscopists who had no dedicated training prior to performing the CE procedures. Conversely, Carballal *et al*[49] prospectively examined a cohort of IBD patients undergoing dysplasia surveillance between 2012-2014. The study protocol required that each colonic segment was evaluated with white light followed by 0.4% indigo carmine CE. When assessing for differences between expert (endoscopists who had performed > 20 CE-based dysplasia surveillance procedures) and non-expert endoscopists, the dysplasia detection rate was not found to be significantly different between the two groups (18.5% *vs* 13.1%, *P* = 0.20).

Cost concerns and technical disadvantages associated with CE

The equipment required to perform chromoendoscopy usually includes one of the absorptive, contrast or reactive stains; these stains are generally inexpensive but have had issues with availability at times. Additionally, when performing chromoendoscopy, a spray catheter may be used to apply a uniform mist of the staining agent. The cost of these spray catheters is between approximately $50-200. The equipment used to perform chromoendoscopy is compatible with most commonly used colonoscopies and the staining dyes are thought to add no additional risk to the patient[54]. While the equipment may only add a small amount of cost to the procedure, the cost of additional time to perform high quality chromoendoscopy harder to quantify. The data on cost-effectiveness of this technique is quite limited. One formal cost effectiveness study has been conducted by Konijeti *et al*[55]. The authors utilized a Markov model to analyze the cost effectiveness of CE relative to WLE or no endoscopy for CRC surveillance in UC patients. This study design was chosen to better analyze need for surveillance and optimal surveillance intervals given increasing data about decreasing rates of CRC in patients with IBD. CE was found to be more effective and less costly than WLE at all surveillance intervals. However, compared with no surveillance, CE was cost effective only at surveillance intervals of at least 7 years, with an incremental cost-effectiveness ratio of $77176. While this study suggests that CE may be more cost effective than white-light endoscopy, it only demonstrates a cost benefit over no surveillance if intervals are stretched out to greater than every 7 years. Overall, the question on whether chromoendoscopy offers a cost savings when used in a real-world surveillance program remains unanswered and more studies are required to truly clarify this.

One additional barrier that may prevent gastroenterologists in implementing CE is the additional procedure time. In the meta-analysis conducted by Subramanian *et al*[44], taking data from experienced centers, CE increased procedure time by 11 min overall. In the previously mentioned study by Kiesslich *et al*[43], procedure time was increased from 35 to 44 min (with CE) overall. However, this procedure time also included time dedicated for random biopsies. If a practice of conducting only targeted biopsies of suspicious lesion were employed, the additional procedure time added by using CE would likely be less. Additionally, increasing experience with CE may translate into shorter procedure times. In an implementation study by Leong *et al*[56], the authors observed that withdrawal time decreased with experience, ranging from 31 min for fewer than 5 procedures to 19 min for more than 15 procedures completed.

CLINICAL IMPACT OF CHROMOENDOSCOPY

CE is highlighted as a more effective modality than high definition white light endoscopy for detecting "invisible

dysplasia". However, it is important to consider whether there is truly a significant clinical impact of missed, "invisible" dysplastic lesions on CAC-related outcomes. To answer this question, Rubin et al[25] conducted a retrospective review of all cases of dysplasia or CRC in UC between November 1994 and October 2004. There were 1339 surveillance examinations in 622 patients with UC; forty-six patients were found to have dysplasia or CRC. seventy-five separate dysplastic or cancerous lesions were identified, 38 of 65 dysplastic lesions (58.5%) and 8 of 10 cancers (80.0%) were visible to the endoscopist as 23 polyps and masses, 1 stricture, and 22 irregular mucosa. Moreover, van den Broek et al[57] conducted a retrospective analysis of 1010 colonoscopies from 1998-2008. In total, 475 patients with UC were included in the study. Of all colonoscopies, 466 were performed for surveillance (in 167 patients) during which 11772 random biopsies were taken (median 29). Dysplasia was detected in random biopsy specimens alone in 5 colonoscopies (0.5%) in 4 patients (0.8%). Of these 4 patients, 2 had had visible dysplasia in previous colonoscopies, 1 had unifocal low-grade dysplasia that was not confirmed in 3 subsequent colonoscopies, and 1 had multifocal low-grade dysplasia and suspicious appearing ulcerations and underwent proctocolectomy, which confirmed the presence of neoplasia. Thus, dysplasia uncovered *via* random biopsy changed the management of only 1 of 475 patients (0.2%). In comparison, targeted biopsy specimens were positive for neoplasia in 83 colonoscopies (8.2%), and major therapeutic decisions (endoscopic resection or colectomy) were made in 61 of these cases (73%). This data suggests that "invisible dysplasia" detected on random biopsy is infrequent and of unclear clinical relevance. Though recent published data has shown promising results for a targeted biopsy approach to dysplasia surveillance[38], the issue of invisible dysplasia likely remains an open issue that requires future investigation before eliminating random biopsy protocols altogether.

Does dysplasia detection affect long-term outcomes?

In a meta-analysis by Subramanian et al[44], the authors assessed the diagnostic yield, for detection of dysplasia between white light endoscopy and CE. In 6 studies involving 1277 patients, the difference in yield of dysplasia between CE and white light endoscopy was 7% (95%CI: 3.2-11.3) with a number needed to treat of 14.3. The difference in proportion of lesions detected by targeted biopsies was 44% (95%CI: 28.6-59.1) and flat lesions was 27% (95%CI: 11.2-41.9) in favor of CE. The aforementioned prospective studies, derived from expert centers, have demonstrated a significant difference in dysplasia detection with the utilization of CE[42,43,50-53]. It must be noted, however, that most of these studies follow a cross-sectional design in which the number of detected lesions using CE is compared with the number of lesions detected using standard definition white-light endoscopy.

The intended goal of surveillance strategies is to detect early lesions that would lead to decreased colon cancer morbidity and mortality as well as unnecessary colectomies. Although chromoendoscopy may help to increase dysplasia detection compared to white light endoscopy, the clinical implications of this increased detection yield are largely unknown. In a follow-up[58] to an initial index study[50] looking at 102 high-risk IBD patients undergoing surveillance comparing CE and SD-WLE with random biopsy, 68 patients were longitudinally followed over a median of 27.8 mo to compare the techniques for dysplasia detection. CE was found to be more likely to detect dysplasia compared to targeted WLE (OR = 2.4, 95%CI: 1.4-4.0) and random biopsy (OR = 5.4, 95%CI: 2.9-9.9) Furthermore, in the 10 patients who underwent colectomy, CE was found to have better overall agreement between endoscopy and colectomy findings regarding the presence or absence of dysplasia which was 80% in CE, 20% for random biopsy and 10% in targeted WLE. Furthermore, a negative result from CE was the best indicator of dysplasia free outcome which may play a role in future decisions regarding recommended screening intervals. There is recent data with conflicting results regarding the impact of lesions detected with CE compared to WLE. In a retrospective study evaluating the implications of LGD found during surveillance in a Dutch cohort, 159/1065 patients evaluated were found to have LGD (133 visible lesions and 26 invisible lesions) for an overall incidence rate of 1.34 per 100 patient-years for all LGD lesions. There was a total of 10 cases which advanced to either HGD (5/10) or CRC (5/10) with no significant difference in the risk of advanced neoplasia during follow-up for index lesions detected with either WLE or CE[59]. Though there was no difference in advancement in lesions detected by HD-WLE *vs* CE, this may have been limited by the overall low number of neoplastic lesions.

Finally, these findings are supported by a recent systematic review that demonstrated a superiority of CE over WLE in dysplasia detection when compared to SD-WLE only with no direct evidence of prevention of cancer-related mortality and time to interval cancer in patients who received CE[60]. As described in this paper, there have been consistent data suggesting increased dysplasia detection with CE, however data showing an impact in cancer related outcomes are still lacking. More longitudinal head to head studies comparing CE with HD-WLE are needed to compare the outcomes of surveillance techniques and to confirm whether the clinical significance of these lesions are indeed comparable.

FUTURE DIRECTIONS

CE appears to increase the rate of colonic dysplasia detection in IBD patients undergoing CAC surveillance. CE with targeted biopsies is now an alternative to random biopsies for CAC surveillance. However, we currently do not have sufficient data to suggest that

there is a clear "real-world" benefit of CE including reduction in cancer rates or improved survival. As such, further studies are required to assess the effect on CAC outcomes, not only dysplasia detection rates. Patients are likely to seek answers from their gastroenterologist regarding the "best" way to prevent CRC. It is important that we are prepared to explain to patients how CE fits into their care.

It is likely that the future of CAC will be increasingly complex as our understanding of dysplasia in IBD and technologies available to detect and treat dysplasia evolve. Risk stratification will likely play a larger role in identifying patients most at risk for CAC who would most likely benefit from aggressive CAC surveillance, including CE.

It is imperative that more studies, particularly longitudinal studies should be done to clarify the role of CE in achieving the ultimate goal of reducing patient morbidity and mortality from CAC while also reducing unnecessary colectomies in patients with clinically insignificant lesions.

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Evolution of stereoscopic imaging in surgery and recent advances

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Abstract

In the late 1980s the first laparoscopic cholecystectomies were performed prompting a sudden rise in technological innovations as the benefits and feasibility of minimal access surgery became recognised. Monocular laparoscopes provided only two-dimensional (2D) viewing with reduced depth perception and contributed to an extended learning curve. Attention turned to producing a usable three-dimensional (3D) endoscopic view for surgeons; utilising different technologies for image capture and image projection. These evolving visual systems have been assessed in various research environments with conflicting outcomes of success and usability, and no overall consensus to their benefit. This review article aims to provide an explanation of the different types of technologies, summarise the published literature evaluating 3D *vs* 2D laparoscopy, to explain the conflicting outcomes, and discuss the current consensus view.

Key words: Three-dimensional laparoscopy; Endoscopy; Three-dimensional displays; Minimally invasive surgery; Stereoscopic

Core tip: Capture of true stereopsis from the operative field is crucial for the subsequent projection of a high quality stereoptic image. The latest three-dimensional (3D) systems using dual channel stereoendoscopes and passive polarizing stereoscopic projection generate high quality 3D images for minimally invasive surgery. There is subjective and objective laboratory based evidence supporting use of 3D *vs* two-dimensional for surgeons of all experience. However, their clinical application has yet to be addressed with Level 1 evidence.

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INTRODUCTION

When Phillipe Bozzini first designed and used his "Lichtleiter" in 1803 to peer into the human body, the medical world unwittingly became reliant on observing the endoscopic view of the human body in only two-dimensions (2D).

In 1838 Charles Wheatstone[1] was the first to accurately describe and publish the phenomenon of stereopsis - "... the mind perceives an object of three dimensions by means of the two dissimilar pictures projected by it on the two retinae ...". He described in his paper how the illusion of light projecting outwards from the surface of a metal plate that had been turned on a lathe had brought him to this realisation. He demonstrated the validity of his proposed mechanism of stereopsis by creating the "Wheatsone Stereoscope". This created an illusion of stereopsis simply by projecting different images to each eye of the viewer. By adjusting each image to give an impression of the perspective that would have been seen by that eye the viewer was left with a sense of a three-dimensional (3D) image.

The first endoscopic procedures were performed with single eyepiece rigid scopes which provided a monocular view for the operating surgeon. In the 1970s these images were relayed *via* a camera to a video monitor. Thus was born the modern era of "off screen" videoscopic operating. In the late 1980s the first laparoscopic cholecystectomies were performed and popularity for laparoscopic surgery began to increase exponentially. This prompted a sudden rise in surgical and technological innovations as the benefits and feasibility of minimal access surgery became more universally recognised. As minimal access surgery became more widely adopted the steepness of the learning curve for surgeons became more apparent. In particular the monocular laparoscopic view providing two-dimensional viewing, and associated reduced depth perception, became the focus of technological advances. Attention therefore turned to producing a usable 3D endoscopic view for surgeons, utilising different technologies for image capture and image projection. These evolving visual systems have been assessed in various research environments with conflicting outcomes of success and usability, and no overall consensus to their benefit.

This review article aims to provide an explanation of the different types of technologies, summarise the published literature evaluating 3D *vs* 2D laparoscopy, to explain the conflicting outcomes, and discuss the current consensus view.

First stereoptic views

Binocular microscopes were first used in 1922 in otolaryngology to overcome the lack of depth perception associated with monocular operating microscopes by surgeon Gunnar Holmgren (1875-1954), Head of the University Clinic of Stockholm[2]. These provided a stereoptic magnified view of the operating field and were quickly adopted by Otolaryngology, Neurosurgery and Orthodontics. In the 1980s, a German surgeon, Dr. Gerhard Buess[3], pioneered Transanal Endoscopic Microsurgery (TEMS) utilising the first "stereoendoscope" with two optical channels, viewed through binocular eye pieces. In 1992, his team trialled the first prototype laparoscopic stereoendoscope in animal studies and clinically during laparoscopic cholecystectomies, and concluded the stereopsis facilitated complex laparoscopy[4].

Image capture

In the laparoscopic settling, an image of the operative field may be captured in one of two ways. A traditional rod-lens laparoscope may be used to transmit the light from the image to outside the patient where a video camera then captures the image and sends it as an electrical signal to an image processor. Rod lens technology is now being superseded by "chip on the tip" technology utilizing small camera chips which capture the image at the tip of the laparoscope and then transmit the electrical signal along the laparoscope to an image processor.

The technology used to capture the 3D characteristics of the operating field includes the laparoscope, the camera and the image processor. Various systems have been developed and trialed in the literature. Single channel systems attempt to extract two perspectives of the operative field from a single point of view by splitting the image either with a prism or filter. The result is therefore not a true binocular image[5]. Dual channel systems provide two horizontally separated images and thus produce two truly different perspectives of the operative field. "Insect eye" scopes allow for multi images to be captured and processed simultaneously. There is significant variety in the design of the video capture systems, which results in differences in the quality of the perceived image.

Projection systems

Projection systems aim to deliver the 3D view to the observer. Early systems used active shuttering projection, where alternate left and right views are displayed at high frequency on a display. With these systems the operator wears active shuttering glasses so that each eye receives only the corresponding right or left eye image. Robotic systems evolved to use a fixed viewing environment, where, like in a microscope, the observer has a separate image displayed to each eye. This concept was used in Head Mounted Displays (HMDs) where each eye was provided with its own screen to achieve stereopsis. The latest commercial projection systems use passive polarizing technology, which allows for two images to be projected simultaneously in different polarized waveforms. A high definition image is made

up of 1080 horizontal pixel lines. For passive polarizing projection the image projected has odd horizontal pixel lines emitting light polarized vertically and even lines emitting light polarized horizontally. The user then wears lightweight polarizing glasses to separate the correct image to each eye. The horizontal resolution of the image is therefore reduced by half to 540 pixels but the vertical resolution remains at 1080 pixels and the resulting image therefore remains high quality. When this technology was transferred from cinema projection systems to home television monitors the opportunity to use this system in the operating theatre became a possibility.

More recently there has been the experimental development of complex waveform projection systems (advanced systems based on anaglyph separation), autostereoscopic "glass-free" displays and holographic displays.

LITERATURE REVIEW

We aimed to identify from the literature, all published work evaluating 3D laparoscopic systems compared to 2D standard "classical laparoscopic" systems. PubMed, EMBASE, Ovid and Medline where used as search engines to identify any published full English language papers since 1996 which referenced stereopsis, 3D, *vs* two-dimensional or 2D, laparoscopy, endoscopic surgery, imaging and 3D. Overall, 361 titles were identified and 275 were discounted on further review of their titles. Of the 86 abstracts reviewed, 45 were further discounted as they didn't compare 3D with 2D. Review of these 41 papers acknowledged another six papers not identified by the original search. In total, 47 papers reported assessing 3D imaging systems against 2D systems in laparoscopic surgery. A further four titles were discounted on reading the whole paper, leaving 43 to be assessed. Ninety-six percent of the studies describe laboratory based experiments, involving a variety of laparoscopic skills tasks, some from validated curriculum programmes and others designed to mimic advanced laparoscopic skills. The studies also use a variety of subjects from non-surgical participants to those with a variety of experience in laparoscopic surgery.

The number of tasks, repetitions, cross over in visual systems, assessment of a learning curve and number of individual subjects involved varied in each study. Universally, the common themes assessed in the majority of studies were the time for task completion and performance, either by clearly defined errors or by other assessment defined scoring systems.

There has been speculation for the last 18 years over the benefit of 3D operating visual systems, largely based on conflicting reports in the literature and the ongoing evolution of the system technology. We separated data by the type of optical or projection system in order to clarify the results and explain the conflicting outcomes observed by different researchers.

Single channel endoscope studies

We identified 13 studies which used single channeled scopes to capture the laparoscopic view (Table 1). Seven of these studies[6-12] utilised active shuttering projection systems with only one study[7] identifying a significant improvement in outcomes using the 3D system compared to the 2D standard. All of these studies also reported poor subjective outcomes associated with the 3D systems, including visual strain, headaches and nausea as well as an awareness of flickering of the screen. Four studies[13-16] assessed a second-generation 3D system, which used a single channel scope and projected left and right images to head mounted display systems, allowing individual eye projection without loss of light or image quality. Three of the studies reported significant improvement in performance for novices. The HMDs, although bulky, did not cause any of the cortical disturbances reported by the active shuttering systems. The final two studies[17,18] used single channel scopes and the latest passive polarizing systems. Neither identified a significant difference in respective outcomes with the 3D systems. Both studies reported that a period of adaptation was required to overcome any higher processing symptoms that the 3D visual system induced[17].

Dual channel endoscope studies

Robotic "fixed screen" studies: Nine studies investigated the effect of stereopsis in laparoscopic surgery utilising the Da Vinci robotic system (Intuitive, California United States) (Table 2)[19-27]. Stereopsis is achieved with a binocular endoscope and two camera heads for separate left and right image capture. Each image is received by the respective eye, simultaneously using a fixed console, alleviating the need for shuttering, polarizing or head mounted projection. All studies reported significant improvement in performance with the Da Vinci system in 3D mode over 2D mode. Notably, performance advantages were independent of participant experience[27].

Studies using screen projection and eye-glass technology

Five studies reported outcomes with binocular stereo-endoscopes (Table 3), alternating screen image and active shuttering glasses[28-32]. Four of the five studies reported significant improvements in performance with 3D systems[28-32]. In the one study (Wentink *et al*[30], 2002) the screen was placed very close to the surgeon while the working environment from the stereoendoscope was 12 cm. This produces conflict between convergence and focus for the operating surgeon, and it is therefore unsurprising that the 3D system showed poorer performance.

Eight studies evaluated passive polarizing screen and glass technology (Table 3)[33-40]. Two of these studies retrospectively compared a series of operations (laparoscopic cholecystectomies and laparoscopic

Table 1 Single channelled scopes

Ref.	Year	Projection system for 3D	Who and what assessed	Objective outcomes	Subjective outcomes
McDougall *et al*[6]	1996	Active shuttering screen and glasses	22 urological and gynaecological surgeons, non-novice Pig-lab, laparoscopic vessel dissection and securing, suturing and knot tying	Time for completion. No significant difference found	3D not felt to enhance image quality or enhance performance. Blurred vision and eye fatigue with 3D
Dion *et al*[7]	1997	Active shuttering screen and glasses	Surgeons and non-surgeons. Lab visual ($n = 8$) and motor skills ($n = 9$)	Time and errors. Improvement in both with 3D	Glasses bothersome and dizziness reported
Chan *et al*[8]	1997	Active shuttering screen and glasses	32 surgeons, 11 with and 21 without laparoscopic experience 1 × lab based skills task	Time for completion in 2D and 3D (1 repetition). No significant difference	50% felt no improved performance although 66% felt depth perception improved 40% felt reduced image quality and dimmer; 10% reported dizziness and eyestrain
Hanna *et al*[9]	1998	Active shuttering screen and glasses (A/S)	4 surgical SpRs performing 60 laparoscopic cholecystectomies	Time for completion and errors No significant difference	Visual strain, headache and facial discomfort with 3D system
Mueller *et al*[10]	1999	Active shuttering screen and glasses	30 subjects (10 with and 20 without laparoscopic experience) 4 × lab based skills tasks for all, then experienced did suturing tasks	Time for attempts, and success/failure of attempt No significant difference	Reported loss of concentration, headaches and distraction with 3D system
Herron *et al*[11]	1999	3D (active shuttering screen and glasses) and 3D HMD	50 laparoscopic novices 3 × lab based skills tasks	Time to completion of 3 skills tasks in each visual system (2 × repitions) No significant difference	Although 48% preferred 3D A/S screen over all, 7% and 25% respectively reported headaches with 3D screen and 3D HMD. 82% found HMD uncomfortable
Mueller-Richter *et al*[12]	2003	3D (active shuttering screen and polarising glasses) and 3D Autostereoscopic screen	59 laparoscopic novices 3 × lab based skills tasks	Number of completions in time limit and subjective difficulty No significant difference	Flickering reported with both 3D systems
Bhayani *et al*[13]	2005	HMD	24 surgical residents, minimal laparoscopic experience. 1 × lab based skills task	Time for completion in 2D and 3D (1 repetition) Significant reduction in time	> 50% preferred the 3D system and found task easier in 3D No subjective assessment on physical symptoms
Patel *et al*[14]	2007	HMD	15 novices and 2 experts 5 × lab based skills tasks	Time and accuracy in 2D and 3D (1 repetition) of the novices compared to the experts Significant difference in both for novices only in 3D	NA
Bittner *et al*[15]	2008	HMD	2 novices, 2 intermediate and 2 experts 2 × lab based suturing tasks (based on handedness, visual system and articulating needle holder)	Time and accuracy in 2D and 3D (multi repetitions with each variable) No significant difference	83% felt improved depth perception. No reported physical symptoms
Votanopoulos *et al*[16]	2008	HMD	36 surgical residents and medical students (11 with and 25 without laparoscopic experience) 6 × lab based skills tasks (rpt 3/12 later)	Time and errors in 2D and 3D (1 repetition) Significant improvement in time and errors in novice group only	NA
Kong *et al*[17]	2009	Passive polarising screen and glasses	21 novices and 6 experienced surgeons 2 × lab based skills tasks	Time and errors in 2D and 3D (4 repetitions of each over 4 d) Significant reduction in errors in 3D novices, no other significant difference noted	Dizziness and eye fatigue in novice with 3D system which improved with time
Mistry *et al*[18]	2013	Passive polarising screen and glasses	31 medical students (novices) 4 × lab based skills tasks (MISTELS)	Task Performance in 2D and 3D as per MISTELS scoring system No significant difference	No detrimental symptoms with 3D

NA: Not available; 3D: Three-dimensional; 2D: Two-dimensional; HMD: Head mounted display.

Table 2 Dual channel laparoscopes - Robotic fixed screen

Ref.	Year	Projection system for 3D	Who and what assessed	Objective outcomes	Subjective outcomes
Falk *et al*[19]	2001	Da Vinci	15 experienced laparoscopic surgeons 6 × lab based skills tasks (increasing difficulty)	Time and errors in 2D and 3D and 2DHD (I repetition in each view) Significant differences in time and errors in 3D	Only 33% felt 3D better view No detrimental symptoms reported
Munz *et al*[20]	2004	Da Vinci	11 experienced laparoscopic surgeons 4 × lab based skills tasks	Errors and performance (ICSAD assessment - time, no. movements and distance moved) Significant difference in both in 3D	NA
Moorthy *et al*[21]	2004	Da Vinci	10 surgeons of varying experience Lab based suturing task	Time and distance travelled of instruments in 2D and 3D Significant difference in both in 3D	NA
Badani *et al*[22]	2005	Da Vinci	7 surgeons (3 experienced with Da Vinci, 4 not) 2 × lab based suturing tasks	Time and errors Significant difference in 3D in all areas	NA
Blavier *et al*[23]	2007	Da Vinci	40 medical students Lab based skills task	Errors, performance and learning curve Significant difference in 3D	No detrimental symptoms reported
Byrn *et al*[24]	2007	Da Vinci	12 surgeons of varying experience 4 × lab based skills tasks	Time and errors in 2D and 3D Significant difference in 3D	No detrimental symptoms reported
Blavier *et al*[25]	2007	Da Vinci	60 medical students 4 × lab based skills task (increasing difficulty)	Specific performance metric score Significant difference in 3D in all tasks	No detrimental symptoms reported
Fishman *et al*[27]	2008	Da Vinci and prototype Ames stereoscopic camera	12 subjects of varying exposure to stereoptic systems	Time for completion while altering binocular disparity of stereoptic camera until 0% (matching 2D vision)	NA
Blavier *et al*[28]	2009	Da Vinci	Lab based skills task using Da Vinci manipulator 80 subjects (60 novice individuals and 20 expert laparoscopic surgeons) Lab based task	Significant difference with 3D from binocular disparity Time for task completion and estimation of time in 2D or 3D not both Significant difference in 3D for novices, similar results for experts	NA

NA: Not available; 3D: Three-dimensional; 2D: Two-dimensional.

Table 3 Dual channel laparoscopes - Screen projection and glasses

Ref.	Year	Projection system for 3D	Who and what assessed	Objective outcomes	Subjective outcomes
Birkett *et al*[26]	1994	Active shuttering screen and Active glasses then polarised glasses *vs* 2D	10 Subjects? experience 2 × lab based skills tasks	Time take for repetitive cycles; No difference in simples task, reduced time in complex task	NA
Peitgen *et al*[29]	1996	Active shuttering screen and glasses	60 subjects (20 novices, 20 beginners, 20 advanced laparoscopic surgeons) 2 × lab based skills tasks	Time and accuracy of tasks Both significantly improved in 3D, independent of experience	NA
Wentink *et al*[30]	2002	Active shuttering screen and polarised glasses *vs* TFT display *vs* projection *vs* standard (2D)	8 surgeons with laparoscopic experience Lab based skills task	Time for task completion, 10 repetitions but only 2 surgeons per visual system No improvement with 3D	Felt image quality poorer with 3D
Jourdan *et al*[31]	2004	Active shuttering screen and glasses	8 experienced laparoscopic surgeons 5 × lab based skills tasks	Time and errors, 10 repetitions each, in each visual system Significant improvement in both in 3D	NA
Feng *et al*[32]	2010	Active shuttering screen and polarised glasses (SD *vs* 2D SD *vs* 2D HD)	27 subjects (16 novices, 11 with varying laparoscopic experience) Lab based skills task	Time and economy of movement Time significantly improved over both 2D systems in 3D, economy of movement improved in 3D *vs* HD, not SD 2D	Felt improved depth perception in 3D
Hubber *et al*[33]	2003	Prototype passive polarising screen and glasses	16 Medical Students (novices) Lab based skills tasks	Time and performance (ICSAD) Improvements in 3D significant over 2D	NA
Honeck *et al*[34]	2012	Passive polarising screen and glassed	10 novices and 10 experienced laparoscopic surgeons 5 × lab based skills tasks	Time and errors (1 × repetition, in only 1 of the visual systems) No significant improvement in time, reduction in errors significant in both groups in 3D	No impairment felt in subjective feedback when using the 3D system
Smith *et al*[35]	2012	Passive polarising screen and glassed	20 novices 4 × lab based skills tasks	Time and errors (10 repetitions of each task in each visual condition) Significant improvement in time and errors in 3D	NA

Bilgen *et al*[36]	2013	Passive polarising screen and glassed	3 surgeons Clinical - 11 laparoscopic cholecystectomies performed in 3D (compared to 11 performed retrospectively in 2D)	Time Significant reduction in time when performed in 3D, compared to case matched lap choles performed previously in 2D	NA
Sinha *et al*[37]	2013	Passive polarising screen and glassed	Retrospective analysis of 451 clinical gynaecological surgery performed in 3D Case matched assessment of 200 hysterectomies performed in 3D *vs* 2D	Time Significant reduction in operating time and morcellation time when performed in 3D	NA
Cicione *et al*[38]	2013	Passive polarising screen and glassed	33 subjects (10 experts and 23 novices) 5 × lab based skills tasks (Basic Laparoscopic Urological Skills)	Time and errors Overall, significant improvement in time and errors (although experts only improved time in 1 task in 3D)	Subjective Questionnaire - felt tasks were easier in 3D universally
Lusch *et al*[39]	2014	Passive polarising screen and glassed	24 subjects (10 medical students, 7 residents, 7 expert surgeons) 6 × lab based skills tasks	Time and errors 4 out of 5 skills tasks had significantly improved time and errors when done in 3D, independent on experience	Optical resolution and depth perception improved in 3D
Smith *et al*[40]	2014	Passive polarising screen and glassed	20 experienced surgeons 4 × lab based skills tasks	Time and errors (10 repetitions of each task in each visual condition) Significant improvement in time and errors in 3D	Subjective assessments using NASA Task Load Index - improvements with 3D all sections

NA: Not available; 3D: Three-dimensional; 2D: Two-dimensional; HMD: Head mounted display.

gynaecological operations) with case matched procedures in standard 2DHD systems[36,37]. Both reported a significant reduction in operating times for case matched procedures. Six laboratory based studies identified significant improvements in most of the tested parameters when tasks were performed in 3D[33-35,38-40]. Two other studies (Honeck *et al*[34], 2012, and Cicione *et al*[38], 2013) found varied performance improvements in 3D. Honeck found reduced errors but no significant time improvements, while Cicione *et al*[38] (2013) found an overall significant improvement with 3D over 2D. These advantages were only observed in the expert subgroup when performing one task, the "Peg Transfer". However both studies only allowed for a single repetition of tasks in 3D and 2D before comparison. In studies which allowed for repetitions and plateauing of the learning curve in both visual environments before comparison, there was a universal improvement when comparing 3D over 2D, independent of experience[33,35,39,40].

Comparing different scopes and projection systems
Four papers described using more than one type of 3D system in their comparison of 3D *vs* 2D (Table 4)[41-44]. Hanna *et al*[42] (2000) assessed single-channel scope and dual-channel scope systems, both using active shuttering screen/glasses systems compared to a standard 2D system when performing laboratory based bowel anastomosis. The 3D systems were evaluated together, rather than separately and showed no significant difference in time or precision compared to 2D. However, closer analysis of the data implies the dual channel scope demonstrated a trend of improved time and precision compared to its single channel

counterpart. Visual strain was reported using both stereoendoscopes. Wilhelm *et al*[43] (2014) reported all performance parameters were superior in 3D over 2D using a variety of experimental and commercially available systems, although visual disturbance related to the autostereoscopic screen only. Finally, Wagner *et al*[44] (2012), compared single channel scope with HMD technology (in 3D and 2D settings) with robotic dual channel fixed screen technology (2D and 3D settings) and demonstrated significant time reductions with robotic 3D across all other laparoscopic outcomes.

Other prototype projection systems
Four publications assessed prototype projection systems (Table 5)[45-48]. Three used autostereoscopic screen technology with binocular scopes thus negating the need for eyewear[45,46,48]. Improvements in all outcomes were seen with the 3D group. Storz *et al*[47] (2011) used a novel projection system with a wavelength multiplex camera and monitor with wavelength polarizing eyewear (a technology based on original anaglyph systems). This again returned a true sense of stereopsis and improvements in outcomes were significant in 3D over 2D.

DISCUSSION
There is subjective and objective laboratory based evidence supporting use of 3D *vs* 2D for surgeons of all experiences as it provides the most realistic view of the operating field. It is also evident that stereoscopic imaging technology is continuing to evolve to generate higher quality 3D images.

Table 4	Comparing multisystems				
Ref.	Year	Projection system for 3D	Who and what assessed	Objective outcomes	Subjective outcomes
van Bergen *et al*[41]	1998	2 × single channelled and 2 × dual channelled scopes + active shuttering screen *vs* 2D	40 subjects - novices Variety of different models and skills tasks	Times and errors Objectively - significant improvement in 3D throughout	Subjectively - all tasks judged easier in 3D
Hanna *et al*[42]	2000	Single-channel scope + active shuttering screen and glasses; double-channel scope + active	10 experienced surgeons Lab based endoscopic anastomotic suturing	Time, precision of suture placement and pressure leakage score of anastomosis (2 × repetitions in each visual system) 3D systems evaluated together, no significant difference noted in 3D	Visual strain reported with 3D systems
Wilhelm *et al*[43]	2014	Dual channel scope + passive polarising screen and glasses *vs* 2D *vs* autostereoscopic screen	48 subjects, varying experience Lab based suturing task	Time, economy of movement (electromagnetic tracking) and workload assessments (using NASA Task Index Score All performance parameters were superior in 3D	No symptoms in 3D PP system, visual disturbance reported with autostereoscopic display
Wagner *et al*[44]	2012	Single-channel scope + HMD *vs* robotic dual channel scope + fixed head view	34 subjects (18 novices) 3 × lab based skills tasks	Time 3D robotic performance faster than all others, significantly	NA

NA: Not available; 3D: Three-dimensional; 2D: Two-dimensional; HMD: Head mounted display.

Table 5	Other prototype projection systems				
Ref.	Year	Projection system for 3D	Who and what assessed	Objective outcomes	Subjective outcomes
Taffinder *et al*[45]	1999	Dual channel scope with autostereoscopic/glass free screen	28 subjects (16 novices and 12 experienced laparoscopic surgeons) Novices = basic grasping and cutting lab based skills Experienced = suturing and complex cutting lab based skills	Time and performance score (ICSAD assessment tool) Significant improvement in 3D over 2D laparoscopy	No side effects reported with 3D
Ohuchida *et al*[46]	2009	Dual channel scope with "Cyberdome" projection system	23 novices 6 × lab based skills tasks	Time, errors and performance Significant improvement in all parameters in 3D with cyberdome over 2D	NA
Storz *et al*[47]	2011	Dual-channel scope + wavelength multiplex camera and monitor with polarising glasses	30 subjects (20 medical students and 10 experienced laparoscopic surgeons) 5 × lab based skills tasks	Time and errors In 4 out 5 tasks, significant reduction in time in 3D, in 4out of 5 tasks, significant reduction in errors	NA
Khoshabeh *et al*[48]	2012	Dual-channel scope + Multiview autostereoscopic display/glass free screen	3 experienced laparoscopic surgeons 2 × lab based skills tasks	Time and errors Reduced time and errors using 3D	NA

NA: Not available; 3D: Three-dimensional; 2D: Two-dimensional.

Capture of true stereopsis from the operative field is crucial for the subsequent projection of a true stereoptic image. However, with such focus on producing an effective projection system, the acquisition and true stereopsis of the image has sometimes been overlooked. It is clear from this review that in systems that compromised on the capture of two truly separate images of the operative field, they yielded no advantage for the participants using 3D over 2D. In studies using dual channel stereoendoscopes, the separate lenses within the laparoscope provided a greater spatial impression of stereopsis[49-51]. Consequently, for the operator, there is a more accurate appreciation of depth. Fishman *et al*[27] (2008) concluded there was deterioration in laparoscopic performance by reducing

horizontal lens separation in an experimental dual channel scope (thereby reducing stereopsis impression). However single channel systems produce images of greater clarity and resolution due to the greater size of the single optic channel for light transfer[52]. Single channel optics can produce convincing stereopsis only at close operating distances, whereas dual channel systems provide significant stereopsis in larger cavities, where there is greater distance from the end of the stereoendoscope to the operating site[51]. Close operating or near field objects with dual channel systems can cause visual discomfort due to the fixed focal point of the two lenses and our natural convergence conflicting. Therefore it is not surprising that the majority of studies which utilised single channel

laparoscopes did not show a benefit of 3D laparoscopy as all used target operating points distant to the scopes key stereoptic capabilities, irrespective of the projection system employed.

Modern projection systems attempt to provide as true a representation of the natural 3D view as possible, whilst balancing comfort and visual ease for the observer(s) and maintaining the brightness and resolution quality of the image. Active systems caused visual disturbances, headaches and symptoms of nausea due to the conflict of convergence and accommodation, as well as flickering and discomfort for the viewer due to the cumbersome battery powered glasses.

Early 3D images had poor resolution and luminosity as early cameras could not cope with low light levels or capture at high resolution. Projection systems were equally constrained by low refresh rates, low resolution and brightness. This added to discomfort and degraded the early 3D view[51]. Falk *et al*[19], 2001, demonstrated that image quality is vital for precision and surgical performance, as 2DHD systems produced better results when compared with standard view 2D and 3D. The use of polarizing glasses and filters over the shuttering screen provides a more comfortable wear experience for the observer but this is at the expense of image brightness.

Head-mounted displays provide good quality images with no degradation in quality or light and preserve the normal hand-eye axis[53]. However open sided head units, which do not block surrounding visual stimuli, can cause headaches and dizziness due to conflicting information from visual input and body position whilst with sealed units the surgeons are isolated from their surroundings and unable to react to unforeseen environmental incidents[42].

The Da Vinci robotic system (intuitive, United States) allows for fixed console viewing and so provides an unparalleled quality of stereopsis for the surgeon. All the studies which assessed binocular and biocular (same view through each eye, therefore 2D view)[51], showed statistically significant advantages with 3D performance for time and errors, reduced motion, and all other comparative markers for surgical performance. There can be no doubt that the advantages noted were purely due to the improvement in view provided by reintroduction of natural stereoptic depth cues. However use of the robot is limited to a relatively small number of procedures where advantage of the robotic platform over standard laparoscopic techniques has been established.

Later studies (Table 3), which used binocular endoscopes and the latest passive polarizing projection systems, identified no subjective impairment or "side effects" to using the 3D systems. The majority identified significant differences in their respective markers of surgical performance when comparing classical laparoscopy to 3D systems. Whilst surgeon experience does affect outcomes, it must be appreciated that experience in classical laparoscopy leads to the development of techniques to overcome the lack of stereopsis. This therefore favours poorer outcomes with the 3D system in studies where the assessment was made after short exposure times and single repetition of skills[34,38,39]. Studies which accounted for learning curves by allowing familiarisation with the system with multiple repetitions and well powered sample sizes demonstrate clearly the benefits in performance achievable with 3D laparoscopy[31,33,35,40].

High quality experimental studies have shown that the latest 3D systems using dual channel stereo-endoscopes and passive polarizing technology provide a "near natural" view, almost comparable to that observed by the Da Vinci. However, their clinical application has yet to be addressed with Level 1 evidence. The only randomised clinical trial assessing 3D systems[9], and addressed by Cochrane review[54], showed no discernible difference for laparoscopic cholecystectomy performance. However, this study is over ten years old and the system assessed used a single channel scope and active shuttering projection, which was unlikely to have provided a true spatial impression of the operating field throughout. Studies that investigated the clinical application of the latest 3D systems identify performance advantages but are underpowered[36,37]. Establishing the benefits of these systems can only truly be addressed within randomised clinical trials, using appropriately powered sample sizes.

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Endoscopic ultrasonography - emerging applications in hepatology

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Abstract

The inspection of the liver is a valuable part of the upper endoscopic ultrasonography (EUS) studies, regardless of the primary indication for the examination. The detailed images of the liver segments provided by EUS allows the use of this technique in the study of parenchymal liver disease and even in the diagnosis and classification of focal liver lesions. EUS has also emerged as an important tool in understanding the complex collateral circulation in patients with portal hypertension and their clinical and prognostic value. Recently, EUS-guided portal vein catheterization has been performed for direct portal pressure measurement as an alternative method to evaluate portal hemodynamics. In this review, the authors summarize the available evidence regarding the application of EUS to patients with liver diseases and how we can apply it in our current clinical practice.

Key words: Endoscopic ultrasonography; Portal hypertension; Gastroesophageal varices; Focal liver lesions; Liver biopsy

Core tip: This review summarizes the current status of the available evidence regarding the application of endoscopic ultrasonography (EUS) to patients with liver diseases, focusing on recent breakthroughs and its potential application on clinical practice. We highlight the

emerging role of EUS in the study of parenchymal liver disease as well as in the diagnosis and classification of focal liver lesions. Finally, we emphasise the crucial role of EUS in the understanding of the complex collateral circulation in patients with portal hypertension.

INTRODUCTION

In the recent years, there has been remarkable improvement in hepatology, with new treatments for viral hepatitis, recommendations for the follow-up of cirrhotic patients and treatment of portal hypertension complications. These advances have brought an increased need for the assessment of liver function and liver histologic characterization.

Endoscopic ultrasonography (EUS) has become an important tool, not only in the diagnosis of several gastrointestinal lesions, but also in performing various therapeutic manoeuvres[1]. Due to the close proximity of the transducer to the liver, from the transgastric and transduodenal routes, EUS allows a clear visualization of the liver anatomy and its vasculature providing accurate and detailed images[2,3] (Figure 1). As experience grows with this technique new indications for EUS continue to emerge, and endosonographers have made an effort to define a clinical role for EUS in liver diseases.

This review summarizes the available evidence regarding the application of EUS to patients with liver diseases and how it can be applied in a current clinical practice.

EUS AND LIVER PARENCHYMAL DISEASE

Although non-invasive tests, such as elastography or serologic markers for liver fibrosis, have been developed, the liver biopsy remains an important part of the liver disease evaluation and management[4].

Liver biopsy has been commonly performed by percutaneously image-guided. A transjugular fluoroscopy-guided approach is used when the percutaneous route is not safe, because of coagulopathy or ascites[5,6].

EUS-guidance represents an emerging method of liver biopsy. EUS provides images of both lobes of the liver, moreover biopsy needle can be safely directed into the liver under image guidance, and intervening vessels and organs can be avoided.

EUS-guided liver biopsy (EUS-LB) for studying parenchymal liver disease has largely been studied with the use of different needles. Since a tissue core biopsy with a preserved architecture is crucial to diagnosis and fully characterization of the hepatic diseases,

needles specifically designed for core biopsy have been used. The ability to obtain specimens of liver tissue for histologic examination with a Tru-Cut biopsy needle dedicated for EUS-guided biopsy, the Quick-Core® needle (Cook® Medical), were demonstrated in some published studies[7,8]. In a study by DeWitt *et al*[8], 21 consecutive patients underwent liver biopsy by using a Quick-Core® needle. Liver biopsy specimens were able to provide diagnostic clinical information in only 15 of 21 patients (71%), the total specimen length was a median of 9 mm, with a median of 2 complete portal tracts. The technique was safe and feasible. However the samples were smaller than those traditionally considered adequate for histologic assessment.

The Tru-Cut biopsy needle failed to reach widespread use due to technical difficulties with its utilization. To overcome the main limitations of a Tru-Cut biopsy needle, the same manufacture developed a new needle, the ProCore® needle (Cook® Medical). Sey *et al*[9] compared the diagnostic yield of a 19-gauge ProCore® needle with a Quick-Core® needle. A total of 45 patients underwent liver biopsy by using the Quick-Core® and 30 patients the ProCore® needle. The ProCore® needle group required fewer passes (median 2 *vs* 3, *P* < 0.0001), produced a longer median specimen length (median 20 mm *vs* 9 mm, *P* < 0.0001) with more complete portal tracts (median 5 *vs* 2, *P* = 0.0003) and also allowed a histologic diagnosis more frequently (97% *vs* 73%).

Other studies have also been published demonstrating the adequacy of liver tissue sampling by a 19-gauge FNA needle. Stavropoulos *et al*[10] presented a study in which patients underwent a EUS-LB with a 19-gauge FNA needle. All patients underwent EUS with a 7.5-MHz linear echoendoscope (Olympus GF-UC140P-AL5; Olympus, Tokyo, Japan) as the initial procedure. Twenty-two patients underwent a EUS-LB of the left lobe of the liver, a median of 2 passes (range 1-3) yielded a median specimen length of 36.9 mm, with a median of 9 complete portal tracts and a diagnostic yield of 91%, without post-procedure complications. The authors concluded that EUS-LB by using a 19-gauge FNA needle was feasible, safe, with an excellent diagnostic yield and sample adequacy for histologic examination.

To evaluate the diagnostic yield of EUS-LB in a large patient cohort, Diehl *et al*[11] recently presented a prospective, multicentre study with 110 patients who underwent EUS-LB at eight centres. EUS examination was performed with a linear echoendoscope (GF-UC140P, Olympus America, Center Valley, PA, United States). The biopsy was performed using a 19-gauge FNA needle, with or without a stylet, 7-10 to-and-fro motions of the needle were made per pass (1-2 pass were made), using the fanning technique and almost all endoscopists preferred to use full suction for the needle aspiration. Adequate liver biopsy specimens for pathological diagnosis were obtained in 98% of patients, with a median specimen length of 38 mm, with median of 14 complete portal tracts. There were five patients whose tissue yield was
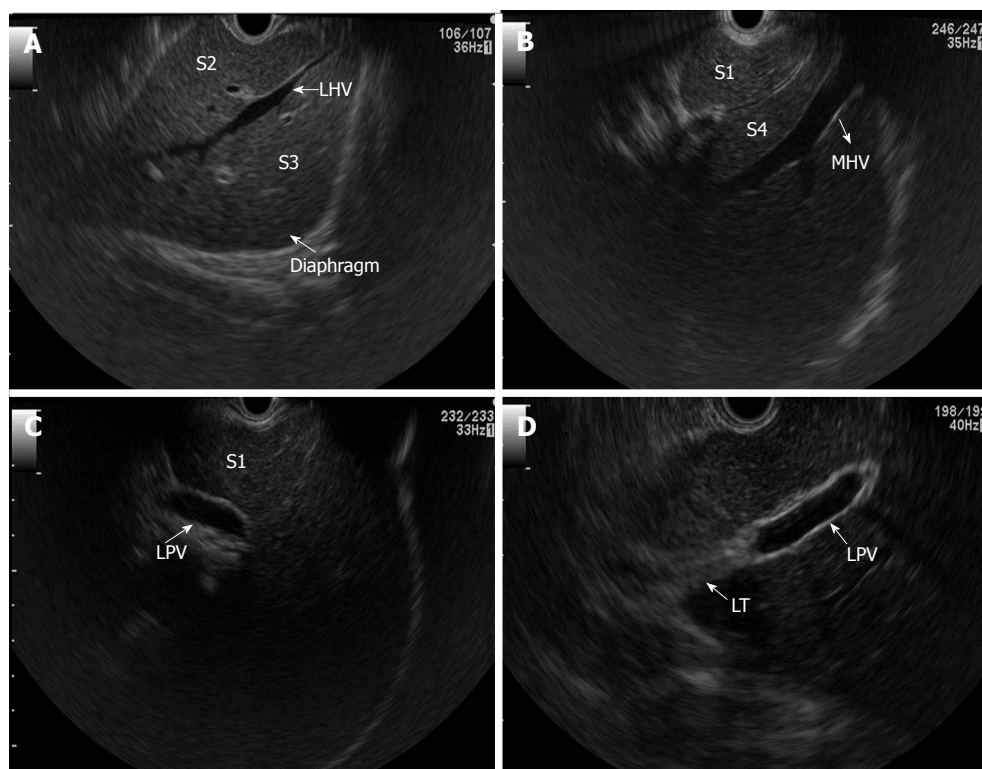
Figure 1 Endoscopic ultrasonography images of the hepatic structures from the proximal stomach: The left lateral segments (S2 and S3) (A); S1 (caudate lobe) and segment 4 (S4) (B); S1 with portal vein behind it (C); Umbilical part of the left portal vein (D). Images recorded using the curved linear scanning echoendoscope (GF-UCT 180; Olympus Medical Systems, Tokyo, Japan) coupled with a ProSound Alpha 10 processor (Aloka, Tokyo, Japan). LHV: Left hepatic vein; MHV: Middle hepatic vein; LPV: Left portal vein; LT: Ligamentum teres.

less than 6 complete portal tracts with aggregate length less than 15 mm. Nevertheless it has been possible to obtain a histological diagnosis in samples from four patients. There was no statistical difference in the yield between bilobar, left lobe only, or right lobe only biopsies. There was, however, one complication, where self-limited bleeding (pericapsular hematoma) occurred in a patient with coagulopathy and thrombocytopenia (platelets, 64000; INR, 1.42), evaluated for abnormal transaminases.

In a recent study by Pineda *et al*[12] the EUS-LB was for the first time compared with the other methods of liver biopsy (percutaneous and transjugular). The EUS-LB was obtained in widely separated regions of the liver or one single region only using a 19-gauge FNA needle. There were 68 EUS-LB cases when both lobes were biopsied, the left lobe only in 34 cases and transduodenal liver biopsy only in 8 cases. A sample of 27 percutaneous liver biopsies and 38 transjugular liver biopsies were selected. EUS-LB of both liver regions produced significantly more tissue in terms of both total specimen length (40 mm *vs* 25 mm, *P* < 0.001) and complete portal tracts (17 *vs* 10, *P* < 0.001) compared to a percutaneous liver biopsy. EUS-LB produced significantly longer total specimen length than transjugular liver biopsy (40 mm *vs* 34 mm, *P* = 0.01) and similar complete portal triads (17 *vs* 15.5, *P* = 0.22). Those EUS-LB cases in which the left lobe only was sampled were not statistically different compared

to percutaneous and transjugular liver biopsy.

Nowadays the EUS-LB could be considered a procedure with several advantages. The liver can be sampled under ultrasonographic visualization, which is important to avoid vessels and organs. The biopsy of both left and right lobes of the liver can overcome the concerns about sampling error, since a more accurate representation of liver histology can be provided. Another potential advantage is that the patient is sedated for the EUS procedure, making the experience less unconfortable.

All previous reports excluded patients with international normalized ratio (INR) > 1.5, thrombocytopenia (platelets < 50000/uL) and antiplatelet agents within 5 d of the procedure. Although the needle puncture occurs under ultrasonographic guidance, Glisson's capsule is punctured, and bleeding remains a concern, thus the use of EUS for these patients is not recommended. The Table 1 summarizes the data from the main studies of EUS-LB.

EUS AND FOCAL LIVER LESIONS

Focal liver lesions are frequently incidentally discovered during an imaging test, such as ultrasonography (US) or computed tomography (CT). Other times they are found in patients with risk factors for hepatic malignancy or even during a preoperative staging of extra-hepatic malignancies. Accurate characterization of these lesions remains an integral part of patients' evaluation, as the

Table 1 Data from the main studies of endoscopic ultrasonography-guided liver biopsy

Ref.	Study design	Needle	Passes	Specimen length (median)	Complete portal tracts (median)	Histological diagnosis
DeWitt *et al*[8]	Prospective unicentre study *n* = 21	Quick-Core[1]	1-4	9 mm	2	71%
Diehl *et al*[11]	Prospective multicentre study *n* = 110	19G (FNA) Expect[1]	1-2	38 mm	14	98%
Stavropoulos *et al*[10]	Prospective unicentre study *n* = 22	19G (FNA) Echotip[2]	1-3	36.9 mm	9	91%
Sey *et al*[9]	Prospective unicentre study *n* = 75	Quick-Core[1] ProCore 19G[1]	1-7 1-3	9 mm 20 mm	2 5	73% 97%

[1]Cook® Medical; [2]Boston Scientific. FNA: Fine needle aspiration.

extent of liver involvement may change clinical stage and management.

The inspection of the liver is a valuable part of the upper EUS studies, regardless of the primary indication for the examination. Recently, EUS and EUS-guided fine needle aspiration (EUS-FNA) has emerged as an important tool in the diagnosis and classification of liver lesions. Most of the liver segments can be visualized with the echoendoscope[3] and the proximity of the ultrasound probe to the liver parenchyma provides exceptional images of the liver parenchyma, which may have a key role in the detection, characterization and even in the definitive diagnosis of liver lesions.

Awad *et al*[13] evaluated the feasibility of EUS for the detection and diagnosis of liver lesions in 14 patients with known or suspected hepatocellular carcinoma (HCC) and metastatic liver lesions. Consecutive patients referred for EUS with suspected liver lesions were evaluated. EUS not only successfully identified all previously hepatic lesions described by CT scan, but also identified new or additional lesions in 4 patients (28%), all less than 0.5 cm in size. Nine patients underwent EUS-FNA of hepatic lesions, with a 22-gauge needle and two passes for each lesion, and all FNA yielded adequate specimens. The authors suggested that EUS is an adequate pre-operative staging tool for liver lesions suspected to be HCC or metastatic lesions, as EUS can detect small hepatic lesions previously undetected by dynamic CT scans.

Singh *et al*[14] have conducted a prospective trial to compare the accuracy of EUS and EUS-FNA with other imaging modalities for the detection of primary liver tumors in subjects at high risk of HCC. Seventeen subjects were enrolled in the study. The EUS has detected more HCC lesions than US (8 *vs* 2, *P* = 0.06), CT (19 *vs* 8, *P* = 0.06) or magnetic resonance imaging (MRI) (14 *vs* 7, *P* = 0.25), although not statistically significant. Moreover, EUS has detected small HCC lesions that has been missed by CT and MRI, with the smallest lesion visualized by EUS and confirmed by FNA having 4 mm in size. Thus, EUS-FNA helped in the determination of the cytological nature of liver nodular lesions that were indeterminate on CT and MRI. A diagnostic algorithm has been proposed in which EUS could be used for high-risk patients with inconclusive CT, or poorly accessible lesions requiring tissue confirmation.

In a study by DeWitt *et al*[15], the sensitivity of EUS features and EUS-FNA for benign and malignant solid liver lesions was described. The EUS-FNA was performed on 77 different liver lesions, a total of 45 aspirates (58%) were diagnostic for malignancy (true positives), of these, 44 were metastatic and one was a HCC. In 25 patients (55%), the FNA provided both the primary diagnosis and upstaged the malignancy and in nine subjects (20%) the EUS-FNA made the initial diagnosis, upstaged the tumor, and prevented surgery. Three lesions previously classified as benign were lately, by intraoperative findings or percutaneous-FNA, reclassified as malignant (false negatives). The EUS features predictive of malignant hepatic lesions were the presence of regular outer margins (60% *vs* 27%, *P* = 0.02) and the detection of two or more lesions (38% *vs* 9%, *P* = 0.03). EUS-FNA was performed using a 22-gauge needle and no complications were reported. This study concluded that EUS is a safe and sensitive procedure that can have a significant impact on patient management. The Table 2 summarizes the reported data from the studies of EUS of Focal liver lesions.

The diagnosis of portal vein thrombosis (PVT) secondary to HCC invasion is of paramount importance since it preclude a therapeutic approach[16]. Non-tumor PVT has usually a similar appearance to portal vein tumor thrombosis, the last could enhance with contrast or have Doppler sign, however sometimes this differentiation is difficult and the diagnosis remains doubtful until proven otherwise. Although percutaneous US-guided FNA of a PVT has been well documented[17], this technique presents some difficulties, especially in accessing thrombus in the centrally located main portal vein. The EUS-FNA could overcome some limitations of a percutaneous US-guided FNA, as it provides an excellent view of the liver hilum which facilitates the puncture of a PVT. Some case reports have been published which the EUS-FNA was used to diagnose

Table 2 Reported diagnostic yields of endoscopic ultrasonography of focal liver lesions

Ref./ study design	Study population	Patient number/ EUS-FNA	EUS diagnostic yield	EUS-FNA diagnostic yield
Awad *et al*[13] Prospective unicenter study	Suspected HCC or metastatic liver carcinoma	14/9	EUS identified all hepatic lesions (*n* = 14) previously reported by CT 4 new/additional lesions identified by EUS	All FNA passes yielded adequate specimens (malignant: *n* = 8; benign: *n* = 1)
Singh *et al*[14] Prospective unicenter study	High risk for HCC	17/16	The diagnostic accuracy of US, CT, MRI, and EUS/EUS-FNA were 38%, 69%, 92%, and 94%	Cytologic diagnosis of primary liver tumor was established in 8 cases (HCC = 7; cholangiocarcinoma = 1)
DeWitt *et al*[15] Retrospective unicenter study	Staging EUS examinations for known or suspected malignancy	77/77	EUS features predictive of malignant hepatic lesions were the presence of regular outer margins and the detection of two or more lesions	45 aspirates were diagnostic for malignancy (metastasis: *n* = 44; HCC = 1)

HCC: Hepatocellular carcinoma; EUS: Endoscopic ultrasonography; FNA; Fine needle aspiration; US: Ultrasonography; CT: Computed tomography; MRI: Magnetic resonance imaging.

HCC in patients with portal vein thrombosis[18-21]. In two cases the procedure was performed with a 25-gauge needle[18,19], while the other cases were performed with a 22-gauge needle[20,21] and all patient have tolerated the procedure well, without any immediate or delayed complications.

After a careful study and analysis of these articles we can easily conclude that the EUS and EUS-FNA may be helpful in the management of a subset of patients with a high suspicion for small liver lesions and to approach lesions that remain difficult to sample by percutaneous US-guided techniques. However some important issues remain unanswered[22,23], the risk of needle track spread of HCC from EUS-FNA remains undefined and the quality of the visualization of peripheral lesions, such as the areas under the dome of the diaphragm and the inferior-posterior portion of the right lobe of the liver.

Other potential concerns are related to the risks associated with EUS-FNA. In a large international survey[24], in which centres with large experience participated, the EUS-FNA of the liver lesions, in expert hands, proved to be a safe procedure. The complication rate was 4%, although this included one major complication (death) and several minor complications (bleeding, infection, abdominal pain). The dead occurred in a patient with a pancreatic mass. The patient was suspected to have an occluded biliary stent at the time of the EUS and a cholangitis resulted from the introduction of bacteria into an obstructed bile duct by the needle. For this reason it is recommended that antibiotics are administered prophylactically and biliary drainage is established rapidly if fine needle aspiration of the liver is to be performed in the setting of obstructive jaundice. Despite these results more information about the risks and complications in specific groups is necessary, especially in patients with a particular propensity for liver lesions, such as patients with cirrhosis or portal hypertension. Prospective studies comparing the accuracy and complication rate of the EUS-FNA and percutaneous FNA techniques for the diagnosis of liver tumors are also still needed.

The therapy of HCC guided by EUS has also been reported in some case reports. In 2011, Di Matteo *et al*[25] reported a case of a hepatocellular carcinoma located in the caudate lobe unsuitable for surgical resection, liver transplant and percutaneous treatment. The embolization failed and an EUS-guided neodymium: Yttrium-aluminium-garnet (Nd: YAG) laser ablation was performed. The ablation of hepatocellular carcinoma was effective without adverse events. Nakaji *et al*[26] reported another case of EUS-guided hepatocellular carcinoma treatment this time with ethanol injection. These two cases have shown the significant innovative options to treat lesions that are difficult to reach by conventional methods.

EUS AND ENDOSCOPIC THERAPY OF GASTROESOPHAGEAL VARICES

Gastroesophageal varices are the most important portosystemic collaterals that can be developed as a consequence of portal hypertension[27]. The venous anatomy of the lower esophagus and stomach in patients with portosystemic collaterals is complex. The dilated submucosal veins can be readily seen during an upper endoscopy. This superficial venous plexus is connected, through the perforating vessels, with the deep venous plexus, periesophageal and paraesophageal veins[28].

The endoscopic and ultrasound images provided by the EUS allows the visualization of the collateral vessels within and outside the esophageal wall[29-31] (Figure 2), and its role in the diagnosis and management of gastroesophageal varices is now well established.

In a study by Faigel *et al*[32] the presence and diameter of varices surrounding the esophagus and proximal stomach (paraesophageal and paragastric varices) were correlated with the presence and degree of liver disease and portal hypertension and represented a risk factor for variceal bleeding.

Since the previous reports about the role of collaterals in patients with portal hypertension and its clinical significance, some studies have analyzed the role of the EUS in the evaluation of the outcome of endoscopic

Figure 2 Esophageal collateral vessels (arrow) (A), esophageal varices seen as hypoechoic structures inside the esophageal wall (arrows) (B); and paraesophageal varices and perforating veins (C). Images recorded using the radial scanning echoendoscope (GF-UE160-AL5; Olympus Medical Systems, Tokyo, Japan) coupled with a ProSound Alpha 10 processor (Aloka, Tokyo, Japan).

therapeutics for esophageal varices, thereby allowing the selection of these patients for more intensive therapy or follow-up[33].

Endoscopic band ligation (EBL) has become the preferred method of treatment for esophageal varices, as it has proved to be as effective as injection sclerotherapy with fewer serious adverse events[34], however the risks of recurrence and rebleeding still remain a concern.

Recently, Masalaite *et al*[35] have assessed the role of the EUS in predicting the recurrence of esophageal varices following EBL. The study has shown that the presence of severe or multiple periesophageal collateral veins were independent prognostic factors for variceal recurrence. Similar results have been previously reported[36-38].

The effects of sclerotherapy and EBL on esophageal varices are considered to be different, which might be explained by different results of each technique in the ablation of collateral veins.

Lo *et al*[39] conducted a study to access the correlation between paraesophageal varices and esophageal variceal recurrence/rebleeding in patients who underwent sclerotherapy and EBL. Patients with more severe paraesophageal varices have presented a significantly higher rate of variceal recurrence and rebleeding. The prevalence of paraesophageal varices was 86% in the EBL group compared to 51% in the sclerotherapy group (*P* = 0.002).

In a study by de Paulo *et al*[40], the EUS was used to guide sclerotherapy for esophageal varices and although no significant benefit was found in the EUS-guided sclerotherapy in relation to the mean number of sessions necessary for eradication, the presence of collateral vessels, associated with bleeding recurrence, was less frequent in the EUS-guided group.

A possible explanation for these results could be appointed as the sclerotherapy causes fibrosis and obliteration of the perforating veins, while during EBL collateral vessels, in deeper layers, could remain untouched.

In order to identify factors that contributed to recurrence of varices and bleeding after endoscopic treatment some authors have also used color Doppler EUS. The

association of Doppler to ultrasound images obtained by EUS allows both the visualization of varices and its collaterals and the understanding of the hemodynamics of the portal venous system and even the effects of endoscopic and pharmacological therapeutics for esophageal varices[41]. In a study by Hino *et al*[42] the color Doppler EUS was used to study the hemodynamics changes and morphology pattern of the left gastric vein (the main feeder vessel of esophageal varices). The hepatofugal flow velocity in the left gastric vein was studied in 31 patients with high risk esophageal varices. This study has demonstrated that patients showing anterior branch dominant pattern of left gastric vein and high hepatofugal flow velocity may present a high risk of an early recurrence of esophageal varices. Posteriorly, these results were validated by the same authors in a larger study of 68 patients[43].

The Table 3 summarizes the reports about the role of EUS in the evaluation of the outcome of endoscopic therapeutics for esophageal varices.

Currently, there are no specific recommendations for the EUS in the diagnosis or treatment management of patients with esophageal varices. However, the previously reported studies report information that may be important for the selection of optimal treatment for esophageal varices. The identification of collateral veins after endoscopic treatment would allow us to identify patients who are at higher risk of variceal recurrence and rebleeding and to select those who require a closer follow-up and even a more aggressive endoscopic approach.

Gastric varices occur in approximately 17% of patients with portal hypertension[44]. The endoscopic diagnosis of high risk for bleeding of gastric varices is not always easy to assess, and sometimes they are mistaken for large gastric folds or submucosal tumors. The magnetic resonance and CT allow the visualization of the entire portal venous system, however the accuracy of these techniques in distinguishing between submucosal gastric varices and perigastric collateral veins remains limited[41].

The EUS equipped with Doppler can significantly

Table 3 Role of endoscopic ultrasonography in the evaluation of the outcome of endoscopic therapeutics for esophageal varices

Ref.	Study design	Endoscopic findings	EUS findings
Masalaite *et al*[35]	Prospective The role of EUS in predicting the recurrence/ rebleeding of esophageal varices: EBL (*n* = 40)	Recurrence of esophageal varices: 19 (47.5%) within 12 mo of EBL	EUS independent prognostic factors for variceal recurrence: Severe esophageal collaterals (OR= 24.39) multiple esophageal collaterals (OR = 24.39)
Lo *et al*[39]	Prospective The role of EUS in predicting the recurrence of esophageal varices: ES (*n* = 35) *vs* EBL (*n* = 44)	Recurrence of esophageal varices: 43% ES *vs* 70% EBL	Paraesophageal varices: 51% ES *vs* 86% EBL
de Paulo *et al*[40]	Prospective The role of EUS-guided ES: ES (*n* = 25) *vs* EUS-guided ES (*n* = 25) of esophageal collateral vessels	Mean number of sessions until eradication: 4.3 ES group *vs* 4.1 for the EUS-ES Recurrence of esophageal varices: 16.7% ES *vs* 8.3% EUS-ES	Esophageal collaterals at the end of the sclerotherapy program: 8 patients in ES *vs* 0 patients in EUS-ES

EUS: Endoscopic ultrasonography; EBL: Endoscopic band ligation; ES: Endoscopic sclerotherapy.

improve the detection of gastric varices and the understanding of the feeding vein, according to each type and the evaluation of vascular blood flow, which could be important in defining the therapeutic strategy[45,46]. With EUS-Color Doppler, Iwase *et al*[47] visualized small gastric varices that were difficult to detect by endoscopic observation, and were able to identify the feeding vein for each type of gastric varices. In a recent study by Imamura *et al*[48] the gastric varices diameter, which was independent from endoscopic view, Child-Pugh classification and the presence of hepatocellular carcinoma, have been correlated with flow volume measured by the EUS.

Sato *et al*[49] have also studied the role of the EUS-Color Doppler in the diagnosis and prediction of bleeding risk of gastric varices. The EUS-Color Doppler has allowed a clear sonographic visualization of the gastric varices and the evaluation of its morphology. In addition, the authors have showed that a smaller thickness of the gastric wall was a significant predictor of a high bleeding risk.

The presence of isolated gastric varices without esophageal varices can also be observed in patients with non-cirrhotic portal hypertension, which can occur in patients with splenic vein obstruction (left-sided portal hypertension). The role of the EUS color Doppler in patients with isolated gastric varices related to splenic vein occlusion has also been studied by Sato *et al*[50]. In this study the authors have provide specific findings that may be regarded as hallmarks of gastric varices due to splenic vein occlusion, namely a flow clearly depicted a round fundal region at the centre, with varices expanding to the curvatura major of the gastric body.

Endoscopic procedures, mainly the injection of tissue adhesives, such as cyanoacrylate (CYA), have become the therapy of choice for the treatment of gastric varices[51], although it is known to be associated with risk of clinical adverse events[52]. An innovative endoscopic option for the management of gastric varices includes the EUS-guided therapy.

The EUS can not only provide a clear image of the varix lumen, but also of the main feeding vein, and thus guiding the treatment directly to the perforating feeder vessel, which may theoretically minimize the amount of CYA needed to achieve the obliteration of gastric varices.

In a small study conducted by Romero-Castro *et al*[53] the EUS was used to guide the CYA injection in gastric varices. The EUS-guided CYA injection at the entrance of the perforating veins was successful in eradicating gastric varices in all the 5 patients treated, without recurrent bleeding or other subsequent complications. The authors have reported that the most difficult and time-consuming issue was the identification of the perforating vein of gastric varices and rule out what would be the outflowing vein. To be sure that the targeted vessel was the perforator, they carefully displayed the vascular anatomy by EUS and checked by fluoroscopy that the CYA-lipiodol mixture would not go downstream if an outflowing vein was mistakenly punctured.

Despite the reported success of the EUS-guided CYA injection, the concerns about the risks of embolization still remain. In a study by Binmoeller *et al*[54], coils, that are currently used for intravascular embolization treatments, were delivered into the varix under the EUS-guidance and previous to CYA injection, in order to reduce or eliminate the risk of glue embolization. The procedure was successful in all patients (thirty patients) with immediate hemostasis achieved in patients with active gastric varices bleeding (two patients). There was no damage to the echoendoscope, related to glue injections and non-procedure-related complications

In a multicentre study by Romero-Castro *et al*[55], EUS-guided coil application *vs* cyanoacrylate for the embolization of feeding gastric varices was studied. Thirty patients, 11 patients in the coil group and 19 patients in cyanoacrylate group, were included. Both techniques were effective in the gastric variceal obliteration. However coil application required fewer endoscopies and tended to have fewer adverse events.

An advantage of the EUS-guided treatment is the lack of dependency on direct varix visualization. In a case study reported by Tang *et al*[56] the point

of rebleeding of a fundal gastric varices, which was persistently obscured due to ongoing bleeding and blood clots, was identified by the EUS, followed by CYA injection and real-time Doppler confirmation of vascular signal loss in gastric varices.

Transesophageal EUS-guided coil or CYA injection of gastric varices is feasible and deserves further studies to determine whether these approaches can improve safety and efficiency over standard endoscopic injection of CYA alone. Although the EUS-guided gastric variceal therapy offers many potential advantages, a review by Fujii-Lau *et al*[46] lists several pitfalls that should be considered before applying the technique, such as the risk of damage the echoendoscope if glue lodged within the channel, the smaller aspiration channel, compared to a therapeutic endoscope, which could be important in cases of active bleeding, the limited retroflexion of the echoendoscope making the approximation to the fundal mucosa difficult, the importance of a fluoroscopy guidance to monitor for the immediate embolization and the complexity of the entire procedure making it time-consuming.

EUS FOR THE EVALUATION OF HEMODYNAMIC CHANGES IN PORTAL HYPERTENSION

Portal hypertension is a common adverse event of liver cirrhosis as this syndrome develops in the majority of patients with cirrhosis being responsible for severe complications such as gastrointestinal variceal bleeding, ascites, hepatorenal syndrome and hepatic encephalopathy[57]. The hepatic venous pressure gradient, an acceptable indirect measurement of portal pressure, predicts the development of complications of portal hypertension[58], whilst its use has also been proposed in the evaluation of the efficacy of pharmacological therapeutics in patients with portal hypertension[59]. Hepatic venous pressure gradient is traditionally measured by a transjugular approach, an invasive procedure, with radiation and intravenous contrast exposure and not readily available in all centres. The EUS-Guided portal vein catheterization for direct portal pressure measurement has been reported in some studies.

The possibility of direct EUS-guided portal vein catheterization using a 25-gauge needle and accurate pressure measurement has been demonstrated in animal models. In a study by Huang *et al*[60] a novel EUS-guided system using a 25-gauge FNA needle (Cook® Medical, Winston-Salem, NC, United States), and a compact manometer with non-compressible tubing (Cook® Medical, Bloomington, Ind, United States) has been used to directly measure portal pressure gradient and to evaluate its performance and clinical feasibility. Under the EUS guidance a 25-gauge FNA needle with attached manometer has been used to puncture (transgastric-transhepatic approach) and to measure pressures in the portal vein, right hepatic vein, inferior vena cava, and

aorta in 3 animal models and the results were correlated with the standard transjugular approach. There has been an excellent correlation between the two methods and no adverse events have been reported. Recently, the same group[61] has presented the first human pilot study of the EUS-guided portal pressure gradient measurement (EUS-PPGM) in patients with liver disease. The procedure has been performed with a linear echoendoscope and the same equipment previously described. Twenty-eight patients underwent EUS-PPGM, 15 of 28 (57.1%) had evidence of portal hypertension based on portal pressure gradient of which 10 of 15 (66.7%) had clinical significant portal hypertension. There has been an excellent association between portal pressure gradient and clinical evidence of cirrhosis, presence of varices, portal hypertensive gastropathy and thrombocytopenia. There have not been technical failures or reported intraprocedural or post-procedural adverse events. This was the first study demonstrating that the EUS-PPGM can be safe and accurate in humans, even in the context of suspected cirrhosis.

The EUS-guided measurements of portal pressure gradient provide an alternative method to evaluate portal hemodynamics. More studies are still needed, mainly in cirrhotic patients with impaired hemostasis, and therefore there is a possibility to use this new method to evaluate the effect of pharmacological therapy on portal hypertension.

CONCLUSION

There is evidence to suggest that the EUS alone or with FNA represent a significant advance in the evaluation and treatment of liver diseases and its complications. The EUS is able to provide an early detection and the biopsy of small focal liver lesions that are either not visualized by other imaging modalities or visualized during routine staging procedures of gastrointestinal malignancies. Thus, the EUS is another potential method for a guided liver biopsy for study parenchymal liver disease.

The EUS proves to be really helpful in managing portal hypertension being used to stratify patients who are at risk of recurrence and rebleeding of gastroesophageal varices and providing support for more aggressive therapy with frequent endoscopic treatments including direct treatment to the perforating veins. Concerning gastric varices, it can be used to guide cyanoacrylate injection in an effort to achieve total occlusion of the varices and decrease the recurrence rate and complications.

More recently, the EUS has been described as a method for guiding interventions such as portal vein catheterization for direct portal pressure measurement. However most of the studies in this field are performed in animal models, and safety date in humans, mainly cirrhotic patients, are still lacking.

The diagnostic and therapeutic role of EUS in hepatology is emerging and the available evidence suggests that the EUS has the potential to be a valuable

alternative imaging modality in the study of liver diseases and its complications. Several methods are still under development and need to be validated, but the authors expect that in the near future applications of the EUS in hepatology will become an integral part of the evaluation of patients with liver diseases.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Clinical impact of confocal laser endomicroscopy in the management of gastrointestinal lesions with an uncertain diagnosis

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Abstract

AIM

To evaluate the clinical impact of confocal laser endomicroscopy (CLE) in the diagnosis and management of patients with an uncertain diagnosis.

METHODS

A retrospective chart review was performed. Patients who underwent CLE between November 2013 and October 2015 and exhibited a poor correlation between endoscopic and histological findings were included. Baseline characteristics, indications, previous diagnostic studies, findings at the time of CLE, clinical management and histological results were analyzed. Interventions based on CLE findings were also analyzed. We compared the diagnostic accuracy of CLE and target biopsies of surgical specimens.

RESULTS

A total of 144 patients were included. Of these, 51% (74/144) were female. The mean age was 51 years old.

In all, 41/144 (28.4%) lesions were neoplastic (13 bile duct, 10 gastric, 8 esophageal, 6 colonic, 1 duodenal, 1 rectal, 1 ampulloma and 1 pancreatic). The sensitivity, specificity, positive predictive value, negative predictive value, and observed agreement when CLE was used to detect N-lesions were 85.37%, 87.38%, 72.92%, 93.75% and 86.81%, respectively. Cohen's Kappa was 69.20%, thus indicating good agreement. Changes in management were observed in 54% of the cases.

CONCLUSION
CLE is a new diagnostic tool that has a significant clinical impact on the diagnosis and treatment of patients with uncertain diagnosis.

Core tip: Endoscopic and histopathological findings are not always certain, thus potentially leading to inaccurate diagnoses and inappropriate therapeutics. The use of confocal laser endomicroscopy has a significant clinical impact on the diagnosis and treatment of patients with uncertain diagnoses.

INTRODUCTION
Conventional histology is the gold standard procedure in evaluating lesions in the gastrointestinal tract. However, endoscopic and histological findings are sometimes poorly correlated, thus hindering accurate diagnosis and subsequent clinical management[1-5]. The probability of sampling error has been found to be 20%-30% and is affected by several factors, such as inadequate macroscopic interpretation and minimal biopsy acquisition[6].

Confocal laser endomicroscopy (CLE) is a technique that is used *in vivo* during endoscopy to evaluate the mucosal epithelium of the gastrointestinal tract, the bile duct and pancreatic cysts[5,7]. Furthermore, it provides dynamic information including blood flow and contrast up-take[8].

Multiple studies have shown that CLE has a diagnostic accuracy above 90% when standardized parameters are used to evaluate specific lesion features[9-17]. However, there is minimal information in the literature regarding the influence of CLE on the evaluation and management of patients with GI lesions of uncertain diagnosis. The aim of this study was to evaluate the clinical impact of CLE in this group of patients.

MATERIALS AND METHODS
Study design
This study was an observational, analytical, retrospective, cross-sectional single-center study. Prospective data from November 2013 to September 2015 were collected at the Ecuadorian Institute of Digestive Diseases (IECED) Omni Hospital Academic Tertiary Care Center, Guayaquil, Ecuador. The study protocol was approved by the Institutional Ethical and Review Board and conducted according to the guidelines in the declaration of Helsinki.

Demographic data, indications, previous diagnostic findings, CLE findings, clinical management and histological results are described. Records from previous endoscopies [*i.e.*, upper endoscopy (UE), colonoscopy with high definition magnification and digital chromoendoscopy, endoscopic retrograde cholangiopancreatography (ERCP) with brushing sample and endoscopic ultrasound (EUS)], computed tomography (CT), magnetic resonance imaging (MRI) cholangiopancreatography and tests for tumor markers were analyzed.

Population selection
Inclusion criteria: Patients who underwent CLE (Cellvizio®, Mauna Kea Technology, France) as a result of an uncertain diagnosis (an absence of correlation between endoscopic and histological findings) in gastrointestinal diseases, including neoplastic (N) or non-neoplastic (NN) lesions (Table 1). Patients ≥ 18 years old; Patients who agreed to participate; Patients with no previous p-CLE.

Exclusion criteria: Pregnant patients and patients with allergies and/or contraindication to fluorescein.

Endoscopy and CLE procedures
All participants underwent CLE according to the standard protocol. Sedation was accomplished with propofol in UE and colonoscopy and general anesthesia in ERCP and EUS. In UE and colonoscopy, the CLE was performed with Gastroflex® and Coloflex® probes (Cellvizio®, Mauna Kea Technology, France) through the working channel of a standard video-endoscope. In ERCP procedures, CLE was performed through cholangioscopy (SpyGlass® system, Boston Scientific®), and in EUS, CLE was performed through a 19G needle (Expect® needle, Boston Scientific) with Cholangioflex® and AQ-flex® probes (Cellvizio®, Mauna Kea Technology, France).

After the GI mucosa was inspected, the areas with suspected pathology were further examined. The probe was carefully advanced to the mucosa, and *in vivo* microscopy images were scanned at 1000 ×

Table 1 Baseline characteristics *n* (%)

	Biopsy/surgical specimen diagnosis			*P* value
	Total (*n* = 144)	Neoplastic lesions (*n* = 41)	Non-neoplastic lesions (*n* = 103)	
Sex (female)	74 (51.4)	19 (46.3)	55 (53.4)	0.445
Age, yr, mean ± SD	51.33 ± 16.5	56.73 ± 17.1	49.19 ± 15.8	0.014
Initial endoscopy indication				< 0.001
Suspected tumor	70 (48.6)	32 (78.0)	38 (36.9)	
Other	74 (51.4)	9 (22.0)	65 (63.1)	
Location				0.187
Vater ampulla	2 (1.4)	1 (2.4)	1 (1.0)	
Colon	14 (9.7)	6 (14.6)	8 (7.8)	
Duodenum	4 (2.8)	1 (2.4)	3 (2.9)	
Esophagus	24 (16.7)	8 (19.5)	16 (15.5)	
Stomach	59 (41.0)	10 (24.4)	49 (47.6)	
Ileum	1 (0.7)	0 (0.0)	1 (1.0)	
Pancreas	8 (5.6)	1 (2.4)	7 (6.8)	
Rectum	3 (2.1)	1 (2.4)	2 (1.9)	
Bile duct	29 (20.1)	13 (31.7)	16 (15.5)	

SD: Standard deviation.

magnification by using CLE. These video images were transmitted in a real-time onto a screen situated next to the endoscopy monitor. For tissue contrast, 5 mL of 10% fluorescein was injected in all patients.

All lesions were analyzed in real-time after an endoscopic assessment. Micrographs and videos obtained during CLE were stored for further examination. The images were interpreted according to methods previously published in esophageal[18,19], gastric[14,20,21] and colonic[22-24] lesions. The Miami[25,26], Paris[13], and CONTACT[11] study criteria for using CLE were used in bilio-pancreatic tract and cystic pancreatic lesions.

Definitions

An uncertain diagnosis in a case of gastrointestinal lesions was defined as a lack of correlation between a histological report and findings on initial endoscopy (*e.g.*, UE, colonoscopy, ERCP, EUS). Neoplastic (N) lesions included dysplasia, adenomas and carcinomas that were located at any level of the GI tract, pancreas or biliary duct. Any other lesion was defined as a non-neoplastic (NN) lesion (Figures 1 and 2).

We defined a "change in management" resulting from CLE in cases of uncertain diagnosis when the results of CLE changed the management strategy that was initially based on the original biopsy or when no further diagnostic methods were used.

Statistical analysis

Baseline characteristics, including demographic data, indications, CLE findings, histological results and changes in management, were described as percentages and ranges or means and standard deviations, as appropriate. The overall diagnostic accuracy of CLE in an N-lesion was determined by comparing the CLE findings to the final post-CLE histopathological report (*e.g.*, biopsy or surgical specimen). The following measurements were used for this purpose: Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), simple percentage agreement (observed agreement) and inter-rater agreement (Cohen's Kappa). Cohen's Kappa was interpreted by using Landis and Koch-Kappa's Benchmark Scale. Changes in management and redirected biopsy samples were described as percentages. The characteristics of N-lesions and NN-lesions groups were compared using Student's *t*-test for continuing variables and χ^2 and Fisher's test for categorical variables. A *P* value < 0.05 was considered to be statistically significant. The statistical methodology used in this study was reviewed by the IECED institutional Biostatistician. Statistical calculations were performed in SPSS software suite v.22.

RESULTS

A total of 144 patients were included. The mean age of the patients was 51.33 years old (range 18-86), and 51.4% (74/144) were female. There were 41/144 N-lesions, including 13 bile duct, 10 gastric, 8 esophageal, 6 colonic, 1 duodenal, 1 rectal, 1 ampulloma and 1 pancreatic lesion (Table 1). The findings included Barrett's esophagus with or without dysplasia, adenocarcinomas and mucosal inflammation in different segments of the digestive tract, gastric metaplasia and dysplasia, carcinoid tumors, ampulloma, mucinous and serous pancreatic cysts, pseudocysts, adenoma and adenocarcinoma of the biliary tract and inflammation related to parasites.

The sensitivity, specificity, PPV and NPV for detecting N-lesions between CLE and target biopsies or surgical specimens were 85.37%, 87.38%, 72.92% and 93.75%, respectively. The observed agreement was 86.81%, and Cohen's Kappa value was 69.20%, thus indicating good agreement (Table 2). Changes in management were noted in 78/144 (54.2) cases (Table 3). These changes resulted from the improved ability of CLE to acquire targeted biopsies, which avoided the need for further diagnostic methods.

Figure 1 Colonic polyp. A: A sigmoid flat polyp was viewed using digital chromoendoscopy with high definition by i-scan, which revealed a pit pattern suggestive of a hyperplastic lesion in a patient with cirrhosis and important coagulation disorders; B: CLE showing dysplasia (image optimized by using a green-white image color palette in Cellvizio® viewer software); C: A histological analysis of the specimen confirmed the dysplasia. CLE: Confocal laser endomicroscopy.

Figure 2 Undetermined stenosis of the biliary tract. A: ERCP was performed in a patient with undetermined stenosis who was cytobrush-negative for malignancy; B: Spyglass cholangioscopy showing a reddish area that was not suspected of malignancy; C: CLE showing dark clumps that were suspected of malignancy (image optimized using the "black-red-yellow" image color palette in Cellvizio® viewer software); D: The histological results of a target biopsy confirmed a diagnosis of cholangiocarcinoma. CLE: Confocal laser endomicroscopy; ERCP: Endoscopic retrograde cholangiopancreatography.

Table 2 Confocal laser endomicroscopy overall diagnostic accuracy with either confocal laser endomicroscopy target biopsy or surgical specimens as the Gold Standard *n* (%)

	Biopsy/surgical specimen diagnosis			*P* value
	Total (*n* = 144)	Neoplastic lesions (*n* = 41)	Non-neoplastic lesions (*n* = 103)	
CLE diagnosis				< 0.001
Neoplastic lesion	48 (33.3)	35 (85.4)	13 (12.6)	
Non-Neoplastic lesion	96 (66.7)	6 (14.6)	90 (87.4)	
CLE overall diagnostic accuracy				
Sensitivity, *n*/T (%; 95%CI)		35/41	(85.37; 70.83-94.43)	
Specificity, *n*/T (%; 95%CI)		90/103	(87.38; 79.38-93.11)	
PPV, *n*/T (%; 95%CI)		35/48	(72.92; 61.46-81.97)	
NPV, *n*/T (%; 95%CI)		90/96	(93.75; 87.71-96.93)	
Observed agreement, *n*/T (%)		125/144	-86.81	
Cohen's Kappa, % (95%CI)		69.2	(56.50-81.90)	

PPV: Positive predictive value; NPV: Negative predictive value; CI: Confidence interval; CLE: Confocal laser endomicroscopy.

Table 3 Patients with changes in management following biopsy/surgical specimen diagnosis, listed according to organ *n* (%)

	Biopsy/surgical specimen diagnosis			*P* value
	Total (*n* = 78)	Neoplastic lesions (*n* = 30)	Non-neoplastic lesions (*n* = 48)	
Location				0.707
Vater ampulla	1 (1.3)	1 (3.3)	0	
Colon	9 (11.5)	4 (13.3)	5 (10.4)	
Duodenum	4 (5.1)	1 (3.3)	3 (6.3)	
Esophagus	10 (12.8)	5 (16.7)	5 (10.4)	
Stomach	17 (21.8)	5 (16.7)	12 (25)	
Ileum	1 (1.3)	0	1 (2.1)	
Pancreas	6 (7.7)	1 (3.3)	5 (10.4)	
Rectum	3 (3.8)	1 (3.3)	2 (4.2)	
Bile duct	27 (34.6)	12 (40)	15 (31.3)	

DISCUSSION

CLE is an imaging method that has demonstrated substantial benefit for diagnosing GI tract, bile duct and pancreatic lesions. Several previous reports have supported CLE's efficacy by showing CLE and histological findings are well correlated[15-17]. Recent studies[11,18] have demonstrated that CLE has high accuracy in differentiating benign from malignant lesions in bile duct and pancreas pathology (mean accuracy, 81%)[21], malignant gastric lesions (94%-96%)[20] and polyps (82%)[22]. In addition, the American Society for Gastrointestinal Endoscopy has reported that CLE has at least 90% sensitivity and 98% NPV when it is used to detect Barrett's esophagus-associated dysplasia[18]. The Miami classification criteria for bile duct lesions have been demonstrated to have a higher accuracy when they are used to diagnose malignant strictures rather than biopsy samples (81% *vs* 75%, respectively)[12]. However, these criteria have some limitations when they are used to differentiate inflammatory from malignant strictures, thus leading to false positives. On the basis of this finding, Caillol *et al*[13] have developed the Paris Classification, which has increased sensitivity and specificity in characterizing indeterminate bile duct strictures[13,27]. Additionally, in colonoscopy, CLE has been demonstrated to be very useful. Neumann *et al*[23,24] have found that CLE, when used in inflammatory

bowel disease (IBD) surveillance, is a simple technique that facilitates the accurate and early detection of related lesions.

Our study focused on the clinical impact and management changes resulting from the use of CLE to evaluate GI (upper and lower) lesions, including bile duct pathology and pancreatic cysts, in a subgroup of patients with uncertain diagnoses due to non-conclusive previous tests.

CLE was found to have a high accuracy in detecting neoplastic bilio-pancreatic lesions, which accounted for 80% of all lesions found in the bile ducts and pancreas. In 54% of such cases, the use of CLE resulted in a change in the diagnostic and therapeutic approach. However, 71% of all lesions in patients with an inconclusive diagnosis were NN benign lesions, and CLE resulted in an observed agreement, PPV and NPV of 86%, 72% and 93%, respectively. These results were similar to those reported in previous publications that have explored lesions in the upper and lower portions of the gastrointestinal tract[1,22-30].

The main advantages of using CLE include its ability to differentiate *in vivo* lesions and guide targeted biopsies, thereby avoiding the potential complications associated with endoscopic mucosal resections (*e.g.*, perforation or bleeding). Additionally, using CLE prevents a need for further unnecessary invasive and noninvasive diagnostic methods (*e.g.*, repeated endo-

scopy, ERCP, EUS, or other imaging modalities, such as CT and MRI), thus decreasing patient risk and economic burden associated with such procedures. However, our study has limitations, including its single-center retrospective design and lack of randomization.

Conclusion
The results of this study suggest that CLE is a valuable diagnostic tool for patients with an uncertain diagnosis (neoplastic or non-neoplastic). CLE can be used to perform real-time evaluation of the GI mucosa, thus allowing endoscopists to target biopsies and having a significant clinical impact when it is used to improve and modify diagnoses and treatment strategies.

COMMENTS

Background
Confocal laser endomicroscopy (CLE) is a technique that can be used *in vivo* during endoscopy to evaluate the mucosal epithelium of the gastrointestinal tract, the bile duct and pancreatic cysts.

Research frontiers
The authors evaluated the clinical impact of CLE in patients with an uncertain diagnosis in gastrointestinal lesions.

Innovations and breakthroughs
The observed agreement was 86.81% and had a Cohen's Kappa value of 69.20%, thus indicating good agreement. Changes in management were noted in 78/144 (54.2) cases and were associated with the improved acquisition of targeted biopsies, thus avoiding the need for further diagnostic tests.

Applications
CLE is a new diagnostic tool that can be used in patients with uncertain diagnosis, in whom it has a significant clinical impact on diagnosis and treatment.

Terminology
Confocal laser endomicroscopy; *in vivo* microscopy.

Peer-review
Overall the paper is interesting and points out discrepancy between endoscopic and histopathologic findings.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Impact of laparoscopic liver resection on bleeding complications in patients receiving antithrombotics

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Abstract

AIM
To assess the impact of laparoscopic liver resection (LLR) on surgical blood loss (SBL), especially in patients with antithrombotics for thromboembolic risks.

METHODS
Consecutive 258 patients receiving liver resection at our institution between 2010 and 2016 were retrospectively reviewed. Preoperative antithrombotic therapy (ATT; antiplatelets and/or anticoagulation) was regularly used in 100 patients (ATT group, 38.8%) whereas not used in 158 (non-ATT group, 61.2%). Our perioperative management of high thromboembolic risk patients included maintenance of preoperative aspirin monotherapy for patients with antiplatelet therapy and bridging heparin for patients with anticoagulation. In both ATT and non-ATT groups, outcome variables of patients undergoing LLR were compared with those of patients receiving open liver resection (OLR), and the independent risk factors for increased SBL were determined by multivariate analysis.

RESULTS
This series included 77 LLR and 181 OLR. There were 3 thromboembolic events (1.2%) in a whole cohort, whereas increased SBL ($\geq$ 500 mL) and postoperative bleeding complications (BCs) occurred in 66 patients (25.6%) and 8 (3.1%), respectively. Both in the ATT and non-ATT groups, LLR was significantly related to reduced SBL and low incidence of BCs, although LLR was less performed as anatomical resection. Multivariate analysis showed that anatomical liver resection was the most

significant risk factor for increased SBL [risk ratio (RR) = 6.54, $P < 0.001$] in the whole cohort, and LLR also had the significant negative impact (RR = 1/10.0, $P < 0.001$). The same effects of anatomical resection (RR = 15.77, $P < 0.001$) and LLR (RR = 1/5.88, $P = 0.019$) were observed when analyzing the patients in the ATT group.

CONCLUSION
LLR using the two-surgeon technique is feasible and safely performed even in the ATT-burdened patients with thromboembolic risks. Independent from the extent of liver resection, LLR is significantly associated with reduced SBL, both in the ATT and non-ATT groups.

Key words: Laparoscopic liver resection; Two-surgeon technique; Antithrombotic therapy; Increased surgical blood loss; Bleeding complication

Core tip: Analyzing consecutive 258 patients undergoing liver resection using the two-surgeon technique, we showed that laparoscopic liver resection is significantly associated with reduced surgical blood loss and low postoperative bleeding complications even in antithrombotic-burdened patients with thromboembolic risks.

INTRODUCTION

In recent years, with the arrival of an aging society, surgical cases with heart disease and cerebrovascular disease have become more common, and most of them are undergoing antithrombotic therapy [ATT; antiplatelet therapy (APT) and/or anticoagulation therapy (ACT)] to prevent thromboembolism. Although the indication for ATT is expanding, perioperative management of antithrombotic drugs during gastroenterological surgery is often at high risk of hemorrhagic and thromboembolic complications and can become difficult[1-4].

In our institution, a protocol of risk stratification and perioperative antithrombotic management has been established for patients receiving ATT ("Kokura Protocol")[5,6]. So far, the feasibility and safety of the Kokura Protocol during laparoscopic and/or open abdominal surgery have been reported[5,6]. Moreover, our recent paper demonstrated that laparoscopic liver resection (LLR) using the "two-surgeon technique" is safely performed without critical intraoperative or postoperative bleeding even in patients receiving APT[7]. But the effect of LLR on increased surgical blood loss

(SBL) and postoperative bleeding complications (BCs), especially in patients undergoing ATT, still remains unclear.

The aim of the current research is to investigate the impact of LLR on increased SBL and BCs with special reference to the presence or absence of ATT.

MATERIALS AND METHODS

Patients
Following institutional review board approval, we searched potentially relevant cases from the single institution prospectively collected surgery database. After excluding cases with emergency surgery or other types of surgery, we included 258 consecutive liver resections performed from January 2010 to October 2016 in the current study (Figure 1). ATT was regularly used in 100 patients (ATT group, 38.8%) whereas not used in 158 patients (non-ATT group, 61.2%). Background, perioperative and outcome variables of the patients were collected through the surgery database as well as hospital and clinic charts.

The status of patients' symptoms and functions regarding ambulatory status was described according to the ECOG scale of performance status (PS)[8]. Postoperative complications were assessed and categorized by Clavien-Dindo classification (CDC)[9] and CDC class Ⅱ or higher was considered significant. Postoperative bleeding and thromboembolic complications were defined as previously described[5,6]. BCs included luminal bleeding, abdominal bleeding, and abdominal wall hematoma; thromboembolic complications included myocardial infarction, cerebral infarction, mesenteric infarction, and pulmonary thromboembolism. Operative mortality included death within 30 d after surgery.

Surgical procedures in this cohort included 163 partial liver resection and 95 anatomical liver resection. All procedures were performed by or under the guidance of one of the board-certified attending surgeons at our institution. We have adopted the "two-surgeon technique" during open liver resection (OLR)[10], and also introduced and maintained this procedure even in LLR, in order to perform safe liver parenchymal transection without critical intraoperative bleeding[7]. The indications for LLR at our institution were initially limited to the lesions in S2, S3, S5, S6 and the ventral side of S4, but were later expanded to almost all areas including S1. Patients having a large tumor more than 10 cm in diameter, those requiring bile duct resection or lymph node dissection, those with tumors involving major hepatic veins or inferior vena cava were excluded. We currently perform both pure and hybrid LLR and select the procedure depending on the tumor location and patient condition. Especially, if the ATT-burdened patients with high thromboembolic risks require major anatomical resection, we definitely choose hybrid LLR or open hepatectomy to avoid elevation of thromboembolic risks due to reduced central venous pressure.

Figure 1 Consort diagram in the current study. Pts: Patients; ATT: Antithrombotic therapy; LLR: Laparoscopic liver resection; OLR: Open liver resection.

Figure 2 Perioperative management protocol ("Kokura Protocol") for patients undergoing antithrombotic therapy in case of elective surgery. The management generally consists of interrupting ATT 5 to 7 d before surgery and early postoperative reinstitution in low thromboembolic risk patients. In patients with high thromboembolic risks, aspirin monotherapy is continued in patients with APT, and/or ACT was substituted by bridging heparin. ATT: Antithrombotic therapy; APT: Antiplatelet therapy; ACT: Anticoagulation therapy; Ope.: Operation; ASA: Aspirin; TPs: Thienopyridines.

The primary outcome included increased SBL (500 mL or more) and BCs. Both in the ATT and non-ATT groups, background characteristics, perioperative factors, and outcome variables of patients undergoing LLR were compared with those of patients receiving OLR, and the independent risk factors for increased SBL were determined by multivariate analysis.

Perioperative management of antithrombotic drugs
We have established our perioperative antithrombotic management system including thromboembolic risk stratification and perioperative antithrombotic management protocol ("Kokura Protocol"), and have shown that both open and laparoscopic abdominal surgeries in patients with antithrombotic therapy can be performed safely under Kokura Protocol[5,6]. Figure 2 demonstrated perioperative flowchart of patients with ATT in the Kokura Protocol. The management generally consisted of interrupting ATT 5 to 7 d before surgery and early postoperative reinstitution in low thromboembolic risk

Table 1 Background characteristics of patients in the cohort *n* (%)

Variables	Total (*n* = 258)	ATT (*n* = 100)			Non-ATT (*n* = 158)		
		LLR (*n* = 35)	OLR (*n* = 65)	*P* value	LLR (*n* = 42)	OLR (*n* = 116)	*P* value
Age, yr, median (range)	69 (36-89)	78 (59-90)	76 (52-92)	0.067	71 (45-89)	69 (36-86)	0.106
Gender				0.312			1
Female	80 (31.0)	10 (28.6)	12 (18.5)		15 (35.7)	43 (37.1)	
Male	178 (69.0)	25 (71.4)	53 (81.6)		27 (64.3)	73 (62.9)	
BMI				0.662			1
< 30 kg/m^2	247 (95.7)	34 (97.1)	60 (92.3)		41 (97.6)	112 (96.6)	
≥ 30 kg/m^2	11 (4.3)	1 (2.9)	5 (7.7)		1 (2.4)	4 (3.4)	
Performance status				0.124			1
0, 1	242 (93.8)	30 (85.7)	62 (95.4)		40 (95.2)	110 (94.8)	
2, 3	16 (6.2)	5 (14.3)	3 (4.6)		2 (4.8)	6 (5.2)	
Concurrent diseases							
Diabetes mellitus	58 (22.5)	10 (28.6)	17 (26.2)	0.817	7 (16.7)	24 (20.7)	0.656
Hx of congestive heart failure	21 (8.1)	8 (22.9)	11 (16.9)	0.594	1 (2.4)	1 (0.9)	0.462
Coronary artery disease							
Hx of PCI	49 (19.0)	17 (48.6)	31 (47.7)	1	1 (2.4)	0 (0.0)	0.266
Hx of CABG	7 (2.7)	4 (11.4)	3 (4.6)	0.236	0 (0.0)	0 (0.0)	-
Hx of cerebral infarction	26 (10.1)	5 (14.3)	17 (26.2)	0.212	0 (0.0)	4 (3.4)	0.574
Current hemo-/peritoneal dialysis	11 (4.3)	2 (5.7)	5 (7.7)	1	1 (2.4)	3 (2.6)	1
Anticoagulation therapy	30 (11.6)	8 (22.9)	22 (33.8)	0.360	-	-	-
Periop. heparin bridging	26 (10.1)	7 (20.0)	19 (29.2)	0.350	-	-	-
Preop. aspirin continuation	35 (13.6)	14 (40.0)	21 (32.3)	0.382	-	-	-

ATT: Antithrombotic therapy; LLR: Laparoscopic liver resection; OLR: Open liver resection; BMI: Body mass index; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft; periop.: Perioperative; preop.: Preoperative.

patients. However, in case of high thromboembolic risks, single aspirin therapy is continued for APT patients, and ACT was substituted by bridging heparin; early reinstitution of the antithrombotic drugs is executed. In patients using both APT and ACT, perioperative management of APT was also combined with those of ACT.

Statistical analysis

The collected data were checked and statistically analyzed by using the package of SPSS software. The categorized variables between the groups were compared by Fisher's exact probability test. The continuous data, expressed as a median with range, and non-parametric variables were compared by Kruskal-Wallis test or Student's *t* test. The analytic method of multivariable logistic regression model was performed to assess significant risk factors affecting increased SBL and BC. Statistical significance was determined at the level of $P < 0.05$.

RESULTS

The current cohort included 77 LLR and 181 OLR. Table 1 demonstrates various characteristics of patient background in the both groups. The type of patient race in the present cohort was exclusively Asian. Both in the ATT and non-ATT groups, age, gender, the rate of high body mass index, and PS class were identical between LLR and OLR. Also, there were no differences between LLR and OLR groups in the occurrence of underlying diseases including history of coronary artery

disease, congestive heart failure, cerebral infarction, or diabetes mellitus. Among the ATT group, the rates of APT and ACT were 32.6% (84/258) and 11.6% (30/258), respectively. Totally, 57 (22.1%) of patients, including 35 (13.6%) of APT patients and 26 (10.1%) of ACT patients, were regarded as high thromboembolic risk and required to continue preoperative aspirin monotherapy and/or bridging heparin.

Table 2 shows factors concerning operative procedures and postoperative morbidity in the both groups. Totally, the diagnoses of the diseases were hepatocellular carcinoma (HCC) in 97 (37.6%) and other diseases in 161 (62.4%), including liver metastases from gastrointestinal malignancy and benign diseases. Type of operation consisted of partial resection in 163 (63.2%), sub-sectionectomy (S5, S6 or S8) in 9 (3.5%), left lateral sectionectomy in 19 (7.4%), and other anatomical hepatectomy (mono-/bi-/tri-sectionectomy) in 67 (26.0%). Both in the ATT and non-ATT groups, there was no difference in the type of liver diseases, although LLR comprised less anatomical resections (ATT, $P < 0.001$; non-ATT, $P = 0.004$), shorter duration of operations (ATT, $P = 0.011$; non-ATT, $P = 0.049$), and less SBL (ATT, $P < 0.001$; non-ATT, $P = 0.007$). Increased SBL (≥ 500 mL) was more frequently observed in OLR compared to LLR in the whole cohort [34.3% (62/181) *vs* 5.2% (4/77), $P < 0.001$]. One patient (0.4%) undergoing LLR in the non-ATT group was converted to open surgery due to massive bleeding but none was converted in the ATT group.

An overall rate of postoperative complication was

Table 2 Factors concerning operative procedures and postoperative morbidity *n* (%)

Variables	Total (*n* = 258)	ATT (*n* = 100)			Non-ATT (*n* = 158)		
		LLR (*n* = 35)	OLR (*n* = 65)	*P* value	LLR (*n* = 42)	OLR (*n* = 116)	*P* value
Liver diseases				0.393			0.271
HCC	97 (37.6)	15 (42.9)	22 (33.8)		19 (45.2)	41 (35.3)	
Non HCC	161 (62.4)	20 (57.1)	43 (66.2)		23 (54.8)	75 (64.7)	
Type of operation				< 0.001			0.004
Partial resection	163 (63.2)	24 (68.6)	38 (58.5)		31 (73.8)	70 (60.3)	
Sub-sectionectomy (S5, 6, 8)	9 (3.5)	0 (0.0)	2 (3.1)		4 (9.5)	3 (2.6)	
Lateral sectionectomy	19 (7.4)	9 (25.7)	1 (1.5)		4 (9.5)	5 (4.3)	
Other anatomical hepatectomy	67 (26.0)	2 (5.7)	24 (36.9)		3 (7.1)	38 (32.8)	
Duration of ope., min, median (range)	230 (74-705)	198 (98-418)	257 (86-587)	0.011	204 (104-420)	242 (74-705)	0.049
Surgical blood loss, mL, median (range)	200 (1-11070)	80 (1-850)	310 (5-2100)	< 0.001	50 (1-530)	265 (2-11070)	0.007
Intraoperative RBC transfusion	45 (17.4)	4 (11.4)	12 (18.5)	0.408	3 (7.1)	26 (22.4)	0.035
Postop. complication							
None	217 (84.1)	34 (97.1)	50 (76.9)	0.009	41 (97.6)	92 (79.3)	0.005
Superficial SSI	8 (3.1)	0 (0.0)	2 (3.1)		1 (2.4)	7 (6.0)	
Deep SSI	5 (1.9)	0 (0.0)	3 (4.6)		0 (0.0)	2 (1.7)	
Bile leakage	11 (4.3)	0 (0.0)	4 (6.2)		0 (0.0)	7 (6.0)	
Bleeding complication	8 (3.1)	0 (0.0)	3 (4.6)		0 (0.0)	5 (4.3)	
Major bleeding	6 (2.3)	0 (0.0)	3 (4.6)		0 (0.0)	3 (2.6)	
Minor bleeding	2 (0.8)	0 (0.0)	0 (0.0)		0 (0.0)	2 (1.7)	
Thromboembolic complication	3 (1.2)	0 (0.0)	1 (1.5)		0 (0.0)	2 (1.7)	
Cerebral infarction	2 (0.8)	0 (0.0)	0 (0.0)		0 (0.0)	2 (1.7)	
Coronary stent thrombosis	1 (0.4)	0 (0.0)	1 (1.5)		0 (0.0)	0 (0.0)	
Cardiopulmonary arrest	1 (0.4)	1 (2.9)	0 (0.0)		0 (0.0)	0 (0.0)	
Operative mortality	1 (0.4)	1 (2.9)	0 (0.0)	0.350	0 (0.0)	0 (0.0)	-
Length of postop. stay, d, median (range)	14 (4-103)	12 (7-23)	15 (8-103)	0.174	11 (6-19)	15 (4-92)	0.321

ATT: Antithrombotic therapy; LLR: Laparoscopic liver resection; OLR: Open liver resection; HCC: Hepatocellular carcinoma; RBC: Red blood cell; ope.: Operation; postop.; Postoperative; SSI: Surgical site infection.

15.9% (41/258), and LLR included less complications both in the ATT group (2.9% *vs* 23.1%, *P* = 0.009) and non-ATT group (2.4% *vs* 20.7%, *P* = 0.005). The most common complication was bile leakage (8/258, 4.3%), all of which were experienced after OLR. Only 3 thromboembolic complications (1.2%) occurred after OLR (cerebral infarction in 2 and coronary stent thrombosis in 1), but LLR was free from these events. Eight BCs were experienced only after OLR (3.1%), including 6 major and 2 minor bleedings, although there was no postoperative BC after LLR. One case of operative mortality was experienced in the ATT group. This patient had high thromboembolic risks, including long-term treatment of hemodialysis and history of multiple DES implantation, underwent partial LLR for HCC under continuation of aspirin monotherapy, and had a good postoperative course, but just the day before discharge (10 d after surgery), suddenly developed cardiopulmonary arrest (pulmonary embolism or coronary thrombosis were denied by urgent cardiopulmonary catheterization) and expired. The cause of arrest was unknown, but may not be related to surgical procedures.

Table 3 shows potential factors affecting increased SBL in the whole cohort (*n* = 258) and in the ATT group (*n* = 100). In the whole cohort, male gender (*P* = 0.009), HCC (*P* = 0.008), OLR (*P* < 0.001), and anatomical liver resection (*P* < 0.001) were the factors affecting increased SBL. When the analysis target was narrowed

down to the ATT group, however, not only OLR (*P* = 0.013) and anatomical liver resection (*P* < 0.001) but also use of multiple APT (*P* = 0.035) and preoperative aspirin continuation (*P* = 0.046) were significantly associated with increased SBL. To control potential confounding and interaction, multivariate analyses for increased SBL in the whole cohort and in the ATT group were performed and shown in Figure 3 as forest plots. In the whole cohort, anatomical liver resection was the most significant risk factor for increased SBL [risk ratio (RR) = 6.54, *P* < 0.001] and LLR also had the significant negative impact (RR = 1/10.0, *P* < 0.001). The same effects of anatomical resection (RR = 15.77, *P* < 0.001) and LLR (RR = 1/5.88, *P* = 0.019) were observed when analyzing the patients in the ATT group.

DISCUSSION

Various types of abdominal surgery are currently being performed laparoscopically thanks to development of many energy devices and techniques. Compared to OLR, many reports have demonstrated advantages of LLR, such as minimal degree of body wall damage, fewer intra- and post-operative complications, and decreased SBL[11-14]. However, the impact of LLR on SBL and BC in patients receiving ATT has not been investigated and is still largely unknown. Our study demonstrates that the cohort comprised 258 liver resection, including 77 LLR and 181 OLR, among

Table 3 Univariate analysis of increased surgical blood loss (≥ 500 mL) in the whole cohort (*n* = 258) and in the antithrombotic therapy group (*n* = 100, %)

Variables	Increased surgical blood loss (≥ 500 mL)			
	The whole cohort (*n* = 258)		ATT group (*n* = 100)	
	Present/total	*P* value	Present/total	*P* value
Total	66/258 (25.6)		23/100 (23.0)	
Age		0.664		0.811
≥ 75 yr	25/105 (23.8)		14/57 (24.6)	
< 75 yr	41/153 (26.8)		9/43 (20.9)	
Gender		0.009		0.389
Female	12/80 (15.0)		3/22 (13.6)	
Male	54/178 (30.3)		20/78 (25.6)	
BMI		0.734		0.332
< 30 kg/m^2	64/247 (25.9)		23/94 (24.5)	
≥ 30 kg/m^2	2/11 (18.2)		0/6 (0.0)	
Performance status		1		0.192
0, 1	62/242 (25.6)		23/92 (25.0)	
2-4	4/16 (25.0)		0/8 (0.0)	
ASA class		0.148		0.789
Ⅰ, Ⅱ	34/153 (22.2)		5/25 (20.0)	
Ⅲ, Ⅳ	32/105 (30.5)		18/75 (24.0)	
Diabetes mellitus		0.733		1
Yes	16/58 (27.6)		6/27 (22.2)	
No	50/200 (25.0)		17/73 (23.3)	
Hx of PCI		0.589		0.234
Yes	14/49 (28.6)		14/48 (29.2)	
No	52/209 (24.9)		9/52 (17.3)	
ATT used		0.468		-
Yes	23/100 (23.0)		-	
No	43/158 (27.2)		-	
Multiple APT used		0.117		0.035
Yes	11/29 (37.9)		11/29 (37.9)	
No	55/229 (24.0)		12/71 (16.9)	
Preop. aspirin continuation		0.215		0.046
Yes	12/35 (34.3)		12/34 (35.3)	
No	54/223 (24.2)		11/66 (16.7)	
Liver diseases		0.008		0.138
HCC	34/97 (35.1)		12/37 (32.4)	
Non HCC	32/161 (19.9)		11/63 (17.5)	
Laparoscopic liver resection		< 0.001		0.013
Yes	4/77 (5.2)		3/35 (8.6)	
No	62/181 (34.3)		20/65 (30.8)	
Anatomical liver resection		< 0.001		< 0.001
Yes	46/95 (48.4)		19/38 (50.0)	
No	20/163 (12.3)		4/62 (6.5)	

ATT: Antithrombotic therapy; BMI: Body mass index; ASA: American Society of Anesthesiologists; PCI: Percutaneous coronary intervention; APT: Antiplatelet therapy; HCC: Hepatocellular carcinoma; Preop.: Preoperative.

which 38% of patients received ATT regularly. LLR was significantly related to reduced SBL and low incidence of BC. Multivariate analyses also showed that both in the whole cohort and in the ATT group, not only anatomical liver resection was significantly associated with increased SBL, but also LLR independently had the impact on reduction of SBL. This is the first study to elucidate the effect of LLR on reduced SBL in patients receiving ATT. Using the two-surgeon technique, LLR is feasible and safely performed without increase of SBL or thromboembolic events even in the ATT-burdened patients with thromboembolic risks.

Minimizing intraoperative SBL during liver resection is one of the most important tasks, and improvement of several technical aspects has been reported, such as the liver hanging manoeuvre, Pringle manoeuvre, and the two-surgeon technique[10,15,16]. The two-surgeon technique during liver surgery, which was first recommended by Aloia, is a novel technique for decreasing SBL and postoperative bile leakage as well as shortening operative time by allowing two surgeons to simultaneously participate in the parenchymal transection[10]. The primary surgeon dissects the liver parenchyma by ultrasonic dissection device; the assistant surgeon performs meticulous hemostasis using the saline-linked electrocautery. We also applied this manoeuvre during both conventional OLR and LLR.

In our hospital, the occurrence of ATT-received patients who need to undergo major hepatobiliary/pancreatic surgery is as many as 40%, and the number

A HR of increased surgical blood loss (≥ 500 mL) in the whole cohort (*n* = 258)

Risk factors	HR an 95%CI	Statistics for each factor			
		HR	Lower	Upper	*P* values
Laparoscopic liver resection		0.10	0.03	0.30	< 0.001
ATT used		0.40	0.15	1.00	0.059
Multiple APT used		1.01	0.21	4.79	0.990
HCC		1.11	0.52	2.37	0.793
Continuation of APT		1.55	0.33	7.20	0.581
Male gender		2.16	0.93	5.00	0.072
ASA class ≥ 3		2.19	0.93	5.17	0.073
Anatomical liver resection		6.54	3.19	13.42	< 0.001

0.01 0.1 1 10 100
Odds ratio

B HR of increased surgical blood loss (≥ 500 mL) in the ATT group (*n* = 100)

Risk factors	HR an 95%CI	Statistics for each factor			
		HR	Lower	Upper	*P* values
Laparoscopic liver resection		0.17	0.04	0.70	0.019
History of CI		0.36	0.06	2.40	0.292
HCC		0.48	0.12	1.97	0.309
History of PCI		0.67	0.13	3.56	0.634
Multiple APT used		1.31	0.23	7.40	0.763
Continuation of APT		1.99	0.34	11.60	0.444
Anatomical liver resection		15.77	3.66	67.95	< 0.001

0.01 0.1 1 10 100
Odds ratio

Figure 3 Forest plots showing hazard ratios of increased surgical blood loss. A: Hazard ratios in the whole cohort (*n* = 258); B: Hazard ratios in the ATT group (*n* = 100). HR: Hazard ratio; ATT: Antithrombotic therapy; APT: Antiplatelet therapy; HCC: Hepatocellular carcinoma; ASA: American Society of Anesthesiolgists; CI: Cerebral infarction.

is increasing further in the future. In ATT-burdened patients undergoing major hepatobiliary/pancreatic surgery, both excessive surgical stress and inappropriate antithrombotic management are considered to affect bad postoperative outcome. The surgical stress has been demonstrated to make an inflammatory response which generates plaque fissure and subsequently causes acute thrombosis[17,18]. Therefore, we should consider an application of LLR to even more troublesome ATT-burdened patients. If the patient has high thromboembolic risks and preoperative ATT cannot be stopped, the intraoperative and postoperative bleeding risks will increase. To minimize SBL especially in this critical patient population, we thought that the appropriate devices and techniques for rigid hemostasis must be applied during LLR. As shown in our previous report, LLR using the two-surgeon technique is safe and feasible, and can be applied to even ATT-burdened patients[7].

Minimizing SBL to maintain a dry operative field is extremely crucial especially during pure LLR. To control hepatic inflow, Pringle maneuver (intermittent hepatic vascular inflow occlusion) is usually employed during liver parenchymal transection. To control backflow bleeding from the hepatic vein, the maintenance of low central venous pressure (CVP) is commonly used, and decreasing CVP combined with the maintenance of low airway pressure and high pneumoperitoneum pressure (PPP) is also reported to be useful[19-22].

However, maintenance of low CVP and high PPP during liver parenchymal transection in pure LLR may expose the ATT-burdened patients to the elevated risks of thromboembolism. Therefore, if the patients with high thromboembolic risks require major anatomical resection, we definitely choose and perform "hybrid LLR" (in which the parenchymal transection is performed through mini-laparotomy) or OLR under the maintenance of normal CVP levels to avoid low CVP-induced thromboembolic events. Our data demonstrated that even though the procedures were associated with increased bleeding tendency due to normal CVP levels, hybrid LLR using the two-surgeon technique was performed safely without increase of SBL or thromboembolic complications.

Concerning perioperative thromboembolic complications including cerebrovascular stroke, pulmonary embolism, or major adverse cardiovascular event (MACE), the rates of perioperative thromboembolisms vary depending on differences in target patient population, study design, and changing of clinical practices. The reported incidence of stroke following noncardiac, nonneurosurgical surgery ranges between 0.1%-0.4% overall, and 2.9%-3.5% in patients at risk of perioperative stroke[23-26]. In consideration of thromboembolic events after liver resection, the prevalence of thromboembolism seems to be higher. Schroeder *et al*[27] reported that analyzing 587 patients undergoing liver resection from ACS-National Surgical Quality Improvement Program (NSQIP) database, rates

of MACE and overall thromboembolic complications after liver resection were at 4.4% and 3.6%, respectively. Another research of 5227 liver resections from ACS-NSQIP database showed that the rate of critical cardiac complications including myocardial infarction and cardiac arrest after liver resection was at 4.8% in patients with underlying cardiac disease and at 1.6% in those without[28]. The present study demonstrated that the incidence of perioperative thromboembolic complication was maintained at 1.2%, a relatively low rate compared to the previous report. Hence, it is suggested that liver resections including both OLR and LLR can be performed safely under the Kokura Protocol, the rigorous perioperative antithrombotic management protocol, with successful inhibition of thromboembolic events even in high thromboembolic risk patients.

There are limitations to the present study. This single-center retrospective observational design of the current study has inherent potential for bias, which lessens the effect of the statistical analysis. This restriction will be alleviated by follow-up investigation, or by multi-institutional prospective studies. Since we continuously manage ATT-received cases that are required to undergo liver resection using the Kokura Protocol and the same surgical policies, we are going to analyze more cases to investigate the safety and feasibility of LLR on this high-risk patient population.

Conclusion

LLR using the two-surgeon technique is feasible and safely performed without increase of SBL or thromboembolic events even in the ATT-burdened patients with thromboembolic risks. Independent from the extent of liver resection, LLR is significantly associated with reduced SBL, both in the ATT and non-ATT groups.

COMMENTS

Background

Nowadays, patients who have histories of cardiovascular or cerebrovascular diseases have been seen more often with aging of patients, and those patients frequently receive antithrombotic therapy (ATT) for the purpose of primary and secondary prevention of thromboembolic diseases. While indications for ATT use have expanded, antithrombotic management during gastrointestinal and/or hepatobiliary-pancreatic surgery is difficult and always bothersome because of high risks of perioperative bleeding or thromboembolic events. Recently, laparoscopic liver resection (LLR) using the "two-surgeon technique" is safely performed without critical intraoperative or postoperative bleeding even in patients receiving ATT, but the effect of LLR on increased surgical blood loss (SBL) and postoperative bleeding complications (BCs), especially in patients undergoing ATT, still remains unclear.

Research frontiers

In the authors' institution, a protocol of risk stratification and perioperative antithrombotic management has been established for patients receiving ATT ("Kokura Protocol"). So far, the feasibility and safety of both open and laparoscopic abdominal surgeries under the Kokura Protocol have been reported. Moreover, the authors' recent paper demonstrated that LLR using the "two-surgeon technique" is safely performed without critical intraoperative or postoperative bleeding even in patients receiving ATT.

Innovations and breakthroughs

The impact of LLR on BCs in patients receiving ATT has not been investigated

and is still largely unknown. The authors' study demonstrates that the cohort comprised 258 liver resection, including 77 LLR and 181 OLR, among which 38% of patients received ATT regularly. LLR was significantly related to reduced SBL and low incidence of postoperative BCs. Multivariate analyses also showed that both in the whole cohort and in the ATT group, LLR independently had the impact on reduction of SBL. This is the first study to elucidate the effect of LLR on reduced SBL in patients receiving ATT.

Applications

Using the two-surgeon technique, LLR is feasible and safely performed without increase of SBL or thromboembolic events even in the ATT-burdened patients with thromboembolic risks.

Terminology

ATT includes antiplatelet therapy (APT) and/or anticoagulation therapy (ACT) for the purpose of primary and secondary prevention of thromboembolic diseases. LLR has been innovated and currently accepted as minimally-invasive procedures for both hepatocellular carcinoma and metastatic liver diseases in selected patients. LLR is reportedly related to reduced degree of body wall damage, fewer intraoperative and postoperative complications, and decreased SBL.

Peer-review

It is an interesting work.

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ORIGINAL ARTICLE

Retrospective Study

Correlation of abnormal histology with endoscopic findings among mycophenolate mofetil treated patients

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Abstract

AIM
To describe all abnormal histological findings and their associated endoscopic presentation in patients using mycophenolate mofetil (MMF).

METHODS
A retrospective review of all individuals prescribed MMF within 6 mo of a colonoscopy or flexible sigmoidoscopy between 07/2009 and 09/2015 was performed within Northwell Health system. Records were analyzed for age, gender, procedure indication, MMF indication, and both gross and microscopic findings. Only reports with abnormal histology were included.

RESULTS
One hundred and eighty-four procedures from 170

patients were found, of which 39 met inclusion criteria. Fifty-one point three percent were female. MMF was used for solid organ transplant in 71.8%. Diarrhea was the indication for 71.8% of colonoscopies. Fifty-nine percent of reports revealed gross and microscopic abnormalities while 41.0% had only microscopic findings. Only 11 patients' reports (28.2%) indicated a specific histopathology of MMF colitis. Among the entire group, only 23.1% of abnormal histology was isolated proximal to the splenic flexure.

CONCLUSION

Our results demonstrate a high rate of left sided disease and microscopic findings without gross mucosal abnormalities among patients using MMF. Also, a broader definition of MMF-colonopathy may be appropriate, with a majority of our abnormal histology falling outside of the more narrowly defined MMF-colitis category. Given the high frequency of isolated microscopic abnormalities and distal disease, sigmoidoscopy with random biopsies may be an appropriate, less invasive initial endoscopic examination in selected MMF patients.

Key words: Mycophenolate mofetil; Colitis; Colonoscopy; Diarrhea

Core tip: Gastrointestinal complaints are common among patients using mycophenolate mofetil (MMF). Little information exits to guide an effective endoscopic workup in this population. A retrospective review of all patients prescribed mycophenolate within 6 mo of an endoscopic procedure was performed. Our results demonstrate a high rate of left sided disease and microscopic findings without gross mucosal abnormalities among patients using mycophenolate. A broader definition of MMF-colonopathy may be appropriate, with a majority of our abnormal histology falling outside of the more narrowly defined MMF-colitis category. Our findings suggest sigmoidoscopy with random biopsies may be an appropriate initial evaluation.

INTRODUCTION

Mycophenolate mofetil (MMF) is an immunosuppressive agent that is used mainly for the prevention of organ transplant rejection, but is increasingly used for autoimmune and hematologic disorders[1,2]. Mycophenolic acid (MPA) is the active metabolite of MMF. MPA prevents the proliferation of lymphocytes by inhibiting inosine monophosphate dehydrogenase, an enzyme in the *de novo* pathway of purine synthesis[3]. Other mechanisms of MPA immunosuppression have been reported, including apoptosis of activated T-lymphocytes, decreased recruitment of lymphocytes to sites of inflammation, and decreased nitric oxide-mediated tissue damage[4]. Enterocytes are also dependent on the *de novo* pathway of purine synthesis and become potential targets for MPA[1,4]. This can lead to gastrointestinal toxicity, which typically manifests as diarrhea, and can occur in up to 36% of patients[1].

For many patients using MMF who develop diarrhea, the severity of complaints may prompt a formal workup. In cases with negative stool studies for infectious causes, endoscopic examination either with flexible sigmoidoscopy or colonoscopy may be performed[5]. In those individuals with abnormal histology, it is then critical to differentiate MMF-related colitis from colitis of other etiologies such as new onset inflammatory bowel disease (IBD) or atypical infection. Accurate diagnosis is critical to proper use of MMF, as dose modification and/or discontinuation of MMF risks organ rejection or reactivation of autoimmune disease[2,6].

Prototypical histopathology of MMF colitis has been described as "prominent crypt cell apoptosis and reactive/reparative changes including enterocyte cytologic atypia, increased neuroendocrine cells, and glandular architectural distortion"[7]. While a pathologist informed of MMF usage may identify a typical pattern of MMF related injury[1,2,4], and specify a finding as "MMF colitis", a broader spectrum of abnormal histology associated with MMF appears to exist[2]. In addition, the endoscopic findings related to MMF colitis, and other MMF associated abnormal histology, are not well described - including the gross nature of lesions and typical distribution within the colon. Most prior studies have been limited to case reports and retrospective studies and have focused on abnormal histopathology associated with MMF usage without addressing the endoscopic appearance or patterns of distribution within the GI tract[4].

As with other disorders such as Crohn's disease and microscopic colitis, knowledge of anatomic disease distribution and associated presence or absence of gross mucosal abnormalities are critical to guide an effective work up. Our aim was to describe all abnormal histological findings and their associated endoscopic presentation in all patients undergoing colonoscopy while using MMF.

MATERIALS AND METHODS

We conducted a retrospective review of all patients who were 18 years of age and older and had documented use of MMF within 6 mo of undergoing a colonoscopy or flexible sigmoidoscopy from July 2009 to September 2015. The study was conducted within the North Shore-LIJ Health System (now Northwell Health) after obtaining institutional review board approval. Only

Table 1 Demographic of mycophenolate mofetil treated patients and procedures (170 patients, 184 procedures) (%)

Characteristic	
mean age	57.05
Female	89 (48.4)
Indication for procedure[2]	
Screening	72 (39.1)
Diarrhea	51 (27.7)
Bleeding	24 (13.0)
Anemia	20 (10.9)
Abdominal pain	14 (7.7)
Constipation	3 (1.6)
Weight loss	3 (1.6)
Abnormal imaging	3 (1.6)
Bloating	1 (0.52)
Other (history of IBD, amyloid, stricture)	9 (4.9)
Indication for MMF	
Organ transplant (kidney, liver, lung)	116
Autoimmune	35
Blood disorder	7
Unknown indication	26
Abnormal mucosa (gross)	40
With normal biopsies	10
With abnormal biopsies	25 (2 duplicates)
Without biopsies[1]	5
Normal mucosa (gross)	144
With normal biopsies	44 (normal biopsy or polypectomy, 1 for mass)
With abnormal biopsies	17 (1 duplicate)
Without biopsies[1]	83

[1]Without biopsies done or with reports unavailable; [2]Some procedures with multiple indications documented. MMF: Mycophenolate mofetil; IBD: Inflammatory bowel disease.

sigmoidoscopy or colonoscopy reports with abnormal histology described on the official pathology report were included in the review. Sigmoidoscopy or colonoscopy reports with normal pathology or missing pathology report were excluded. In patients with multiple eligible colonoscopies or sigmoidoscopies, the procedure report nearest to the date of MMF prescribing was the one included in the analysis. If a patient had both an eligible colonoscopy and flexible sigmoidoscopy, the colonoscopy report was used.

Demographic information, indication for colonoscopy, indication for MMF, gross and histological findings were recorded. All pathology samples were evaluated by experienced gastrointestinal pathologists. Only pathology reports specifically citing MMF use as the likely etiology were classified as "MMF-colitis". All remaining abnormal findings were broadly classified as "other" abnormal findings, and sub-categorized according to their description in the pathology report. Abnormal histology findings proximal to the splenic flexure were defined as right colonic; findings distal to the splenic flexure were defined as left colonic. Abnormal findings occurring both proximal and distal to the splenic flexure were defined as pancolonic. Location and description of abnormal gross findings on colonoscopy/sigmoidoscopy examination also corresponded to the official procedure report. Our goals

were to describe abnormal histological findings, their location within the colon, and the presence or absence of associated gross endoscopic findings.

RESULTS

A total of 184 colonoscopies and sigmoidoscopies from 170 patients were reviewed during the study period. Overall, screening was the most common indication for a procedure, with organ transplant as the most common indication for MMF use (Table 1). Of these, 34 colonoscopies and 5 sigmoidoscopies from 39 individual patients met inclusion criteria. Fifty-one point three percent were female. Average age at time of procedure was 51.44 years old. For this group with abnormal histology, diarrhea was the most common indication, accounting for 71.8% of the combined sigmoidoscopies and colonoscopies. Two patients had procedures for history of inflammatory bowel disease. Indications for MMF therapy were: Solid organ transplant (71.8%), hematologic disorders (17.9%) and autoimmune disease (10.3%). Of the 28 solid organ transplant patients, 27 were from renal transplants and 1 was from a lung transplant. Demographics of colitis among MMF treated patients (Table 2).

Of the 39 patient reports meeting inclusion criteria, only 11 patient pathology reports (28.2%) indicated a specific histopathology of MMF colitis. Notably, only 9 of 39 (23.1%) specimen request forms sent to pathology provided history of MMF use. Non-specific colitis was identified in 30.8% of the reports. Four reports indicated graft *vs* host disease (GVHD), and all were from patients who were on MMF for leukemia or lymphoma and underwent stem cell transplant. The remaining twelve cases are included in Table 3.

Overall 23 (59.0%) of abnormal histology corresponded to a reported gross endoscopic abnormality, while 16 (41.0%) demonstrated abnormal histology without a gross abnormality. Of the 28 procedures performed for an indication of diarrhea, 13 (46.4%) of abnormal histology corresponded to a gross endoscopic abnormality, while 15 (53.6%) demonstrated abnormal histology without a gross abnormality. Among the entire 39 cases reviewed only 23.1% of abnormal histology was isolated to the right colon. Among the subgroup of 11 MMF-colitis cases, only one (9.1%) was isolated to the right colon, Figure 1.

DISCUSSION

In our study out of 184 procedures performed on 170 patients using MMF, only 39 colonoscopies/sigmoidoscopies had abnormal pathology. Of these, only 28.2% demonstrated a specific histopathology of MMF colitis. Endoscopic and histological evidence of colitis in patients who developed diarrhea while using MMF have been previously studied[4]. Those reports, which evaluated the histopathological findings of this MMF-colitis, have shown a variety of features including

Table 2 Demographic of colitis among mycophenolate mofetil treated patients *n* (%)	
Characteristic	
n	39
mean age	51.44
Female	20 (51.3)
Indication for procedure	
Diarrhea	28 (71.8)
Bleeding	2 (5.1)
Anemia	1 (2.6)
Screening	4 (10.3)
Abnormal imaging	2 (5.1)
Other (history of IBD)	2 (5.1)
Indication for MMF	
Organ transplant	28 (71.8)
Autoimmune	4 (10.3)
Blood disorder	7 (17.9)

MMF: Mycophenolate mofetil; IBD: Inflammatory bowel disease.

Figure 1 Distribution of histopathology in confirmed mycophenolate mofetil colitis and other abnormal findings.

prominent crypt cell apoptosis and reactive/reparative changes including enterocyte cytologic atypia, lamina propria inflammation, and crypt architectural disarray[8]. In our study, similar findings were described for MMF-colitis, with the most common feature being cell apoptosis. While the presence of apoptosis is regarded as more typical of a true MMF-related colitis[8], there is no consensus regarding the spectrum of abnormal histology related to MMF use. Our findings of frequent nonspecific colitis and other histological abnormalities suggests that a broader definition of MMF-colonopathy may be required, with a majority of our abnormal histology falling outside of the more narrowly defined MMF-colitis category.

Prior case series and reports were able to categorize abnormal histological findings in patients on MMF into IBD-like, GVHD-like, ischemic-like, acute colitis, or non-specific colitis[2,9]. In our study, 30.8% of the reports indicated non-specific colitis. This high frequency of non-specific colitis was also found by de Andrade *et al*[9]. In addition to non-specific colitis, there were 4 reported cases of GVHD in our study, all in patients with hematologic disease and a history of bone marrow transplant. This suggests that the transplant itself is the cause of the abnormal findings rather than the MMF, although previous studies have described GVHD-like pathology in patients on MMF following solid organ transplant[1,2,4]. Additionally, it can be difficult to histologically differential between GVHD and MMF colitis. Star *et al*[10] have found that high eosinophilic count, absence of neuroendocrine cell clusters and apoptotic microabscess are more suggestive of MMF colitis over GVHD. Ischemic-like pathology can also be found in patients on MMF. Johal *et al*[8] described MMF-induced segmental colitis mimicking ischemic colitis. There was one case of ischemic-like pathology found in our study, however, given lack of multiple biopsies, it is unknown if this patient had segmental colitis. Regardless of the pathology, most of these patients underwent col-

onoscopy due to diarrhea.

Gastrointestinal toxicity, usually manifested as diarrhea, is the most common side effect of MMF[8]. The reported incidence of diarrhea is variable and can range from 13% to 64%[4]. Diarrhea was the most common indication for colonoscopy in our study population (71.8%). Even though the exact mechanism of MMF induced diarrhea is unknown, different etiologies have been proposed[4]. In addition to the impact on the quality of life, diarrhea can lead to non-compliance, weight loss, and physician-directed MMF dose reduction[1].

Data describing the presence of macroscopic abnormalities and distribution of findings associated with MMF-related colitis is limited. Calmet *et al*[4] found macroscopic findings ranging from erythema to erosions and ulcers. About half of the patients they studied had normal macroscopic findings, similar to our findings of abnormal histology without endoscopic mucosal changes in 41% patients, with others demonstrating erythema, friability, granularity, loss of vascularity, and ulcerations. These findings were found across MMF-related colitis including GVHD, AML, and MMF colitis as shown in Figure 2. Along with Calmet *et al*[4], our results showing such a high rate of isolated microscopic abnormalities strongly support a diagnostic protocol including random biopsies of normal appearing mucosa in patients on MMF with colitis-like complaints.

Our patients also demonstrated a low frequency of abnormal histology (23.1%) limited to the right colon, proximal to the splenic flexures. This finding was even more pronounced for the subgroup of MMF-colitis, of which only one case was isolated proximal to the splenic flexure. This appears similar to the findings of Calmet *et al*[4]. In a smaller sample of 20 patients they found that 25% of MMF related colitis was found in the right colon, though "right colon" was not explicitly defined[4]. Our findings suggest that a viable strategy for evaluation in this patient population could be to initially perform by a sigmoidoscopy, moving on to full colonoscopy only if distal findings are negative. While sigmoidoscopy is

Table 3 Abnormal histological findings by mycophenolate mofetil indication

	Solid organ transplant (*n*)	Autoimmune (*n*)	Blood disorder (*n*)	Total (*n*)
MMF colitis	10	1	0	11
Graft *vs* host disease	0	0	4	4
Nonspecific colitis	11	0	1	12
Other	3 (hyperplastic), 1 (lymphoid aggregate), 1 (kayexalate), 1 (ischemic), 1 (amyloid)	1 (IBD), 1 (lymphoid aggregate), 1 (hyperplastic)	1 (AML), 1 (reactive)	12

MMF: Mycophenolate mofetil; IBD: Inflammatory bowel disease.

Figure 2 These findings were found across mycophenolate mofetil-related colitis. A: Mycophenolate mofetil (MMF) colitis: erythematous hyperemic mucosa (sigmoid colon); B: MMF colitis: coarse appearing colonic mucosa (ascending colon); C: AML: multiple small ulcers and erosion (rectum); D: GVHD: patchy areas of mucosa (transverse colon).

no longer commonly used for colon cancer screening purposes, it remains a valuable tool for the evaluation of other gastrointestinal conditions. Notably, it may be used for the diagnosis and monitoring of response to therapy in ulcerative colitis due to the near universal involvement of the rectum and left-colon typical of the disorder. Our findings suggest a similar role for sigmoidoscopy for the workup of lower gastrointestinal complaints in patients using MMF. Significant advantages to sigmoidoscopy compared to colonoscopy include avoidance of sedation and lower risk of perforation. Also, since so many of these patients have a history of renal transplantation, the avoidance of a full bowel preparation, required by colonoscopy but unnecessary for sigmoidoscopy, lowers the risk of renal compromise, which has been associated with certain colonoscopy preparations[11].

In our current series we found a relatively small number of abnormal histology reported with a diagnosis specific for MMF colitis. Notably, a similarly small number of samples that were sent to pathology directly specified usage of MMF. This implies that

some pathologists, if they are not aware of MMF use, or are less familiar with MMF-related colitis, may not consider the diagnosis of MMF-related colitis, leading to decreased specificity of findings and lingering diagnostic uncertainty. It would likely be of value to pathologists to make them aware of MMF usage, so as to improve the rate at which MMF-related colitis is appreciated in pathology samples. Alternatively, as discussed, a more broadly defined MMF-colonopathy may need to be considered when evaluating and managing patients with any abnormal histology using MMF.

Our study had some limitations. The total number of patients we analyzed for abnormal histological findings, while large by comparison to other case series, was still small in absolute numbers due to the rareness of MMF use and occurrence of these findings. Also, though the electronic medical record (EMR) allowed us to track MMF prescribing, we could not confirm patient compliance. In addition, though we did analyze a significant amount of demographic information, there were limits to the EMR, such as our inability to consider patient race/ethnicity as part of our analysis.

In summary, ours is the largest study correlating all abnormal pathology associated with MMF use with both gross endoscopic findings and disease distribution. Our findings reinforce the importance of random biopsies of grossly normal appearing colonic mucosa towards making an accurate diagnosis. Importantly, our findings also support a first line diagnostic approach using a less invasive, lower risk sigmoidoscopy coupled with routine biopsy in selected MMF patients with appropriate complaints. Moving forward, valuable avenues of research would include outcomes analysis of patients diagnosed with MMF-related colonic abnormalities after intervention, whether that be *via* dose modification or discontinuation of MMF or other means of treatment. This would be valuable in further confirming the clinical significance of these findings, as well as the therapeutic benefit of accurately confirming such a diagnosis

COMMENTS

Background
Gastrointestinal complaints are common among patients using mycophenolate mofetil (MMF). Abnormal biopsy findings have been described in this population, but little information exits to guide an effective endoscopic workup of those on MMF such as the presence or absence of gross endoscopic findings and their anatomic distribution.

Research frontiers
Abnormal biopsy findings have been described in patients treated with MMF. The current research focus is to evaluate the endoscopic findings and the proper endoscopic workup in patients with gastrointestinal complaints on MMF.

Innovations and breakthroughs
Prior studies have only described the histology in a limited number of patient on MMF. Most of these studies were limited to renal transplant patients. The authors looked at all patients treated with MMF for a variety of illnesses. Also, there is very limited information describing gross mucosal findings and anatomic distribution of abnormal findings within the MMF population. The authors results demonstrate a high rate of left sided disease and microscopic findings without gross mucosal abnormalities among patients using MMF.

Applications
A broader definition of MMF-colonopathy may be appropriate, with a majority of the authors' abnormal histology falling outside of the more narrowly defined MMF-colitis category. The authors findings support sigmoidoscopy with random biopsies may be an appropriate initial endoscopic evaluation in patients with bowel complaints using MMF.

Terminology
MMF is an immunosuppressive agent that is used mainly for the prevention of organ transplant rejection. This can lead to gastrointestinal toxicity, which typically manifests as diarrhea. Right colonic findings were defined as abnormal histology findings proximal to the splenic flexure. Left colonic findings were defined as abnormal histology findings distal to the splenic flexure.

Peer-review
This paper study the correlation of abnormal histology with endoscopic findings among Mycophenolate Mofetil treated patients, the sample is large.

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ORIGINAL ARTICLE

Retrospective Study

Usefulness of the Hook knife in flexible endoscopic myotomy for Zenker's diverticulum

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Abstract

AIM
To investigate the outcome of flexible endoscopic myotomy performed with the Hook knife in patients with symptomatic Zenker's diverticulum (ZD).

METHODS
All consecutive patients treated for ZD at our institution between 7/2012 and 12/2016 were included. The flexible endoscopic soft diverticuloscope-assisted technique with endoclips placement and Hook knife myotomy were performed in all patients. Here we report a retrospective review of prospectively collected data. Demographics, dysphagia score (Dakkak and Bennett), associated symptoms and adverse events were collected pre-procedure, at 2 and 6 mo post-procedure, and at the end of the follow-up period. Clinical success was defined as at least 1-point improvement in dysphagia score and a residual dysphagia score $\leq$ 1, with no need for reintervention. Dysphagia scores were compared before treatment and at end-of-follow-up using the Wilcoxon test.

RESULTS
Twenty-four patients were included. Mean size of ZD was 3.0 cm (range 2-8 cm). Mean number of sessions

was 1.17/patient (range 1-3 sessions). Overall clinical success was 91.7%. Two adverse events (8.3%) occurred, and both were managed conservatively. No bleeding or perforation was reported. Mild pain was reported by 9 patients (37.5%). Median hospital stay was 1 d (range 1-6). Median follow-up was 19.5 mo (range 6-53). Mean ± SD dysphagia score was 2.25 ± 0.89 before treatment and decreased to 0.41 ± 0.92 at end-of-follow-up ($P < 0.001$). Regurgitation and cough dropped from 91.7% and 50% to 12.5% and 0% at the end of follow-up, respectively. Recurrence was observed in 3 patients, and all 3 were symptom-free after one more session.

CONCLUSION
The Hook knife, used in the soft diverticuloscope-assisted technique setting, is efficient and safe for treatment of ZD.

Key words: Zenker's diverticulum; Flexible endoscopy

Core tip: Zenker's diverticulum can cause uncomfortable symptoms such as dysphagia, regurgitation and cough, and sometimes weight loss or aspiration pneumonia. Soft diverticuloscope-assisted flexible myotomy is used worldwide and has proven to be safe and efficient. In terms of adverse events, perforation remains the major concern. The most effective tool for performing myotomy in this setting has yet to be determined. Here we treated 24 patients with the Hook knife, resulting in 91.7% overall success, a 13% recurrence rate, and only 2 mild adverse events reported.

INTRODUCTION
Zenker's diverticulum (ZD), an acquired rare condition that typically occurs in the elderly[1], is a pulsion diverticulum developing on the posterior wall of the esophagus through Killian's triangle. ZD development is thought to be caused by dysfunction of the cricopharyngeal muscle resulting in increased intraesophageal pressure[2]. ZD can cause symptoms such as dysphagia, regurgitations, or chronic cough. Weight loss and aspiration pneumonia are potentially severe complications. Treatment basically consists in myotomy of the cricopharyngeal muscle. Endoscopic myotomy was introduced decades ago, has been widely evaluated since, and is now considered a first-line treatment option[3]. In Europe, the mini-invasive flexible endoscopic soft diverticuloscope-

Table 1 The Dakkak and Bennett score of dysphagia[7]	
Grade 0	No dysphagia
Grade 1	Solids
Grade 2	Semi-solids
Grade 3	Liquids
Grade 4	Aphagia

assisted technique with endoclip(s) placement, as described by Huberty *et al*[4], is common practice and has proven safe and effective. However, various tools are used to perform the myotomy. Submucosal dissection knives have been described in this indication, and appear to be safe and effective[5]. Myotomy must be continued deep enough to improve clinical symptoms, but dissection must be limited to muscle fibers to avoid perforation. The key issue is where to stop the myotomy[6]. The Hook knife (Olympus endotherapy, Tokyo, Japan) is designed with a distal tip consisting in a 5 mm-long, rotatable, hook-shaped knife, allowing pulling tissues before cutting. We posit that the Hook knife is the most appropriate tool for this intervention. Here we report short and mid-term outcome and adverse events of soft diverticuloscope-assisted flexible endoscopic myotomy with the Hook knife.

MATERIALS AND METHODS
Population
All consecutive patients treated at our institution by flexible endoscopy for symptomatic ZD between July 2012 and December 2016, and with at least 6 mo of follow-up at December 2016, were included in the study. We performed a retrospective review of prospectively collected data. Demographics, dysphagia score, symptoms, outcome, and adverse events were recorded. The Dakkak and Bennett dysphagia score was used (Table 1)[7]. All patients were seen as outpatients before and at 2 and 6 mo after the procedure, and were asked to phone anytime in case of recurrence. At the end of the follow-up period, all patients were interviewed by phonecall.

This study was conducted according to the ethical principles of the Declaration of Helsinki and in compliance with good clinical practice. Informed consent was obtained from all patients. This study was reviewed and approved by our center's Institutional Review Board, reference 2016/CE 91.

Endoscopic treatment
All patients were treated by a single endoscopist (Olivier Rouquette). All procedures were performed under general anesthesia, with orotracheal intubation, in supine position. All patients were administered amoxicillin-clavulanic acid prophylaxis beforehand. Anticoagulant therapy was discontinued 5 d before procedure and bridged with low molecular-weight heparin. Low-dose aspirin was continued. Other antiplatelet agents were

Figure 1 Endoscopic procedure. A: Soft diverticuloscope in place, affording optimal exposure. Esophageal lumen is identified by the guidewire; B: The Hook knife is locked in 12 o'clock position; C: After initial incision, myotomy is performed, pulling the muscle fibers up before cutting; D: End of procedure, with 2 endoclips in place.

discontinued 5 d before procedure and replaced with low-dose aspirin. Anticoagulant and antiplatelet therapies were resumed on the day after the procedure.

Figure 1 describes the endoscopic procedure. First, a complete upper endoscopy, using a standard gastroscope (GIF H180, GIF H190; Olympus, Tokyo, Japan), is performed to rule out any other esophageal or gastric disorder that could explain dysphagia. A 0.035-inch guidewire is advanced in the gastric lumen and left in place for later identification of the esophageal lumen. Then, the soft diverticuloscope (ZDO-22-30, Cook Endoscopy, Winston-Salem, NC) is fitted over the gastroscope and advanced gently, after lubrication, as far as the black mark is located roughly near the incisor line. The endoscope is then slowly withdrawn to allow visualization of the diverticulum and adjust diverticuloscope position across the septum, which is then seen as a bridge, and optimal exposure of the operative site. Once septum exposure is good, myotomy of the cricopharyngeal muscle is performed with the Hook knife (Endocut Q mode, effect 3, 120 W cutting, 40 W soft coagulation; VIO 300; ERBE, Tübingen, Germany). The hook is locked in 12 o'clock position. The initial incision is performed at the top of the bridge. Then, the cricopharyngeal myotomy is continued progressively downward, using the hook to gently pull the muscle fibers before cutting, allowing precise dissection. Myotomy is stopped when the muscle fibers are completely cut. Finally, anterior ZD and posterior esophageal walls are cut up to 5 mm above the bottom of the diverticulum, and one or more

endoclips are placed to prevent delayed perforation or bleeding. If no complication is suspected, oral semi-liquid diet is resumed and patients are discharged from hospital on day one post-surgery.

Primary endpoint was clinical success. Recurrence and adverse event rates were also investigated. Clinical success was defined as at least a 1-point improvement in dysphagia score and a residual dysphagia score $\leqslant 1$, with no need for reintervention. Recurrence was defined as dysphagia score > 1 after initial clinical success. Any event resulting in readmission or unexpected length of hospital stay post-surgery (> 1 d) was regarded as an adverse event. Bleeding was considered an adverse event if any medical or endoscopic reintervention was needed. Perforation was defined as presence of cervical subcutaneous crepitus, cervical abscess, or free air on computed tomography.

Statistical analysis

The statistical review of the study was performed by a biomedical statistician. Characteristics of the study population are expressed as proportion and means ± SD. The Wilcoxon matched-pairs signed-rank test was used to compare pre- *vs* post-treatment dysphagia scores comparison. Statistical significance was set at $P < 0.05$ (two-sided). Statistics were computed using Stata12 (Stata Corp, College Station, TX).

RESULTS

The study included 24 consecutive patients [18 men

Table 2 Patient characteristics *n* (%)	
Characteristics	
Variable	*n* = 24
Male	18 (75)
Median age (yr)	77
Mean time from onset of symptoms (mo)	18.5
Dysphagia score before treatment	
Grade 1	6 (25)
Grade 2	7 (29)
Grade 3	10 (42)
Grade 4	1 (4)
Weight loss	11 (46)
Mean size of diverticula (cm ± SD)	3.0 ± 1.63

(75%), median age 77 years (range 44-90 years)]. Before procedure, seven patients were treated with anticoagulant therapy and 6 with antiplatelet agents. ZD diagnosis was based on esophagogastroscopy in 12 (50%) patients, and/or barium swallow in 18 (75%) patients or computed tomography in 3 patients. Mean size of ZD was 3.0 cm (2-8 cm). Mean time from onset of symptoms was 18.5 mo. Four patients had a previous rigid endoscopic treatment (CO_2 laser). All patients presented with dysphagia. Other symptoms included regurgitation (*n* = 22, 91.7%), chronic cough (*n* = 12, 50%) and aspiration pneumonia (*n* = 2, 8.3%). Patient characteristics are reported in Table 2.

A total of 28 endoscopic procedures were performed in our 24 patients (mean 1.17 procedures per patient): One procedure in 21 patients, two procedures in two patients and three procedures in one patient. Diverticuloscope insertion and good septum exposition were achieved in all patients. One or two endoclips were placed in all patients. Median follow-up was 19.5 mo (6-53).

Clinical success was obtained in 21 (87.5%) patients after the first procedure. Two patients developed recurrence, at 4 and 8 mo post-procedure, respectively: One was successfully treated with a second session, the other declined any reintervention. Initial failure was observed in 3 (12.5%) patients: One patient with an 8-cm ZD was contraindicated for general anesthesia for a second session, and two patients with ≤ 3 cm ZD underwent a second procedure. Symptoms resolved in both patients, but one experienced recurrence 6 mo later, which was successfully treated by a third session. Overall clinical success was obtained in 22/24 patients (91.7%). Overall recurrence rate was 13% (3/23). Mean ± SD dysphagia score was 2.25 ± 0.89 before treatment and decreased to 0.25 ± 0.74 at end-of-follow-up ($P < 0.001$). At end-of-follow-up, 19/22 (86.4%) and 12/12 patients were free from regurgitation and cough, respectively. Among 11 patients with preoperative weight loss, 10 (90.9%) regained weight (mean +4.2 kg) at two months post-treatment. Median time to recurrence was 6 mo. Figure 2 and Table 3 summarize treatment outcome. Overall adverse effect rate was 8.3%: Two patients developed

Figure 2 Clinical outcome of endoscopic myotomy.

fever with elevated CRP, without evidence of perforation on CT scan with contrast agent ingestion. Conservative management with antibiotics was successful in both patients, who were discharged from hospital on day 4 and day 6 post-procedure, respectively. No perforation or post-procedural bleeding was recorded. Nine patients (37.5%) reported mild pain, lasting a median 3 d. All of them were treated with acetaminophen as outpatients. Mild bleeding during myotomy occurred in two (8.3%) patients and was treated by soft coagulation applied with a Coagrasper (Olympus endotherapy, Tokyo, Japan). These two patients were not treated with anticoagulant or antiplatelet agents, and both were discharged from hospital on day 1 post-procedure. One asymptomatic patient died of unrelated cause during follow-up, at 29 mo after myotomy. Median hospital stay was 1 d (1-6).

DISCUSSION

Open surgery is mainly considered after endotherapy failure or for large diverticula[2,8]. Along with endoscopic stapling, flexible endoscopic myotomy is a first-line treatment option for symptomatic ZD. The use of a soft diverticuloscope stabilizes the endoscope and provides better exposure of the septum, resulting in a lower adverse events rate[9]. We perform diverticulotomy in supine position in order to increase the stability of the gastroscope, which may slip out of the diverticuloscope if the patient is lying in left lateral position. Most authors agree with placing endoclips at the end of the procedure to prevent delayed complications[4]. Nevertheless, various tools are used to perform the myotomy: Argon plasma coagulation has been practically abandoned as it needs multiple procedures and carries a high complication rate[10], whereas favorable outcome is

Table 3 Dysphagia score before treatment and at end-of-follow-up

Before treatment	End of the follow-up period			
	0	1	2	3
1	n = 6	n = 0	n = 0	n = 0
2	n = 7	n = 0	n = 0	n = 0
3	n = 7	n = 1	n = 1	n = 1
4	n = 1	n = 0	n = 0	n = 0
Total	21	1	1	1

reported with the use of needle-knife[11], submucosal dissection knives[5], a Zimmon needle (Cook endoscopy, Winston-Salem, NC)[4], or endoscopic scissors[12,13]. The SB-knife® (Sumimoto Bakelite Ltd, Tokyo, Japan), an endoscopic scissor, seems to be safe, fast and effective[13]. Myotomy with the SB-knife consists in cutting the full thickness of the septum without individualization of muscle fibers, anterior and posterior walls of the diverticulum. It remains unclear where dissection should be stopped in this setting. The most reliable device for diverticulotomy has yet to be determined[14]. A major concern is perforation risk if dissection extends too deeply. The Hook knife provides advantages for this purpose, as its design allows pulling the muscle fibers upward before cutting. Extensive myotomy can be achieved with complete visual control, and the risk of coagulation-induced injury risk may be reduced by pulling tissues upward instead of pushing downward with most other tools. Unlike previous series on submucosal dissection knives[5], we believe that these devices-but not the Hook knife-do not confer an optimal visualization, especially in the final steps of the myotomy, before cutting the posterior ZD and anterior esophageal walls, whereas pulling with the hook is helpful to assess the nature and amount of tissue before cutting.

Our 91.7% overall clinical success rate is in line previous papers. A 95% overall success rate was reported in a series of 46 patients treated with the Hook knife[15]. However, in this series, initial clinical success was 100%, but recurrence rate was high at 30%, leading to frequent retreatment (mean 1.39 sessions/patient). This might be explained by the interruption of the myotomy 5 to 10 mm above the bottom of the diverticulum, regardless of complete cut of muscle fibers and diverticulum size. Indeed, post-treatment size $\geq$ 10 mm is suspected to be a risk factor for recurrence at 48 mo[8]. Moreover, diverticula were larger (median size 42 mm) than in our series. Although diverticulum size was not significantly associated with recurrence rate, pre-treatment size $\geq$ 50 mm may be an independent factor for clinical failure at 6 mo[8], and this could also explain such a high recurrence rate. Lower (from 50%) or higher (to 100%) success rates have been reported before[8,16,17]. With the Zimmon needle, overall success, recurrence and complication rates were respectively 84%, 23.1% and 2.2%[4]. With a needle knife, overall

success rates ranged from 69%[8] to 84%[17] at 6 mo, recurrence rates from 15%[8] to 30%[17], and adverse event rates from 3%[8] to 23%[17]. Laquière *et al*[5] described the use of the Dual-knife® (Olympus endotherapy, Tokyo, Japan) and the HybridKnife® (Erbe elektromedizin GmbH, Tuebingen, Germany), with an overall success rate, recurrence rate and complication rate of respectively 91.7%, 14% and 7.1%. Endoscopic myotomy with the SB-knife® resulted in a 87.1% overall success rate, a 6.5% recurrence rate, and a 3.2% complication rate, with a limited median follow-up of 7 mo[13]. These variations might be related to how tightly clinical success was defined: Dysphagia score ≤ 1[4], or < 1[8] have been proposed. Moreover, composite scores investigating respiratory symptoms or hoarseness and their weekly frequency have been included in clinical success definition by some authors[9], resulting in lower success rates. Here however, in our definition of clinical success, no further intervention was needed, which means patients were satisfied with the functional result on the ZD-related symptoms. The initial failure rate of 12.5% and the recurrence rate of 13% are consistent with previous studies given the small mean size of ZD in our series; septotomy length $\leq$ 25 mm is suspected to be an independent prognostic factor for clinical failure and recurrence (HR = 6.34 at 6 mo and 2.20 at 48 mo)[8].

Only two patients experienced mild adverse events. No bleeding was reported, when anticoagulant or antiplatelet therapy was resumed the day post-procedure in more than half of patients. No perforation occurred. Moreover, after all but two procedures, patients were discharged from hospital on day 1, demonstrating the safety of this technique.

Retrospective analysis, single-center design, and lack of comparison with other devices are limitations to this study. Even with a minimal follow-up of 6 mo, our median follow-up of 19.5 mo might still be too short to investigate long-term recurrences: Even though another study reported a mean time to recurrence after diverticulotomy with the Hook knife of 4.4 mo[15], recurrence rate may be underestimated, as success rate for dysphagia decreased between 6 and 48 mo in a large study including 89 patients with a 24-mo minimum follow-up[8].

Conclusion

The Hook knife is a reliable tool for flexible endoscopic soft diverticuloscope-assisted myotomy in patients with symptomatic Zenker's diverticula. It is safe and efficient and could therefore be considered a device of choice in this indication. Larger comparative studies, with extended follow-up, are needed to determine which tool is the best.

COMMENTS

Background

Zenker's diverticulum can cause dysphagia, regurgitations, and sometimes life-

threatening complications. Endoscopic treatment is a first line option.

Research frontier

Flexible endoscopic myotomy can be performed with various tools. Safety (perforation risk) and efficacy are major concerns. The ideal tool has yet to be determined.

Innovations and breakthroughs

The Hook knife allows precise dissection of muscle fibers and complete myotomy in a safe way, by pulling up tissues before cutting. It results in high clinical success rate and low complication and recurrence rates.

Applications

The Hook knife may be a device of choice for flexible endoscopic diverticulotomy.

Peer-review

The manuscript was well written and helpful.

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CASE REPORT

Russell body gastritis with Dutcher bodies evaluated using magnification endoscopy

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Institutional review board statement: This case report was approved by the institutional review board of the Japanese Red Cross Kochi Hospital.

Informed consent statement: The patient described in this case report provided written informed consent.

Conflict-of-interest statement: All the authors have no conflicts of interests to declare.

Abstract

Russell body gastritis (RBG) is an unusual type of chronic gastritis characterized by marked infiltration of Mott cells, which are plasma cells filled with spherical eosinophilic bodies referred to as Russell bodies. It was initially thought that *Helicobacter pylori* (*H. pylori*) infection was a major cause of RBG and that the infiltrating Mott cells were polyphenotypic; however, a number of cases of RBG without *H. pylori* infection or with monoclonal Mott cells have been reported. Thus, diagnostic difficulty exists in distinguishing RBG with monoclonal Mott cells from malignant lymphoma. Here, we report an unusual case of an 86-year-old-Japanese man with *H. pylori*-positive RBG. During the examination of melena, endoscopic evaluation confirmed a 13-mm whitish, flat lesion in the gastric antrum. Magnification endoscopy with narrow-band imaging suggested that the lesion was most likely a poorly differentiated adenocarcinoma. Biopsy findings were consistent with chronic gastritis with many Mott cells with intranuclear inclusions referred to as Dutcher bodies. Endoscopic submucosal dissection confirmed the diagnosis of RBG with kappa-restricted monoclonal

Mott cells. Malignant lymphoma was unlikely given the paucity of cytological atypia and Ki-67 immunoreactivity of monoclonal Mott cells. This is the first reported case of RBG with endoscopic diagnosis of malignant tumor and the presence of Dutcher bodies.

Key words: Russell body gastritis; Mott cell; Dutcher body; Mucosa-associated lymphoid tissue lymphoma; Plasmacytoma; Magnification endoscopy with narrow-band imaging

Core tip: We report Russell body gastritis (RBG) evaluated by magnification endoscopy with narrow band imaging and pathological evaluation by endoscopic submucosal dissection. The endoscopic features of RBG are exclusively inflammatory; however, our detailed endoscopic evaluation led to misdiagnosis of the lesion as poorly differentiated adenocarcinoma. The histological features of RBG were also unique because the presence of Mott cells with light chain restriction and Dutcher bodies suggested malignant lymphoma. Pathologists should be aware of the existence of this pathological entity, and clinicians should consider RBG as a differential diagnosis in cases where detailed endoscopic examination reveals poorly differentiated early gastric cancer.

INTRODUCTION

Russell body gastritis (RBG) was first described by Tazawa *et al*[1] in 1998 and is considered as a unique form of chronic gastritis characterized by infiltration of plasma cells filled with spherical eosinophilic cytoplasmic globules, referred to as Russell bodies. The endoscopic features of RBG are most in keeping with an inflammatory condition, and biopsy is required to confirm the pathological diagnosis. RBG is considered a reactive condition; however, monoclonal Mott cells have been shown in a number of cases of RBG, and therefore whether or not RBG with monoclonal Mott cells is benign remains debatable. This uncertainty is due to the fact that monoclonal Mott cells can show regional lymph node metastasis[2] and have been identified in mucosa-associated lymphoid tissue (MALT) lymphoma with extreme plasmacytoid differentiation[3]. Here, we report a unique case of RBG with endoscopic features of a malignant tumor, which consisted of monoclonal Mott cells with Dutcher bodies identified histologically following endoscopic submucosal resection.

CASE REPORT

An 86-year-old Japanese man with a history of rheumatoid arthritis, type 2 diabetes mellitus, and hypertension was referred to our medical center with melena. He took non-steroidal anti-inflammatory drugs for arthralgia but did not take immunosuppressive drugs. Physiological examination was unremarkable. Laboratory findings revealed anemia (Hb 6.5 g/dL) and no other abnormal results. Endoscopic evaluation of the upper and lower digestive tracts did not reveal any active bleeding. *Helicobacter pylori* (*H. pylori*) infection was confirmed on a positive serum anti-*H. pylori* antibody test. The patient was initially diagnosed with atrophic and erosive gastritis secondary to *H. pylori* infection, and eradication therapy was initiated. The first esophagogastroduodenoscopy revealed a 13-mm flat lesion (Figure 1A and B) of white and slightly brown discoloration in the lesser curvature of the antrum. A magnification endoscope (Gastrointestinal fiber-H260Z, Olympus, Tokyo, Japan) with a narrow-band imaging (NBI) system (EVIS LUCERA SPECTRUM ELITE system, Olympus) was used, and magnification endoscopy with NBI (M-NBI) of the lesion showed loss or irregularity of microsurface pattern, irregular microvascular proliferation, and a demarcation line (Figure 1C and D). Poorly differentiated adenocarcinoma was suspected, and a biopsy was performed. The duodenum appeared to be intact. The biopsy specimen (Figure 2A-D) showed chronic gastritis with infiltration of lymphocytes, plasma cells, eosinophils, and small-to large-sized granulated cells (Figure 2B-D). Spiral-shaped bacilli were focally located in the mucin on the foveolar epithelium, confirming the diagnosis of *H. pylori*. Substantial amounts of granulated cells with eosinophilic cytoplasmic granules and eccentric nuclei were seen (Figure 2B), which were of a similar size to the eosinophilic granules (Figure 2C). The small-sized granulated cells showed plasmacytoid morphology with eccentric and cartwheel-like nuclei, while ballooning large granulated cells showed histiocytoid morphology (Figure 2C). Intranuclear eosinophilic granules were also observed in some granulated cells (Figure 2D) but were not apparent in infiltrating plasma cells without cytoplasmic granules. Lymphoid follicles were not observed. Neither lymphoepithelial lesions nor monotonous proliferation of centrocyte-like cells or monocytoid-B cells were observed. The cytoplasmic granules were stained by phosphotungstic acid-hematoxylin (PTAH) and periodic acid Schiff with or without diastase treatment. Immunohistochemically, the granulated cells including histiocytoid cells were positive for CD79a (Clone HM57, DAKO, Glostrup, Denmark) and multiple myeloma oncogene 1 (Clone MUM1p, DAKO, Glostrup, Denmark) and negative for pancytokeratin (Clone CAM5.2, Becton Dickinson, CA), CD20 (Clone L26, DAKO, Glostrup, Denmark), CD138 (Clone MI15, DAKO, Glostrup, Denmark), CD68 (Clone KP-1, DAKO, Glostrup, Denmark), CD163

Figure 1 Endoscopic imaging of the antral lesion before and after the eradication. A: An endoscopic image before the eradication shows a 13-mm whitish/slightly brownish lesion (arrow) on the lesser curvature of the antrum; B: Indigo carmine dye spray reveals that the antral lesion (arrow) is almost flat; C: Magnification endoscopy with narrow-band imaging shows the lesion (C, right side) exhibits loss or irregularity of the microsurface pattern and irregular microvascular proliferation compared to the background mucosa (C, left side). A demarcation line (D, arrowheads) is seen at the periphery of the lesion. E-F: Endoscopic images after the eradication therapy exhibit that the mucosal lesion (arrow) decreases in size to 7 mm in diameter (E) and preserves the gross appearance with indigo carmine dye spray (F).

(10D6, Thermo scientific), CD1a (Clone 10, DAKO, CA), S100 (polyclonal, DAKO, Glostrup, Denmark), c-KIT (polyclonal, DAKO, Glostrup, Denmark), mast cell tryptase (Clone AA1, DAKO, Glostrup, Denmark), and Ki-67 (Clone MIB-1, DAKO, Glostrup, Denmark). Thus, the granulated cells were considered to be plasma cells and identified as Mott cells with cytoplasmic eosinophilic globules (Russell bodies). Intranuclear eosinophilic granules in some Mott cells were considered to be Dutcher bodies. Immunohistochemically, the Mott cells appeared to be negative for light chains and immunoglobulin G (IgG, polyclonal, Novocastra Laboratories Ltd., Newcastle, United Kingdom), IgA (polyclonal, Novocastra Laboratories Ltd., Newcastle, United Kingdom), and IgM (polyclonal, Novocastra Laboratories Ltd., Newcastle, United Kingdom), while plasma cells without Russell bodies showed polytypic light chain staining pattern and were reactive for IgG, IgA, or IgM in varying proportions. Taken together, these findings were most in keeping with a diagnosis of RBG, but malignant lymphoma, particularly MALT lymphoma, was a differential diagnosis. However, chest-abdomen-pelvis computed tomography showed no abnormal mass, no swollen lymph nodes, and no lytic bone lesion. Two months after completion of eradication therapy, the patient consented to undergo endoscopic submucosal dissection (ESD), which was performed with the aim of histologically evaluating the entire lesion.

After eradication therapy, the mucosal lesion decreased in size to 7 mm in diameter (Figure 1E-F) and loss or irregularity of the microsurface pattern, irregular microvascular proliferation, and a demarcation line with M-NBI were seen. ESD was successfully performed. The patient was discharged without any complications and there was no endoscopic evidence of recurrence 14 mo after the ESD treatment.

Pathological diagnosis on ESD specimens
The endoscopically resected tissue was extended on a board with pins, fixed in 10% formalin for 24 h, cut into 2- to 3-mm thick sections, and embedded in paraffin. Four μm-thick sections were obtained from the paraffin blocks and stained with hematoxylin and eosin. Pathology showed that the mucosal lesion had regional accumulation of substantial amounts of granulated cells associated with mild lymphocytic and plasma cell infiltration (Figure 2E and F). The immunohistochemical results of ESD were similar to those of the biopsy specimens (Figure 2G and H). In situ hybridization revealed that the Mott cells showed kappa light chain restriction (Figure 2I and J), whereas the plasma cells without Russell bodies were polyphenotypic. Cellular atypia and mitosis were not seen in the plasma cells or Mott cells, and less than 1% of the infiltrating cells were Ki67-positive, whereas no Mott cells were Ki67-positive. At the periphery of the lesion and in the background

Figure 2 Pathological features of the antral lesion. The biopsy specimen stained by hematoxylin and eosin shows chronic gastritis with crowded granulated cells (A, B). The histiocytoid cells have fine eosinophilic granules similar to those of eosinophils (C). Intranuclear cytoplasmic granules suggesting Dutcher bodies are observed (D). E-F: The ESD specimen stained by hematoxylin and eosin shows that the lesion (E, indicated by a dotted line) is edematous and demarcated and includes many granulated cells (F). G-J: Immunohistochemical (G-H) and in situ hybridization (I-J) findings with ESD specimens show that the granulated cells (arrowheads) are positive for CD79a (G), multiple myeloma oncogene 1 (H), and kappa (I) and negative for lambda (J), while plasma cells without cytoplasmic granules are polyphenotypic.

mucosa and submucosa, Mott cells and Dutcher bodies were absent. Lymphoid follicles were observed in the periphery of the lesion and the background mucosa, but not within the collection of Mott cells. There were no pathological features suggestive of carcinoma or MALT lymphoma. Amyloid deposition was unlikely because no amorphous materials were identified, and there was no characteristic apple green birefringence noted when the Congo Red stained section was viewed under polarized light. Thus, our final diagnosis was Russell body gastritis. However, the diagnostic assessment utilized had several limitations, as we did not assess for the presence of M protein in the serum, Bence-Jones protein in the urine, or genetic alterations in the immunoglobulin locus, and we did not perform cytopathological examination of the bone marrow.

DISCUSSION

We presented a unique case of RBG with *H. pylori* infection. Russell body gastritis is characterized by a dense accumulation of plasma cells with Russell bodies, referred to as Mott cells[1]. Russell bodies are eosinophilic spherical or globular cytoplasmic inclusions in plasma cells that were first described by Russell *et al*[4] in 1890. The globules differ from normal secretory granules in that they are larger and much more electron dense, and they lie in the distended cisternae of the rough endoplasmic reticulum[5]. These globules mainly consist of condensed immunoglobulin[6] and are

related to abnormalities in the synthesis, trafficking, or excretion of immunoglobulin[7]. The Russell bodies seen in the present case were much smaller compared to those in previous reports; however, the granules were stained positive by periodic acid Schiff and PTAH, as described in previous case reports of RBG[8,9].

Table 1 summarizes the results of 31 previously published cases of RBG, including our own[1,8-25]. We excluded two cases reported as RBG[26] and Russell body carditis[27] because in these cases the inflammation site was at the esophagogastric junction. One case of RBG associated with advanced signet ring cell cancer[28] was also excluded because the authors did not describe whether or not RBG was present in the background gastric mucosa. The mean age of the patients described in previous case reports of RBG was 60 (range 24 to 86) years old, and our patient was the oldest. The male (*n* = 19) to female (*n* = 12) ratio was approximately 2:1. Twenty-one cases (68%) of RBG accompanied *H. pylori* infection, and the majority of patients in all cases presented with non-specific symptoms. The gastric antrum appears to be the predominant location for RBG, although there is one reported case of an immunocompromised patient with RBG associated with Russell body enterocolitis[25].

The endoscopic features of RBG are non-specific, and in most cases, the inflammatory phenotype of the condition has been attributed largely to the presence of swollen, erythematous mucosa. The pathological features of RBG can mimic those of gastric xanthoma[19]. To the best of our knowledge, this is the first case of RBG with a clinical diagnosis highly suggestive of a malignant tumor. In the present case, M-NBI confirmed a flat mucosal lesion in the antrum with a demarcated line, loss of microsurface pattern, and irregular microvascular proliferation. Nishimura *et al*[29] also reported that partial loss of microsurface structure and abnormal microvessels were observed in a case of RBG with M-NBI, but the demarcation line of RBG was not reported. Magnification endoscopy permits visualization of mucosal details that cannot be seen with standard endoscopy, and NBI is a novel endoscopic approach to visualize the microvasculature on the tissue surface. M-NBI has been proven to be highly sensitive, specific, and accurate at detecting early gastric neoplasms. Pathological evaluation revealed that the lesion was characterized by regional and intramucosal accumulation of Mott cells. The proliferation of Mott cells might induce expansion of the lamina propria, decrease the density of gastric glands and pits, and influence the microvasculature of the lesion. At present, RBG is considered a rare entity, but its incidence may increase in the future secondary to the increased use of M-NBI. It may be better that clinicians raise RBG as a differential diagnosis of poorly differentiated early gastric cancer upon examination by M-NBI.

Of pathological interest, Mott cells were monoclonal and had Dutcher bodies, which caused difficulty in making a histological diagnosis. Only two cases[8,12]

of RBG and Dutcher bodies have been described in the literature to date, and both failed to identify a Dutcher body in the lesion. Considering the presence of monoclonal Mott cells and Dutcher bodies, the differential diagnoses that we considered were plasma cell neoplasm, MALT lymphoma, and lymphoplasmacytic lymphoma. In the present case, MALT lymphoma could not be diagnosed on account of the lack of histological features suggestive of MALT lymphoma, such as a lymphoepithelial lesion and proliferation of monocytoid B-cells or centrocyte-like cells. Moreover, Mott cells showed neither cellular atypia nor mitotic activity. Plasma cell neoplasm was excluded due to hypoproteinemia, lack of osteolysis in computed tomography images, and lack of nuclear atypia or mitotic activity of monoclonal Mott cells, although paraproteinemia was not evaluated *via* serum protein electrophoresis. Lymphoplasmacytic lymphoma was ruled out because of an absence of splenomegaly and lymphadenopathy. Monoclonal gammopathy of undetermined significance[13], which can be associated with *H. pylori*-positive RBG, could not be evaluated in this case.

The pathogenesis of RBG remains unknown. Tazawa *et al*[1] firstly postulated that RBG might be induced by *H. pylori* infection, and this is in keeping with previously published literature, in which two thirds of RBG cases were *H. pylori*-positive (Table 1). A recent study[30] showed that *H. pylori* with vacA m1 genotype produces more prominent Russell bodies in the antrum but not in the body. Indeed, the literature review revealed that the incidence of antral RBG was higher in *H. pylori*-positive cases (70%) than in *H. pylori*-negative cases (40%). On the other hand, our case showed endoscopic regression of the lesion from 13 mm to 7 mm at 2 mo after eradication of *H. pylori,* and similar findings were observed in previous studies[16,18,19,21]. These observations suggest that the successful eradication of *H. pylori* may eliminate the proliferative stimulation of Mott cells. However, case reports of RBG without *H. pylori* infection have also been described, although those cases were complicated by HIV infection[11], post-transplant status[25], or monoclonal gammopathy of uncertain significance[13]. Therefore, it is likely that *H. pylori*-unrelated pathogenesis of RBG is present, and an immunocompromised status may be partly related to the occurrence of RBG. In our case, the patient was elderly and had a history of rheumatoid arthritis; therefore, it is possible that the occurrence of RBG in this patient may have been due, in part, to his immunocompromised status.

RBG is considered to be a benign condition, and clinical follow-up data of 19 cases of RBG to date has failed to reveal any malignant change (Table 1). Among the 19 cases described in the literature, ten cases received *H. pylori* eradication therapy after diagnosis of RBG, and most of these showed endoscopic or histological resolution at three months, whether or not monoclonal Mott cells were present. Thus, follow-

Table 1 Literature review of clinicopathological findings of Russell body gastritis

Ref.	Age/sex	Endoscopic finding or diagnosis (size)	Site of mott cells	HP	Mott cells	ET and follow-up
Tazawa *et al*[1] (1998)	53/M	Multiple ulcer scars with redness and swelling	Antrum	Yes	Poly	Follow-up biopsy after ET showed no RBG Follow-up period was not available
Erbersdobler *et al*[8] (2004)	80/F	Circumscribed irregular swelling (30 mm)	Fundus	No	Poly	NA
Ensari *et al*[10] (2005)	70/M	Pangastritis/flattened, edematous gastric folds	Body and antrum	Yes	Poly	ET was performed, but patient refused to be re-examined endoscopically
Drut *et al*[11] (2006)	34/M	A raised, swollen area (20 mm)	Body	No	Poly	NA
Paik *et al*[12] (2006)	47/F	Focal erythematous swelling	Antrum	Yes	Poly	ET was performed. Follow-up data: NA
	53/F	A geographical yellowish raised lesion (25 mm)	Body	Yes	Poly	ET was performed Follow-up data: NA
Wolkersdorfer *et al*[13] (2006)	54/M	Mild erythema and small erosions with slight edema	Antrum	Yes	Mono (λ chain)	One year after ET, the lesion had not resolved macroscopically, but biopsy found resolution of Mott cells
Pizzolitto *et al*[14] (2007)	60/F	Minute-raised granular areas	Antrum	Yes	Poly	ET was performed, and clinical follow-up was uneventful
Licci *et al*[15] (2008)	59/M	Mild hyperemia	Antrum	Yes	Poly	Mott cells were absent in biopsy specimen taken 3 mo after ET
Tabata *et al*[16] (2010)	72/M	Multiple ulcers	Body and antrum	Yes	Mono (κ chain, IgG)	Mott cells were absent in biopsy specimen taken 3 mo after ET
Habib *et al*[17] (2010)	75/M	Noduar chronic active gastritis	Antrum	No	Poly	NA
Miura *et al*[18] (2012)	63/F	Low elevated lesions in the antrum	Antrum	Yes	Mono (λ chain)	Mott cells were absent in biopsy specimen taken 4 mo after ET
Yoon *et al*[19] (2012)	57/M	A slightly raised whitish lesion with a mild central depression (20 mm)	Body	Yes	Poly	The lesions were cleared 3 mo after ET. A follow-up biopsy was not performed
	43/M	A whitish oval shaped flat lesion with a slight central depression (20 mm)	Antrum	Yes	Poly	The lesions were cleared 2 mo after ET. A follow-up biopsy was not performed
Choi *et al*[20] (2012)	55/M	A mucosal elevation with a central depression (10 mm)	Antrum	Yes	Mono (λ chain)	NA
Karabagli *et al*[21] (2012)	60/M	Erythema (body) and ulcer (incisura angularis)	Body and antrum	Yes	Poly	Three months and 6 mo after ET, Mott cells were decreased and absent in biopsy specimens, respectively
Coyne *et al*[22] (2012)	49/M	Severe, raised, erosive gastritis	NA (Biopsy site; NA)	No	Mono (κ chain, IgM)	NA
Araki *et al*[9] (2013)	74/F	Open ulcer	Gastric angle	Yes	Mono (κ chain, IgM)	NA
Zhang *et al*[23] (2014)	78/F	Uneven mucosa	Body, incisura angularis, antrum	No	Mono (κ chain)	Clinical follow-up evaluations were uneventful
	77/F	Uneven mucosa	Incisura angularis	Yes	Mono (κ chain)	
	77/F	punctiform erosion	Body	Yes	Mono (κ chain)	
	56/M	Raised erosions	Antrum	Yes	Mono (κ chain)	
	76/M	Erythema	Body	Yes	Mono (κ chain)	
	50/M	Flat and raised erosions	Antrum	Yes	Mono (κ chain)	
	28/M	Erythema	Antrum	No	Mono (κ chain)	
	24/F	Erythema	Antrum	No	Mono (κ chain)	
	66/M	Ulcer, stage A2	Incisura angularis	No	NA	
Klair *et al*[24] (2014)	76/F	Cobblestoned, whitish, raised, and irregular mucosa	Fundus	No	Poly	NA
Muthukumarana *et al*[25] (2015)	44/M	Diffuse mild erythematous gastric mucosa	Stomach, duodenum, terminal ileum, colon	No	Poly	NA
Nishimura *et al*[29] (2016)	64/F	A white, granular lesion (2 cm)	Body	Yes	Poly	The lesion had grown larger 15 mo after the diagnosis, and the lesion had disappeared 15 mo after eradication
Present case	86/M	A demarcated whitish flat lesion (13 mm)	Antrum	Yes	Mono (κ chain)	Two months after ET, the lesion decreased in size. There was no evidence of recurrence 14 mo after ESD

HP: *Helicobacter pylori*; ET: Eradication therapy; Poly: Polyclonal; Mono: Monoclonal; RBG: Russell body gastritis; NA: Not available; Ig: Immunoglobulin.

up might be a better approach for the present case. However, whether or not RBG with monoclonal Mott cells is a reactive or neoplastic phenomenon remains debatable. To date, a total of 15 cases (50%, 15/30) of RBG with monoclonal Mott cells, including our case, have been described, and all of these RBG cases–had uneventful clinical follow-up. Brink *et al*[31] reported a case with a rectal tubulovillous adenoma accompanied by a proliferation of monoclonal Mott cells and concluded that the phenomenon indicated an inflammatory response. As Araki *et al*[9] discussed, monoclonal B cell proliferation can be seen in cases of chronic inflammation such as lymphoid follicle-forming gastritis[32], Sjögren's syndrome[33], Hashimoto's thyroiditis[34], and chronic liver disease secondary to hepatitis C virus[35]. Thus, the above data support the theory that RBG with monoclonal Mott cells is a benign condition. However, Fujiyoshi *et al*[2] described a gastric tumor consisting of monoclonal Mott cells which metastasized to the perigastric lymph nodes, and they concluded that the gastric tumor was most likely an extramedullary plasmacytoma or a MALT lymphoma. Joo[3] and Kai *et al*[36] also showed that monoclonal Mott cells can be a neoplastic component of MALT lymphoma with extreme plasmacytoid differentiation. Fujiyoshi *et al*[2], Joo[3], and Kai *et al*[36] did not describe cellular atypia or mitotic activity in monoclonal Mott cells in their cases, and therefore the histopathological distinction of monoclonal Mott cells in RBG and in MALT lymphoma and plasmacytoma remains unknown. In the present case, we concluded that the monoclonal Mott cells were non-neoplastic cells mainly because of the absence of cellular atypia and mitotic activity. Nevertheless, future studies are warranted to clarify the distinction between RBG with monoclonal Mott cells and MALT lymphoma or plasmacytoma.

In conclusion, we presented an unusual case of an 86-year-old man with *H. pylori*-positive RBG. This is a valuable case of RBG evaluated by M-NBI and pathological evaluation of the entire lesion. The detailed endoscopic evaluation led to the clinical diagnosis of a poorly differentiated adenocarcinoma, despite the fact that previous endoscopically diagnosed cases of RBG were exclusively inflammatory. Pathological evaluation of ESD-obtained specimens confirmed the presence of regional proliferation of kappa-restricted Mott cells within the mucosal lesion and failed to identify an epithelial malignancy. RBG is a rare condition whose incidence is expected to increase in proportion to the increased use of M-NBI. Therefore, it is of great clinical importance to increase our understanding of the pathological features of RBG in order to effectively diagnose and manage future cases.

ACKNOWLEDGMENTS

COMMENTS

Case characteristics
An 86-year-old Japanese man with melena and a history of rheumatoid arthritis and type 2 diabetes mellitus.

Clinical diagnosis
The patient was initially diagnosed with atrophic and erosive gastritis secondary to *Helicobacter pylori* (*H. pylori*) infection, and the first esophagogastroduodenoscopy revealed a 13-mm flat lesion of white and slightly brown discoloration in the lesser curvature of the antrum.

Differential diagnosis
Findings of magnification endoscopy with a narrow-band imaging (M-NBI) of the flat gastric lesion suggested poorly differentiated adenocarcinoma.

Laboratory diagnosis
Laboratory findings revealed anemia and a positive serum anti-*H. pylori* antibody test.

Imaging diagnosis
M-NBI of the lesion showed loss or irregularity of microsurface pattern, irregular microvascular proliferation, and a demarcation line, which suggested poorly differentiated early gastric cancer.

Pathological diagnosis
The final diagnosis was Russell body gastritis (RBG) with substantial infiltration of granulated plasma cells. Although the granulated plasma cells showed kappa light chain restriction and the presence of Dutcher bodies, malignant lymphoma was unlikely partly because of the paucity of the cellular atypia and mitotic activity.

Treatment
Endoscopic submucosal dissection (ESD) was selected for therapeutic diagnosis.

Related reports
Thirty-one previously published cases of RBG, including the authors own, has been reported, and this is the first reported case of RBG with the endoscopic diagnosis of malignant tumor with M-NBI, pathological evaluation of the entire lesion with ESD-obtained specimens, and the presence of Dutcher bodies.

Term explanation
RBG is considered as a unique form of chronic gastritis characterized by infiltration of plasma cells filled with spherical eosinophilic cytoplasmic globules, referred to as Russell bodies.

Experiences and lessons
The endoscopic features of RBG are exclusively inflammatory; however, clinicians should consider RBG as a differential diagnosis in cases where detailed endoscopic examination reveals poorly differentiated early gastric cancer. Pathologists should be aware of the existence of this pathological entity, because histological features of RBG can overlap with those of malignant lymphoma.

Peer-review
Excellent case report article.

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CASE REPORT

Simultaneous Courvoisier's and double duct signs

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Abstract

Presence of Courvoisier's or double duct signs in a jaundiced patient is suggestive of malignant obstruction of the pancreaticobiliary ductal system. The oncologic impact of the simultaneous occurrence of these signs on the survival of patients with periampullary cancer is unknown. We report a case of obstructive jaundice secondary to an ampullary cancer demonstrating the Courvoisier's sign on clinical examination and a double duct sign on imaging. The patient underwent a pancreaticoduodenectomy which confirmed an ampullary adenocarcinoma.

Key words: Ampullary cancer; Obstructive jaundice; Double duct sign; Courvoisier's law; Prognosis

Core tip: Presence of Courvoisier's or double duct signs in a jaundiced patient is indicative of obstruction of the pancreaticobiliary ductal system most likely of malignant etiology. This study reports classic clinical and radiologic findings in ampullary adenocarcinoma. The oncologic impact of the simultaneous occurrence of these signs on the survival of patients with ampullary cancer is unknown.

INTRODUCTION

Recent studies validate Courvoisier's observation that gallbladder distension seldom occurs in stone obstruction of the bile duct and is usually seen with other causes of biliary obstruction[1,2]. The radiographic double duct sign comprising of the simultaneous dilation of the common bile duct (CBD) and main pancreatic duct (MPD) se-

condary to biductal obstruction is highly suggestive but not diagnostic of pancreatic cancer[3,4]. Despite a common etiology there is little data on the simultaneous occurrence of the two signs.

CASE REPORT

A 52-year-old male presented to the clinic with complaints of yellow discoloration of eyes and generalized pruritis since one month. He denied fever, chills or weight loss and maintained a normal appetite. He denied abdominal pain or backache. He quit smoking 15 years ago and denied consumption of alcohol. His past medical, surgical or family history were noncontributory. On examination he was icteric with no supraclavicular lymphadenopathy. Abdominal examination revealed a palpable liver edge 3 cm below the costal margin and a distended gall bladder consistent with a Courvoisier's sign. Laboratory tests were remarkable for elevated liver function tests- total bilirubin 5.4 mg/dL, direct bilirubin 4.4 mg/dL, glutamic-oxalacetic transaminase (AST) 107 IU/L, alanine aminotransferase (ALT) 189 IU/L, alkaline phosphatase 489 U/L with a normal tumor marker CA 19-9.

Abdominal ultrasound (US) demonstrated hepatomegaly, distended gallbladder with sludge, dilated MPD, CBD and intrahepatic biliary radicles. Pancreatic protocol computed tomography (CT) demonstrated a sessile enhancing mass in the medial wall of the second portion of the duodenum in the region of the ampulla with upstream dilation of the CBD, MPD, IHBR and a distended gallbladder. CBD and MPD measured 16 mm and 7 mm respectively and pancreatic parenchyma was normal (Figure 1). MR cholangiopancreatography confirmed an ampullary mass, a double duct sign with MPD dilated in its entire course and a prominent cystic duct (Figure 2). Upper gastrointestinal endoscopy demonstrated a periampullary tumor with surface ulceration and biopsy confirmed an adenocarcinoma (Figure 2, inset). The patient underwent a classic pancreaticoduodenectomy or Whipple operation. Postoperative course was unremarkable and the patient was discharged home on postoperative day six. Surgical pathology demonstrated a $pT_1N_1M_0$ ampullary adenocarcinoma with vascular invasion. Adjuvant chemotherapy was administered and the patient remains without evidence of tumor recurrence at 18 mo following surgery.

DISCUSSION

The lack of gallbladder distension in 80.4% patients with calculous obstruction of the CBD was first reported by Courvoisier and is typically explained by fibrotic or atrophic changes in the gallbladder wall secondary to repeated inflammatory episodes however, recent data suggests that gallbladders are equally distensible regardless of the underlying pathology and it is the markedly higher and sustained elevation in ductal pressure in malignant obstruction that results in a

Figure 1 Double duct sign in a 52-year-old male with ampullary adenocarcinoma. Contrast-enhanced CT scan shows dilatation of the main pancreatic duct (short arrow) and common bile duct (long arrow).

Figure 2 MR cholangiopancreatography shows a distended gallbladder, dilatation of the common bile duct (long arrow) and main pancreatic duct (short arrows) consistent with a double duct sign. A mass is noted in the region of the ampulla of Vater (arrowhead) and a periampullary tumor (black arrow) is confirmed on upper gastrointestinal endoscopy (inset).

distended gallbladder in contrast to the intermittent obstruction produced by gallstones[1,5,6]. The double duct sign initially described on endoscopic retrograde cholangiopancreatography (ERCP) has also been seen with US, CT or MRCP and is usually caused by cancer of the pancreatic head or ampulla of Vater and less commonly, chronic pancreatitis or ampullary stenosis[3]. Other malignant causes include cholangiocarcinoma, metastatic lymphadenopathy, lymphoma and rare causes include primary retroperitoneal fibrosis, Kaposi sarcoma or parasitic infestation of the bile ducts[3]. The prevalence of malignancy in patients with the double duct sign varies from 58%-85% particularly, in association with obstructive jaundice[4,7,8]. However, the MPD caliber is normal in 20% patients with pancreatic cancer and isolated dilation of the MPD (single duct dilation) is due to chronic pancreatitis in the majority of the patients[9,10].

Biductal obstruction of the CBD and MPD may result in the Courvoisier's and/or double duct signs and the diagnostic value of these signs in the evaluation of a patient with obstructive jaundice is widely accepted. Despite extensive evaluation of the etiology,

pathogenesis and mechanism of these signs no study has reported the incidence or prognostic significance of the simultaneous occurrence of these signs in a patient with an ampullary cancer. The impact of the simultaneous occurrence of the Courvoisier's and double duct signs on survival outcome is unknown and an area for future investigation.

COMMENTS

Case characteristics

A 52-year-old male presented to the clinic with obstructive jaundice and abdominal examination revealed a palpable liver edge and a distended gall bladder consistent with the Courvoisier's sign. Abdominal imaging revealed an ampullary mass and a double duct sign. Upper endoscopy and biopsy confirmed ampullary adenocarcinoma. A classic pancreaticoduodenectomy was performed. Postoperative recovery was uneventful and adjuvant chemotherapy was administered. The patient remains without evidence of tumor recurrence at 18 mo following surgery.

Clinical diagnosis

Obstructive jaundice with ampullary tumor.

Differential diagnosis

Ampullary adenoma.

Laboratory diagnosis

Blood investigations confirmed obstructive jaundice.

Imaging diagnosis

Triphasic computed tomography and magnetic resonance cholangio-pancreatography confirmed an ampullary mass, a double duct sign with the common bile and main pancreatic ducts dilated in thier entire course.

Pathological diagnosis

Ampullary adenocarcinoma on esophagogastroduodenoscopy and biopsy.

Treatment

A classic pancreaticoduodenectomy (Whipple Operation).

Experiences and lessons

A double duct sign in a patient with obstructive jaundice is indicative of an ampullary tumor. A pancreaticoduodenectomy is potentially curative for ampullary adenocarcinoma.

Peer-review

This is a good clinical case report with good quality imaging studies to support the case.

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FLYLEAF

EDITORS FOR THIS ISSUE

Laparoscopic splenectomy: Current concepts

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Abstract

Since early 1990's, when it was inaugurally introduced, laparoscopic splenectomy has been performed with excellent results in terms of intraoperative and post-operative complications. Nowadays laparoscopic splenectomy is the approach of choice for both benign and malignant diseases of the spleen. However some contraindications still apply. The evolution of the technology has allowed though, cases which were considered to be absolute contraindications for performing a minimal invasive procedure to be treated with modified laparoscopic approaches. Moreover, the introduction of advanced laparoscopic tools for ligation resulted in less intraoperative complications. Today, laparoscopic splenectomy is considered safe, with better outcomes in comparison to open splenectomy, and the increased experience of surgeons allows operative times comparable to those of an open splenectomy. In this review we discuss the indications and the contraindications of laparoscopic splenectomy. Moreover we analyze the standard and modified surgical approaches, and we evaluate the short-term and long-term outcomes.

Key words: Laparoscopy; Splenectomy; Splenomegaly; Hand-assisted-laparoscopic-splenectomy; Lymphoma

Core tip: With the advent of laparoscopic techniques, laparoscopic splenectomy has become the procedure of choice for benign and malignant diseases of the spleen. Splenomegaly can be alternatively treated with modified hand-assisted approach. In addition the introduction of advanced laparoscopic tools for ligation and electrocauterization contributed to reduced blood loss at surgery and minimal morbidity.

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INTRODUCTION

Since the late 80's, minimal invasive surgical techniques have been widely used for numerous operations in General Surgery. Less intraoperative bleeding, subordinate postoperative pain, shorter hospital stay, and better cosmetic results are some of the advantages that made laparoscopy nowadays the standard approach for many surgical procedures. Therefore, laparoscopic splenectomy since 1991 when was first described by Delaitre and Maignien[1] is widely accepted as a safe and feasible technique for most splenectomy cases. Like appendix and gallbladder, spleen does not require reconstruction on removal, and its anatomic landmarks are often consistent, so it can be considered as an ideal organ for laparoscopic removal. The spleen, especially in benign diseases, can be safely morcellated prior to removal, fact that suits in laparoscopic procedures, as the specimen can be removed through a small skin incision. The development of technology and the introduction of new alternatives to classic laparoscopic splenectomy such as the single-port procedure imply that in the near future laparoscopic splenectomy will be considered as the standard approach, even in trauma cases.

In this study we review the indications for a laparoscopic splenectomy and discuss the contraindications of it. Moreover, we analyze the current technical aspects of the procedure and compare the outcomes in comparison to open splenectomy.

INDICATIONS

In general, indications for laparoscopic splenectomy are the same as those of open splenectomy, except for the trauma cases, where the role of laparoscopy is still debatable. We can divide the indications for undergoing a splenectomy into three major categories: (1) benign hematologic diseases; (2) malignant hematologic diseases; and (3) splenic cysts.

Benign hematologic diseases

It is well established that splenectomy can be a curative therapy for most of benign hematologic diseases, especially in patients with immune thrombocytopenic purpura, which is the most common indication for splenectomy (excluding trauma). ITP is an acquired autoimmune disorder characterized by a peripheral blood platelet count $< 100 \times 10^9$/L, without abnormalities in the erythroid and myeloid/lymphoid lineages[2]. The incidence of ITP in adults is estimated at 2.2-3.9 per 10^5 persons per year[3]. The curative role of splenectomy for ITP underlies in the pathophsysiology of the disease. The ITP-associated thrombocytopenia is the result of the production of antiplatelet antibodies

which bind to the platelets resulting in the destruction of the platelets through phagocytosis. This phagocytosis occurs throughout the reticuloendothelial system, but spleen is considered as the primary site not only for antiplatelet antibodies production, but also for antibody-bound platelet destruction as well[4]. Therefore, removal of spleen can reverse the pathophysiology of the disease. However, splenectomy is considered a second-line therapy, mainly for patients with chronic ITP (presence of the disease for > 12 mo), as the first-line therapy consists of high doses of corticosteroids and/or intravenous immunoglobulin[5]. A decision for a splenectomy is taken when the patient has persistent thrombocytopenia after a 6-wk therapy with steroid or intravenous immunoglobulin[6], as a remission after that time is unlikely to occur. Lately however it is suggested that a remission can occur up to 1 or 2 years after onset, so a splenectomy can be preserved for thereafter[7]. A splenectomy can be suggested also in patients who receive near-toxic doses of immunosuppressive therapy[8], in order for a complete remission to be achieved. Finally, splenectomy is preferred also in patients who had achieved a remission under medical therapy, but the thrombocytopenia has relapsed. In these cases actually laparoscopic splenectomy is considered a method of choice[9]. In the above cases, the spleen is usually normal-sized, therefore splenectomy can be successively performed with laparoscopy.

It is well established that splenectomy had excellent results in terms of *ITP* remission; in some studies the rates of complete and partial remission after laparoscopic splenectomy were superior to medical therapies[10]. In the systematic review by Kojouri *et al*[11], 66% of patients who had undergone splenectomy had a complete response (defined as a platelet count of $> 100 \times 10^9$/L) and 88 had a complete or partial response (defined as a platelet count of $> 50 \times 10^9$/L), whereas relapse of ITP occurred in 15% of all patients. High complete remission rates were found also in the study by Vianelli *et al*[12]; complete response was found in 66% of patients and a complete or partial response in 86% of patients, although the relapse rate was higher (23% with a median time to relapse of 8 mo). Many studies have tried to find prognostic factors for complete response after splenectomy, but none of them is widely accepted. Young age (< 50 years), previous response to corticosteroid and IV Ig therapies, preoperative platelet count (> 70 ×) have been occasionally proposed as prognostic factors[13]. Nevertheless, Kojouri *et al*[11], showed that none of them is a statistically significant independent predictor of a good response to splenectomy.

Patients with hereditary spherocytosis are also candidates for laparoscopic splenectomy, again under certain circumstances, as the first line therapy is mainly medical[14]. Splenectomy is preserved for moderate or severe forms of the disease, where medical therapy has nothing more to offer. In his recent meta-analysis,

Guizzetti[15] has shown encouraging results in patients with hereditary spherocytosis undergoing total or partial splenectomy; a general qualitative resolution of anemia was reported. The hemoglobin concentration increased by an average of 2.20 g/dL in patients after partial splenectomy, and the increase of hemoglobin concentration was significantly higher (3.60 g/dL) following total splenectomy. Interestingly, splenectomy showed to have a durable result, as the hemoglobin concentration remained at almost same levels after a follow-up time of four years. Moreover, the European Association of Endoscopic Surgery states that minimal invasive surgery is safe and feasible method for total splenectomy in patients with hereditary spherocytosis[9], as perioperative and postoperative complications are found in less than 1% of all patients[15]. The laparoscopic approach allows also a simultaneous cholecystectomy, which in the majority of patients with hereditary spherocytosis is required due to symptomatic cholelithiasis.

Thrombocytopenic thrombotic purpura is another indication for laparoscopic splenectomy, although it is rarely performed, as plasma therapy has very good response rates. Splenectomy is indicated in patients with primarily refractory or with progressive disease despite plasma exchange, where perioperative and postoperative mortality can reach up to 40%[16]. The response rates however are considered decent, as relapse of the disease occurs in 8% and 17% of splenectomized patients with refractory and progressive disease respectively[17]. Patients with autoimmune hemolytic anemia can be also benefited from a laparoscopic splenectomy. Lechner *et al*[18] had proposed that splenectomy is the best second-line therapy, when glycocorticoids fail to manage adequately the disease because of a high short-term efficacy and a good evidence of a long-term response. Other benign hematologic diseases that can be partially or completely treated with a laparoscopic splenectomy are Evans syndrome and hemoglobinopathies, such as sickle cell anemia, β-thalassemia and hemoglobin sickle cell disease[19]. It is mandatory to be noted though, that for all benign hematologic diseases and especially for autoimmune hematologic disorders, a routine preoperative search for accessory splenic tissue should be undergone. Many studies have reported disease recurrence due to accessory spleen(s)[20] which were not found preoperatively or intraoperatively. Some surgeons claim that minimal invasive approach restricts spotting of accessory splenic tissue, however it is well established that a thorough search of the peritoneal cavity during the laparoscopic splenectomy has similar detection rates compared to open splenectomy[21,22]. Definitively, a preoperative screening with a high-resolution CT is obligatory, as it can detect nearly 100% of accessory splenic tissue, irrespective of their size[23].

Malignant hematologic diseases
Unlike benign hematologic diseases, in malignant hematologic diseases a minimal invasive approach serves mainly diagnostic and palliative purposes but it can be also used for cure. Patients with Hodgkin's lymphoma can be benefited when the staging procedure[24], is undergone through laparoscopy, as this has fewer postoperative complications and decreased length of hospital stay[25]. Nevertheless, many surgeons hesitate to perform a staging laparoscopy for Hodgkin lymphoma, mostly for two reasons; firstly, finding infiltrated nodes, especially in iliac and celiac regions is considered to be more difficult through laparoscopy. This fact is widely accepted, however, Baccarani *et al*[25] have found that although a staging laparoscopy was associated with longer operative time, not only more infiltrated nodes were found, but also disease did not relapse in patients who underwent staging laparoscopy, proving that through a minimal invasive procedure a more accurate diagnosis can be acquired. The second reason is that when a splenectomy is required, the spleen must be removed intact for pathologic analysis and for avoiding tumor cells dissemination. Considering the fact that the majority of patients with Hodgkin's lymphoma have splenomegaly, it is proposed that an additional 8-10 cm incision should be made, in order for the spleen to be removed unattached, or alternatively a hand-assisted-laparoscopic-splenectomy (HALS) should be considered. In non-Hodgkin lymphomas the role of laparoscopic splenectomy is restricted to palliative purpose, when the patient suffers from abdominal pain and obstipation, due to splenomegaly, or for correction of cytopenia[26]. An elective laparoscopic splenectomy can be performed in patients with non Hodkin lymphoma for acquiring a histological diagnosis. In fact, a pathologic analysis of spleen tissue is considered to be the gold standard for non-Hodgkin lymphomas and additionally it is not necessary for the spleen to be removed intact[27]. It is doubtful though, whether a splenectomy is worthwhile in this case, as it may delay the curative chemotherapy[28]. The laparoscopic approach in this case may be useful, as it may minimize postoperative complications, allowing early beginning of chemotherapy.

Other malignancies in which a laparoscopic splenectomy can have a diagnostic or a therapeutic role are myeloproliferative diseases (*e.g.,* myelofibrosis*),* and lymphoproliferative diseases*, (e.g.,* chronic lymphocytic leukemia or chronic myelogenous leukemia). Lately it is believed though that splenectomy for hairy cell leukemia should be abandoned, due to efficiency of existing medical therapy. Primary splenic malignancies are very rare, comprising mostly lymphangiosarcomas, malignant vascular tumors (*e.g.,* hemangiosarcomas) or malignant lymphomas[29]. Most splenic tumors are *metastatic* (*e.g.,* of malignant melanoma or ovarian cancer)[30]. In all these malignancies, patients usually present with splenomegaly, so special issues for undergoing a laparoscopic splenectomy should be considered (see below).

Undoubtedly, laparoscopic splenectomy for mali-

gnant diseases is more challenging. Fraser *et al*[31] compared patients who underwent laparoscopic splenectomy for malignant and non-malignant diseases, and found that patients with malignant diseases were significantly older (61 years *vs* 50 years, *P* = 0.0004). Moreover, spleens removed from patients with malignancies were statistically significant larger (*P* = 0.0004) and 73% of malignant cases are considered to have splenomegaly, resulting in bigger conversion rates (30% *vs* 16%). Nevertheless, postoperative complications were not significantly increased in patients with malignant diseases, showing that although a laparoscopic splenectomy is technically more difficult in malignant cases, no difference in outcome was found. In another study by Silecchia *et al*[32] was also manifested that laparoscopic splenectomy is associated with longer operating times, larger spleen size and a higher conversion rate, the intraoperative complications were fewer though. It is generally believed that an additional incision for removal of the intact specimen for histopathologic evaluation should be made in patients with malignancies, in order to keep the conversion rate low[29,33]. Alternatively, a HALS procedure should be used, which also results in low conversion and morbidity rates[34].

Splenic cysts

Nowadays the use of imaging studies is arising, and, along with the improvement of diagnostic tools such as abdominal sonography and computed tomography, has contributed to an increased incidence of splenic cysts which in the past remained undiagnosed. Splenic cysts can be classified in three large categories; infectious (abscess or hydatid cysts), nonparasitic (congenital or post-traumatic) or malignant ones. Nonparasitic cysts represent approximately 75% of splenic cysts[35] and are usually asymptomatic, therefore their true incidence can be higher, as the majority of cases remain undiagnosed or untreated. Rarely can nonparasitic cysts cause symptoms, mainly abdominal pain, fullness, nausea, vomiting, flatulence and diarrhea, and irritation of the left diaphragm followed by cough or pneumonia. It is believed that the presence of symptoms is due to the large size of cysts, usually greater than 5 cm, at which point it is unlikely that the cyst will resolve automatically, and rupture even with minor trauma is likely to occur[36]. Although a laparoscopic partial splenectomy is rarely indicated in adults[9], in cases of large nonparasitic cysts a partial splenectomy, cystectomy, or cyst decapsulation can be performed, preferably through laparoscopy[9], as this preserves the immunologic function of the spleen and therefore prevents the potentially fatal complication of postsplenectomy sepsis. In addition, laparoscopy seems to have better outcomes compared to open procedure in terms of postoperative morbidity[37]. Of course, this minimally invasive approach is associated with higher possibility of cyst recurrence[38]. In contrast to the asymptomatic course of nonparasitic cysts,

patients with infectious cysts, and especially splenic abscesses, may present with sepsis, and if they remain untreated, the mortality rate is high. Infectious cysts are usually produced from septic emboli from especially in a pre-installed sepsis or immunodeficiency conditions[39]. An open splenectomy is considered still the standard approach for treatment, mainly due to the need of an emergency procedure in a usually compromised patient; however, it has been shown that infectious cysts can be successfully managed with a laparoscopic procedure and/or conservative therapy[39-41]. The lower postoperative morbidity that a minimal invasive approach can offer is of high significance for the immunocompromised patients.

Finally, splenic artery aneurysms are relatively rare, with a prevalence of 0.04%[9] and commonly asymptomatic. Treatment of splenic aneurysms is indicated if the aneurysms become symptomatic, in women of childbearing age, in the presence of portal hypertension, before liver transplantation, if the diameter exceeds 2 cm, and in case of pseudoaneurysm formation, regardless of size[42-44]. Here interventional therapies are in first line; however if these therapies are not applicable, a laparoscopic removal of the aneurysm or a laparoscopic partial splenectomy has to be undergone[9].

Special considerations

Splenomegaly: Although splenomegaly was considered to be a contraindication for a minimally invasive approach, the evolution of the technology and the acquired experience of surgeons have allowed the use of laparoscopic splenectomy in many cases of splenomegaly. Therefore, it is strongly suggested that when the spleen is up to 1000 g (or its maximal diameter is up to 15 cm), it should be removed with the laparoscopic approach[9]. However, the laparoscopic technique is correlated with longer operative times, increased blood loss, higher conversion rates, more perioperative complications and longer total length of hospital stay[45]. For that reason, laparoscopic splenectomy in cases of splenomegaly should be performed by experienced surgeons. When the spleen size exceeds 1000 g the role of laparoscopy is controversial, as the working space in the abdominal cavity is significantly restricted, due to the spleen size, and preparation of the spleen as well as dissection around the splenic structures are burdensome, and finally the specimen cannot be removed easily. In these cases, especially when the maximal diameter of the spleen is longer than 19 cm, a HALS should be performed, for easier manipulation and removal of the organ[46]. Kaban *et al*[47] shown that when HALS is performed, a minimal invasive approach is feasible, with low conversion rates and few perioperative complications. Moreover lower operating times can be achieved through HALS[48]. Some studies have suggested that an interventional preoperative ablation of the splenic artery can reduce the size of the spleen, allowing for the completion of the operation laparoscopically[49], but this is

not well established. However, spleen weight over 2000 g (or maximal diameter > 23 cm) is considered to be a contraindication for laparoscopic splenectomy, and open laparotomy is preferable[9,50].

Trauma: A splenic rupture is often present in patients with blunt abdominal trauma. The management of splenic injuries has evolved considerably lately, so the classic explorative laparotomy and splenectomy, when needed, has given its place to interventional, nonoperative therapy. Splenic artery angio-embolization has been described as an alternative to operative management of splenic injuries. It is true that lower grades of injury correspond to higher success rates for this approach. However, nonoperative treatment in general fails to manage the rupture in up to 40% of all cases[51]. Unfavourable results of nonoperative treatment are mainly found in older patients (> 55 years), in patients with severe splenic trauma [Injury Severity Score (ISS) > 25], in patients in which the splenic injury is well manifested in imaging studies and in patients with evidence of hemoperitoneum in more than two recesses or in the pelvis[52,53]. In these patients, nonoperative treatment is associated with higher morbidity and mortality rates[54], therefore surgical treatment with splenorraphy or splenectomy should be done. It is widely accepted that when it comes to trauma, an open splenectomy is preferred; however there is a limited number of studies which describe a minimal invasive approach of splenectomy after trauma. This approach offers better detection and identification of possibly simultaneous diaphragmatic and visceral injuries[55], along with other general benefits of laparoscopy. Although it is not abundantly described, laparoscopic splenectomy for splenic injuries seems to be feasible, even though exploratory laparotomy remains the gold standard treatment. In a recent study by Ermolov *et al*[56], it has been shown that although a laparoscopic splenectomy for splenic injury was associated with significantly longer operating time compared to open splenectomy, patients after laparoscopy had better recovering conditions. The authors highlighted though that when a hemodynamic instability and high bleeding rate (> 500 mL/h on serial ultrasound examinations) are established, the laparoscopic approach should be avoided.

Portal vein hypertension: Portal hypertension is found usually in case of liver cirrhosis but it can be also the consequence of other pathologies. In an established portal hypertension, gastric varices usually coexist, therefore the risk of intraoperative hemorrhage is high[57]. Nevertheless, portal hypertension is not an absolute contraindication for laparoscopic splenectomy. In the study by Cobb *et al*[58], laparoscopic splenectomy was associated with significantly longer operative time (mean operative time 192 min), but acceptable intraoperative blood loss (mean 193 mL), and hospital length of stay (mean 3.5 d), showing that laparoscopic

splenectomy for Child A and B liver cirrhosis is feasible and safe. In addition, Hashizume *et al*[59] found that although a minimally invasive procedure in patients with portal hypertension had prolonged operative times and relatively significant intraoperative blood loss, the conversion rate was relatively low (4.1%), supporting that laparoscopic splenectomy is not only safe and feasible, but also should be considered as the procedure of choice. To date the role of laparoscopy in preexisting portal hypertension is not adequately established; therefore it is still suggested that patients with portal hypertension from liver cirrhosis should undergo an open splenectomy when needed.

SURGERY

In all patients scheduled for an elective laparoscopic splenectomy, the spleen size and volume should be preoperatively measured with an abdominal sonography. The acquired information can be very useful not only for planning the right approach, but also for diagnosing coexistent conditions, which should be intraoperatively evaluated (*e.g.,* cholelithiasis in patients with hereditary spherocytosis). As we mentioned above, patients with immune thrombocytopenic purpura or malignant diseases should undergo also a high-resolution computed tomography of abdomen, to detect any existing accessory spleens. In addition, in elective operations it is recommended that vaccination against *S. pneumoniae*, *H. influenzae* and *N. meningitidis* should be carried out preferably 15 d prior to surgery[9]. Of course vaccination can be performed also 10 d after the operation, especially when the patient is operated on an emergency basis[60]. Moreover it is recommended that patients with autoimmune thrombocytopenia and platelet count less than 20×10^9/L should be preoperatively treated with corticosteroids and/or immunoglobulins, in order to reduce intraoperative blood loss.

Positioning of the patient is a matter of debate. There are three patient's position described: anterior, hemilateral and lateral. Anterior position was the first one described[1]. At this position omental pouch and splenic hilum are well visualized. Moreover, in an anterior position, concurrent procedures (*e.g.,* cholecystectomy, biopsy) and conversion to open laparotomy (if required) can be easily performed[61]. However, anterior position has the disadvantage of moderate visualization and therefore dissection of the ligament structures and dorsal vessels and procedures in the area of splenic hilum could be burdensome, especially when the hilum is close to the pancreatic tail[62]. In hemilateral position the patient is positioned in the right lateral decubitus position at an angle of approximately 45°. Hemilateral position allows easy division of short gastric vessels and better access to the posterior surface of the spleen and perisplenic ligaments. Additionally, dissection and ligation of hilar vessels is easier, because pancreatic tail is spared[63]. Hemilateral positions is currently preferred by the majority of surgeons as it is widely adjustable

and provides better access to anatomic landmarks[63,64]. In lateral position, patient's abdomen is vertical to operating table. Here the dissection of ligaments and hilar landmarks is even easier than in other positions, thus an injury to the pancreas can be avoided[65]. In a series compared lateral *vs* anterior positions, lateral position was associated with shorter operative time, fewer perioperative and postoperative complications and shorter length of hospital stay[66]. Lateral approach has the disadvantage though, that a conversion to open laparotomy may require repositioning of the patient. Nevertheless, position of the patients depends on the surgeon's preference.

Standard laparoscopic approach

The operation begins with obtaining abdominal access, usually with an open cutdown technique, but the use of a Veress needle is also allowed, except for patients with massive splenomegaly, due to the high risk of injury. Regardless of checking for accessory spleens, it is recommended that before initiating splenic mobilization, diagnostic laparoscopy should be performed. Thereafter working trocars are placed; the placement depends mostly on surgeon's preference. In general, one trocar can be placed just off the midline/subxiphoid region in the left subcostal position and another one can be placed in the anterior axillary line in the left subcostal region. After mobilization of the splenic flexure, an additional trocar may be placed laterally off the tip of the 11th rib, as it may be highly assistive in cases of splenomegaly. Then posterior avascular attachments and short gastric vessels are divided and the spleen is retracted in order to obtain complete access to the splenic hilum and the pancreatic tail. The splenic hilum is then divided with an endoscopic stapler with a vascular load. Endovascular stapler provides easy and stable division of hilum[66]. After hilum division, hemostasis is ensured and staple line bleeding can be controlled with clips or hemostatic agents. At this point however, an injury of the pancreatic tail is possible, so when this procedure is not completely safe, the hilar vessels can be alternatively divided with an electrothermal bipolar vessel sealer or ultrasonic coagulating shears. These are reported to be safe, providing low blood loss and short operative time[67]. Now the spleen can be grasped by the handle of the splenocolic ligament placed into a strong bag. Here it is important to avoid spillage of splenic tissue, especially in patients with malignancies. The spleen is mainly removed morcellated, except cases where intact removal of the spleen is needed. A use of drainage is not recommended[9]; Delaitre *et al* has shown higher morbidity rates in cases when a drainage tube was placed[68]. Of course, when a pancreatic injury has occurred or is suspected, drainage is mandatory[9].

HALS

HALS is an alternative to laparoscopic splenectomy that combines benefits of both open and laparoscopic techniques. It is used in cases of massive splenomegaly that otherwise would not be amenable to a standard laparoscopic splenectomy and a conversion would be required. (craniocaudal length > 22 cm or width > 19 cm). HALS splenectomy can be used with the anterior, hemilateral or lateral postitioning. The essential difference between HALS and standard laparoscopy is that the surgeon's nondominant hand is inserted through hand-assist devices (in order to maintain the pneumoperitoneum) into the abdominal cavity. For that reason, an additional incision, not greater than 7-8 cm (or 1 cm less than the surgeon's glove size), should be performed in upper or lower midline or right abdomen, depending on the surgeon's preference, but generally the incision should be located 2-4 cm caudal to the inferior pole of the enlarged spleen. This technique facilitates the surgical procedure and especially the medial retraction, rotation, and elevation of the spleen. Moreover, intraoperative complications such as hemorrhage may be better controlled. The removal of the spleen in this way is easier, as with the hand the spleen is placed easier and faster in the strong bag and it is removed *via* the additional incision, usually without morcellation. It has been well reported that, as we mentioned above, HALS for patients with splenomegaly is associated with fewer intraoperative complications, lower conversion rate, shorted operative time and therefore significantly shorter total length of hospital stay[47,48,69]. Interestingly, although HALS involves an additional incision, the general benefits of laparoscopic procedures such as less postoperative pain and early resumption of the oral diet are succeeded, making this approach the best alternative for patients with massive splenomegaly (maximal spleen diameter > 22 cm)[70]; however patients with smaller spleen size should not undergo HALS[9,71,72].

Single-incision laparoscopic splenectomy

The rapid advance of technology has led to a struggle for an even more "scarless techniques". In that principle, single-incision laparoscopic procedures have been introduced, which have been tested successfully in various operations. Laparoscopic splenectomy has been also reported that can safely and successfully be done through a single incision, using a single port through which the working trocars are inserted in the abdominal cavity. The basic concepts of laparoscopy are also followed in single-incision laparoscopic splenectomy (SILS); an umbilical or periumbilical incision is made and a specific port system is applied; either 2 or 3 single ports through this incision only, or 1 single-incision port (*e.g.,* SILS™ port of Covidien, Mansfield, MA) are applied. Then the operation is continued just like standard laparoscopic splenectomy. Undoubtedly, a SILS is considered to be more technically challenging; Barbaros *et al*[73] compared SILS *vs* standard laparo-scopic approach in patients with ITP, and they found that operative time was statistically significant longer in SILS compared to standard laparoscopy, and the blood loss during SILS was also more. These technical difficulties

come as a result of the proximity of surgical tools, which are not specially designed for SILS. Nevertheless, SILS has almost the same conversion rate, morbidity and mortality rate as standard laparoscopy[74], and patients who underwent SILS seems to have less postoperative pain[73]. Further technological evolution and more experience on single-incision procedures can make SILS more popular.

OUTCOMES

Intraoperative complications

It is widely accepted that laparoscopic splenectomy is safe, however does not lack intraoperative complications. Bleeding is the main intraoperative complication, and the main reason to convert the operation to open. It usually comes as a result of injuries of the hilar or short gastric vessels, the splenic capsule, and/or splenic parenchyma during the surgical procedures and especially during the ligation of the vessels mentioned above, or during the dissection and ligation of the splenic hilum. When an intraoperative bleeding cannot be safely and promptly managed, conversion should be considered[9]. Through a converted to open approach bleeding is easily managed, however, the postoperative complications of every open procedure are found also here[75]. Laceration of adjacent organs and structures, especially the pancreas and gastric or diaphragmatic wall damage can occur. The incidence of these complications seems not to be associated with the experience of surgeons[9], however, an enlarged spleen may be responsible for technical difficulties which can lead to injuries. In a large review of possible complications after laparoscopic splenectomy by Chand *et al*[76] the incidence of pancreatic injury was 15%, which in most cases resulted in pancreatic fistula. Therefore, it is important to place a drainage tube when a pancreatic injury is suspected; otherwise it can be placed postoperatively through a CT-guided cannulation. As we mentioned above, a HALS in cases of splenomegaly can significantly reduce the incidence of injuries.

Postoperative complications

Early postoperative complications after laparoscopic splenectomy may include postoperative *bleeding*, subphrenic collections or abscess, deep vein thrombosis, thrombosis of the splenoportal axis, pneumonia and atelectasis, pancreatitis, ileus, abdominal wall infections, abdominal wall hematomas and abdominal wall hernias. These are treated according to general standards.

Special consideration should be made for portal or splenic vein thrombosis (PSVT)*,* which may occur even within months after surgery and can be proved lethal[77]. It is a potentially life-threatening complication that can occur within months after surgery. Consequences of PSVT are intestinal infarction/intestinal ischemia and portal hypertension. The incidence rate of PSVT reported varies, from 0.7%[78] to 14%[79], but it can

reach up to 80%[80]. It is unclear whether the minimal invasive approach is associated with high incidence of PSVT; nevertheless, there are some underlying diseases which are correlated with PSVT, these are myeloproliferative disorders, hemolytic anemia, hypersplenism or hematologic malignancy and splenomegaly[81]. Interestingly the bigger the size of the spleen, the higher the incidence of PSVT[80-82]. Diagnosis of PSVT may be challenging as its symptomatology is unspecified. Therefore it is recommended that patients with high risk of PSVT should receive postoperatively anticoagulation therapy as prophylaxis[9,83]. When the diagnosis of PSVT is secured, immediate anticoagulant therapy with intravenous administration of heparin should be started, in order to achieve best treatment outcomes[80].

Another splenectomy-associated postoperative complication is the overwhelming postsplenectomy infection (OPSI). OPSI is suspected when a patient after splenectomy presents with sudden systemic infection, occasionally dermatorrhagia and DIC, whereas no obvious site of the infection is present[84]. Although the pathogenesis of OPSI remains unclear, it has a fast, overwhelming onset. It starts as a simple respiratory infection, but it rapidly progresses to hyperpyrexia, headache, shivering, jaundice, anuria, septic shock, acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome (MODS), coma, and death. The primary pathogenic bacteria of OPSI are S. pneumoniae, N. meningitides, and H. influenza. In a prospective study by Theilacker *et al*[85] it was shown that S. pneumonia was the most important cause for severe sepsis development. They also showed that due to proper vaccination of patients after splenectomy, incidence of OPSI has been substantially reduced compared to the past. Although laparoscopic splenectomy is clearly superior to standard laparotomy in terms of postoperative infections, incidence of OPSI remains similar because this complication is related more to spleen removal than to the surgical approach[86].

CONCLUSION

Laparoscopic splenectomy has been established as a safe and feasible minimally invasive procedure. It can be used in almost all cases that a splenectomy is required, having in the majority of cases better results than open splenectomy in terms of intraoperative and postoperative complications. However, there are some special conditions, such as splenic trauma, in which the role of laparoscopy is not widely accepted. The evolution of the technology has allowed though, cases which were considered to be absolute contraindications for performing a minimal invasive procedure to be treated with modified laparoscopic approaches, such as the HALS for splenomegaly. The further improvement of laparoscopic tools as well as the increased experience of surgeons in minimal invasive procedures allows

lower operative times and conversion rates, along with less intraoperative complications, such as blood loss. Therefore it is strongly believed that laparoscopic splenectomy will become in the near future the standard procedures for almost all cases of splenectomy.

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Endoscopic diagnosis and treatment of early esophageal squamous neoplasia

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Abstract

Esophageal cancer is one of the leading causes of cancer-related death and is associated with high morbidity and mortality. It carries a poor prognosis as more than half of patients present with advanced and unresectable disease. One contributing factor is the increased risk of lymph node metastases at early stages of disease. As such, it is essential to detect squamous cell neoplasia (SCN) at an early stage. In order to risk stratify lesions, endoscopists must be able to perform image enhanced endoscopy including magnification and Lugol's chromoendoscopy. The assessment of both the horizontal extent and depth of any lesion is also of utmost importance prior to treatment. Endoscopic mucosal resection and submucosal dissection remain the standard of care with literature supportive their respective use. Radiofrequency ablation and other endoscopic treatments are currently available although should not be considered first line at this time. Our objective is to review the current options for the endoscopic diagnosis and treatment of esophageal SCN.

Key words: Esophageal squamous cell neoplasia; Image enhanced endoscopy; Esophageal squamous cell carcinoma; endoscopic detection; Chromoendoscopy; Endoscopic mucosal resection; Endoscopic submucosal dissection

Core tip: Esophageal squamous cell carcinoma is one of the leading causes of cancer death. Improving the detection of early stage lesions remains of utmost importance as these lesions can be cured with endoscopic therapy. Endoscopists have many advanced imaging modalities available to assist in risk stratifying lesions. Endoscopic mucosal resection and submucosal dissection remain the standard of care with literature supportive their respective use. Radiofrequency ablation and other endoscopic treatments are currently available although should not be considered first line at this time. As we await improved endoscopic technologies, endoscopists everywhere must remain vigilant in their endoscopic evaluation of the esophagus during each and every endoscopy performed.

INTRODUCTION

Esophageal cancer is one of the leading causes of cancer-related death and is associated with high morbidity and mortality[1,2]. There are two predominant histologic types of esophageal cancer; squamous cell carcinoma (SCC) and Barrett's esophagus related adenocarcinoma. The incidence of SCC is higher along two geographic belts, one from North-central China through central Asia to Northern Iran, and the other from Eastern to Southern Africa. Despite the predominance of esophageal ade-nocarcinoma in Western countries, SCC remains the most common subtype worldwide. It carries a poor prognosis as more than half of patients present with advanced and unresectable disease[3]. One contributing factor to this phenomenon is the increased risk of lymph node metastases at early stages of disease. While the risk of lymph node metastases is almost zero for EP (intraepithelial) and LPM (lamina propria) lesions, the risk increases to 8%-15% for lesions invading into the muscularis mucosa (MM), 11%-53% for lesions invading SM1 (submucosal layer to 200 μm or less) and 30%-54% for SM2 and deeper lesions[4-7]. For patients with adenocarcinoma confined to the MM however, the rate of lymph node metastases ranges from 0%-4% and has been estimated at 15%-25% for those with submucosal invasion[8-10]. With data showing a higher risk of lymph node metastases in SCC, detecting squamous cell neoplasia (squamous high grade intraepithelial neoplasia, HGIN, and early SCC) at an early stage becomes extremely important with subsequent inter-ventions that can improve patient outcomes.

The objective of this article is to review the current options for the endoscopic diagnosis and treatment of esophageal squamous cell neoplasia (SCN).

ESOPHAGEAL SCC

Esophageal SCC is most prevalent in the sixth and seventh decades; with a male to female ratio of 3:1[11]. Known risk factors include regular alcohol consumption, smoking, aldehyde dehydrogenase type 2 deficiency, low fruit and vegetable intake, selenium, zinc, and vitamin E deficiency, high exposure to areca nuts and polycystic aromatic hydrocarbons and poor oral hygiene. Caustic injuries, tylosis, achalasia, and human papillomavirus (HPV) infection are other known risk factors[3,12-15]. As well, the risk of developing synchronous and/or metachronous lesions is high in patients with a history of head and neck and esophageal SCC. All of the aforementioned risk factors must be considered when determining who may benefit from screening.

There is currently no globally accepted endoscopic screening program for esophageal SCC. This is in spite of an improved understanding of the risk factors. The data in support of screening is not as robust as for Barrett's esophagus and the detection of Barrett's associated dysplasia. Studies on endoscopic surveillance for high-risk patients with histories of head and neck cancer have shown that it is feasible and effective[16-18]. A recent study from China revealed that endoscopic screening and intervention significantly lowered mortality caused by esophageal SCC[2]. Wei *et al*[2] compared the incidence and mortality of esophageal SCC in two communities (endoscopic screening *vs* control). In the intervention group, detected lesions were treated according to their respective stages. Although there was an initial increased incidence of SCC in the intervention group, likely related to the effect of screening, the cumulative incidence (over the full ten year follow-up period) of esophageal SCC in the screened group became lower than in the control group (4.2% *vs* 5.9%, respectively, *P* < 0.01). A reduction in cumulative mortality was seen in the intervention group (3.35% *vs* 5.05% respectively, *P* < 0.001). This study supports the notion that screening (and subsequent intervention) can lead to a reduction in the incidence of and mortality from esophageal SCC.

ENDOSCOPIC DETECTION

Endoscopic screening/detection is performed by using a combination of conventional and high-definition white light imaging (WLI), Lugol's chromoendoscopy (CE), and image-enhanced endoscopy (IEE). The detection of early lesions with WLI can be challenging since the mucosal abnormalities present are often difficult to observe. The features used to detect dysplasia using WLI include the disappearance of the mucosal vascular network, nodular surface, subtle white coating, and erythema. The endoscope should be maneuvered slowly and carefully to allow for a thorough assessment of the entire esophagus paying special attention to commonly missed areas on the right lateral wall and in the narrow cervical esophagus. Observation using moderate insufflation is recommended as excessive insufflation may make it more difficult to identify flat lesions. Lao-Sirieix *et al*[19] showed that the sensitivity and specificity of WLI for the detection of severe dysplasia or cancer was 62% and 79% respectively. One must also pay close attention to the oropharynx when inserting the gastroscope, especially in patients known to have esophageal squamous neoplasia given the high risk of synchronous lesions. A recent study showed that 8.6% of patients followed over the 2-year study period were found to have metachronous head and neck SCC even after treatment of their esophageal SCC[20]. Asking patients to perform a valsalva maneuver can be considered to facilitate clear visualization of the hypopharyngeal area.

Figure 1 **Chromoendoscopy with Lugol's iodine.** A: Unstained area seen within the marking after spraying diluted Lugol's solution with spray catheter; B: After observing for several minutes, the unstained area turned into pink color, suggesting HGIN and squamous cell carcinoma.
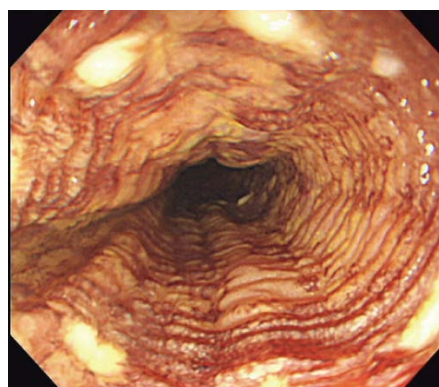

Figure 2 **"Tatami sign" is commonly seen after iodine staining.** It is characterized by regular, fine circular folds of the Lugol's unstained area. This is typically seen when lesions are confined to the muscularis mucosal.

Chromoendoscopy with Lugol's iodine has become the standard of care for the detection of esophageal SCC and synchronous lesions as well as defining the extent of lesions. Lugol's iodine adheres to the glycogen of normal squamous epithelium leading to staining. Neoplastic lesions lack glycogen and therefore remain unstained. A thorough examination with Lugol's CE includes an assessment for the following: (1) pink color sign (PC sign): This finding can be seen following Lugol's staining where unstained areas change to a pink color after 2-3 min. While not well understood, it is thought that this phenomenon is most likely related to an absence of the keratinous layer[21]. This finding can be used to distinguish HGIN and SCC from LGIN, inflammation, and epithelial atrophy and has been shown to have high diagnostic accuracy with a 91.9% sensitivity and 94.0% specificity[22] (Figure 1); (2) tatami sign: This is the pattern commonly seen after iodine staining and is named after "Tatami", a type of mat used as flooring material in traditional Japanese rooms. This is seen as regular, fine circular folds of the unstained area. This occurs with lesions invading no deeper than the MM[23] (Figure 2); and (3) multiple iodine unstained areas: This is a frequent finding seen in patients with esophageal SCN and is also known as "leopard-skin appearance". This finding implies a high risk of synchronous lesions and/or metachronous recurrence[24]. A recent study following patients for

2 years after treatment of esophageal SCC revealed that 24.7% of patients who had 10 or more Lugol's unstained areas developed metachronous SCC[20].

By picking up on the above findings with Lugol's CE, lesions requiring endoscopic treatment can be identified. However, there are some disadvantages to using it. Firstly, staining with Lugol's iodine is known to cause retrosternal chest discomfort and carries a risk of allergic reaction. Secondly, the aforementioned finding of unstained areas has been shown to have high sensitivity but low specificity for detecting HGIN and early SCC. Finally, re-epithelialization after mucosal damage, often caused by the chemical esophagitis from Lugol's staining, may obscure delineation of lesions when performing subsequent endoscopic resection[25]. To overcome some of these concerns, less concentrated Lugol's solution with concentrations of 0.5%-1% or less (vs 3% traditionally) are now used to reduce mucosal irritation. In addition, spraying 20 mL of 20% sodium thiosulfate solution (STS; 10% Detoxol, Banyu Pharmaceutical Co. Ltd., Tokyo, Japan) can be performed to neutralize the Lugol's iodine solution[26]. Aspiration of the residual Lugol's iodine from the stomach also minimizes mucosal irritation.

IEE augments the detection, diagnosis and treatment of esophageal SCN. Narrow-band imaging (NBI) (Olympus, Japan), Pentax I-Scan (Pentax, Japan), and the Fujinon Intelligence Colour Enhancement system (FICE, Fujinon Corporation, Japan) are frequently applied electronic-based endoscopic modalities that target the microvessels of the mucosa. Although all of the above can be utilized to detect early esophageal SCN, narrow-band imaging (NBI) is used most commonly. It uses specific blue and green wavelength light to illuminate blood vessels more distinctly in comparison to WLI. Non-magnification NBI (NM-NBI) allows endoscopists to recognize esophageal SCN as brownish areas (Figure 3). In Japan, it is standard to utilize IEE during the observation of the oropharynx and esophagus during endoscope withdrawal. As opposed to Lugol's CE, using IEE is safe and easily performed with the push of a single button on the endoscope.

Figure 3 Brownish areas seen under non-magnifying narrow-band imaging can be seen with inflammation, low-grade and high-grade intraepithelial neoplasm, and squamous cell carcinoma.

White-light imaging vs image enhanced endoscopy vs Lugol's chromoendoscopy

A multicenter, prospective, randomized, controlled trial conducted in 2010 comparing WLI and NM-NBI revealed a significantly higher detection rate of small (< 5 mm), early SCC lesions with NM-NBI when compared to WLI[27]. Nagami *et al*[28] compared NM-NBI and Lugol's CE in 202 patients with risk factors for esophageal SCC. The operating characteristics of NM-NBI were superior to that of Lugol's CE as the accuracy, sensitivity, and specificity of NM-NBI were 77.0%, 88.3%, and 75.2% respectively, compared with 68.0%, 94.2%, and 64.0% respectively for unstained areas detected by Lugol's CE. This study was limited, however, by the fact that the authors did not incorporate the pink color sign into their assessments. Goda *et al*[29] conducted a randomized, non-inferiority trial comparing ME-NBI to the PC sign seen on Lugol's CE. They found no sig_nificant differences between these two techniques. ME-NBI showed a significantly shorter examination time with similar accuracy, however was less reliable in patients with multiple Lugol's unstained areas. As such, the optimal use of these modalities remains unclear. We recommend that a standard scr-eening endoscopy should include WLI and NM-NBI. When mucosal changes are seen on WLI or brownish areas identified on NM-NBI, ME-NBI or Lugol's CE should be considered for further assessment.

Lateral margin assessment

After detecting a lesion, it is important to delineate the lateral extent of the lesion in order to achieve R0 resection. This is accomplished *via* careful inspection with a combination of WLI, IEE, and Lugol's CE[30-32]. Typically, the assessment of lateral extent is done with Lugol's CE. It is important to keep in mind that if the preoperative assessment is done with Lugol's CE, it may cause chemical esophagitis resulting in re-epithelialization thereby complicating the demarcation of tumors at the time of endoscopic treatment[25]. As such, there is a theoretical advantage to performing Lugol's CE and endoscopic resection during the index endoscopy and/or using IEE alone (without Lugol's CE) to examine the lateral margins of a lesion.

Depth assessment

After detecting esophageal SCN, it is of utmost importance to predict a lesion's depth of invasion to determine if endoscopic resection is possible. Such assessment begins with WLI and the use of the Paris classification[33]. Paris 0-IIa, 0-IIb, 0-IIc lesions, which are flat or slightly elevated/depressed lesions, are generally confined to the EP and LPM. Slight color change with redness and irregular elevation/depression raise the possibility of deeper invasion into the MM and SM1. If the lesion has a large, broad-based protrusion, crater, and/or stiffened wall, the lesion likely invades deeper. A majority of protruded (Paris classification 0-I) and/or excavated (0-III) lesions usually represent invasion into the submucosa or deeper. A recent multicenter, prospective study showed that the accuracy of invasion depth using WLI alone was 71.4%. The sensitivity and specificity for MM lesions was 61.1% and 77.4% respectively[34].

Recently, ME-NBI has been utilized to assess lesion depth. This allows for the assessment of the surface capillary microvasculature or intraepithelial papillary capillary loop (IPCL), a superficial fine vascular network of the esophageal mucosa. Attention should be made to the four signs of abnormal vessels which include dilatation, tortuosity, caliber change, and non-uniformity. The IPCL is known to change morphologically depending on the severity of structural irregularities in the eso-phageal mucosa. The Japanese Esophageal Society has developed a simplified magnifying endoscopic classification for estimating invasion depth based on the degree of irregularity of the microvascular morphology[35]. The microvessels are classified into two main categories; Type A or B. Microvessels are considered Type B vessels when all four features of abnormal IPCL (dilatation, tortuosity, caliber change, and non-uniformity) are seen. Type B can be further sub-classified into B1, B2, and B3. B1 vessels can be seen as dot-like microvessels under NM-NBI or low magnification ME-NBI (Figure 4). B2 vessels can be recognized as stretched and markedly elongated microvessels. B3 vessels are dilated and abnormal vessels (Figure 5). When type B1, B2, B3 microvessels are identified on ME-NBI, the extent of invasion is likely into the EP-LPM, MM-SM1, and SM2 or deeper, respectively. Goda *et al*[36] reported that ME-NBI could differentiate intramucosal cancer from submucosal cancer with a sensitivity and specificity of 78% and 95% respectively. On the other hand, a recent multicenter, prospective study showed no additional benefit of adding ME-NBI to WLI for the assessment of invasion depth[34].

Endoscopic ultrasound (EUS) is another modality used to assess the depth of invasion of esophageal SCC. Its utility is to rule out invasion into the muscularis propria and detect regional lymphadenopathy. A meta-analysis reported that among patients with T1 disease, EUS had a pooled sensitivity in differentiating T1a and

Figure 4 Abnormal intraepithelial papillary capillary loop, a superficial fine vascular network of the esophageal mucosa. Type B1 vessels, shown here, are identified as dot-like microvessels under non-magnifying narrow-band imaging or low magnified ME-NBI.

Figure 5 Abnormal intraepithelial papillary capillary loop. Type B2 (black arrow) can be recognized as stretched and markedly elongated microvessels *vs* type B3 (white arrow) microvessels which are highly dilated, abnormal vessels.

T1b lesions of 84% and 83%, and a specificity of 91% and 89%. For T4 lesions, EUS had a pooled sensitivity of 84% and specificity of 96%. The overall accuracy of EUS for T-staging was 79% and 71% for N-staging[37]. In spite of its limitations (time, expertise required, expense and resolution), EUS is currently considered a standard modality used in the evaluation of lesion extent and regional lymphadenopathy. CT scan and PET-CT scan are adjunct modalities that should be considered in the evaluation of regional lymphadenopathy[32].

Other diagnostic modalities

There are other emerging advanced diagnostic imaging modalities such as confocal laser endomicroscopy (CLE) and optical coherence tomography (OCT) that may play a role in screening and/or diagnosis of SCC. Probe-based confocal laser endomicroscopy (pCLE) allows for real-time *in-vivo* histologic imaging of the esophagus. Its use has been shown to improve the detection of BE-associated dysplasia when compared to WLE alone[38]. Although there are proposed diagnostic criteria for the detection of squamous epithelial cells with pCLE (irregular arrangement, increased diameter, irregular shape and long branching of the IPCL), the diagnostic accuracy of pCLE is not well known[39]. pCLE is limited by its imaging depth and field of view and thus standard imaging with WLE and chromoendoscopy is required for detecting lesions. Recently, Guo *et al*[40] described the diagnostic value of pCLE for esophageal SCN. The authors reported high sensitivity, specificity, and accuracy of pCLE for SCN as 94.6%, 90.7%, and 92.3% respectively. In the other recent study comparing ME-NBI and probe-based CLE, pCLE possessed higher specificity and accuracy[41].

Volumetric laser endomicroscopy, a second-generation optical coherence technology, is an advanced, non-invasive imaging modality that uses infrared light to produce real-time high-resolution cross-sectional images of the GI tract. Its resolution (10-20 μm) is extremely fine approaching that of histopathology. This technology has been applied to the detection of Barrett's esophagus

related dysplasia in clinical practice[42-44]. For esophageal SCC, it has been reported to be useful in assessing tumor invasion depth. Hatta *et al*[45] utilized OCT for pre-operative staging with a high overall accuracy rate. Its ability to select lesions for endoscopic resection was significantly better than EUS (94.6% *vs* 80.6%, *P* < 0.05). OCT is limited by its inability to accurately detect dysplasia and therefore requires further study, like pCLE, before it can be incorporated into clinical practice. In addition to the aforementioned limitations, we have futher concerns with respect to cost effectiveness, acquisition of expertise in image interpretation and indication standardization that may limit widespread use.

TREATMENT OF ESOPHAGEAL SQUAMOUS CELL NEOPLASIA

Traditionally, esophagectomy and lymph node dissection have been the standard of care for the treatment of esophageal cancer including early esophageal SCC. However, the paradigm has shifted to less invasive therapy with improved techniques in endoscopic resection. There are two widely accepted endoscopic resection methods: Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). These are indicated when there is minimal to no risk of lymph node metastases.

EMR

EMR has been widely accepted as a safe and effective treatment for early esophageal SCC. Cap-assisted mucosectomy (EMR-C) and EMR-ligation (EMR-L) are the two methods of performing EMR. A randomized trial comparing EMR-L with multiband mucosectomy (MBM) and EMR-C for endoscopic piecemeal resection of large SCN (2-6 cm, maximum 2/3 of esophageal circumference) has been conducted[46]. Both methods were highly effective and safe, however EMR-L with MBM was faster and less expensive. Although large lesions can be treated with piecemeal EMR, this

technique is limited by its inability to achieve oncologic (R0) resections. In the aforementioned study, a high local recurrence rate was seen in lesions exceeding 2 cm and in lesions subject to piecemeal resection in five or more pieces. The optimal size for EMR is still debatable. To overcome the limitation of piecemeal resection, endoscopic submucosal dissection (ESD) has become the treatment of choice for *en bloc* resection of larger lesions.

ESD

ESD was initially introduced in the 1990s to allow *en bloc* resection with detailed pathological assessment regardless of lesion size[47]. This method spread rapidly as it optimized the rate of *en bloc* resection in gastric and colonic lesions. Yet, ESD is known to be more time consuming and associated with higher rates of complications such as bleeding and perforation. This is especially true in the esophagus. Esophageal ESD is technically more challenging than gastric ESD due to a narrower lumen thus limiting endoscopic maneuvers. Movement due to heartbeat and respiration are other factors making this technique more challenging. Moreover, the esophagus has a thin muscle wall and an absence of serosal fat leading to higher perforation rates. Previous literature in Japan has shown that ESD in the esophagus has a high *en bloc* resection rate (95%-100%), a low local recurrence rate (0%-1%), and is a relatively safe procedure with perforation occurring in 0%-6% of cases. However, most early studies were limited by small sample sizes and short follow-up. Tsujii *et al*[48] recently reported clinical outcomes of ESD in a multicenter, retrospective, cohort study. A total of 368 superficial esophageal neoplasms in 307 patients were treated by ESD at 11 hospitals. The *en bloc* resection and complete resection rates were 96.7% and 84.5% respectively. Perforation, bleeding and esophageal strictures occurred in 5.2%, 0%, and 7.1% of patients, respectively. All complications were successfully managed conservatively[48]. More recent studies show an *en bloc* resection rate between 83%-100%, R0 resection rate between 78%-100% and local recurrence rates of 0%-6%[49-57]. The experience of Western endoscopists with ESD in esophageal SCC was recently published. Probst *et al*[58] reported the outcome of 24 SCC undergoing ESD resulting in *en bloc* resection in 100% and R0 resection in 91.7% of the cases. Disease-specific survival was 95.8% and overall survival was 66.7% over a mean follow-up period of 38 mo[58].

EMR vs ESD

Although there is ongoing debate as to what size lesions should be resected by ESD *vs* EMR, the European Society of Gastrointestinal Endoscopy (ESGE) recommends endoscopic *en bloc* resection for superficial esophageal SCC without obvious submucosal involvement. EMR may be considered for lesions smaller than 20 mm if *en bloc* resection is feasible. If not, ESD should be performed. According to the Japanese Esophageal Society, absolute

indications for endoscopic mucosal resection are: flat intramucosal cancers confined to the epithelium and lamina propria that occupy less than 2/3 of the circumference of the lumen of the esophagus. Relative indications include cancers involving the muscularis mucosa or < 200 μm of invasion into the submucosa, and lesions extending more than ¾ of the circumference of the lumen[59].

The literature comparing these two methods is scant. Ishihara *et al*[60] analyzed the outcomes of EMR and ESD in 171 superficial esophageal SCC's less than 20 mm in diameter. For lesions less than 15 mm, there was no difference in local recurrence, R0 resection, and *en bloc* resection concluding that EMR is feasible for treating lesions this small. Recently, another retrospective study compared the efficacy and safety of EMR-L using MBM and ESD. They found no statistical difference in the rate of complete resection between the two methods. For lesions over 15 mm however, ESD had a significantly higher rate of *en bloc* (100%) and curative resection (92.3%) compared to MBM (44.8 and 41%, *P* < 0.05). As expected, ESD procedure times were longer (84 ± 35 min *vs* 38 ± 11 min). In addition, ESD had higher rate of major bleeding (16.7% *vs* 1.85%) and perforation (8.3% *vs* 0%). As such, EMR appears safe and effective for the treatment of lesions 15 mm or smaller leaving ESD as the treatment of choice for larger lesions[61].

Post-endoscopic resection strictures

One of the major complications of endoscopic resection for large SCN is esophageal stricturing, which can severely affect patients' quality of life. Treatment related strictures requiring multiple sessions of endoscopic dilation can occur when resecting lesions involving over half of the esophageal circumference. Lesions greater than or equal to 3/4 of the circumference of the lumen are strongly associated with stricturing[62,63]. In addition, muscle layer damage and defects larger than 5 cm after circumferential ESD were significant factors associated with refractory stenosis[64]. Typically, steroids injected locally and/or taken orally are used to prevent post-ESD strictures for lesions involving over 3/4 of the esophageal circumference. There are differences in the timing of administration, route of administration (local *vs* oral), and the dosages among institutions. The most common strategy in Japan is to inject triamcinolone into the base of the post-ESD ulcer directly post-procedure or on post-procedure day one. With the prevalence of this complication, more studies are needed to further elucidate the ideal prevention strategies post-endoscopic resection.

Post-endoscopic resection therapy

Treatment post-endoscopic resection is determined based on the pathological evaluation of the resected specimen. No additional treatment is required for EP and LPM lesions with no lymphovascular invasion as the probability of lymph node metastases approaches

0%. Although MM and SM1 lesions have a risk of lymph node metastases, most can be predicted based on the presence of lymphovascular invasion or poor differentiation in the resected specimen. In 2011, Moriya *et al*[65] showed that well-differentiated MM and SM1 tumors without lymphovascular invasion had minimal risk of lymph node involvement. Therefore, close follow-up is acceptable for such lesions. Surgery and/or chemoradiation should be considered for lesions with lymphovascular invasion or SM2 or deeper involvement. The 5-year overall survival rate for patients with EP, LPM, MM, and SM cancers is 90.5%, 71.1%, and 70.8% respectively[66]. As mentioned, it is very important to consider the risk of metachronous lesions in patients with esophageal SCC and therefore, close endoscopic surveillance is needed.

Radiofrequency ablation

Radiofrequency ablation (RFA) has emerged as the ablative technique of choice for Barrett's esophagus related dysplasia. Since a multicenter, randomized, sham-controlled study demonstrated decreased disease progression to malignancy along with high rates of dysplasia and intestinal metaplasia eradication, RFA has been used to treat BE in patients with HGD[67]. However, the role of RFA in squamous neoplasia remains unclear. RFA involves the direct application of thermal energy to the targeted area using either a balloon for circumferential treatment (HALO360; BARRX, Sunnyvale, California, United States), a probe attached to the scope (HALO90, HALO60, HALO-ultra; BARRX) or a through-the-scope catheter for focal therapy (Channel Catheter; BARRX). The clear benefit and role of radiofrequency ablation in SCN has not yet been proven. There are reports with small patient populations describing a possible role for RFA in early esophageal SCN[68-70]. The largest study consists of a total of 96 patients including 42 patients with HGIN and 9 with early SCC. At 3 and 12 mo post-RFA treatment, 73% (70/96) and 84% (81/96) showed an absence of dysplasia and SCC (considered a complete response). Two patients progressed in spite of RFA (MGIN to HGIN and HGIN to SCC respectively) however both were treated endoscopically and achieved complete response with additional ablations. Strictures occurred in 20 patients (21%), all of whom underwent circumferential RFA. Lugol's CE with RFA (12 J/cm^2, single application, no cleaning) was the favored baseline circumferential RFA technique. In patients with SCN, RFA appears to be associated with a high response rate and an acceptable safety profile[70].

The clear disadvantage of ablative therapy is that no tissue is obtained for histopathological assessment. Proper staging and risk stratification with various endoscopic techniques described above must be done prior to treatment to appropriately select patients thereby avoiding treatment failures. On the other hand, there may be a role for RFA in cases where endoscopic resection is challenging. The feasibility of RFA for treating early SCC on or adjacent to esophageal varices

was recently reported. While this study was limited to only 8 patients (5 HGIN and 3 SCC), 6 patients achieved complete response after a single circumferential treatment. All achieved a complete response at 12 mo with further focal ablation therapy. Although there is data revealing that RFA is both safe and efficacious, it should only be considered when the lesion is deemed to be non-invasive. Currently, endoscopic resection with histological evaluation should be the first choice and we believe that we should be conservative on applying RFA to squamous cell neoplasia. We need more studies regarding safety and efficacy of RFA in squamous cell neoplasia.

Other ablative therapies such as photodynamic therapy (PDT), argon plasma coagulation (APC) and Nd: YAG laser have been discussed in the literature[71-74]. Recently, PDT was described as a palliative or less-invasive salvage treatment option for local failure after chemoradiotherapy (CRT). Retrospective analysis of 130 patients treated with PDT for local failure (T2 lesions without metastases) after CRT was performed[75]. The complete response rate, progression-free survival and the overall survival rates at 5 years after salvage PDT were 58.4%, 22.1% and 35.9% respectively. The treatment-related death rate was 1.8%. APC is another ablative therapy used to safely treat lesions that are not endoscopically resectable and to control the recurrence after endoscopic resection or chemoradiotherapy[76]. However, the literature supporting this technique is lacking.

CONCLUSION

Esophageal SCC remains one of the leading causes of cancer death. Improving the detection of early stage lesions remains of utmost importance as these lesions can be cured with endoscopic therapy. With improvements in advanced imaging modalities, we will better be able to detect, assess, and treat lesions at earlier stages. As we await improved endoscopic technologies, endoscopists everywhere must remain vigilant in their endoscopic evaluation of the esophagus during each and every endoscopy performed.

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Laparoscopic resection of gastrointestinal stromal tumors: Does laparoscopic surgery provide an adequate oncologic resection?

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of the GI tract. Surgical resection remains the mainstay of non-metastatic disease. However, the ability to provide an adequate oncologic resection using laparoscopic surgery is still an area of debate. This is a thorough review of the current literature, looking particularly at the use of laparoscopic surgery for larger GISTs and the long-term oncologic outcomes compared to the results of open surgery. Laparoscopic resections provide an adequate oncologic result for GISTs of all sizes, including those greater than 5 cm in size.

Key words: Gastrointestinal stromal tumors; Oncologic; Laparoscopy; Surgery

Core tip: Laparoscopy is now increasingly being used in cases of gastrointestinal stromal tumors (GISTs). While technically possible to resect these tumors laparoscopically, there has been concern that the oncologic outcomes for these patients could be compromised for tumors greater than 5 cm in size. This review, summarizing the data from several studies, demonstrates that a proper oncologic resection can be achieved laparoscopically, even for larger GISTs.

Abstract

Gastrointestinal stromal tumors (GISTs) are rare tumors

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are rare tu-

mors of the gastrointestinal (GI) tract but are the most common type of mesenchymal tumor found in the GI tract. They account for between 0.1% to 3% of gastrointestinal malignancies with an incidence of 14 to 20 cases per 1 million of the general population per year[1-4]. Treatment has not been standardized; however, surgical resection remains the mainstay for non-metastatic GISTs. Furthermore, the use of minimally invasive techniques has been widely debated. Because of the low incidence of GISTs, published reports have been primarily limited to case reports and retrospective observational studies with no good randomized controlled trials encountered in the literature. This review examines the efficacy of laparoscopic surgery to achieve a proper oncologic resection for GISTs as compared to open while looking at different factors such as the biology, location and size of these tumors.

BIOLOGY OF GIST

The term GIST was originally coined by Mazur and Clark[5] in 1983 and became more frequently diagnosed around the turn of the century. GISTs were historically classified as leiomyomas, leiomyosarcomas, or leiomyoblastomas but with advancements in immunochemistry and the discovery of the tyrosine kinase KIT, GIST tumors have been identified as a separate entity from leiomyomas and its diagnosis has increased 25-fold[1].

GISTs are equally distributed between men and women. While they have been found in patients of all ages, the majority are found in patients between the ages of 40 and 70 with the median age of diagnosis between 60 and 65 years of age[6-8]. GISTs can be found throughout the GI tract with the most common location in the stomach (60%-70%), followed by the small intestine (20%-30%), duodenum (4%-5%), rectum (4%-5%), colon (< 2%), esophagus (< 1%)[3,7,9-11]. They are found and even more rarely outside the GI tract, including the mesentery, omentum, and retroperitoneum.

Originating from the interstitial cell of Cajal, the majority (70%-85%) of GISTs are associated with mutations in the c-KIT pathway and stain positively for CD117. The second most common mutation seen (approximately 10%) is with *PDGFRA* and the two gene mutations are mutually exclusive. Through these mutations, abnormally oncologic signaling is promoted through the mitogen-activated protein kinase (MAPK) and phosphoinositide-3-kinase (PI3K) pathways[11]. In general, these tumors do not spread *via* submucosal invasion or lymphatics. Rather, their spread is mostly expansive and the main routes of metastasis are hematogenous. Chromosomal abnormalities in GISTs that have been associated with malignant progression include deletions on 14q, 22q, 1p, and 9p and gains on chromosomes 8q and 17q[11]. Tumors associated with these alterations are likely to be metastatic in nature and less amenable to resection, either open or

laparoscopic at time of surgery.

DIAGNOSIS OF GISTS

The presentation of a patient with a GIST can be quite variable, based on its location and size. The most common presentation is a GI bleed followed by abdominal pain. These GI bleeds are more often chronic than acute. Other rarer symptoms and signs include anemia, a palpable mass, dysphagia, obstruction, or weight loss[12]. However, a significant number are discovered incidentally on imaging performed for other reasons.

In a review of diagnostic modalities, Scarpa *et al*[12] proposed endoscopy as the first diagnostic tool in the algorithm to diagnose a GIST. On pooled analysis, endoscopy with mucosal biopsy, however, had a diagnostic yield of 33.8%. This is not surprising, given the submucosal nature of GISTs. The diagnostic yields of computed tomography (CT) and magnetic resonance imaging (MRI) were both much higher, at 73.6% and 91.7% respectively ($P = 0.07$). Between the two, CT is usually the first non-invasive imaging modality used due to its cost, ubiquity, and consistency. On CT, a GIST usually enhances with intravenous contrast and has smooth contours. While most GISTs appear solid, larger GISTs can develop areas of necrosis or hemorrhage and appear more complex. CT can also evaluate the abdomen for metastatic disease. MRI can be used as an adjunct if the mass is large and abutting other structures, as it may better demonstrate planes of dissection.

While CT and MRI have excellent diagnostic yields, the most definitive diagnosis can be obtained using an endoscopic ultrasound with fine needle aspiration (EUS-FNA). The diagnostic yield of simple EUS was 68.7%, which was significantly improved with the addition of an FNA during the procedure (84.0%) ($P = 0.01$)[12]. If there is a high suspicion for GIST based on CT or MRI, and the lesion appears resectable, a tissue diagnosis is not required. However, a biopsy can be used to confirm the diagnosis if there appears to be metastatic disease or in large, locally advanced lesions that may benefit from preoperative treatment with imatinib.

LAPAROSCOPIC RESECTION OF GISTS

Historical perspective
The multidisciplinary management of GIST has changed over time. With further research into the molecular biology of these tumors, there has been development of better treatments for advanced GISTs, including imatinib and newer therapeutic agents such as sunitinib and regorafenib[1,13-15]. Despite these advancements, the accepted management of non-metastatic GIST remains surgical resection.

The advent of minimally invasive surgery has affected how many procedures are being performed. With the generalized advantages of decreased pain, shorter

hospital stay and faster recovery to normal activity, laparoscopic surgery is fast becoming the standard of care for many procedures. One area of contention with minimally invasive surgery is its use in oncologic procedures. There has been extensive research in colon cancer that has shown that a laparoscopic approach can be safe and produce a safe oncologic margin. Similarly, lung cancers are routinely resected thoracoscopically. In other cases, such as low rectal cancer requiring abdominoperineal resection, the debate still continues whether a laparoscopic approach is as efficacious and provides as good an oncologic result as an open procedure. Because GISTs are a relatively newly identified entity and a rare neoplasm, there has been little consensus on the role of minimally invasive techniques in their resection.

Unresectable and metastatic GISTs are usually very aggressive and often fatal with a median survival of approximately 6-18 mo[16]. In 2002, Fletcher *et al*[17] proposed a risk stratification classification for recurrence based on tumor size, mitotic rate, and tumor location. This was updated in 2006 by Miettinen *et al*[18] and accepted by the National Comprehensive Cancer Network (NCCN) Task Force report in 2010[19]. Because chemotherapy and radiotherapy are ineffective in treating GISTs, imatinib is the only approved agent for unresectable/metastatic GIST at this time. With the poor prognosis of metastatic and recurrent GISTs, it is vital that a good oncologic procedure be completed at the time of resection.

The surgical management of GIST has changed significantly since Lukaszczyk and Preletz[20] reported the first laparoscopic removal of a gastric GIST found incidentally during a cholecystectomy. Since then, others have explored the use of laparoscopy for GIST removal. Although there is still no consensus on the role of minimally invasive techniques in their resection, the biological behavior of these tumors lend themselves to laparoscopic resection. Because submucosal and lymphatic invasion is rare, local excision rather than formal organ resection has become the treatment of choice for GISTs which allows laparoscopic resection to be an attractive alternative to more invasive conventional surgery. Historically, wide resection margins were advocated but there has been no correlation with improved survival or recurrence[21]. Therefore, wide margins and lymph node dissections are not necessary. The consensus is that a negative gross surgical margin is the important factor in decreasing the risk of local recurrence and metastatic spread of GISTs.

However, in 2004 the National Comprehensive Cancer Network and The European Society of Medical Oncology released consensus statements recommending that the use of laparoscopy be limited for GISTs less than 2 cm in size due to concerns of tumor rupture and seeding of the peritoneum and the ability to achieve an adequate oncologic margin[19,22]. Despite these concerns, surgeons continued to resect GISTs laparoscopically with excellent results which resulted

in the NCCN updating their recommendations in their Task Force Report of 2010 to include GISTs up to 5 cm as acceptable for laparoscopic resection[9]. The surgical management of GIST resection is based on the principles of maintaining an intact capsule to prevent tumor spillage and obtaining a negative margin to ensure complete excision of localized disease[23].

LOCATION OF GISTs

GISTs are most frequently located in the stomach followed by the small bowel. The most frequently cited comparison studies between laparoscopic and open GIST resections were for gastric tumors. These papers identified several laparoscopic techniques for resection for these gastric tumors. They ranged from laparoscopic wedge resections, trans-gastric tumor-everting resection, and distal and proximal gastrectomies depending on the size and location of the tumors with appropriate reconstruction. Depending on the size and location of the tumor, endoscopy may be required to identify the location of the tumor intraoperatively. This is particularly true for smaller GISTs which may not be able to be easily identified grossly from outside the gastric lumen. Shu *et al*[24] showed that in their comparison study, operative time and complication rates between open and laparoscopic procedures were comparable while overall time to bowel function and hospital stay were significantly longer in the open group. These findings were confirmed in a more recent meta-analysis which included 17 studies and over 700 patients looking specifically at laparoscopic *vs* open techniques for gastric GIST resections. The study showed that complication rates and operative times were no different, but times to first flatus, oral intake and hospital stay were all significantly different in favor of the laparoscopic group. From an oncologic perspective, the recurrence rates between the laparoscopic group and the open group were not significantly different[25]. Koh *et al*[26] found similar results in their meta-analysis with shorter times to flatus and oral intake and shorter hospital stays for the laparoscopic resections while finding no differences in margin positivity, local recurrence rates, recurrence free survival and overall survival when comparing laparoscopic to open resections.

GISTs located in the small bowel are less frequently identified and similarly are less frequently cited in the literature. Due to the location though, there are several techniques that can be used to resect and reconstruct the small bowel. These can range from any combination of resecting and re-anastomosing the small bowel intracorporeally or extracorporeally as well as with any combination of stapler and suture[27]. In addition, the re-anastomosis can be performed in either a side-to-side or isoperistaltic fashion. There are many factors involved with these surgical decisions including the size of the tumor, the location of the tumor within the small bowel, body habitus of the patient, as well as technical

proficiency with intracorporeal techniques. Several studies have shown that presentation of small bowel GISTs are more likely to be gastrointestinal bleeding as compared to gastric GISTs. Although endoscopy is often unable to be performed for these small bowel tumors, it is usually unnecessary as these tumors grow outwards from the intestinal lumen and rarely cause obstruction. In one of the few studies comparing laparoscopic compared to open resection of GISTs in the small bowel, the results were similar to those seen with gastric GISTs. Operative time and complication rates were similar, yet time to bowel function and hospital stay were significantly different with shorter times in favor of the laparoscopic group[28]. Another study comparing laparoscopic *vs* open resection for small bowel GISTs up to 10 cm in size indicated that operative times and length of stay were shorter for the laparoscopic group while complications rates were similar. Additionally, there was no difference found in overall survival and recurrence-free survival between the two groups, concluding that laparoscopic resection was safe for these small bowel GISTs[29].

While the use of laparoscopy for resection for GISTs in the rectum has been limited, Fujimoto *et al*[30] published a series of five patient who underwent laparoscopic sphincter-preserving surgery for rectal GISTs after having received neoadjuvant imatinib. All had significant decreased in tumor size with imatinib and all were resected with negative margins. All five were recurrence free at a mean follow-up time of 36 mo, demonstrating that these cases can be performed safely laparoscopically.

SIZE OF GISTs

One of the primary benefits of laparoscopy is in using small incisions and thereby foregoing the pain and morbidity associated with a large laparotomy incision. Unfortunately, the size of the tumor dictates the length of the incision of the extraction site and as can be imagined, the larger the tumor is, the less the incision is able to be minimized. In addition, the larger the tumor, the more unwieldy it becomes to manipulate with the laparoscopic instruments and the danger of tumor capsule rupture increases. Because of these concerns, currently the NCCN guidelines advocate for the use of laparoscopy for GISTs less than 5 cm in size.

In one of the first major series of laparoscopic GIST resections, Nguyen *et al*[27] showed that laparoscopic resection for larger GISTs were possible. The series consisted of 43 patients with the average size of the resected gastric GIST was 4.6 cm and resected small bowel GIST was 3.7 cm. Since then, there have been several other studies that looked at tumors greater than 5 cm that were laparoscopically resected with good results including a 20 cm GIST by Sokolich[29,31-37]. Additionally, Kim *et al*[38] reviewed 24 patients that underwent laparoscopic gastric resections for GISTs ranging from 5-10 cm in size. They had no incidence of capsular rupture and had similar operative and complication rates as compared to open surgery.

ROLE OF NEOADJUVANT THERAPY

The American College of Surgical Oncology group in 2009[13] showed that adjuvant imatinib after resection significantly improved recurrence free survival compared to placebo leading to the FDA approving imatinib for adjuvant therapy. Others studies have confirmed the effectiveness of imatinib for adjuvant therapy in certain populations[39,40]. The use of imatinib for neoadjuvant therapy was recommended by the NCCN[41] for patients in whom cytoreduction would be beneficial including marginally resectable tumors and tumors that would lead to significant surgical morbidity.

Studies have since shown the effectiveness of neoadjuvant therapy with imatinib, resulting in dramatic reduction in tumor size and rendering locally advanced or previously unresectable tumors to be resected with decreased morbidity for the patients[42,43]. The use of minimally invasive techniques after neoadjuvant therapy has not been well studied. While these trials were based on open resections, there have been case reports and case series where laparoscopic resections were successful. Cavaliere *et al*[44] reported a patient with an approximately 10 cm × 15 cm perigastric GIST that underwent 12 mo of neoadjuvant imatinib. The treatment resulted in a greater than 50% reduction in diameter, allowing laparoscopic resection with negative margins and disease free survival at 12 mo. Pandey *et al*[45] reported a 5.5 cm × 4.5 cm gastric GIST the decreased in size to a 3.3 cm × 3 cm and was then resected laparoscopically with no evidence of recurrence at 18 mo. Similarly, Cao *et al*[46] reported a patient with a 10 cm × 15 cm gastric GIST with three liver metastases that underwent six months of neoadjuvant imatinib with a greater than 50% reduction in the tumor burden. He then had a successful laparoscopic resection of both the gastric GIST and the liver metastases with 11 mo of disease free survival. Fujimoto *et al*[30] reports a five-patient case series of patients with rectal GIST that underwent 4-12 mo of neoadjuvant imatinib prior to successful laparoscopic sphincter-preserving surgery. All tumors were initially thought to require an abdominoperineal resection or other extended surgery which would result in a permanent stoma. At a median follow-up of 36 mo, all diverting ostomies had been reversed with maintenance of bowel continence and no evidence of recurrence. While there is not a lot of data yet, it appears that there is a role for laparoscopic surgery after neoadjuvant imatinib therapy.

REVIEW OF LITERATURE

We reviewed 32 independent case series which were all observational studies reviewing outcomes of laparoscopic GIST resections with or without a comparison group that had undergone open resection. This

Table 1 Review of case series

| | All cases included | | Study period 2000 onward | | Follow-up 24+ mo | |
	LAP	OPEN	LAP	OPEN	LAP	OPEN
Total	1062	811	478	463	818	691
Conversion to OPEN	6.03% (64)	-	6.07% (29)	-	6.11% (50)	-
Complications	6.78% (72)	18.74% (152)	6.90% (33)	21.60% (100)	6.85% (56)	20.84% (144)
Mean/median size	2.7-6.1 cm[1]	3.15-9.2 cm	2.7-5.5 cm[1]	3.15-9.2 cm	2.7-6.1 cm[1]	3.15-9.2 cm
Follow-up	8-74 mo	18-91 mo	8-41 mo	21-91 mo	24-74 mo	36-91 mo
Margin positive	0.66% (7)	5.92% (48)	0.42% (2)	3.46% (16)	0.61% (6)	6.08% (42)
Recurrence	3.24% (31)[2]	7.16% (50)[3]	2.74% (11)[4]	4.80% (19)[5]	3.52% (25)[6]	7.61% (44)[7]
GIST-related mortality	0.85% (9)	3.33% (27)	0.42% (2)	0.86% (4)	0.86% (7)	3.91% (27)

[1]Not including series of 4 patients and series where all tumors 2-5 cm (means not included); [2]Out of 958 cases; [3]Out of 698 cases; [4]Out of 401 cases; [5]Out of 396 cases; [6]Out of 710 cases; [7]Out of 578 cases. Summary of the experience of 32 independent case series: All the studies were observational studies reviewing outcomes of laparoscopic gastrointestinal stromal tumor resections, with or without a comparison group that had undergone open resection. This compilation amounted to 1873 cases, 1062 of which were laparoscopic[4,24,26,28,29,31-38,47-49,51-67]. LAP: Laparoscopic; OPEN: Open surgery.

compilation amounted to 1873 cases, 1062 of which were laparoscopic. The analyzed data is compiled in Table 1.

Regarding size of the GISTs resected, the range of the mean/median for the laparoscopic (LAP) cases was 2.7-6.1 cm while the resections by conventional open surgery (OPEN) was 3.15-9.2 cm. These ranges did not include an observational series of 4 laparoscopic cases where the mean size was 10 cm (including a 20 cm GIST) and one laparoscopic series of 37 where only masses between 2-5 cm were resected and the mean/median size was not reported.

The conversion rate from a laparoscopic to an open procedure was 6.03% (64 cases) and the complication rate was 6.78% in the LAP group and 18.74% in the OPEN group. The margins were positive on the pathology in 0.66% of the LAP cases and 5.92% of the OPEN cases. The range of mean/median follow-up periods was 8-74 mo for the LAP group and 18-91 mo for the OPEN group with a 3.24% recurrence rate in the LAP group compared to 7.16% in the OPEN group. Overall, the GIST-related mortality was approximately 0.85% for the LAP group and 3.33% for the OPEN group.

Subgroup analysis was done on those studies that started in 2000 or later. The rationale for this was to see if there was a trend towards better laparoscopic results due to the further experience and knowledge of working with GISTs since the original laparoscopic resection in 1992. A total of 941 cases (478 LAP, 463 OPEN) were included in this subgroup. The conversion rate was similar (6.07%) as were the complication rates for the LAP (6.9%) and OPEN (21.6%) groups. The rate of positive margins was slightly lower for the LAP group (0.42%) compared to the entire LAP cohort (0.66%). Similar trend was seen in the recurrence rate (2.74%) and GIST-related mortality (0.42%) for LAP group.

A subgroup analysis was performed looking at those studies that had a mean/median follow-up of 24 mo or greater. A total of 1509 cases (818 LAP, 691 OPEN) were included in this subgroup. The conversion rate was

similar (6.11%) as were the complication rates for the LAP (6.85%) and OPEN (20.84%) groups. The rate of positive margins was approximately the same in the LAP group (0.61%) compared to the entire LAP cohort (0.66%). The recurrence rate was similar (3.52%) when compared to the entire LAP cohort (3.23%) and the GIST-related mortality was the same (0.86% *vs* 0.85%).

In addition, many studies have shown the benefits of laparoscopic resection over open resection with benefits including decreased operative blood loss, decreased postoperative pain, shorter length of hospital stay, and better quality of life after operation[35,47,48]. This data shows that the complication rate is significantly lower in the LAP group (6.78%) compared to the OPEN group (18.74%). Therefore, from a recovery standpoint, laparoscopic surgery appears to be superior to open surgery.

The data demonstrated that the ability to obtain negative margins (0.66% positive margin) is not compromised with the use of laparoscopic surgery. Furthermore, the recurrence rate (3.24%) is superior compared to open cases (5.92%). However, this finding may be biased by the selection process for choosing between open and laparoscopic resection. None of the studies are randomized control trials, so the surgeons decided which tumors to resect laparoscopically. In all the series, the mean/median size of those that had undergone laparoscopic resection was smaller than those that had undergone open procedures. In many studies the size difference was not found to be significantly different, but the trend is certainly noticeable. In most studies, there was a trend towards the OPEN group having a higher risk stratification than the LAP group. This could also account for the difference in GIST-related mortality (0.85% LAP *vs* 3.33% OPEN). However, Karakousis *et al*[47] and Lee *et al*[49] reported size-matched comparisons of patients with gastric GIST and demonstrated that there was no difference in the efficacy of the oncologic resection (margin, recurrence, overall and recurrence-free survival) while showing

that these patients had decreased operative blood loss, faster return of bowel function, and shorter hospital stay. Furthermore, there were no reports of spillage of tumor during the laparoscopic resections.

Most recurrences occur within the first two years after resection and the risk stratification should determine the course of follow-up[50]. DeMatteo *et al*[21] reported a recurrence rate of approximately 30% in their series of 200 patients followed out to a median of 24 mo. Lee *et al*[49] reported a similar size-matched series comparing laparoscopic and open resections of submucosal tumors and found that the resections were oncologically equivalent. Some of the studies reviewed did not have sufficient follow-up beyond this 24 mo period during which most recurrences were seen. For this reason, a subgroup analysis was done of the studies that had a mean/median follow-up of at least 24 mo. This analysis showed that the recurrence rate (3.52%) was similar to the overall recurrence rate (3.24%) for laparoscopic resections and lower than the recurrence rate of open cases (7.16%) and the general recurrence rate reported in the literature overall.

A further subgroup analysis looked only at those studies whose enrollment was from 2000 onward in order to see if there was an improvement in conversion rate, obtaining a negative margin, and recurrence rate, given more experience with dealing with GISTs. We found that the conversion rate was the same (6.07% *vs* 6.03% overall) while obtaining a negative margin was slightly better (0.42% *vs* 0.66% overall). Also, there was a decrease in the recurrence rate for both laparoscopic (2.74% *vs* 3.24% overall) and open (4.80% *vs* 7.16% overall) resections. The GIST-related mortality rate was lower for both laparoscopic (0.42% *vs* 0.85% overall) and open (0.86% *vs* 3.33% overall) resections. These differences could be due to improvements in surgical technique and experience, but are more likely credited to advancements in non-surgical therapy (imatinib) and slightly shorter follow-up periods.

CONCLUSION

More comparison studies need to be performed but based on retrospective data, there appears to be no difference in terms of complications between open and laparoscopic resection of GISTs in either the stomach or small bowel. Our review strongly suggests that laparoscopic resection for GISTs provides a good oncologic result with rates equal or better than would be expected for open procedures when evaluating negative margins, recurrences, and GIST-related deaths. Also, the data suggests that laparoscopic resection is associated with lower rate of complications and short hospital stay. Ultimately, to conclusively show that laparoscopy is superior, randomized control trials are needed. However, due to the low incidence of this pathology, obtaining the proper number of participants would be difficult. Despite the current NCCN recommendations of open resection for GISTS > 5 cm, many published series have shown

laparoscopic surgery is feasible and can be efficacious in larger GISTs as long as the principles of oncologic resection are followed. The limiting factor is being able to manipulate large tumors without violating the capsule and being able to remove the tumor of significant size through a laparoscopic incision. Furthermore, the role of neoadjuvant imatinib for cytoreduction prior to laparoscopic resection appears to be promising but requires further investigation. Ultimately, the decision to resect using a laparoscopic or open technique is currently based on the surgeon preference and experience. However, the data shows that laparoscopic resection of almost all GISTs does provide an oncologic result similar to conventional open resection.

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MINIREVIEWS

Lumen apposing metal stents for pancreatic fluid collections: Recognition and management of complications

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Abstract

For patients recovering from acute pancreatitis, the development of a pancreatic fluid collection (PFC) predicts a more complex course of recovery, and introduces difficult management decisions with regard to when, whether, and how the collection should be drained. Most PFCs resolve spontaneously and drainage is indicated only in pseudocysts and walled-off pancreatic necrosis when the collections are causing symptoms and/or local complications such as biliary obstruction. Historical approaches to PFC drainage have included surgical (open or laparoscopic cystgastrostomy or pancreatic debridement), and the placement of percutaneous drains. Endoscopic drainage techniques have emerged in the last several years as the preferred approach for most patients, when local expertise is available. Lumen-apposing metal stents (LAMS) have recently been developed as a tool to facilitate potentially safer and easier endoscopic drainage of pancreatic fluid collections, and less commonly, for other indications, such as gallbladder drainage. Physicians considering LAMS placement must be aware of the complications most commonly associated with LAMS including bleeding, migration, buried stent, stent occlusion, and perforation. Because of the patient complexity associated with severe pancreatitis, management of pancreatic fluid collections can be a complex and multidisciplinary endeavor. Successful and safe use of LAMS for patients with pancreatic fluid collections requires that the endoscopist have a full understanding of the potential complications of LAMS techniques, including how to recognize and manage expected complications.

Key words: Pancreatic fluid collection; Lumen apposing metal stent; Endoscopic necrosectomy; Cystgastrostomy

Core tip: Pancreatic fluid collections (PFC) are a recognized complication of pancreatitis, trauma or surgical injury to the pancreas. Over the years, management has included surgical, radiologic or endoscopic intervention. Endoscopic interventions are now at the forefront for management of PFCs, and development of lumen apposing metal stents (LAMS) have made endoscopic drainage more accessible

and easy. It is important for practitioners to understand the risks of LAMS including bleeding, stent migration, buried stent, stent occlusion, and perforation, as well as proper management approaches to these complications.

INTRODUCTION

Acute pancreatitis (AP) leads to 275000 admissions annually and $2.5 billion in healthcare costs worldwide[1]. Pancreatic fluid collections (PFCs) are a burdensome, sometimes devastating complication of AP. PFCs can arise after interstitial or necrotizing pancreatitis. Acute peripancreatic fluid collections occur commonly in interstitial AP, generally resolve, and require no intervention. When an acute PFC does not resolve, a wall forms around the collection, signaling the evolution into a pancreatic pseudocyst. Pseudocysts require intervention only if they are symptomatic. Necrotizing pancreatitis that fails to resolve spontaneously can develop into walled-off necrosis (WON). As with pseudocysts, WON warrants intervention only when symptomatic or if there is clear evidence of infection[2]. Infected pancreatic necrosis, which may occur before or after a collection becomes walled-off, carries a mortality rate of 30%, compared to only 2% of all AP and 10% of patients with sterile necrosis[1].

Historically, PFCs were drained or debrided surgically or percutaneously; however, these techniques have a high risk of complications and morbidity. Endoscopic cystgastrostomy and necrosectomy have emerged as an alternative to these approaches in many cases. An endoscopic approach requires close contact between the GI lumen and PFC and is not an appropriate alternative for surgical indications other than drainage, such as bleeding or perforation[3]. For pseudocysts, endoscopic cystgastrostomy has been demonstrated to be as effective as surgical cystgastrostomy when it is technically feasible, but with shorter hospital stays, lower costs and higher patient physical and mental health scores[4]. A 2016 Cochrane review of randomized control trial data for management of pancreatic pseudocysts concluded that endoscopic ultrasound (EUS)-guided drainage leads to better short term healthcare quality of life and lower costs compared to surgical drainage[5]. For necrotic collections, the rate of surgical complication is as high as 72%[6,7]. When it can be utilized, endoscopic necrosectomy has been shown to result in lower rates of major complications and death[3]. While there is strong data now supporting lower morbidity/mortality for endoscopic approaches over surgical approaches

in PFCs, there is limited data comparing percutaneous approaches and endoscopic approaches. The main limitations of percutaneous approaches are: (1) the need for external drainage catheters; (2) the potential development of a drain tract/fistula; and (3) diameter limitations of external drainage catheters which can limit their effectiveness for WON.

Early techniques for endoscopic management of PFCs involved radiologic and endoscopic identification of an area of extrinsic gastric or duodenal compression, creation of a cystgastrostomy with a needle-knife sphincterotome, wire passage, and use of a Seldinger technique to balloon dilate the tract and place double pigtail plastic stents to maintain its patency and allow drainage[8]. Over the ensuing years, techniques and technologies have evolved. Endoscopic ultrasound guidance is now almost universally used for confirmation of PFC location and identification of an avascular path for drainage[5]. While plastic stents continue to be used commonly for simple pseudocysts, self-expanding metal biliary and esophageal stents have also been used for PFC drainage, as these have the advantage of a larger lumen, which is particularly useful in the setting of WON and in some cases to enable endoscopic necrosectomy[9]. Traditional self-expanding metal stents (SEMS) are designed to anchor in place in a stricture; however, when used for PFC management, there is a significant migration risk, as the size and shape of available biliary and esophageal SEMS are not specifically designed for management of pancreatic collections[10].

The first clinical experiences with LAMS were described in 2012, and over the last several years LAMS have been increasingly preferred by many endoscopists for cystgastrostomy and pancreatic necrosectomy procedures[11,12]. LAMS address the need for a larger lumen for drainage and endoscopist entry into the cyst cavity, and are designed with a "dumbbell" shape with flanged ends to oppose the gastrointestinal and cyst lumens in order to reduce stent migration[11]. There are numerous studies showing safety and efficacy of LAMS[10-15]. There is also data showing the superiority of LAMS to double pigtail stents (DPS) for drainage of WON[16].

In early studies of both WON and pseudocysts, the use of LAMS has been associated with higher rates of clinical success, fewer required endoscopic sessions, shorter procedure times, shorter hospital stays and lower costs compared to DPS[16–20]. In the United States, the Axios stent (Boston Scientific) is used most commonly, but internationally, other LAMS stent designs including the Spaxus stent (TaeWoong Medical) and Nagi stent (TaeWoong Medical) are available, among others[21].

COMPLICATIONS OF LAMS

While much has been written regarding the technical advantages of LAMS, there has been more limited discussion of their complications. Reported complication

Author	Year	Single/multi-center	*n*	PFC type	Bleeding	Perforation	Migration	Buried stent	Failure to deploy
Itoi *et al*[11]	2012	Single	15	6 WON, 9 PC[2]	0%	0%	7%	0%	0%
Yamamoto *et al*[12]	2013	Multi	9	4 WON, 5 PC	11%	0%	11%	0%	0%
Chandran *et al*[14]	2015	Multi	54	9 WON, 39 PC	6%	0%	19%	6%	2%
Shah *et al*[10]	2015	Multi	33	11 WON, 18 PC	0%	0%	3%	0%	9%
Walter *et al*[39]	2015	Multi	61	46 WON, 15 PC	0%	2%	10%	0%	2%
Rinninella *et al*[24]	2015	Multi	93	4 APFC, 37 PC, 52 WON	1%	2%	1%	0%	1%
Mukai *et al*[40]	2015	Single	21	19 WON, 2 PC	10%	0%	19%	0%	0%
[1]Mukai *et al*[17]	2015	Single	43	WON	0%	2%	5%	0%	0%
[1]Siddiqui *et al*[19]	2016	Multi	86	WON	7%	3%	0%	3%	2%
[1]Bang *et al*[25]	2016	Single	12	WON	25%	0%	0%	17%	-
[1]Lang *et al*[26]	2016	Single	19	9 WON 10 PC	21%	0%	0%	0%	-
[1]Bapaye *et al*[18]	2017	Single	72	WON	3%	0%	3%	0%	0%
[1]Ang *et al*[16]	2017	Multi	12	8 WON, 8 PC[3]	0%	0%	8%	0%	-
Lakhtakia *et al*[37]	2017	Single	205	WON	3%	1%	1%	1%	1%

[1]Study includes multiple stent types, only LAMS cases are included here; [2]PFC type not explicitly defined, inferred based on description of cyst contents; [3]Study includes patients with multiple stent types. Number of subjects is not equal to sum of PFC types. LAMS: Lumen-apposing metal stents; WON: Walled off necrosis; PC: Pseudocyst; APFC: Acute pancreatic fluid collection.

rates vary widely. Several studies report complication rates under 10%[22-24]. Conversely, one group recently published their experience of conducting an interim audit during a randomized controlled trial and ultimately changing their study protocol and clinical practice due to a higher than expected complication rate of 50% in the LAMS arm of their trial[25]. The variations may be at least partially attributable to different definitions of complications in the studies. Given that these series represent the experiences of earlier adopters of the technology who are therapeutic endoscopists at high volume centers, broader use of these devices may either decrease complication rates, as technical experience and approaches evolve, or may increase complication rates, as these procedures become more commonly performed in centers with less clinical experience and expertise. The most common complications encountered in PFC drainage with LAMS include bleeding, stent migration/dislodgement, buried stents, stent occlusion, and perforation (Table 1). While these complications are not unique to LAMS placement, the prevalence and management of these complications is somewhat different than for prior endoscopic drainage techniques.

Bleeding
Cystgastrostomy, and indeed any transenteric procedure, carries a risk of hemorrhage. This can include acute bleeding, at the time of initial access and tract creation, and delayed bleeding, which can occur due to a variety of mechanisms, weeks or months after the initial procedure[25]. A major advantage of EUS guidance is that Doppler ultrasound helps identify an avascular path, which should reduce procedural bleeding risk. Acute bleeding or oozing at the site of mucosal entry can still occur, and can often be managed by tissue tamponade from either balloon dilation or stent placement and radial expansion. The more serious bleeding complication of endoscopic cystgastrostomy and endoscopic necro-

sectomy is bleeding within the PFC. The reported rate of bleeding can be as high as 25%, but is lower in most studies (Table 1). Acute or delayed bleeding within the PFC is often not endoscopically manageable, in part due to limited visualization. Rapid bleeding, whether acute or delayed, may require immediate referral to angiographic embolization or surgery (Figure 1). Pseudoaneurysm development and variceal formation are expected complications in patients with severe pancreatitis and may increase the risk of bleeding during PFC management (Figure 2).

A comparison of LAMS and DPS in PFC drainage found that while the two treatment groups had similar rates of PFC resolution at 6 mo, there were significantly higher rates of bleeding (19% *vs* 1%, *P* = 0.0003) in the LAMS group compared to the DPS group. The bleeding events in the LAMS group included a splenic artery pseudoaneurysm, 2 collateral vessel bleeds, and an intracavitary variceal bleed; whereas the single bleeding event in the DPS group was an erosion of the stent into the gastric wall[26].

In a second trial comparing LAMS to DPS for management of WON, three major bleeding events requiring transfusion and ICU admission among the first 12 patients randomized to the LAMS arm were reported. All three events occurred in a delayed fashion, at 3 wk (*n* = 1) and 5 wk (*n* = 2) from LAMS placement. As a result of this experience, the authors changed their study protocol and clinical practice and now perform a CT scan 3 wk after LAMS placement to assess for PFC resolution, rather than 6 wk as is their practice for DPS and their original study protocol[25]. Similarly, another comparison between LAMS and DPS in WON describes erosion of the LAMS into the splenic artery as the cause of 2 bleeding complications, both of which were delayed (Table 1)[18].

The primary concept that has been proposed to explain the increased bleeding risk reported in the early

Figure 1 Delayed bleeding after lumen apposing metal stent placement, which required angiographic embolization.

Figure 2 Pulsatile pseudoaneurysm seen on left of screen after endoscopic entry into cyst cavity, several weeks after initial lumen apposing metal stent placement for walled off necrosis.

LAMS literature is that the more rapid collapse of the collection which may occur due to the large diameter of LAMS, may lead to direct impingement of the stent on blood vessels on the cyst wall, leading to risk of pseudoaneurysm and hemorrhage. Furthermore, plastic stents are softer and more flexible, and may be less likely to cause bleeding if they encounter a vascular structure. The data regarding bleeding risk should become clearer as a larger experience develops with LAMS use. Based on the available evidence, our approach is to perform short term CT imaging after LAMS placement, typically within 3-4 wk, with the plan to endoscopically remove the stent after cyst collapse is demonstrated. In recurrent pseudocysts for which long-term drainage is desired, use of plastic stents may be preferable based on our current understanding. We also strongly recommend that physicians considering LAMS placement should have experienced angiography and surgical teams available to help manage bleeding when it occurs. This is in keeping with recommended approaches for all patients with pancreatic fluid collections, which should typically involve multidisciplinary care involving a gastroenterologist, surgeon, and radiologist.

Migration

While the LAMS flanged ends are intended to anchor the stent in place, there remains some risk of stent migration after placement. Migration rates of up to 19% have been reported (Table 1). Migration can occur either into the cyst cavity, or back into the gut lumen. Migration can occur immediately due to improper deployment of the stent, but may also occur spontaneously, weeks after stent placement, and also due to subsequent manipulation of the stent during endoscopic debridement procedures[27]. While some endoscopists prefer to place a double pigtail stent through the LAMS to "stabilize" the LAMS, it is currently unknown whether this approach may reduce the risk of LAMS migration, and we do not currently recommend this practice.

In the case of migration into the gastric lumen, the stent may either remain in the stomach (Figure 3), or

pass spontaneously. Small bowel obstruction has been reported in association with LAMS migration, requiring surgical exploration for stent retrieval[28]. Migration of the stent into the cyst cavity can be more problematic as the cystgastrostomy tract may partially or completely close.

If stent migration is recognized during routine imaging or endoscopy, endoscopic removal of the stent should be pursued urgently. In the case of migration into the lumen, retrieval is straightforward if the stent is in the stomach or proximal small bowel. More distal migration of the stent may be managed with a deep enteroscopy attempt at removal, or conservatively with serial abdominal X-rays to confirm passage, and prompt surgical management if bowel obstruction occurs. Migration of the stent into the cyst cavity requires re-establishing the cyst gastrostomy tract with wire passage, dilation, and subsequent re-introduction of the endoscope into the cavity for stent retrieval using a snare or forceps. If stent retrieval is not possible endoscopically, then surgical removal is indicated.

Buried stent

The term "buried stent" refers to the situation when gastric or enteric mucosa grows over the flanged end of the LAMS. This complication may occur with LAMS due to the tight apposition of the gastric and PFC lumen and the relatively low stent profile. Buried stent has been reported in up to 17% of cases in reported series (Table 1). The management of this issue has been described in several case reports[29-31].

Given that buried stent is a relatively uncommon occurrence, the specific risk factors for this event are not clear. Some have proposed that placing the stent across the gastric antrum (rather than the gastric body), may increase the risk of buried stent because of the significant motility of the gastric antrum[32].

Techniques for removing buried stents have included the use of a needle knife device and argon plasma coagulation to partially uncover the enteric side of stent, prior to removal with a snare or forceps. Dilation of the stent and tract may also facilitate removal. When

Figure 3 Endoscopic removal of lumen apposing metal stent that migrated into gastric lumen.

Figure 4 Closure of a perforation in the stomach after lumen apposing metal stents maldeployment and removal (a second gastric location was subsequently chosen for successful lumen apposing metal stents placement).

adequate exposure of the buried enteric side of the stent is not feasible, an alternative approach is to dilate the stent, enter the cavity with the endoscope through the stent, and subsequently capture the internal flange of the stent in order to facilitate removal[31]. Aggressive attempts at removal of a buried stent may increase the risk of bleeding, and potentially separation of the cyst cavity from the enteric wall.

Perforation
The risk of perforation when performing an upper GI endoscopy including EUS is low, at less than 0.05%[33]. The reported risk of perforation in endoscopic drainage of PFCs is less than 5% (Table 1)[34]. Peritonitis or pneumoperitoneum caused by gastric perforation or separation of the cyst wall and stomach are perhaps the most feared complications of endoscopic cystgastrostomy and similar techniques. These challenges are not specific to the use of LAMS and can occur in any endoscopic PFC drainage procedures.

While LAMS are designed to make endoscopic access into PFCs easier, and potentially safer, initial data does not suggest that LAMS use eliminates the risk of perforation. In one study comparing DPS, SEMS and LAMS, 3 cases of perforation were reported in the LAMS group (*n* = 86), all resulting from stent maldeployment. One was fixed endoscopically with an "over the scope" clip (OTSC) and two required surgical repair. In the DPS and SEMS groups (*n* = 227), there were only 2 such perforations[19].

Patients in whom a perforation is not immediately recognized and closed endoscopically may present immediately post procedure with abdominal/chest pain, hemodynamic instability or in a more delayed fashion with worsening clinical status including sepsis. Because patients recovering from severe pancreatitis may have pre-procedural abdominal pain, and, in some situations, features of systemic inflammatory response syndrome, post-procedural perforation may not be immediately obvious. Physicians must be alert to the risk of perforation, and initiate clinical investigation early if there is evidence of clinical deterioration or increased abdominal pain after LAMS placement. Initial

management includes imaging studies such as a CT scan with contrast to assess extent. Conservative, nonsurgical management with nothing by mouth, nasogastric/nasoduodenal tube placement and intravenous antibiotics can be considered in clinically stable patients. A small perforation/leak after successful stent placement may lead to fluid or air in the peritoneum, and can potentially be followed conservatively. However, the surgical team should be consulted at time of presentation to evaluate the role of surgical intervention.

When a perforation is recognized, the endoscopist should describe the size and location of the perforation in clear terms. Endoscopic treatment of the perforation can include endoscopic clip placement, OTSC placement, endoscopic suturing, or a combination of these tools (Figure 4)[35]. For gastric perforations less than 1cm, monotherapy with these tools should be considered; however, for gastric perforations of 1-3 cm, a combination of techniques may be required[35]. If it is clear that the stent has been deployed outside of the PFC, either from incorrect deployment or separation of the cavities, the stent should be removed and the site closed endoscopically with standard clips, OTSC, or endoscopic suturing.

For PFCs, perforation/pneumoperitoneum risk can be minimized by choosing a site with clear wall apposition (with ideally less than 1cm of distance) between the gut lumen and cyst wall on EUS. Carbon dioxide is also strongly preferred for all LAMS placements as this may lower the risk of tension-pneumothorax, pneumomediastinum, pneumopericardium, or abdominal compartment syndrome[35].

Stent occlusion
LAMS placement is intended to allow fluid and debris to flow out of the cyst cavity, and also to permit digestive juices to flow in, which may facilitate clearance of the cavity. When the stent lumen becomes occluded, either with food debris (Figure 5), or with cyst contents (Figure 6), drainage is impaired[36]. The prevalence of stent occlusion has not been clearly reported in the available

Figure 5 Food debris occluding lumen apposing metal stent lumen.

Figure 6 Necrotic debris occluding lumen apposing metal stent lumen.

literature, as this has not been included in the described list of complications in most available reports. While some physicians advocate placing double pigtail plastic stents through the LAMS at the time of initial placement in order to reduce the likelihood of stent occlusion, the benefit of this approach, if any, has not been evaluated in clinical trials.

LAMS occlusion is important to recognize as it may slow the rate of cyst resolution, and lead to early "closure" of a partially drained cyst may also increase the risk of infection. Stent occlusion should be considered in patients who have a sudden clinical worsening (for instance new abdominal pain or fever), after initial improvement or stability following LAMS placement, and also in patients where follow-up clinical imaging demonstrates lack of improvement in cyst cavity size. Management of stent occlusion is generally straightforward, endoscopically, requiring standard techniques of debris removal, with a forceps or retrieval net, in order to re-establish the stent lumen.

An active, step-up approach to managing WON has been proposed, which employs early assessment for stent occlusion and clearing stent debris as a first re-intervention step for cases that do not resolve after LAMS placement[37]. If resolution still does not occur, the algorithm employs nasocystic tube with hydrogen peroxide and saline lavage, and, ultimately direct endoscopic necrosectomy for the most persistent cases.

CONCLUSION

LAMS technology is a welcome and important addition to the armamentarium of gastrointestinal endoscopists managing PFCs. While these devices represent an important leap forward with regard to ease of rapid endoscopic drainage, promoting lumen apposition and limiting stent migration compared to off-label use of other stent designs, LAMS do not eliminate the risk of complications of endoscopic cystgastrostomy and endoscopic necrosectomy and may even carry some of their own unique risks. The continued study of these devices as they become more commonly used will be critical to more precisely characterize their risks and the

best techniques to avoid them.

Specific questions which will be important to address in future research will include: (1) what is the appropriate/safe duration between LAMS placement and removal? (2) what are the ideal intervals of radiologic and endoscopic follow-up to reduce the risk of stent migration and buried stent? and (3) does the use of double pigtail stents placed through a LAMS have any effect on the risk migration, occlusion, or other complications? The consistent application of deliberately developed and refined protocols should help drive down the rate of LAMS complications, and will allow for safer application of these important devices as their clinical usage broadens over time[38].

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ORIGINAL ARTICLE

Case Control Study

Clinical predictors for sessile serrated polyposis syndrome: A case control study

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Abstract

AIM

To compared individuals with serrated polyposis syndrome (SPS) to those with sessile serrated adenoma (SSA) and adenomas in the setting of endoscopists with high adenoma detection rates at a secondary and tertiary academic centre.

METHODS

Retrospectively we collated the clinical, endoscopic and histological features of all patients with SPS at St Vincent's public and private hospital in the last 3 years. Patients were identified by searching through 2 pathology databases. Variables explored included smoking status, symptoms, and family history of concurrent colorectal cancer, number and location of polyps. Patients with SPS were matched to two cohorts (1) patients with SSA not meeting World Health Organization (WHO) criteria for SPS over 3 years; and (2) patients with exclusively adenomas. The control cases were also matched according to gender and endoscopist. Adenoma detection rates ranged from 25% to 40%.

RESULTS

Forty patients with SPS were identified and matched with 40 patients in each control group. In total 15452 colonoscopies were performed over the study period which

amounts to a prevalence of 1: 384 patients (0.26%) with SPS. Fourteen patients (35%) required more than 1 year to accumulate enough polyps to reach WHO criteria for SPS. The diagnosis of SPS was largely incidental and 5% SPS patients were diagnosed with colorectal cancer over 3 years. The chance of detecting a meta-synchronous adenoma was similar in those with SPS (42%) and those with SSA (55%), P = 0.49. The majority of patients (75%) meeting criteria for SPS were women. The mean age of those with SPS (45 years) was significantly lower than both cohorts with SSA (57 years) and adenomas (63 years), P = 0.01. On univariate analysis cigarette exposure, first-degree family history of colorectal cancer and a high BMI weren't significantly more associated with SPS compared to patients with SSA or patients with adenomas. However, patients with SPS (97%) and patients with SSAs not meeting SPS criteria (98%) were significantly more likely to be Caucasian compared to patients with adenomas (79%), P = 0.01.

CONCLUSION

The prevalence of SPS in our study was 0.26%. The vast majority of patients diagnosed with SPS were women. As a group, they were significantly younger compared to patients with SSA not meeting WHO criteria and patients with adenomatous polyps by more than a decade. Patients with SPS were no more likely to have a first degree relative with colorectal cancer or smoking history than the other two groups. Patients with serrated polyps were more likely to be Caucasian than patients with adenomas.

Key words: Serrated lesions; Colonoscopy; Colorectal polyps; Polyposis syndrome; Colorectal cancer

Core tip: At the time of diagnosis, sessile serrated polyposis syndrome (SPS) is associated with a high risk of concurrent colorectal cancer. Early diagnosis of SPS is crucial and this case-control study aim to delineate differences in risk factors for SPS and other types of polyps. The vast majority of patients diagnosed with SPS in our study were women. They were younger and more likely to be Caucasian compared to patients with adenomatous and patients with serrated adenomas not meeting World Health Organization criteria. SPS patients were no more likely to have a family history of colorectal cancer or cigarette exposure than other polyp groups.

INTRODUCTION

In the past decade, serrated polyps have garnered rapid interest as they cause colorectal cancer *via* a different pathway compared to adenomas. This pathway features hyper-methylation, CpG island methylator phenotype (CIMP) and mutations in proto-oncogene BRAF. Sessile Serrated adenoma (SSA), hyperplastic polyps and traditional serrated adenoma all fall under the classification of serrated polyps.

Serrated polyposis syndrome (SPS), distinguished by numerous serrated polyps distributed throughout the colon is associated with increased risk of colorectal cancer. Its prevalence is unclear. In a systematic review, it ranges from as low as 1:1800 in average risk screening population and as high as 1:150 in patients in a Faecal immunochemical testing programme[1,2]. In comparison, Familial Adenomatous Polyposis Syndrome (FAP), has lower prevalence rate of 1:13000 in average risk screening population and has a known genetic mutation[3]. However a genetic basis for SPS has not been discovered despite large multi-centre studies looking into a variety of germline mutations[4]. The definition of SPS is essentially a clinical one, based on endoscopic findings and histopathology of polyps removed. In 2010, the condition was arbitrarily defined by the World Health Organization (WHO) as follows: (1) at least 5 histologically diagnosed serrated lesions proximal to the sigmoid colon, of which 2 should be > 10 mm in diameter; (2) any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative (FDR) with SPS; or (3) > 20 serrated polyps distributed throughout the colon. The definition is a cumulative one, whereas many years and multiple colonoscopies can pass before patient reach the criteria for the diagnosis of SPS[5].

Concurrent colorectal cancer (CRC) is often encountered at the time of SPS diagnosis, at rates as high as 16%-29%[5]. The propensity for a delay in diagnosis in SPS and the inclusion of patients with symptoms suspicious for cancer accounts for the high prevalence rates in these previous studies. Once patients enter a surveillance program and undergo the recommended yearly colonoscopies, the absolute 5-year CRC risk falls to 1.5%[2]. Hence, early diagnosis of SPS is crucial as it radically change the natural history of patients with the disorder. Serrated and adenomatous polyps share many clinical risk factors, however it is unclear if certain risk factors have a stronger association with one polyp subtype compared to another[6]. Despite there being a small number of studies investigating the differences in risk factors for distinct polyp subtypes, no study to date has included SPS as one of the comparators.

MATERIALS AND METHODS

A case-control retrospective study was conducted in 2 centres; St Vincent's public hospital, Sydney, Australia a tertiary referral teaching hospital and St Vincent's clinic, a secondary referral private centre in the same campus. The colonoscopies were performed by 7 experienced endoscopists, each performing more than 450 colonoscopies per year and having high adenoma

detection rate between 25%-40%. Patients undergoing a colonoscopy with polypectomy with a diagnosis of SPS between December 2013 and December 2016 were identified by searching through two pathology databases. The colonoscopies were performed with high definition white light endoscope with NBI capability (190 series, Evis Extera Ⅲ CV190 processor Olympus, Tokyo, Japan). Bowel preparation was used using either Moviprep split dose (a polyethylene glycol preparation) or Prep Kit C (Sodium picosulfate and Glycoprep). Bowel preparation was considered adequate if the Boston scale score was more than 6 points. Those with poor bowel preparation were excluded. Procedures were performed with the patients under deep sedation with Propofol administered by an anaesthetist. We collated the clinical, endoscopic and histological features of all SPS patients and matched them to two cohorts (1) patients with SSA not meeting WHO criteria for SPS over 3 years; and (2) patients with exclusively adenomas. The control cases were matched according to gender and endoscopist in order to minimise bias secondary to variations in endoscopic recognition and technique.

Variables collected for each patient included age, ethnicity, smoking status, weight, height, symptoms, family history of colorectal cancer, presence/absence of concurrent colorectal cancer, number, size and location of polyps. Since the diagnosis of SPS is dependent on a cumulative polyp count, the number of colonoscopies and years required to meet criteria were also analysed. Whether the diagnosis of SPS was made on the first "index" colonoscopy or subsequent followup colonoscopy during followup was also distinguished. Adenoma detection rates for each endoscopist involved in the study was extracted from Quality Assurance data from each centre. The study was approved by the Institutional Review Board.

Statistical analysis

Univariate analysis of co-variates was analysed using Fisher's exact test or χ^2 test as appropriate. Age and BMI was assessed using the Independent student *T*-test. Quantitative variables were summarized using mean standard variation and mean values. Frequencies were used to summarise categorical values. SPSS statistics software version X (SPSS, Inc Chicagi, Illionois, United States) was used to analyze the data. The statistical methods of this study were reviewed by Dr. Yang Wu from Department of Gastroenterology, St Vincent's Hospital, NSW, Australia. Nancy Briggs from Stats Central, statistical consulting unit established at University of NSW, also reviewed the statistical methods of this study.

RESULTS

During the 3 years period, 40 patients were diagnosed with SPS and equal number of patients matched in the control groups: Patients with SSA not meeting the WHO criteria for SPS and patients with only adenomatous polyps. Bowel prep was reported as adequate in all the

Table 1 Characteristics of patients with serrated polyposis syndrome *n* (%)

Study population (*n* = 40)	
Women	30 (75)
Age in years, mean ± SD	45 ± 18.54
Ethnicity	
Caucasian	39 (98)
Other	1 (2)
First Degree Relative with CRC	
Present	12 (35)
Absent	22 (65)
Smoking status	
Current Smoker/Ex-smoker	318 (48)
BMI (kg/m^2), mean ± SD	25 ± 4.7
WHO Criteria	
1	30 (75)
2	0
3	10 (25)
Mean number of total polyps	13
Mean number of serrated polyps during first colonoscopy	7
Mean size of largest polyp (mm)	17
Location of largest polyp	
Caecum	13 (32)
Ascending colon	16 (40)
Transverse colon	5 (13)
Descending colon	2 (5)
Sigmoid colon	4 (10)

SPS: Serrated polyposis syndrome.

cases. The majority, 26 patients had enough polyps to meet criteria at their first "index" colonoscopy. However 14 patients (35%) required more than 1 year to accumulate enough polyps to reach WHO criteria for SPS, with 7 patients requiring 2 years and 7 patients requiring 3 years to reach criteria. In total 15452 colonoscopies were performed over the study period across the two sites which amounts to a prevalence of 1: 384 patients (0.26%) with SPS.

The mean age of the patients with SPS was 45 years old and women made up 75% of the cohort. Characteristics of the 40 patients with SPS are included in Table 1. There was substantial heterogeneity in the indications for colonoscopy in patients with SPS, ranging from abdominal pain to per rectal bleeding. 7/40 patients underwent colonoscopy due to a history of colonic polyps in the past, sometimes discovered at other endoscopy centres not involved in the study. For the remaining patients, SPS diagnosis was largely unrelated to the pretest suspicion of the referring doctor. Only 1/40 patient had their procedure initiated by a positive Faecal Occult Blood Test (FOBT). The indication for colonoscopy is not a reliable predictor factor for finding SPS.

The mean number of serrated polyps removed during the first colonoscopy was 7 (range 1 to 30) and the mean total number of polyps detected over 3 years was 13 (range 6 to 30). The mean size of the largest serrated polyp removed was 17 mm, ranging from 10 mm to 40 mm. Interestingly, 17/40 patients with SPS also had concurrent adenomas ranging from

Figure 1 Polyp groups according to age distribution. SPS: Serrated polyposis syndrome; SSA: Sessile serrated adenoma.

Figure 2 Relationship between polyp groups and predominance for polyp location in right/left colon. SPS: Serrated polyposis syndrome; SSA: Sessile serrated adenoma.

1-6 adenomas detected over 3 years. The age of this subpopulation ranged from 32 to 72 years old.

A small proportion 5% (2/40), were diagnosed with colorectal cancer during the 3 years and neither of the patient displayed symptoms classic of malignancy. Interestingly, both patients met WHO criteria for SPS not during their index colonoscopy but during the followup colonoscopy when their colorectal cancer was diagnosed. Neither patients had a family history of colorectal cancer. One patient was a 76 years old woman with history of one SSA removed from ascending colon in 2014 and subsequently developed a colorectal cancer in hepatic flexure plus five right-sided SSA in 2016. Molecular markers for the colorectal cancer showed positivity for BRAF, Microsatellite instability (MSI) and MLH1. The second patient was a 64 years old woman with one SSA removed in 2013 at different endoscopy centre and subsequently developed a colorectal cancer in the ascending colon along with three adenomas and thirteen SSAs in 2016. This cancer was BRAF and MSI negative. Both patients had localised disease and had surgery with curative intent in 2016.

The mean age of patients with SPS was 45 years (SD: 18.54), significantly lower than 57 years (SD: 15.56) in patients SSAs not meeting SPS criteria and 63 years (SD: 10.58) in patients with adenomas, *P* = 0.01. Figures 1 and 2 shows the difference in age distribution between the three polyp groups. The SPS polyp group had a higher rate of family history of colorectal cancer in a first degree relative (31%) compared to the SSA group (26%) and adenoma group (30%), but this didn't reach statistical significance. Patients with SPS (97%) and patients with SSAs not meeting SPS criteria (98%) were significantly more likely to be Caucasian compared to patients with adenomas (79%), *P* = 0.01. Past or present cigarette exposure was reported at a higher proportion in patients with SPS (47%) compared to SSA group (32%) and Adenoma group (33%) but this wasn't statistically significant, *P* = 0.39. BMI was not significantly different across the three groups with the SPS group associated with mean BMI of 26 kg/m^2,

SSA group associated with mean BMI of 23 kg/m^2 and Adenoma group with mean BMI of 25 kg/m^2, *P* = 0.61.

Evaluating clinical risk factors between the 26 patients who met WHO criteria for SPS at their first "index" *vs* 14 patients who required more than 1 year to accumulated enough polyps to be diagnosed with SPS, there was no significant difference in rates of family history of colorectal cancer, smoking or age.

Endoscopically, each polyp group has distinct characteristics. Polyps were predominantly discovered in the right colon in 84% of SPS patients *vs* 46% of patients with SSAs and 43% of patients with exclusively adenomas, *P* = 0.003.

In 4/40 patients with SPS and in 4/40 patients with SSA not meeting WHO criteria, an adenoma was the largest polyp discovered, not a serrated polyp. In the rest of the group, 36 patients, the largest polyp was a serrated polyp. Concentrating only on patients whose largest polyp was serrated, the distribution of largest or dominant polyp was significantly different between the SPS patients and SSA patients.

Figure 3 illustrates the differences in the distribution of the largest Serrated polyp in the SPS group compared with the SSA group. In both groups, the largest serrated polyp was most frequently found in ascending colon. However in SSA group, there was a more even spread of large serrated polyps throughout the colonic segments with 5 patients having their largest polyp in his/her sigmoid colon.

The proportion concurrent adenoma 17 (42%) in patients who were diagnosed with SPS was comparable to those with SSAs not meeting SPS criteria 21 (52%). Table 2 describes that patients with SPS have a mean total polyp count significantly higher than the other two groups, but this is expected given the intrinsic requirement of multiple polyps to meet the criteria for SPS. Similarly a greater proportion of patients with SPS have a polyp > 15 mm compared to the other groups. The mean size of largest polyp for SPS (17 mm) was significantly greater than the mean size of largest polyp

Table 2 Endoscopic features of each polyp groups

	SPS *n* = 40 Number/mean	Adenoma *n* = 40 Number/mean	SSA *n* = 40 Number/mean	*P* value for comparison between groups
Patients with concurrent adenoma				0.49
Yes	17 (42)		21 (52)	
No	23 (58)		19 (48)	
Total Number of Polyps	13	1.4	3.4	0.001
Patients with a polyp > 15 mm				
Yes	30 (75)	3 (7.5)	21 (52)	0.04
No	10 (25)	37 (92.5)	19 (48)	
Size of largest polyp (mm)	17	7.8	13.5	0.014

SPS: Serrated polyposis syndrome; SSA: Sessile serrated adenoma.

Figure 3 Distribution of the largest serrated polyp according to colonic segments in ser-rated polyposis syndrome patients and patients with sessile serrated polyps not meet-ing serrated polyposis syndrome criteria. SPS: Serrated polyposis syndrome; SSA: Sessile serrated adenoma.

found in the SSA group (14.3 mm) and the adenoma group (7.8 mm), *P* = 0.014.

Missing data was most frequently encountered in collating BMI (10%) and documentation of family history of colorectal cancer (15%). Information on smoking status and indication for colonoscopy were almost universally available. Alcohol intake of the patients were sparsely and inconsistently documented in the clinical records. We were unable to precisely quantify alcohol intake for the majority of the patients, hence this variable, an important risk factor for adenoma polyp development, wasn't analysed in our study.

DISCUSSION

It is estimated that 20%-30% of all CRCs develop through the serrated neoplasia pathway[7]. It has been hypothesised that the imperceptible nature of serrated polyps and inconsistent bowel preparation have been responsible for the relative failure of colonoscopy to protect from proximal colon carcinoma.

In this study, we describe the phenotypic features in a group of patients with SPS from a secondary and tertiary gastroenterology centre over 3 years. The prevalence of SPS in our study, 1:384, is higher than the

measurements reported in previous studies performed in screening populations 1:1800[1]. The contrast between these figures may reflect the expertise and vigilance of the local gastroenterologist in detecting serrated lesions. All adenoma detection rates of the endoscopists involved in this study were above the national benchmark on quality in colonoscopy. A shift towards switching split preparation in recent years may have also influenced the ability to detect serrated lesions. Another strength in our data is that there is little ascertainment bias as our data isn't collected from genetic clinics or bowel cancer screening programs. Limitations in our study include the retrospective assessment of the data, the smaller number of patients with SPS relative to recent multi-center studies[8], and the inability to analyse alcohol intake as a variable due to missing data points.

Two of our 40 patient with SPS (5%) were diagnosed with colorectal cancer during the 3 year evaluation period, neither of whom reported symptoms suggestive of malignancy. Quantification of the magnitude in which SPS increases the risk of CRC is difficult. Early case series have reported rates of 16%-29% in synchronous cancer at the time of SPS diagnosis, however theses risk estimates were likely inflated due to inclusion of many patients symptomatic of cancer not patients undergoing screening. In 2015 Carballal *et al*[8] described a cumulative CRC incidence of 1.9% over 5 years in a group of 296 patients with SPS in Spain. Forty-seven patients (15.8%) developed cancer during follow-up, with 4/47 (8.5%) developing tumours during surveillance. One of our two patients who developed colorectal cancer had a previous colonoscopy at a different endoscopy centre, where the optical training of the endoscopist and bowel preparation quality is unclear and the diagnosis of SPS could have been missed.

Consistent with previous reports, our cohort with SPS demonstrated some phenotypic heterogeneity[9]. Patients diagnosed with the syndrome were aged from 23 years to 73 years and had an overall polyp count ranging from 7 to 40 polyps, with the largest polyp resected ranging from 10 mm to 40 mm. However, there were some clinical features that were distinct for patients with SPS compared to those with SSAs not meeting WHO criteria and patients with adenomas. SPS patients were significantly younger and more likely to be

caucasian. The polyp groups were matched according to gender hence the gender distribution across the three groups were identical, but the over-representation of women in 75% of patients with SPS suggests that being a women is likely a positive predictor for SPS. Having a first degree relative with CRC was no more strongly associated with SPS than any other polyp groups, somewhat supportive of the lack of genetic causality found in SPS patients so far. Cigarette exposure was found in greater number of patients with SPS than other groups but this didn't reach statistical significance. Our data adds to the controversy in current literature on whether or not smoking is a risk factor in the serrated pathway[10,11]. Past population-based studies have shown that cancers arising from serrated pathways are specifically associated with cigarette smoking but Liang *et al*[12] published a meta-analysis in 2009 showing a stronger association with smoking and distal/rectal cancer.

The endoscopic features of our SPS cohort were intrinsic to definition of the disease. Compared to other polyp groups, a greater total number of polyps were discovered in SPS and the size of the dominant polyp was also bigger. SPS was also significantly associated with polyps found with predominance for the right colon. Somewhat surprisingly, the spread of the largest polyp in patients with SSA not meeting WHO criteria was evenly across both right and left colon. In Carballal's study on CRC risk factors, 53% of the cancers found in a cohort of 293 patients with SPS were discovered in the distal colon[8]. Coupled with the fact that 42% of our SPS patients and 52% of our SSA patients had concurrent adenomas, it seems the pathway to colorectal cancer is indeed a complex interplay between various carcinogenic pathways we are yet to fully untangle.

The cumulative definition of SPS isn't widely known as it not consistently included in published versions of the WHO criteria. In our study, 14/40 patients could have potentially been mis-diagnosed if the endoscopist didn't recognise that their cumulative polyp load over successive colonoscopy during the study period were enough to qualify for SPS diagnosis. Although no pre-endoscopic risk factors was found be distinguish the subgroup of SPS diagnosed at index colonoscopy from the subgroup with cumulated polyp count, the fact that both patients with colorectal cancer were diagnosed at a follow-up colonoscopy suggest that there may be important differences in the two groups. Discussion about how to manage patients who may soon develop SPS seems to be sparse. Currently ASGE and ESGE guidelines for patients with SSAs that don't meet WHO criteria is very similar to adenomas, stratified according to size and number. The earliest recommended followup colonoscopy for serrated polyps without dysplasia is 3 years[13]. Contrasting this with patients with established SPS, the recommended followup colonoscopy is 1 year. Recently, Rivera-Sanchez *et al*[14] assessed the incremental rate of SPS diagnosis in 191 patients with proximal serrated lesions larger than 5 mm after a

positive FOBT. One year after the index colonoscopy's where they found 11 patients with SPS, they performed a reassessment colonoscopy in 71 patients and found 20 new patients with SPS. It is postulated that the polyps found on reassessment colonoscopy were either missed during initial colonoscopy or newly grown and early reassessment colonoscopy at 1 year substantially improved SPS detection rate in patients with proximal serrated lesions. Results of our study indicate that there is a substantial number of patients with a polyp load that is borderline for fulfilling WHO criteria and Rivera-Sanchez showed there is good yield in performing reassessment colonoscopy as early as 1 year. Hence, we suggest that there is a population of patients with SSAs that are at risk of developing SPS in near future or have missed serrated polyps that would benefit from earlier endoscopic follow up than currently recommended. Larger prospective studies are required to stratify exactly which threshold qualify a patient for earlier screening, but a revision of guidelines to encourage more accurate and earlier detection SPS would be prudent.

COMMENTS

Background
At the time of diagnosis, sessile serrated polyposis syndrome (SPS) is associated with high risk of concurrent colorectal cancer. However once patients enter a surveillance program and undergo the recommended yearly colonoscopies, the absolute 5-year colorectal cancer (CRC) risk falls dramatically. Hence, early diagnosis of SPS is crucial as it radically change the natural history of patients with the disorder. Serrated and adenomatous polyps share many clinical risk factors; however it is unclear if certain risk factors have a stronger association with one polyp subtype compared to another.

Research frontiers
Despite there being a small number of studies investigating the differences in risk factors for distinct polyp subtypes, no study to date has included SPS as one of the comparators.

Innovations and breakthroughs
Patients diagnosed with SPS were younger and more likely to be Caucasian compared to patients with adenomatous polyps and patients with serrated adenomas not meeting World Health Organization (WHO) criteria. The vast majority of SPS patients diagnosed were women. Patients with SPS were no more likely to have a family history of colorectal cancer or cigarette exposure than other polyp groups. In addition, 14 out of 40 patients with SPS could have potentially been mis-diagnosed if the endoscopist didn't recognise that their cumulative polyp load over successive colonoscopy over 3 years were enough to qualify for the diagnosis. This suggest that patients with a polyp load that is borderline for fulfilling WHO criteria have a good chance of qualifying for a SPS diagnosis if reassessment colonoscopy is performed as early as 1 year.

Applications
There is a population of patients with sessile Serrated adenoma that are at risk of developing SPS in near future or have missed serrated polyps that would benefit from earlier endoscopic follow up than currently recommended. Larger prospective studies are required to stratify exactly which threshold qualifies a patient for earlier screening, but a revision of guidelines to encourage more accurate and earlier detection SPS would be prudent.

Terminology
SPS refers to sessile serrated polyposis syndrome. It is defined by a set of

clinical and histo-pathological features by World Health Organisation.

Peer-review

Well-documented study highlighting the main possible risk factors which could interfere in SPS development. Even though the number of participants in the study is small, the statistical analysis seems to reveal interesting information as concerns the SPS background and the potential of shortening the surveillance interval of the syndrome.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Colonoscopy quality with Entonox® *vs* intravenous conscious sedation: 18608 colonoscopy retrospective study

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Abstract

AIM
To compare colonoscopy quality with nitrous oxide gas (Entonox®) against intravenous conscious sedation using midazolam plus opioid.

METHODS
A retrospective analysis was performed on a prospectively held database of 18608 colonoscopies carried out in Lothian health board hospitals between July 2013 and January 2016. The quality of colonoscopies performed with Entonox was compared to intravenous conscious sedation (abbreviated in this article as IVM). Furthermore, the quality of colonoscopies performed with an unmedicated group was compared to IVM. The study used the following key markers of colonoscopy quality: (1) patient comfort scores; (2) caecal intubation rates (CIRs); and (3) polyp detection rates (PDRs). We used binary logistic regression to model the data.

RESULTS

There was no difference in the rate of moderate-to-extreme discomfort between the Entonox and IVM groups (17.9% *vs* 18.8%; OR = 1.06, 95%CI: 0.95-1.18, *P* = 0.27). Patients in the unmedicated group were less likely to experience moderate-to-extreme discomfort than those in the IVM group (11.4% *vs* 18.8%; OR = 0.71, 95%CI: 0.60-0.83, *P* < 0.001). There was no difference in caecal intubation between the Entonox and IVM groups (94.4% *vs* 93.7%; OR = 1.08, 95%CI: 0.92-1.28, *P* = 0.34). There was no difference in caecal intubation between the unmedicated and IVM groups (94.2% *vs* 93.7%; OR = 0.98, 95%CI: 0.79-1.22, *P* = 0.87). Polyp detection in the Entonox group was not different from IVM group (35.0% *vs* 33.1%; OR = 1.01, 95%CI: 0.93-1.10, *P* = 0.79). Polyp detection in the unmedicated group was not significantly different from the IVM group (37.4% *vs* 33.1%; OR = 0.97, 95%CI: 0.87-1.08, *P* = 0.60).

CONCLUSION

The use of Entonox was not associated with lower colonoscopy quality when compared to intravenous conscious sedation using midazolam plus opioid.

Key words: Gastrointestinal endoscopy; Colonoscopy; Caecal intubation; Benzodiazepine; Polyp detection; Nitrous oxide; Entonox; Midazolam; Sedation; Unsedated

Core tip: Previous studies have shown that colonoscopies performed with Entonox® gas are not associated with more patient discomfort, or lower caecal intubation rates, than those performed with intravenous conscious sedation. We have completed the largest and most comprehensive real-world retrospective study of Entonox use in colonoscopy. In particular, we compare colonoscopy quality with Entonox against intravenous conscious sedation using midazolam plus opioid. This study shows that Entonox is not associated with lower colonoscopy quality when compared to intravenous conscious sedation. Based on the results of this study, Entonox remains an attractive option for colonoscopy analgesia and sedation.

INTRODUCTION

Nitrous oxide gas (N2O) has well established analgesic and sedative properties[1-4]. It is likely that the analgesic effect of nitrous oxide is opioid receptor-mediated[5,6].

Furthermore, and although less well characterised, animal models suggest that the anxiolytic effect of nitrous oxide is benzodiazepine receptor-mediated[7].

Entonox® (50% nitrous oxide: 50% oxygen) is routinely used as a patient-controlled inhaled analgesic and sedative. In particular, it is used in various emergency, orthopaedic, and obstetric procedures[8,9]. It is not as frequently used in gastrointestinal (GI) endoscopy, with intravenous conscious sedation (benzodiazepine use in combination with an opioid) being the standard sedation regime in the United Kingdom[10].

A useful way of examining standards in colonoscopy practice is to use the framework of "colonoscopy quality"[11-13]. The aim of current colonoscopy quality guidelines [jointly adopted by the Joint Advisory Group on GI Endoscopy, the British Society of Gastroenterology (BSG), and the Association of Coloproctology of Great Britain and Ireland] is to improve patient care[14]. Three important markers of colonoscopy quality are: (1) < 10% of patients should experience moderate or severe discomfort; (2) the caecal intubation rate (CIR) should be ≥ 90%; and (3) the polyp detection rate (PDR) should be ≥ 15%[14].

Welchman *et al*[15] conducted a systematic review of Entonox use in colonoscopy. Their review, which included a total of 623 patients, was based on data from 9 small randomised controlled trials (RCTs). The authors concluded that "N2O provides comparable analgesia to *i.v.* sedation". A Cochrane review of 547 patients (from 7 of the RCTs), where the primary outcome was adequate pain relief during the procedure, similarly, reached the conclusion that Entonox was "as efficient" as intravenous sedation in reducing pain/discomfort during colonoscopy[16].

Neither the Welchman *et al*[15] and Aboumarzouk *et al*[16] nor Cochrane reviews found (based on more limited data) any difference in CIRs when Entonox and intravenous sedation groups were compared directly. However, CIRs were found, in a large prospective study by Radaelli *et al*[17], to be higher in the intravenous benzodiazepine (*n* = 3701; CIR = 83.1%) *vs* unsedated (*n* = 5737; CIR = 76.1%) groups (OR = 1.460, 95%CI: 1.282-1.663). Radaelli *et al*[17] also demonstrated that PDRs were higher in intravenous benzodiazepine (*n* = 3701; PDR = 26.9%) *vs* unsedated (*n* = 5737; PDR = 26.5%) groups (OR = 1.121, 95%CI: 1.016-1.236). A small study at a UK private hospital found a higher adenoma detection rate (but not PDR) in the Entonox group compared to the intravenous sedation group[18].

Endoscopic procedure data from UK endoscopy units have been used to retrospectively analyse colonoscopy quality associated with different types of analgesia/sedation. Two independently conducted retrospective studies of NHS endoscopy units (one of 2873 patients at Altnagelvin Area Hospital, Northern Ireland[19] and another of 322 patients at Furness General Hospital, England[20]) have found that CIRs, PDRs, and patient comfort scores were similar in patients receiving

Entonox *vs* intravenous sedation.

In this study we assessed the quality of colonoscopies performed with Entonox against intravenous conscious sedation (abbreviated in this article as IVM) using intravenous midazolam plus opioid. We also compared colonoscopy quality with an unmedicated group against IVM. We used the following markers of colonoscopy quality: (1) patient comfort scores; (2) CIRs; and (3) PDRs.

MATERIALS AND METHODS

Study design and setting
Eighteen thousand six hundred and eight colonoscopies were undertaken between July 2013 and January 2016 at one of four NHS colonoscopy units within Lothian health board: (1) the Royal Infirmary of Edinburgh; (2) the Western General Hospital, Edinburgh; (3) St John's Hospital, Livingston; or (4) Roodlands Hospital, Haddington. Relevant patient and procedural data was recorded by the endoscopist/nurse at the time of colonoscopy using Unisoft's electronic GI Reporting Tool (Unisoft Medical Systems, Enfield, United Kingdom). The database was retrospectively analysed.

Procedures were performed using Olympus XQ 240 and XQ260 and Fuji EC530WL and EC600WL colonoscopes. Generally during the procedures the endoscopist and two nurses where present, regardless of regime type, and patients routinely had blood pressure, heart rate and oxygen saturation monitoring.

At each of these units, throughout this timeframe, patients were offered the choice of either: (1) Entonox; (2) intravenous conscious sedation (IVM) with midazolam plus or minus opioid; or (3) no sedation or analgesia (*i.e.*, unmedicated), each administered by the performing endoscopist. Patients offered Entonox had the option of fentanyl plus or minus midazolam as an adjunct if required and clinically appropriate. There were 234 individual cases of patients receiving both Entonox and midazolam sedation (1.26% of the total), and all these cases were all excluded from the analysis. This situation could have arisen in the case where the patient was not adequately responding to IVM and Entonox was then introduced as an adjunct or vice versa. Ninety-nine percent of patients receiving IVM had a combination of fentanyl analgesia and midazolam sedation at the start of the procedure.

Local exclusion criteria for Entonox
Local exclusion criteria for the use of Entonox are head injury or altered GCS, maxillo-facial injuries, drug or alcohol intoxication, pneumothorax or chest trauma, decompensated respiratory disease, decompression sickness or recent underwater diving, the first sixteen weeks of pregnancy, middle ear occlusion, high risk infection, *e.g.,* MRSA/VRE or vitamin B12 deficiency (see the regulator-approved summary of product characteristics[21]).

Measured variables
A "polyp" was defined as such by the performing endoscopist when reporting the investigation. For the purpose of this study polyps were either detected or not detected. Caecal intubation was confirmed by identification of caecal landmarks and recording these in the reporting software with supporting photo-documentation where possible. For the purpose of this study caecal intubation was either achieved or was not achieved.

Patient comfort score was endoscopist/nurse reported and recorded as either: "no discomfort", "mild discomfort", "moderate discomfort", "severe discomfort", or "extreme discomfort".

In the primary analysis "moderate", "severe", and "extreme" discomfort were combined into a single "moderate-to-extreme" discomfort binary variable because this was felt to be the most clinically relevant approach and is consistent with the current United Kingdom colonoscopy quality guidelines[14]. A secondary analysis compared rates of mild discomfort between sedation groups. This analysis only included the subgroup of patients that had either "no" or "mild" discomfort, *i.e.,* patients with either "moderate, "severe", and "extreme" discomfort were excluded from the analysis. Therefore, in this secondary analysis, the new patient comfort variable was again a binary variable.

Statistical analysis
The data were exported from the Unisoft GI reporting tool to an Excel 2016 spreadsheet (Microsoft Corporation, WA, United States). The statistical analysis was subsequently performed by importing the data into the software package R Version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria). The caecal intubation and polyp detection variables were separately analysed using binary logistic regression to assess for an association with different types of colonoscopy analgesia/sedation. The caecal intubation and polyp detection fields were treated as binary dependent variables. Patient age and gender were included as independent variables.

RESULTS

Patient characteristics and analgesia/sedation regimes
One thousand five hundred and one colonoscopies were excluded for one or more of 5 reasons: (1) the patient was a child under the age of 18 ($n = 35$); (2) the comfort score was not recorded ($n = 154$); (3) the patient had undergone a general anaesthetic ($n = 26$); (4) the patient was administered both Entonox and midazolam ($n = 234$); and (5) the patient had opioid alone ($n = 1091$). This left a total of 17107 patients to be included in the final analysis (Table 1).

Patient comfort score
A graphical representation of comfort scores by analgesia/sedation type and gender is shown in Figure 1.

Figure 1 Patient comfort scores by sedation type used and patient gender. This figure uses 100% stacked bars to provide a graphical representation of the proportions of each level of patient discomfort (see legend; inset right) with each sedation type in females (A) and males (B).

Table 1 Descriptive statistics of demographic and medication variables for patients receiving different analgesia/sedation regimes

Variable	Type of analgesia/sedation		
	Midazolam ± opioid	Entonox ± opioid	Unmedicated
Gender			
Female (% of females)	6753 (76.0%)	1609 (18.1%)	520 (5.9%)
Male (% of males)	4613 (56.1%)	2239 (27.2%)	1373 (16.7%)
Median age/yr (IQR)	61.1 (50.7-70.1)	60.4 (50.8-69.1)	63.8 (54.3-71.4)
Median midazolam dose/mg (IQR)	2.5 (2.0-3.0)		
Opioid, mcg			
Number (%) given fentanyl	10255 (90.2%)	258 (6.7%)	0 (0.0%)
Number (%) given pethidine	1060 (9.3%)	27 (0.7%)	0 (0.0%)
Total number (%) given an opioid	11299 (99.4%)	284 (7.4%)	0 (0.0%)
Median fentanyl equivalent dose (IQR)	75.0 (50.0-100.0)	75.0 (50.0-100.0)	

IQR: Interquartile range.

There was no difference in the rate of moderate-to-extreme discomfort in the Entonox group compared to the IVM group (17.9% *vs* 18.8%; OR = 1.06, 95%CI: 0.95-1.18, *P* = 0.27) (Table 2). Patients in the unmedicated group were less likely to experience moderate-to-extreme discomfort than those in the IVM group (11.4% *vs* 18.8%; OR = 0.71, 95%CI: 0.60-0.83, *P* < 0.001).

There was no statistical association of age with moderate-to-extreme discomfort (OR = 1.00, 95%CI: 1.00-1.01, *P* = 0.08). Males were less likely to experience moderate-to-extreme discomfort than females (11.3% *vs* 23.9%; OR = 0.40, 95%CI: 0.36-0.43, *P* < 0.001).

Amongst only those patients experiencing mild or no discomfort, Entonox was associated with greater likelihood of mild discomfort compared to IVM (64.7% *vs* 58.9%; OR = 1.46, 95%CI: 1.33-1.61, *P* < 0.001).

Caecal intubation
In addition to the exclusions listed at the beginning of this section, 74 cases where the extent of intubation was listed as "anastomosis" were excluded from the caecal intubation calculation. A further 3 cases where the extent of intubation was not recorded were also excluded.

There was no difference in caecal intubation between the Entonox and IVM groups (94.4% *vs* 93.7%; OR = 1.08, 95%CI: 0.92-1.28, *P* = 0.34) (Table 3). Furthermore, there was no difference in caecal intubation between the unmedicated and IVM groups (94.2% *vs* 93.7%; OR = 0.98, 95%CI: 0.79-1.22, *P* = 0.87).

There was a negative association of age with caecal intubation (OR = 0.98, 95%CI: 0.97-0.98, *P* < 0.001). Males had higher caecal intubation compared to females (95.3% *vs* 92.7%; OR = 1.61, 95%CI: 1.41-1.85, *P* < 0.001).

PDR
Polyp detection in the Entonox group was not significantly different from the IVM group (35.0% *vs* 33.1%; OR = 1.01, 95%CI: 0.93-1.10, *P* = 0.79) (Table 4). Furthermore, polyp detection in the unmedicated group

Table 2 Moderate-to-extreme against none-mild discomfort by analgesia/sedation type

Variable[1]	No. with moderate-to-extreme discomfort (%)[2]	Odds ratio (95%CI)[1]	*P* value[1]
Sedation type			
Midazolam ± opioid	2137 (18.8)	Reference	
Entonox ± opioid	689 (17.9)	1.06 (0.95-1.18)	0.27
Unmedicated	215 (11.4)	0.71 (0.60-0.83)	< 0.001
Age		1.00 (1.00-1.01)	0.08
Gender			
Female	2114 (23.9)	Reference	
Male	927 (11.3)	0.40 (0.36-0.43)	< 0.001

[1]The dichotomous "moderate-to-extreme"/"none-mild" discomfort dependent variable was regressed on the sedation type, age, and gender independent variables using binary logistic regression. Output is expressed as odds ratios and *P* values; [2]This column lists the number (simple percentage) of patients with moderate-to-extreme discomfort in each sedation type and gender group.

Table 3 Caecal intubation for patients receiving different analgesia/sedation regimes

Variable[1]	Caecal intubation rate, *n* (%)[2]	Odds ratio (95%CI)[1]	*P* value[1]
Sedation type			
Midazolam ± opioid	10562 (93.7)	Reference	
Entonox ± opioid	3612 (94.4)	1.08 (0.92-1.28)	0.34
Unmedicated	1763 (94.2)	0.98 (0.79-1.22)	0.87
Age		0.98 (0.97-0.98)	< 0.001
Gender			
Female	8159 (92.7)	Reference	
Male	7778 (95.3)	1.61 (1.41-1.85)	< 0.001

[1]The dichotomous caecal intubation dependent variable was regressed on the sedation type, age, and gender independent variables using binary logistic regression. Output is expressed as odds ratios and *P* values. [2]This column lists the number (simple percentage) of patients in which caecal intubation was achieved in each sedation type and gender group.

Table 4 Polyp detection for patients receiving different analgesia/sedation regimes

Variable[1]	Polyp detection rate, *n* (%)	Odds ratio (95%CI)[1]	*P* value[1]
Sedation type			
Midazolam ± opioid	3755 (33.1)	Reference	
Entonox ± opioid	1345 (35.0)	1.01 (0.93-1.10)	0.79
Unmedicated	707 (37.4)	0.97 (0.87-1.08)	0.6
Age		1.03 (1.03-1.03)	< 0.001
Gender			
Female	2454 (27.7)	Reference	
Male	3353 (40.8)	1.83 (1.71-1.96)	< 0.001

[1]The dichotomous polyp detection dependent variable was regressed on the sedation type, age, and gender independent variables using binary logistic regression. Output is expressed as odds ratios and *P* values. 2This column lists the number (simple percentage) of patients in which polyp(s) was/were detected in each sedation type and gender group.

was not significantly different from the IVM group (37.4% *vs* 33.1%; OR = 0.97, 95%CI: 0.87-1.08, *P* = 0.60).

There was a positive association of age with polyp detection (OR = 1.03, 95%CI: 1.03-1.03, *P* < 0.001). Males had higher polyp detection compared to females (40.8% *vs* 27.7%; OR = 1.83, 95%CI: 1.71-1.96, *P* < 0.001).

DISCUSSION

Previous systematic reviews of the clinical trial data, although limited by the small sample sizes of the constituent trials, show nitrous oxide to be as effective as IVM in controlling patient discomfort during colonoscopy. Furthermore, they show that CIRs are comparable between the two groups[15,16]. The two independently conducted retrospective studies of real-world colonoscopy data have also suggested equivalence between nitrous oxide and IVM. However, in addition to their relatively small sample size, these latter studies were notably limited by the way in which they analysed the data using descriptive and basic inferential statistics[19,20]. There has therefore been a need for a larger and more comprehensive retrospective study.

In our study we used binary logistic regression to model the data. We found no difference in moderate-to-

extreme discomfort experienced, caecal intubation, and polyp detection between the intravenous medication and Entonox groups.

Our study therefore supports and strengthens the data from existing studies in suggesting that using Entonox is not associated with lower colonoscopy quality than IVM.

The key implication of this finding is that patients can continue to be offered the same level of choice with respect to their colonoscopy analgesia/sedation. There are many factors associated with Entonox use that may be attractive to patients relative to IVM. For example, some patients are likely to be attracted by the rapid post-procedure recovery associated with Entonox use[15,16]. In particular, after using Entonox patients have the potential to be discharged after just 30 min[22], are safe to drive[23], and do not require overnight home supervision by a responsible person. This could manifest itself in improved patient satisfaction levels with their post-procedural care. Furthermore, although outside the remit of this study, it could contribute to efficiency and cost savings in the endoscopy department by optimising patient flow.

As measured by CIR and PDR the overall quality of colonoscopy performed in the included centres was good. All groups met the ≥ 90% (CIR) and ≥ 15% (PDR) BSG/Joint Advisory Group on GI Endoscopy/ Association of Coloproctology standards[14]. Furthermore we were gratified, because of its implication of good colonoscopy technique, to see that the unmedicated group experienced a lower level of discomfort compared to the IVM group. We are not aware of any previous studies demonstrating an association of no sedation with lower levels of patient discomfort. Ristikankare *et al*[24] found no significant difference in patient experience between an intravenous midazolam sedation group and a no intravenous cannula control group. Furthermore, studies have demonstrated the feasibility of unsedated colonoscopy[25,26]. The NordICC study is a large population-based RCT into the effectiveness of colonoscopy screening for colorectal cancer. The NordICC study group has published an interim data analysis showing that overall "pain during colonoscopy was not significantly associated with the use of sedation (adjusted odds ratio, 0.91; 95%CI: 0.61-1.35)"[27].

Within this analysis the CIR and PDR of the un-medicated group where not significantly different compared with the IVM patients.

Polyp detection rate was used rather than adenoma detection as analysis was based on reports written during and immediately following the procedure, and as such prior to histological differentiation of the polyp.

The way that Entonox is used by GI endoscopists in the UK varies. In particular, some endoscopists use Entonox as a primary agent, whereas others use it as an adjunct to another standard analgesia/sedation regime. Within Lothian health board Entonox is principally used as a primary agent. In only 234 cases, 1.26% of the total number, were patients administered both Entonox and intravenous midazolam. Consequently, variability in Entonox use with respect to its primary or adjunctive status was not something that could be addressed by this study.

The introduction of comfort scores in the assessment of colonoscopy quality was initially recommended by the BSG Endoscopy Committee in order to monitor whether, in striving to achieve total colonoscopy to the caecum, endoscopists were causing unacceptable pain and distress to patients[13,28]. However, it has been demonstrated that the best colonoscopists (typically those performing the most procedures per annum) have "a higher CIR, use less sedation, cause less discomfort and find more polyps"[28]. This highlights the importance of the technical skill of the endoscopist in relation to patient comfort during colonoscopy. Indeed, the initial data from the NordICC study show that individual endoscopist performance is associated with significant variability in CIRs, adenoma detection rates, and the percentage of participants with moderate or severe pain[27].

Interestingly, among the subgroup of patients experiencing "none" or "mild" discomfort, Entonox was associated with more patients having "mild" discomfort when compared to IVM. This was a secondary analysis, as it was felt that (in line with the UK guidelines and the ongoing NordICC study) patient discomfort is most important when it is moderate or worse[14,27]. Furthermore, there have been differences reported in the way that nurses, endoscopists, and patients report comfort. In particular, Rafferty *et al*[29] found that nurses tend to give higher comfort scores, in other words report more discomfort, than the endoscopist and the patient. This suggests that the distinction between "none" and "mild" discomfort is potentially not meaningful. Furthermore, the use of the Entonox apparatus during colonoscopy is likely to be associated with a learning curve, with colonoscopy technique modification required to maximise its effect. As such there is likely to be inter-operator variability in outcomes with Entonox. Within this study there was no data collected on the individual endoscopists experience in relation to patient outcomes but further discussion and study into the importance of the endoscopist with respect to Entonox would be highly beneficial.

There was a marked gender effect in our patient population. Females experienced significantly worse patient comfort scores, CIRs, and PDRs. Indeed, these gender differences in comfort scores[27,30-32], caecal intubation rates or times[33,34], and PDRs/adenoma detection rates[35,36] are well established in the literature. The difference with respect to comfort scores can potentially be accounted for by two physical factors. Firstly, females have a pelvic anatomy, and a longer colon that are more predisposed to "looping" than in males[37,38]. Secondly, gynaecological surgery can result in anatomical distortion and pelvic or abdominal adhesions that make colonoscopy more difficult, and therefore more uncomfortable for the patient.

This is supported by the evidence that previous hysterectomy is associated with greater discomfort during colonoscopy[31,39,40]. It has been postulated that responses to pain and discomfort may be related to psychosocial factors[41]. However, we are not aware of any study that has sufficiently differentiated these factors from past surgical history and other considerations. Within our analysis procedures with the limit listed as "anastomosis" have been removed. As further surgeries have been incompletely documented they have not been corrected for. Overall, the uncertainty of the relative importance of these factors highlights the need for future clinical research in colonoscopy analgesia and sedation to consider the possibility of important gender differences generally, as well as more specifically in relation to response to sedation.

There was the potential in this study for patient and endoscopist selection bias. This might explain the observation that unmedicated patients experienced lower levels of discomfort when compared to the IVM group. Patients who had previous high tolerance of colonoscopy for example would be likely to select the unmedicated option. Endoscopist and nurse reporting of comfort scores may also have significant inter-observer variability. Furthermore, patient comfort scores were entirely endoscopist or nurse reported. There was no data recorded on analgesics being taken regularly prior to the procedure or whether the recorded procedure was their first.

Although data was collected on the indications for colonoscopy these were similar between the groups and as such not included in the final analysis.

Procedures were carried out by a combination of gastroenterologists, surgeons and nurse endoscopists with varying experience. This information, and the personal experience of the endoscopist was not included within this study.

Bowel preparation, its quality, colonoscopy technique and complication rates were not included within the data analysed. Within the endoscopy departments a Moviprep based schedule was most commonly used. The predominant technique employed was air insufflations although carbon dioxide insufflation was also common and exceptions to this are likely to be equally distributed among the groups.

This is a large retrospective study whose merits lie not in the systematic elimination of bias but rather in observing the real-world quality markers associated with the different analgesia and sedation regimes. This type of study is therefore important for its ability to encourage and facilitate quality and service improvement.

In conclusion, this study shows that Entonox is not associated with lower colonoscopy quality when compared to intravenous conscious sedation. Entonox therefore remains an attractive option for colonoscopy analgesia and sedation. In most cases, decisions regarding analgesia and sedation are the result of an informed discussion between patient and endoscopist in which several factors, such as patient comorbidities and individual patient preferences, are taken into account.

COMMENTS

Background
Previous small randomised controlled trials have shown that colonoscopies performed with Entonox® gas are not associated with more patient discomfort, or lower caecal intubation rates (CIRs), than those performed with intravenous conscious sedation using intravenous conscious sedation (IVM). Furthermore, the two published retrospective studies of "real-world" colonoscopy data have also suggested an equivalence between nitrous oxide and IVM. However, in addition to their relatively small sample size these studies have been limited by their statistical methodology.

Research frontiers
The authors have now completed the largest and most comprehensive real-world retrospective study of Entonox use in colonoscopy. In particular, the authors have compared colonoscopy quality with Entonox against intravenous conscious sedation using midazolam plus opioid. The study used the following key markers of colonoscopy quality: (1) patient comfort scores; (2) caecal intubation rates (CIRs); and (3) polyp detection rates (PDRs). The authors used binary logistic regression to model the data.

Innovations and breakthroughs
This study shows that Entonox is not associated with lower colonoscopy quality when compared to intravenous conscious sedation.

Applications
Based on the results of this study, Entonox remains an attractive option for colonoscopy analgesia and sedation.

Terminology
Entonox is the proprietary name of the commercially available compressed gaseous mixture of 50% nitrous oxide: 50% oxygen.

Peer-review
This is a large and interesting study which is well written. The authors demonstrated the equal effectiveness between N_2O and intravenous midazolam for patient's anesthesia in performing the colonoscopy.

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ORIGINAL ARTICLE

Retrospective Study

Efficacy and safety of liquid nitrogen cryotherapy for treatment of Barrett's esophagus

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Abstract

AIM
To evaluate the efficacy and safety of liquid nitrogen cryotherapy as a primary or rescue treatment for BE, with and without dysplasia, or intramucosal adenocarcinoma (IMC).

METHODS
This was a retrospective, single-center study carried out in a tertiary care center including 45 patients with BE who was treatment-naïve or who had persistent intestinal metaplasia (IM), dysplasia, or IMC despite prior therapy. Barrett's mucosa was resected *via* EMR when clinically appropriate, then patients underwent cryotherapy until eradication or until deemed to have failed treatment. Surveillance biopsies were taken at standard intervals.

RESULTS
From 2010 through 2014, 33 patients were studied regarding the efficacy of cryotherapy. Overall, 29 patients (88%) responded to cryotherapy, with 84% having complete regression of all dysplasia and cancer. Complete eradication of cancer and dysplasia was seen in 75% of subjects with IMC; the remaining two subjects did not respond to cryotherapy. Following cryotherapy, 15 patients with high-grade dysplasia (HGD) had 30% complete regression, 50% IM, and 7% low-grade dysplasia (LGD); one subject had persistent HGD. Complete eradication of dysplasia occurred in all 5 patients with LGD. In 5

patients with IM, complete regression occurred in 4, and IM persisted in one. In 136 cryotherapy sessions amongst 45 patients, adverse events included chest pain (1%), stricture (4%), and one gastrointestinal bleed in a patient on dual antiplatelet therapy who had previously undergone EMR.

CONCLUSION
Cryotherapy is an efficacious and safe treatment modality for Barrett's esophagus with and without dysplasia or intramucosal adenocarcinoma.

Key words: Barrett's esophagus; Esophageal adenocarcinoma; TruFreeze; Liquid nitrogen cryotherapy; Radiofrequency ablation

Core tip: Liquid nitrogen based cryotherapy is efficacious as a treatment modality for Barrett's esophagus, especially dysplastic Barrett's esophagus, either as a first or second line therapy.

INTRODUCTION

Approximately 17000 people are diagnosed with, and 15600 die of, esophageal cancer each year in the United States[1]. The incidence of esophageal adenocarcinoma has increased greatly over the past several decades, and Barrett's esophagus is a known risk factor for and the sole precursor lesion to esophageal adenocarcinoma[2]. Barrett's without dysplasia has an increased esophageal cancer risk of approximately 0.3% per year[2]. High-grade dysplasia progresses to adenocarcinoma at a rate as high as 10% per year[2,3].

Several endoscopic ablative modalities are available for the treatment of Barrett's esophagus as alternatives to esophagectomy including cryotherapy, argon plasma coagulation (APC), photodynamic therapy, and radiofrequency ablation (RFA). These therapies are often times used in conjunction with endoscopic mucosal resection (EMR) to improve efficacy, especially in long-segment BE[4]. Liquid nitrogen cryotherapy is a noncontact ablation therapy with ease of use compared to other endoscopic modalities[5]. It works *via* a low-pressure spray of liquid nitrogen that freezes tissue at -196℃ (Figure 1)[6]. Its major advantage is the ability to spray large areas without contact, whereas other therapies require precise contact between the probe and esophageal mucosa[7]. This makes it particularly

useful for lesions at the gastroesophageal junction and in cases of complex esophageal anatomy including large hiatal hernias[7].

Current studies regarding the efficacy of cryotherapy are limited by small sample sizes and short observation times; therefore, more data is required so that findings can be compiled into meta-analyses with large numbers of subjects observed over extended periods of time after completion of treatment. Currently available studies have also demonstrated an excellent safety profile with a low risk of adverse events[5,8-13], therefore conferring a unique clinical advantage. The aim of this study was to evaluate the efficacy and safety data for liquid nitrogen cryotherapy as primary or rescue treatment of Barrett's esophagus with intestinal metaplasia, dysplasia, and intramucosal adenocarcinoma at our institution.

MATERIALS AND METHODS

Study design and patients
This was a retrospective, institutional review board-approved study of a Barrett's esophagus database at an academic tertiary referral center (Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania) and included all patients that underwent liquid nitrogen cryotherapy for the treatment of Barrett's esophagus at our institution from January 2010 through December 2014.

Inclusion criteria were adult patients that underwent liquid nitrogen cryotherapy for biopsy-proven Barrett's esophagus of any length including intestinal metaplasia (IM), low-grade dysplasia (LGD), high-grade dysplasia (HGD), and intramucosal adenocarcinoma (IMC). Endoscopic cryotherapy was offered to appropriate patients on a case-by-case basis both as primary and/or rescue therapy after discussion of the risks and benefits. All patients with intramucosal adenocarcinoma or confirmed high-grade dysplasia on pathology underwent endoscopic ultrasound to rule out nodal or local metastatic disease. Patients who did not follow-up for surveillance biopsies after treatment were included only in the data evaluating for adverse events.

Patients were excluded from the study if they were treated with other endoscopic ablative modalities during the study period, if adenocarcinoma extended beyond the muscularis mucosa, or if evidence of metastatic disease was present.

The database was reviewed in 2015 after the study endpoint. The study was reviewed and approved by the Penn State Milton S. Hershey Medical Center Institutional Review Board (IRB #00002498). Informed consent requirement was waived given the retrospective nature of the study.

Intervention
All patients underwent sedated, outpatient, high resolution endoscopy, performed by several experienced therapeutic endoscopists, and mucosal biopsies were obtained if indicated. Patients with intramucosal adenocarcinoma or

Figure 1 Low-pressure spray of liquid nitrogen that freezes tissue at -196 ℃.

high-grade dysplasia underwent endoscopic ultrasound to exclude metastatic or nodal disease; suspicious lymph nodes were sampled to help reassure against occult invasive disease. Endoscopic mucosal resection was performed when nodular Barrett's was encountered prior to initiation of cryotherapy or during the cryotherapy session after cryoablation was complete. The primary goal of cryotherapy was complete regression or downgrading of intestinal metaplasia, dysplasia, and cancer.

The truFreeze® spray cryotherapy system (CSA Medical Inc., Baltimore, Maryland, United States) was used to deliver liquid nitrogen to visible columnar mucosa and the gastroesophageal junction for two cycles of 20 s bursts with observation for adequate freeze and thaw. The timing for dosing was started when ice formation was detected on the treated mucosa. Decompression *via* a separate catheter was ensured. Multiple treatments were performed based on endoscopic findings and the length of the Barrett's segments. Patients returned for additional cryotherapy sessions until there was endoscopic and pathologic evidence of complete eradication of Barrett's esophagus or until treatment was deemed to have failed, defined as lack of responsiveness to therapy confirmed by endoscopy and pathology. Mucosal biopsies were obtained prior to the onset of therapy every 1cm in four quadrants as well as targeted biopsies for areas of concern. Surveillance biopsies using the same technique were at the discretion of the treating endo-scopist during treatment and were performed after complete eradication of visible Barrett's in the entire pre-treatment segment at 3, 6, and 12 mo following completion of therapy.

Adverse events during and immediately after the procedure were recorded. Patient charts were reviewed to determine if patients experienced any adverse effects thereafter, and esophageal stricture formation was noted on the subsequent follow-up endoscopy.

Surveillance

Patients underwent surveillance biopsies at the end of cryotherapy sessions and/or returned for endoscopies with biopsies approximately 3 mo after completion of treatments. Biopsies were taken from visible lesions,

if present, and random four-quadrant biopsies were obtained at visualized columnar and neosquamous epithelium and/or at the gastroesophageal junction every centimeter through the extent of the maximal initial extent of Barrett's.

Pathology

Biopsy specimens were fixed in formalin and reviewed by experienced gastrointestinal pathologists for the presence of intestinal metaplasia with goblet cells, dysplasia, and adenocarcinoma using a standard cla-ssification system. Pathologists were provided with the clinical history and procedural information.

Treatment failure

Cryotherapy treatment failure was defined as lack of response to therapy, demonstrated by persistence of the previously-diagnosed intestinal metaplasia, dysplasia, or cancer, or progression to worsening dysplasia or cancer. In such cases, EMR or ESD (endoscopic submucosal dissection) was performed to resect localized areas and lesions if appropriate and feasible. Subsequent treatment decisions were made on an individualized patient basis after discussing alternative options with patients including esophagectomy in surgical candidates *vs* other ablative modalities.

Study outcomes

For analysis regarding the efficacy of cryotherapy, the primary endpoint of the study was endoscopic and pathologic improvement in baseline cancer, dysplasia, or intestinal metaplasia, as observed on subsequent surveillance biopsies obtained during the study period. The response rate for eradication of all intestinal metaplasia was also calculated.

For analysis regarding the safety of cryotherapy, the incidence of adverse events, including stricture formation, chest pain, perforation, and bleeding were recorded. This data additionally included patients that were not included in the efficacy analysis due to lack of follow-up surveillance data.

Statistical analysis

Descriptive statistics including proportions, mean,

Table 1 Characteristics of the entire cohort and the subset evaluated for efficacy *n* (%)

	Patients analyzed for efficacy *n* = 33	Entire cohort *n* = 45
Age, mean ± SD, yr	66 ± 8.7 (range 47-80)	66 ± 8.7 (range 47-87)
Age > 65 yr	17 (52)	22 (49)
Male gender	21 (64)	32 (71)
Barrett's length, mean ± SD, in cm	3.3 ± 2.1 (range 0.8-7)	3.4 ± 2.2 (range 0.8-8)
Short segment (⩽ 3 cm)	58%	56%
Long segment (4-10 cm)	42%	44%
History of ablative therapy	6 (18)	12 (27)
IM at baseline	5 (15)	7 (16)
LGD at baseline	5 (15)	7 (16)
HGD at baseline	15 (45)	19 (42)
IMC at baseline	8 (24)	12 (27)
Years observed, mean ± SD, yr	2.3 ± 1.1 yr (range 1-4)	Entire study duration (4 yr)

LGD: Low-grade dysplasia; HGD: High-grade dysplasia; IMC: Intramucosal adenocarcinoma.

standard deviation, and median were calculated. Treatment response rates were calculated based on all data available at the end of the study period. All statistical analyses were performed using the GraphPad Software (http://graphpad.com/quickcalcs/).

RESULTS

From January 2010 through December 2014, a total of 45 subjects that underwent cryotherapy at our institution met inclusion criteria for the study. Of these, 33 patients had sufficient surveillance (at least one subsequent endoscopy with biopsies at our institution) to be included in the efficacy data. Characteristics of the entire cohort and the subset evaluated for efficacy are detailed in Table 1. The two groups were similar with respect to age, gender, Barrett's segment length, and proportions of baseline intestinal metaplasia, low-grade dysplasia, high-grade dysplasia, and intramucosal adenocarcinoma. The study included 45 subjects with a mean age of 66 ± 8.7 (range 47-87) years old, 71% male and 29% female.

The 33-patient subset had a mean age of 66 ± 8.7 (range 47-80) years old, 64% male and 36% female. Fifty-eight percent of patients in this group had short segment Barrett's esophagus (⩽ 3 cm) and 42% had long segment (3-8 cm), with a mean length of 3.3 ± 2.1 cm (range 0.8-8 cm) in the entire group. Of this subset, 27% had previously undergone another type of endoscopic ablative therapy, including radiofrequency ablation (RFA) or photodynamic therapy (PDT). Of the group with intramucosal cancer, two subjects had previously undergone RFA with treatment failure. All patients in this group underwent EMR prior to or at initiation of cryotherapy. Amongst the patients with high-grade dysplasia, four had previously undergone other endoscopic ablative modalities. Seven of the patients in this group underwent EMR prior to or at initiation of cryotherapy. In the group with low-grade dysplasia, two had previously undergone RFA. Amongst the patients with intestinal metaplasia without dysplasia or cancer, two had previously undergone RFA. The

median number of cryotherapy sessions was two, with a range of one to nine sessions per patient.

Treatment response

Amongst all subjects, 29 patients (88%) demonstrated a response to cryotherapy, defined by downgrading of the baseline pathology. Overall, 85% of treated patients demonstrated complete response, defined as eradication of all dysplasia and/or cancer. Of 33 patients, 16 showed complete regression to normal epithelium without residual cancer, dysplasia, or intestinal metaplasia. Results are illustrated in Table 2.

Complete eradication of cancer and dysplasia was seen in six of eight subjects (75%) with intramucosal adenocarcinoma after endoscopic mucosal resection of focal nodules and cryotherapy. The remaining subjects, who had long-segment BE, did not respond to cryotherapy and eventually proceeded with alternative therapy. Of 15 patients with high-grade dysplasia, 7% had low-grade dysplasia, 50% had intestinal metaplasia, and 30% had complete regression to normal epithelium at follow-up. One subject maintained high-grade dysplasia and was subsequently transitioned to RFA. Eradication of dysplasia was seen in all five patients with low-grade dysplasia. Three of these five patients (60%) demonstrated complete regression to normal epithelium, and the remaining two patients (40%) had intestinal metaplasia on subsequent surveillance biopsies. Of the five patients with intestinal metaplasia without dysplasia, complete regression occurred in four (80%), and intestinal metaplasia persisted in one (20%).

Overall surveillance time for the entire 33-patient cohort was 2.3 ± 1.1 years (range 1-4 years) from the time of the initial treatment.

Adverse events

For all 45 patients that underwent cryotherapy during the study period, the overall rate of adverse events was 6.6% amongst 136 total sessions of cryotherapy. Reported adverse events included two episodes of transient chest pain (1%), five strictures (4%), and one

Table 2 Treatment response

Baseline Pathology	Pathology after cryotherapy treatments					
	Complete regression	IM	LGD	HGD	IMC	Total
IM	4	1	0	0	0	5
LGD	3	2	0	0	0	5
HGD	5	8	1	1	0	15
IMC	4	2	0	0	2	8

HGD: High-grade dysplasia; LGD: Low-grade dysplasia; IMC: Intramucosal adenocarcinoma.

gastrointestinal bleed (1%). There were no reported occurrences of post-procedural perforation or fever. The gastrointestinal bleed occurred in a patient on dual antiplatelet therapy who had undergone EMR prior to the cryotherapy session; a stricture also occurred in the same patient. This patient presented to an outside hospital eleven days after the cryotherapy treatment with hematemesis, and an EGD revealed esophageal ulcerations and a visible bleeding vessel that required epinephrine injection, cauterization, and clipping to achieve hemostasis.

One patient that developed a stricture had previously undergone RFA, ultimately with treatment failure. Two of the strictures occurred in the same patient. One of the two episodes of transient chest pain was in a patient that had previously undergone mediastinal radiation. Overall, 5 of the 8 patients that developed adverse events had long-segment BE.

DISCUSSION

Current data shows cryotherapy-induced eradication of high-grade dysplasia in 87%-95% of patients and complete eradication of intestinal metaplasia in 57%-96%[9,14-16]. Additionally, in early-stage esophageal cancer, cryotherapy has been shown to eliminate mucosal cancer in 75%[10-14], including as rescue therapy in patients who have failed other modalities[17].

In 2005, Johnston *et al*[8] reported a single-center study of cryotherapy in 11 patients with metaplasia and/ or dysplasia; of the nine patients that completed the study, all had eradication of metaplasia and dysplasia at six months. Therapy was well tolerated with no reports of severe chest pain, strictures, or perforation[13,18]. Canto *et al*[9] (2008) subsequently reported a single-center study of 33 subjects with high-grade dysplasia or intramucosal carcinoma who had previously failed EMR and/or photodynamic therapy. There was a preliminary 72% reduction in Barrett's esophagus after a mean of three treatments. Again, therapy was well-tolerated without any chest pain, perforation, or strictures[13,19].

In 2009, Dumot *et al*[10] presented a single-center study of cryotherapy in 30 high-risk patients with HGD and/or intramucosal carcinoma; 90% of subjects had downgrading of pathology stage after cryotherapy. Median follow-up time was one year. Three (10%) subjects reported severe chest pain and three (10%) had strictures requiring dilation; one gastric perforation developed in a patient with Marfan's syndrome[13,20].

Greenwald *et al*[6] (2010) later conducted a four-center study in which 77 subjects with metaplasia, low-grade dysplasia (LGD), HGD, intramucosal carcinoma, invasive carcinoma, or severe squamous dysplasia were treated with cryotherapy (323 total treatments). Ninety-four percent of 17 patients with HGD had complete eradication, 88% had eradication of dysplasia, and 53% had eradication of intestinal metaplasia after cryotherapy. Complications included strictures requiring dilation in three patients and moderate to severe chest discomfort in 3.7%[8,13].

Few studies have followed biopsy surveillance for patients with Barrett's esophagus with dysplasia and intramucosal adenocarcinoma for greater than one year. Overall, our institutional data demonstrated that the use of liquid nitrogen cryotherapy is efficacious and safe as primary or rescue treatment for Barrett's esophagus, including in patients with dysplasia and intramucosal adenocarcinoma. Response rates were 88%, with complete eradication of all dysplasia and cancer in 84% of patients, including most subjects with baseline pathology showing high-grade dysplasia and/or intramucosal adenocarcinoma. More data regarding the safety and effectiveness of liquid nitrogen cryotherapy with extended observation times would be useful, and analysis of large sample sizes (*i.e.,* by meta-analysis) is needed.

COMMENTS

Background
Several modalities exist to try and treat Barrett's esophagus, especially dysplastic Barrett's prior to progression into esophageal adenocarcinoma.

Research frontiers
The primary two modalities are radiofrequency ablation and endoscopic mucosal resection. Spray cryotherapy is another ablation technique with limited long term efficacy described in the literature.

Innovations and breakthroughs
These results further clarify and define long term efficacy of spray liquid nitrogen cryotherapy for treatment of Barrett's esophagus including long-term follow-up in a large cohort. Liquid nitrogen cryotherapy is an efficacious first or second line therapy for the treatment of dysplastic and even non-dysplastic Barrett's esophagus.

Peer-review
This is a single center retrospective study on effectiveness of liquid nitrogen

cryotherapy in the treatment of Barrett's esophagus. The authors admit the clinical usefulness of this technique.

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ORIGINAL ARTICLE

Retrospective Study

Novel and supplementary management of pancreatic fluid collections: Endoscopic ultrasound-guided drainage

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Institutional review board statement: The study was reviewed and approved by the Ethics Committee of Huashan Hospital, Fudan University.

Informed consent statement: Patients were required to give informed consent to the study and the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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Abstract

AIM

To compare efficacy and safety of endoscopic ultrasound (EUS)-guided and surgical drainage in pancreatic fluid collection management.

METHODS

Data were obtained retrospectively from January 2012 to December 2016. Patients with pancreatic fluid collection were performed EUS-guided or surgical procedure. Main outcome measures including clinical efficiency, complication, duration of procedures, hospital stay and cost were analyzed.

RESULTS

Thirty-six patients were enrolled into the study, including 14 in endoscopic group while 22 in the surgical group. Twelve (86%) patients were treated successfully by endoscopic approach while 21 (95%) patients benefited through surgical procedure. Endoscopic treatment had higher recurrence and complication rates than surgery, resulting in more re-interventions. Meanwhile, duration of procedure, hospital stay and cost were significantly lower in endoscopic group.

CONCLUSION

Both approaches were effective and safe. EUS-guided

approach should be the first-line treatment in mild and simple cases, while surgical approach should be considered as priority in severe and complex cases.

Core tip: This retrospective study was to compare efficacy and safety of endoscopic ultrasound (EUS)-guided and surgical drainage in pancreatic fluid collection management after acute pancreatitis or pancreatic surgery. Of all the 36 patients, 14 patients were performed EUS-guided drainage while 22 patients were performed surgical procedure. Endoscopic treatment had higher recurrence and complication rates than surgery, resulting in more re-interventions. Meanwhile, duration of procedure, hospital stay and cost were significantly lower in endoscopic group. Both approaches were effective and safe. EUS-guided approach should be the first-line treatment in mild and simple cases, while surgical approach should be considered as priority in severe and complex cases.

INTRODUCTION

Pancreatic fluid collection (PFC), including acute peri-pancreatic fluid collection (APFC), acute necrotic collection (ANC), pseudocyst and development of walled-off necrosis (WON), arises as a complication of acute pancreatitis and pancreatic surgery[1]. Part of PFC will resolve spontaneously. The indications for PFC treatment are symptom driven, including fever, upper abdominal pain, satiety, gastric outlet obstruction, weight loss, or jaundice[2].

Open surgical drainage has long been first choice for PFC treatments[3]. However, patients often suffered tremendous injury from operation with an unsatisfied modality and mobility. During the last 20 years, endoscopic ultrasound (EUS) guided drainage, which is minimally invasive, has been increasing utilized to help manage PFCs[4]. Fluid collection can be aspirated by EUS-guided puncture. Furthermore, the procedure creates a fistula using stent or naso-cystic catheter between the PFC and the gastric lumen (cyst-gastrostomy). However, EUS-guided drainage of PFCs is technically challenging which requires experienced expertise and centers.

Although both approaches have been demonstrated different efficacy in previous studies, there is still a scarcity of data to decided which one is optimal.

In this study, we tried to compare endoscopic and surgical treatment regarding clinical success, complication rate, recurrence, duration of procedures, hospital stay and cost with emphasis on selection of patients.

MATERIALS AND METHODS

Patients

Thirty-six patients were enrolled retrospectively at the Department of Pancreatic Surgery and Department of Gastroenterology and Digestive Endoscopy, Huashan Hospital, Shanghai, China, from January 2012 to December 2016. All patients suffered symptomatic or asymptomatic PFCs after acute pancreatitis or pancreatic surgery. Symptomatic associated with PFC included fever, abdominal pain, biliary or gastric outlet obstruction. All patients provided written informed consent to undergo the procedures.

Patients were identified from the clinical databases, and clinical data and CT scan were individually reviewed. Patient and PFC characteristics, treatment outcomes and complications were recorded. As the EUS-guided drainage is an evolving treatment modality, the choice between endoscopic *vs* surgical treatment was made according to the patients' current opinion and doctors' experience.

Definitions

Treatment success means complete resolution of PFC or a decrease in size to 2 cm or smaller on CT scan with the relief of symptoms at 72 h after procedure. Treatment failure was defined as symptoms persists or worsen with PFC increased in size or remained 2 cm in size on CT scan at 6 wk afterwards. Recurrence means PFC found on CT scan with symptoms at 72 h after an initial procedure. Re-intervention means the need for repeat procedure, surgery or endoscopy, because of persistent symptoms with PFC not less than half of the original size on follow-up imaging[5]. The cost was determined by the expenditure of procedure, anesthesia, peri-treatment medications, facility fees and hospital stay.

Procedures

A contrast-enhanced abdominal CT scan was performed 24 to 48 h before undergoing either treatment. The PFC was categorized and graded according to the Atlanta classification[6], based on CT scan imaging reviewed by two experienced radiologists. All patients with pancreatic pseudocyst, or necrosis in the setting of uncontrolled pancreatitis underwent placement of naso-jejunum feeding tubes, to provide symptomatic relief and nutrition support. Third generation cephalosporin was intravenously administered in the peri-procedure period.

All EUS procedures were performed with EUS guidance by an experienced endoscopist while the

	Endoscopic group, $n = 14$	Surgical group, $n = 22$	P value
Age (yr)	56.3	58.7	0.102
Gender (male, %)	6 (43)	9 (41)	0.143
Etiology			0.223
Acute pancreatitis	5 (36)	18	
Post-op. pancreatic leakage	9 (64)	4	
Type of PFC			0.138
APFC	7	3	
ANC	2	3	
Pseudocyst	3	9	
WON	2	7	
ASA grade			/
I - II	14	21	
III - V	0	1	
Occurrence time			0.557
Early (within 14 d)	9	14	
Late (after 14 d)	5	8	

Table 1 Epidemiology characteristics of patients with pancreatic fluid collection

PFC: Pancreatic fluid collection; APFC: Acute peripancreatic fluid collection; ANC: Acute necrotic collection; WON: Walled-off necrosis.

patient was under conscious sedation. Once the PFC was identified, it was accessed using a 19-gauge needle, fluid was aspirated. Furthermore, a 0.035-inch guidewire was inserted into the PFC through the needle with fluoroscopic guidance. And needle was removed afterwards. needle knife was inserted through the guidewire guidance to extend a bigger fistula. Finally, a wire-guided balloon was used to dilate the gastric wall perforation to 10 mm. Two double pig-tail plastic stents or a metal stent were chosen to be deployed to facilitate the drainage of pseudocyst contents into the stomach. A naso-cystic catheter was inserted if there was necrotic debris.

All operations were performed by experienced pancreatic surgeon. An incision was made from the umbilicus to xiphoid process, to allow access to the abdomen. If the PFC were diffuse, debridement and drainage were performed and necrotic tissue were cleansed. If the PFC were localized such as pseudocyst or WON, cyst-gastrostomy was performed in the lowest point of the cyst. The abdominal drainage tubes were set if needed. Patients were discharged when pain control was adequate and a soft diet was tolerated.

During the process of drainage, all patients remained hospitalized. The cavity was lavage daily with saline solution through naso-cystic catheter after endoscopic procedure. All patients were evaluated with CT scan within 72 h after PFC drainage. If the PFC re-appears after procedure, re-intervention was considered. In patients with treatment success, cyst-gastrostomy stents, naso-cystic catheter, and the nose-jejunum feeding tube were removed. The patients with PFC decreased in size partially underwent transmural stents replacement and were re-evaluated by CT scan after 1 mo; With resolved PFC, then the patients were managed

as treatment success. The patients with treatment failure suffered endoscopic therapy repeatedly or turn to surgery. All patients were follow-up during 6 mo.

Statistical analysis
Descriptive statistics for continuous variables are presented as means or medians with SD, respectively. Categorical variables are reported as absolute values and percentages. Differences between groups were analyzed for categorical variables with the χ^2 test. We considered $P < 0.05$ as statistically significant. Statistical analysis was performed with SPSS version 20.0 for Windows.

RESULTS
A total of 36 patients had an intervention for PFC over the period from January 2012 to December 2016. 22 patients (61%) were treated surgically and 14 (39%) endoscopically. In 23 patients (64%), PFC were caused by acute pancreatitis in early or late stage. Of them, 5 in endoscopic group while 18 in surgical group. Thirteen patients (36%) suffered post-operative pancreatic leakage which resulted in PFC, and 9 in endoscopic group while 4 in surgical group. The type of PFC was divide into four categories. In endoscopic group, acute PFC were the leading type while pseudocyst, ANC and WON followed. In contrast, pseudocyst and WON were the majority in the surgical group (Table 1).

Endoscopic approach was performed in the patients with PFC in the distal pancreas mainly. PFC around head of pancreas relied more on surgical treatment. Moreover, 2 patients with diffuse PFC in the abdomen have underwent surgical approach. The size of the PFC in both group had no significant difference. Overall two-third of the patients had PFC with infection, which had fever, high WBC value, or microbiologic evidence. But infection was not the influencing factor of deciding the treatment approach. Contrasted with the operation, endoscopic treatment of PFC benefits in duration of procedure, hospital stay after procedure and the medical costs (Table 2).

Fourteen patients with PFC underwent endoscopic treatment in the study. Seven of them were diagnosed with APFC and simple aspiration were performed through EUS-guided puncture. Among these patients, 2 patients suffered re-intervention because of fluid collection re-appears within 72 h. Two patients with ANC were treated by combination of naso-cystic catheter and double pig-tail tube successfully. Three patients with pseudocyst were treated by different method, including naso-cystic catheter, double pig-tail tube and metal stent. Both patients with WON were treated by metal stent, one of which suffer the serious bleeding after procedure and turned to emergency surgery (Table 3).

Overall, 12 patients (86%) in the endoscopic group were treated successful (Figure 1) while the surgical group were 21/22 (95%) success. One of the failed

Figure 1 Endoscopic ultrasound-guided drainage of pancreatic fluid collection. A: CT scan before procedure; B: CT scan after procedure (24 h); C: CT scan after procedure (1 mo); D: EUS imaging of PFC; E and F: endoscopic imaging of double pig-tail tubes implantation. EUS: Endoscopic ultrasound; PFC: Pancreatic fluid collection; CT: Computed tomography.

Table 2 Comparison of pancreatic fluid collections between endoscopic and surgical group

	Endoscopic group, *n* = 14	Surgical group, *n* = 22	*P* value
Location			0.127
Head of pancreas	2	8	
Distal pancreas	12	12	
Peripancreatic (diffuse)	0	2	
Long axis (cm)	4.32 ± 1.13	5.17 ± 3.18	0.098
Infection			0.081
+	10	14	
-	4	8	
Duration for procedure (min)	94.4 ± 23.5	127.2 ± 61.9	0.038
Hospital stay (d)	7.4 ± 2.8	12.5 ± 8.1	0.019
Cost (RMB)	24311.48 ± 3211.76	48119.93 ± 6723.25	0.003

cases in the endoscopic group turned to surgery due to complication and then underwent operation successfully (No. 10). In the surgical group, the fail case died within 72 h due to serious bleeding from WON to digestive tract. Three patients in the endoscopic group suffered PFC recurrence and 2 of them underwent re-intervention (Nos. 2 and 12, Figure 2). The other one failed and chose conventional therapy and follow-up when PFC recurrence appeared (No. 3, Figure 3). Two patients in the endoscopic group had complication after procedure. One case mentioned above were serious bleeding (No. 10) and the other were secondary infection after metal stent implantation (No. 8). In the

other hand, surgical group had satisfying efficiency and safety (Tables 3 and 4).

DISCUSSION

In this retrospective study, we indicate that there are no statistical differences in clinical success, complications and mortality rate between the two approaches (endoscopic drainage and surgical drainage) in the PFC treatment. Procedure time, cost and hospital stay were lower statistically in the endoscopic group. However, recurrence and re-interventions rates in the endoscopic group were significantly higher than those of surgical group.

Regarding hospital cost and stay, endoscopic approach has some advantages compared with surgery: Minimal invasion, shorter procedure time and rapid recovery. As previously reported in a retrospective analysis of 19 PFC, only about one-third of patients required hospitalization. The authors indicated that endoscopic treatment is a feasible method for some selected outpatient with PFC[7]. We found that the cost of surgical treatment was about twice cost of endoscopic approach, which agrees with the previous study[6,8]. These savings were mostly the result of early patient discharge, lower medication costs and use of conscious sedation for endoscopy. As comparison of costs in this study pertained to the China only, it may not be applicable to other countries. Due to a lower professional income for surgeons in China, we assume the gap between endoscopic group and surgery group would be larger in other countries.

Figure 2 Re-intervention of pancreatic fluid collection drainage. A: Computed tomography (CT) scan before procedure; B: CT scan after first procedure (72 h); C: CT scan after re-intervention (72 h); D: CT scan after procedure (1 mo).

Figure 3 Failed case of pancreatic fluid collection drainage. A: Computed tomography (CT) scan after procedure (24 h); B: CT scan after procedure (72 h); C: CT scan after procedure (3 mo); D: CT scan after procedure (1 year).

In the study, the treatment success rate in short-term was 95% in surgical group *vs* 86% in Endoscopic group, which is agreed with previous reports[9,10]. Surgery is successful technically in almost all patients

Table 3 Drainage pathway of patients in endoscopic group

No.	Type	Simple suction	Nasogastric tube	Double pig-tail tube	Metal stent
1	APFC	O			
2	APFC	OO[1,2]			
3	APFC	O[1,3]			
4	Pseudocyst		O		
5	Acute necrosis		O	O	
6	Acute necrosis		O	O	
7	APFC	O			
8	Pseudocyst				O[4]
9	APFC	O			
10	WON		O		O[3,4]
11	Pseudocyst			O	
12	APFC	O[1,2]			
13	APFC	O			
14	WON				O

[1]Recurrence; [2]Re-interventions; [3]Treatment failure; [4]Complication. APFC: Acute peripancreatic fluid collection; WON: Walled-off necrosis.

Table 4 Comparison of procedure efficiency between endoscopic and surgical group

	Endoscopic group, $n = 14$	Surgical group, $n = 22$	*P* value
Treatment success	12	21	0.858
Treatment failure	2	1	0.041
Recurrence	3	0	0.035
Re-interventions	2	0	0.017
Complications	2	0	0.051
Bleeding	1	1	
Secondary infection	1	0	

who meet the criteria for a cyst-gastrostomy, while not all PFCs may be amenable for EUS-guided drainage. Especially for patients with thick viscosity of necrotic fluid and solid debris or the PFC tracked deep into the pelvic cavity, Endoscopic treatment may be not adequate. Insufficient drainage may potentially result in persistence of symptoms and infection, thus causing recurrence, even re-intervention.

With the advantage of real-time imaging and revealing the presence intervening vasculature, EUS-guided cyst-gastrostomy is increasingly being performed in pancreatic fluid collections. Unlike walled-off necrosis, current treatment outcomes for endoscopic drainage of pseudocysts are excellent[11,12]. With increasing experience, EUS-guided drainage has extended its use in many complicate cases such as pancreatic necrosis, even with infection[13,14]. Several studies have introduced new techniques, such as large diameter, lumen-apposing, self-expanding metal stent with bilateral flanges[15] or multiple transluminal gateway treatment (MTGT)[16]. However, there is no definite evidence showing metal stents are better than plastic ones, or which kind of plastic stent is better than others[17]. Also, there have not adequate studies reported about the efficacy of MTGT in the treatment of PFC. In a study of 211 patients with symptomatic PFCs, the reported success rate for treating sterile and infective pseudocysts was 93.5%, but only 63.2% when treating a WON[11]. Another study reported by adopting endoscopic necrosectomy, a more aggressive endoscopic approach, the success rates up to 81% when treating a WON[18]. We must point out that endoscopic necrosectomy carries risks of bleeding and perforation, even costs patients' life with internal hemorrhage. During the poorly drainage process of treatment and collapse, tiny, narrow connections were formed, causing unilocular separated into sub-cavities. Since there are undrained sub-cavities, pancreatic fluid collections are less responsible to any endoscopic treatment.

In 2011, a retrospective study was published

discussing the long-term outcomes of patients underwent endoscopic treatment of PFC[19]. The results showed that the long-term success rate was 72.5% (58/80 patients), and 28% of patients turned to surgery. It was perforation in four patients, endoscopically inaccessible areas in two patients, inadequate drainage and recurrent fluid collections in sixteen patients, respectively. Surgical drainage is a multidisciplinary decision and should be considered for patients who have a high potential recurrence, or not suits endoscopic or percutaneous drainage.

In our study, 3 patients experienced recurrence due to continuous pancreatic leakage after distal pancreatectomy, 2 of which need a re-intervention with octreotide therapy afterward. The other one chose conventional treatment and the PFC absorbed significantly after one year follow up. It seems like we had higher recurrence rate than other studies, but we found the 3 cases were APFC after distal pancreatectomy, which was free and connected with main pancreatic duct while most studies focus on the pseudocyst or WON, which is limited by fibrous tissue. If we excluded the APFC case, we had no recurrence case in ANC, pseudocyst and WON cases. 2 patients suffered complications in the endoscopic group while surgical group had one. Both endoscopic complications were caused by metal stents implantation. Repeated rubbing between the stent and the cyst wall or necrotic tissue may lead to internal hemorrhage. The placement of stent may increase the risks of secondary infection in sterile pseudocyst.

Additional, another advantage of EUS-guided drainage for PFC is that an additional diagnosis is made in approximately 5% of patients with drainage of pseudocyst[10]. There is about 1.25% risk of cancer in patients with PFC and no clear evidence in imaging scans[20]. As necrotic tissue and debris in the pancreatic fluid collections are morphologically similar to mural nodules in mucinous cystic neoplasm, it is necessary to perform a contrast-enhanced ultrasound before the EUS puncture.

There are several limitations to this study. Firstly, it is a retrospective study performed by a single center. Our department is a highly specialized tertiary academic endoscopic unit, which may lead to overestimation of procedures' results. Secondly, the small size of the enrolled patient group may also represent a bias.

Another important selection bias is the fact that patients referred to surgical cyst-gastrostomy were sicker and required more definitive therapy.

In conclusion, in this retrospective study, we demonstrated that EUS-guided drainage and surgical drainage were both effective and safe technique, which were complementary to each other. For patients with uncomplicated pancreatic pseudocysts, EUS-guided cyst-gastrostomy should be the first-line treatment, because the approach has less expenditure and shorter length of hospital stay. For patients with PFC connected to pancreatic duct or with complex situations such as pancreatic necrosis, even with infection, surgical cyst-gastrostomy may be better choice due to its low recurrence rate.

COMMENTS

Background

Pancreatic fluid collection (PFC), arises as a complication of acute pancreatitis and pancreatic surgery. Part of pancreatic fluid collections will resolve spontaneously, while others needs aggressive management. Open surgical drainage has long been first choice for PFC treatments. However, patients often suffered tremendous injury from operation with an unsatisfied modality and mobility. Minimally invasive endoscopic ultrasound (EUS) guided drainage has been increasing utilized to help manage PFCs in decades. PFCs can be aspirated by EUS-guided puncture. Furthermore, the procedure creates a fistula using stent or naso-cystic catheter between the PFC and the gastric lumen (cyst-gastrostomy). Although both approaches have been demonstrated different efficacy in previous studies, there is still a scarcity of data to decided which one is optimal. In this study, the authors tried to compare endoscopic and surgical treatment regarding clinical success, complication rate, recurrence, duration of procedures, hospital stay and cost with emphasis on selection of patients.

Research frontiers

Many studies have focus on the efficacy and feasibility of the new approach for PFCs, and the researches have concluded that the efficacy and safety of EUS-guided drainage is satisfying. But comparing with the surgical drainage, a traditional treatment, the endoscopic method has not shown comprehensive advantage. There is still a scarcity of data to decided which one is optimal.

Innovations and breakthroughs

Both EUS-guided and surgical drainage were both effective and safe technique, which were complementary to each other. For patients with uncomplicated pancreatic pseudocysts, EUS-guided cyst-gastrostomy should be the first-line treatment, because of cost saving and shorter length of hospital stay. For patients with PFCs connected to pancreatic duct or with necrosis or infection, surgical cyst-gastrostomy may be better choice due to its low recurrence rate.

Applications

The study suggested that EUS-guided and surgical drainage can be complementary to each other. If the patients with simple pseudocysts or acute peripancreatic fluid collection (APFC), the EUS-guided drainage should be firstly considered. If the patients suffer complicate PFCs, including necrosis or infection, surgical drainage is always be the better choice.

Terminology

PFC: Pancreatic fluid collection; APFC: Acute peripancreatic fluid collection; ANC: Acute necrotic collection; WON: Walled-off necrosis.

Peer-review

This article is well-written.

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CASE REPORT

Successful endoscopic removal of three embedded esophageal self-expanding metal stents

Xiao-Qin Liu, Min Zhou, Wen-Xin Shi, Yi-Ying Qi, Hui Liu, Bin Li, Hong-Wei Xu

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Abstract

In the report, we describe a case of refractory benign esophageal strictures from esophageal cancer after an operation for the placement of three partially covered self-expanding metal stents (SEMSs), which were all embedded in the esophageal wall. Using the stent-in-stent technique, the three embedded SEMSs were successfully removed without significant complications. To the best of our knowledge, few cases of the successful removal of multiple embedded esophageal SEMSs have been reported in the literature. This case also highlights that the stent-in-stent technique is effective for removing multiple embedded esophageal SEMSs.

Key words: Esophageal stricture; Self-expanding metal stent; Multiple; Stent-in-stent; Gastroscopy

Core tip: Stent embedding is a common complication that precludes the safe removal of stents. The article reports a case of benign esophageal strictures with three stents embedded and remained in place for over a year. We successfully removed the three embedded stents by using the stent-in-stent technique. The stent-in-stent technique is effective for the removal of multiple stents that are embedded in the esophageal wall.

Liu XQ, Zhou M, Shi WX, Qi YY, Liu H, Li B, Xu HW. Successful endoscopic removal of three embedded esophageal self-expanding metal stents. *World J Gastrointest Endosc* 2017; 9(9): 494-498

INTRODUCTION

The placement of esophageal self-expanding metal stents (SEMSs) is commonly used to treat benign and malignant esophageal disorders, such as esophageal strictures and fistulas. SEMSs should be removed in a timely manner to avoid severe long-term complications for benign esophageal diseases. However, stent embedding is a common complication that precludes the safe removal of stents. This article reports the successful removal of three embedded esophageal SEMSs from a patient with benign esophageal strictures by using the stent-in-stent technique.

CASE REPORT

A 65-year-old male patient underwent a radical resection of distal esophageal carcinoma more than 2 years ago. The esophageal tumor located in 32 cm from the upper incisors, and there was no lymph node metastasis. Excision of inferior segmental esophagus and cardia of stomach and high intrathoracic anastomosis using gastric tube were performed in the patient. The postoperative pathological diagnosis was moderately differentiated esophageal squamous cell carcinoma. The first partially covered SEMS was placed at the local hospital for treating a gastroesophageal anastomotic fistula, which occurred ten days after the surgery. There was a benign stricture which was located the upper of stent after nine months the first stent placement. The second and third partially covered SEMSs were successively placed for the palliation of dysphagia from a benign esophageal stricture at another hospital, without the removal of the first stent. The patient was admitted to our hospital with recurrent dysphagia. A barium meal meal examination showed three visible metal stents and severe esophageal stricture (Figure 1A). Gastroscopy revealed a benign esophageal stricture located 25 cm from the upper incisors, which a conventional gastroscope (GIF-XQ260; Olympus Medical Systems, Tokyo, Japan) could not pass (Figure 2A). The proximal cup of the third stent was completely embedded in hyperplastic tissue. An ultrathin endoscope (GIF-XQ260N; Olympus Medical Systems, Tokyo, Japan) was subsequently used to scrape through the strictures and demonstrated that no embedded distal cups of stents. Removal of the embedded stents was attempted, but failed. Then, the fourth SEMS was placed inside the original stents to achieve pressure necrosis (Figure 2B and C). After the stent placement, the dysphagia was alleviated and the quality of the patient's life was significantly improved. A month later, the fourth stent was retrieved by endoscopy. Meanwhile, we attempted but failed to remove the other

Figure 1 Barium meal examination of the upper gastrointestinal tract. A: The three metal stents were placed in the esophagus, and the esophageal stricture was on the upper end of the stents. Those three white arrows indicated first, second, and third stent from bottom to top; B: After the removal of all stents, the stricture was alleviated without the occurrence of an esophageal fistula.

three stents (Figure 2D). A week later, we attempted to retrieve the stents again and successfully removed all the initial stents without significant complications (Figure 2E). The upper gastrointestinal contrast X-ray study revealed no contrast extravasation, and the patient was allowed a semi-liquid diet (Figure 1B). The patient developed recurrent dysphagia 5 wk after stent removal, which was resolved after the temporary placement of a fully covered SEMS for 4 wk (Figure 3). No dysphagia or further complications occurred during 6-mo follow-up period.

DISCUSSION

Stent placement is widely used in the treatment of a variety of benign and malignant esophageal strictures, which can quickly and effectively dilate strictures and relieve dysphagia[1,2]. The temporary placement of an esophageal stent has become an effective treatment for refractory benign esophageal strictures owing to its longer-lasting dilatation effects, ability to maintain luminal patency and simultaneous stretching of the strictures[3-5]. However, for the management of benign esophageal strictures, the long-term placement of stents is deprecated because of the potential for adverse events, such as migration, bleeding, fistula formation, hyperplastic tissue overgrowth or ingrowth stent restenosis and damage to surrounding organs[6]. The optimal stenting duration remains unclear and should be individualized depending on the type and characteristics of the stricture. Generally, it is recommended that stents remain in place for 4-8 wk and no more than 16 wk for benign esophageal strictures to maximize the success and minimize the risk of a hyperplastic tissue reaction[1,7]. If stents need to be in place for a long time, upper endoscopy performed at 4-wk intervals is necessary to determine whether the stent has become embedded in the esophageal wall[7].

In our patient's case, three SEMSs remained in place for over a year, and the upper ends of them were

Figure 2 Gastroscope images of esophagus and stents. Gastroscopy showed (A) an esophageal stricture beginning 25 cm from the incisor teeth; B: The fourth stent was placed and (C) remained in place for 4 wk; D: The previous stents became visible after the removal of the fourth stent; E: Outcomes after the removal of all stents were diffuse, but minor bleeding and mucosal tears, and the imprint of the stent mesh was visible in the esophageal mucosa; F: The three original stents were completely retrieved.

Figure 3 Endoscopic appearances of the esophageal stricture after all the stents were removed. A: The esophageal stricture located 25 cm from the incisor teeth was worsened 5 wk after the stents were removed, making it difficult to pass the gastroscope; B: A fully covered SEMS was placed and left in place for 4 wk; C: The stricture was significantly wider after the removal of (D) the fully covered SEMS. SEMS: Self-expanding metal stent.

completely embedded. Thus, the removal of stents was difficult and inevitably associated with bleeding and mucosal tears[8]. However, without the removal of the stents, the stricture could not be dilated to an adequate diameter by endoscopic dilatation, which is the most common initial treatment for benign esophageal stri-

Figure 4 The timeline of stents placement.

ctures. In addition, with the successive placement of the stents, the esophageal stricture moved upward, and there was no space to place a new stent. Gastrostomy and nasogastric tube placement are alternative treatment strategies, but they all have negative influences on the patient's quality of life[9]. Percutaneous endoscopic gastrostomy is impossible for patients with intrathoracic stomach. Furthermore, these patients are often unwilling or not in a suitable enough condition to undergo a complex surgical procedure. Therefore, stent removal is imperative, whether for the prevention of long-term complications or for facilitating further treatment.

We temporarily placed a new stent within the initial stents according to the stent-in-stent technique to facilitate the mobilization and safe removal of all stents by inducing pressure ischemia of the granulation tissue. Ultimately, three embedded stents were successfully removed without serious complications (Figure 4). Previous studies have shown that the stent-in-stent technique is a safe and effective method for removing single embedded esophageal stents[10]. This is the first report showing that the stent-in-stent technique also applies to the removal of multiple stents that have become embedded in the esophageal wall.

For the management of benign esophageal strictures, the placement of stents is a minimally invasive treatment option, but it still requires serious consideration because of the potential for adverse events. Even when stent removal is very difficult for benign esophageal diseases, permanent stent placement should be avoided, and the stent-in-stent technique can be attempted.

COMMENTS

Case characteristics
This article reports a case of successful removal of three embedded esophageal self-expanding metal stents (SEMSs) in a patient who has benign esophageal strictures.

Clinical diagnosis
The patient had refractory benign esophageal stricture of esophagus cancer after operation and was placed three partially covered SEMSs.

Differential diagnosis
The benign esophageal stricture differentiated with malignant stricture by pathology inspection.

Laboratory diagnosis
The laboratory testing were tumor markers, and the results are generally

negative.

Imaging diagnosis
Barium meal examination of the patient showed three visible metal stents and severe esophageal stricture.

Pathological diagnosis
The postoperative pathologic diagnosis was moderately differentiated esophageal squamous cell carcinoma.

Treatment
With the assistance of the stent-in-stent technique, the three embedded SEMSs were successfully removed with no significant complications.

Experiences and lessons
For the management of benign esophageal strictures, the placement of stents is a minimally invasive treatment option, but it still requires serious consideration because of the potential for adverse events. Even when stent removal is very difficult for benign esophageal diseases, permanent stent placement should be avoided, and the stent-in-stent technique can be attempted.

Peer-review
The authors reported a case of refractory benign esophageal strictures with three stent embedded in the esophagus and successfully treated with a sten-in-stent technique. The case is interesting and the case report is well-written with nice picture demonstration and therefore is worth to share with the readers who care or treat such patients.

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AIM AND SCOPE

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FLYLEAF

Endoscopic ultrasound: Current roles and future directions

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Abstract

Endoscopic ultrasound (EUS), developed in the 1980s, was initially predominantly used for guidance of fine needle aspiration; the last 25 years, however, have witnessed a major expansion of EUS to various applications, both diagnostic and therapeutic. EUS has become much more than a tool to differentiate different tissue densities; tissue can now be characterized in great detail using modalities such as elastography; the extent of tissue vascularity can now be learned with increasing precision. Using these various techniques, targets for biopsy can be precisely pinpointed. Upon reaching the target, tissue can then be examined microscopically in real-time, ensuring optimal targeting and diagnosis. This article provides a comprehensive review of the various current roles of EUS, including drainage of lesions, visualization and characterization of lesions, injection, surgery, and vascular intervention. With EUS technology continuing to develop exponentially, the article emphasizes the future directions of each modality.

Key words: Endoscopic ultrasound; Future; Trends; Roles

Core tip: In recent years, endoscopic ultrasound (EUS) has evolved and is now used in various applications, both diagnostic and therapeutic. Classically used to differentiate different tissue densities, EUS is now used to characterize and localize tissue with much more precision. Upon reaching the target, tissue can then be examined microscopically in real-time, ensuring optimal targeting and diagnosis. This article provides a comprehensive review of the various current roles of EUS, including drainage of lesions, visualization and characterization of lesions, injection, surgery, and vascular intervention. With EUS technology continuing to develop exponentially, the article emphasizes the future directions of each modality.

INTRODUCTION

Flexible endoscopy was first developed in 1911 and

ultrasound later arrived in 1956. In the 1980s, these modalities were merged to form the endoscopic ultrasound (EUS). EUS allowed the visualization of structures near the gastrointestinal tract. It did not have much of a role in gastroenterology, however, until the advent of the fine needle aspiration (FNA) in 1991. FNA was a major step for EUS; it was the first time structures outside the lumen could be interacted with and explored. It was the first time the vast length of the gastrointestinal tract could truly be exploited as a potential inlet to the rest of the body.

For the last 25 years, EUS has increasingly been used in the field of gastroenterology. This trend is likely to continue as novel technology is developed and the demand for minimally invasive techniques continues to grow. Procedures that utilize EUS-FNA have specifically spearheaded this growth, but EUS itself has also evolved to be useful for many other procedures, both diagnostic and therapeutic.

Certain EUS advances have caught on faster than others, and in this review several of such modalities will be discussed. The focus will be on the current status of each modality and the direction to which each is heading. Each EUS modality will be categorized in terms of its main function, that is, drainage, visualization, injection, surgery, and vascular interventions.

CHARACTERIZATION OF LESIONS

EUS-guided biopsy is the modality of choice to characterize and stage lesions in the GI tract, with the most commonly targeted organs being the pancreas, submucosal lesions, and lymph nodes[1].

Because of its success thus far, much of the EUS research has been focused on improving characterization of lesions. This has led to advancements which have improved the ability to characterize lesions both from afar (ultrasound) and up close (*via* biopsy). Ultrasound imaging is no longer limited to the conventional B mode imaging, and now includes newer, more advanced modalities such as contrast-enhanced ultrasound and elastography. Forward-viewing EUS (FV-EUS) has improved the ability to access lesions, and modern microscopy advancements now enable real-time optical biopsy.

Elastography
EUS elastography is a major recent advancement in EUS characterization of lesions. The underlying principle of elastography is that compression of a target tissue by a probe produces a smaller strain in hard (usually malignant) tissue than in soft (usually benign) tissue; therefore, elastography can indicate which areas are likely to be malignant *vs* benign.

Because elastography can be used in real-time, elastography serves as an important marker that can direct EUS-FNA. The sensitivity in identifying metastatic lymph nodes is at least 85%[2]. Another advantage of

elastography is that it is relatively inexpensive and does not require extensive training, though it is operator-dependent and is therefore inherently subjective. In addition, elastography can be used in the diagnosis of other conditions, such as prostate cancer, and rectal cancer[3]. Elastography can potentially also be used for adrenal tumors and biliary duct cancers because of their proximity to the gastrointestinal tract, but this research is still in its very early stages[2].

Shear wave elastography is a special type of elastography that requires no manual compression of tissue as applied in conventional elastography, and is therefore less operator-dependent. Measurements of shear wave velocity yield additional information on the tissue's elasticity and therefore can help in diagnosis. Thus far shear wave elastography has been used mostly to characterize breast lesions, liver fibrosis, and thyroid lesions[2]. It has also been used in transrectal ultrasonography for prostate cancer[4]. It is anticipated that shear wave elastography will soon be used with EUS procedures.

Despite the promise that elastography has shown thus far, it is currently only used if EUS-FNA results are negative or inconclusive[3]. In the future, elastography may be able to be merged with other imaging techniques, such as fusion imaging, contrast-enhanced EUS, or 3D elastography to increase accuracy even further[2]. Another notable advancement in elastography is the automated histogram, which allows more quantitative, less subjective elastography, thereby increasing accuracy and reducing operator bias[2].

Tissue harmonic echo
Tissue harmonic echo (THE) imaging is a new technology that provides yet another modality of imaging pancreatic cystic lesions. THE mode imaging provides better characterization of lesions than conventional B mode images. The principle behind THE is that the sonogram is produced by higher harmonic frequencies as ultrasonic beams propagate through tissues. It has thus far only been used in abdominal ultrasound, but there is potential for EUS as well. More studies need to be done to determine whether THE significantly improves EUS diagnostics[5].

Contrast enhanced EUS
Contrast enhanced EUS (CE-EUS) is yet another advanced ultrasound modality. Its advantage is that it allows vascularity to be depicted, thereby improving accuracy, sensitivity, and specificity for diagnosing pancreatic masses and lymphadenopathy[3]. CE-EUS can also be used during EUS-FNA to help avoid vessels. Contrast enhanced color and power Color-Doppler sonography (CD-EUS) enable detection of intratumor vasculature, by producing pseudo Doppler signals from microbubbles. Contrast enhanced harmonic EUS (CH-EUS) was more recently developed to overcome the limitations of CD-EUS. CH-EUS can depict the microbubbles themselves rather the entire flow

through the vessels thus allowing visualization of both microvessels and parenchymal perfusion[6].

CE-EUS is an emerging technique with promise, but it has been scrutinized for being qualitative in nature, and therefore research is underway to develop more quantitative techniques[3].

Needle-based confocal laser endomicroscopy

Needle-based confocal laser endomicroscopy (n-CLE) is a technique allowing *in-vivo* "optical" histology using fluorescent contrast. N-CLE therefore can show which areas are most suspicious for malignancy and require biopsy. Preliminary results of n-CLE studies have been very promising, and in the future n-CLE may stand as the second option for diagnosing pancreatic cysts when EUS-FNA is inconclusive[7]. In the near future, n-CLE may become routinely used after EUS-FNA of solid pancreatic masses returns inconclusive[7,8]. Despite how accurate n-CLE proves to be, it will likely catch on slowly due to high cost and the difficulty of predicting pathology based on surface characteristics[9]. N-CLE can theoretically one day deem classical tissue acquisition obsolete, although tissue acquisition will continue to provide diagnostic benefits, such as the ability to perform molecular testing, flow cytometry, and PCR[8]. Ideally, pancreatic cystic neoplasms will eventually be diagnosed in a personalized fashion, implementing the techniques of cytology, nCLE, and molecular markers differently for each patient[9]. With this arsenal, one may be able to accurately predict which lesions will progress quickly, and therefore require urgent treatment such as endoscopic ablation or surgery. At the same time, improved diagnostic techniques may also reveal those lesions that progress slowly and therefore can be followed less closely.

In summary, recent years have brought on many advances in the ability to characterize lesions, most notably pancreatic lesions. This boom has been spear-headed by the improvement of ultrasound technology, the most important currently being CH-EUS and elastography. For now, to obtain the most accurate characterization, a combination of the two are used in clinical practice[3]. In the future, ideally all techniques will be in the armamentarium, so that each patient can receive personalized treatment.

DRAINAGE

Pancreatic fluid collection

Pancreatic fluid collection (PFC) is a common complication of pancreatitis. The decision whether or not to drain depends on multiple factors, namely, clinical presentation, duration, size, and location. If drainage is indicated, it must be decided whether to intervene surgically, endoscopically, or radiologically (percutaneously). Currently, surgery is performed when a wall has not yet formed around the collection. Alternatively, if a wall has already formed, endoscopic drainage is considered[10]. Walled-off collections include both pseudocysts (fluid) and walled off

necrosis (WON; solid). Studies have shown endoscopic drainage to have higher rates of treatment success than percutaneous drainage, as well as lower rates of re-interventions[11]. ERCP is considered if the collection communicates with the pancreatic duct.

Endoscopic drainage is aided by EUS guidance specifically when there is either no intraluminal bulge, portal hypertension, nearby collateral vessels, necrosis, or calcification in the wall[12,13]. EUS drainage is performed *via* either a transgastric or transduodenal approach, and therefore requires the collection to be near ($\leqslant$ 1 cm) the GI lumen[14]. EUS provides precise localization of the collection as well as precise measurement of the thickness of the wall and distance from the GI lumen.

EUS-guided drainage can be enhanced in many instances with the use of a self-expanding metallic stent (SEMS). This stent provides a wider diameter for drainage, thus leading to a quicker resolution of symptoms[15]. SEMS is most useful in WON, as it allows for repeated access for necrosectomy[16]. SEMS has greatly improved EUS-guided drainage, though additional research is needed on SEMS, as it is still a relatively new tool.

Alongside the current recommendations and considerations listed above, the decision how to drain ultimately depends not only on the actual collection but also the institution, local expertise, and the patient preference.

Pancreatic duct

EUS guidance may be helpful in decompression of the pancreatic duct during an obstruction. Currently, EUS is only used when ERCP-guided cannulation fails or when the papilla is inaccessible (*e.g.*, gastric or duodenal obstruction or surgically altered anatomy)[16]. The pancreatic duct can be drained either by the rendezvous procedure or translumenally, through the stomach or duodenum[16].

Biliary

Similar to pancreatic duct drainage, biliary drainage may be done endoscopically with EUS guidance when ERCP cannulation has failed, the papilla is inaccessible, or anatomy is surgically altered. Classically, the alternatives to ERCP have been percutaneous or surgical methods, but EUS provides a safer alternative[17], and internal drainage is considerably preferable from a patient perspective.

Like pancreatic duct drainage, EUS-guided biliary drainage can be done in three different ways[18]: Trans-papillary rendezvous, or translumenally *via* either choledochoduodenostomy or hepaticogastrostomy. The data is still limited at this point, but many believe that the results are promising for EUS-guided biliary drainage, with the overall success rate around 90%[19] with a minimal complication rate. EUS-guided biliary drainage results have been so promising that experts increasingly argue that EUS should become the first-

line treatment, ahead of percutaneous drainage[16]. It is argued that EUS-guided drainage is superior because it both reduces adverse event rates and the need for re-interventions, thereby reducing costs of therapy[20].

As in PFC drainage, SEMS is also being used more often for biliary drainage. Forward viewing-EUS, a new tool discussed below, combined with a SEMS, has been shown to be the best method when performing EUS guided choledochoduodenostomy for malignant distal biliary obstruction[21]. Preliminary results suggest that, in the future, gastroenterologists may assume the responsibility of biliary drainage from surgeons, whether it be for ERCP or EUS.

Gallbladder
The gallbladder needs to be drained in cholecystitis if the patient is unfit for surgery or has an unresectable pancreatic cancer, or if the cholecystitis is refractory to antibiotics. Classically, drainage has been performed percutaneously, although studies have shown that EUS-guided endoscopic drainage is equally as successful as percutaneous drainage[22]. Drainage by EUS can be performed either with a plastic stent, metal stent, or naso-gallbladder/nasobiliary drain.

Abscesses
EUS has developed into a favorable alternative to traditional percutaneous drainage of abscesses[16]. Accessible abscesses include those in the mediastinum, lesser sac, perihepatic and subphrenic spaces, and pelvic and perirectal regions.

INJECTION

Nerve block
Nerve blocks are administered to reduce transmission through a nerve, thereby reducing chronic pain and the resulting need for opioids and analgesics. Nerve blocks are often conducted using neurolysis, in which cytolytic agents, commonly alcohol or phenol, are injected to damage the nerves. The nerves most commonly targeted are in the celiac plexus for pancreatic cancers and, less commonly, chronic pancreatitis. Neurolysis can be performed percutaneously or endoscopically by EUS. The percutaneous approach has been the more widely used approach, though studies have shown that endoscopic approach may provide more lasting results[16,23], as the injection is delivered under greater control.

Tattooing
EUS-guided fine-needle tattooing (EUS-FNT) is a technique in which carbon particle labels are injected into pancreatic lesions *via* EUS guidance. These labels then serve as markers during laparoscopic distal pancreatectomy, which ultimately reduces operating time, cost, and amount of healthy pancreas that is inadvertently resected[24].

Targeted destruction of lesions
Alcohol ablation: Alcohol can be injected using EUS guidance in order to ablate pancreatic lesions, neuroendocrine tumors, or metastases from the abdomen. Alcohol ablation has proven very effective, especially for certain pancreatic lesions, particularly when combined with taxols or other agents. Currently, alcohol ablation of neuroendocrine tumors is only indicated if the patient is unfit for surgery. It is uncertain how effective alcohol ablation has been for neuroendocrine tumors because there is not yet sufficient data for predicting prognoses.

Radiotherapy: Fiducials, which are small 3-5 mm radiopaque metal markers, may be placed in tumors or lymph nodes using EUS guidance and a 19-gauge FNA needle[17]. These fiducials act as points of reference for targeted external beam radiation therapy[25]. Alternatively, EUS can guide injection of seeds through 19-gauge needles for brachytherapy (internal radiotherapy, various plasmids).

Chemotherapy: Chemotherapeutic agents, commonly paclitaxel, have been injected using precise EUS guidance. Chemotherapy injection can be combined with other therapeutic methods such as alcohol ablation. EUS-guided chemotherapy has been used for pancreatic cysts and tumors and esophageal cancers, but much more research is needed to understand the long-term results[18].

Photodynamic therapy: Photosensitizing drugs can also be injected using EUS guidance. Exposure to the specific wavelength of light leads to cytotoxic effects, vascular effects, and inflammatory reactions, thereby leading to necrosis of the targeted site.

SURGERY

Natural orifice transluminal endoscopic surgery
Natural orifice transluminal endoscopic surgery (NOTES) is a surgical technique that uses the body's natural orifices as inlets to reach various organs *via* EUS guidance. Pioneered by Dr. Anthony Kalloo, NOTES procedures have a number of potential benefits. Without external incisions, there are no scars or risks of skin infection, and thus the NOTES approach offers a potentially quicker recovery and therefore shorter hospital stay. Furthermore, less anesthesia may be required. NOTES procedures are currently being developed to: Create anastomoses - Gastroduodenal anastomosis by NOTES has succeeded as a minimally invasive approach for certain gastrointestinal bypass procedures. These bypass procedures include treatment of obstructions, such as duodenal stenosis or gastric outlet obstruction. NOTES can also be used for gastrojejunal bypass, as a malabsorptive-type bariatric procedure. Studies are needed, however, to compare these NOTES procedures

directly with conventional surgical approaches[26].

Remove and biopsy organs-NOTES also has the potential to become a minimally invasive alternative to routine laparoscopic procedures. NOTES can be used for liver biopsy, cholecystectomy, appendectomy, thyroidectomy, and procedures involving mediastinal and spinal tissues. The transgastric approach has been the most studied inlet to date. So far, however, the majority of human NOTES procedures have been transvaginal cholecystectomy and appendectomy. More human research is needed on the transgastric and transrectal approaches.

NOTES has many advantages and therefore much potential, although it has undoubtedly been slow to catch on. Devices designed specifically to facilitate NOTES are needed. Despite NOTES being an endoscopic procedure and therefore inherently within a gastroenterologist's "jurisdiction", its ultimate procedural goal is often that of a surgeon. Techniques such as NOTES obscure the distinct borders of each specialist, and the medical community must come together and decide who is best trained to perform each procedure. To do so, it must first be decided how to base the decision; should the decision be based on the approach or the ultimate goal of the procedure? If based on the approach, it must then be asked if NOTES should be considered a surgical approach? How do we even define surgery today? Should a NOTES cholecystectomy be considered surgery even though EUS-FNA is not? If a consensus is reached among the medical community, NOTES may, like the arrival of laparoscopy in 1901, lead to a momentous step forward in medicine.

VASCULAR

Angiography
Angiography is another novel application of EUS. EUS can guide access into small vessels, such as the celiac branches and hepatic vein. Although thus far only conducted in animals, EUS can also be used to measure portal vein pressure and therefore guide portal hypertension therapy[25].

Bleeding control
EUS can also be applied to control gastrointestinal bleeding, such as treatment of varices, insertion of porto-systemic shunts, pseudoaneurysm control, embolization, and coil application. Studies have shown notable success, concluding that EUS should be considered when managing patients who have failed with conventional therapy[27]. Studies are still in their early stages, however, and much research on EUS and vascular interventions is on the horizon[18].

NOVEL TOOLS

Forward viewing EUS
Forward viewing EUS (FV-EUS), a relatively novel tool,

is believed by some experts to be an upgrade to the conventional curved linear array EUS (CL-EUS)[21]. FV-EUS gives the endoscopist better and more stable access into cysts. It also is easier to maneuver because of its short, hard tip, thereby allowing for more dexterity during interventional procedures. This allows the endoscopist to reach more difficult locations within the GI tract; this is especially true in the lower GI tract, as FV-EUS has been shown to allow for easier cecal intubation[21]. FV-EUS also enables a shorter training time, which may lead to a more widespread usage than the conventional curved linear array EUS. In addition to its technical advantages over CL-EUS, some studies have also shown that FV-EUS can detect additional gastrointestinal lesions[28].

Disadvantages do exist though; the EUS view is reduced from 180 to 90 degrees; this however, reportedly, does not pose difficulty for experienced endosonographers. It is also more difficult with FV-EUS to intubate the cervical esophagus. It may also be more difficult to aspirate pancreatic pseudocysts because of the lack of fixation of the guide-wire without an elevator. Also regarding NOTES procedures, it is unclear if FV-EUS or CL-EUS is superior; a multicenter randomized trial, comparing the two endoscopes, found the same success rates, mean procedure times, and ease of access and complication rates[29]. FV-EUS and CL-EUS shared the same diagnostic yield of upper GI subepithelial lesions, though FV-EUS led to a shorter procedure time and a larger tissue sample area[30]. Clearly, more studies are needed on FV-EUS to determine when it provides significant advantage over the CL-EUS.

3D reconstruction
Three-dimensional imaging has been found useful in gynecologic ultrasound, and may also find a place in gastrointestinal EUS if proven advantageous.

CONCLUSION
EUS has come a long way in the last 25 years. Ultrasound has become much more than a tool to differentiate different tissue densities; tissue can now be characterized in great detail; the extent of vascularity within a tissue and how malignant the tissue appears can now be learned with increasing precision, all in real-time and without radiation. Using these techniques, targets for biopsy can be precisely pinpointed. Upon reaching the target, tissue can then be examined microscopically in real-time, to ensure optimal targeting and diagnosis.

EUS and its associated advancements have begun to take advantage of the fact that the gastrointestinal tract runs medially throughout the majority of the body and is very accessible; the gastrointestinal tract is now beginning to be used as an inlet to the rest of the body. After having brought ultrasound technology inside the gastrointestinal tract in the 1980s, EUS is

now being used as a guide outside the lumen. Many of these recent technologic advancements are in early stages and have not yet been studied extensively. The years ahead are therefore expected to be bright for EUS, as more research concludes and as these various technologies begin being implemented into clinical practice.

ACKNOWLEDGMENTS

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Endoscopic ultrasound elastography for solid pancreatic lesions

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Abstract

Elastography is one of technologies assisting diagnosis of solid pancreatic lesions (SPL). This technology has been previously used for measuring the stiffness of various organs based on a principle of "harder the lesions, higher chance for malignancy". Two elastography techniques; strain and shear wave elastography, are available. For endoscopic ultrasound (EUS), only the former is existing. To interpret results of EUS elastography for SPL, 3 methods are used: (1) pattern recognition; (2) strain ratio; and (3) strain histogram. Based on results of existing studies, these 3 techniques provide high sensitivity but low to moderate specificity and accuracy rate. This review will summarize all available information in order to update current situation of using elastography for an evaluation of SPLs to readers.

Key words: Elastography; Endoscopic ultrasound; Solid pancreatic lesions; Pancreatic cancer; Chronic pancreatitis

Core tip: Elastography is a technology that can measure tissue stiffness. Endoscopic ultrasound (EUS) elastography has been increasingly used for an evaluation of solid pancreatic lesions (SPL). Several interpretation methods of EUS elastography for this purpose have been described in many previous studies. This review focuses on how to read and interpret findings of EUS elastography obtained from SPL. Readers should be competent for applying EUS elastography for diagnosing SPL after finishing reading the review.

INTRODUCTION

The diagnosis of solid pancreatic lesions (SPL) is a

challenging clinical problem. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is the most commonly used diagnostic method. It has high specificity but moderate sensitivity. Due to the aggressiveness and poor outcomes of pancreatic cancer, several methods such as elastography or contrast enhancement have then been developed to assist in the diagnosis of SPL. Certainly, these software technologies cannot replace EUS-FNA because they are not pathological diagnostic tools, but they can help clinicians in many clinical scenarios such as in lesions with remarkably low EUS-FNA diagnostic yield including mass-forming chronic pancreatitis. Several previous studies have shown various efficacy values for these adjunctive technologies in their results. Elastography is one of these current assisting technologies diagnosing SPL. This technology measures the stiffness of the target lesion. In this review, the results of EUS elastography in the evaluation of SPL will be summarized.

This review summarizes characteristic findings of each SPL by EUS elastography. We searched the PubMed database for English-language journals with human studies published between 1988 and 2016. The following keywords were used in combination with EUS: Elastography, pancreas, and solid lesions. References to those identified articles were also examined for potentially relevant studies.

HISTORY OF ELASTOGRAPHY

Since 1988, the concepts of tissue deformability and elasticity of solid tumor has been described[1]. In 1991, tissue elasticity measurements were made by evaluation of the elastic modulus after applying a pressure (Figure 1); hence, the term "elastography" was first reported[2]. This led to the development of real-time imaging and the combination of elastography imaging with B mode imaging using a combined autocorrelation method in 2001[3]. Since then, elastography has been applied to the diagnosis of solid tumors of various organs such as breast, thyroids, lymph nodes and liver. In 2006, elastography for SPL was firstly reported[4]. The interpretation of elastography findings from SPL have been developed and applied to clinical management.

TYPES OF ELASTOGRAPHY

Elastography is classified into two categories based on different mechanical properties: Strain and shear wave elastography. The former evaluates tissue stiffness by measuring tissue distortion after applying pressure and the latter assess tissue stiffness by measuring tissue distortion after applying the acoustic radial force impulse[5]. However, only strain elastography is available for EUS.

STRAIN ELASTOGRAPHY MEASUREMENT METHODS

Strain elastography evaluates tissue stiffness *via*

the displacement caused by manual compression or cardiovascular pulsation[6]. Larger strain or tissue displacement values represent softer tissue (Figure 2). The degree of strain-the relative indicator-can be displayed *via* three methods[6].

Pattern recognition
This method is to display as colors, with the green color as the mean stiffness, blue color represents harder tissue and red color represents softer tissue. This is the only method considered qualitative method whereas following methods are quantitative ones.

Strain ratio
This method is to display as gray scale image and compare strain ratio (SR) of area of interest with reference area.

Strain histogram
Pattern recognition: Color pattern analysis of elastography was first described in transcutaneous ultrasound elastography of the breast[7]. The EUS elastography pattern in pancreatic lesion was first described by Giovannini (Figure 3)[4] with 100% sensitivity but only 67% specificity in differential diagnosis of benign and malignant SPL. The same author later classified the previous 5-scale elastic score into 3 scores: A, B and C, representing benign, indeterminate, and malignant lesions, respectively[8]. This classification has 92.3% sensitivity and 80% specificity in differential diagnosis between benign and malignant SPL. Reports of different pattern analyses results in different clinical efficacy have been published. Another report by Janssen *et al*[9] classified color patterns into 3 types: Type 1 with homogeneous pattern, type 2 with 2 or 3 colors, and type 3 with a honeycomb pattern. In this report, however, the use of elastography in differential diagnosis between benign and malignant lesions was disappointing. Another study done by Iglesias-Garcia[10], classified the elastography into 4 patterns with 100% sensitivity and 85.5% specificity in the diagnosis of malignant SPL. The comparison of each report as well as sensitivity and specificity is shown in Table 1.

SR: SR compares the strain between the target area and other reference areas to provide more objective qualitative data[11]. In breast lesions, the strain of the lesion is compared to the strain of the surrounding fat tissue. Many studies use SR to differentially diagnose pancreatic carcinoma and chronic pancreatitis[11-14]. In some studies, the strain of the area surrounding the pancreas was used as the baseline compared with the strain of the lesion[11,15]. The peripancreatic surrounding the soft tissue was used as the baseline in other studies[12,13]. Moreover, according to the phantom study, the depth of the reference area has a significant impact on the evaluation of the SR[16]. The area of selection and cut-off point in each study are demonstrated in Table 2. Studies have correlated SR and chronic pancreatitis.

Figure 1 The principle of strain elastography is illustrated by coil spring appearance. A: After applying pressure, more deformation is demonstrated in tissue with higher elasticity; B: The strain on each tissue depends on the tissue stiffness; C: Higher strain is seen in softer tissue after compression (Adapted from Ophir[2]).

Figure 2 The principle of endoscopic ultrasound elastography for solid pancreatic lesions. A: Pancreatic carcinoma has more stiffness than normal pancreas; B: The strain elastography measured the degree of displacement after applying manual pressure or vascular pulsation; C: The degree of displacement is represented as colors: Green is the average stiffness, blue is stiffer tissue, and red is softer tissue.

Table 1 Results of 4 large studies using pattern recognition of elastography for diagnosis of solid pancreatic lesions

Author	Giovannini *et al*[4], 2006		Giovannini *et al*[8], 2009		Janssen *et al*[9], 2007			Iglesias-Garcia *et al*[10], 2009	
	Elastic score /pattern	Interpretation	Score	Inter-pretation	Type	Color	Interpretation	Pattern	Interpretation
Score and interpretation	Distortion for entire low echo area	Normal pancreas	A (elastic score 1 and 2)	Benign	Homogeneous	A = blue	B = normal pancreas	Homogeneous green	Normal pancreas
	No distortion on low echo area even for a part	Fibrosis, chronic pancreatitis						Heterogenous green	Inflammatory pancreas
	Distortion at the edge of low echo area, even for a part	Small adeno-carcinoma	B (elastic score 3)	Indeter-minate	2 or 3 colors	B = green/ yellow		Homogeneous blue	Ductal pancreatic adenocarcinoma
	No distortion for entire low echo area	Endocrine tumor	C (elastic score 4 and 5)	Malignant	Heterogeneous	C = red	A/B = chronic pancreatitis and neoplasia	Heterogeneous blue	Neuroendocrine tumor
	No distortion on low echo area and surrounding	Advanced adeno-carcinoma							
Sensitivity	100		92.3		65.9 (chronic pancreatitis), 93.8 (neoplasia)			100	
Specificity	67		80		56.9 (chronic pancreatitis), 65.4 (neoplasia)			85.5	
Accuracy	NA		89.2		60.2 (chronic pancreatitis), 73.5 (neoplasia)			94	

NA: Not available.

Elastic score	Elastography	Pattern	Condition
1		Distortion for entire low echo area	Normal pancreas
2		No distortion on low echo area even for a part	Fibrosis, chronic pancreatitis
3		Distortion at the edge of low echo area, even for a part	Small adenocarcinoma
4		No distortion for entire low echo area	Endocrine tumor
5		No distortion on low echo area and surrounding	Advanced adenocarcinoma

Figure 3 Classification of elastography findings proposed by Giovannini[4].

Iglesias-Garcia reported a cut-off of 2.25 for the diagnosis of chronic pancreatitis with a sensitivity of 91.2% and a specificity of 91% using the surrounding soft tissue as a reference[17]. Another study reported the correlation of SR and the presence of pancreatic exocrine insufficiency (PEI) with 87.0% probability of PEI in those with SR higher than 4.5 compared with 16.3% probability of PEI in those with SR lower than 4.5[18]. In this study, the normal surrounding gut wall was used as the reference. Iglesias-Garcias reported the mean elastic value to be 0.47%, 0.23%, 0.02% and 0.01% for normal pancreas, chronic pancreatitis, pancreatic cancer, and endocrine tumor, respectively[14]. Another report from South Korea demonstrated a mean elastic value of 0.53% for the normal pancreas and 0.02% for pancreatic cancer[19].

Many studies are based on the SR method, but there is no standardization for the reference area yet[5]. Moreover, the distance of the reference area from the ultrasound probe significantly impacted the SR measurements[16]. These two factors significantly impacted the reliability of the SR methods as a diagnostic test for SPL.

Strain histogram
The strain histogram is another type of the quantitative image analysis. To analyze the strain histogram, the color image of the elastography is converted into the gray scale (value) of 256 tones. It ranged from 0 to 255 with 0 representing the blue area (hard) and 255 representing the red area (soft) (Figure 4). The distribution of the gray scale is then calculated into various parameters as shown (Table 3). In some reports, the histograms were performed separately from the individual red/green/blue color[20]. The correlations of the parameters with the degree of pancreatic fibrosis have been published[21]. With increasing fibrosis, the mean and standard deviation decrease, while skewness and kurtosis increase. On the other hand, the histogram could be analyzed using the neural network analysis. The correlation between a cut-off mean level > 175 in pancreatic carcinoma

Table 2 Results of studies using strain ratio of elastography for an evaluation of solid pancreatic lesions

Ref.	Diseases of comparison (*n*)	Reference area	Cut off point	Sensitivity	Specificity
Iglesia-Garcia *et al*[14]	PC (49) *vs* CP (27)	Soft tissue	6.04	100	96.3
	PC (49) *vs* PNET (6)		26.63	100	87.8
Itokawa *et al*[11]	PC (72), PNET (9), CP (20), normal pancreas (8)	Normal pancreas	23.66 in MFP *vs* 39.08 in PC		
Dawwas *et al*[12]	Malignant (87): (PC, PNET, metastatic cancer) And benign (17) (pancreatitis)	Soft tissue	4.65	100	16.7
Kongkam *et al*[13]	PC (23), PNET (5), Meatastasis (1), CP (2), AIP (3), other (4)	Soft tissue	3.17	86.2	66.7
			6.04	75.9	77.8

PC: Pancreatic cancer; PNET: Pancreatic neuroendocrine tumor; CP: Chronic pancreatitis; AIP: Autoimmune pancreatitis.

Table 3 The histogram parameters[5,21,45]

Images	Parameters	Information	Interpretation
Gray scale images	Mean	Mean of the gray levels	Higher mean value indicates softer tissue
	Standard deviation	Standard deviation of the gray levels	Higher value indicating heterogeneous hardness
	ASM	Measure of the homogeneity on the gray scale image	
	Contrast	Measure of local gray level variation on the gray scale image	
	Correlation	Measure of gray level linear dependence on the gray scale image	
	Entropy	Measure of the randomness of gray level distribution	
	IDM	Measure of the homogeneity on the gray scale image	
	Skewness	Measure of the asymmetry of the gray level distribution	Higher value indicating higher or lower hardness
	Kurtosis	Measure of the "peakedness" of the gray level distribution	Higher value indicating concentration of a specific hardness
Black and white image	% area	Percentage of the white area (= hard area)	
	Mean of Complexity	Complex ratio of the shape of the white area (= hard area) and is calculated as periphery^2/area of the white area	

had a sensitivity of 91.4%-93.4% and a specificity of 66%-87.9%[22,23]. Another report analyzed the histogram by comparing the histogram of the tumor over the adjacent part of the pancreas[24]. The strain histogram's ratio with cut-off value of 1.15 indicated pancreatic malignancy with 98% sensitivity, 58% specificity, and 69% accuracy.

CLINICAL IMPLICATIONS

Pancreatic adenocarcinoma vs mass-forming chronic pancreatitis

Pancreatic adenocarcinoma is the most common type of pancreatic tumor, and it is characterized by many desmoplastic reactions[25]. Increased amounts of extracellular matrix including type I and type V collagen and fibronectin are found similar to those found in alcoholic chronic pancreatitis and tumor-induced chronic pancreatitis[26]. The differential diagnosis between pancreatic adenocarcinoma and mass-forming pancreatitis-especially on the background of chronic pancreatitis-remains a challenging problem. It is well known that the incidence of pancreatic adenocarcinoma is higher in patients with chronic pancreatitis[27]. Moreover, some features of chronic pancreatitis, such as calcification, may hinder the detection of pancreatic cancer[28]. Moreover, EUS-FNA of the pancreatic cancer (standard method for tissue acquisition from SPL) results in only 50%-73.9%

sensitivity but with 73.7%-100% specificity in the presence of chronic pancreatitis[29-31]. In elastography, pancreatic adenocarcinoma usually manifests as a hard tumor with a predominate blue color pattern (Table 1 and Figure 5). It has a higher SR than mass-forming chronic pancreatitis. Another single report compared pancreatic adenocarcinoma and autoimmune pancreatitis. This demonstrated that in autoimmune pancreatitis the stiffness area not only forms the mass area but also the surrounding pancreatic tissue[32].

Pancreatic neuroendocrine tumor

Pancreatic neuroendocrine tumors (PNETs) are a rare type of solid pancreatic tumor that are characterized histologically by tumor cells arranged in solid nest, trabecular, or gland like formation surrounded by thin vascular stroma[33]. The elastography pattern of PNET was described as homogeneous blue and heterogeneous blue by Giovannini[4] and Iglesias-Garcia[10], respectively. In one prospective study that included 6 patients with PNET, the SR of PNET is 56.73-higher than the 17.41 SR seen in pancreatic adenocarcinoma[17].

Solid pseudopapillary neoplasm

Elastography studies in solid pseudopapillary neoplasm (SPN) are rare. Only one study with 1 SPN case was found. It had a SR near 15[17].

Figure 4 Histogram analysis using MATLABver 1.6.7. A and B: The color image of the elastography is converted into the gray scale (value) of 256 tones ranging from 0 to 255:0 represents the blue area (hard) and 255 represents the red area (soft); C: The distribution of the gray scale is presented as a histogram from which the parameters are calculated.

Figure 5 Endoscopic ultrasound elastography of pancreatic adenocarcinoma. The color pattern showed predominant blue color pattern without distortion of surrounding area.

OTHER UNCOMMON TUMORS

For pancreatic acinar cell carcinoma, there are limited reports of EUS elastography. Only one report of elastography in pancreatic acinar cell carcinoma has been published[34]. In this report, there was no specific pattern of elastography, and the pattern varied according to the acinar cell tumor pathologic phenotype. The data for more uncommon types of pancreatic cancers such as anaplastic cell carcinoma and adenosquamous cell carcinoma have not yet been reported.

Chronic pancreatitis

Elastography has been used in both the diagnosis of chronic pancreatitis and as a predictor of post-operative pancreatic fistula. Despite the usefulness of EUS in the diagnosis of pancreatic lesions, there are only limited data in EUS elastography studies in chronic pancreatitis. Many studies of elastography in chronic pancreatitis

using transabdominal ultrasound with shear wave elastography for the detection of pancreatic fibrosis both in chronic pancreatitis and tumor-related fibrosis have been reported[35-38]. Apart from the transabdominal ultrasonography, intraoperative ultrasound elastography has been published. This demonstrated correlation between "soft pancreas" and the development of a post-operative pancreatic fistula[39,40].

In EUS studies, one prospective study demonstrated a higher SR in chronic pancreatitis with 91.2% sensitivity, 91.0% specificity, and 91.1% accuracy with a cut-off point of 2.25[17]. In this study, the SR also varied across groups according to Rosemond criteria for the diagnosis of chronic pancreatitis with a higher SR up to 8.12 in cases that fulfilled all criteria of chronic pancreatitis. Moreover, in patients with chronic pancreatitis, elastography with higher SR was seen in those with evidence of pancreatic enzyme insufficiency (SR 4.89 *vs* 2.99)[18]. This finding was consistent with another study demonstrating higher stiffness in more advanced pancreatic fibrosis using EUS elastography with histogram analysis[21]. A retrospective study of EUS elastography using histograms for analysis also demonstrate the correlation of mean value with the stage of chronic pancreatitis *via* the Rosemont criteria. This used cutoffs of 90.1 ± 19.3, 73.2 ± 10.6, 63.7 ± 14.2, and 56.1 ± 13.6, in normal pancreas, indeterminate for chronic pancreatitis, suggestive of chronic pancreatitis, and consistent with chronic pancreatitis, respectively[41].

Aging can cause several changes similar to early chronic pancreatitis[42]. A study using EUS also demonstrated abnormalities similar to chronic pancreatitis in elderly subjects without clinical chronic pancreatitis-particularly after the age of 60[43]. Elastography studies in aging populations also showed increased pancreatic stiffness with age demonstrated by both EUS[44]. and transabdominal ultrasonography[45]. These changes

become significant after age 40 to 60[44,45]. In one study, the mean histogram below 50 was more suggestive of chronic pancreatitis than usual aging changes[44].

COULD EUS ELASTOGRAPHY REPLACED TISSUE DIAGNOSIS?

While many studies have demonstrated excellent efficacy of elastography in the diagnosis of SPL, the value of elastography in cases with negative EUS FNA remains inconsistently demonstrated in all studies. Moreover, the method of image analysis is not yet standardized. Most reports demonstrated high sensitivity but low specificity, and the interpretation was performed by a center with many experienced elastographers. Hence, elastography cannot replace EUS-FNA for diagnosis[46].

CONCLUSION

In summary, EUS elastography is an improvement in the differential diagnosis between benign and malignant SPL in many studies. The main role of elastography in SPL is as an adjunct with other modalities in making diagnoses. Especially in chronic pancreatitis, EUS still has a promising role in both the diagnosis of early chronic pancreatitis and the prediction of complication. However, the overlapping of early chronic pancreatitis and aging changes makes the decision more difficult.

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Retrospective Study

Oral esomeprazole *vs* injectable omeprazole for the prevention of hemorrhage after endoscopic submucosal dissection

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Abstract

AIM
To evaluate the effectiveness of oral esomeprazole (EPZ) *vs* injectable omeprazole (OPZ) therapy to prevent hemorrhage after endoscopic submucosal dissection (ESD).

METHODS
A case-control study was conducted using a quasi-randomized analysis with propensity score matching. A total of 258 patients were enrolled in this study. Patients were treated with either oral EPZ or injectable OPZ. The endpoint was the incidence of hemorrhage after ESD.

RESULTS
Data of 71 subjects treated with oral EPZ and 172 subjects treated with injectable OPZ were analyzed. Analysis of 65 matched samples revealed no difference in the incidence of hemorrhage after ESD between the oral EPZ and injectable OPZ groups (OR = 0.89, 95%CI:

0.35-2.27, $P \geqslant 0.99$).

CONCLUSION
We conclude that oral EPZ therapy is a useful alternative to injectable PPI therapy for the prevention of hemorrhage after ESD.

Key words: Endoscopic submucosal dissection; Proton pump inhibitors; Hemorrhage

Core tip: Proton pump inhibitors (PPIs) have been reported to be effective for suppressing hemorrhage after endoscopic submucosal dissection (ESD); however, it remains unclear whether oral PPI therapy or injectable PPI therapy is preferable. The results of the present study indicate that oral effectiveness of oral esomeprazole therapy is a useful alternative to injectable PPI therapy for the prevention of hemorrhage after ESD.

INTRODUCTION
Endoscopic submucosal dissection (ESD) allows *en-bloc* resection of even large and ulcerated gastric tumors[1,2]. It enables accurate histopathological diagnosis and reduces the risk of local recurrence[3], and is a standard treatment for selected gastric tumors. However, ESD is technically difficult and is associated with a higher risk of adverse events than conventional endoscopic mucosal resection (EMR)[3-5]. Among the adverse events, hemorrhage is a frequently encountered and serious problem[6]. Hemorrhage after ESD can occur at a later stage than other complications of ESD, such as perforation, sometimes occurring even after hospital discharge. Furthermore, hemorrhage after gastric ESD can be serious, as it can be massive and complicated by life-threatening hemorrhagic shock[7]. Thus, the importance of preventing hemorrhage after ESD cannot be overemphasized. While some previous studies have reported the risk factors for hemorrhage after ESD[6-14], no consensus has been arrived at yet in respect of the risk factors. Proton pump inhibitors (PPIs) have been reported to be effective for controlling hemorrhage after ESD[15]. However, to the best of our knowledge, there have been no studies yet to compare the efficacy of oral PPI therapy *vs* injectable PPI therapy for the control of hemorrhage after ESD. It remains unclear whether oral PPI therapy or injectable PPI therapy is preferable for the

prevention of hemorrhage after ESD.

Esomeprazole (EPZ) is the S-isomer of omeprazole (OPZ) and has more favorable pharmacokinetic and pharmacodynamic profiles than OPZ[16]. However, injectable EPZ is not available at present in our hospital. In the current study, therefore, we compared the efficacy of oral EPZ therapy with that of injectable OPZ (in place of EPZ) therapy for the prevention of hemorrhage after ESD by propensity score-matched analysis.

MATERIALS AND METHODS
Patients and methods
We conducted a retrospective study with propensity score-matched analysis. We registered patients who had undergone ESD for gastric tumors at our hospital between March 2008 and March 2014 (n = 258). The research protocol was approved by the Hospital Ethics Committee. Written informed consent was obtained from each of the participants of the study.

Treatment
Figure 1 shows the treatment protocol used. The patients received either oral EPZ (20 mg daily) for 8 wk after ESD (oral EPZ group) or injectable OPZ (20 mg twice daily) for the first 5 d, followed by oral OPZ (20 mg daily) from day 6 to the end of 8 wk after the ESD (injectable OPZ group). Additionally, all the patients underwent an endoscopic examination on day 2 and a third endoscopy on day 6 after the ESD. All patients were given sucralfate from day 2 to the end of 8 wk after the ESD. Antiplatelet/anticoagulant drugs were discontinued before the ESD.

ESD procedure
ESD was performed using a videoendoscope (GIF-Q260J), Electric scalpel for endoscopic surgery (IT-Knife2) (Olympus Corporation, Tokyo, Japan) and an electrosurgical unit (ICC 200) (ERBE Elektromedizin GmbH, Tubingen, Germany). After tumor resection, all the visible vessels in the created ulcer were coagulated using a coagulation device (Coagrasper) (Olympus Corporation).

Hemorrhage
Hemorrhage after ESD was defined as the presence of clinical evidence of hemorrhage, such as the occurrence of melena or hematemesis confirmed by the hospital staff, or confirmation of the presence of blood or bleeding spots in the post-ESD ulcer at the second or third endoscopy. Preventive hemostasis for visible vessels not showing evidence of hemorrhage during the second or third endoscopy was not included as evidence of hemorrhage after ESD. We also defined clinically significant hemorrhage after ESD as hemorrhage necessitating emergency endoscopy or blood transfusion.

Statistical analysis
Data are presented as mean ± SD or number, and the diagnostic outcomes were examined using the χ^2 test.

Figure 1 Treatment protocol for the two groups. EGD: Esophagogastroduodenoscopy; ESD: Endoscopic submucosal dissection; EPZ: Esomeprazole; OPZ: Omeprazole.

The variables and incidence of hemorrhage after ESD in the oral EPZ group were compared with those in the injectable OPZ group using the χ^2 test. Furthermore, propensity score matching was performed to control and reduce the selective bias[17-19]. Ten variables that could potentially influence the incidence of hemorrhage after ESD, listed below, were used to generate propensity scores using logistic regression: Patient age, patient sex, history of use of antiplatelet/anticoagulant drugs, location of the lesion, lesion depth, presence/absence of ulceration, diameter of the lesion, duration of operation, macroscopic type of the lesion, and the operator experience (beginners: Surgeons who had performed < 50 gastric ESDs; experts: Surgeons who had performed > 50 gastric ESDs). A propensity score-matched cohort was created by trying to match each patient given oral EPZ with a patient given injectable OPZ (a 1:1 match), using the nearest pair method. After matching, a coarse comparison of the matched cohorts was performed using χ^2 test. *P* values of < 0.05 were considered to indicate significance. Statistical analyses were performed using the JMP 10.0 software (SAS, North Carolina, United States).

RESULTS

Background characteristics of the patients

A total of 258 patients were enrolled in this study. Fifteen following reasons: Failure of resection of the lesion *en-bloc* (*n* = 8); presence of perforation (*n* = 5); interruption of the ESD (*n* = 1); previous history of gastrectomy (*n* = 1). Data of the remaining 243 patients were evaluated. Of the 243 patients, 172 who had undergone ESD before November 2012 received injectable OPZ, and the remaining 71 patients who had received ESD after November 2012 received oral EPZ (Figure 2). The data of 71 patients of the oral EPZ group and 172 patients of the injectable OPZ group were analyzed.

Among the 243 patients included in the analysis, 33 developed hemorrhage after the ESD (13.6%), with the hemorrhage being clinically significant in 10 of these cases (4.1%). Table 1 shows the baseline characteristics of the study population. A univariate analysis identified operator experience as the only risk factor for hemorrhage after ESD (beginner *vs* OR = 2.16; 95%CI: 1.03-4.55, *P* = 0.039). Hemorrhage after ESD was observed within 6 d of the procedure in all the cases.

Propensity score matching

A quasi-randomized experiment can be created using propensity score matching. That is, two subjects assigned to each group are equally likely to receive oral EPZ or injectable OPZ (Tables 2 and 3). Nearest-neighbor matches were performed using a caliper with 0.25 standard deviation of the propensity score (log odds scale). The predictive performance of the treatment model was evaluated using the χ^2 statistic that can take values from 0.5 for chance prediction to 1.0 for perfect prediction[20]. The propensity score allowed clear distinction between cases with and without hemorrhage after ESD, with a *c*-statistic of 0.77.

Among the matched samples, the incidence of hemorrhage after ESD was 15.4% (10/65) in the oral EPZ group and 16.9% (11/65) in the injectable OPZ group, with no statistically significant difference seen between the two groups (EPZ group *vs* OPZ group, OR = 0.89, 95%CI: 0.35-2.27, *P* $\geqslant$ 0.99). The incidence of clinically significant hemorrhage was 6.2% (4/65) in the oral EPZ group and 4.6% (3/65) in the injectable OPZ group, with no significant difference of this parameter between the two groups either (EPZ group *vs* OPZ group, OR = 1.36, 95%CI: 0.29-6.31, *P* $\geqslant$ 0.99). No significant differences in any of the other variables examined were found between the two groups.

Figure 2 Selection of cases for study. ESD: Endoscopic submucosal dissection; EPZ: Esomeprazole; OPZ: Omeprazole.

Table 1 Background characteristics of the patients in relation to the bleeding status

	Hemorrhage after ESD		*P* value
	Negative	**Positive**	
Number	210	33	
Age (yr)	73.9 ± 8.0	71.7 ± 9.4	0.14
Gender (M/F)	151/59	8/25	0.65
Antiplatelet/anticoagulant drugs (-/+)	161/49	8/25	0.91
Hypertension (-/+)	123/87	20/13	0.83
Diabetes mellitus (-/+)	186/24	4/27	0.52
H. pylori infection (-/+)	90/120	13/20	0.89
Location (U/M/L)	28/96/86	2/15/16	0.45
Depth (m/sm)	190/20	5/28	0.35
Ulcer (-/+)	205/5	33/0	0.37
Diameter of the lesion (mm)	40.7 ± 15.3	40.4 ± 13.9	0.89
Duration of the operation (min)	106.9 ± 64.1	123.8 ± 98.5	0.2
Macroscopic type of the lesion (elevated or flat/combined/depressed)	130/29/51	5/10/2018	0.49
Pathological findings (Adenoma/Differentiated ca/Undifferentiated ca)	76/126/8	12/21/0	0.32
Lymphatic/venous invasion (-/+)	206/4	Jan-32	0.67
Anastomosis (-/+)	200/10	33/0	0.2
Operator type (expert/beginner)	129/81	14/19	0.0392
Bleeding during ESD (good/poor control)	164/46	9/24	0.49

P value calculated by the χ^2 test (Fisher's exact test or Pearson's test). ESD: Endoscopic submucosal dissection; *H. pylori*: *Helicobacter pylori*.

DISCUSSION

EPZ is the first optical isomer developed as a PPI. Previous studies have demonstrated the efficacy of oral EPZ in the treatment of GERD[21,22]. Recently, Bunno *et al*[23] reported that oral EPZ was effective for ulcer healing after ESD. However, no studies have assessed the efficacy of oral EPZ for the control of hemorrhage after ESD. Recent studies have reported that oral EPZ therapy is a useful alternative to injectable PPI therapy to prevent recurrent hemorrhage in hemorrhagic gastric ulcer patients[24,25]. Laine *et al*[26], who compared oral and injectable lansoprazole, showed a difference in the intragastric pH only during the first hour after PPI administration, with no difference in the intragastric pH seen between the two groups at ≥ 1.5 h after the drug administration. Javid *et al*[27] demonstrated an equivalent ability of injectable and high oral doses of various PPIs in suppressing gastric acid secretion, and no significant difference in effect among various PPIs given through different routes on the gastric pH ≥ 6 for 72 h after successful endoscopic hemostasis. Our results were consistent with the findings of these previous studies. Oral EPZ therapy has the advantages of a lower cost and easier administration as compared to injectable PPI therapy, whereas injectable PPIs will still be needed for patients who cannot receive oral medications. Therefore, we conclude that oral EPZ therapy is a useful alternative to intravenous PPI therapy for the prevention of hemorrhage after ESD.

Table 2 Background characteristics of the patients according to the treatment group before the propensity score matching

	EPZ group	OPZ group	P value
Number	71	172	
Age (yr)	75.3 ± 7.1	72.9 ± 8.5	0.0361
Gender (M/F)	52/19	124/48	0.86
Antiplatelet/anticoagulant drugs (-/+)	50/21	136/36	0.15
Hypertension (-/+)	40/31	103/69	0.61
Diabetes Mellitus (-/+)	Sep-62	151/21	0.92
H. pylori infection (-/+)	29/42	55/117	0.19
Location (U/M/L)	10/34/27	20/77/75	0.7
Depth (m/sm)	57/14	161/11	0.0019
Ulcer (-/+)	71/0	167/5	0.15
Diameter of the lesion (mm)	42.2 ± 17.2	40.14 ± 14.1	0.31
Duration of the operation (min)	115.9 ± 87.3	106.4 ± 61.1	0.34
Macroscopic type of the lesion (elevated or flat/combined/depressed)	46/16/9	102/18/52	0.003
Pathological findings (Adenoma/Differentiated ca/Undifferentiated ca)	26/42/3	62/105/5	0.86
Lymphatic/venous invasion (-/+)	Jan-70	168/4	0.65
Anastomosis (-/+)	Mar-68	163/9	0.74
Operator type (expert/beginner)	31/40	112/60	0.002
Bleeding during ESD (good/poor control)	55/16	134/38	0.94
Hemorrhage after ESD (-/+)	149/23	Oct-61	0.88
Clinically significant bleeding (-/+)	165/7	Mar-68	0.96

P value calculated by the χ^2 test (Fisher's exact test or Pearson's test). EPZ: Esomeprazole; OPZ: Omeprazole; ESD: Endoscopic submucosal dissection.

Table 3 Background characteristics of the patients according to the treatment group after the propensity score matching

	EPZ group	OPZ group	P value
Number	65	65	
Age (yr)	75.2 ± 7.3	75.0 ± 7.5	0.9
Gender (M/F)	46/19	44/21	0.85
Antiplatelet/anticoagulant drugs (-/+)	46/19	44/21	0.85
Hypertension (-/+)	37/28	33/32	0.6
Diabetes Mellitus (-/+)	Aug-57	Dec-53	0.47
H. pylori infection (-/+)	26/39	23/42	0.72
Location (U/M/L)	5/33/27	10/24/31	0.19
Depth (m/sm)	Sep-56	Jun-59	0.58
Ulcer (-/+)	65/0	65/0	0
Diameter of the lesion (mm)	41.9 ± 18.5	39.6 ± 12.1	0.4
Duration of the operation (min)	110.6 ± 85.7	102.0 ± 54.9	0.5
Macroscopic type of the lesion (elevated or flat/combined/depressed)	42/14/9	10/8/1947	0.6
Pathological findings (Adenoma/Differentiated ca/Undifferentiated ca)	26/37/2	29/35/1	0.76
Lymphatic/venous invasion (-/+)	Jan-64	Feb-63	≥ 0.99
Anastomosis (-/+)	Mar-62	Mar-62	≥ 0.99
Operator type (expert/beginner)	29/36	27/38	0.86
Bleeding during ESD (good/poor control)	51/14	49/16	0.84
Hemorrhage after ESD (-/+)	Oct-55	Nov-54	≥ 0.99
Clinically significant bleeding (-/+)	Apr-61	Mar-62	≥ 0.99

P value calculated by the χ^2 test (Fisher's exact test or Pearson's test). EPZ: Esomeprazole; OPZ: Omeprazole; ESD: Endoscopic submucosal dissection.

Previous studies have reported the incidence and risk factors for hemorrhage after ESD, although the results are conflicting. We also assessed the risk factors for hemorrhage after ESD, and our analysis identified only the operator experience as a significant predictor of hemorrhage after ESD. Adequate coagulation of the vessels at the ulcer base after ESD is important to prevent delayed hemorrhage. As some experience is required for such coagulation, the incidence of hemorrhage after ESD differs between beginners and experts. A previous study also identified the operator experience as a significant risk factor for hemorrhage after ESD[11]. On the other hand, several studies have reported the absence of any significant effect of the operator experience on the risk of hemorrhage after ESD[6-10,12-14]. These differences in the outcomes were likely caused by the diversity of the ESD procedures and treatments employed. Further investigation is required to clarify the unified risk factors for hemorrhage after ESD.

Our study had some limitations. First of all, injectable EPZ is not available at our hospital; therefore, we compared oral esomeprazole with injectable OPZ. Second, we could not carry out a non-inferiority study, because the number of cases was small. Third, hemorrhage after

ESD is usually defined as bleeding, including hematemesis or melena, that necessitates endoscopic treatment and has been reported to occur in 1.3% to 11.9% of patients undergoing ESD[28]. We observed only 10 cases (10/243) with hemorrhage after ESD fulfilling this conventional definition, which made a reasonable comparison between oral EPZ and injectable OPZ difficult. Therefore, in this study, we defined hemorrhage after ESD as described in the text above. This was the reason why the frequency of hemorrhage after ESD was relatively high in this study, while the frequency of clinically significant hemorrhage was comparable to that reported from other studies. Fourth, this study was a 6-year clinical study. During this period, ESD has gradually become more and more popular. Individual learning curves, introduction of new devices, and establishment of education programs over the last few years make reasonable comparisons difficult.

In conclusion, in the present study, we assessed the frequency of hemorrhage after ESD after oral EPZ and injectable OPZ treatments. No difference was seen in the incidence of hemorrhage after ESD between the oral EPZ and injectable OPZ groups. This is the first study to investigate the effectiveness of oral EPZ therapy to prevent hemorrhage after ESD. Further large-scale trials are necessary to clarify the effectiveness of oral EPZ therapy. Oral PPI therapy shows a clear cost benefit and is easier to administer as compared to injectable PPI therapy. Thus, we conclude that oral EPZ therapy is a useful alternative to intravenous PPI therapy for the prevention of hemorrhage after ESD.

COMMENTS

Background
Endoscopic submucosal dissection (ESD) is technically difficult and is associated with a high risk of adverse events. Among the adverse events, hemorrhage is a frequently encountered and serious problem. Proton pump inhibitors (PPIs) have been reported to be effective for controlling hemorrhage after ESD. In this study, the authors compared the efficacy of oral effectiveness of oral esomeprazole (EPZ) therapy with that of injectable injectable omeprazole (OPZ) therapy for the prevention of hemorrhage after ESD.

Research frontiers
No comparison of the efficacy of oral PPI therapy *vs* injectable PPI therapy for the control of hemorrhage after ESD has been carried out previously. Therefore, whether oral PPI therapy or injectable PPI therapy is preferable for the prevention of hemorrhage after ESD remains uncertain. The results of this study contributed to clarifying the efficacy of oral EPZ therapy *vs* injectable OPZ therapy for the prevention of hemorrhage after ESD.

Innovations and breakthroughs
A quasi-randomized experiment was created using propensity score matching. Among the matched samples, the incidence of hemorrhage after ESD was 15.4% (10/65) in the oral EPZ group and 16.9% (11/65) in the injectable OPZ group. No statistically significant difference was seen between these groups.

Applications
This study suggests that oral EPZ therapy is a useful alternative to intravenous PPI therapy for the prevention of hemorrhage after ESD. Oral PPI therapy shows a clear cost benefit and is easier to administer as compared to injectable PPI therapy.

Terminology
ESD: An endoscopic technique allows *en-bloc* resection even for large or ulcerated gastric tumors.

Peer-review
The study is very well described and the results are clear. In this study, the authors investigated to compare EPZ *vs* intravenous omeprazole therapy to prevent hemorrhage after ESD using a quasi-randomized analysis with propensity score matching.

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CASE REPORT

Two case reports of acute upper gastrointestinal bleeding from duodenal ulcers after Roux-en-Y gastric bypass surgery: Endoscopic diagnosis and therapy by single balloon or push enteroscopy after missed diagnosis by standard esophagogastroduodenoscopy

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Institutional review board statement: William Beaumont Hospital IRB approved/exempted study on 12/16/16.

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Abstract

The diagnosis and opportunity for endoscopic therapy of gastric or duodenal lesions may be missed at esophago-gastroduodenoscopy (EGD) because of technical difficulty in intubating at EGD the postoperatively excluded stomach and proximal duodenum in patients status post Roux-en-Y gastric bypass (RYGB). Two cases are reported of acute upper gastrointestinal bleeding 10 or 11 years status post

RYGB, performed for morbid obesity, in which the EGD was non-diagnostic due to failure to intubate the excluded stomach and proximal duodenum, whereas subsequent push enteroscopy or single balloon enteroscopy were diagnostic and revealed 4-cm-wide or 5-mm-wide bulbar ulcers and even permitted application of endoscopic therapy. These case reports suggest consideration of push enteroscopy, or single balloon enteroscopy, where available, in the endoscopic evaluation of acute UGI bleeding in patients status post RYGB surgery when the EGD was non-diagnostic because of failure to intubate these excluded segments.

Key words: Morbid obesity; Bariatric surgery; Roux-en-Y gastric bypass surgery; Upper gastrointestinal bleeding; Esophagogastroduodenoscopy; Push enteroscopy; Single balloon enteroscopy; Therapeutic endoscopy; Double balloon enteroscopy

Core tip: After Roux-en-Y-gastric-bypass (RYGB) surgery, the surgically excluded distal stomach/duodenum may be difficult to intubate and examine during esophago-gastroduodenoscopy (EGD). Two cases are reported of acute upper gastrointestinal (UGI) bleeding many years after RYGB surgery, in which EGD was non-diagnostic due to failure to intubate these excluded segments. However, single balloon or push enteroscopy successfully permitted this intubation, enabling endoscopic diagnosis and therapy of bulbar ulcers at high risk of rebleeding. These case reports suggest using single balloon or push enteroscopy to endoscopically evaluate acute UGI bleeding in patients status-post-RYGB-surgery when EGD was non-diagnostic because of failure to intubate the excluded gastroduodenal segments.

INTRODUCTION

Anastomotic ulcers are the most common cause of upper gastrointestinal (UGI) bleeding after Roux-en-Y gastric bypass (RYGB), the most popular form of bariatric surgery[1], but such patients can also bleed from ordinary gastric or duodenal (peptic) ulcers[2]. Ulcers in the proximal duodenum or stomach may, however, be missed at esophagogastroduodenoscopy (EGD) after RYGB surgery because deep intubation of the proximal afferent limb is technically difficult

at EGD. Two patients with UGI bleeding status post RYGB surgery are reported who had non-diagnostic EGDs because of this technical difficulty, but then had 4-cm-wide or 5-mm-wide bulbar ulcers diagnosed and endoscopically treated after successfully intubating the proximal duodenum by push enteroscopy or single balloon enteroscopy. This work alerts physicians about this potential limitation of EGD in patients status post RYGB surgery, and suggests use of push enteroscopy or single balloon enteroscopy as alternatives for endoscopic diagnosis and therapy.

Methods
The literature was systematically reviewed *via* PubMed using the following medical subject headings or keys words: ("Roux-en-Y gastric bypass") AND ("duodenal ulcer" or "gastric ulcer" or "missed ulcer" or "peptic ulcer" or "esophagogastroduodenoscopy" or "push enteroscopy" or "single balloon enteroscopy" or "double balloon enteroscopy" or "therapeutic endoscopy") OR ("excluded segment" and "esophagogastroduodenoscopy") OR ("bariatric surgery" and "endoscopy" and "upper gastrointestinal bleeding"). The term esophagogastro-duodenoscopy (EGD) is used to describe what is technically esophagogastrojejunoscopy (EGJ) in patients status post RYGB, in accordance with common usage. The IRB at William Beaumont Hospital, Royal Oak, approved/exempted this study on December 16, 2016.

CASE REPORT

Case 1
A 44-year-old woman with prior RYGB 11 years earlier for morbid obesity presented to a community hospital with recurrent melena, weakness, and orthostatic dizziness for 1 wk. She had been taking non-steroidal anti-inflammatory drugs (NSAIDs) about two days per month for several months, but was not taking proton pump inhibitors (PPIs). She was a non-smoker and non-alcoholic. Physical examination revealed stable vital signs, pallor, and a benign abdominal examination. Rectal examination revealed melena and no visible hemorrhoids. On admission the hemoglobin (Hgb) was 4.1 g/dL. She was intravenously infused crystalloid solutions, transfused 4 units of packed erythrocytes, and intravenously administered PPI. EGD did not reveal any source of UGI bleeding, but the excluded proximal duodenum and stomach were not intubated and viewed. Colonoscopy did not reveal any etiology of lower GI bleeding. The patient was discharged with Hgb = 8.0 g/dL.

The patient was readmitted 1 d later to the same hospital, and then transferred to William Beaumont Hospital, a tertiary care hospital, for recurrent GI bleeding, with Hgb decline to 5.8 g/dL. Physical examination revealed stable vital signs, pallor, and a benign abdominal examination. Rectal examination revealed dark red blood and no visible hemorrhoids.

Figure 1 Endoscopic findings and therapy during single balloon enteroscopy in Case 1. A: Diagnostic findings. Single balloon enteroscopy performed in a 44-year-old woman, status post Roux-en-Y gastric bypass (RYGB) surgery 11 years earlier for morbid obesity, who presented with acute melena and a hemoglobin decline to 5.8 g/dL demonstrates a 4-cm-wide bulbar ulcer with a non-bleeding visible vessel in the afferent limb. Note the retrograde view of the duodenal bulb with the pylorus seen in the distance. Esophagogastroduodenoscopy performed 3 d earlier for melena had revealed no upper gastrointestinal lesions, but the afferent limb of the Roux-en-Y, including the excluded proximal duodenum and stomach, had not been intubated and visualized because of technical difficulties at esophago-gastroduodenoscopy; B: Endoscopic therapy. Single balloon enteroscopy showing the ablated bulbar ulcer after dual therapy of dilute epinephrine injection and heater probe thermocoagulation.

Laboratory tests revealed a normal mean corpuscular volume, platelet count, and coagulation panel. Serum blood urea nitrogen:creatinine (BUN:Cr) ratio = 36. Liver function tests were within normal limits, except for albumin = 1.6 g/dL. She was medically stabilized with transfusions of packed erythrocytes. Abdominal computed tomography (CT) with intravenous contrast was within normal limits. Single balloon enteroscopy revealed a non-bleeding, 4-cm-wide bulbar ulcer with a non-bleeding visible vessel in the afferent limb and no other lesions (Figure 1A). The visible vessel was ablated by injection of 10 mL of dilute epinephrine 1:10000 and by heater probe thermocoagulation using coaptation with 13 pulses of 25 W for one second each (Figure 1B). The visible vessel was almost completely flattened by the thermocoagulation. After 72 h the patient had another episode of melena and the Hgb acutely declined from 9.5 to 6.5 g/dL. A technetium-labeled erythrocyte (bleeding) scan and an abdominal arteriogram did not reveal an actively bleeding source. Exploratory laparotomy revealed a giant, posterior, bulbar ulcer, which was oversewn. A Warthin-Starry stain of gastric biopsies did not reveal *Helicobacter pylori* (*H. pylori*). Serology for IgG antibodies against *H. pylori* was negative (low titer). No significant postoperative complications occurred. The patient is doing well at 3 mo follow-up, with no further GI bleeding.

Case 2

A 64-year-old woman with prior RYGB for morbid obesity 10 years earlier presented acutely with melena and hematochezia, associated with dyspnea, fatigue, and syncope. She was taking ibuprofen about 800 mg/d for about 2 d per week for arthralgia, but had stopped about 3 mo ago. She was not taking PPIs, did not drink alcohol, and had stopped smoking cigarettes (1 pack/d) 12 years earlier. Physical examination on admission revealed stable vital signs, pallor, and a normal abdominal examination. Rectal examination revealed melena and no visible hemorrhoids. Laboratory analysis revealed Hgb = 7.4 g/dL (baseline recent Hgb = 13.3 g/dL), evident iron deficiency anemia with ferritin = 25 ng/mL, platelet count = 62000/L, and serum BUN: Cr ratio = 100. Liver function tests and coagulation panel were within normal limits. She was intravenously infused crystalloid solutions, transfused 4 units of packed erythrocytes, and intravenously administered a PPI. EGD revealed no lesions, including no anastomotic ulcers, but the afferent limb was not intubated. Colonoscopy revealed no lesions. Both computed tomographic enterography and capsule endoscopy were within normal limits. Bleeding slowly resolved and she was discharged with Hgb = 8.0 gm/dL.

The patient was readmitted 3 d later for recurrent melena. Laboratory analysis revealed Hgb = 5.1 g/dL, platelets = 201000/L, and BUN:Cr ratio = 40. A technetium labeled erythrocyte (bleeding) scan did not reveal active GI bleeding. Push enteroscopy with intubation of the afferent limb revealed a 5-mm-wide acute bulbar ulcer with a visible vessel that was oozing blood, and an otherwise normal examination (Figure 2A). The visible vessel was endoscopically treated with dilute epinephrine injection, hemoclips, and argon plasma coagulation (APC) (Figure 2B). Serologic tests for IgG antibodies against *H. pylori* were negative (low titer). The patient had one further, minor, episode of melena, after which the bleeding resolved, and the patient was discharged. She has had no further GI bleeding during 3 mo of follow-up.

DISCUSSION

The prevalence of obesity in adults is currently 13% worldwide, and 34%-36% in the United States[3]. From 1960 to 2008 the prevalence of morbid obesity [body mass index (BMI) > 40 kg/m^2 or > 35 kg/m^2

Figure 2 Endoscopic findings and therapy during push enteroscopy in Case 2. A: Diagnostic findings. Push enteroscopy performed in a 64-year-old woman status post RYGB surgery 10 years earlier for morbid obesity who presented with acute melena and a hemoglobin of 5.1 g/dL demonstrates a 5-mm-wide bulbar ulcer, which is actively oozing blood. EGD performed 5 d earlier for melena had revealed no upper gastrointestinal lesions, but the afferent limb of the Roux-en-Y, including the excluded proximal duodenum and stomach, had not been intubated and visualized because of technical difficulties at EGD; B: Endoscopic therapy. Push enteroscopy showing the bulbar ulcer after endoscopic treatment with dilute epinephrine, argon plasma coagulation, and hemoclips. RYGB: Roux-en-Y gastric bypass; EGD: Esophagogastroduodenoscopy.

Figure 3 Sketch showing coronal axis of upper gastrointestinal tract during intubation of afferent (biliopancreatic) limb using a push enteroscope in a patient status post Roux-en-Y gastric bypass for morbid obesity. After Roux-en-Y gastric bypass (RYGP) direct continuity between the proximal and distal stomach is severed and the stomach is surgically divided and reconstructed to form two pouches: A small proximal gastric pouch that connects directly to the proximal jejunum *via* a surgical anastomosis (efferent limb) and a large distal pouch that connects retrograde only to the duodenum *via* the duodenal bulb (afferent limb). Surgical reconstruction of a small proximal gastric pouch promotes weight loss by causing early satiety due to limited proximal gastric pouch capacity, and by causing decreased appetite by reducing ghrelin synthesis. The sketch shows that the afferent (biliopancreatic) limb is hard to reach and intubate using a routine esophagogastroduodenoscope after RYGP because of the long distance traversed (through the jejunum) to reach the afferent limb, and sharp angulation at the anastomosis between the afferent and efferent limbs. Failure to intubate the afferent limb results in missing lesions in this limb, as occurred in the 2 currently reported cases in which duodenal bulb ulcers with high risk stigmata of recent hemorrhage were missed.

with significant obesity-related disorders) increased from 0.9% to 6%, and the prevalence of obesity (BMI > 30 kg/m^2) increased from 13.4% to 34.3% in the United States[4]. This epidemic of obesity has led to a surge in the number of bariatric surgeries, from 13365 annually in 1998 to 205000 annually in 2008 in the United States[5,6]. The direct annual costs of bariatric surgery are > 10 billion dollars per annum in the United States[7]. RYGB is the most common and most effective bariatric surgery performed in the United States[5,8].

Anastomotic ulcers are a common, important cause of UGI bleeding after RYGB, which most commonly occur in patients actively smoking or taking NSAIDs[9]. Such ulcers are usually easily detected and readily treated at EGD[10]. Contrariwise, bleeding from ordinary duodenal or gastric ulcers is rarely reported after RYGB, with only 22 reported cases[2,11-13]. Proposed mechanisms for these ulcers after RYGB include: An acidic environment within the excluded segment[14,15], deprivation of the buffering effect of ingested food in the excluded segment[16], bile acid reflux into the excluded stomach and duodenal bulb, excessive alcohol consumption, frequent NSAID use, and *H. pylori* infection[5,12]. In both reported cases, excessive alcohol consumption, frequent NSAID use, recent cigarette smoking, and *H. pylori* infection were excluded as risk factors for the peptic ulcers or GI bleeding by patient history and laboratory tests.

Diagnosis of ulcers in the excluded segment after RYGB is challenging because intubating the excluded stomach and proximal duodenum (afferent limb) is technically difficult due to sharp bowel angulation, deep intubation to reach the excluded segment (afferent limb) through the jejunum, endoscopic looping, and inability to adequately distend the gastric remnant with air (Figure 3). However, intubation of only the efferent limb at EGD would result in missing lesions in the afferent limb. CT or magnetic resonance imaging (MRI) virtual gastroduodenoscopy can provide excellent intra-luminal views, but cannot provide a tissue diagnosis[17]. Percutaneous endoscopic gastrostomy has been successfully used to endoscopically access the excluded segments[1]. Alternatively, patients have undergone intraoperative endoscopy or gastrostomy to identify and treat bleeding duodenal ulcers after RYGB surgery. Some authors have even suggested placing

Figure 4 **Flow diagram showing a proposed diagnostic/therapeutic algorithm for patients status post Roux-en-Y gastric bypass surgery presenting with acute gastrointestinal bleeding that is highly likely from an upper gastrointestinal source (*e.g.*, patient presenting with melena).** The important difference in this algorithm from a general patient with UGI bleeding (who is not status post RYGB) is the addition of push enteroscopy, single balloon enteroscopy, or possibly double balloon enteroscopy if the EGD was non-diagnostic but the excluded stomach and duodenum (afferent limb) had not been intubated and viewed at EGD. Alternative management algorithms include: (1) performing push enteroscopy or single balloon enteroscopy initially instead of EGD in patients status post RYGB; or (2) performing colonoscopy before performing push enteroscopy or single balloon enteroscopy (or double balloon enteroscopy) after a non-diagnostic EGD. RYGB: Roux-en-Y gastric bypass; EGD: Esophagogastroduodenoscopy.

a gastrostomy tube within a radiopaque silastic ring during primary RYGB surgery to facilitate subsequent percutaneous endoscopic access to the excluded stomach[1].

There are no standard recommendations in RYGB patients who present with obscure GI bleeding. Eid *et al*[9] recommended that examination of the bypassed stomach and duodenum should be attempted before performing colonoscopy to evaluate for a lower GI source and before performing capsule endoscopy to evaluate for a small bowel source. This work adds to the literature by suggesting the diagnostic and therapeutic benefits of push enteroscopy or single balloon enteroscopy if EGD was non-diagnostic and the excluded segments were not intubated at EGD in patients status post RYGB surgery (Figure 4). These alternative endoscopies can be performed either before or after colonoscopy and capsule endoscopy, depending on the likelihood of the patient having had an UGI bleed. Push enteroscopy or

single balloon enteroscopy can even be done initially instead of EGD in patients status post RYGP to increase the diagnostic yield and therapeutic efficacy of the initial endoscopy. Push enteroscopy, however, can sometimes fail to reach the desired area. Double balloon enteroscopy is a promising alternative technique that requires an experienced endoscopist and is currently offered primarily at tertiary care centers. Double balloon enteroscopy was approximately 83% successful in intubating the excluded segment in a study of 6 patients status post RYGB[18,19]. Cappell *et al*[20] in 1992 reported 3 cases in 2 patients of severely symptomatic gastric ulcers within the surgically excluded gastric segment in patients status post vertical banded gastroplasty that were missed at EGD and only diagnosed at laparotomy. Whereas the ulcers in the surgically excluded segment status post vertical banded gastroplasty were endoscopically inaccessible, the currently reported ulcers in the excluded segment status post RYGB are often accessible using push enteroscopy

or single balloon enteroscopy.

Angiography with embolization should be considered in actively bleeding and hemodynamically unstable patients. Emergency surgery, possibly including resection of the bypassed stomach, should be considered for patients with refractory bleeding, but such surgery without prior endoscopic localization of the bleeding site increases the surgical failure rate[9]. Some authorities even suggest resection of the excluded stomach, which can be performed during the initial bypass surgery[21]. Advantages of this resection include: (1) decreased acid production because of resection of most of the gastrin-releasing part of the stomach; (2) removal of difficult to access parts of the stomach; and (3) avoiding gastro-gastric fistulization. Disadvantages of this resection include: (1) risk of duodenal stump leakage; (2) risk of intraoperative or postoperative bleeding; (3) potential abscess formation from necrosis of omental fat; (4) bacterial overgrowth in the biliopancreatic blind pouch; and (5) nutrient deficiencies, including vitamin B12 deficiency. Due to the rarity of bleeding or perforation from peptic ulcers in the excluded segment after RYGB, surgical treatment should be individualized[21,22].

RYGB patients also face potentially delayed diagnosis of GI cancers in the excluded segment due to technically difficult endoscopic access, but RYGB patients have a lower incidence of gastric cancer as compared to the general population[18,23]. Five cases have been reported in the excluded segment of gastric adenocarcinoma, most of which were advanced cancers[18,24], and several cases of lymphoma or gastrointestinal stromal tumors have been reported[25]. Another problem in diagnosing these cancers are the limitations of virtual gastroduodenoscopy, including: (1) lack of visualization of fine mucosal detail, especially vascularity; (2) missing small, flat lesions; (3) confusion of residual intragastric food with a gastric mass; and (4) inability to obtain biopsy specimens for histological diagnosis[17]. Voellimger *et al*[26] suggested that resection of the bypassed stomach should be considered during the primary RYGB operation in patients with precancerous gastroduodenal lesions.

This study is limited by reporting only 2 cases and the retrospective methodology.

Despite the two currently reported diagnostic su-ccesses, these advanced endoscopic techniques may be non-diagnostic because of absence of lesions in the excluded segments or potential inability to sometimes intubate the excluded segments with these enteroscopes. Furthermore, endoscopic therapy of ulcers with stigmata of recent hemorrhage (SRH) may not necessarily pre-vent recurrent bleeding; one of the currently reported patients required surgery for re-bleeding despite the therapeutic endoscopy. Nonetheless, endoscopic therapy of ulcers with high risk SRH significantly reduces the risk of rebleeding and is therefore recommended despite occasional therapeutic failures[27]. This work should prompt a large, prospective, study to determine the technical success rate of single or double balloon enteroscopy *vs* standard EGD in intubating the excluded

gastroduodenal segment (afferent limb) in patients status post RYGB.

In conclusion, intubation of the excluded stomach and duodenum at EGD is technically difficult in patients status post RYGB, and therefore the diagnosis and opportunity for endoscopic therapy of gastric or duodenal lesions may be missed. Two cases are reported of UGI bleeding 10 or 11 years status post RYGB in which the EGD was non-diagnostic due to failure to intubate the excluded stomach and proximal duodenum, whereas single ba-lloon enteroscopy or push enteroscopy successfully diagnosed duodenal ulcers and provided for endoscopic treatment of these ulcers. These case reports suggest consideration of push enteroscopy, or single balloon enteroscopy, where available, in the evaluation of acute UGI bleeding in patients status post RYGB surgery when EGD was non-diagnostic because of failure to intubate these excluded segments. The results of this study require confirmation by a large study that is preferentially prospective, randomized, and controlled.

COMMENTS

Case characteristics
In case 1, a 44-year-old woman with prior Roux-en-Y gastric bypass (RYGB) 11 years earlier for morbid obesity presented with melena, weakness, and orthostatic dizziness for 1 wk. She had been taking non-steroidal anti-inflammatory drugs (NSAIDs) about two days per month for several months, but was not taking proton pump inhibitors (PPIs). She was a non-smoker and non-alcoholic. Physical examination revealed stable vital signs, pallor, and a benign abdominal examination. Rectal examination revealed melena and no visible hemorrhoids. In case 2, a 64-year-old woman with prior RYGB for morbid obesity 10 years earlier presented acutely with melena and hematochezia, associated with dyspnea, fatigue, and syncope. She was taking ibuprofen about 800 mg/d for about 2 d per week for arthralgia, but had stopped about 3 mo ago. She was not taking PPIs, did not drink alcohol, and had stopped smoking cigarettes (1 pack/d) 12 years earlier. Physical examination on admission revealed stable vital signs, pallor, and a normal abdominal examination. Rectal examination revealed melena and no visible hemorrhoids.

Clinical diagnosis
In case 1, the clinical history of melena, weakness, and orthostatic dizziness strongly suggests acute gastrointestinal bleeding. Melena strongly suggests acute upper GI bleeding, but lower GI bleeding cannot be completely excluded by this history. The symptoms of weakness and orthostatic dizziness suggest that the bleeding caused hypovolemia and was therefore physiologically significant and severe. In case 2, the clinical history of melena suggests acute upper GI bleeding, although occasionally melena may occur secondary to lower GI bleeding. The symptoms of dyspnea, fatigue, and syncope all suggest severe GI bleeding that is causing symptoms of end-organ injury or insufficiency from hypovolemia: Syncope from insufficient cerebral blood perfusion; and dyspnea and fatigue from profound anemia with decreased oxygen-carrying capacity of the blood.

Differential diagnosis
In case 1, the history of prior RYGB surgery in a patient presenting with melena suggests possible bleeding from an anastomotic (marginal) ulcer, but other common causes of upper GI bleeding are in the differential diagnosis, including ordinary peptic ulcer disease, hemorrhagic gastritis, hemorrhagic reflux gastritis, as well as relatively uncommon lesions. Bleeding from esophageal varices is unlikely because of no history of chronic liver disease, absence of stigmata of chronic liver disease, and normal biochemical parameters of liver function. Also lower GI lesions must be considered in the differential diagnosis of patients presenting with melena when the EGD is non-diagnostic. The patient lacked potential risk factors for peptic ulcers or other causes of upper

GI bleeding including known *H. pylori* infection, frequent NSAID use, smoking cigarettes, or alcoholism. In case 2, the melena suggests likely upper GI bleeding. Most prominent in the differential diagnosis in a patient status post RYGB with melena is an anastomotic (marginal) ulcer. However, other common causes of upper GI bleeding are in the differential diagnosis, including ordinary peptic ulcer disease, hemorrhagic gastritis, hemorrhagic reflux gastritis, as well as relatively uncommon lesions. Bleeding from esophageal varices is unlikely because of no history of chronic liver disease, absence of stigmata of chronic liver disease on physical examination, and normal biochemical parameters of liver function. Also lower GI lesions must be considered in the differential diagnosis of patients presenting with melena when the EGD is non-diagnostic. The patient lacked risk factors for peptic ulcer disease or other causes of upper GI bleeding including known *H. pylori* infection, recent NSAID use, recently smoking cigarettes, and alcoholism.

Laboratory diagnosis

In case 1, on admission the hemoglobin level was 4.1 g/dL. This profound anemia demonstrated the importance of relatively rapidly transfusing the patient to prevent end organ injury from hypovolemia, and the patient was transfused 4 units of packed erythrocytes. A coagulopathy was not contributing to the bleeding as the coagulation profile was normal. The blood urea nitrogen: creatinine ratio was 36, consistent with upper rather lower GI bleeding. These findings are consistent with severe, upper GI bleeding. In case 2, laboratory analysis revealed hemoglobin = 7.4 g/dL (recent baseline hemoglobin = 13.3 g/dL), evident iron deficiency anemia with ferritin = 25 ng/mL, platelet count = 62000/L, and serum BUN:Cr ratio = 100. Liver function tests and coagulation panel were within normal limits. The current very low hemoglobin level that has recently declined from a normal hemoglobin level suggests acute, severe, GI bleeding. The iron deficiency anemia suggests the bleeding has been sufficiently long and severe to deplete iron stores. Melena usually arises from an upper GI source, but can occasionally result from a lower GI source, especially when associated with hematochezia. The highly elevated BUN: creatinine ratio strongly suggests that the melena is from upper rather than lower GI bleeding.

Imaging diagnosis

In case 1, EGD did not reveal any source of UGI bleeding, but the excluded duodenum and distal stomach were not intubated and examined. This was due to the difficulty in intubating the afferent limb status post RYGB surgery because of the long intubation needed to reach the afferent limb and acute angulation at the anastomosis to the afferent limb. Colonoscopy was performed because the EGD was non-diagnostic and did not reveal any etiology of lower GI bleeding. The patient experienced recurrent GI bleeding, with hemoglobin decline to 5.8 g/dL for which the patient was again medically stabilized. Abdominal computerized tomography with intravenous contrast was within normal limits. Single balloon enteroscopy, with intubation of the afferent limb, revealed a non-bleeding, 4-cm-wide bulbar ulcer with a non-bleeding visible vessel in the afferent limb and no other lesions. The diagnosis of a giant duodenal ulcer by single balloon enteroscopy after a non-diagnostic EGD due to failure to intubate the afferent limb at EGD is notable. In case 2, EGD did not reveal any source of UGI bleeding, including no anastomotic ulcers, but the excluded duodenum and distal stomach (afferent limb) status post RYGB surgery was not intubated and examined. This was due to the difficulty in intubating the afferent limb status post RYGB surgery because of the long intubation needed to reach the afferent limb and acute angulation at the afferent limb anastomosis. Colonoscopy was performed because of the history of melena and a non-diagnostic EGD, but did not reveal any etiology of lower GI bleeding. Both computed tomographic enterography and capsule endoscopy were within normal limits. Bleeding slowly resolved and she was discharged with hemoglobin level of 8.0 g/dL. The patient was readmitted 3 d later for recurrent melena with a hemoglobin level of 5.1 g/dL. A technetium labeled erythrocyte (bleeding) scan did not reveal active GI bleeding. Push enteroscopy revealed a 5-mm-wide acute bulbar ulcer with a visible vessel that was oozing blood, and an otherwise normal examination. The visible vessel was endoscopically treated with dilute epinephrine injection, hemoclips, and argon plasma coagulation.

Pathological diagnosis

In case 1, giant duodenal ulcer in excluded gastroduodenal segment in afferent limb after RYGB surgery which was diagnosed by single-balloon enteroscopy and confirmed at surgery. The lesion was not resected and therefore the diagnosis was by endoscopic and intraoperative examination without a pathologic diagnosis. In case 2, peptic ulcer in the duodenal bulb in the excluded gastroduodenal segment (afferent limb) after RYGB surgery, as diagnosed by enteroscopy. The bulbar ulcer was not resected and therefore the diagnosis was by enteroscopy, without a pathologic diagnosis.

Treatment

In case 1, the visible vessel was ablated at single-balloon enteroscopy by injection of dilute epinephrine and by heater probe thermocoagulation. However, the patient had another episode of melena and the hemoglobin acutely declined from 9.5 g/dL to 6.5 g/dL 72 h after therapeutic single balloon enteroscopy. Failure despite use of two methods of endoscopic hemostasis (dilute epinephrine injection and heater probe thermocoagulation) was most likely related to the exceedingly large size of the duodenal ulcer (4 cm diameter). A technetium-labeled erythrocyte (bleeding) scan and an abdominal arteriogram did not reveal an actively bleeding source. Exploratory laparotomy revealed a giant, posterior, bulbar ulcer (which had been detected at single-balloon enteroscopy), which was oversewn. The patient was discharged with no further bleeding during the hospitalization or for three months of follow-up. In case 2, the patient received intravenously infused crystalloid solutions, transfused 4 units of packed erythrocytes, and intravenously administered a PPI. The duodenal ulcer lesion was endoscopically treated with dilute epinephrine injection, hemoclips, and argon plasma coagulation (APC) because it was oozing blood at the endoscopy. The patient had one further, self-limited, episode of melena, after which the bleeding resolved, and the patient was discharged. She has had no further GI bleeding during 3 mo of follow-up.

Related reports

This work reports two cases of duodenal ulcers occurring after RYGB, supplementing 22 prior case reports of peptic ulcers after RYGB.

Term explanations

RYGB is an acronym for Roux-en-Y gastric bypass surgery, a popular form of bariatric surgery, in which a large part of the stomach and the duodenum is surgically excluded from the normal stream of food. This surgery leads to weight loss from decreased assimilation and absorption of food, from early satiety because of the very small residual stomach pouch, and from decreased production of ghrelin which acts as a "hunger hormone". The afferent limb (also called the biliopancreatic limb) is composed of the duodenum which is excluded from the alimentary track after RYGB. The gastrojejunal (alimentary) limb connects directly from the proximal gastric pouch to the jejunoileum after RYGB surgery. After RYGB surgery the distal gastric pouch, duodenal bulb and rest of the duodenum are excluded from continuity with the rest of the alimentary tract.

Experiences and lessons

These two cases report bleeding giant or moderately-sized duodenal ulcers being missed at routine EGD performed for acute upper GI bleeding because of inability to intubate the afferent limb (excluded segment) due to acute angulation and the need for deep intubation. This finding has been previously reported in case reports. This work reports that the afferent limb was successfully intubated by either a single balloon enteroscope or push enteroscope. This work further confirms the findings in previous isolated case reports. Use of these specialized endoscopes (enteroscopes) permitted the diagnosis of the etiology of the acute upper GI bleeding as peptic ulcers, permitted identification of high-risk stigmata of recent hemorrhage (SRH) consisting of either a visible vessel or active oozing of blood, and permitted performance of therapeutic endoscopy for hemostasis. Although recurrent GI bleeding from only one of the two high risk peptic ulcers was prevented by the endoscopic therapy and the second patient required GI surgery for recurrent GI bleeding, these two cases illustrate the usefulness of specialized enteroscopes rather than standard esophagogastroduodenoscopes to intubate, examine, and diagnose lesions in the excluded gastroduodenal segment (afferent limb) status post RYGB surgery. This work adds to the literature by emphasizing the potential diagnostic and therapeutic benefits of push enteroscopy or single balloon enteroscopy if EGD was non-diagnostic in patients status-post RYGB surgery. This work points out the need for a prospective, large study comparing the diagnostic yield of enteroscopy *vs* EGD in patients with upper GI bleeding

status post RYGB surgery.

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Cap polyposis refractory to *Helicobacter pylori* eradication treated with endoscopic submucosal dissection

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Abstract

Cap polyposis is a rare intestinal disorder. Characteristic endoscopic findings are multiple inflammatory polypoid lesions covered by caps of fibrous purulent exudate. Although a specific treatment has not been established, some studies have suggested that eradication therapy for *Helicobacter pylori* (*H. pylori*) is effective. We report a case of a 20-year-old man with cap polyposis presenting with hematochezia. Colonoscopy showed the erythematous polyps with white caps from the sigmoid colon to rectum. Histopathological findings revealed elongated, tortuous, branched crypts lined by hyperplastic epithelium with a mild degree of fibromusculosis in the lamina propria. Although *H. pylori* eradication was instituted, there was no improvement over six months. We then performed *en bloc* excision of the polyps by endoscopic submucosal dissection (ESD), which resulted in complete resolution of symptoms. ESD may be a treatment option for cap polyposis refractory to conservative treatments. We review the literature concerning treatment for cap polyposis and clinical outcomes.

Key words: Endoscopic submucosal dissection; Cap polyposis; Eradication therapy; *Helicobacter pylori*

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Core tip: Although for cap polyposis, conservative treatment should be selected as first-line therapy, the optimal treatment of cap polyposis refractory to conservative treatment has not been established. Endoscopic submucosal dissection may be a treatment option for cases refractory to conservative treatment.

INTRODUCTION

Cap polyposis is a rare intestinal disorder with unique clinical, endoscopic, and histological findings. Clinical symptoms include mucoid and bloody diarrhea, abdominal pain, tenesmus, weight loss, and dysplasia. Endoscopy typically reveals multiple reddish, mucus-capped inflammatory polyps in the rectosigmoid area with normal mucosa interspersed between the polyps[1]. Pathologically, the surfaces of these inflammatory polyps are covered by a thick layer of fibrinopurulent exudate, hence the term "cap"[1]. However, the etiology of cap polyposis is unclear and its clinical course varies from spontaneous clinical and endoscopic remission without treatment[2-4] to persistent disease refractory to conservative treatment[5-7], requiring surgical resection. Little is known about its long-term course.

The optimal treatment for cap polyposis has not been established[2-16]. Some cases have been treated successfully by the avoidance of straining at defecation[8], antimicrobial agents (*i.e.,* metronidazole)[9], steroids[2], immunomodulators (*i.e.,* infliximab)[12], endoscopic therapy[13,14] and surgical resection[5-7]. Recently, the efficacy of *Helicobacter pylori* (*H. pylori*) eradication therapy for *H. pylori*-positive patients with cap polyposis has been reported[10,11,15,16], and in 2016 the Japanese Society for *Helicobacter* Research added cap polyposis as a possible *H. pylori*-associated disease in its treatment guidelines. However, no treatments for *H. pylori*-negative cap polyposis or *H. pylori*-positive cases refractory to eradication therapy have yet been established.

Here, we report a case of *H. pylori*-negative cap polyposis refractory to *H. pylori* eradication therapy that was successfully treated with endoscopic submucosal dissection (ESD). We also review the literature concerning conservative and endoscopic treatments for cap polyposis.

CASE REPORT

A 20-year-old Japanese man presented with a 1-year history of hematochezia and tenesmus. He denied straining at stool and had no history of anal prolapse. His past medical and family history were unremarkable. Laboratory tests revealed mild hypoproteinemia (serum albumin 3.9 g/L), but no hepatic or renal dysfunction, leukocytosis, elevation of C-reactive protein, or anemia. Colonoscopy revealed the characteristic appearance of cap polyposis, with approximately 20-30 erythematous variform inflammatory polyps with white caps of fibrinopurulent exudate from the sigmoid colon to the rectum (Figure 1A and B). Magnification endoscopy with narrow-band imaging showed amorphous exudate in the white caps overlying long branching tortuous crypts in the basal part of the polyps (Figure 1C and D). Endoscopic ultrasonography (EUS) with radial array scanning showed significant thickening of the mucosa without evidence of invasion into the submucosa (Figure 1E). Histologic findings from a polyp revealed elongated, tortuous, branched crypts lined with hyperplastic epithelium with inflammatory cell infiltration and a mild degree of fibromusculosis in the lamina propria (Figure 2). The surface of the polyps was covered by thick inflammatory granulation tissue with exudate (Figure 2). The intervening mucosa between lesions was histologically normal. Computed tomography and magnetic resonance imaging showed multiple elevated lesions thickening the walls of the sigmoid colon and rectum (Figure 3A and B). Barium enema showed multiple raised mucosal lesions without stenosis or sclerotic changes in the sigmoid colon and rectum (Figure 3C). The differential diagnosis included the mucosal prolapse syndrome, inflammatory polyps, colon cancer, malignant lymphoma, inflammatory bowel disease, and adenomatous polyposis. We diagnosed cap polyposis based on the endoscopic and histopathological characteristics.

The patient had no evidence of *H. pylori* infection by urea breath test, anti-*H. pylori* antibody, or endoscopic findings (*i.e.,* gastric mucosal atrophy or diffuse redness of gastric mucosa). However, according to previous evidence that *H. pylori* eradication therapy was effective for patients with cap polyposis[10,11,15,16], *H. pylori* eradication therapy with vonoprazan 20 mg, amoxicillin 750 mg and clarithromycin 200 mg twice daily for 7 d was initiated. Abdominal symptoms (*i.e.,* hematochezia and tenesmus), bowel habits, and endoscopic findings did not improve over the six months after therapy. Therefore, as conservative alternative treatment, we performed *en bloc* excision of the polyps with ESD (Figure 4). After resection, the patient's symptoms disappeared and he had no endoscopic evidence of recurrence for six months.

DISCUSSION

We report a case of a patient with cap polyposis refractory to *H. pylori* eradication therapy who then underwent *en bloc* excision of polyps by ESD with good results. This is the first report of the efficacy of ESD for treatment of cap polyposis. More studies of ESD as a treatment option for cap polyposis are needed to validate

Figure 1 Endoscopic findings of multiple inflammatory polyps. A and B: Caps of fibrinopurulent exudate from the sigmoid colon to the rectum interspersed with normal colonic mucosa; C and D: Magnifying endoscopy shows an area in the cap of amorphous fibrinopurulent exudate and tortuous and long branching crypts under the cap; E: Endoscopic ultrasonography showed significant thickening of the colonic mucosa layers.

Figure 2 Microscopic findings of inflammatory polyps show elongated, tortuous, branched, and dilated crypts with epithelial hyperplasia, inflammatory granulation tissue and a mild degree of fibromusculosis in the lamina propria. Hematoxylin-Eosin stain, × 4 (A) and × 20 (B).

its use instead of surgical resection.

Diagnosis of cap polyposis

Cap polyposis can be difficult to diagnose. It can resemble mucosal prolapse syndrome (MPS). There has been a debate about whether cap polyposis is a specific form of inflammatory disorder or part of a spectrum of MPS[12]. MPS and cap polyposis share some clinical, endoscopic, and histological features. Both diseases show infiltration of inflammatory cells with elongated stroma and fibromuscular obliteration of the lamina propria. However, the fibromuscular obliteration is more marked in cap polyposis. MPS is usually confined to the rectum, but cap polyposis usually involves the sigmoid and/or descending colon as well as the rectum. EUS findings in cap polyposis show significant thickening of the mucosa[9], whereas MPS is characterized by smooth, diffuse thickening of the submucosa and minimal thickening of the lamina propria[17].

Cap polyposis and protein loss

Common clinical features of cap polyposis are hematochezia (82%), chronic straining (64%), and mucous diarrhea (46%)[1]. When mucous diarrhea is severe and/or continuous for long periods, excessive protein loss is observed as a result[1,5]. Direct loss of protein was

Figure 3 Multiple elevated lesions with wall thickening in the sigmoid colon. Rectum on computed tomography (A) and magnetic resonance imaging (B); Barium enema shows a collection of small sessile polyps in the sigmoid colon and rectum (C).

Figure 4 Endoscopic submucosal dissection. Post-dissection ulcers after endoscopic submucosal dissection at the sigmoid colon and rectum (A). Fresh specimen of cap polyposis after endoscopic submucosal dissection (B) and fixed specimen (C). The fixed specimen revealed bleeding into the polyps. Microscopic findings of inflammatory polyps [HE stain, × 4 (D)].

demonstrated in a case of cap polyposis by scintigraphy with technetium 99m-labeled diethylenetriaminepentaacetic acid complexed to human serum albumin[18]. In our case, blood tests revealed mild hypoproteinemia, with an albumin level 39 g/L, possibly secondary to protein loss from mucous diarrhea.

Cap polyposis and H. pylori infection

Cap polyposis has been attributed to colonic dysmotility, immune abnormalities, bacterial infection (*i.e.*, *H. pylori*) or other unknown pathogens. Géhénot *et al*[19] suggested the possibility of bacterial infection, reporting on a cap polyposis patient who had no evidence of

colonic dysmotility and who was successfully treated with metronidazole. Of the myriad gut microbiota, although *H. pylori* is not detected in mucosa obtained from cap polyposis lesions[10], most cases of cap polyposis with *H. pylori* infection have resolved after *H. pylori* eradication therapy[10,11,15,16,18]. *H. pylori* infection is well-known to cause not only gastroduodenal diseases, but also diseases such as idiopathic thrombocytopenic purpura and chronic idiopathic urticaria[20,21]. In addition, eradication therapy often induces regression of mucosa-associated lymphoid tissue (MALT) lymphoma in the rectum and thyroid[22]. Although an *H. pylori*-associated immune reaction may play a role in the development of some cases of cap

polyposis, there is no evidence for efficacy of *H. pylori* eradication therapy in *H. pylori*-negative cap polyposis patients, as in our case. Because the development of cap polyposis with active inflammation in the colonic mucosa may be related to other bacterial infections that are also sensitive to the antimicrobial agents used in *H. pylori* eradication therapy (*i.e.*, clarithromycin, amoxicillin, and metronidazole), we selected eradication therapy as the first-line treatment. Although eradication failed to cure the cap polyposis, further studies will be required to investigate whether other pathogens are related to this diagnosis, and whether their eradication can effect resolution.

Cap polyposis and endoscopic treatment
The efficacy of endoscopic treatment, such as poly-pectomy and endoscopic mucosal resection (EMR), for cap polyposis has been reported[12,14]. However, *en bloc* excision is difficult to perform with conventional EMR, and the use of surgical resection is more frequent[5-7]. Although there have been no reports of malignant transformation, surgical resection may be excessive for the treatment of cap polyposis. We consider ESD *en bloc* excision to be less invasive, and also can prevent recurrence.

ESD, an endoscopic procedure that originated in Japan and Korea in the late 1990s which has since spread rapidly to other nations, is now commonly used to treat gastrointestinal tumors[23,24]. ESD allows complete pathological assessment, proving this technique sup-erior to polypectomy or conventional EMR to prevent recurrence[25]. To date, no case of cap polyposis treated with ESD has been reported. Our present case suggests that ESD may be an effective treatment for intractable cap polyposis, with lower invasiveness than surgical resection. Our patient remains under surveillance for recurrence.

Conclusion
For cap polyposis, conservative treatment should be selected as first-line therapy. In particular, we recom-mend eradication therapy for *H. pylori* infection. To our knowledge, however, the optimal treatment of cap polyposis refractory to conservative medical treatment has not been established. This is the first report of cap polyposis refractory to conservative medical treatment effectively treated with ESD. We believe that ESD is less invasive and more effective than surgical resection in cases refractory to conservative treatment. ESD may be a treatment option for cap polyposis cases refractory to conservative medical treatments, such as *H pylori* eradication, metronidazole, steroids, and infliximab. Further investigation is required.

COMMENTS

Case characteristics
A 20-year-old Japanese man with cap polyposis located in sigmoid colon and rectum refractory to *Helicobacter pylori* (*H. pylori*) eradication and resected with endoscopic submucosal dissection.

Clinical diagnosis
Cap polyposis.

Differential diagnosis
Although the differential diagnosis includes the mucosal prolapse syndrome (MPS), inflammatory polyps, colon cancer, malignant lymphoma, inflammatory bowel disease, and adenomatous polyposis, MPS is most possible disease as differentiation disease, because cap polyposis and MPS share some clinical, endoscopic, and histological features.

Laboratory diagnosis
Although mild hypoproteinemia was revealed, there was no hepatic or renal dysfunction, leukocytosis, elevation of C-reactive protein, or anemia.

Imaging diagnosis
Colonoscopy revealed the characteristic appearance of cap polyposis, with approximately 20-30 erythematous variform inflammatory polyps with white caps of fibrinopurulent exudate from the sigmoid colon to the rectum.

Pathological diagnosis
Pathological findings revealed elongated, tortuous, branched crypts lined with hyperplastic epithelium with inflammatory cell infiltration and a mild degree of fibromusculosis in the lamina propria in the polypoid lesion and thick inflammatory granulation tissue in the surface of the polyps.

Treatment
Because this case was refractory to *H. pylori* eradication as the first-line therapy, *en bloc* excision of polyposis with endoscopic submucosal dissection (ESD) was selected as second-line therapy.

Related reports
Previously, although endoscopic treatment including polypectomy and EMR, and conservative medical treatments including *H. pylori* eradication, metronidazole, steroids, and infliximab, had been reported, the optimal treatment for cap polyposis has not been established.

Experiences and lessons
ESD may be a treatment option for cap polyposis cases refractory to conservative treatments (*i.e., H. pylori* eradication, metronidazole, steroids, and infliximab).

Peer-review
The paper is well written.

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Endoscopic ultrasound-guided pancreaticogastrostomy for symptomatic pancreatic duct obstruction caused by migrated pancreatic stent

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Abstract

Endoscopic pancreatic stenting has been widely used in various pancreatic conditions. With the increasing use of pancreatic stents, many complications have been recognized. Especially, proximal stent migration presents a serious condition because of subsequent pancreatic duct obstruction, impaired drainage, ductal dilation, and pancreatic pain. Although endoscopic retrieval is the preferred treatment for proximally migrated pancreatic stents, it is not always successful, resulting in conversion to surgery. To date, endoscopic ultrasound-guided pancreatic duct drainage (EUS-PD) has never been reported for treatment of pancreatic duct obstruction caused by proximally migrated pancreatic stent. We herein describe a case of pancreatic duct rupture and obstruction caused by proximally migrated pancreatic stent that was successfully treated by EUS-guided pancreaticogastrostomy while keeping the former stent *in situ* after failed endoscopic retrograde cholangiopancreatography. We believe that this report adds to the increasing evidence of symptomatic pancreatic duct obstruction being successfully treated by EUS-PD.

Key words: Endoscopic retrograde cholangiopancreatography; Pancreatic stent; Stent migration; Pancreatic duct obstruction; Endoscopic ultrasound-guided pancreatic duct drainage

Core tip: Stent migration is a rare complication of pancreatic stenting. Especially, proximal migration presents a serious condition because of subsequent pancreatic duct obstruction, impaired drainage, and pancreatic pain.

We described a case of symptomatic pancreatic duct obstruction caused by proximally migrated pancreatic stent that was successfully treated by endoscopic ultrasound-guided pancreatic duct drainage (EUS-PD) while keeping the former stent *in situ*. To the best of our knowledge, EUS-PD has never been reported for relief of pancreatic duct obstruction caused by proximally migrated pancreatic stent, and this report adds to the increasing evidence of the safety and effectiveness of EUS-PD.

INTRODUCTION

Endoscopic pancreatic stenting has become an accepted therapy for various pancreatic diseases, including pancreatic duct obstruction due to benign strictures, stones, or tumors, drainage of pancreatic pseudocysts, symptomatic pancreaticobiliary anomalies, and preventing post-ERCP pancreatitis (PEP)[1,2]. With the increasing use of pancreatic stents, various complications have been recognized, such as bleeding, infection, stent occlusion, duodenal perforation, stent fracture, and PEP. Especially, proximal stent migration is a rare complication and presents a serious condition because of subsequent pancreatic duct obstruction, impaired drainage, ductal dilation, and pancreatic pain[3]. Although endoscopic removal of proximally migrated stents can be quite effective, it is not always successful, resulting in conversion to surgery[4]. Endoscopic ultrasound-guided pancreatic duct drainage (EUS-PD) is a promising option for pancreatic duct decompression after failed endoscopic retrograde cholangiopancreatography (ERCP)[5], however, it has never been reported for relief of pancreatic duct obstruction caused by proximally migrated pancreatic stent. We herein report a case of a 78-year-old woman with symptomatic pancreatic duct obstruction caused by proximally migrated pancreatic stent that was recovered *via* EUS-guided pancreaticogastrostomy (EPG).

CASE REPORT

A 78-year-old woman was admitted to our hospital with epigastric discomfort of three months' history. On admission, she appeared ill, vitally stable, not jaundiced, and her abdomen was soft but mild tenderness over the epigastrium. Laboratory data were within the normal ranges. Abdominal computed tomography (CT) showed a bright linear object extending from the main pancreatic duct (MPD) and parenchyma into the lesser omental bursa along with a dilated distal MPD (Figure 1).

The patient's medical history revealed recurrent acute pancreatitis during the past 7 years. At 71 years of age, she experienced the first attack of acute pancreatitis. Further examination excluded the possibilities of biliary, alcoholic or hyperlipidemic causes. ERCP was then performed and demonstrated a stricture of the head segment of MPD. A positron emission tomography/computed tomography (PET-CT) was performed for further evaluation and no pancreatic mass was detected. For reliving the stricture of MPD, a pancreatic stent was inserted by ERCP and the patient achieved symptomatic relief at discharge. However, regular stent exchange was refused by the patient for fear of endoscopic procedure. Thereafter, she had several episodes of acute pancreatitis and occasional epigastric pain which were all managed conservatively. She could not remember which type of pancreatic stent was used after 7 years.

In view of her medical history and imaging findings, a possibility of pancreatic duct obstruction due to a proximally migrated pancreatic stent was considered and we attempted to drain the MPD to relieve her symptoms. Endoscopic transpapillary treatment was failed because of pyloric deformation preventing access to the second portion of the duodenum. After a brief discussion with the patient's family and obtaining their consent, we decided to perform endoscopic ultrasound-guided pancreaticogastrostomy (EPG) while keeping the former stent *in situ*. The dilated MPD was punctured transgastrically with a 19-gauge needle (Echotip 19A; Cook Medical Inc., United States) (Figure 2A), and a sample was aspirated for further testing. Under fluoroscopy, pancreatogram displayed the dilated pancreatic duct proximal to complete obstruction (Figure 2B). After introduction of a 0.035-inch guidewire (Jagwire, Boston Scientific) into the MPD, the EUS needle was removed (Figure 2C), and a 6 Fr cystotome (Cook Endoscopy) was used to dilate the tract. Finally, the pancreaticogastrostomy was then stented with a 6-Fr double pigtail stent (Figure 2D). The amylase concentration of the effusion was 72450 U/L, while CEA and CA-199 were within the normal range. The patient revealed great resolution of abdominal pain, which was confirmed by CT scanning performed after 1 wk (Figure 3). There were no adverse events, and the patient remains asymptomatic at present (five months after the EPG procedure). We planned to make the follow-up investigations (endoscopic ultrasonography) for the possible stent occlusion and pancreatic duct obstruction after 6 mo and then once a year. Stent exchange under EUS is planned if recurrent acute pancreatitis occur.

DISCUSSION

Stent migration is an infrequent complication of endoscopic pancreatic stenting. Distal stent migration has been reported in 7.5% of pancreatic stent placement[3]. This rarely presents a problem since the stent can clear from the intestine spontaneously. However, proximal stent migration can result in serious complications, including ductal damage, recurrent pancreatitis, impaction and subsequent difficulty to retrieve the migrated stent[3]. In

Figure 1 Abdominal computed tomography. A: Computed tomography image showing a pancreatic stent; B and C: An endoprosthesis extending from the main pancreatic duct (MPD) and parenchyma into the lesser omental bursa with a dilated distal MPD.

Figure 2 Endoscopic ultrasound-guided pancreaticogastrostomy. A: Endoscopic ultrasound-guided puncture; B and C: Contrast injection and cystotome advancement; D: Double pigtail stent placement.

the case presented, the proximal stent tip migrated into the lesser omental bursa, which resulted in duct distortion and obstruction, and eventually symptomatic pancreatic duct hypertension. This patient had never undergone stent

Figure 3 Successful decompression of the dilated main pancreatic duct.

revision or retrieval since its placement 7 years earlier. Her history of long term recurrent acute pancreatitis might indicate stent migration and subsequent pancreatic duct obstruction, however, which was unfortunately ignored during her previous hospitalization.

Currently, ERCP is the preferred procedure for treating pancreatic duct obstruction. However, it may not be feasible in approximately 3% to 10% of patients because of surgically altered anatomy, complete ductal obstructions, or disrupted ducts. In these cases, percutaneous radiologic intervention or surgical treatment is required[6]. However, both methods have been associated with significant morbidity and mortality rates. The development of EUS allowed the ability to visualize the pancreatic ductal system, and introduction of the therapeutic linear echoendoscope allowed access to the pancreatic duct with a needle in the case of ERCP failure. EUS-PD was first described by Bataille *et al*[7] in 2002. Following this report, several case series with satisfactory results have been published[8-10]. Technically, EUS-PD can either be performed *via* a rendezvous technique, combining EUS and ERCP, or *via* a transluminal technique. The former should be attempted in patients with accessible ampulla. Actually, in the present case, the echoendoscope cannot access the second part of duodenum because of pyloric deformation, and EUS-PD with transmural stenting seems to be the primary intervention.

To date, EUS-PD remains one of the most technically challenging endosonography interventions[11]. Success rates vary widely and adverse events occur in approximately 15% of reported cases[12]. Mainly, EUS-PD might be associated with complications such as pancreatitis, hemorrhage, stent migration, stent dysfunction, perforation, pneumoperitoneum, pancreatic juice leakage as well as abscess formation. Although there was no procedure related mortality, severe adverse events were noted when pancreatic drainage failed, and EUS-PD should be performed in endoscopic units experienced in therapeutic endoscopy[13].

Endoscopic retrieval is the primary treatment modality for proximally migrated pancreatic stents[4]. Matsumoto *et al*[4] reported that the successful endoscopic retrieval rate for proximally migrated pancreatic stents was approximately 80%. In the presented case, endoscopic

transpapillary removal of the migrated stent was impossible because of pyloric deformation, and surgical intervention is too invasive for patients with benign cause. Once the pancreatic duct decompression was achieved, it does not seem necessary to remove the migrated pancreatic stent, which entails little damage to her health.

In conclusion, proximal migration of a pancreatic stent into the lesser omental bursa resulting in distortion and obstruction of the MPD, and symptomatic pancreatic duct dilation is a rare and catastrophic complication of pancreatic stenting. EUS-PD appears to be an effective and safe treatment for MPD decompression when conventional ERCP fails. This report adds to the increasing evidence of symptomatic pancreatic duct obstruction being successfully treated by EUS-PD.

COMMENTS

Case characteristics
A 78-year-old woman with endoscopic pancreatic duct stenting 7 years earlier presented with epigastric discomfort of three months' history.

Clinical diagnosis
The patient had a history of recurrent acute pancreatitis within 7 years. After admission to the hospital, CT scan showed a bright linear object extending from the main pancreatic duct (MPD) and parenchyma into the lesser omental bursa along with a dilated distal MPD.

Laboratory diagnosis
All laboratory data were within normal limits.

Imaging diagnosis
Computed tomography scan revealed a bright linear object extending from the MPD and parenchyma into the lesser omental bursa along with a dilated distal MPD.

Treatment
Endoscopic ultrasound-guided pancreatic duct drainage (EUS-PD) was performed after failed endoscopic retrieval.

Related reports
There is no related report about EUS-PD for pancreatic duct obstruction caused by proximally migrated pancreatic stent.

Experiences and lessons
Proximal stent migration is an infrequent complication of endoscopic pancreatic stenting and can sometimes result in serious complications including pancreatic duct obstruction, pancreatic pain and acute pancreatitis. Endoscopic retrieval is the primary treatment modality for proximal migrated pancreatic stents. EUS-PD is feasible and safe for pancreatic duct drainage, as well as symptomatic relief if endoscopic retrieval has failed.

Peer-review
The authors propose the migration of a proximal pancreatic duct stent, which cannot be removed by ERCP, as a new indication for EUS-PD. This interesting case report adds to the increasing evidence of the use of EUS-PD as an effective and safe treatment for pancreatic duct decompression.

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FLYLEAF

EDITORS FOR THIS ISSUE

ORIGINAL ARTICLE

Retrospective Study

Colonoscopy procedural volume increases adenoma and polyp detection rates in gastroenterology trainees

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Abstract

AIM

To investigate changes in polyp detection throughout fellowship training, and estimate colonoscopy volume required to achieve the adenoma detection rate (ADRs) and polyp detection rate (PDRs) of attending gastroenterologists.

METHODS

We reviewed colonoscopies from July 1, 2009 to June 30, 2014. Fellows' procedural logs were used to retrieve colonoscopy procedural volumes, and these were treated as the time variable. Findings from screening colonoscopies were used to calculate colonoscopy outcomes for each fellow for the prior 50 colonoscopies at each time

point. ADR and PDR were plotted against colonoscopy procedural volumes to produce individual longitudinal graphs. Repeated measures linear mixed effects models were used to study the change of ADR and PDR with increasing procedural volume.

RESULTS
During the study period, 12 fellows completed full three years of training and were included in the analysis. The average ADR and PDR were, respectively, 31.5% and 41.9% for all fellows, and 28.9% and 38.2% for attendings alone. There was a statistically significant increase in ADR with increasing procedural volume (1.8%/100 colonoscopies, $P = 0.002$). Similarly, PDR increased 2.8%/100 colonoscopies ($P = 0.0001$), while there was no significant change in advanced ADR (0.04%/100 colonoscopies, $P = 0.92$). The ADR increase was limited to the right side of the colon, while the PDR increased in both the right and left colon. The adenoma per colon and polyp per colon also increased throughout training. Fellows reached the attendings' ADR and PDR after 265 and 292 colonoscopies, respectively.

CONCLUSION
We found that the ADR and PDR increase with increasing colonoscopy volume throughout fellowship. Our findings support recent recommendations of $\geqslant 275$ colonoscopies for colonoscopy credentialing.

Core tip: Adenoma and polyp detection rates are important colonoscopy quality indicators. Competence in colonoscopy is measured by motor skills and not adenoma detection rate (ADR) and polyp detection rate (PDR). Recent guidelines recommend at least 275 colonoscopies to achieve competence. In this study, we found that ADR, PDR, adenoma per colon, and polyp per colon significantly increase throughout fellowship training. Fellows achieve the ADR and PDR of attendings after 262 and 292 colonoscopies. The variability of polyp detection among fellows suggests that ADR and PDR could be used during fellowship as part of periodic feedback.

INTRODUCTION
Colorectal cancer (CRC) is the third most common cancer and second leading cause of cancer deaths in the United States[1]. Colonoscopy is the preferred modality for screening for colon cancer[2], and an essential follow-up procedure when other screening tests are positive. Several studies found that colonoscopy and polypectomy decrease colon cancer-specific mortality[3-5]. However, this is dependent on the quality of colonoscopy, and the ability of the endoscopist to detect and remove precancerous polyps. The adenoma detection rate (ADR), the most important quality indicator of colonoscopy, was found to be inversely associated with risk for interval colon cancer[6,7]. Most interval cancers are related to missed lesions during a screening colonoscopy[8]. Current practice guidelines include a recommendation for a minimum ADR of 20% in women and 30% in men to ensure adequate colonoscopy quality[9]. During gastroenterology training, competency in colonoscopy has been traditionally measured by the ability of the trainee to achieve cecal intubation in a timely manner (< 15 min) and resect polyps independently. The current Accreditation Council for Graduate Medical Education (ACGME) guidelines include a recommendation that fellows perform at least 140 colonoscopies during training to achieve competence. However, previous studies found that the number of procedures needed to achieve competence is much higher (275-500)[10-13]. Furthermore, polyp and adenoma detection, which is an essential goal of colonoscopy, is not part of competency assessment. Therefore, it is important to examine the change in adenoma and polyp detection as fellows increase their colonoscopy volume, and determine the number of colonoscopies that allows fellows to achieve an adequate polyp and adenoma detection rate.

In a retrospective study, it was found that the ADR was higher among third year fellows than among first and second year fellows[14]. Other studies found no change in adenoma and polyp detection with increasing fellowship training level[15,16]. In a prospective tandem colonoscopy study it was found that fellows with a higher colonoscopy volume had lower adenoma miss rates (AMR), and it was estimated that 450 colonoscopies would be required to achieve an AMR of < 25%[17]. In a retrospective study in which trainees were followed throughout their fellowship training, it was found that fellows' ADRs and polyp detection rates (PDR) improved when the fellows had conducted > 140 colonoscopies[18]. There are several limitations to these studies, including the small number of procedures performed by the fellows, inclusion of non-screening colonoscopies in calculating the ADR, and including fellows from various stages of training during only a limited part of their fellowship. In addition, none of these studies examined the change in individual fellow's ADRs and other colonoscopy metrics throughout fellowship training.

Our primary aim for the present study was to evaluate changes in the ADR, PDR, and advanced ADR with increasing colonoscopy procedural volume among gastroenterology trainees. Our secondary aims were to investigate changes in other colonoscopy metrics, such as adenoma per colon, polyp per colon, and left *vs* right-

MATERIALS AND METHODS

Data source and database creation

For this retrospective study, which was approved by the Emory University Institutional Review Board, we used the endoscopic procedure database at Grady Memorial Hospital in Atlanta, Georgia. Informed consent was waived by the Institutional Review Board due to the large sample size, retrospective study design, and the fact that this study does not affect the welfare of the patients. Information about all endoscopic procedures performed in the gastroenterology endoscopy unit is prospectively collected and entered into the database, and includes variables such as procedure type, patient's medical record number, age, race, procedure indication, endoscopist, and fellow participation in the procedure. We reviewed screening colonoscopies for patients aged 40-85 performed by gastroenterology fellows who completed their entire gastroenterology training between July 1, 2009 and June 30, 2014. Gastroenterology trainees in the training program rotate through three different sites: Grady Memorial Hospital, Veterans Affairs Medical Center, and Emory University Hospital. However, all screening colonoscopies are performed at Grady Memorial hospital. For each training fellow we created a separate Microsoft Excel dataset that included all of his or her screening colonoscopies performed at Grady throughout their fellowship training. This included the patient's age, race (black or non-black), and sex; colon preparation ("prep") quality (good, fair-adequate, fair-inadequate, poor) and success at cecal intubation; and polyp size (1-5 mm, 6-9 mm, $\geq$ 9 mm), number, location, and histology. Procedures with unsuccessful cecal intubation, fair-inadequate prep or poor prep were considered "inadequate" procedures, while those with successful cecal intubation in addition to fair-adequate or good prep were considered "adequate" procedures. Polyp location was categorized as right colon (cecum, ascending colon, hepatic flexure, and transverse colon) and left colon (splenic flexure, descending colon, sigmoid, and rectum). Adenomatous polyps were categorized as advanced and non-advanced adenomas. Advanced adenomas included adenomas larger than 9 mm in size and those that had histologic features of tubulovillous/villous structure, high-grade dysplasia, or adenocarcinoma.

We then sorted the colonoscopies in ascending temporal order, starting with the first day a screening colonoscopy was performed and continuing until the last screening colonoscopy was performed during fellowship. Next, we reviewed the fellow's procedure logs that contained the total number of colonoscopies (for all indications) performed at all training locations. Using this information, we assigned a procedure number that reflected the "rank" of each screening colonoscopy for that fellow. In assigning the rank, all colonoscopies performed by fellows for screening, polyp surveillance, and diagnostic indications at all locations contributed to the procedural volume. However, only screening colonoscopies were included in the analysis to calculate procedural outcomes. Patients with a personal history of colon cancer or prior colonic surgery were excluded from analysis. Procedural outcomes were defined as follows: Adenoma detection rate (ADR) - the percentage of screening colonoscopies with at least one histologically proven adenoma; polyp detection rate (PDR) - the percentage of screening colonoscopies with at least one polyp removed during the colonoscopy; and advanced ADR - the percentage of screening colonoscopies with at least one advanced adenoma (see above). The mean number of adenoma per colon (APC) was calculated by dividing the total number of adenomas by the number of screening colonoscopies performed. The mean number of polyps per colon (PPC) was calculated by dividing the total number of polyps by the number of screening colonoscopies performed.

Starting at the 50th screening colonoscopy, we calculated procedural outcomes for the current colonoscopy and the previous 49 colonoscopies (50 procedures for each outcome measurement). We also calculated the mean age and the percentage of patients in this block of 50 procedures who were male, black, and had an adequate exam. With each additional screening colonoscopy, these outcomes and control variables were recalculated until the last screening colonoscopy in the dataset was reached. The final dataset contained observations organized in ascending order by colonoscopy procedure rank number. Each ranked observation, starting at the 50th screening colonoscopy, contained colonoscopy outcome measures and time varying percentages as mentioned above. This process was conducted for each of the 12 fellows. Finally, we merged the 12 individual spreadsheets into one longitudinal dataset that contained the fellows' ID code, the procedural rank variable, time varying outcomes (ADR, PDR, APC, PPC), and time varying control variables (percentage of male patients, black patients, procedures with inadequate prep, and mean age).

To obtain a reference standard to which to compare the fellow's performance, we reviewed all screening colonoscopies performed by the attending physicians alone without the involvement of fellows at Grady Memorial Hospital. We used the same inclusion and exclusion criteria mentioned above for the fellows' procedures. The demographic characteristics of the patients who underwent screening colonoscopies were similar to those of the patients included in the calculation of outcomes for the fellows' procedures. We calculated the ADR, PDR, APC, and PPC for the attending-alone

group. These values were used as target levels to estimate the number of procedures it takes for fellows to achieve attendings' level of polyp detection.

Screening colonoscopy information

At our hospital, patients are referred for screening colonoscopy by their primary care physician or their gastroenterologist. For bowel preparation, patients received 4 L of polyethylene glycol solution as a single dose regimen the evening before the procedure. All procedures were performed with moderate sedation. During the study period, there were 8 attendings who supervised the 12 fellows who performed the colonoscopies. The fellow began the procedure and attempted insertion of the colonoscope to the cecum. The attending physician assisted when there was difficulty passing an area of the colon. The attending usually returned the scope to the fellow once the problematic area of the colon was traversed, though this varied per procedure, attending, and fellow level of training. The attending physicians were present and monitored fellows throughout the duration of the procedure. In the attending-alone group, the attending started and completed the procedure with no fellow involvement.

Statistical analysis

All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, United States) statistical software. Descriptive statistics, including means, ranges, and frequencies, were used to characterize the study population. For each fellow, from their measurement time points, we calculated ranges and mean values for each predictor and outcome. We constructed individual and combined graphs to illustrate the change in colonoscopy outcome with increasing colonoscopy procedural volume, which was used as a proxy measure of the time variable. To examine the individual and combined trajectories of all fellows, defined as change in colonoscopy outcome with increasing colonoscopy volume, we used repeated measures linear mixed effects longitudinal models. The unconditional growth model to investigate the individual fellows' trajectories included the outcome and procedural volume (main exposure), and accounted for the random effect of the intercept with an unstructured covariance matrix. For the combined trajectories, the models included the outcome and procedural volume (main exposure), and mean age, percentages of black patients, sex, and inadequate prep as time-varying predictors, and accounted for the random effect of the intercept and procedural volume with an unstructured covariance matrix. The time varying predictors were centered to their mean, and the procedural volume was centered to procedure $n = 50$ to ease the interpretation of the initial status. The unconditional means model was used to calculate the mean outcome for the entire cohort. This included the outcome in the model statement

and accounted for the variable effect of the intercept. The results are reported as the estimated means and 95%CIs. A *P*-value $\leqslant 0.05$ (two-sided) was used to assess statistical significance. We used the results of the longitudinal growth model (initial status and rate of change) to estimate the number of colonoscopies required to achieve the attending-alone group mean ADR, PDR, APC, and PPC.

RESULTS

Between July 1, 2009 and June 30, 2014, 12 fellows completed their full three-year clinical fellowship training. A total of 3123 screening colonoscopies performed by these fellows were included in the analysis. The attending physicians performed 2174 procedures without fellow involvement. The characteristics of the screening colonoscopies performed by the fellows and the attendings alone are summarized in Table 1. The overall mean ADR, PDR, and advanced ADR for all fellows were 31.5%, 41.9%, and 7.8%, respectively. There was substantial inter- and intra-individual variation in the ADR, PDR, and advanced ADR. The mean ADR ranged from 21.6% to 39.8%, and ADR values ranged from 8% to 52% throughout all measurement time points. The mean PDR ranged from 32.5% to 53.8%, while PDR values ranged from 14% to 70%. The overall ADR and PDR of the attending-alone group during the study period were 28.9% and 38.2%, respectively.

Primary outcomes

Plots of individual and combined fellows' ADR, PDR, and advanced ADR are shown in Figure 1. There was a statistically significant increase in the ADR among all fellows (1.8% per 100 colonoscopies, $P = 0.002$) (Figure 1A). Similarly, there was a statistically significant increase in the PDR among all fellows (2.8% per 100 colonoscopies, $P = 0.0001$) (Figure 1B). Overall, there was no substantial or statistically significant change in the advanced ADR with increasing procedural volume (0.04% per 100 colonoscopies, $P = 0.92$) (Figure 1C).

Secondary outcomes

In addition to increasing ADR and PDR, the adenoma per colon (APC) and polyp per colon (PPC) also increased with increasing procedural volume (Figure 2A and B, and Table 2). The mean APC for the entire cohort was 0.58, and it increased by 0.05 per 100 colonoscopies, ($P = 0.0001$). The mean PPC was 0.84, and there was positive trend of 0.09 per 100 colonoscopies for this metric ($P < 0.0001$). However, there was a difference in the trends for detecting polyps in the right *vs* the left colon. The right-side ADR (ADR-right) increased with increasing procedural volume (1.9% per 100 colonoscopies, $P = 0.006$), while the left-side ADR (ADR-left) increased slightly (0.6% per 100 colonoscopies, $P = 0.05$) (Figure 2C and D). This was also observed for the APC, for which where APC-right

Table 1 Characteristics of screening colonoscopies performed by 12 gastroenterology fellows throughout their 3 years of clinical training (*n* = 3123), and 8 attendings alone (*n* = 2174), July 1 2009 to June 30 2014									
Fellow	Number of screening colonoscopies	Total colonoscopy procedure volume	Patient's mean age (yr)	Male patients (%)	Black patients (%)	Adequate exam (%)	Mean ADR (%)	Mean PDR (%)	Mean advanced ADR (%)
A	326	751	58.5	39.4	86.3	90.5	31.0	38.1	6.9
B	277	702	58.2	36.3	83.1	91.9	28.4	34.9	9.1
C	282	680	57.8	39.1	88.7	90.8	28.8	42.4	6.7
D	328	668	58.4	35.4	87.1	92.8	31.2	37.5	10.7
E	214	566	57.8	35.4	89.2	92.6	35.7	53.8	8.9
F	275	546	57.9	37.7	86.1	93.1	32.7	47.8	6.7
G	254	561	58.4	41.2	87.7	85.3	21.6	32.5	8.6
H	226	689	58.0	35.9	90.4	81.1	31.5	41.2	6.5
I	229	600	57.0	37.9	85.2	89.4	34.6	41.8	7.5
J	206	586	58.0	35.2	90.8	91.7	28.2	36.5	4.8
K	244	549	58.2	36.5	84.0	91.8	34.5	44.8	5.7
L	261	569	58.6	35.7	90.5	91.7	39.8	51.5	12.0
All fellows	3123	7467	58.1	37.2	87.3	89.8	31.5	41.9	7.8
Attendings alone	2174		57.9	36.3	89.3	90.1	28.9	38.2	8.5

Adequate colonoscopies were those in which the cecum was reached and the preparation quality was either good or fair-adequate. ADR: Adenoma detection rate; PDR: Polyp detection rate.

Figure 1 Individual and combined change trajectories of adenoma detection rate, polyp detection rate, and advanced adenoma detection rate for 12 fellows throughout their fellowship training. A: ADR per rank; B: PDR; C: Advanced ADR. The black lines represent individual fellows and the red line represents the mean for the entire group of fellows. The numbers in the bottom right corner of each panel represent the slope (absolute percentage increase in outcome per 100 screening colonoscopies) and its associated *P* value. Models included the outcome, procedural volume (main exposure), and mean age, percentages of black patients, sex, and inadequate prep as time-varying predictors. ADR: Adenoma detection rate; PDR: Polyp detection rate.

increased by 0.04 per 100 colonoscopies, *P* = 0.001; while the estimated increase in APC-left was only 0.01 per 100 colonoscopies and not statistically significant (*P* = 0.24) (Figure 2G and 2H). The PDR and PPC for both

A Adenoma per colon
B Polyp per colon
C ADR left
D ADR right
E PDR left
F PDR right
G Adenoma per colon-left
H Adenoma per colon-right

Figure 2 Individual and combined change trajectories colonoscopy metrics. A: Adenoma per colon (APC); B: Polyp per colon (PPC); C: Left-sided Adenoma detection rate (ADR); D: Right-sided ADR; E: Left sided polyp detection rate (PDR); F: Right-sided PDR; G: Left-sided APC; H: Right-sided APC; I: Left-sided PPC; J: Right-sided PPC.

Table 2 Adjusted mean polyp-related outcomes, estimated initial status, and changes in outcomes per 100 screening colonoscopies[1] among the entire group of fellows (*n* = 12)

Outcome[1]	Overall mean[2] (95%CI)	Mean after first 50 colonoscopies (95%CI)	Change in outcome per 100 colonoscopies (95%CI)	*P* value[3]	Number of procedures to achieve mean attending value[4]
ADR (%)	31.5 (28.7-34.3)	25.1 (21.1-29.2)	1.8 (0.8-2.7)	0.002	265
ADR-right (%)	22.3 (20.1-24.4)	15.3 (10.6-20.0)	1.9 (0.7-3.2)	0.01	
ADR-left (%)	14.2 (12.4-16.0)	11.6 (8.3-14.9)	0.6 (0.001-1.3)	0.05	
PDR (%)	41.9 (37.9-45.9)	31.4 (26.7-36.0)	2.8 (1.7-3.9)	0.0001	292
PDR-right (%)	26.5 (23.8-29.2)	16.0 (10.6-21.4)	2.9 (1.5-4.3)	0.001	
PDR-left (%)	24.9 (21.5-28.3)	18.7 (13.1-24.3)	1.6 (0.3-2.9)	0.02	
AADR (%)	7.8 (6.6-9.1)	7.4 (4.6-10.2)	0.04 (-0.80-0.90)	0.92	
APC	0.58 (0.52-0.65)	0.39 (0.28-0.49)	0.05 (0.03-0.07)	0.0001	399
APC-right	0.37 (0.32-0.42)	0.20 (0.12-0.28)	0.04 (0.02-0.06)	0.001	
APC-left	0.22 (0.19-0.25)	0.18 (0.11-0.26)	0.01 (-0.01-0.02)	0.24	
PPC	0.84 (0.74-0.94)	0.51(0.36-0.66)	0.09 (0.06-0.12)	< 0.0001	375
PPC-right	0.45 (0.39-0.50)	0.21 (0.11-0.31)	0.06 (0.04-0.09)	< 0.0001	
PPC-left	0.40 (0.34-0.46)	0.30 (0.21-0.39)	0.03 (0.01-0.05)	0.01	

[1]From linear mixed effects regression models, controlling for age, sex, race, and inadequate procedure; [2]Mean from all screening colonoscopies over all 3 years of training; [3]*P* value associated with the rate of change; [4]Mean attending values were: ADR 28.9%, PDR 38.2%, APC 0.57, and PPC 0.80. ADR: Adenoma detection rate; PDR: Polyp detection rate; AADR: Advanced ADR; APC: Mean adenoma per colon; PPC: Mean polyp per colon. Right colon included the cecum, ascending colon, hepatic flexure, and transverse colon. Left colon included splenic flexure, descending colon, sigmoid, and rectum.

sides of the colon increased with increasing procedural volume; however, the increase in PDR-right was higher than PDR-left (2.9%, *P* = 0.0001 *vs* 1.6%, *P* = 0.02, respectively), and the increase in PPC-right was higher than PPC left (0.06, *P* < 0.0001 *vs* 0.03, *P* = 0.01) (Figure 2E, F, I, J). In the attending-alone group, the overall APC and PPC were 0.58 and 0.8, respectively.

The numbers of colonoscopies required to achieve the outcomes (ADR, PDR, APC, and PPC) of those of attendings estimated using the results of longitudinal analysis are shown in Table 2. Overall, on average, fellows achieved the attendings' level of ADR and PDR after 265 and 292 colonoscopies, respectively. The corresponding numbers for the APC and PPC were 399 and 375.

Changes in the trajectories of the ADR, PDR, and advanced ADR for individual fellows throughout their fellowship training are shown in Figure 3. The ADR for

most fellows statistically significantly increased with increasing procedural volume. The ADR for eight fellows increased, while for two fellows it remained the same, and for two it decreased (Figure 3A). Similarly, the PDR for nine fellows statistically significantly increased, whereas for three fellows it remained relatively stable (Figure 3B). The trends for change in the advanced ADR were variable among fellows; some fellows had increasing rates, some had decreasing rates, and others remained stable (Figure 3C).

DISCUSSION

Our results indicate that there are clinically important increases in the ADR, PDR, APC, and PPC as gastroenterology fellows increase their colonoscopy procedural volume. This strongly suggests that polyp detection is a learned skill that improves as fellows perform more

A

ADR

Adenoma detection rate

Number of colonoscopies performed

B

PDR

Polyp detection rate

Number of colonoscopies performed

C

Advanced ADR

Figure 3 Individual change trajectories of the three main quality metrics for 12 fellows throughout their fellowship training. A: ADR; B: PDR; C: Advanced ADR. The numbers in the top right corner of each panel represent the slope (absolute percentage increase in outcome per 100 screening colonoscopies). The [a] represents statistically significant ($P < 0.05$) slopes. Models included the outcome and procedural volume (main exposure). ADR: Adenoma detection rate; PDR: Polyp detection rate.

procedures. This is highly plausible because polyp detection requires skill in colon distension, residual stool cleanup, and deliberate and systematic examination of each colon fold. The improvement in adenoma detection (as measured by the ADR and APC) was mainly observed in the right colon. The reason behind this finding is unclear. In our study, all patients received a single dose colon preparation the night prior to the colonoscopy. This may have led to the presence of residual stool preferentially in the right colon[20], which needs to be cleaned adequately to improve polyp detection. Previous studies found that cleaning the colon of residual stool by using air, water, and suction is an important motor skill in colonoscopy that improves with increasing procedural volume[13]. Therefore, it is possible that as this skill improved in our fellows, ADR and PDR increased in the right colon.

Traditional ways of assessing competence in colonoscopy have not included polyp detection, but rather focused on other metrics such as cecal intubation rate (> 90%), cecal intubation times, rate of ileocecal valve intubation, patient comfort level, and number of biopsy forceps passes for removal of small polyps. More recently, a dedicated colonoscopy skill assessment tool was developed [Assessment of Competency in Endoscopy (ACE) tool] that incorporates several motor

and cognitive skills, in addition to polyp detection. In a multicenter prospective assessment of the ACE tool that included gastroenterology fellows at various stages of training over a one-year period, there was a gradual increase in the PDR from 24% early in training to 65% by the end of training[13]. The ACE tool does not include the ADR or other metrics (APC, PPC). In our study, we found a similar overall upward trend in the ADR and PDR throughout fellowship training. This suggests that measurement of the PDR for competency assessment, while not ideal, could be sufficient for assessing fellows' polyp detection skills. However, it is important to mention that the PDR is a "corruptible" measure of quality, with potential for the endoscopists (including fellows) to artificially inflate their PDR by removing insignificant diminutive polyps. The ADR remains the most objective and validated quality measure of colonoscopy.

The number of colonoscopies needed to achieve competence is a matter of continuous debate. It has been consistently found in retrospective and prospective studies that the previously recommended number of 140 colonoscopies is inadequate for achieving competence[10,11,13,17,21]. Furthermore, there is a general shift towards performance-based assessment of competency, and away from merely documenting the

number of procedures performed[21]. Nevertheless, our findings support the need for a higher number of colonoscopies. Using the ADR and APC of attendings as a reference standard, we found that it requires 265 and 400 procedures to achieve the reference ADR and APC, respectively. This is in accordance with the most recent literature and guidelines for privileging and credentialing, which recommend a minimum of 275 colonoscopies before assessment of competence and seeking of privileges[22]. It is noteworthy that we did not use the recommended minimal quality metrics (ADR of 25%) in calculating the number of required procedures because the average initial ADR for the fellows in the study was already 25.1% at the first measurement occasion.

Our study has several strengths. To our knowledge, we included the largest number of fellows to be followed longitudinally throughout their fellowship training. Our unique method of analysis allowed us to evaluate individual as well as combined trajectories of change in polyp detection. Previous studies used a linear regression analysis method to examine the change in the ADR with procedural volume[23]. This method of analysis is suboptimal because the observations are not independent, but are interrelated and performed by the same gastroenterology fellows over time. A longitudinal analysis method considers the individual and combined change trajectories, examines the change in outcome with time, and allows for estimation of outcome at different time points by using the initial ADR and other detection rates and their rates of change. Furthermore, this method allows comparison of different trends even if values are not available for all fellows at all time points. When calculating the ADR and other outcomes, we only included screening colonoscopies and excluded colonoscopies performed for polyp surveillance and for diagnostic indications; nevertheless, we included all colonoscopies in the calculation of procedural volume. We believe that this approach provides a valid estimation of the ADR and other outcomes, while still incorporating an accurate measure of procedural experience. Previous studies examined differences in polyp detection among fellows according to their year of training. However, using procedural volume is likely a better approach because fellows perform a variable number of procedures during their years of training. The ADR and other polyp detection outcomes were measured using a fixed number of colonoscopies at each time point (50 procedures) which eliminated the variability in these values that can occur if a different number of procedures is used at each time point. We also adjusted for important time-varying predictors of polyp detection in the combined model to account for the varying contribution of these factors on colonoscopy outcomes. Our study extends the traditional analysis of polyp detection beyond the ADR and PDR to include other outcomes such as the advanced ADR, APC, and PPC, and the right- *vs* left-side detection rates, thereby providing more insight into changes in these

outcomes with increasing procedural volume and skill in colonoscopy.

The study also has several limitations. We did not evaluate the exact involvement of fellows in the procedure. Part of the withdrawal could have been performed by the attendings, especially for first year fellows. We did not evaluate other features of fellows' performance such as independent cecal intubation rates, insertion, and withdrawal times. This would have given more insight into the learning curves of the fellows in respect to motor skills in addition to polyp detection, and would have helped evaluate whether withdrawal times are linked to higher polyp detection by fellows. Our study was limited to one gastroenterology training program with a small number of supervising attendings, and our results may not be generalizable to other gastroenterology programs. This study focused on procedural volume as a determinant of improvement in polyp detection. However, the quality of the endoscopic and didactic training of fellows is also important when considering improvement in their polyp detection skills.

Measurement of the ADR is an essential component of continuous quality improvement in colonoscopy, and is an important metric for all practicing gastro-enterologists. Yet there are no requirements for mea-suring the ADR or PDR during fellowship training, and there seems to be a gap in trainee knowledge when it comes to quality in colonoscopy. In a survey of gastroenterology trainees, less than 50% of respondents correctly identified the recommended national bench-marks for ADR[24]. The inclusion of the ADR (or the less preferred PDR) as a component of the colonoscopy assessment tool is a critical step towards a more objective measure of trainee performance, and provides the needed emphasis on quality of colonoscopy during training. It is likely that fellows achieve a 90% cecal intubation rate long before they acquire the necessary skills to improve their polyp detection skills. Therefore, we recommend establishing a separate category of "colonoscopy quality" for assessing colonoscopy skills. To do this, fellows can be evaluated using objective colonoscopy assessment tools (*e.g.*, the ACE tool) and periodically given an overall motor skill score, cognitive skill score, and quality score (ADR or PDR). Despite the overall increase in the ADR and PDR, we found that fellows vary substantially in their individual polyp detection rates (Table 1 and Figure 1). In addition, there are intra-individual variations and fluctuations in ADR, PDR and AADR throughout fellowship training (Figure 3), which are likely substantially related to variations in the characteristics of patients undergoing colonoscopy (*e.g.*, true numbers of polyps/adenomas, age, prep quality). Therefore, it is important to measure these metrics at multiple intervals throughout fellowship in order to evaluate trends rather than inappropriately weighing a single value. A few fellows had a relatively low ADR and PDR even in their later stages of training. Such trainees could benefit from targeted feedback and training to improve their polyp detection. Some

studies found that providing a quality report card to gastroenterologists results in an improved ADR[25,26]. It is unclear whether this would have a similar effect on trainees during fellowship. Nevertheless, continuous measurement of the ADR during fellowship could instill the habit of quality monitoring, provide opportunities for self-improvement, and prepare fellows for similar activities when they start practicing as independent gastroenterologists.

In summary, we found that the ADR, PDR, and other indicators of polyp detection increase with increasing colonoscopy volume during training, and that it requires between 265-400 colonoscopies for fellows to reach the adenoma detection level of attendings. We recommend increased focus on colonoscopy quality during fellowship training, with establishment of a separate colonoscopy quality score for each fellow to be incorporated in periodic trainee feedback and evaluations.

COMMENTS

Background
Adenoma and polyp detection rates (ADR and PDR) are important quality metrics for colonoscopy. Several studies found that participation of gastroenterology fellows in screening colonoscopies is associated with increased ADR and PDR. During gastroenterology training, competency in colonoscopy is measured by the ability of the trainee to achieve cecal intubation in a timely manner (< 15 min) and resect polyps independently.

Research frontiers
In addition to traditional milestones of competence in colonoscopy, it is important to examine the effect of procedural volume on the quality of colonoscopy performed by fellows under the supervision of attendings. The aim of this study was to investigate changes in polyp detection throughout fellowship training, and estimate the colonoscopy volume required to achieve the ADRs and PDRs of attending gastroenterologists.

Innovations and breakthroughs
The authors performed a retrospective cohort study of 12 fellows who completed three full years of training. The authors examined the change in ADR, PDR, and advanced ADR for each individual fellow and as a group using longitudinal modelling. The majority of fellows increased their ADR and PDR throughout their fellowship training as they performed more colonoscopies. The ADR increase was limited to the right side of the colon, while the PDR increased for both the right and left colon. The adenoma per colon and polyp per colon also increased throughout training, providing further evidence that polyp detection is a skill that continues to improve throughout fellowship. Fellows reached ADR and PDR levels similar to those of the attendings' average values after 265 and 292 colonoscopies, respectively.

Applications
This study provides important insight into the progression of polyp detection skills of trainees throughout fellowship. It also supports the recent recommendations of ≥ 275 colonoscopies for colonoscopy credentialing. Quality metrics during fellowship training could complement other evaluation tools for colonoscopy training. Fellows should monitor their own ADR throughout fellowship and strive for continued improvement.

Peer-review
The manuscript written by Qayed *et al* analyzed the relation between adenoma or polyp detection rates and colonoscopy volume. They found that ADR and PDR increase with increasing colonoscopy volume throughout fellowship. The data are well analyzed and important.

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Safety of gastrointestinal endoscopy with conscious sedation in obstructive sleep apnea

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Abstract

AIM

To perform a systematic review and meta-analysis to assess the safety of conscious sedation in patients with obstructive sleep apnea (OSA).

METHODS

A comprehensive electronic search of MEDLINE and EMBASE was performed from inception until March 1, 2015. In an effort to include unpublished data, abstracts from prior gastroenterological society meetings as well as other reference sources were interrogated. After study selection, two authors utilizing a standardized data extraction form collected the data independently. Any disagreements between authors were resolved by consensus among four authors. The methodological quality was assessed using the Newcastle Ottawa tool for observational studies. The primary variables of interest included incidence of hypoxia, hypotension, tachycardia, and bradycardia. Continuous data were summarized as odds ratio (OR) and 95%CI and pooled using generic inverse variance under the random-effects model. Heterogeneity between pooled studies was assessed using the I^2 statistic.

RESULTS

Initial search of MEDLINE and EMBASE identified 357 citations. A search of meeting abstracts did not yield any relevant citations. After systematic review and exclusion consensus meetings, seven studies met the a priori determined inclusion criteria. The overall methodological

quality of included studies ranged from moderate to low. No significant differences between OSA patients and controls were identified among any of the study variables: Incidence of hypoxia (7 studies, 3005 patients; OR = 1.11; 95%CI: 0.73-1.11; P = 0.47; I^2 = 0%), incidence of hypotension (4 studies, 2125 patients; OR = 1.10; 95%CI: 0.75-1.60; P = 0.63; I^2 = 0%), incidence of tachycardia (3 studies, 2030 patients; OR = 0.94; 95%CI: 0.53-1.65; P = 0.28; I^2 = 21%), and incidence of bradycardia (3 studies, 2030 patients; OR = 0.88; 95%CI: 0.63-1.22; P = 0.59; I^2 = 0%).

CONCLUSION
OSA is not a significant risk factor for cardiopulmonary complications in patients undergoing endoscopic procedures with conscious sedation.

Key words: Conscious sedation; Obstructive sleep apnea; Endoscopy; Complications; Safety; Meta-analysis

Core tip: Patients with obstructive sleep apnea (OSA) often receive monitored anesthesia care in lieu of conscious sedation due to a perceived elevated risk of complications. However, prior studies have failed to note any clinically significant variations in cardiopulmonary parameters in OSA patients when compared to controls during endoscopy but studies have been underpowered due to small sample sizes. The objective was to perform a systematic review and meta-analysis to assess the safety of conscious sedation in patients with OSA. This meta-analysis showed OSA is not a significant risk factor for cardiopulmonary complications in patients undergoing endoscopic procedures with conscious sedation.

INTRODUCTION
Obstructive sleep apnea (OSA) is an increasingly common disorder. Because of a presumed elevated risk, endoscopic evaluation in patients with OSA may be delayed, denied or achieved at a higher level of care resulting in substantial healthcare expenses. In the general population, adverse events during endoscopy are rare with an approximate adverse event rate of 0.1% and 0.2% for upper gastrointestinal and lower gastrointestinal procedures respectively[1-4]. Non-significant variations in cardiopulmonary parameters are usually noted during routine endoscopy and have been well studied[5-7]. Several published studies, including a recently reported prospective study evaluating the risk of cardiopulmonary

complications in patients with OSA undergoing endoscopy with conscious sedation have not supported the need for extra precaution[8]. We recently published a prospective analysis in the veteran population undergoing upper and lower endoscopy which did not find any significant cardiopulmonary variation in control and OSA patients[8].

Despite their comparable findings, these conclusions are limited by small sample sizes in conjunction with low adverse event rates. No systematic reviews or meta-analyses have been performed on this topic to date. The present study aims to systematically review the literature and perform a meta-analysis of all selected published and unpublished data meeting search criteria on patients with OSA undergoing endoscopic procedures.

MATERIALS AND METHODS
Selection criteria
A comprehensive electronic search of MEDLINE and EMBASE was performed from inception until March 1, 2015. A total of 119 MEDLINE references were identified using the following search strategy: (apnea) OR "sleep apnea") OR sleep apnea) OR obstructive sleep apnea) OR "obstructive sleep apnea") OR sleep disordered breathing) OR "sleep disordered breathing") AND (sedation) OR conscious sedation) OR "conscious sedation") OR moderate sedation) OR "moderate sedation") AND endoscopy. A total of 238 EMBASE references were identified using the following strategy: Endoscopy AND (Apnea OR (sleep AND disordered AND breathing) OR "sleep disordered breathing" OR "obstructive sleep apnea" OR "sleep apnea" OR (sleep AND apnea) OR (obstructive AND sleep AND apnea) AND (Sedation OR "conscious sedation" OR (conscious AND sedation) OR "moderate sedation" OR (moderate AND sedation) AND human. Two authors evaluated the combined 357 candidate studies independently. Studies performed on patients with obstructive sleep apnea undergoing endoscopy with conscious sedation and at least one the following variables of interest were considered for inclusion: Incidence of hypoxia, hypotension, tachycardia, and bradycardia.

Data collection
Two authors extracted all data independently utilizing a standardized data extraction form. Once the data was entered into a dataset, a random data check was performed for accuracy. All disagreements between authors were resolved by consensus with a third author. Data were collected on study and patient characteristics, OSA groups, use of conscious sedation and the incidences of hypoxia, hypotension, tachycardia, and bradycardia when available. The methodological quality was assessed using the Newcastle Ottawa tool for observational studies[9]. The primary variables of interest included incidence of hypoxia, hypotension, tachycardia, and bradycardia. The systematic review was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Figure 1 Flow diagram of study selection[22-25]. OSA: Obstructive sleep apnea.

guidelines[10].

Statistical analysis
Continuous data were summarized as odds ratio (OR) and 95%CI and pooled using generic inverse variance under the random-effects model. Heterogeneity between pooled studies was assessed using I^2 statistic and categorized as low (< 30%), moderate (30%-50%), or high (> 50%)[11]. All analyses were performed using Review Manager 5.1 software[12].

Biostatistics
The statistical methods of this study were performed and reviewed by a biomedical statistician, Ambuj Kumar, MD, MPH from Comparative Effectiveness Research, Morsani College of Medicine, University of South Florida, Tampa, FL, United States.

RESULTS

Study selection
A comprehensive search of MEDLINE and EMBASE identified 357 eligible citations. In an effort to capture unpublished data, conference abstracts from the last 3 meetings (2013-2015) of the American College of Gastroenterology and Digestive Disease Week were also reviewed. No studies were identified to meet inclusion criteria. The following sites were also interrogated for possible study inclusion: ClinicalTrials.gov, Roche clinical trial protocol registry (www.roche-trials.com), Novartis clinical trials database (www.novctrd.com), Australian New Zealand Clinical Trials Registry (ANZCTR), and the

metaRegister of Controlled Trials. No additional studies were identified for inclusion.

After systematic review and exclusion consensus meetings, seven studies met the a priori determined inclusion criteria (Figure 1). None of the references from the included studies yielded additional studies eligible for inclusion. The overall methodological quality of the included studies ranged from moderate to low as assessed by the Newcastle Ottawa tool for observational studies[9].

Hypoxia
Seven studies identified for inclusion contained data on the incidence of hypoxia. A total of 3005 patients were included for analysis. No significant differences between OSA patients and controls were identified with regards to the incidence of hypoxia (OR = 1.11; 95%CI: 0.73-1.11; *P* = 0.47, Figure 2). The heterogeneity among the studies was low (I^2 = 0%).

Hypotension
Four studies identified for inclusion contained data on the incidence of hypotension. A total of 2125 patients were included for analysis. No significant differences between OSA patients and controls were identified with regards to the incidence of hypotension (OR = 1.10; 95%CI: 0.75-1.60; *P* = 0.63, Figure 3). The heterogeneity among the studies was low (I^2 = 0%).

Tachycardia
Three studies identified for inclusion contained data on the incidence of tachycardia. A total of 2030 patients were included for analysis. No significant differences between OSA patients and controls were identified with regards to the incidence of tachycardia (OR = 0.94; 95%CI: 0.53-1.65; *P* = 0.28, Figure 4). The heterogeneity among the studies was low (I^2 = 21%).

Bradycardia
Three studies identified for inclusion contained data on the incidence of bradycardia. A total of 2030 patients were included for analysis. No significant differences between OSA patients and controls were identified with regards to the incidence of bradycardia (OR = 0.88; 95%CI: 0.63-1.22; *P* = 0.59, Figure 5). The heterogeneity among the studies was low (I^2 = 0%).

DISCUSSION
OSA is a growing problem in the United States especially among the veteran population. Moderate to severe OSA is estimated to affect approximately 13% of men and 6% women between the ages of 30-70[13]. Per the ASGE sedation guidelines, patient with OSA are considered to be at a higher risk regarding sedation-related cardiopulmonary complications in relation to upper and lower endoscopy[14]. These patients are routinely recommended MAC anesthesia for endoscopic

Study or subgroup	Sleep apnea		No sleep apnea		Weight	Odds ratio M-H, random, 95%CI	Odds ratio M-H, random, 95%CI
	Events	Total	Events	Total			
Andrade, 2015	13	244	15	243	31.2%	0.86 [0.40, 1.84]	
Cha, 2013	1	30	7	65	4.0%	0.29 [0.03, 2.43]	
Gill, 2011	1	200	0	200	1.8%	3.02 [0.12, 74.46]	
Khiani, 2009	10	90	7	143	18.1%	2.43 [0.89, 6.63]	
Mador, prospective 2011	2	351	1	553	3.2%	3.16 [0.29, 35.02]	
Mador, retrospective 2011	12	509	3	130	11.1%	1.02 [0.28, 3.68]	
Qadeer, 2009	17	30	125	217	30.7%	0.96 [0.45, 2.08]	
Total (95%CI)		1454		1551	100%	1.11 [0.45, 1.71]	
Total events	56		158				

Heterogeneity: Tau^2 = 0.00; χ^2 = 5.58, df = 6 (P = 0.47); I^2 = 0%
Test for overall effect: Z = 0.50 (P = 0.62)

Figure 2 Incidence of hypoxia[8,17-21].

Study or subgroup	Sleep apnea		No sleep apnea		Weight	Odds ratio M-H, random, 95%CI	Odds ratio M-H, random, 95%CI
	Events	Total	Events	Total			
Andrade, 2015	41	244	39	243	62.2%	1.06 [0.65, 1.71]	
Cha, 2013	0	30	0	65		Not estimable	
Mador, prospective 2011	4	351	7	553	9.4%	0.90 [0.26, 3.09]	
Mador, retrospective 2011	49	509	10	130	28.4%	1.28 [0.63, 2.60]	
Total (95%CI)		1134		991	100%	1.10 [0.75, 1.60]	
Total events	94		56				

Heterogeneity: Tau^2 = 0.00; χ^2 = 0.30, df = 2 (P = 0.86); I^2 = 0%
Test for overall effect: Z = 0.49 (P = 0.63)

Figure 3 Incidence of hypotension[8,17,20,21].

Study or subgroup	Sleep apnea		No sleep apnea		Weight	Odds ratio M-H, random, 95%CI	Odds ratio M-H, random, 95%CI
	Events	Total	Events	Total			
Andrade, 2015	19	244	24	243	52.0%	0.77 [0.41, 1.45]	
Mador, prospective 2011	9	351	8	553	28.0%	1.79 [0.69, 4.69]	
Mador, retrospective 2011	10	509	4	130	20.0%	0.63 [0.19, 2.05]	
Total (95%CI)		1104		926	100%	0.94 [0.53, 1.65]	
Total events	38		36				

Heterogeneity: Tau^2 = 0.06; χ^2 = 2.55, df = 2 (P = 0.28); I^2 = 21%
Test for overall effect: Z = 0.22 (P = 0.82)

Figure 4 Incidence of tachycardia[8,20,21].

evaluation. Cardiopulmonary complications are the most feared unfavorable events among patients with OSA including episodes of tachycardia, bradycardia, hypotension, and hypoxia[5-7]. It is believed that OSA patients especially tend to have poor respiratory drive and effort which can be exacerbated by sedation[15,16]. Contrary to that belief, our meta-analysis and review does not show any significant difference in regards to hypoxia in OSA patients. It is also well studied that sedation tend to lower overall mean blood pressure. When looking at cardio-circulatory parameters including bradycardia, tachycardia and hypotension, our review failed to show any significant difference in regards to those parameters. Therefore, in patients undergoing endoscopy with conscious sedation, OSA does not seem to be a clinically important risk factor for unfavorable outcomes. In short, significant differences between OSA patients and controls were not identified among any of

the study variables: Incidence of hypoxia, hypotension, tachycardia or bradycardia. This is in correlation with regards to the recent publication from our institution highlighting the cardiopulmonary parameters in the OSA and non-OSA patients[8]. OSA patients are perceived as high risk for endoscopy and are offered monitored anesthesia care routinely although this meta-analysis suggests otherwise. Moving forward, endoscopists should be cognizant that OSA does not predispose patients to higher risk compared to non OSA patients. In addition, using conscious sedation for OSA patients may reduce overall healthcare burden with cost saving measures as MAC anesthesia care has not necessarily shown any overall reduction in adverse events. A major limitation of the study includes the overall methodological quality of the included studies ranged from moderate to low. Further, for patients undergoing endoscopic procedures with conscious sedation, OSA does not appear to be a

Study or subgroup	Sleep apnea		No sleep apnea			Odds ratio	Odds ratio
	Events	Total	Events	Total	Weight	M-H, random, 95%CI	M-H, random, 95%CI
Andrade, 2015	73	244	83	243	74.0%	0.82 [0.56, 1.20]	
Mador, prospective 2011	15	351	24	553	24.7%	0.98 [0.51, 1.90]	
Mador, retrospective 2011	6	509	0	130	1.3%	3.37 [0.19, 60.20]	
Total (95%CI)		1104		926	100%	0.88 [0.63, 1.22]	
Total events	94		107				

Heterogeneity: $Tau^2 = 0.00$; $\chi^2 = 1.07$, df = 2 ($P = 0.59$); $I^2 = 0\%$
Test for overall effect: $Z = 0.79$ ($P = 0.43$)

Figure 5 Incidence of bradycardia[8,20,21].

significant risk factor for cardiopulmonary complications. Future prospective studies must be conducted to evaluate the cost effectiveness and safety of endoscopy with MAC in the OSA population.

COMMENTS

Background
Patients with obstructive sleep apnea (OSA) often receive monitored anesthesia care in lieu of conscious sedation due to a perceived elevated risk of complications. However, prior studies have failed to note any clinically significant variations in cardiopulmonary parameters in OSA patients when compared to controls during endoscopy but studies have been underpowered due to small sample sizes. The authors aim was to perform a systematic review and meta-analysis to assess the safety of conscious sedation in patients with obstructive sleep apnea (OSA).

Research frontiers
This meta-analysis has demonstrated that OSA does not appear to be a significant risk factor for cardiopulmonary complications in patients undergoing endoscopy. Future prospective studies are needed to look at both the safety and cost-effectiveness of endoscopy with MAC in the OSA population.

Innovations and breakthroughs
This meta-analysis showed OSA is not a significant risk factor for cardio-pulmonary complications in patients undergoing endoscopic procedures with conscious sedation, which has typically been the standard of care. These results further open the consideration of endoscopy without MAC in patients with OSA but future prospective studies are needed to look at both the safety and cost-effectiveness of endoscopy with MAC in the OSA population.

Applications
These findings can be considered by endoscopists when performing endoscopy with MAC in the OSA population in assessing their risk for procedural cardio-pulmonary complications.

Terminology
Conscious sedation - The use of a sedative during a medical procedure that allows for a quick recovery; OSA - A sleep disorder that causes breathing to start and stop during sleep due to airway obstruction during sleep; Endoscopy - A procedure which uses an endoscope, or a long flexible tube with a camera to examine the upper GI tract.

Peer-review
The author gave a systematic review and meta-analysis about the safety of gastrointestinal endoscopy with conscious sedation in patients with OSA. The manuscript was concise and helpful for us to be cognizant that OSA does not appear to be a clinically significant risk factor for adverse outcomes in patients undergoing endoscopy with conscious sedation.

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Efficacy of Prucalopride in bowel cleansing before colonoscopy: Results of a pilot study

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Abstract

Colonoscopy is a crucial diagnostic instrument for colorectal cancer screening and an adequate bowel preparation is definitely decisive for the success of the procedure. Especially in elderly patients, bowel cleansing is considered a big issue, because it is often poorly tolerated for many reasons (like inability to swallow large volume of liquids or unlikable taste); this can cause a suboptimal preparation that may lead to miss a neoplastic lesion. There is relatively little data about how to improve preparation tolerability. The purpose of our pilot study was to analyze the effect of prucalopride (Resolor®), a highly selective serotonin 5HT4 receptor agonist used for chronic constipation for its ability to stimulate gastrointestinal peristalsis, undertaken the day before colonoscopy, followed by half volume of polyethylene glycol solution. We found that this can be a good and safe method to achieve an adequate and better-tolerated colon cleansing.

Key words: Bowel cleansing; Colonoscopy; Prucalopride; Screening; Colorectal cancer

Core tip: Efficacy of bowel cleansing is of crucial importance in screening colonoscopies for the prevention and early detection of colorectal cancer. Many categories of patients however cannot tolerate the large volume of liquids that make up standard bowel cleansing regimens. Aim of our pilot study was to test the efficacy of prucalopride, a highly selective 5HT4 receptor agonist that increases bowel movements, in improving bowel cleansing and reducing the necessary volume of liquids.

Corleto VD, Antonelli G, Coluccio C, D'Alba L, di Giulio E. Efficacy of Prucalopride in bowel cleansing before colonoscopy: Results of a pilot study. *World J Gastrointest Endosc* 2017; 9(11): 558-560 Available from: URL: http://www.wjgnet.com/1948-5190/full/v9/i11/558.htm DOI: http://dx.doi.org/10.4253/wjge.v9.i11.558

| Semiliquid lunch | Prucalopride 2 mg | 1 It Peg Asc. solution | Colonoscopy |
| h 15:00 | h 18:00 | h 20:00 | h 9:00 |

Figure 1 Time scale of Prucalopride preparation scheme.

| Semiliquid lunch | 1 It Peg Asc. solution | 1 It Peg Asc. solution | Colonoscopy |
| h 15:00 | h 18:00 | h 20:00 | h 9:00 |

Figure 2 Time scale of standard preparation scheme.

Table 1 Demographic and anthropometric characteristics *n* (%)		
	Standard preparation (2 L PEG-ASC) (*n* = 30)	Prucalopride + 1 L PEG-ASC (*n* = 30)
Age median (range)	53 (46-67)	55 (48-64)
Sex	14 (47)	14 (47)
BMI median (range)	26.7 (18.4-32.8)	25.4 (17.3-31)
Boston scale ≥ 7	26 (87)	25 (83)
Boston scale ≤ 6	4 (13)	5 (17)
Exam indication		
Screening	18 (60)	16 (53)
Follow up	12 (40)	14 (47)
Adenoma detection rate (%)	32	29
Time to preparation (h) median (range)	11.30 (10.45-12.30)	11.45 (10.30-12.45)
Colonoscopy insertion time (min), median (range)	8.2 (3.3-36)	7.6 (3.1-47)

PEG: Polyethylene glycol; BMI: Body mass index.

TO THE EDITOR

Adequacy of preparation is one of the most important factors[1] in screening and early detection of colorectal cancer (CRC), which still has a high incidence and mortality. Poor colon cleansing however still affects as many as 20% of colonoscopies, increasing burden for patients and total costs of colon cancer screening programs[1,2]. Patient tolerability is strongly affected by the chosen preparation and manner in which it is administered. Many factors have been identified to influence bowel preparation such as unappealing taste of the solution or inability to swallow large volumes of liquids. There have been many efforts to improve bowel cleansing like smaller volume solutions, tablets consumed with water and split-dose regimens[3,4].

Prucalopride, a highly selective serotonin 5HT4 receptor agonist used for treatment of chronic constipation, stimulates gastrointestinal peristalsis and colon movements[5,6]. It is a generally well tolerated drug, contraindicated only in patients on dialysis or with bowel perforation or obstruction. The most common side effects are fatigue, appetite loss, diarrhea and headache at first dose administration[5,6]. In the present pilot study we tested the hypothesis that a previous dose of Prucalopride followed by a low volume of polyethylene glycol (PEG) solution, might achieve a satisfactory colon cleansing.

A total of 30 consecutive patients, 16F, 14M, mean age 55 years (48-62) (complete characteristics available in Table 1), all with regular bowel movements, after written informed consent, agreed to use the following preparation schedule: on the day before the examination, 3 h after a semi-liquid midday meal, 2 mg of Prucalopride, and later in the evening, 1 L of PEG-Asc. solution followed by the assumption of water or other clear liquids (> 1 L) (Figure 1). A control group of 30 patients with comparable characteristics followed the standard 2 L PEG-ASC. Preparation schedule (Figure 2). All patients underwent colonoscopy either for CRC screening or for periodical survey. All had four days of low fiber diet and all examinations were performed the following morning. The colonoscopies were performed by senior endoscopists who were unaware of the preparation schedule at the time of the examination. Twelve out of 14 patients of the Prucalopride group, who were undergoing colonoscopy for follow up of previous examinations, declared that the new preparation schedule was more acceptable compared to the standard one. Specifically, none of them reported nausea and/or retching during assumption of the PEG-ASC.

Colonoscopy was completed (caecal intubation) in all patients studied. Insertion time is reported in Table 1. The colon cleansing was rated good/optimal (Boston scale 7-9) in 26/30 (87%) and in 25/30 (83%) in study and controls group respectively. The adenoma detection rate (ADR) among the two groups was comparable (Table 1). Among patients receiving Prucalopride, two patients had mild headache in the following three hours after its administration. Among patients receiving standard dose, two patients reported nausea and one patient reported mild abdominal pain during assumption.

Our pilot study shows that previous Prucalopride administration followed by half dose PEG solution produced comparable colon cleansing quality than regular

standard dose. Faster intestinal transit with intestinal residuals removal stimulated by previous Prucalopride administration might explain why a reduced volume of preparation solution could achieve a satisfactory bowel cleansing. These results must be further investigated by a wider, prospective, randomized control trial that can confirm these preliminary findings and facilitate colon cleansing for those patients that are unable to drink large volumes of liquid.

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FLYLEAF

Retrospective Study

Gastric endoscopic submucosal dissection as a treatment for early neoplasia and for accurate staging of early cancers in a United Kingdom Caucasian population

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Author contributions: Ang Y designed the study, supervised the project, obtained the data and wrote the manuscript; Sooltangos A coordinated the study, obtained and analysed the data, and wrote the manuscript; McGrath S reviewed all pathology reports and contributed to data analysis; George R and Ang Y performed the ESD and analysed the data; Vickers J, Senapati S and Akhtar K performed surgery and analysed the data.

Informed consent statement: All the data used in this study have been anonymised.

Conflict-of-interest statement: None to declare.

Data sharing statement: All data are under the control of the gastroenterology team at Salford Royal NHS Foundation Trust.

Abstract

AIM

To investigate the efficacy of endoscopic submucosal dissection (ESD) at diagnosing and treating superficial neoplastic lesions of the stomach in a United Kingdom Caucasian population.

METHODS

Data of patients treated with or considered for ESD at

a tertiary referral center in the United Kingdom were retrieved for a period of 2 years (May 2015 to June 2017) from the electronic patient records of the hospital. Only Caucasian patients were included. Primary outcomes were curative resection (CR) and were defined as ESD resections with clear horizontal and vertical margin and an absence of lympho-vascular invasion, poor differentiation and submucosal involvement on histological evaluation of the resected specimen. Secondary end-points were reversal of dysplasia at 12 mo endoscopic follow-up and/or at the latest follow up. Change in histological diagnosis pre and post ESD was also analysed.

RESULTS
Twenty-four patients were initially identified with intention to treat. 19 patients were eligible after mapping gastroscopy and ESD was attempted on a total of 25 ESD lesions, 4 of which failed and had to be aborted mid-procedure. Out of 21 ESD performed, en-bloc resection was achieved in 71.4% of cases. Resection was considered complete on endoscopy in 90.5% of cases compared to only 38.1% on histology. A total of 6 resections were considered curative (28%), 5 non-curative (24%) and 10 indefinite for CR or non-CR (24%). ESD changed the histological diagnosis in 66.6% of cases post ESD. Endoscopic follow-up in the "indefinite" group and CR group showed that 50% and 80% of patients were clear of dysplasia at the latest follow-up respectively; 2 cases of recurrence were observed in the "indefinite" group. Survival rate for the entire cohort was 91.7%.

CONCLUSION
This study provides early evidence for the efficacy of ESD as a therapeutic and diagnostic intervention in Caucasian populations and supports its application in the United Kingdom.

Key words: Endoscopic resection; Endoscopic submucosal dissection; Endoscopic mucosal resection; Dysplasia; Early gastric cancer; United Kingdom

Core tip: Endoscopic submucosal dissection (ESD) is a minimally invasive technique used to diagnose or treat early neoplastic lesions of the gastrointestinal tract. Imported from Far East countries, where it is extensively used, this intervention has proven to be highly effective in carefully selected patients and to constitute a viable alternative to radical surgery. ESD is relatively new in the West and local evidence to support its use in the United Kingdom lacking. This retrospective study provides early evidence in favour of the use of ESD in the United Kingdom.

INTRODUCTION

Endoscopic resection (ER) is a minimally invasive technique aimed at staging or curing dysplastic lesions and intramucosal cancers of the gastrointestinal tract. ER includes endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), their respective application mainly depending on the size of the tumour[1]. EMR was the first endoscopic treatment proven to be as effective as gastrectomy at managing early gastric cancers, with curative rates as high as 85%[1]. However, in lesions larger than 20mm, ESD is preferred as it can achieve higher rates of en-bloc resections and consequently lower recurrence rates[1-7]. *En-bloc* resections almost constitute a prerequisite for accurate histological evaluation of the resected specimen.

ER is also considered the only definitive method of excluding invasion in otherwise precancerous lesions, where time and again, endoscopic biopsies and endoluminal ultrasound have proven inadequate[2,8,9]. ER can change the diagnosis in up to 40% of cases, more commonly resulting in an upstaging[10-12]. It provides vital information about the depth of invasion of the tumour and as the latter constitutes the strongest predictor of lymph node metastasis[13,14], it is used to guide subsequent management decisions, in particular the indication for surgery. When compared to surgery, ESD appears to have comparable oncologic outcomes with the advantage of shorter operation times, shorter hospital stays and lower complication rates[15].

Most evidence for the efficacy and safety of ESD comes from Eastern countries, where ESD has been shown to achieve curative resection (CR) rates as high as 97% in lesions that meet the Japanese Gastric Cancer Association (JGCA) guidelines[16-18]. Despite being a technically challenging procedure and carrying a high risk of adverse events in inexperienced hands[19], ESD is gradually gaining popularity in Western countries, partly facilitated by technological advancements[20]. However, evidence for ESD is still scarce in Western populations. One of the few studies carried out in Germany showed promising results with a high rate of en-bloc resections and remarkably low recurrence rates of 1.5%[21]. In the United Kingdom, the JGCA criteria guidelines are used to select lesions amenable to ESD. However, since the outcomes of ESD are heavily dependent on the level of skills of the endoscopist, more local studies are crucial[22,23]. The National Institute of Health and Care Excellence in the United Kingdom only take into account United Kingdom studies when formulating local clinical guidelines. No studies have considered the efficacy of gastric ESD in a United Kingdom Caucasian population

MATERIALS AND METHODS

This retrospective study is part of our service development and audit and aims to investigate the efficacy of ESD at treating early neoplastic lesions of the stomach in a Caucasian population at a tertiary referral centre in the United Kingdom and secondly, its application for staging early cancers.

Inclusion criteria: Data was obtained for a period of 2 years from May 2015 to June 2017. Only Caucasian patients with gastric cancers staged at or below T1a N0M0 on the basis of computed tomography (CT) scans (or Positron Emission Tomography-Computed Tomography (PET-CT) in a few cases) and Endoscopic Ultrasound (EUS) were included in this study.

Exclusion criteria: Patients with gastric cancers staged at T1bN0M0 or above were excluded from the study on the basis of CT scans (or PET-CT scans in a few cases) and EUS .

Mapping oesophagogastroduodenoscopy (mapping OGD, a pre-ESD check to evaluate if the case is suitable for ESD) was used to assess the macroscopic appearance of the lesions, the position and size, the presence of ulceration, any field changes and importantly whether the lesions were liftable. The degree of lift of each lesion was graded according to the Kato classification where Kato 1 denotes lifting without any resistance, Kato 2 lifting with some resistance and Kato 3 no lifting[24]. Endoscopic imaging enhancements used included White Light Imaging, Olympus Narrow Band Imaging (NBI) or Fuji Fluorescent Intelligent Chromoendoscopy, indigo carmine spray and acetic acid spray. Biopsies were taken prior to any intervention to assess or re-assess the type of neoplasia present and the degree of differentiation. Poor differentiation and non-lifting sign (Kato 3) precluded ESD except in one patient whose co-morbidities notably liver cirrhosis Child's Grade A made him unfit for surgery. Endoscopy reports, histology reports and multi-disciplinary team (MDT) meeting letters were retrieved from the electronic patient record of the hospital. The information about each patient's demographic data, pre-ESD endoscopic assessment, index procedure, follow-up endoscopy, surgery and outcome at the latest follow up were recorded. Microsoft Excel has been used to record all data and for all statistical analyses.

Olympus Double Channel Double-Headed Scope or Fuji Dual Channel Endoscope were used in all procedures and the procedures were jointly performed by two experienced interventional gastroenterologists. The ESD procedure was carried out in theatre (operating room) with the patient under general anaesthesia. The patient was intubated with the assistance of an anaesthetist and endoscopy performed using carbon dioxide gas only. The ESD equipment used for dissection included Olympus ITknife2 Electrosurgical Knife (KD-611L), Olympus ITknife nano Electrosurgical Knife (KD-612L/U), Fujifilm Flush Knife, Fujifilm Clutch Clutter and ERBE Hybrid O Knife. A soft transparent hood (D-201-13404; Olympus,

Tokyo, Japan) was attached to the tip of the endoscope to obtain good endoscopic views of the submucosal layer. In some cases, additional image enhancing techniques (as outlined above) had to be used. This was done through a 2-channel scope equipped with multibending and water jet functions attached to the tip of the endoscope. The lesions were lifted with EMR solution and marking dots were placed using argon on the normal mucosa at approximately 5 mm from the tumour margin to provide safety margins. EMR solution (consisting of a small amount of indigo carmine and 0.1% lidocaine) was then injected into the submucosal layer and a mucosal incision made outside the marking dots. In case of poor mucosal elevation due to ulceration of the lesion or extensive fibrosis of the submucosal layer, hyaluronic acid solution was added to the injection solution to achieve better lift. After mucosal incision, dissection of the submucosal layer was performed, thus achieving *en bloc* resection.

Each patient was given oral Omeprazole 40 mg, twice daily for at least 3 mo (or another equivalent proton pump inhibitor) after the procedure.

The resected specimen was cut into 4-mm-thick slices after formalin fixation. The histological type, size, depth of invasion, horizontal and vertical margins (HM and VM respectively), and lympho-vascular invasion were evaluated in each slice according to the JGCA Japanese Classification of Gastric Carcinoma criteria. To reconcile and allow for the efficacy of ESD to be more accurately investigated in Western populations, a more systematic approach to reporting histological findings such as the Vienna classification was also used[25]. The measure of efficacy in this study is CR. A resection is considered curative if it achieves clear vertical and horizontal margins and if histological evaluation of the resected specimen shows neither poor differentiation, nor lympho-vascular invasion nor submucosal involvement[3]. An ESD resection is coded as non-CR if it fails to meet all aforementioned criteria and as "indefinite" if data is inadequate to confirm either CR or non-CR. All resected lesions were coded as "complete resection on endoscopy" unless otherwise specified; a resection was considered to be "complete resection on histology" if the VM and the horizontal margin (HM) were clear on histology. The position of lesion was coded as Upper stomach if it was found in the cardia or fundus, as Mid stomach if in the body and as Lower stomach if in the antrum, pylorus or incisura. The age of the patient was at the time of the index procedure.

The secondary end-point was complete reversal of dysplasia at 12 mo endoscopic follow-up and/or at the latest follow-up and was investigated in the "indefinite" group and the CR group. The schedule for endoscopic surveillance for site check is 3 mo after the procedure and then 6 monthly for first year and then yearly thereafter, for 5 years. This outcome considers a patient as one entity, regardless of the number of ESD resections he/she may have had. The change in histological diagnosis pre and post ESD has also been recorded to assess the ability of ESD to influence diagnosis. The histological diagnosis is recorded as the worst histological

Figure 1 Prisma diagram showing how patients have been selected and their respective outcomes. CR: Curative resection.

grade reported for each lesion.

RESULTS

There were 24 patients with gastric dysplasia and/or neoplasia who were considered for endoscopic treatment using ESD. The demographic data of patients included in the study are shown in Table 1. Out of the 24 patients identified for the study, 19 were deemed suitable for ESD after mapping OGD. ESD was attempted on a total of 25 dysplastic or neoplastic lesions, among which 21 were completed and the patients then followed up or offered further treatment based on histology of the resected specimens, and 4 aborted (Figure 1). There were 5 patients who were found to be unsuitable for ESD after mapping OGD.

Pre-ESD endoscopic assessment
Most lesions were reported as Kato 1, one lesion

as Kato 2 and one as Kato 2 to 3. The mean size of lesions resected was 24.7 mm (standard deviation 11.7 mm; range 10-50 mm). Figure 2 shows a lesion suitable for ESD and the procedure in sequence. The main contraindicative features in lesions unsuitable for ESD were ulceration and poor differentiation. Poor lift, large size and deeper invasion constituted other contraindications (Table 2; Figure 2). In one patient, a severe oesophageal stricture prevented passage of the endoscope to assess the lesion. Features of the lesions deemed suitable for ESD are shown in Table 3.

Index procedure: Gastric endoscopic submucosal dissection
Of the 21 resections completed successfully, en-bloc resection was achieved in 71.4% of cases. Resection was considered complete on endoscopy in 90.5% of cases compared to only 38.1% on histology (Table 4). 6 achieved a definite CR (5 patients), 5 were confirmed to

Figure 2 Endoscopic appearance of the gastric lesions considered for resection with endoscopic submucosal dissection. A-E: Macroscopic appearance of lesion with mapping OGD and thus suitable for ESD. This is an area extending from the antrum through to the pyloric ring. The ESD procedure is highlighted here; F: Macroscopic appearance of lesion with suspected sm3 or deeper on mapping OGD and thus unsuitable for ESD. This is an area extending from the cardia through to the upper body. ESD: Endoscopic submucosal dissection.

Table 1 Demographic data of patients included in the study *n* (%)

Variable	Value, *n* = 24
Number of patients assessed for ESD, *n*	24
Age, Mean ± SD, yr	73.0 ± 10.7
Age, range, yr	44-86
Gender, male	20 (83.3)
Gender, female	4 (16.7)
Caucasian ethnicity	24 (100)

ESD: Endoscopic submucosal dissection.

Table 2 Features found to make endoscopic submucosal dissection unsuitable in 5 patients

Patient	Reasons
A	Ulcerated lesion
B	SM3 or deeper invasion; Poorly differentiated lesion
C	Large size: 4-5 cm; Ulcerated over 3 cm
D	Severe oesophageal stricture prevented passage of scope
E	KATO 3; Deeply ulcerated; Poorly differentiated

Table 3 Features of lesions on which endoscopic submucosal dissection has been attempted *n* (%)

Variable	Value, *n* = 25
Location of lesion	
Upper stomach	4 (16)
Mid stomach	7 (28)
Lower stomach	14 (56)
Average of longer axis of lesion (mm)	
Mean ± SD	24.7 ± 11.7
Range	10-50
Histological grade at baseline	
IMC	13 (52)
HGD	8 (32)
LGD	3 (12)
Invasive	1 (4)

LGD: Low grade dysplasia; HGD: High grade dysplasia; IMC: Intramucosal carcinoma.

be non-curative (4 patients) and 10 were indefinite (10 patients) (Figure 3). In the latter group, only 2 patients were considered potential candidates for surgery. The

Table 4 Results of endoscopic submucosal dissection *n* (%)

Variable	Value, *n* = 21
Average number of ESD per patient (including failed ESD)	1.3
Number of en-bloc resections	15 (71.4)
Number of pieces in which lesions were resected	
Mean ± SD	1.5 ± 1.4
Range	1-7
Unspecified but > 1	2
Rate of complete resection on endoscopy	19 (90.5)
Rate of complete resection on histology	8 (38.1)
Margins clear on histology of ESD specimen	
Both VM and HM	8 (38.1)
VM only	1 (4.8)
HM only	1 (4.8)
Neither VM nor HM	1 (4.8)
Not specified or difficult to interpret specimen due to coagulation effect/poor preservation of tissue	10 (47.6)

ESD: Endoscopic submucosal dissection.

Primary outcomes (CR rates)

CR 28%
Non-CR 24%
Indefinite 48%

Figure 3 Pie chart showing the rate of primary outcomes: CR (6), non-CR (5) or indefinite (10) when data is inadequate to definitively qualify a resection as CR or non-CR. CR: Curative resection; Non-CR: Non-curative resection.

Figure 4 The appearance of the stomach wall on endoscopic follow-up of the patient in which endoscopic submucosal dissection had to be aborted twice due to profuse bleeding. The patient had a high INR and was a poor candidate for ESD at baseline but co-morbidities precluded surgery in his case. Note the 2 metachronous malignant sessile polyps Paris 2a and the marked mucosal friability evident from bleeding. ESD: Endoscopic submucosal dissection.

rest were only offered endoscopic follow-up as complete resection had been achieved on endoscopy and no other poor prognostic features (*e.g.,* poor differentiation) were present. Adjuvant chemo or radio therapy were not given as patients initially selected for this study had no evidence of lymph node involvement or distant metastases on CT and/or PET-CT scans. The histological diagnoses of non-CR patients post ESD are shown in Table 5.

Complications are classified as acute (during the procedure), early (< 48 h after the procedure) or late (> 48 h after the procedure). The most common acute complication reported was oozing small blood vessels (6). In 4 of these cases, bleeding was mild and treated with argon, coagulation forceps or endo-clips. In the other 2, the procedure had to be aborted due to profuse bleeding. Both cases were in the same patient. The patient was on anti-coagulation for atrial fibrillation and had a normal INR after stopping warfarin for 5 d prior to ESD. The marked mucosal friability resulted in bleeding even on mild trauma from the water jet used during endoscopy (Figure 4). A further 2 cases also had

to be aborted, one due to the location of the lesion, which would have led to gastric outlet obstruction in due course and the other due to extensive scarring secondary to a previous ESD attempt. There was only one case of early complication involving vomiting within 24 h of the procedure. No cases of late complications were reported.

The median duration of the ESD procedures was found to be 120 min (with factors such as the size of the lesion, its location and tissue factors influencing the length of time required to complete the procedure).

Change in histological grade post endoscopic submucosal dissection

Gastric ESD changed the histological grade in 66.6% of the resected lesions (*n* = 21) (Figure 5), equally

Table 5 Histological grade of 5 non- curative resection

Patient	Histological grade at baseline	Histopathologic diagnosis on ESD specimen of non-CR
A	IMC	IMC with lympho-vascular invasion
A	IMC	Invasive adenocarcinoma; Lympho-vascular invasion
B	IMC	Invasive adenocarcinoma; Poorly differentiated; Diffuse (signet ring) type; Tumour extends into submucosa; Further de-differentiation noted at the invasive aspect
C	Highly suspicious of IMC	Adenocarcinoma with deep margin involvement; Moderately to poorly differentiation; Vascular invasion
D	Invasive adenocarcinoma	Invasive adenocarcinoma; Well differentiated; No lympho-vascular invasion

ESD: Endoscopic submucosal dissection; CR: Curative resection; IMC: Intramucosal carcinoma.

Table 6 Secondary outcome in the cohort' indefinite for curative resection or non- curative resection

Variable	Indefinite, *n* = 10	CR, *n* = 5
Number of patients under endoscopic follow-up, *n* (%)	9 (90)	5 (100)
Median follow-up, mo	2	3
Mean follow-up, mo	5.1	8.5
Range, mo	0-19	0-22
Length of time since ESD, mean ± SD, mo	13.3 ± 11.3	12.2 ± 11.1
Length of time since ESD, range, mo	2 - 38	0 - 26
Number of patients with metachronous or synchronous disease post ESD, *n*	2	0

ESD: Endoscopic submucosal dissection; CR: Curative resection.

downgrading and upgrading the histological diagnoses. Most resected specimens were found to have HGD (5) and IMC (5), compared to the higher proportion of IMC prior to ESD. In addition, as shown in Figure 6, lympho-vascular invasion and invasive cancer were observed in 5 cases compared to only one case pre ESD. Of these 5 cases, 1 resection was found to be completely clear of dysplasia and a further case indefinite for any dysplasia on histology, but with clear evidence of invasion in both cases. LGD was present in 4 cases. In all cases except one, the change in histological grade, if any, was by one stage.

Endoscopic follow-up

In the "indefinite" cohort of 10 patients, one declined further endoscopic follow-up and has been scheduled for a CT scan instead. In addition, 2 patients had not had any follow-up yet at the time of data collection. One passed away 1 mo after his last follow-up endoscopy (the cause of death is unrelated to his gastric diagnosis). The median follow-up period was 2 mo and the mean 5.1 mo for the "indefinite" cohort (Table 6). Complete reversal of dysplasia was observed in 10% and 50% of patients at 12-mo and the latest follow-up respectively in the "indefinite" cohort (Figure 7). Recurrence was observed in 2 patients - both had in fact been considered poor candidates for ESD at baseline due to multiple comorbidities. In the cohort considered to have achieved CR with ESD, 80% were found to be free of dysplasia at their latest endoscopic follow-up at a mean follow-up period of 6.8 mo (Figure 8). Hence, with both cohorts (CR and 'indefinite') combined, 9

Change in histological grade post ESD, *n* = 21

Figure 5 Pie chart showing how endoscopic submucosal dissection changed the histological grade of the resected lesions. Down: Downstaged; Up: Upstaged; ESD: Endoscopic submucosal dissection.

Figure 6 Column chart showing the difference between pre-ESD and post-ESD histological grade for all 16 resected lesions. LGD: Low grade dysplasia; HGD: High grade dysplasia; IMC: Intramucosal carcinoma; LV: Lympho-vascular invasion; ESD: Endoscopic submucosal dissection.

of the 11 patients (81.8%) who had had at least one endoscopic follow-up were found to be free of dysplasia on endoscopy at their latest follow-up at a mean follow-up period of 7.7 mo.

Surgery

Overall, 6 patients were considered for surgery after ESD. In the "indefinite" group, the 2 patients with

Secondary outcome for indefinite for CR or Non-CR, *n* = 10

Figure 7 Column chart showing secondary outcomes *i.e.* complete reversal of dysplasia at 12 mo endoscopic follow-up and/or at latest follow-up in the group indefinite for curative resection or non-curative resection post endoscopic submucosal dissection. CR: Curative resection.

Secondary outcome in CR group, *n* = 5

Figure 8 Column chart showing secondary outcomes *i.e.* complete reversal of dysplasia at 12 mo endoscopic follow-up and/or at latest follow-up in the group curative resection post endoscopic submucosal dissection. CR: Curative resection.

recurrence at follow-up were referred for surgery but neither was sufficiently fit to proceed. ESD was attempted again but failed in both patients. They were thus listed for endoscopic surveillance. Metachronous or recurrent polyps were observed at the latest follow-up for both patients at 11 and 19 mo respectively. In the group of 4 patients found to be non-CR, surgery was considered a treatment option in all of them but only one patient was sufficiently fit to proceed with gastrectomy. The rest of non-CR patients were offered either further ESD or endoscopic surveillance or palliative care.

Only 2 of the 5 patients considered unfit for ESD underwent surgery (Patients B and E; Table 2). Post-op staging were pT3N3MxR1 and pT1bN1MxR0 (moderate to poor differentiation) respectively.

Survival rate
One ESD patient died 4 mo after ESD. ESD on this patient was considered curative and endoscopic follow-up at 3 mo post ESD showed no macroscopic recurrence but biopsies could not be taken due to the patient's high INR. Cause of death is unrelated to his primary gastric diagnosis. Survival rate in ESD patients was 94.7% (18 out of 19 patients) at a mean follow-up period of 15 mo.

Another patient in the group found unsuitable for ESD died 5 mo after an attempted mapping OGD. The patient was suffering from a severe oesophageal stricture and was receiving parenteral nutrition. The overall survival rate in the entire cohort was thus 91.7% (22 out of 24 patients).
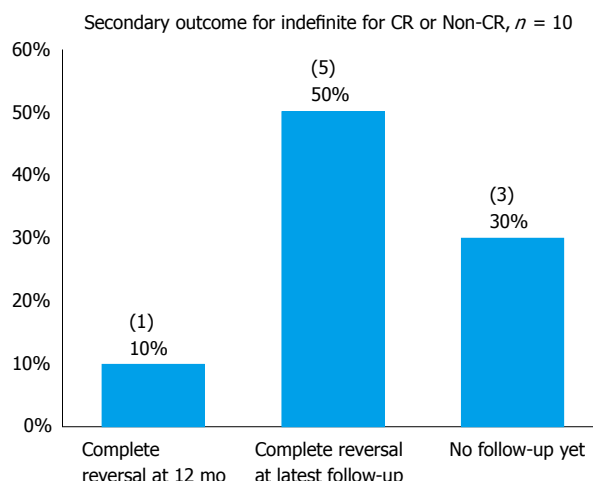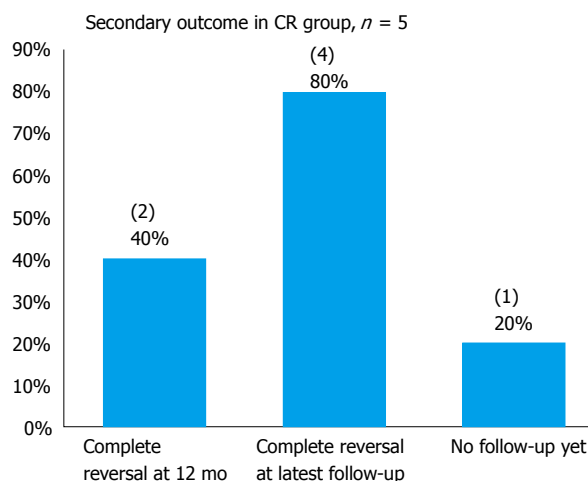
DISCUSSION
Despite the small sample size, the ability of ESD to achieve CR in carefully selected patients has been demonstrated. Approximately 28% of ESD resections (6) were considered curative. Moreover, 4 of the 5 CR

patients were free of dysplasia at the latest follow-up while the fifth patient had not had any follow-up yet, thus corroborating previous studies that demonstrated the positive long-term outcomes in patients with a CR, as defined by the JGCA criteria.

Positive long-term outcomes were also observed in a large proportion of the "indefinite" patients, despite the inability to confirm CR on histology. In the 2 patients who had recurrence of disease, histological evaluation of the ESD specimens had been particularly challenging due to marked inflammation in one case and very severe distortion of the tissue in the other. The specimen in fact reached the pathology laboratory outside formalin. Non-CR could therefore not be confidently excluded in these 2 patients and was in fact made more likely by a pre-ESD diagnosis of IMC. It was clear however on endoscopic follow-ups that these 2 patients had more advanced disease than suspected prior to ESD, as suggested by the presence of several metachronous and/or synchronous - polyps. Overall, despite the inability to always confirm CR on histology, gastric ESD has proven itself highly effective at clearing neoplastic growth if complete resection can be achieved on endoscopy. It also points to the importance of MDT discussions to avoid unnecessary surgery in patients indefinite for CR or non-CR.

The main reason for uncertainty regarding the completeness of excision on histology was the poor preservation of the resected specimens. In many instances, the specimen had been pinned down too deeply into the polystyrene board thus inflicting substantial trauma to the tissue. Other artefacts such as diathermy changes at the periphery, excision margins not clearly defined and inflammation also hindered accurate interpretation. In one case, the lesion had to be resected piecemeal. Other reasons included missing report and lack of mention of margin clearance. Hence, it is clear that to allow for the efficacy of ESD to be more accurately investigated in the future, ways

to satisfactorily preserve the resected specimen in its original state and implementing a more systematic approach to reporting histological findings are required.

This study also demonstrates the importance of careful selections of patients at baseline. Out of the 5 non-CR resections, 3 already contained poor prognostic features at baseline. However, the MDT consensus was to proceed with ESD given the patients' multiple co-morbidities that made them unfit for surgery. In one case, poor differentiation was seen prior to ESD while in the other two, invasive carcinoma had been identified. In the rest of non-CR cases, deeper invasion would have been left unnoticed had the lesion not been resected by ESD. ESD effectively identified lympho-vascular invasion in these 2 lesions presumed to be IMC only prior to ESD. This observation lends support to the status of ESD as the only definitive tool to exclude invasion. Moreover, ESD changed the histological grade in 66.6% of resected lesions. Unlike more large-scale studies however, ESD equally downgraded and upgraded histological diagnoses. In one exceptional case, the histological grade changed from IMC pre-ESD to clear of any dysplasia or malignancy post ESD. Further investigations into this case revealed observer bias in the interpretation of pre-ESD biopsy specimen at the patient's local hospital. ESD thus enabled the correct diagnosis to be made. This however points to a potential source of error in this study, *i.e.,* bias in interpretation of histology slides.

Only one patient underwent surgery after a non-CR ESD. Interestingly, in this patient, the ESD scar was still present on endoscopic follow-up after the surgery. Deep biopsies taken from this site were all found to be clear of dysplasia, even at the latest endoscopy performed 30 mo post ESD. In this patient, ESD had revealed a well-differentiated invasive adenocarcinoma without any lympho-vascular invasion. This "invasion" constituted the indication for surgery even though the exact depth of invasion was not reported. Hence, it may be possible that ESD patients are being unnecessarily referred for surgery and that ESD alone could be sufficient to treat more advanced diseases with the advantage of shorter hospital stays and fewer complications.

Some of the other limitations of this study include relatively short follow-up periods preventing more accurate assessment of the long-term outcomes and potential bias in letters and endoscopy reports. Hence we plan to study a larger number of patients and have a longer follow-up period in order to reduce bias and truly assess the efficacy of ESD in our Caucasian United Kingdom population.

In conclusion, these results although modest are promising and provide early evidence in favour of the use of ESD in Caucasian populations in the United Kingdom. Despite the wealth of evidence for the efficacy of gastric ESD in Far Eastern countries, the National Institute of Health and Care Excellence (NICE) United Kingdom still views upper GI ESD as a procedure to be applied on a case-by-case basis only with an MDT

approach[22], thus demonstrating the need for further, larger-scale studies into this technique in the United Kingdom and other Western countries.

ARTICLE HIGHLIGHTS

Research background
Endoscopic submucosal dissection (ESD) is a minimally invasive technique used to treat early superficial lesions of the gastrointestinal tract. It is popular in Far East countries where its outstanding efficacy has been proven by multiple studies. Technological advances have recently made ESD more accessible worldwide. In the United Kingdom, this intervention is still relatively new and local evidence to support its use still scarce.

Research motivation
This study aims to evaluate the application of ESD in Caucasian patients in the United Kingdom and seeks to compensate for the lack of evidence in the literature in favour of its use in this country. Larger scale studies will be required in the future.

Research objectives
This study constitutes a step forward in providing the evidence necessary to support the application of ESD among Caucasian patients in the United Kingdom as well as to help produce standardised clinical guidelines to inform local clinical practice for this relatively new intervention.

Research methods
This retrospective study uses data obtained from the Department of Gastro-enterology at Salford Royal NHS Foundation Trust in the United Kingdom, a tertiary centre for gastrointestinal interventions. Data for a period of 2 years has been analysed using Microsoft Excel.

Research results
Of the 21 lesions resected with ESD, 6 achieved curative resection (CR), 10 were "indefinite" for CR or non-CR, and 5 were considered non-CR. A favourable long-term outcome was observed in the CR and "indefinite" groups, with clearance of dysplasia observed overall in 81.8% of patients who had had at least one endoscopic follow-up. ESD also changed the histological diagnoses in 66.6% of cases. These results are promising and provide early evidence in favour of the use of ESD in the United Kingdom.

Research conclusions
ESD as applied to Caucasian patients in the United Kingdom can produce promising results as shown by this study. There have not been similar studies in the United Kingdom in the past and thus larger scale studies are required to fully evaluate the efficacy and safety profile of ESD as applied to upper gastrointestinal cancers.

Research perspectives
To better assess the effectiveness of ESD at clearing early neoplastic lesions of the stomach and other upper gastrointestinal cancers among Caucasian patients in the United Kingdom, a prospective study involving a larger sample of such patients is required.

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ORIGINAL ARTICLE

Observational Study

Lumen-apposing metal stents for benign gastrointestinal tract strictures: An international multicenter experience

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Abstract

AIM

To investigate technical feasibility, outcomes and adverse events of the lumen-apposing metal stent (LAMS) for benign gastrointestinal (GI) tract strictures.

METHODS

Between July 2015 and January 2017, patients under-going treatment by LAMS for benign GI strictures at

three tertiary referral centers were included in this study. Primary outcomes included technical success, short-term clinical success, long-term clinical success, and adverse events. Short-term clinical success was defined as symptom resolution at 30 d after stent placement. Long-term clinical success was defined by symptom resolution at 60 d in patients who continued to have indwelling stent, or continued symptom resolution at 30 d after elective stent removal.

RESULTS

A total of 21 patients (mean age 62.6 years, 47.6% males) underwent placement of LAMS for benign GI strictures. A 15 mm × 10 mm LAMS was placed in 16 patients, a 10 mm × 10 mm LAMS was placed in 2 patients, and a 16 mm × 30 mm LAMS was placed in 3 patients. Technical success was obtained in all cases. Short-term clinical success was achieved in 19 out of 21 cases (90.5%), and long-term clinical success was achieved in 12 out of 18 (66.7%). Mean (range) stent indwell time was 107.2 (28-370) d. After a mean (range) dwell time of 104.3 (28-306) d, 9 LAMSs were removed due to the following complications: ulceration at stent site (n = 1), angulation (n = 2), migration (n = 4) and stricture overgrowth (n = 2). Migration occurred in 4 cases (19.0%), and it was associated with stricture resolution in one case. Median (range) follow-up period was 119 (31-422) d.

CONCLUSION

Utilization of LAMS for benign strictures has shown to be technically feasible and safe, but adverse events highlight the need for further study of its indications.

Key words: Endoscopy; Stent; Gastrointestinal diseases; Stricture; Biomedical technology

Core tip: Treatment of benign short gastrointestinal (GI) tract strictures has primarily involved endoscopic balloon dilation, intralesional steroid injection and the conventional fully-covered metal stent. The lumen-apposing metal stent (LAMS), which has been used to drain pancreatic fluid collections, may serve as a more effective alternative. This study measures technical feasibility and potential short and long-term effectiveness of LAMS for benign GI strictures at three tertiary referral centers. Although results are promising, complications include angulation, stricture overgrowth and ulceration at stent site. These highlight the need for further study to better specify which patients should receive LAMS and how to minimize burden of complications.

INTRODUCTION

Benign etiologies of gastrointestinal (GI) strictures include ulcers, caustic ingestion, post-operative anastomotic states and inflammation[1]. The management of benign GI strictures has typically entailed endoscopic balloon dilation (EBD). However, EBD often does not provide definitive treatment and carries risks of bleeding and perforation[2,3]. Intralesional steroid injections may serve as an adjunct to endoscopic dilation that leads to increased efficacy of dilation and decreased number of total dilations[4]. Conventional fully-covered self expandable metal stent (cSEMS) has offered an alternative for therapy in cases that are refractory to EBD and steroid injections[5,6]. The cSEMS holds advantages over uncovered and partially-covered stents due to the relative ease of deployment and retrieval[7]. Furthermore, cSEMS may provide a gradual and continuous dilation of the stenotic segment. However, the use of cSEMS has demonstrated high rates of migration that may occur early in the period after stent placement, which may ultimately compromise long-term clinical success. Endoscopic suturing of cSEMS to tissue has been a recent advance that has mitigated this issue of migration[8], but this procedure is expensive and can be technically challenging[9].

Recently, lumen-apposing metal stents (LAMS) have become widely available for drainage of pancreatic fluid collections that exhibit lumen-apposing and dual anchoring capabilities[10]. These design features allow for robust pseudocyst drainage and the passage of an endoscope with a lower risk of stent migration due to anchoring. The AXIOS™ stents (Boston Scientific, Marlborough, United States) are 10 mm in saddle length, 10 mm or 15 mm in diameter, and with flanges that are 21 mm or 24 mm in diameter.

The NAGI™ stent (Taewoong Medical Co., Ltd., Ilsan, South Korea) is another type of LAMS that has been feasible in treating both pancreatic pseudocysts and walled-off necrosis. The presence of flared edges allows for its dual-anchoring capabilities, and the inclusion of a retrieval string also facilitates the removal of the stent. These LAMS are 10-30 mm in length, 10-16 mm in diameter, and contain flared edges 20 mm in diameter. Overall, the dimensions of the AXIOS™ and NAGI™ stents allow for potential use in treating short-length strictures that are less than or equal to 10 mm with a low risk of migration due to the anchoring flanges.

Prior studies have thus far supported LAMS as a potentially safe and effective measure to treat benign GI strictures (Table 1). Majumder *et al*[11] demonstrated that in a group of 5 patients, the placement of AXIOS™ stent led to successful resolution of symptoms with no stent-related adverse events during a median follow-up period of 120 d. Irani and colleagues found that in a

Table 1 Summary of prior studies on lumen-apposing metal stent for benign strictures *n* (%)

	Majumder *et al*[11] (2015)	Irani *et al*[12] (2016)	Yang *et al*[13] (2017)
Total cases	5	25	30
Age	47.4 (mean)	54 yr (median)	51.6 (mean)
Females	4 (80.0)	18 (72.0)	19 (63.3)
Underwent prior endoscopic dilation	3 (60.0)	20 (80.0)	27 (90.0)
Prior cSEMS	1 (20.0)	1 (4.0)	8 (29.6)
LAMS used			
AXIOS 15 mm × 10 mm	5 (100.0)	25 (100.0)	29 (96.7)
AXIOS 10 mm × 10 mm	0	3 (12.0)[1]	1 (3.3)
Technical success	Not described	25 (100)[2]	29 (96.7)[3]
Clinical success	Not described		
Short-term		15 (60)[4]	27 (90.0)[5]
Long-term			19 (82.6)[6]
Migration	0	2 (7.0)	2 (8.0)
Median stent dwell time (range)	Not described	92 d (3-273, median)	Not described
Median follow-up, d (range)	120 (84-140)	301 (62-681)	100 (60-139)

[1]Three patients initially had an AXIOS 10 mm × 10 mm placed, which was immediately upsized to 15 mm × 10 mm; [2]Technical success was defined as appropriate stent placement across the stricture verified endoscopically and fluoroscopically; [3]Technical success was defined as successful placement of the LAMS across the stricture; [4]Clinical success was defined as resolution of underlying symptoms for at least 6 mo after stent placement; [5]Short-term clinical success was defined as symptom improvement/resolution with indwelling stent; [6]Long-term clinical success was defined as symptom improvement/resolution after stent removal. LAMS: Lumen-apposing metal stent.

group of 25 patients with benign GI strictures refractory to standard therapies, the placement of AXIOS™ stent led to resolution of symptoms at 6 mo in 60.0% of cases[12]. Yang *et al*[13] demonstrated in a group of 30 patients, an indwelling AXIOS™ stent led to resolution of symptoms in 90.0% of cases, and 82.6% continued to have improved symptoms after LAMS removal. The data remains limited, and the prior studies solely involve the AXIOS™ stent. We describe the feasibility, safety and efficacy of treating benign GI strictures with two types of LAMS in an international multicenter setting.

MATERIALS AND METHODS

Between July 2015 and January 2017, patients who had undergone treatment by LAMS for benign GI strictures at three tertiary referral centers were identified. All cases were reviewed for demographic information, clinical presentation, initial diagnosis, anatomic location and prior endoscopic therapies. Inclusion criteria were patients with benign strictures that were not amenable to placement of cSEMS or had failed prior endoscopic therapies.

Primary outcomes evaluated included technical success, short-term clinical success, long-term clinical success, and adverse events. Technical success was defined by appropriate stent placement across the stricture verified endoscopically and fluoroscopically. Short-term clinical success was defined as symptom resolution at 30 d after stent placement, inclusive of patients with indwelling stents at day 30 and patients who had elective removal prior to day 30. Long-term clinical success was defined by symptom resolution at 60 d in patients who continued to have indwelling stent, or symptom resolution at 30 d after elective stent removal. Early complications were defined by adverse

events pertaining to the stent that occurred either at the time of placement or within 24 h after placement. Late complications were defined by adverse events pertaining to the stent that occurred after 24 h the stent was verified to be placed. Follow-up of stent placement took place *via* clinic visits, telephone calls, imaging studies and endoscopic surveillance appointments.

RESULTS

A total of 21 patients (mean age 62.6 years, 47.6% males) underwent placement of LAMS for benign GI strictures over the study period at the three centers (Table 2). Anatomic location of strictures included proximal esophagus (5, 23.8%), distal esophagus (4, 19.0%), stomach (6, 28.6%), duodenum (4, 19.0%), and colon (2, 9.5%). Etiology of GI strictures in this study included prior surgical anastomosis (10, 47.6%), prior surgical anastomosis and radiation therapy (4, 19.0%), caustic injury (3, 14.3%), peptic strictures (3, 14.3%) and chronic pancreatitis (1, 4.8%). Sixteen patients (76.2%) had at least one prior endoscopic therapy, which included EBD (*n* = 14), placement of cSEMS (*n* = 3), and stricturoplasty (*n* = 1).

In all cases, procedures were performed using a forward-viewing therapeutic endoscope. A standard guidewire was passed across the stricture under fluoroscopic guidance and contrast may have been utilized *via* injection to confirm stricture length. Upon the discretion of the endoscopist, the decision was made to use an AXIOS™ stent of 10 or 15 mm in diameter, or a NAGI™ stent measured at 16 mm × 30 mm (Figure 1). The LAMS were deployed under fluoroscopic and endoscopic guidance.

A 15 mm × 10 mm LAMS was placed in 16 patients, a 10 mm × 10 mm LAMS was placed in 2 patients,

Table 2 Demographics and stricture characteristics

	Proximal esophagus (*n* = 5)	Distal esophagus (*n* = 4)	Stomach (*n* = 6)	Duodenum (*n* =4)	Colon (*n* = 2)	Total (*n* = 21)
Age, mean (yr)	54	68.5	59	65.8	77	62.6
Gender						
Male	3 (60.0)	3 (75.0)	2 (33.3)	2 (50.0)		10 (47.6)
Female	2 (40.0)	1 (25.0)	4 (66.7)	2 (50.0)	2 (100.0)	11 (52.4)
Etiology						
Post-surgery/radiation	4 (80.0)	3 (75.0)	4 (66.7)	1 (25.0)	2 (100.0)	14 (65.2)
Peptic			1 (16.7)	2 (50.0)		3 (13.0)
Chronic pancreatitis				1 (25.0)		1 (4.3)
Caustic ingestion	1 (20.0)	1 (25.0)	1 (16.7)			3 (13.0)
Types of prior treatments						
Balloon dilatation						
1			1	1	1	3
2	4	2	2			8
3			1		1	2
> 3		1				1
Fully-covered stents	1	1		1		3
Prior migration	1	1		1		3
Stricturoplasty	1					1

Table 3 Results of lumen-apposing metal stent placement

	Proximal esophagus (*n* = 5)	Distal esophagus (*n* = 4)	Stomach (*n* = 6)	Duodenum (*n* =4)	Colon (*n* = 2)	Total (*n* = 21)
LAMS						
15 mm × 10 mm AXIOS	5 (100.0)	2 (50.0)	3 (50.0)	4 (100.0)	2 (100)	16 (76.2)
10 mm × 10 mm AXIOS			2 (33.3)			2 (9.5)
16 mm × 30 mm NAGI		2 (50.0)	1 (16.7)			3 (14.3)
Mean stent dwell time (d)	67.6	56.5	151.2	167.5	55.5	107.2
Technical success	5 (100.0)	4 (100.0)	6 (100.0)	4 (100.0)	2 (100)	21 (100.0)
Clinical success						11
Short-term	5 (100.0)	3 (75.0)	5 (83.3)	4 (100.0)	2 (100)	19 (90.5)
Long-term	1 (25.0)	2 (66.7)	5 (100.0)	3 (75.0)	1 (50.0)	212 (66.7)
Reasons for stent removal						
Angulation	1	1				2
Stent migration	1	1		2		4
Stricture overgrowth			2	1		2
Ulceration			1			1
Resolution	1			11		3
Treatments after stent failure						
Balloon dilation		2				2
cSEMS	1					1
15 mm × 10 mm AXIOS		1	1	1		3
16 mm × 30 mm NAGI	2	1				3

and a 16 mm × 30 mm NAGI stent was placed in 3 patients (Table 3). Technical success was obtained in 21 out of 21 cases (100.0%). Short-term clinical success was achieved in 19 out of 21 cases (90.5%) (Figure 2). Long-term clinical success was achieved in 12 out of 18 (66.7%). Three cases did not qualify for evaluation for long-term clinical success due to: Currently indwelling at a period of less than 60 d or a period of less than 30 d after already electively removed. Mean (range) dwell time of all cases was 107.2 (28-370) d.

There were no early adverse events in any of the cases such as bleeding or perforation. There were no serious delayed adverse events in any of the cases. However, after a mean (range) dwell time of 104.3 (28-306) d, 11 LAMS (52.4%) needed to be removed

due to the following complications: Ulceration at stent site (*n* = 1), angulation (*n* = 2), migration (*n* = 4), tissue overgrowth (*n* = 2), and stricture resolution (*n* = 3). Two patients with LAMS removal did not require further intervention. Overall, there were four cases (19.0%) that involved migration; in one of the cases, it was found that migration occurred likely due to resolution of the stricture. In the 8 cases in which the patients continued to be symptomatic after LAMS removal, the patients underwent repeat dilation, placement cSEMS or repeated placement of LAMS. Median (range) follow-up period was 119 (31-422) d.

Stent placement by site
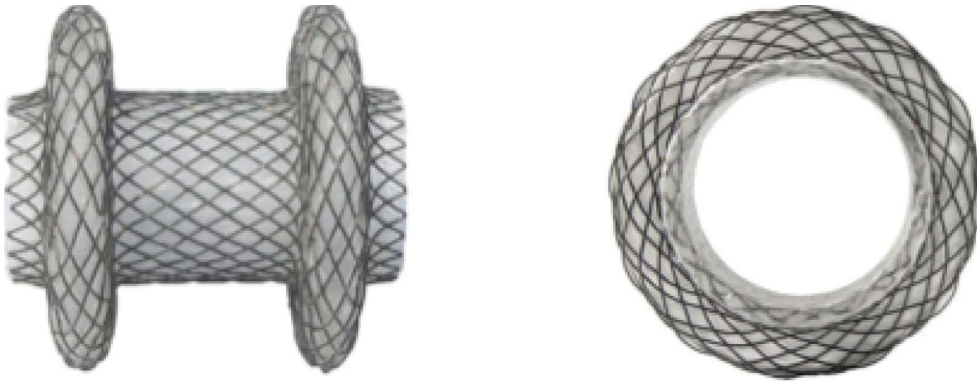Of the 5 proximal esophageal strictures, 4 (80.0%)

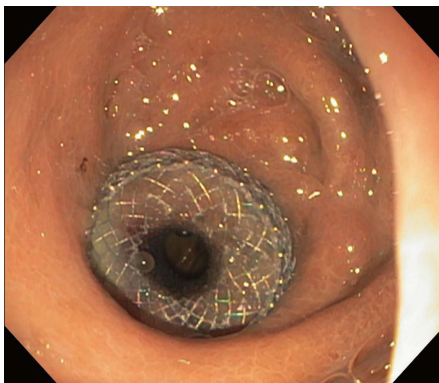Figure 1 AXIOS™ stent and delivery system.

Figure 2 AXIOS™ 15 mm × 10 mm stent across gastrojejunal anastomotic stricture.

Figure 3 Angulation of AXIOS™ 15 mm × 10 mm that was placed across a distal esophageal anastomotic stricture.

were due to prior surgical anastomosis and 1 (20.0%) was due to caustic ingestion. All five underwent prior treatments that included balloon dilatation and placement of cSEMS, which were complicated by recurrence and migration, respectively. All five underwent placement of 15 mm × 10 mm AXIOS™ LAMS. All five cases achieved technical success. All five cases (100.0%) achieved short-term clinical success. One case did not qualify for long-term clinical success evaluation because the patient had an indwelling LAMS less than 60 d. Only one of the remaining four (25%) cases achieved long-term clinical success. The first case that did not meet long-term clinical success involved removal of an AXIOS™ stent after indwell time of 90 d due to perceived resolution of stricture; however, it was found that the stricture had recurred. The second case that did not meet long-term clinical success involved an AXIOS™ stent that had distally migrated after 110 d. The third case that did not meet long-term clinical success involved an AXIOS™ stent that had angulation at stent site after 40 d, in which the lumen of the stent was abutting the oesophageal wall (Figure 3). This led to odynophagia and vomiting that necessitated removal of LAMS.

Of the 4 distal esophageal strictures, 3 (75%) were due to prior surgeries and 1 (25.0%) was due to caustic ingestion. Three (75%) underwent prior therapies

including balloon dilatation and placement of cSEMS, which were complicated by recurrence and migration, respectively. Two underwent placement of 15 mm × 10 mm AXIOS™ LAMS, and two underwent placement of 16 mm × 30 mm NAGI™ LAMS. All four cases achieved technical success. Three (75%) achieved short-term clinical success. The one case that did not achieve short-term clinical success was due to a NAGI™ stent that migrated prior to 30 d after stent placement, leading to recurrent symptoms and removal of the stent; thus, this case did not qualify for long-term success evaluation. Two out of the remaining three cases (67%) achieved long-term clinical success. The one case that did not achieve long-term clinical success was due to angulation of a 15 mm × 10 mm AXIOS™ LAMS at the stent site that occurred 45 d after stent placement, which led to vomiting and subsequent removal of the stent.

Of the 6 gastric strictures, 4 (67.7%) were due to prior surgery, 1 (16.7%) was due to caustic injury, and 1 (16.7%) was due to peptic ulcer. Three (67.7%) underwent prior therapy, which was balloon dilation that failed due to recurrence. Three underwent placement of 15 mm × 10 mm AXIOS™ LAMS, two underwent placement of 10 mm × 10 mm AXIOS™ LAMS, and one underwent placement of NAGI™ LAMS. All 6 stent placements achieved technical success. Five (83.3%) achieved short-term clinical success. One (16.7%)
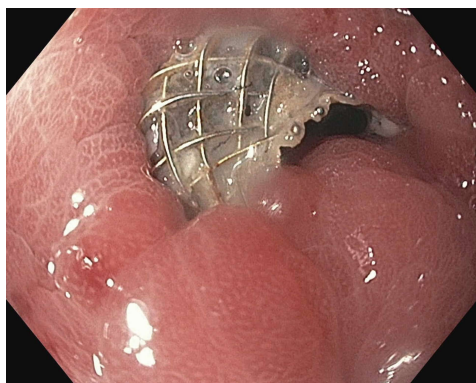
Figure 4 Stricture overgrowth of AXIOS™ 10 mm × 10 mm that was placed across a gastrogastric anastomotic stricture.

Figure 5 Stricture overgrowth of AXIOS™ 10 mm × 10 mm that was placed across a prepyloric stricture.

placement of 15 mm × 10 mm LAMS was complicated by an ulcer at 28 d, requiring removal of LAMS; thus, this case did not qualify for long-term clinical success evaluation. The remaining five cases achieved long-term clinical success. Of note, one case involved a patient that developed tissue overgrowth at the site of a 10 mm × 10 mm AXIOS™ stent placement across a gastrogastric anastomotic stricture after 306 d, which resolved with stricturoplasty (Figure 4). Another case involved a patient that developed tissue overgrowth at the site of a 10 mm × 10 mm AXIOS™ stent placement across a prepyloric anastomotic stricture after 183 d, which led to stent removal (Figure 5).

Of the 4 duodenal strictures, 2 (50%) were peptic ulcer disease, 1 (25%) was due to chronic pancreatitis, and 1 (25%) was an anastomotic stricture from prior Whipple procedure. Two (50%) underwent prior therapies including balloon dilatation and placement of cSEMS, which failed due to recurrence and migration, respectively. All four cases underwent placement of 15 mm × 10 mm AXIOS™ LAMS. All cases achieved technical success and short-term clinical success. Three (75%) cases achieved long-term clinical success. The one case that failed to achieve clinical success was due to proximal migration of AXIOS™ stent that occurred after an indwell time of 150 d, requiring the placement of another AXIOS™ stent. Of note, another case resulted in distal migration of AXIOS™ stent after 60 d. However, upon removal of this stent, the stricture was resolved and no further intervention was needed.

Of the 2 colonic strictures, both were due to prior surgical anastomosis. Both underwent prior treatments with balloon dilatation, which failed due to stricture recurrence. Both underwent placement of 15 mm × 10 mm AXIOS™ LAMS. Technical and clinical successes were obtained in both cases. One case (50%) involved elective removal after indwell time of 48 d due to resolution of the stricture, and patient has been asymptomatic since LAMS removal.

DISCUSSION

The management of benign GI strictures is often challenging due to the refractory nature of these strictures and failure of conventional therapy, EBD. In our study, the majority of patients who underwent LAMS for benign strictures received prior therapies that failed. Those who had prior EBD or stricturoplasty had developed stricture recurrence, and prior placement of cSEMS had led to migration. These complications are consistent with those that have been previously described[2,3,8]. A recent systematic review and meta-analysis on outcomes following stent placement in refractory benign esophageal strictures reported an overall stent migration rate of 28.6%[14]. In order to prevent the occurrence of migration associated with cSEMS, the utilization of stent suturing as a means of fixation has been described. The use of this external fixation method has been associated with lower migration rates[15]. However, stent suturing with cSEMS is also described to be associated with stricture overgrowth. Furthermore, stent suturing involves a more technically challenging approach for the endoscopist that may affect technical success and feasibility.

In our study, the decision was made to proceed with LAMS prior to considering surgical intervention. Although surgery may provide an opportunity to definitively treat benign strictures, rates of postoperative morbidity and mortality are significant[16-18]. Among the population predisposed to developing benign GI strictures, the risk of surgery is compounded by advanced age, poor nutritional status and other related comorbidities among these patients.

For strictures that are refractory to standard endoscopic therapies, we thus would recommend further consideration of endoscopic therapies, in which LAMS may serve as a feasible and safe alternative. Given the length parameters of LAMS, currently LAMS would be appropriate for benign, short strictures. Specifically, this would be for strictures < 10 mm in length for utilization of AXIOS™ LAMS and < 30 mm in length for utilization of NAGI™ LAMS.

In contrast to the conventional SEMS, LAMS imparts lumen apposition *via* its wide flanges and provides anchorage, hence potentially reducing the risk of stent migration. In our study, the migration rate for those

who underwent LAMS placement was 19.0% and this does appear to be higher than other studies on this topic. In the cases of LAMS migrating, the mean period of time before detected migration was 87.5 d, which appears to be a potentially longer period in comparison to the period associated with cSEMS migrating in our experience. Nonetheless, it is important to highlight that migration may occur with LAMS use, as this has not been a common observation in prior studies.

Overall, technical success was achieved in all cases without incidence of any immediate complications. Of note, all stents were placed by interventional endoscopists that were highly experienced in endoscopic stent placement. There were also no difficulties with evaluation of the stented area or removal of the stent. This supports the feasibility of endoscopic follow-up and surveillance in patients with indwelling LAMSs.

This study supports the high short term clinical success rate found in previous case series[12,13]. We chose 30 d after stent placement to be the measure of short term clinical success as recurrent strictures are defined as those unable to maintain a satisfactory luminal diameter for this length of time[19]. The long term clinical success rate in this series fell quite dramatically however largely due to complications occurring after 30 d. The rate of complications in this study that prevented short or long-term clinical success was high relative to other studies at 38.0%[12,13]. Furthermore, we noted complications not mentioned in the literature previously. In addition to migration, we found angulation to be a potential complication, at a rate of 9.5%. This involved the stent lumen/axis of the LAMS being misaligned within the luminal GI tract. Due to the stent lumen facing the luminal walls, patients developed foreign body sensation and obstructive symptoms. In these cases, this likely occurred due to the short length of LAMS coupled with the angled nature of these particular anastomotic strictures. Therefore, assessment of the stricture angle in relation to adjacent lumen may be an important factor when considering LAMS as a potential therapeutic option. Stricture overgrowth was also encountered in this study as a late complication. In our study, there were two cases of tissue overgrowth leading to stent dysfunction. Of note, one case had the stent placed for 183 d and the other 306 d. In one case, stricturoplasty of the tissue overgrowth with needle knife was successful in recanalizing the stent. In another case, the stent was removed and the stricture has since remained patent. The duration of stent dwell time of these cases was much longer than the mean dwell time of this series which might indicate that a scheduled assessment of the LAMS should occur at a specified duration after placement, possibly 180 d, to ensure tissue overgrowth is not occurring.

Limitations of this study include its retrospective nature with lack of a control arm, lack of symptom severity score, and no standardized method of managing complications. Given the lower volume of benign refractory GI strictures relative to other GI pathological processes, it would be difficult to have a robust control arm for analysis. The utilization of a symptom severity score may have also allowed for ability to better categorize the treatment effect. This data would potentially add clinical significance to our evaluation of LAMS, as we would not only categorize how many patients benefited, but also to the extent of symptom improvement. Lastly, the cases took place in 3 different tertiary care centers with no standardized algorithm of stent management. As a result, decisions of clinical and endoscopic follow-up as well as decisions regarding management of stent related complications were made at the endoscopists' discretion and best judgment.

In conclusion, we found that the utilization of LAMS is technically feasible and safe as a primary or salvage therapy for benign GI strictures with a high short term clinical success rate. However, late complications related to stricture overgrowth, stent migration, and angulation prevented a sustained symptom-free period in a large proportion of cases. These adverse events highlight the need for further study in this area to better understand which patients and which strictures are most optimal for management with LAMS prior to widespread adoption of this technique for the treatment of benign GI strictures.

COMMENTS

Background
Treatment of benign short gastrointestinal (GI) tract strictures has primarily involved endoscopic balloon dilation, intralesional steroid injection and the conventional fully-covered metal stent. The lumen-apposing metal stent (LAMS) exhibit lumen-apposing and dual anchoring capabilities. While it has primarily been used to drain pancreatic fluid collections, LAMS may serve as a more effective alternative to standard endoscopic therapies for benign strictures.

Research frontiers
Currently, there are two recent retrospective studies in the literature that describe use of LAMS for benign strictures. Irani and colleagues found that in a group of 25 patients, the placement of AXIOS™ stent led to resolution of symptoms at 6 mo in 60.0% of cases. Yang and colleagues found that in a group of 30 patients, the placement AXIOS™ stent led to resolution of symptoms in 90.0% of cases, and 82.6% continued to have improved symptoms after LAMS removal. The migration rates in the Irani *et al* and Yang *et al* are 7.0% and 8.0%, respectively. Currently there have been no prospective studies using LAMS and this may be worthwhile in the future to truly determine the ideal clinical scenarios when LAMS should be used.

Innovations and breakthroughs
In the authors' group of 21 cases, short-term clinical success was achieved in 90.5% of cases, and long-term clinical success was achieved 66.7% of cases. We also report the outcomes of 16 mm × 30 mm NAGI™ stent that was successfully placed in 3 cases. The migration rate for those who underwent LAMS placement was 19.0%, which appears to be higher than other studies on this topic. Furthermore, in contrast to prior reports, the authors found complications of LAMS placement not described in prior reports. These primarily include angulation and stricture overgrowth, which played significant roles in preventing clinical success in the cases.

Applications
The authors found that the utilization of LAMS is technically feasible and safe as a primary or salvage therapy for benign GI strictures with a high short-term clinical success rate. However, the adverse events as described above highlight the need for further study in this area to better understand which patients and

which strictures are most optimal for management with LAMS. Uncovering this information will contribute towards the potential widespread adoption of this technique for the treatment of benign GI strictures.

Terminology
Covered self-expandable metal stent: This stent has been widely used in malignant obstruction. The presence of a covering membrane allows the lumen to remain patent despite structured tissue overgrowth. Furthermore, it prevents the metal wires from burrowing into the wall, which allows for easier retrieval; LAMS: This newer stent has been widely used for drainage of pancreatic fluid collections. It exhibits lumen-apposing and dual anchoring capabilities. The anchoring flanges are thought to lower the risk of stent migration.

Peer-review
An International Multicenter study that is clinically meaningful. It is a retrospective analysis of LAMS placement in three tertiary care hospitals that add value to the knowledge of benign stricture treatment.

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Retroperitoneal epithelioid sarcoma: A case report

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Abstract

Epithelioid sarcoma (ES), a mesenchymatous malign neoformation, is often diagnosed in later stages and associated with high recurrence index, metastasis and mortality. We report a case of a 65 years old male, with history of abdominal pain and upper gastrointestinal bleeding. Endoscopy demonstrated a posterior duodenal wall perforation communicating with a solid retroperitoneal neoformation. Endoscopic biopsy was performed, with a final report of ES. The patient was submitted for surgical palliation due to the tumor's unresectability. Retroperitoneal ES is an extremely rare condition with limited reports in the literature where guidelines for its optimal treatment are not well established.

Key words: Epithelioid sarcoma; Retroperitoneal; Mesenchymatous neoformation; Duodenal perforation; Endoscopy

Core tip: Epithelioid sarcoma (ES) is a rare malign neoformation, often diagnosed in later stages and associated with high recurrence index and mortality. We report a case of a 65 years old male with a posterior duodenal wall perforation found during endoscopy, communicating with a solid retroperitoneal neoformation. Endoscopic biopsies were sufficient for the diagnosis. Retroperitoneal ES is an extremely rare condition with limited reports, where guidelines for its optimal treatment are not well established.

Coronado JA, Chávez MA, Manrique MA, Cerna J, Trejo AL. Retroperitoneal epithelioid sarcoma: A case report. *World J*

INTRODUCTION

Epithelioid sarcoma (ES) was originally described in 1970 by Enzinger[1]. It is a rare malignant mesenchymatous tumor more frequently found in young patients from 23 to 40 years old; however with a range of presentation between 4 and 90 years of age[2]. Due to its diverse clinical scenario, diagnosis is generally delayed. Usually divided in proximal and distal presentation, with predominant topography on distal zones such as upper extremities, mainly fingers, hands and wrists[3]. The distal form is composed of spindle to polygonal epithelioid cells arranged in nodules with central necrosis. The proximal form was described in 1997, arising in the deep part of the pelvis, perineum and genital tract. It presents large epithelioid carcinoma-like cells and has a more aggressive clinical course than the distal presentation[4].

Microscopic appearance of ES ranges from spindle cells to large polygonal cells with an acidophilic cyto-plasm[5]. Diagnosis can be confirmed with immuno-chemical staining positive for epithelial markers such as cytokeratin and epithelial membrane antigen, a mesenchymatous marker (vimentin) and CD34[6]. Finally, in some small series cytogenetic analysis has been performed, finding genetic alterations at the long arm of chromosome 22[7].

ES is distinguished by its high recurrence rate, with local recurrences reported in up to 77%, and an elevated percentage of node and lung metastasis (36%-44%)[8]. Five year, and 10-year survival are 65.3% and from 25% to 50% respectively[6]. However, the mean time from recurrence to death in patients older than 36 years stands at 5.6 ± 4.5 mo and in younger patients at 15.2 ± 17.2 mo[3]. Furthermore, the specific treatment for this pathology has not been established by international consensus; where a distal type ES tends to avoid amputation, a local recurrence is treated with local excision plus radiotherapy[7]. But, in tumors with unfavorable factors such as, proximal type or size greater than 5 cm, a systemic treatment plus surgical intervention should be evaluated[9].

CASE REPORT

A 65 years old Hispanic male with a remarkable medical history, presented with a one month history of right upper quadrant abdominal pain and upper gastrointestinal bleeding characterized by intermittent melena. Episodes of fever were also reported. Physical examination revealed a palpable right upper quadrant abdominal mass extending up to 4 cm below the costal margin. CT scan reported an infiltrative lesion in duodenum and

Figure 1 Abdominal radiography showing right upper quadrant mass enlargement.
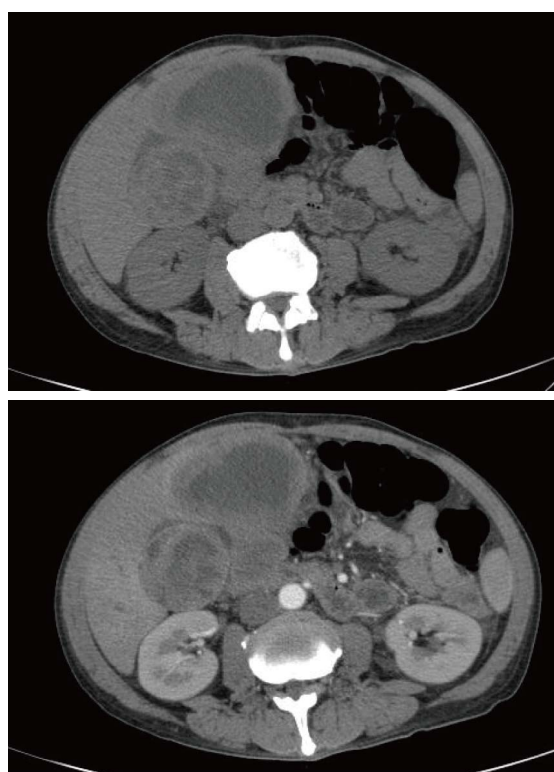

Figure 2 Computed tomography scan (simple and arterial phase) with infiltrative lesion at duodenum and gallbladder.

gallbladder affecting the splenic, hepatic and mesenteric vascularity (Figures 1 and 2). Endoscopy was performed finding a 2 cm opening from the posterior duodenal wall communicating with a solid retroperitoneal mass, irregular, indurated and extremely friable measuring more than 10 cm in diameter (Figure 3).

The patient was treated with palliative surgery, performing a gastro-jejunal anastomosis, with a postoperative report of retroperitoneal tumor invading duodenum and gallbladder. Final histopathological report stated the presence of retroperitoneal ES positive for cytokeratin and vimentin (Figure 4). Lastly, the patient was deceased two weeks after the initial diagnosis.
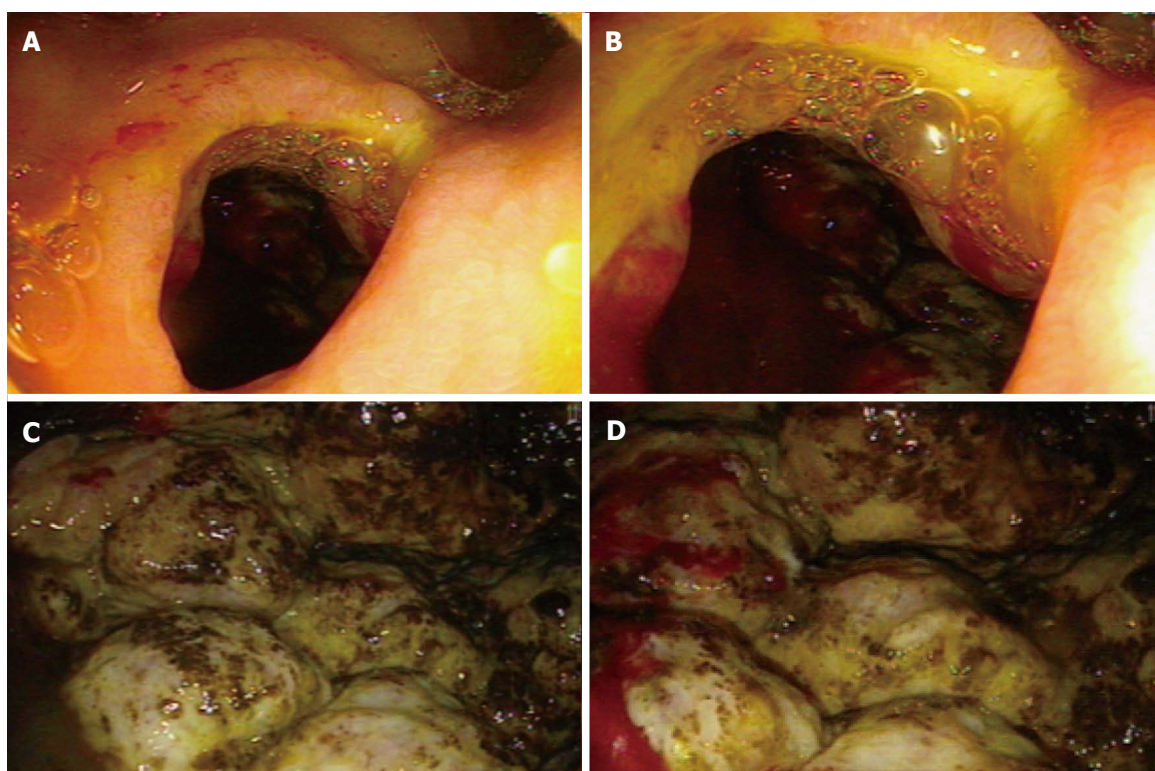
Figure 3 Duodenal posterior wall perforation (A and B), retroperitoneal solid and irregular neoplasia (C), extreme friability and spontaneous bleeding (D).

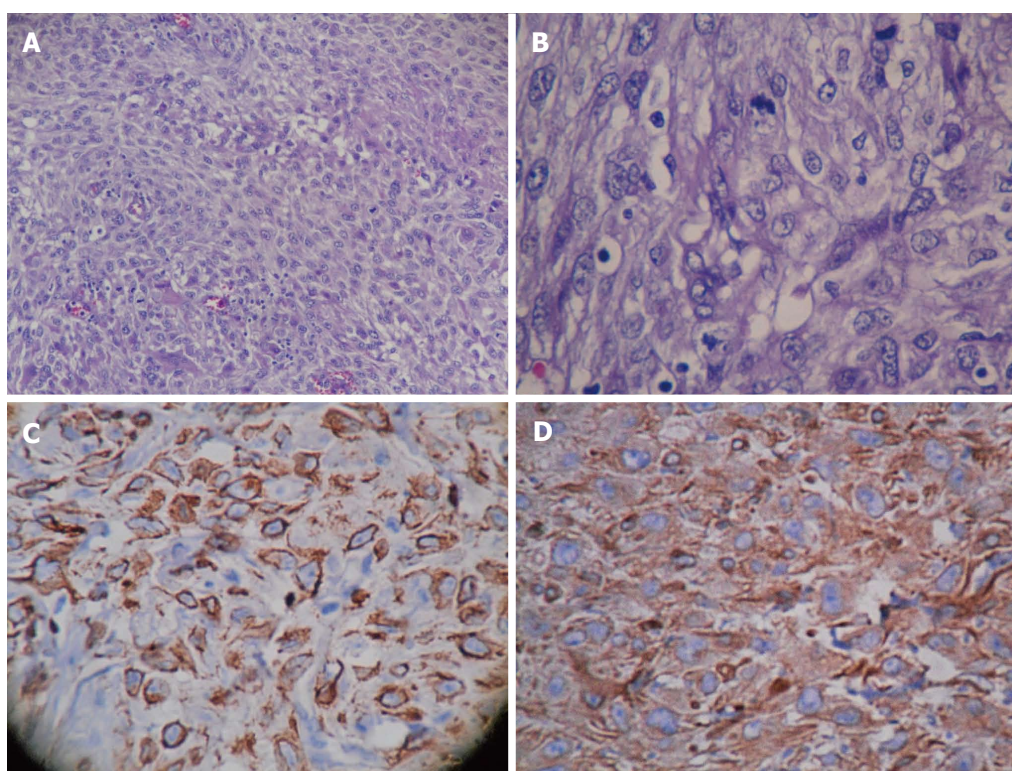**Figure 4 H and E with fusiform and giant pleomorphic cells, increased mitosis (A and B), positive staining for vimentin and cytokeratin respectively (C and D).**

DISCUSSION

ES is a soft tissue malignant entity with a high recurrence rate and mortality. Thus, the importance of reporting this case in order to increase awareness of this rare disease; since it seems only an early diagnosis with

definite surgical treatment can improve prognosis. In this particular case, endoscopy was helpful as the duodenal perforation allowed direct examination and prompt biopsy samples from the lesion. However, urgent surgical consultation was needed once the bowel perforation was found. In conclusion, ES is an infrequent variant of malignant sarcoma, with a very aggressive behavior, and which will only benefit with a prompt diagnosis and intensive multidisciplinary treatment.

COMMENTS

Case characteristics
A 65 years old Hispanic male with right upper quadrant abdominal pain and upper gastrointestinal bleeding characterized by intermittent melena.

Clinical diagnosis
Palpable right upper quadrant abdominal mass extending up to 4 cm below the costal margin.

Differential diagnosis
Primary neoplasm arising from a retroperitoneal structure (pancreas, adrenal glands, kidneys and duodenum), lymphoma.

Laboratory diagnosis
All labs were within normal limits except for chronic moderate anemia.

Imaging diagnosis
CT scan showed an infiltrative lesion in duodenum and gallbladder affecting the splenic, hepatic and mesenteric vascularity.

Endoscopy
Endoscopy showed a 2 cm opening from the posterior duodenal wall communicating with a solid retroperitoneal mass, irregular, indurated and extremely friable measuring more than 10 cm in diameter.

Pathological diagnosis
Retroperitoneal epithelioid sarcoma (ES) positive for cytokeratin and vimentin.

Treatment
Palliative surgery, a gastro-jejunal anastomosis.

Related reports
Epitheliod sarcoma is a malign entity with distal and proximal forms. The proximal form arising in the deep part of the pelvis, perineum and genital tract or retroperitoneum has been very rarely reported.

Term explanation
ES is a rare malignant mesenchymatous tumor more frequently found in young patients from 23 to 40 years old. Usually divided in proximal and distal presentation, with predominant topography on distal zones such as upper extremities, mainly fingers, hands and wrists. The proximal form originates in the deep part of the pelvis, perineum and genital tract. It presents large epithelioid carcinoma-like cells and has a more aggressive clinical course than the distal presentation.

Experiences and lessons
Retroperitonal ES is an extremely rare pathology, the duodenal perforation allowed the passage of a videoendoscope providing a very unusual and direct endoscopic view of the neoformation.

Peer-review
The authors describe a rare and an interesting case of ES.

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CASE REPORT

Endoscopic ultrasound-guided fine-needle aspiration for diagnosing a rare extraluminal duodenal gastrointestinal tumor

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Author contributions: Hayashi K and Kamimura K wrote the manuscript; Hosaka K, Ikarashi S, Kohisa J, Takahashi K, Tominaga K, Mizuno K, Hashimoto S, Yokoyama J, Yamagiwa S, Terai S, Takizawa K and Wakai T diagnosed and treated the patient; Umezu H performed histological analysis; all authors read and approved the final version of the manuscript.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Board of Niigata University.

Informed consent statement: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Conflict-of-interest statement: The authors declare that they have no current financial arrangement or affiliation with any organization that may have a direct influence on their work.

Abstract

Duodenal gastrointestinal stromal tumors (GISTs) are extremely rare disease entities, and the extraluminal type is difficult to diagnose. These tumors have been misdiagnosed as pancreatic tumors; hence, pancreaticoduodenectomy has been performed, although partial duodenectomy can be

performed if accurately diagnosed. Developing a diagnostic methodology including endoscopic ultrasonography (EUS) and fine-needle aspiration (FNA) has allowed us to diagnose the tumor directly through the duodenum. Here, we present a case of a 50-year-old woman with a 27-mm diameter tumor in the pancreatic uncus on computed tomography scan. EUS showed a well-defined hypoechoic mass in the pancreatic uncus that connected to the duodenal proper muscular layer and was followed by endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA). Histological examination showed spindle-shaped tumor cells positively stained for *c-kit*. Based on these findings, the tumor was finally diagnosed as a duodenal GIST of the extraluminal type, and the patient underwent successful mass resection with partial resection of the duodenum. This case suggests that EUS and EUS-FNA are effective for diagnosing the extraluminal type of duodenal GISTs, which is difficult to differentiate from pancreatic head tumor, and for performing the correct surgical procedure.

Key words: Gastrointestinal stromal tumor; Duodenum; Extraluminal type; Pancreatic head tumor; Endoscopic ultrasonography; Endoscopic ultrasound-guided fine-needle aspiration; Partial resection

Core tip: Duodenal gastrointestinal stromal tumors are extremely rare disease entities, and the extraluminal type is difficult to diagnose. Therefore, these tumors have been misdiagnosed as pancreatic tumors; hence, pancreaticoduodenectomy has been performed, although partial duodenectomy can be performed if accurately diagnosed. Recent advances in developing endoscopic ultrasonography and endoscopic ultrasound-guided fine-needle aspiration are helpful for accurate diagnosis of the tumors located in the area and effective for performing the correct surgical procedure.

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are a group of mesenchymal tumors in the gastrointestinal tract that arise from the interstitial cells of Cajal[1]. These tumors contribute to about 1%-3% of all gastrointestinal malignancies and are frequently found in the stomach (60%-70%). Duodenal GISTs are very rare, with 5% rate of occurrence[2]. They are thought to be caused by

a mutation in the *c-kit* gene and alpha-type platelet-derived growth factor receptor gene in the intestinal cells of Cajal or their precursors[3]. Due to its rarity and the complex anatomy of the pancreaticoduodenal region, it is extremely difficult to differentially diagnose duodenal GISTs from pancreatic tumors, especially when it is extraluminal. Because misdiagnosis may lead to an inaccurate choice of surgical procedure, we report our case of extraluminal-type duodenal GISTs correctly diagnosed with endoscopic ultrasonography (EUS) and EUS-guided fine-needle aspiration (EUS-FNA) followed by successful resection of the tumor. To date, the usefulness of these modalities in diagnosing the tumor has not been reported. This case suggests that EUS and EUS-FNA are effective for diagnosing extraluminal type of duodenal GISTs and for performing the correct surgical procedure.

CASE REPORT

A 50-year-old Japanese woman was found to have a pancreatic head tumor by abdominal ultrasonography on a health checkup and was referred to our hospital for further examination. She was in good physical condition, no evidence of melena, and had no remarkable history. The results of her initial physical examination were as follows: Body temperature, 37.0 ℃ blood pressure, 127/78 mmHg; pulse rate, 74 bpm, regular; a flat and soft abdomen without pain or tenderness; and no palpable masses.

Blood tests performed on admission revealed a slight elevated inflammatory response with a white blood cell count of 11370/μL and C-reactive protein level of 0.33 mg/dL. Other laboratory findings were normal including a red blood cell count of 326×10^4/μL and hemoglobin of 13.7 g/dL, indicating no existence of anemia. Tumor markers including carbohydrate antigen 19-9, carcinoembryonic antigen, DUPAN, SPan-1, and soluble interleukin-2 receptor levels were within normal limits.

An abdominal dynamic contrast-enhanced computed tomography (CT) showed a 27-mm diameter tumor in the pancreatic uncus, which was well defined and enhanced starting from the arterial to the venous phase, exhibiting the greatest enhancement in the arterial phase (Figure 1). Magnetic resonance imaging revealed the mass to be hypointense on T1-weighed imaging and slightly hyperintense on T2-weighed imaging. The contrast enhancement study showed a similar pattern on CT suggesting the diagnosis of duodenal GIST or pancreatic head neuroendocrine tumor (NET). Therefore, endoscopic examination was performed for the further diagnosis.

Upper gastroendoscopy showed a slightly elevated lesion located in the inferior angle of the duodenum with normal overlying mucosa detected on upper gastrointestinal endoscopy (Figure 2). EUS showed a well-defined hypoechoic mass placed close to the
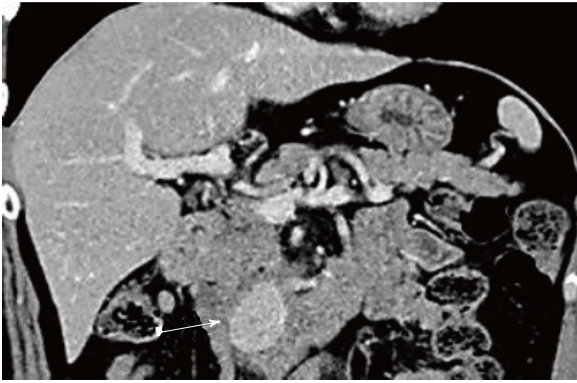
Figure 1 Abdominal dynamic contrast-enhanced computed tomography showed a 27-mm diameter tumor in the pancreatic uncus, which was well defined and enhanced from the arterial phase, exhibiting the greatest enhancement in the arterial phase. White arrow indicates the tumor.
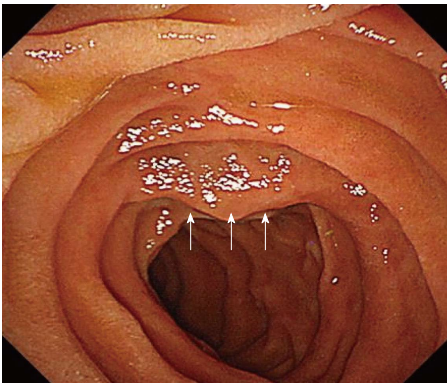

Figure 2 A slightly elevated lesion located in the inferior angle of the duodenum with normal overlying mucosa was detected on upper gastrointestinal endoscopy. White arrows indicate the elevation.

Figure 3 Endoscopic ultrasonography showed a well-defined hypoechoic mass in the pancreatic uncus, and the tumor connected with the muscularis propria layer of the duodenum. Black arrow indicates the tumor and white arrow indicates the muscularis propria layer.

Figure 4 Histological analysis of specimen collected by endoscopic ultrasound-guided fine-needle aspiration. A: Hematoxylin and eosin staining revealed that the tumor was mainly composed of spindle-shaped cells; B: The tumor cells were positive for *c-kit*.

pancreatic uncus; however, the tumor was clearly revealed to be connected to the muscularis propria layer of the duodenum (Figure 3). Based on the EUS findings, duodenal GIST or pancreatic NET was suspected and EUS-FNA was performed for a definitive diagnosis. Histological examination revealed that the tumor was mainly composed of spindle-shaped cells (Figure 4). Immunohistochemistry (IHC) showed that the tumor cells were positive for c-kit, CD34, and S-100, but negative for desmin (Figure 4). Based on these results, the tumor was diagnosed as the extraluminal type of duodenal GIST.

The patient underwent mass resection of the tumor with partial resection of the second part of the duodenum. The tumor showed extraluminal growth and protruded into the pancreas but did not infiltrate the pancreatic parenchyma, consistent with the EUS findings. In addition, there was no ascites and no peritoneal dissemination.

Histopathology of the resected tumor showed a mesenchymal, sharply margined tumor of 30 mm × 22 mm × 22 mm size, consisting of spindle cells without necrosis. Mitosis was detected in 2/50 high-power fields

(HPFs). The tumor cells were positive for c-kit, and MIB-1 labeling index (Ki-67 stain) was < 1% (Figure 5).

No postoperative recurrence has been observed to date, and the patient did not require adjuvant chemotherapy for 2 years.

DISCUSSION

GISTs are the most common mesenchymal tumors in the gastrointestinal tract, contributing about 1%-3% of all gastrointestinal malignancies[1]. GISTs develop most

Figure 5 Histological analysis of resected tumor tissue. A: Macroscopic finding showed 30 mm × 22 mm × 22 mm sized tumor showing extraluminal growth from duodenum (black arrow); B: Hematoxylin and eosin-stained sections showed that the tumor was mainly composed of spindle-shaped cells without necrosis; C: The tumor cells appeared immunohistochemically positive for *c-kit*; D: Mitosis was detected in 2/50 high-power fields, and MIB-1 labeling index (Ki-67 stain) was < 1%.

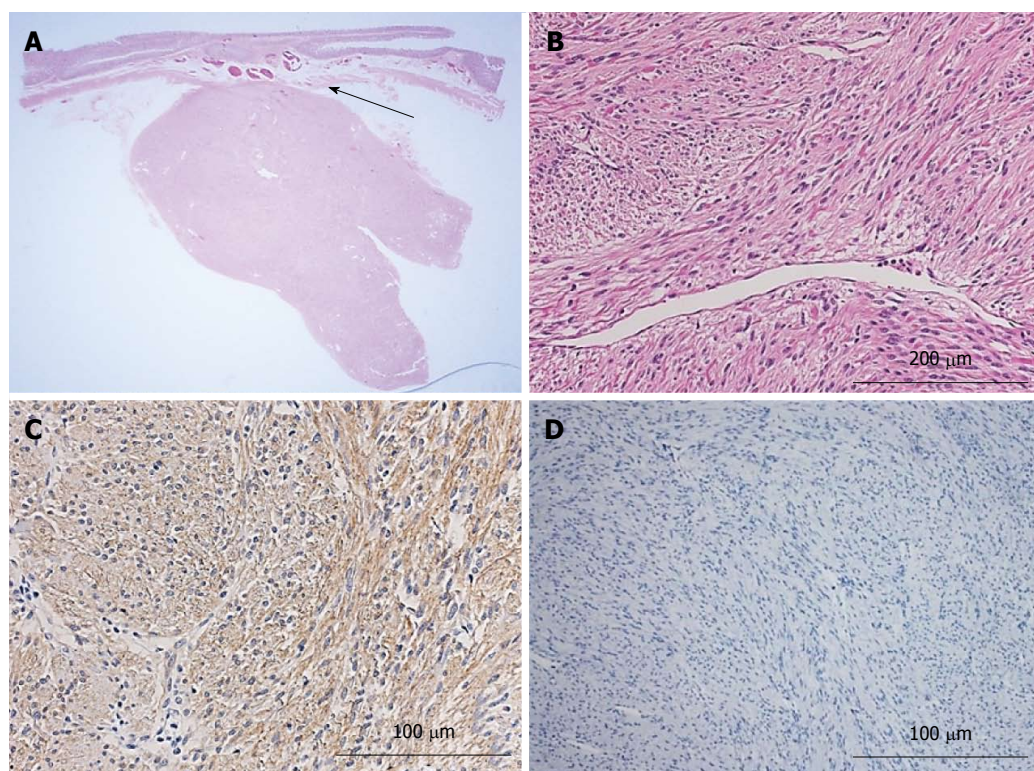frequently in the stomach (60%-70%), followed by the jejunum and ileum (20%-25%), duodenum (5%), colon and rectum (5%), and esophagus (< 5%)[3]. Miettinen *et al*[4] reported that duodenal GISTs most frequently involved the second portion of the duodenum, followed by the third, fourth, and first portions. They also reported that a majority of duodenal GISTs show submucosal tumor with a centrally ulcerated umbilication[4]; therefore, duodenal GISTs present with gastrointestinal bleeding, epigastric pain, a palpable mass, and intestinal obstruction[4].

In our case, the tumor exhibited exclusive extra-luminal growth into the pancreatic head, and there was a slightly elevated lesion without ulceration in the inferior angle of the duodenum; this atypical finding made it difficult to distinguish it from a pancreatic NET[5]. Because the lesion without ulceration is difficult to diagnose by forcep-based biopsy on normal mucosa[6], EUS and EUS-FNA are helpful for its diagnosis. For EUS, it is important to determine whether there is a connection with gastrointestinal wall because it is the most accurate test to distinguish the layer where a lesion is located. The accuracy of the diagnosis was < 50% when using only EUS[7]. The sensitivity of EUS-FNA cytology was 84.4% for GISTs located in the stomach but poor for lesions located in the duodenum[8]. Table 1 summarizes the cases of duodenal gastrointestinal tumors diagnosed with endoscopic ultrasound-guided fine-needle aspiration. Only a few reports show the

usefulness of EUS-FNA for the diagnosis of duodenal GIST, especially when it is extraluminal type. Based on Skandalakis classification, among 11 cases reported, only 3 cases were extraluminal type and 2 showed mixed type. Ueda *et al*[9] reported that they diagnosed intra- and extraluminal growth type duodenal GIST by EUS-FNA. As summarized, while all case showed somewhat level of submucosal elevation, no ulcer was complicated in the lesion and EUS showed clear hypo-echoic mass in nine cases among 11 cases (Table 1). In addition, the connection to the proper muscle layer was shown in nine cases and FNA tissues have successfully performed to determine the histological analyses.

In the reported case, EUS revealed the connection of the tumor and the muscularis propria layer (the fourth EUS layer). EUS-FNA showed that the tumor was composed of spindle-shaped cells, which were positive for c-kit, CD34, and S-100, but not for desmin, reported as a typical IHC result of GIST[10]. An accurate diagnosis helped determine the surgical procedure. Therefore, our case was successfully treated as reported[11].

Prognostic factors are very important for both assessing recurrence risk and the choice of adjuvant and neoadjuvant therapy[12]. The recently proposed "modified National Institutes of Health (NIH) classi-fication" is defined by four factors: Number, size, location, and rupture of mitoses. This classification may offer advantages in the selection of patients who may require adjuvant therapy[13]. All GISTs that occurred in

Table 1 Summary of cases of duodenal gastrointestinal tumors diagnosed with endoscopic ultrasound-guided fine-needle aspiration

Ref.	Age (yr)	Gender	Location in duodenum	Size (mm)	Endoscopic findings			EUS findings				Immunohistochemistry				Skandalakis classification	Treatment	Adjuvant chemotherapy	Clinical course	Follow up period (yr)
					SMT	Central depression	Ulcerative lesion	well-demarcated	Internal echogram	Cystic change	Connected to proper muscles	CD117	CD34	S-100	MIB-1 labeling index					
9	72	F	3rd	26	+	-	-	+	hypo	-	+	+	+	N.A.	<1%	Mixed	Partial duodenectomy	-	No recurrence	N.A.
16	62	F	2nd	40	+	-	-	+	hypo	-	+	+	+	-	0.60%	Eodoluminal	Partial duodenectomy	-	No recurrence	6
16	69	M	1st	15	+	+	-	+	iso	-	+	+	+	N.A.	0.50%	Eodoluminal	No surgery, Follow up	-	SD	5
16	76	M	2nd	35	+	+	-	-	hetero	+	+	+	-	-	0.70%	Eodoluminal	No surgery, Follow up	-	SD	3
17	50s	F	2nd	35	+	-	-	+	N.A.	-	N.A.	+	±	+	<5%	NA	Partial duodenectomy	-	N.A.	NA
18	85	F	2nd	30	+	-	-	+	hypo	-	+	+	±	-	N.A.	Eodoluminal	No surgery, Follow up	-	SD	1.6
19	50s	F	3rd	25	+	+	-	+	hypo	-	+	+	+	-	2%	Eodoluminal	Partial duodenectomy	-	No recurrence	1.3
19	30s	M	3rd	20	±	-	-	+	Aypo	-	+	+	+	-	3%	Extraluminal	Partial duodenectomy	-	No recurrence	1.2
20	75	M	3rd	60	+	-	-	+	hypo	-	-	+	-	-	2%	Extraluminal	Subtotal stomach-preserving Pancreaticoduodenectomy	+	No recurrence	1
21	51	M	2nd	27.5	+	-	-	+	hypo	-	+	+	+	N.A.	N.A.	Mixed	Surgery (no detail available)	N.A.	N.A.	N.A.
Our case	50	F	2nd	30	±	-	-	+	hypo	-	+	+	-	-	<1%	Extraluminal	Partial duodenectomy	-	No recurrence	2

EUS: Endoscopic ultrasound; ALT: Alanine aminotransferase.

the intestines had more than a moderate possibility of metastasis when they were > 5 cm or had > 5 mitoses/50 HPFs. In tumors < 5 cm with a mitotic count < 5/50 HPFs, the intestinal GISTs had a low probability of metastasis[14].

Patients with duodenal GISTs classified as intermediate or high risk for tumor relapse should be treated with 400 mg imatinib daily for 3 years and there is no benefit for patients classified at low risk. As summarized in Table 1, other than 2 cases with no follow up data are available after the surgical treatment, no recurrence after the surgical treatment was confirmed in all other 6 cases for whom the surgery was performed. While other 3 cases showed stable disease with no surgical treatment because of low risk. Our patient was low risk according to the NIH consensus criteria for risk satisfaction of GISTs and has been followed without adjuvant chemotherapy.

After completed tumor resection, follow-up care should be every 3-6 mo, including clinical examination and CT scans of the abdomen and pelvis once a year for 5 years[15]. Our patient has been doing well with no tumor recurrence for 2 years since her surgery and will continue strict CT follow-up.

In summary, we have described a rare extraluminal growth type of duodenal GIST and showed the usefulness of EUS-FNA. This report will aid physicians in diagnosing rare duodenal tumors and contribute to determining the appropriate therapeutic strategy.

COMMENTS

Case characteristics

The authors present a case of a 50-year-old woman with a 27-mm diameter tumor in the pancreatic uncus that connected to the duodenal proper muscular layer and was followed by EUS-guided fine-needle aspiration (EUS-FNA). Histological analysis showed spindle-shaped tumor cells positively stained for c-kit. Therefore, the tumor was diagnosed as a duodenal gastrointestinal stromal tumors (GISTs) of the extraluminal type, and the patient underwent successful mass resection with partial resection of the duodenum.

Clinical diagnosis

A mass in the pancreatic uncus that connected to the duodenal proper muscular layer.

Differential diagnosis

Pancreatic cancer; gastrointestinal stromal tumors; neuroendocrine tumor.

Laboratory diagnosis

Laboratory data showed a slight elevated inflammatory response with a white blood cell count of 11370/μL and C-reactive protein level of 0.33 mg/dL. Tumor markers including carbohydrate antigen 19-9, carcinoembryonic antigen, DUPAN, SPan-1, and soluble interleukin-2 receptor levels were within normal limits.

Imaging diagnosis

EUS showed a well-defined hypoechoic mass in the pancreatic uncus that connected to the duodenal proper muscular layer. Magnetic resonance imaging revealed the mass to be hypointense on T1-weighed imaging and slightly hyperintense on T2-weighed imaging. The imaging studies suggested the diagnosis of duodenal GIST or pancreatic head neuroendocrine tumor (NET).

Pathological diagnosis

IHC showed that the tumor cells were positive for c-kit, CD34, and S-100, but negative for desmin. Based on these results, the tumor was diagnosed as the extraluminal type of duodenal GIST.

Treatment

The patient underwent successful mass resection with partial resection of the duodenum.

Term explanation

GISTs: Gastrointestinal stromal tumors; NET: Neuroendocrine tumor; EUS: Endoscopic ultrasonography; FNA: Fine-needle aspiration.

Experiences and lessons

This case suggests that EUS and EUS-FNA are effective for diagnosing the extraluminal type of duodenal GISTs, which is difficult to differentiate from pancreatic head tumor, and for performing the correct surgical procedure.

Peer-review

This is a well written case.

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Deanxit relieves symptoms in a patient with jackhammer esophagus: A case report

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Abstract

Jackhammer (hypercontractile) esophagus presents with dysphagia and chest pain. Current treatments are limited. We describe a 60-year-old man who presented with dysphagia, chest pain and heartburn for a period of 1 year. His workup showed Barrett's esophagus on endoscopy and high-resolution manometry demonstrated jackhammer esophagus with esophagogastric junction outflow obstruction. The patient was treated with proton pump inhibitor and nifedipine but without resolution of his symptoms. He was followed up to assess the efficacy of treatment with deanxit (flupentixol + melitracen). Dysphagia and chest pain resolved during the therapeutic trial and efficacy was maintained on maintenance treatment without troublesome side effects.

Key words: High-resolution manometry; jackhammer esophagus; Deanxit; Therapy

Core tip: Low-dose antidepressants can improve patients' reaction to the pain associated with esophageal dynamic disorders. The case report describes that deanxit (flupentixol + melitracen) has a positive effect on a new, rare disease, jackhammer esophagus, and speculates upon the potential relationship between mental factors and jackhammer esophagus.

Li JY, Zhang WH, Huang CL, Huang D, Zuo GW, Liang LX. Deanxit relieves symptoms in a patient with jackhammer esophagus: A case report. *World J Gastrointest Endosc* 2017; 9(12):

INTRODUCTION

High-resolution manometry (HRM) has provided a new method for clinical diagnosis and treatment of esophageal motility disorders. Based on HRM techniques, the new Chicago classification has revised the esophageal motility disorder diagnostic criteria, mainly for achalasia and esophageal body motility disorders. Jackhammer esophagus is a new entity within spastic disorders of the esophagus[1]. Moreover, it has recently been described by a new Chicago Classification version 3.0 with at least two swallows with distal contractile integral (DCI) > 8000 mmHg-s-cm[2]. We describe a patient with impaired esophagogastric junction (EGJ) relaxation and hypercontractile peristaltic disorder, accompanying depressive disorder, which has not been reported in China. Treatment with deanxit (flupentixol + melitracen) led to an unusual recovery.

CASE REPORT

A 60-year-old man visited our hospital because of a 1-year history of intermittent and recurrent episodes of dysphagia, chest pain and heartburn in January 2015. In another hospital, he had taken proton pump inhibitors (PPIs) for > 1 mo, but he was not relieved of any symptoms. There was nothing remarkable in his medical history. Physical and laboratory examinations showed no specific findings. Endoscopy showed possible Barrett's esophagus (BE) (Figure 1A). Moreover, esophageal mucosal biopsy suggested gastric mucosa ectopia. A barium esophagogram showed reflux esophagitis and spastic contraction in the distal esophagus (Figure 1B). He underwent HRM (Sierra Scientific Instruments, Los Angeles, CA, United States) and 24-h esophageal impedance-pH monitoring (Sierra Scientific Instruments). HRM showed that the maximum DCI was 8099.9 mmHg-s-cm and the integrated relaxation pressure (IRP) was 21.5 mmHg (Figure 1C). Pathological acid reflux was reported by 24-h esophageal impedance-pH evaluation (Figure 1D). Medical therapy with nifedipine 10 mg twice daily, esomeprazole 20 mg twice daily and teprenone 50 mg twice daily for approximately 10 mo showed no improvement in dysphagia and chest pain, but the symptoms of acid regurgitation and heartburn had relieved.

He was seen in our hospital in December 2015 with worsening dysphagia and chest pain. However, laboratory investigations were normal again including serum troponin level, electrocardiography monitoring and coronary angiography. HRM and 24-h esophageal impedance-pH monitoring were repeated. HRM showed typical hypercontractile contractions (6 swallows with DCI > 8000 mmHg-s-cm in 10 liquid swallows) and IRP 14.7 mmHg (Figure 2A), whereas impedance-pH

monitoring was negative (Figure 2B). Close examination of his medical history revealed long-term sleep disorders, with difficulty falling asleep, worrying about cancer, and anxiety. The patient was judged to be in a depressive state by a psychiatrist. Drug therapy was adjusted to deanxit 0.5 mg/10 mg (one piece) twice daily, rabeprazole 10 mg twice daily and hydrotalcite 1 g three times daily, and the patient's symptoms improved, with no obviously reflux, chest pain, and dysphagia after 5 d treatment. Moreover, he continued this therapy as-maintained basis.

At follow-up 5 mo later, the patient described clinical improvement with only one episode of dysphagia and chest pain, because of stopping his medication without permission. However, symptoms were relieved soon after he takes medicine. He was re-examined by HRM in May 2016, which showed IRP 10.1 mmHg (normal < 15 mmHg) and mean DCI 6750 mmHg-s-cm (Figure 3). The total period of treatment was 6 mo, with deanxit dose gradually reduced until withdrawal under the guidance of a psychologist and gastroenterologist. In June 2017, the patient had recovered well without recurrence of symptoms.

DISCUSSION

Jackhammer esophagus is a rare disorder that occurs in 4% of patients referred to a tertiary center for HRM, and these patients with extreme phenotypes of esophageal hypercontractility present mainly with dysphagia, chest pain, and gastroesophageal reflux symptoms[3]. Nowadays there appears to be no clear consensus about optimal therapy, and options are similar to other esophageal dysmotility disorders. Pharmacological treatment should be considered first, with a combination of nitrates, calcium channel blockers, phosphodiesterase-5 inhibitors and PPIs having potential benefit[4]. Recently, Marjoux *et al*[5] reported that esophageal botulinum toxin was effective for treatment of hypertensive esophageal motility disorders. There were also recently reported cases of successful treatment with peroral endoscopic myotomy[6] and balloon dilatation[7]. Tsutomu *et al*[8] have reported that surgery using thoracoscopic esophageal extended myotomy is beneficial.

Patients with jackhammer esophagus can present with mechanical EGJ outflow obstruction, gastro-esophageal reflux disease, or primary esophageal muscle hypercontractility[3]. Our patient had high IRP; a hypercontractile peristaltic disorder of the esophagus that overlaps with BE. The first treatment strategy of spastic disorders depends on whether there is an accompanying EGJ outflow obstruction[4]. Moreover, there is a lack of evidence for the value of pharmacological treatment alone if EGJ relaxation is impaired. Therefore, we selected medical therapy first. A trial of nifedipine and PPIs have been chosen. The IRP was normal and changed to jackhammer esophagus without EGJ outflow obstruction and pathological acid reflux.
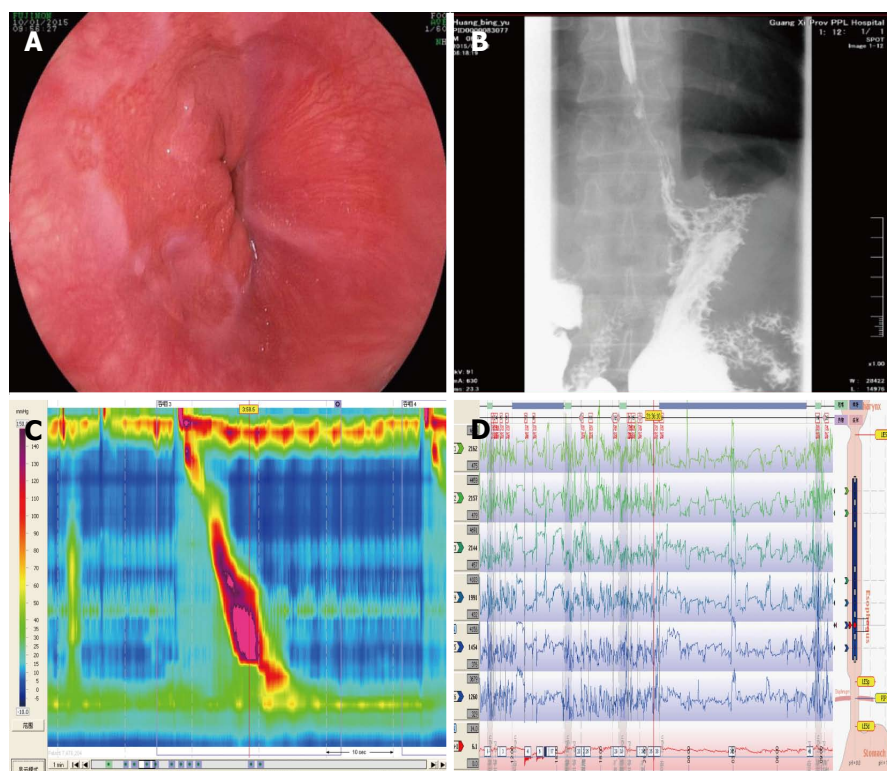
Figure 1 The workup of the patient for the first time. A: Esophageal lesions of the patient under endoscopy, which were suggestive of BE; B: Barium esophagogram showing reflux esophagitis and spastic contraction in the distal esophagus; C: Representative swallow from the patient's initial HRM. The median IRP was high at 21.5 mmHg, and the DCI was elevated to 8099.9 mmHg-s-cm; D: 24-h pH-impedance monitoring. It can monitor 100% acid reflux into the esophagus. DCI: Distal contractile integral; HRM: High-resolution manometry; IRP: Integrated relaxation pressure.
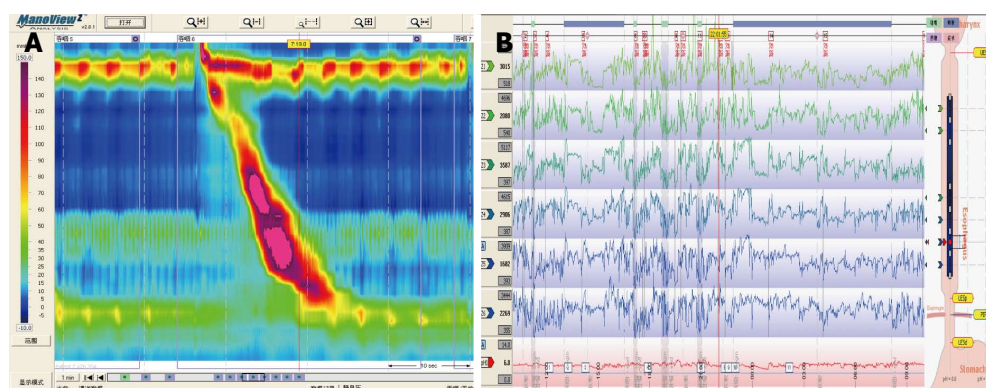

Figure 2 Esophageal test results for the second time. A: Representative swallow from the patient's repeat esophageal HRM. Median IRP was normal at 14.7 mmHg. DCI was higher than normal, which was 8120.1 mmHg-cm-s, and six swallows with DCI > 8000 mmHg-s-cm in 10 liquid swallows. Esophageal manometry was consistent with jackhammer esophagus; B: 24-h pH-impedance monitoring was repeated, which was negative for gastroesophageal reflux disease. DCI: Distal contractile integral; HRM: High-resolution manometry; IRP: Integrated relaxation pressure.

Low-dose antidepressants can improve patients' reaction to pain without objectively improving motility function[9]. Our patient had obvious chest pain and dysphagia with esophageal hypercontractility. We allowed him to take antidepressants (deanxit) because he had depression. The patient's clinical and objective esophageal indexes were improved. Previous studies have established that the psychosocial aspects are related to gastroesophageal reflux disease and functional esophageal disorders, such as functional chest pain, functional dysphagia and hypersensitive esophagus[10,11]. In the present study, we examined the influence of the relationship between mental factors and jackhammer esophagus. Deanxit had surprising efficacy for this patient, so we speculated that his depressive disorder may have caused hypercontractile peristaltic disorder because of nonspecific esophageal motility disorder. Alternatively, it may be that the patient endured painful symptoms for a long period, resulting in psychiatric comorbidity of jackhammer esophagus. The underlying pathological mechanisms in this case are unclear and deserve further study.

In summary, despite the evidence of efficacy, the long-term optimal management of jackhammer esophagus is
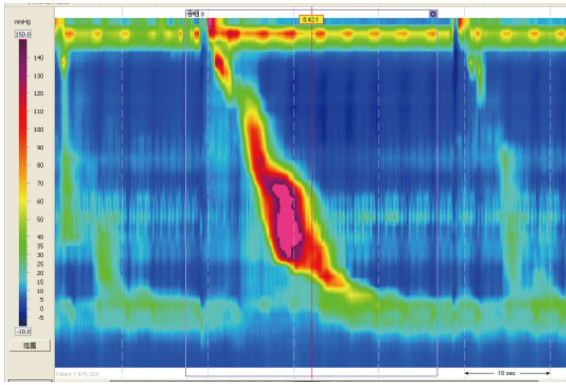
Figure 3 A representative swallow from the patient's repeat esophageal high-resolution manometry after administration of deanxit. Median IRP was elevated at 10.1 mmHg. DCI of each swallow was higher than the normal range but < 8000 mmHg-cm-s, which was improved after treatment. DCI: Distal contractile integral; IRP: Integrated relaxation pressure.

not yet established. In our patient with a rare esophageal motility disorder and depression, antianxiety and anti-depressant agents relieved his symptoms. However, the duration of treatment with antidepressants in patients with jackhammer esophagus and longer follow-up need further discussion.

ARTICLE HIGHLIGHTS

Case characteristics
A 60-year-old man with a 1-year history of intermittent and recurrent episodes of dysphagia, chest pain and heartburn, who had taken PPIs for a long time, but without relief of any symptoms.

Clinical diagnosis
Dysphagia, chest pain and heartburn and depressive state.

Differential diagnosis
Achalasia, gastroesophageal reflux disease, esophageal infections, esophageal carcinoma, coronary heart disease.

Laboratory diagnosis
All laboratory parameters were within normal limits.

Imaging diagnosis
High-resolution manometry (HRM) showed six swallows with distal contractile integral (DCI) > 8000 mmHg-s-cm in 10 liquid swallows and integrated relaxation pressure (IRP) 14.7 mmHg.

Pathological diagnosis
Esophageal mucosa appeared as ectopia of gastric mucosa.

Treatment
Deanxit for 6 mo, gradually reduced until withdrawal.

Related reports
Jackhammer esophagus is a rare disorder, and current treatments are limited,

such as botulinum toxin injection, peroral endoscopic myotomy, and balloon dilatation.

Term explanation
Jackhammer esophagus is a rare esophagus disorder, and patients with extreme phenotypes of esophageal hypercontractility present mainly with dysphagia, chest pain, and gastroesophageal reflux symptoms. Jackhammer esophagus is described by a new Chicago Classification version 3.0 with at least two swallows with DCI > 8000 mmHg-s-cm.

Experiences and lessons
Patients with esophageal hypercontractility present mainly with dysphagia, chest pain, and HRM is the primary diagnostic method. Patients may also have mental illness, so at the time of diagnosis, psychological evaluation is necessary. Antianxiety and antidepressant agents are promising medical treatment to relieve symptoms in patients with jackhammer esophagus combined with psychosocial problems, but longer follow-up is needed.

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