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REVIEW

What are the current and potential future roles for endoscopic ultrasound in the treatment of pancreatic cancer?

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Abstract

Pancreatic adenocarcinoma is the fourth leading cause of cancer-related death in the United States. Due to the aggressive tumor biology and late manifestations of the disease, long-term survival is extremely uncommon and the current 5-year survival rate is 7%. Over the last two decades, endoscopic ultrasound (EUS) has evolved from a diagnostic modality to a minimally invasive therapeutic alternative to radiologic procedures and surgery for pancreatic diseases. EUS-guided celiac plexus intervention is a useful adjunct to conventional analgesia for patients with pancreatic cancer. EUS-guided biliary drainage has emerged as a viable option in patients who have failed endoscopic retrograde cholangiopancreatography. Recently, the use of lumen-apposing metal stent to create gastrojejunal anastomosis under EUS and fluoroscopic guidance in patients with malignant gastric outlet obstruction has been reported. On the other hand, anti-tumor therapies delivered by EUS, such as the injection of anti-tumor agents, brachytherapy and ablations are still in the experimental stage without clear survival benefit. In this article, we provide updates on well-established EUS-guided interventions as well as novel techniques relevant to pancreatic cancer.

Key words: Endoscopic ultrasound; Pancreatic cancer; Palliation; Endoscopic ultrasound-guided celiac plexus neurolysis and block; Endoscopic ultrasound-guided biliary drainage; Endoscopic ultrasound-guided gastrojejunal anastomosis; Endoscopic ultrasound-guided anti-tumor therapy; Endoscopic ultrasound-guided fiducial placement; Endoscopic ultrasound-guided ablation

Core tip: Endoscopic ultrasound (EUS) is an indis-

pensable tool in pancreatic cancer not only for tissue diagnosis and disease staging but also for therapeutic purposes. Although some EUS-guided therapies such as celiac plexus interventions and biliary drainage in the setting of unsuccessful endoscopic retrograde cholangiopancreatography (in expert tertiary referral centers) have become widely accepted interventions for patients with pancreatic cancer, other techniques have yet to evolve. Given the lack of effective systemic treatment for pancreatic cancer at present, further research in therapeutic EUS is warranted.

Oh SY, Irani S, Kozarek RA. What are the current and potential future roles for endoscopic ultrasound in the treatment of pancreatic cancer? *World J Gastrointest Endosc* 2016; 8(7): 319-329 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i7/319.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i7.319

INTRODUCTION

Pancreatic adenocarcinoma is the fourth leading cause of cancer-related death in the United States[1]. Only 20% of patients at diagnosis are amenable to surgical resection[2], which offers the best chance of long-term survival. As a result, the majority of patients are treated with palliative chemotherapy or best supportive care. From a histological standpoint, one of the defining features of pancreatic ductal adenocarcinoma is extensive desmoplastic stroma with fibrotic reaction around the tumor. The fibrotic stroma promotes tumor growth[3], induces resistance to chemotherapy and radiotherapy[4], and constitutes a barrier to the delivery of therapeutic agents[5]. Due to the aggressive tumor biology and late manifestations of the disease, long-term survival is extremely uncommon and the current 5-year survival rate is 7%[6].

Over the last two decades, endoscopic ultrasound (EUS) has evolved from a diagnostic modality to a minimally invasive therapeutic alternative to radiologic procedures and surgery for pancreatic diseases. EUS-guided celiac plexus neurolysis (CPN)/block are widely accepted techniques for pain management in patients with pancreatic cancer. Recently, EUS-guided biliary access in both malignant and non-malignant biliary obstruction has been increasingly utilized. As EUS offers dynamic images, unparalleled access to the pancreas and Doppler to avoid vascular structures, it has a theoretical advantage of targeting the tumor directly through the desmoplastic stroma while minimizing complications. This, coupled with the lack of effective systemic chemotherapies for pancreatic cancer, has prompted researchers to investigate local EUS-guided delivery of anti-tumor agents and ablative therapies over the last decade.

In this article, we provide updates on well-established EUS-guided interventions as well as novel techniques that are in the development for the treatment of pancreatic cancer.

PALLIATIVE/SYMPTOMATIC THERAPIES

EUS-guided celiac plexus interventions

CPN refers to permanent chemical ablation of the celiac plexus and is performed by injecting alcohol or phenol into or around the celiac plexus or ganglion. Celiac plexus block denotes inhibition of pain transmission *via* the celiac plexus by injecting a combination of a corticosteroid and a long acting local anesthetic. Injections can be delivered *via* a percutaneous, surgical or EUS-guided approach. EUS provides access to the celiac plexus which is located adjacent to the proximal gastric wall. The main advantage of this route over a percutaneous one is the ability to avoid vessels with Doppler, in addition to being able to undertake concomitantly at the time of another intervention such as an endoscopic retrograde cholangiopancreatography (ERCP) or fine needle aspiration of the primary mass.

Since the first report of EUS-CPN in 30 patients with intra-abdominal malignancy (25 with pancreatic cancer) showing significant improvement in pain scores[7], multiple randomized controlled and meta-analyses[8-12] have demonstrated that EUS-CPN provided effective pain relief in patients with pancreatic cancer compared with conventional analgesia. There is also evidence that CPN reduces analgesia use. Two meta-analyses showed that CPN (either EUS or percutaneous approach) was associated with a significant reduction in narcotic use[8,11]. Additionally, a randomized controlled trial involving 96 patients with advanced pancreatic cancer reported that morphine consumption was lower at 3 mo in the EUS-CPN group compared to placebo[11]. Nonetheless, approximately 15% of patients may see no reduction in their use of narcotics, and in this group, a repeat EUS-CPN has not been shown to be effective. A study of 24 patients with pancreatic cancer undergoing repeat EUS-CPN showed that repeat CPN was not as effective as index procedure in pain control (67% after the initial CPN *vs* 29% at 1 mo follow-up)[13].

EUS-guided injection can be given centrally into the space between the aorta and the origin of the coeliac trunk, or bilaterally on either side of the coeliac axis. To date, one randomized trial comparing the two techniques demonstrated no difference in the duration of pain relief (11 wk *vs* 14 wk), complete pain relief (2/29 patients *vs* 2/21 patients) or reduction in pain medication (9/29 patients *vs* 7/21 patients)[14]. The decision to inject centrally or bilaterally often depends on the personal preference and experience of an endosonographer and further prospective studies are needed to determine which approach is superior. On the other hand, a Japanese group investigated the efficacy of broad plexus neurolysis (BPN) extending over the superior mesenteric artery with the aim of delivering a larger amount of neurolytic agents[15]. The study found that EUS-BPN patients had significantly greater reductions at days 7 and 30 on the visual analog pain

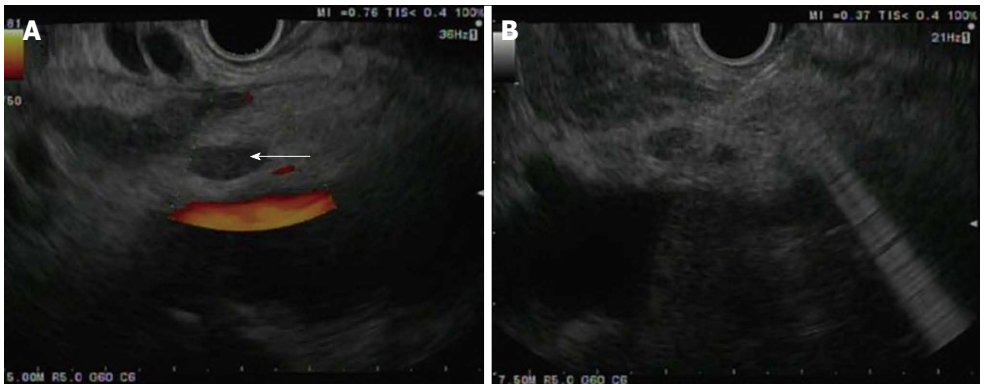

Figure 1 Endoscopic ultrasound-guided injection into the celiac ganglion. A: Celiac ganglion visualized by linear endoscopic ultrasound as a hypoechoic structure anterior to the aorta (arrow); B: 19-gauge needle puncture into the celiac ganglia for neurolysis.

scale scores compared with EUS-CPN group. This technique, however, is yet to be validated in a large, prospective trial.

There has been an interest in direct celiac ganglia injection to improve the efficacy of CPN (Figure 1). Celiac ganglia appear as an oval, hypo to isoechoic structures around the celiac axis and are visible in upwards of 80% of the general population[16,17]. A recent study randomized 34 patients to EUS-celiac ganglia neurolysis *vs* EUS-CPN showed that celiac ganglion neurolysis was associated with more effective pain relief compared with CPN (73.5% *vs* 45.5%, respectively; $P = 0.026$) with a smaller volume of alcohol needed for the ablation[18].

Contraindications to celiac plexus interventions include coagulopathy (international normalized ratio > 1.5), thrombocytopenia (platelets < 50000/L), and hemodynamic or respiratory instability prohibiting adequate sedation. Otherwise, EUS-guided celiac plexus intervention is generally safe. Diarrhea, abdominal pain and hypotension due to the disruption of the autonomic nervous system are usually self-limiting. A paradoxical increase in pain has been shown to occur in 9% of cases but generally resolves spontaneously[19]. Serious adverse events including paralysis from anterior spinal cord infection[20,21], necrotic gastric perforation[22], and celiac artery thrombosis causing infarction[23,24] are rare.

EUS-guided biliary drainage

ERCP for biliary access and drainage is successful in 90% to 95% of cases and is the preferred method of stenting the bile duct in obstructive jaundice from pancreatic cancer. In cases of unsuccessful ERCP due to difficult cannulation or altered anatomy, the alternatives have been precut papillotomy, percutaneous transhepatic biliary drainage (PTBD) and surgical bypass. Recently, EUS-guided biliary drainage has emerged as an alternative to these options. EUS-guided approach spares patients the discomfort of an external drain, and can be performed at the time of an unsuccessful ERCP, reducing the need for additional percutaneous interventions.

Three main approaches for EUS-guided biliary drainage have been described. Rendezvous technique is where a guidewire is placed into the intra or extrahepatic bile duct and passed through the papilla for retrieval by duodenoscopy for retrograde biliary intervention. Direct transgastric (hepaticogastrostomy) or transduodenal (choledochoduodenostomy) route involves the dilation of the tract followed by stenting for transmural biliary drainage (Figure 2). This obviates biliary access *via* the papilla. A third, less frequently performed intervention, involves the antegrade placement of a stent across the papilla *via* a transduodenal approach[25,26]. The transduodenal approach requires at least an intact duodenal bulb[27] and can sometimes be performed after placement of a duodenal stent for gastric outlet obstruction. In patients with obstruction at the level of the pylorus, the transgastric approach almost always requires a dilated intrahepatic biliary system[28].

Available evidence suggests excellent technical and clinical success with EUS-guided biliary drainage in 87% of cases, however, adverse events up to 10%-20% have been reported[29-40]. One of the major shortcomings of the rendezvous technique is a failure rate of 25%, and this can be associated with prolonged procedure times and higher risk of bile leak[31,36,37,40,41]. In contrast, transluminal stenting can be complicated by stent migration or occlusion, bile leak and biliary peritonitis, cholangitis, hemobilia and pneumoperitoneum[27,33-35].

Alternatively, EUS-guided gallbladder drainage may be an option when the previously mentioned approaches are not feasible. As the gallbladder presents a large target in close proximity to the gastric antrum and duodenal bulb, this technique can be performed more easily. However, it would not be beneficial in a non-dilated gallbladder suggesting cystic duct invasion by tumor[42]. Excellent technical success, clinical success and safety profiles with EUS-guided gallbladder drainage in patients with acute cholecystitis have been demonstrated in a randomized controlled trial[43] and its use in the setting of malignancy has been described in case reports and small series[44,45].

At present, experts recommend that EUS-guided biliary drainage should be performed by an advanced

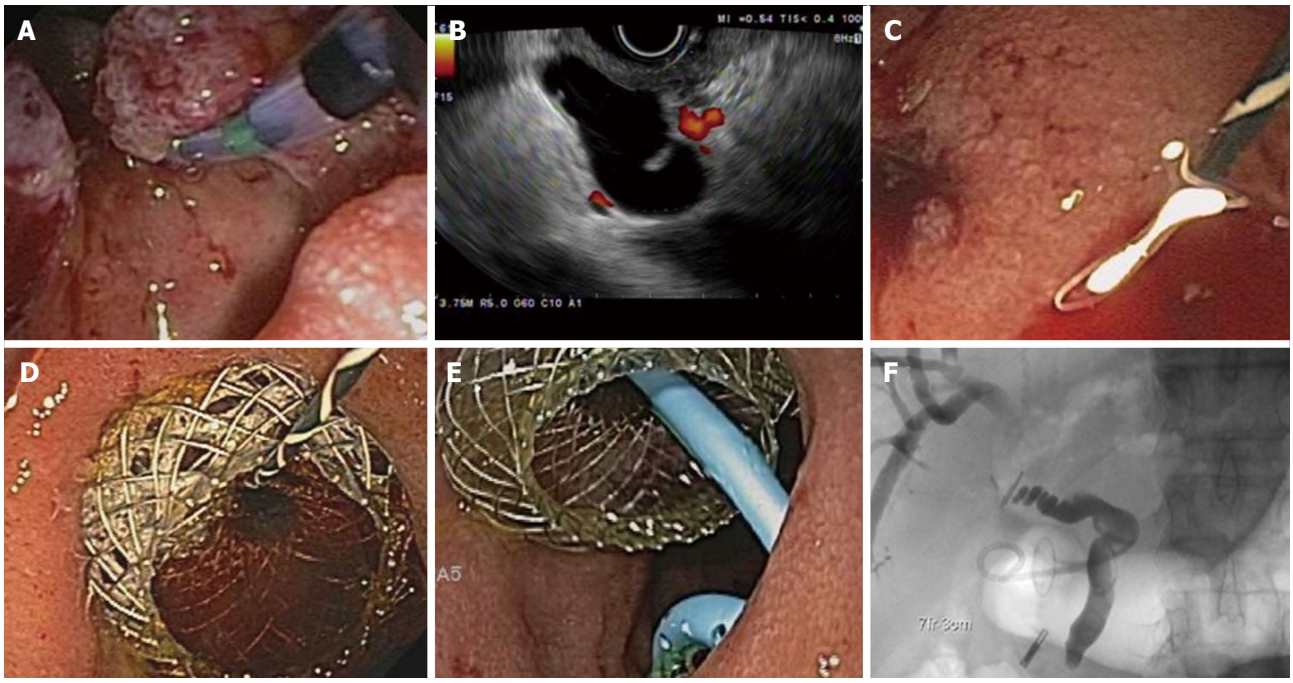

Figure 2 A 84 years old male with duodenal adenocarcinoma causing biliary obstruction underwent endoscopic ultrasound-guided choledochoduodenostomy following unsuccessful endoscopic retrograde cholangiopancreatography. A: Tumor involving the major papilla; B: Endoscopic ultrasound-guided puncture of the common bile duct through the duodenum with a 19-gauge needle; C: Guidewire insertion and balloon dilation of a choledochoduodenal fistula; D: Followed by the placement of a 10 mm × 10 mm lumen-apposing metal stent to create a choledochoduodenostomy; E and F: Endoscopic (E) and flouroscopic (F) view after the placement of a 7 Fr × 3 cm double pigtail stent into the common hepatic duct.

endoscopist with expertise in both ERCP and EUS in a tertiary center, where surgery and radiology unit can provide support to manage adverse events if they arise[46,47].

EUS-guided anastomosis

Gastric outlet obstruction is a common late manifestation of cancer in the head of the pancreas. When endoscopic gastroduodenal stent placement is unsuccessful in relieving obstruction, bypass surgery can be performed to accomplish the anastomosis between the stomach and jejunum. However, in poor surgical candidates, the EUS-guided approach may offer a minimally invasive means of establishing an anastomosis. In this technique, a gastrojejunal fistula is created by obtaining an access to the jejunum *via* EUS-guided needle, placing a guidewire through the needle and dilating the tract over the wire using a dilator catheter, balloon and/or electrical cautery needle. Subsequently, a lumen-apposing stent is placed across the fistula (Figure 3). This has been described in 2 recent case reports[48,49]. EUS-guided gastrojejunostomy using a double-balloon enteric tube to distend the jejunum between the two balloons at the EUS-guided needle puncture has also been reported[50,51].

The use of magnetic compression devices through oral, percutaneous, and surgical introduction of magnets to create gastroenterostomy and cholecystoenteric anastomosis in animal models has been reported[52,53] (Figure 4). Encouraged by the favorable outcomes of the experimental studies, two human trials of endoscopic gastroenteric anastomosis have been performed. The first study evaluated 15 patients with malignant obstruction undergoing gastroenteric anastomosis using magnetic compression devices and a yoyo stent and found that the procedure was successful in 13 (87%) patients[54]. One perforation occurred and was attributed to manipulation of the recently formed fistula. Three stents migrated (2 distal and 1 proximal) and no mortality was reported. Subsequently, a prospective multicenter study evaluated 18 patients who had gastroenteric anastomosis using magnetic compression device and self-expandable stent[55]. The procedure was successful in 12 (67%) patients but the study was terminated after inclusion of 18 patients due to a fatal perforation in 1 patient. Three (25%) patients experienced stent migration. This technique is usually performed by forward-viewing endoscope but can also be performed under the guidance of EUS combined with fluoroscopy. Creation of magnetic biliary anastomoses using endoscopic and radiologic techniques has also been described in case reports[56,57] but there are no large trials to date.

Through-the-scope device for EUS-guided suturing and tissue approximation between two organs has been tested in porcine models[58,59]. A suturing device was developed for suturing under EUS guidance to the desired depth. The device allowed multiple sutures to be placed without withdrawing the echoendoscope. Stitching, knot tying, and thread cutting were achieved through an accessory channel in the echoendoscope. Traction for the insertion of stents and other devices was provided through the lumen of both organs. With-

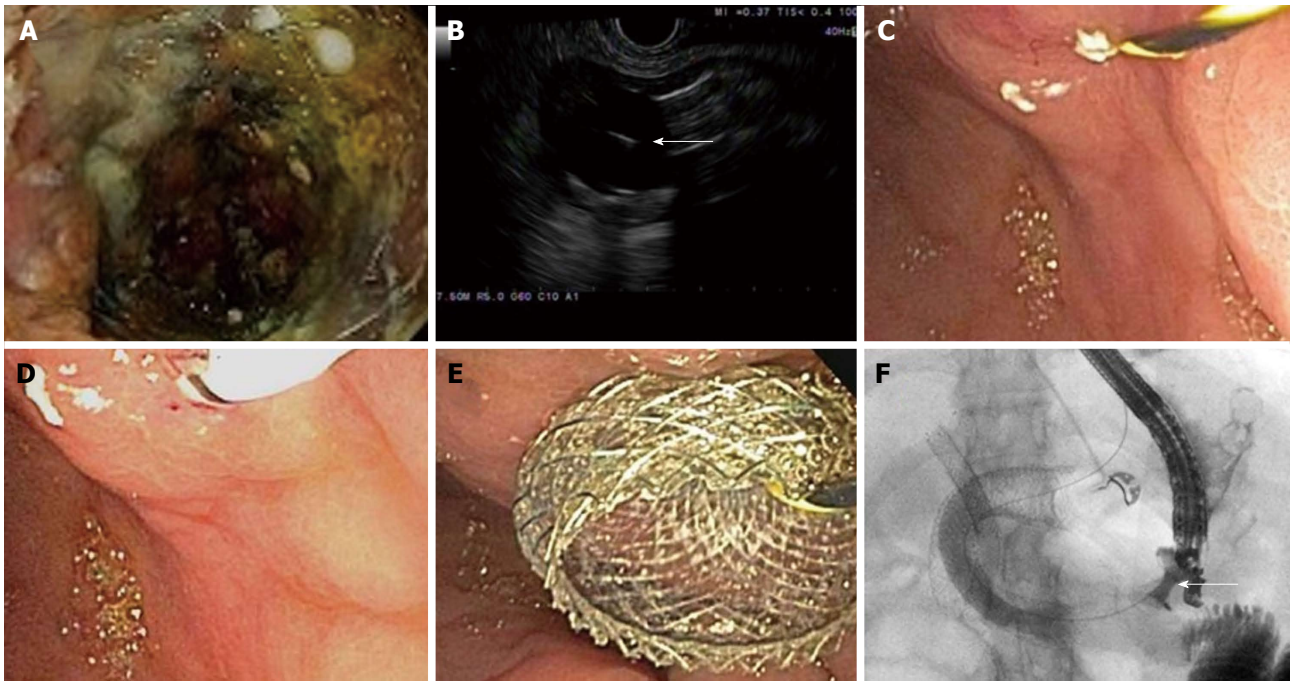

Figure 3 A 66 years old female with metastatic cholangiocarcinoma and gastric outlet obstruction undergoing endoscopic ultrasound-guided gastrojejunostomy. A: Tumor ingrowth into two previously placed duodenal stents; B: Endoscopic ultrasound visualization of a 20 mm balloon inflated in the proximal jejunum followed by a 19-gauge needle puncture (arrow); C and D: Balloon dilation of the gastrojejunal fistula over a 0.035 inch guidewire; E and F: Endoscopic (E) and fluoroscopic (F) demonstration of contrast flow across 10 mm × 15 mm lumen-apposing metal stent (arrow) into the jejunum.

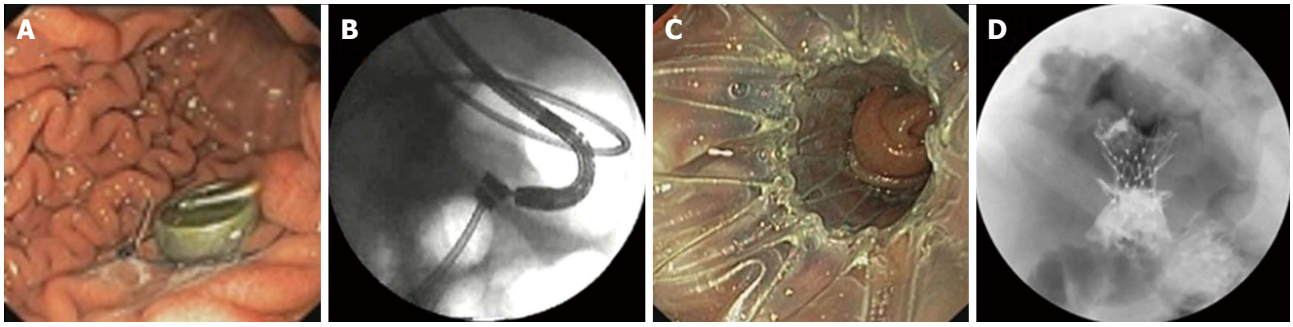

Figure 4 Magnetic anastomosis device to create endoscopic gastrojejunostomy (Images courtesy of Cook Medical). A: Gastric magnent marked with an endoscopy clip; B: Mating of gastric and proximal jejunal magnets under fluoroscopic guidance to create a gastrojejunal fistula; C: Placement of a fully covered stent within the fistula with a proximal flanged edge positioned in the gastric lumen; D: The stent within the fistula functions as a gastrojejunostomy.

in 4 to 7 d, anastomoses had formed between the small intestine and the stomach, and between the gallbladder and the stomach. The initial diameter of the anastomoses ranged from 3 to 9 mm, and no adverse events were reported.

ANTI-TUMOR THERAPIES

EUS-fine needle injection of anti-tumor agents

Cytoimplant: An allogenic mixed lymphocyte culture (Cytoimplant) induces cytokine production and activates the host immune effector mechanism. EUS-fine needle injection (EUS-FNI) of Cytoimplant was examined in a phase I trial of 8 patients with advanced pancreatic cancer[60]. The median survival was 13.2 mo, with 2 partial responses (> 50% reduction in tumor size measured on imaging) and 1 minor response (tumor size reduction of < 50%). The technique was feasible and no major complications were seen.

Immunotherapy/dendritic cells: Immature dendritics cells can stimulate primary T-cell response against tumor antigens. To date, 2 pilot trials have been conducted on EUS-FNI of dendritics for the treatment of unresectable pancreatic cancer. The use of EUS-FNI of immature dendritic cells was reported in a study of 7 patients with advanced pancreatic cancer who previously failed gemcitabine. Injections of 10 billion or more dendritic cells at two to three sites were performed. There was 1 complete response, 3 partial responses and 2 patients had stable disease with a median survival of 9.9 mo. No adverse events were seen[61]. Later, the

use of combined systemic gemcitabine and EUS-FNI of OK432-pulsed dendritic cells, followed by intravenous lymphokine-activated killer cells was reported in 5 patients with unresectable pancreatic cancer. One patient showed a partial response and 2 patients had stable disease over 6 mo[62].

Tumor necrosis factor erade: Tumor necrosis factor (TNF)erade is a replication-deficient adenovirus vector that expresses human TNF-alpha gene regulated by promoter Egr-1, which is inducible by chemotherapy and radiation. Preliminary results from a phase Ⅰ/Ⅱ trial of intratumoral TNFerade injection (either EUS or percutaneous approach) in combination with systemic 5-fluorouracil and radiotherapy in 50 patients with locally advanced pancreatic cancer demonstrated encouraging results[63]. One complete response, 3 partial responses and 12 stable disease with a median survival of 297 d was noted. Interestingly, seven patients had surgical resection, 6 with negative margins, 1 with complete pathologic response and 3 surviving more than 2 years. However, a subsequent large randomized multicenter trial involving 304 patients with locally advanced pancreatic cancer showed no survival benefit of combining intratumoral TNFerade injection with 5-fluorouracil and radiotherapy compared with chemoradiation alone[64]. In addition, the study used either EUS-guided or a percutaneous approach for the injection of TNFerade and found that EUS-FNI was associated with inferior progression-free survival. This was thought to be the operator-dependent nature of EUS-FNI.

ONYX-015: ONYX-015 is a modified adenovirus (deletion in the E1B gene) which preferentially replicates in tumor cells leading to cell death. In a phase Ⅰ/Ⅱ trial using EUS-FNI of ONYX-015 in 21 patients with locally advanced pancreatic cancer, patients received 8 injections and the last injection was administered with systemic gemcitabine[65]. The mean survival was 7.5 mo. Serious adverse events included duodenal perforations and sepsis in 2 patients each, raising concerns over its safety.

BC-819: BC-819 is a DNA plasmid that targets the expression of diphtheria-toxin gene under the control of H19 regulatory sequences and has the potential to treat pancreatic cancer that overexpresses the *H19* gene. In a phase Ⅰ/Ⅱa trial, EUS or computed tomography (CT)-guided FNI of BC-819 was performed in 9 patients with advanced pancreatic cancer treated with concurrent chemoradiation[66]. Three patients achieved partial response and 2 were successfully downstaged for surgery. No serious adverse events were reported.

Radiotherapy and EUS

EUS-guided brachytherapy: Brachytherapy involves the insertion of a radioactive seed directly into the tumor for local destruction. Iodine-125 (125I) is the most common radioactive seed used and has a half-life of 59.7 d and tissue penetration of 1.7 cm[67]. EUS-guided implantation of 125I into pancreatic tumor was first reported in a pilot study of 15 patients with unresectable pancreatic cancer[68]. The study showed partial response in 27%, minimal response in 20% and stable disease in 33%. Reduction in pain was noted in 30% but the effect was short-lived. Two further studies examined the efficacy of combined EUS-brachytherapy and systemic gemcitabine-based chemotherapy in patients with advanced pancreatic cancer, both demonstrating no significant survival benefit but improvement in pain was again noted[69,70].

Stereotactic body radiotherapy and fiducial placement: The main benefit of stereotactic body radiotherapy (SBRT) is that it limits the field of radiation to the organ of interest thereby minimizing irradiation of adjacent normal tissue[71]. One prospective[71] and two retrospective studies[72,73] showed that local tumor control and overall survival following SBRT were comparable with the outcomes of external beam radiotherapy.

Placement of fiducial markers prior to SBRT acts as a landmark and enables precise tumor targeting. Fiducial markers are available in different forms, including radiopaque spheres, coils or seeds and were traditionally placed in or near the tumor using surgical or radiological techniques (Figure 5[74]). However, two recent prospective studies have demonstrated that EUS-guided placement of fiducial markers in pancreatic tumors had excellent technical success rates (88% to 90%) and safety[74,75]. EUS-guided placement is performed by passing fiducials through a 19G or 22G needle and deploying them by using stylet or injecting sterile water into the needle after the needle is punctured to the desired depth[76]. Different types of fiducial markers have also been studied. Khashab *et al*[77] evaluated the EUS-placement of traditional *vs* coiled fiducials in a study of 39 patients with locally advanced pancreatic cancer. Visibility score was significantly better for traditional compared with coil fiducials but no difference in migration rate, number of fiducials placed, technical success or complication rate were seen. The authors recommended the placement of traditional fiducials whenever possible.

EUS-guided ablative techniques

Radiofrequency ablation: Radiofrequency ablation (RFA) works by passing electrical current in the range of radio waves between a needle electrode positioned in the tumor, and grounding pads placed on the patient's skin. Radiofrequency current produces a high level of heat within the tumor leading to protein desaturation and loss of fluids (coagulative necrosis)[78]. Several studies have demonstrated the feasibility of RFA *via* open, percutaneous and laparoscopic approaches in patients with locally advanced pancreatic cancer[79,80].

The application of EUS-guided RFA in porcine models was shown to be effective in destroying pancreatic tissue[78,81,82]. Complications included pancreatitis[81], intestinal wall adhesion[82], and retroperitoneal fibrosis

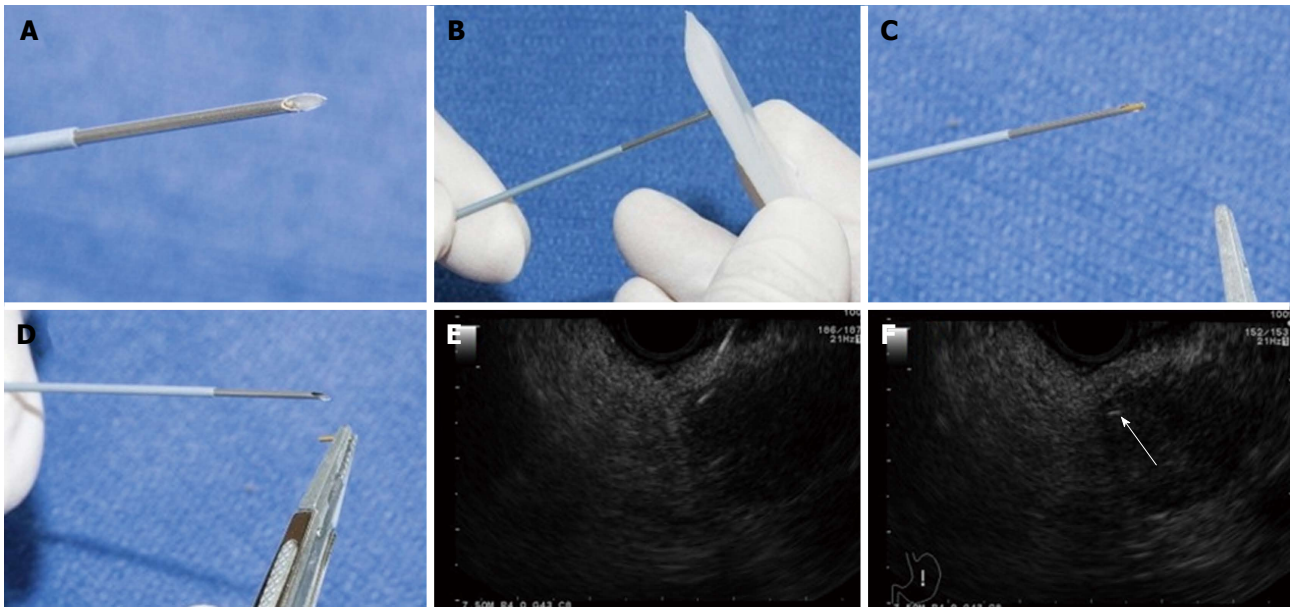

Figure 5 Images courtesy of Sanders *et al*[74]. A: Fiducial loaded into 19-gauge needle with sterile forceps; B: Fiducial within tip of needle; C: Sealing fiducial with sterile bonewax; D: Loaded fiducial ready for advancement down operating channel; E and F: Needle delivering fiducial into pancreatic mass (arrow).

in an adjacent organ[83]. To date, there is only one study that reported the use of EUS-RFA in humans. The study used a cryothermal probe which is a large bore flexible bipolar device that combines radiofrequency with cryogenic cooling in the same session. The probe was successfully applied under EUS guidance in 73% (16/22) of patients with locally advanced pancreatic cancer and the procedure was well tolerated in all patients. In 6/16 patients, reduction in tumor size was noted on follow-up CT[83].

Photodynamic therapy: Photodynamic therapy (PDT) is a technique where a specific wavelength of light is delivered *via* optical fibers threaded through a needle placed in the target tissue[84]. Wavelength light is then activated by a photosensitizing agent which is usually administered intravenously. Photosensitizer is also present in pancreatic cancer at a sevenfold greater concentration compared with normal tissue[85]. The combination of a photosensitizing agent and wavelength light in the presence of oxygen leads to the generation of reactive oxygen species that can damage cellular constituents leading to cell death[86]. Unlike RFA, PDT is collagen sparing and preserves normal tissue architecture[87].

Promising results of PDT on cholangiocarcinoma have been reported including survival benefit[88-94] however its use in pancreatic cancer is still at an experimental stage. Three pilot trials of PDT in patients with locally advanced pancreatic cancer have demonstrated its feasibility and safety[86,95,96].

CONCLUSION

EUS-guided celiac plexus intervention is a useful adjunct to conventional analgesia for pain management in patients with pancreatic cancer. Direct injection into the celiac ganglia may result in a better response.

EUS-guided biliary drainage has emerged as a viable alternative to PTBD in patients who have failed ERCP. However, it should be performed by an interventional endoscopist with expertise in both ERCP and EUS at a tertiary center where surgery and radiology can provide support in case of adverse events.

EUS-guided anastomosis is in the preliminary stage of development and the majority of studies are limited to animal models. Major advancements in technique and prospective human trials are needed before it becomes a feasible alternative to surgery in patients at high risk of operative complications.

Results of trials with EUS-guided anti-tumor injection therapy have been disappointing. The lack of effective anti-tumor agents is a significant barrier to the development in this field.

EUS-guided brachytherapy and fiducial placement can be performed safely and easily. However, there is no available data to suggest clear survival benefit, although clinical benefit from pain relief has been noted in some studies.

The use of EUS-guided ablative therapies is still at an experimental stage. Further human trials are need to determine its clinical benefit.

To summarize, EUS is an indispensable tool in pancreatic cancer not only for tissue diagnosis and disease staging but also for therapeutic purposes. Although some EUS-guided therapies have become widely accepted interventions for patients with pancreatic cancer, others have yet to evolve. Given the lack of effective systemic treatment for pancreatic cancer at present, further research in this field is warranted.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Risk factors for local recurrence after *en bloc* endoscopic submucosal dissection for early gastric cancer

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Abstract

AIM: To investigate factors related to recurrence following *en bloc* resection using endoscopic submucosal dissection (ESD) in patients with early gastric cancer (EGC).

METHODS: A total of 1121 patients (1215 lesions) who had undergone ESD for gastric neoplasia between April 2003 and May 2010 were retrospectively reviewed. Data from 401 patients (415 lesions) were analyzed, following the exclusion of those who underwent piecemeal resection, with deep resection margin invasion or lateral margin infiltration, and diagnosed with benign lesions.

RESULTS: Local recurrence after *en bloc* ESD was found in 36 cases (8.7%). Unclear resection margins, long procedure times, and narrow safety margins were identified as risk factors for recurrence. Lesions located in the upper third of the stomach showed a higher rate of recurrence than those located in the lower third of the stomach (OR = 2.9, P = 0.03). The probability of no recurrence for up to 24 mo was 79.9% in those with a safety resection margin $\leqslant$ 1 mm and 89.5% in those with a margin > 1 mm (log-rank test, P = 0.03).

CONCLUSION: Even in cases in which *en bloc* ESD is performed for EGC, local recurrence still occurs. To reduce local recurrences, more careful assessment will be needed prior to the implementation of ESD in cases

in which the tumor is located in the upper third of the stomach. In addition, clear identification of tumor boundaries as well as the securing of sufficient safety resection margins will be important.

Key words: Early gastric cancer; Endoscopic mucosal resection; Recurrence; *En bloc* resection; Endoscopic submucosal dissection

Core tip: Unclear resection margins, long procedure times, and narrow safety margins were identified as risk factors for recurrence following *en bloc* endoscopic submucosal dissection (ESD) for early gastric cancer. Lesions located in the upper third of the stomach demonstrated more recurrences than those located in the lower third of the stomach. To reduce local recurrences, more careful assessment will be needed prior to the implementation of ESD in cases in which the tumor is located in the upper third of the stomach. In addition, clear identification of tumor boundaries as well as the securing of sufficient safety resection margins will be important.

Lee JY, Cho KB, Kim ES, Park KS, Lee YJ, Lee YS, Jang BK, Chung WJ, Hwang JS. Risk factors for local recurrence after *en bloc* endoscopic submucosal dissection for early gastric cancer. *World J Gastrointest Endosc* 2016; 8(7): 330-337 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i7/330.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i7.330

INTRODUCTION

As regular national gastric cancer screening *via* endoscopy is being implemented in South Korea with an increased interest in health, findings of early gastric cancer (EGC) and precancerous lesions are increasing rapidly[1,2]. In addition, due to advances in the development of endoscopy-related tools and equipment and improvements in the procedural skills of doctors, performing endoscopic treatment for EGC is getting easier[3]. As a result, existing endoscopic mucosal resection (EMR) has led to significant progress in endoscopic submucosal dissection (ESD), in terms of resection techniques, and regardless of the size of the lesions, *en bloc* resection has become possible[4].

The classic EMR method is a simple procedure, but it has limitations in that the ratio of *en bloc* resection to complete resection decreases depending on the size of the lesion[5,6]. In the contrast, the ESD method is a relatively complex procedure with a high level of difficulty, but it has a higher rate of *en bloc* resection than the EMR method, with the capacity to perform accurate post-resection pathological assessment, and it has recently become widely available as a treatment for EGC[5-8]. In endoscopic resection, accomplishing reconstruction of dissected tissues when the resection is performed in a piecemeal fashion and determining whether complete resection of the lesion has been achieved is difficult, and this results in higher rates of local recurrence. Therefore, *en bloc* resection is being suggested as the standard method of ESD as it increases the accuracy of pathological assessment of complete resection and lowers the rate of local recurrence[9]. Incomplete resection procedures have been identified as an independent factor that increases the risk of local recurrence[10], but although *en bloc* resection has been practiced, there have been very few studies on the risk factors associated with local recurrence after *en bloc* resection. To that end, the aim of the current study was to investigate factors related to local recurrence in patients with EGC who underwent *en bloc* resection *via* ESD.

MATERIALS AND METHODS

Study subjects

The medical records of 1121 patients (1215 lesions) who had undergone ESD for the treatment of gastric neoplasia between April 2003 and May 2010 at Keimyung University Dongsan Hospital (Daegu, South Korea) were retrospectively reviewed. Because we aimed to evaluate the risk factors for local recurrence after *en bloc* resection only and to analyze the risk factors depending on the safety resection margin, patients who underwent partial resection, with deep resection margin invasion or lateral margin infiltration, and diagnosed with benign lesions were excluded. Finally, data from 401 patients (415 lesions) were analyzed (Figure 1). Written informed consent was obtained from all patients. This study was approved by the Institutional Review Board of the Keimyung University Dongsan Medical Center, South Korea (DSMC 2015-10-047).

ESD methods

The ESD procedure was performed following a standard method. First the boundaries of the lesions were clarified using a solution of indigo carmine diluted to 10 times its volume, and the margins were marked with a 5 mm space from the boundaries of the lesions using an argon plasma laser connected to an ERBE VIO 300D electrosurgical unit (ERBE United States, Marietta, GA, United States). For submucosal injection, a solution was used consisting of hypertonic saline solution 100 mL, 1:1000 epinephrine 1 mL, and indigo carmine 1 mL. The incision knife was connected to the ERBE VIO 300D electrosurgical unit, a flex knife (Olympus, Tokyo, Japan) was used in mucosal incision, and the IT-2 knife (Olympus, Tokyo, Japan) was used for most submucosal dissection, but in some cases, a hook knife (Olympus, Tokyo, Japan) was used as well. Most procedures were carried out in Endocut Ⅰ mode (Effect 2), and in some portions containing blood vessels, forced coagulation

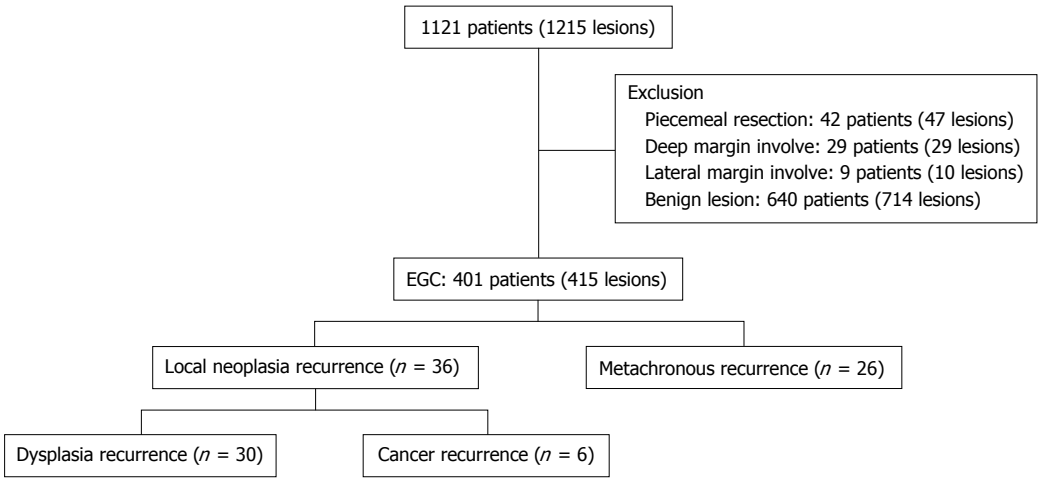

Figure 1 Flow chart of the patients. EGC: Early gastric cancer.

mode (Effect 1) was utilized.

Histopathological evaluation

For histopathological examination, resected specimens were sectioned perpendicularly at 2-mm intervals. The EGC location was classified into upper third, middle third, and lower third according to the location of the center point. The gross type of EGC was classified into type Ⅰ (protruded type), type Ⅱ (superficial type), and type Ⅲ (excavated type) in accordance with the classification methods of the Japan Gastroenterological Endoscopy Society, and type Ⅱ was subdivided again into type Ⅱa (superficial elevated), type Ⅱb (flat type), and type Ⅱc (superficial depressed type)[11]. In cases in which various shapes were mixed in one lesion, it was recorded as the mixed type. Based on the histological findings, tissues of the lesion were classified into differentiated type adenocarcinoma (well or moderately differentiated adenocarcinoma) and undifferentiated type adenocarcinoma (poorly differentiated or signet ring cell adenocarcinoma). Tumor involvement in the lateral and deep margins, lymphatic and vascular involvement, and the presence of submucosal invasion was assessed. In cases of submucosal infiltration, invasion depth was measured and quantified.

Evaluation of outcomes

The following clinical variables were investigated: Patient age, sex, gross tumor type, *en bloc* resection rate, location, size, histology, procedure time, safety margin, local neoplasia recurrence rate, and local cancer recurrence rate.

En bloc resection was defined as a resection in a single piece, whereas piecemeal resection was conducted in multiple pieces. Complete resection was defined as complete reconstruction of the lesion with negative deep and lateral margins with no lymphovascular involvement. The sizes of lesions were categorized into less than 20 mm, 21-30 mm, 31-40 mm, and over 40 mm. When malignant cells were found from the resection site within 3 mo after endoscopic removal of gastric carcinoma, the case was defined as incomplete resection, and when malignant cells or dysplastic cells (low grade, high grade) were found from the resection site during follow-up examinations after 3 mo, the case was defined as local recurrence of neoplasia. When only malignant cells were found from the resection site, the case was defined as local cancer recurrence. In addition, when neoplasia (dysplasia or malignant) was found from a site other than the resection site during follow-up observation, the case was defined as metachronous recurrence. Procedure time was defined as the time from the start of marking to complete removal of the tumor. Safety margins were defined as the distance between the lesion and the edges of the cuts around the resected specimen.

Follow-up observation

Patients were followed up with endoscopic examinations and biopsy at 3, 6, 12 and 24 mo after ESD. To detect local recurrence or metachronous cancer, biopsy was performed at the treatment-related scar in the case of any suspicious abnormalities. The cumulative neoplasia recurrence-free rate was estimated.

Statistical analysis

SPSS software version 18.0 for Windows (SPSS, Inc., Chicago, IL, United States) was used for statistical analysis. For comparison of continuous variables between two groups, the independent samples t-test was used, while for comparison of frequency variables, the χ^2 test was used through cross analysis. Continuous variables were presented as means ± SD, and count variables were presented in the forms of frequency and percentage. Multivariate analysis was performed using binary logistic regression methods. Cumulative recurrence rates and recurrence times were calculated by the Kaplan-Meier method, and they were compared with each other using a log-rank test. A *P* value less than 0.05 was considered statistically significant. The statistical methods of this study were reviewed by Lee YJ and Lee YS.

Table 1 Clinicopathologic feature of the 415 lesions treated with endoscopic submucosal dissection

	No. of lesions *n* = 415
Age, yr (mean ± SD)	64.2 ± 9.8
Sex, *n* (%)	
Male	291 (70.1)
Female	124 (29.9)
Gross type of tumor, *n* (%)	
Protruded (Ⅰ)	29 (7.0)
Superficial elevated (Ⅱa)	146 (35.2)
Flat (Ⅱb)	76 (18.3)
Superficial depressed (Ⅱc)	134 (32.3)
Excavated (Ⅲ)	2 (0.5)
Mixed	28 (6.7)
En bloc resection, *n* (%)	415 (100)
Piecemeal resection, *n* (%)	0 (0)
Tumor location, *n* (%)	
Upper	15 (3.6)
Mid	129 (30.9)
Lower	271 (65.0)
Tumor size, *n* (%)	
≤ 20 mm	116 (28.0)
21-30 mm	77 (18.8)
31-40 mm	122 (29.4)
> 40 mm	100 (24.1)
Histology, *n* (%)	
Well differentiated	195 (47.0)
Moderate differentiated	180 (43.4)
Poorly differentiated	30 (7.2)
Signet ring cell	10 (2.4)
Follow-up period, mo (mean ± SD)	19.7 ± 17.5

RESULTS

Characteristics of patients and lesions

The mean age of patients was 64.2 ± 9.8 years and 291 (70.1) patients were men. For the gross type of tumor, 146 (35.2%) cases were type Ⅱa and this was the most frequent type. Regarding the location of lesions, 271 (65.0%) patients had lesions in the lower third of the stomach, representing the highest frequency, followed by 129 (30.9%) patients with lesions in the mid-third of the stomach, and 15 (3.6%) patients with lesions in the upper third of stomach. Regarding the size of tumors removed by ESD, tumors ≤ 20 mm were found in 110 (28.0%) cases, tumors 21-30 mm were found in 77 (18.8%) cases, tumors 31-40 mm were found in 122 (29.4%) cases, and tumors over 40 mm were found in 100 (24.1%) cases. Histologically, well differentiated adenocarcinoma and moderately differentiated adenocarcinoma were observed in 195 (47.0%) and 180 (43.4%) cases, respectively, constituting ≥ 90%. The mean follow-up period for these patients was 19.7 mo (Table 1).

Comparison of the recurrence group and the non-recurrence group

Local neoplasia recurrence was observed in 36 (8.7%) cases, but there was no significant difference in age at the time of diagnosis, sex, tumor size, location, or degree of differentiation when compared to the non-recurrence group (Table 2). However, there were many recurrences in cases in which tumors had ill-defined margins (33.3% *vs* 17.4%, $P = 0.02$), long procedure times (63.5 min *vs* 48.8 min, $P = 0.02$), and narrow safety resection margins (3.1 mm *vs* 4.2 mm, $P = 0.03$) (Table 2). The performance of multivariate analysis revealed that ill-defined tumor margin was the element factor that related to local neoplasia recurrence ($P = 0.03$) (Table 2).

Factors related to sufficient safety resection margins

When 1 mm was used as the reference value, 63 (15.2%) cases were found to have safety resection margins ≤ 1 mm. There was no difference in age at the time of diagnosis, sex, tumor size, location, or degree of differentiation between the two groups. Nevertheless, the group with safety resection margins ≤ 1 mm was found to have more lesions located in the upper third and mid-third of the stomach ($P < 0.0001$) and had longer operation times ($P = 0.04$) (Table 3). Multivariate analysis revealed that the patients with lesions located in the upper third of the stomach demonstrated more recurrences than those with lesions located in the lower third of the stomach (OR = 2.900, 95%CI: 1.110-7.579, $P = 0.03$) (Table 4). Designating 1 mm as the safety resection margin, there was no difference in recurrence of neoplasia, but there was more frequent recurrence of cancer ($P = 0.006$) (Table 5).

Follow-up observation and cumulative local recurrence rate

During the entire follow-up observation period, 6 cases (6/415, 1.4%) were observed of the recurrence of malignancy at the same site, and 26 cases (26/415, 6.3%) were observed of metachronous gastric carcinoma (Figure 1). In addition, the probability of no recurrence for up to 24 mo was 79.9% in those with safety resection margin ≤ 1 mm and 89.5% in those with margins that exceeded 1 mm, indicating that the local recurrence of neoplasia was observed more frequently in those with safety resection margins ≤ 1 mm, and the difference between the two groups was significant ($P = 0.03$) (Figure 2).

DISCUSSION

In cases of lesions larger than 20 mm, ESD offers far superior *en bloc* resection rates and very low local recurrence rates when compared with EMR[12]. In general, the results of ESD for lesions larger than 20 mm have demonstrated an *en bloc* resection rate of over 90% with little local recurrence, while EMR has demonstrated very low *en bloc* resection rates of about 60% in cases of lesions sized about 10 mm and 14%-40% for lesions sized about 20-30 mm, and the local recurrence rate is about 10%[13,14]. Regarding the *en bloc* resection rate, following the resection, determining complete resection with histological accuracy and thereby significantly reducing the occurrence of any situations that require

Table 2 Risk factor associated with neoplasia recurrence

	Recurrence *n* = 36	No recurrence *n* = 379	Univariate *P* value	Multivariate *P* value
Age, yr (mean ± SD)	66.7 ± 9.0	64.0 ± 9.9	0.11	
Male/female	25/11	266/113	0.93	
Tumor margin, *n* (%)			0.02	0.03
Well-defined	24 (66.7)	313 (82.6)		
Ill-defined	12 (33.3)	66 (17.4)		
Tumor size, *n* (%)			0.62	
⩽ 20 mm	9 (25.0)	107 (28.2)		
21-30 mm	6 (16.7)	71 (18.7)		
31-40 mm	14 (38.9)	108 (28.5)		
> 40 mm	7 (19.4)	93 (24.5)		
Tumor location, *n* (%)			0.05	
Upper	3 (8.3)	12 (3.2)		
Mid	14 (38.9)	115 (30.3)		
Lower	19 (52.8)	252 (66.5)		
Histology, *n* (%)			0.7	
Well differentiated	17 (47.2)	178 (47.0)		
Moderate differentiated	13 (36.1)	167 (44.1)		
Poorly differentiated	6 (16.7)	24 (6.3)		
Signet ring cell	0 (0.0)	10 (2.6)		
Procedure time, min (mean ± SD)	63.5 ± 56.9	48.8 ± 34.3	0.02	0.06
Safety margin, mm (mean ± SD)	3.1 ± 2.1	4.2 ± 2.9	0.03	0.05

Table 3 Factors associated with sufficient safety margin after endoscopic submucosal dissection (Univariate)

	Safety margin ⩽ 1 mm *n* = 63	Safety margin > 1 mm *n* = 352	*P* value
Age, yr (mean ± SD)	65.9 ± 11.1	63.9 ± 9.5	0.14
Male/female	38/25	253/99	0.12
Tumor margin, *n* (%)			0.52
Well-defined	53 (84.1)	284 (80.7)	
Ill-defined	10 (15.9)	68 (19.3)	
Tumor size, *n* (%)			0.55
⩽ 20 mm	21 (33.3)	95 (27.0)	
21-30 mm	12 (19.0)	65 (18.5)	
31-40 mm	14 (22.2)	108 (30.7)	
> 40 mm	16 (25.4)	84 (23.9)	
Tumor location, *n* (%)			< 0.0001
Upper	7 (11.1)	8 (2.3)	
Mid	31 (49.2)	98 (27.8)	
Lower	25 (39.7)	246 (69.9)	
Histology, *n* (%)			0.85
Well differentiated	32 (50.8)	163 (46.3)	
Moderate differentiated	24 (38.1)	156 (44.3)	
Poorly differentiated	3 (4.8)	27 (7.7)	
Signet ring cell	4 (6.3)	6 (1.7)	
Procedure time, min (mean ± SD)	58.9 ± 43.8	48.5 ± 35.4	0.04

Table 4 Factors associated with sufficient safety margin after endoscopic submucosal dissection (Multivariate)

	Multivariate analysis	
	Odds ratio (95%CI)	*P* value
Location		
Upper	2.90 (1.11-7.58)	0.03
Mid	1.10 (0.48-2.55)	0.82
Lower	1 (ref)	
Ill-defined margin	2.32 (1.00-4.96)	0.03

unnecessary additional treatment, re-treatment, or surgical treatment due to local recurrence is possible. Due to these advantages, ESD is being used as a major treatment method for EGC.

The current study investigated the factors related to recurrence in patients with EGC who had undergone *en bloc* resection using ESD. Even in cases in which *en bloc* resection was performed, local recurrence of neoplasia was observed in 36 patients (8.7%). When a comparison was performed between the recurrence group and the non-recurrence group, the identified risk factors for recurrence included unclear resection margins, long procedure times, and narrow safety margins, whereas

Table 5 Neoplasia recurrence and cancer recurrence by safety margin 1 mm *n* (%)

	Safety margin ⩽ 1 mm *n* = 63	Safety margin > 1 mm *n* = 352	*P* value
Neoplasia recurrence	9 (14.3)	27 (7.7)	0.09
Cancer recurrence	4 (6.3)	2 (0.6)	0.006

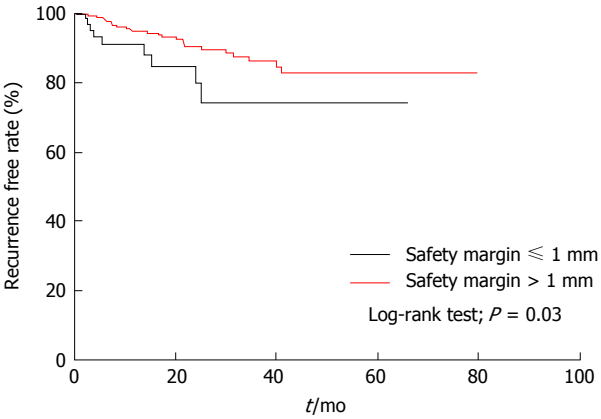

Figure 2 Cumulative neoplasia recurrence free rate according to period after endoscopic submucosal dissection. The probability of no recurrence up to 24 mo was 79.9% in those with the safety resection margin ⩽ 1 mm and 89.5% in those exceeded 1 mm.

among the factors related to sufficient safety resection margins, it was found that the location of the tumor was an important factor. In particular, tumor location in the upper third of stomach was identified as having the greatest association with recurrence.

The visual tumor boundaries and safety resection margins of tumors had been identified as the risk factors for local recurrence. The introduction of ESD has increased the rates of *en bloc* resection and complete resection, but incomplete resection, in which resection margins are found to be positive in the post-ESD pathological testing, remains problematic. This results in cases in which the degree of horizontal invasion at the lesion is not assessed accurately and there is a failure to secure sufficient safety resection margins prior to performing the procedure[15-17]. In the current study as well, the group with visually unclear tumor margins showed a higher rate of post-ESD recurrences (33.3% *vs* 17.4%, $P = 0.03$), and more incidences of recurrent tumors were found among those with safety resection margins ⩽ 1 mm. Thus, good visual observation of the boundaries of lesions and the securing of sufficient safety resection margins before performing the procedures would be helpful in reducing local recurrence. However, since it is better to attempt minimal incision in order to minimize the procedure time and complications, as possible, accurate diagnosis is required before performing ESD. There have been reports suggesting that in cases in which the boundaries of the tumor are unclear, a preoperative biopsy on the ambient area of the lesion could be useful[18,19], and the horizontal degree of invasion of the tumor could be assessed *via* chromoendoscopy[20] or narrow-band imaging magnifying endoscopy[21].

The most important factor that has effects on local recurrence following the implementation of EMR or ESD is whether complete resection is performed. Ono *et al*[22] reported that the rate of local recurrence was 2% in cases of complete resection, while in contrast, recurrence was found in 18% of 85 patients either who had incomplete resection or in whom it was impossible to make assessments. Isomoto *et al*[23] also reported that while only 0.2% of patients who underwent complete resection had experienced local recurrence, 10.3% of patients who had incomplete resection had been found to have local recurrence, indicating that the complete resection group had a statistically significant lower rate of local recurrence in comparison to the incomplete resection group. Takenaka *et al*[6] presented a study on factors affecting local recurrence following ESD. They reported no cases of local recurrence among lesions that had been completely resected, but patients who underwent incomplete resection had local recurrences. Statistical analysis had confirmed that incomplete resection and local recurrence had a very high level of correlation. The authors analyzed the factors that cause incomplete resection and identified tumor size ⩾ 30 mm, tumor location in the mid-third or upper third, and any ulcer or ulcerative scar on the lesion as the risk factors that can cause incomplete resection. Imagawa *et al*[24] also reported that tumor location (upper third, 74% *vs* mid-third, 77% *vs* lower third, 91%, $P < 0.05$) and tumor size (> 20 mm, 59% *vs* < 20 mm, 89%, $P < 0.0001$) were important elements of complete resection. In our study, it was confirmed that the more lesions were located in the upper third, the more frequent local recurrences were. However, according to the results of our study, tumor size was identified as having no significant correlation with recurrence, and it was considered that the procedures were implemented after securing sufficient safety resection margins considering the risk of recurrence as the tumor sizes increased. The underlying causes of more frequent local recurrences when lesions are located in the upper third of the stomach are, first, when the tumor is located nearer to the upper third, the endoscopic approach becomes difficult, resulting in difficult setting of accurate boundaries; second, this region has unclear boundaries of the mucosa in many cases; and third, this area has a larger distribution of blood vessels than any other site, which causes frequent bleeding during the procedure[25]. The use of side-view endoscopes or multi-bending endoscopes can offer easy access to these sites, which is very helpful in performing the procedures[26].

A molecular pathological epidemiology approach, which analyzes tumor molecular pathology of resected tumors, can predict recurrence after ESD. Semba *et al*[27] reported that EGC demonstrating intestinal claudin-positive phenotype has a high risk of synchronous and metachronous gastric neoplasia. Hasuo *et al*[28] investigated the correlation between microsatellite instability (MSI) status and the incidence of metachronous recurrence after initial ESD. They demonstrated that patients with the MSI-type tumors showed a high incidence of metachronous recurrence within a 3-year observation period after initial ESD. These molecular approaches are expected to be of value for decisions regarding therapy and surveillance after ESD.

The advantage of the current study is that it was conducted in patients who underwent *en bloc* resection only, and those patients with deep and lateral resection margin invasion were excluded, so that we could analyze the risk factors depending on the safety resection margins. However, the study also has limitations in that the follow-up periods were different, as it was a retrospective study, and there were differences in the number of biopsies during the follow-up endoscopy.

In conclusion, even in cases in which *en bloc* resection using ESD is performed for EGC, local recurrence occurs. In terms of risk factors related to local recurrence, tumor location and the visual boundaries of the tumor are important. In order to reduce post-ESD local recurrences, more careful assessment will be needed prior to the implementation of ESD in cases in which the tumor is located in the upper third of the stomach. In addition, clear identification of tumor boundaries as well as the securing of sufficient safety resection margins will be important.

COMMENTS

Background

En bloc resection is suggested as the standard method of endoscopic submucosal dissection (ESD) as it increases the accuracy of pathological assessment of complete resection and lowers the ratio of local recurrence. However, although *en bloc* resection has been practiced, there are few studies regarding the risk factors associated with local recurrence after *en bloc* resection.

Research frontiers

The authors aimed to investigate factors related to recurrence in patients who had undergone *en bloc* resection using ESD for early gastric cancer (EGC).

Innovations and breakthroughs

Unclear resection margins, long procedure times, and narrow safety margins were identified as risk factors for recurrence lesions located in the upper third of the stomach demonstrated more recurrences than those located in the lower third of the stomach.

Applications

Even in cases in which *en bloc* resection for ESD is performed, local recurrence occurs. Regarding risk factors related to local recurrence, tumor location and the visual boundaries of the tumor are important. In order to reduce post-ESD local recurrences, more careful assessment will be needed prior to the implementation of ESD in cases in which the tumor is located in the upper third of the stomach. In addition, clear identification of tumor boundaries as well as the securing of sufficient safety resection margins will be important as well.

Terminology

EGC is defined as malignant tumor confined to the mucosa or the submucosa regardless of lymph node metastases. ESD is an endoscopic technique for the treatment of early gastrointestinal neoplasms allowing direct dissection of the submucosal layer of the lesion with *en bloc* resection.

Peer-review

This is a large retrospective study on risk factor for local recurrence after ESD of early gastric cancer. The topic is important and interesting.

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ORIGINAL ARTICLE

Retrospective Study

Stent type used does not impact complication rate or placement time but can decrease treatment cost for benign and malignant esophageal lesions

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Author contributions: McGaw C and Munoz JC designed the research and wrote the initial manuscript; McGaw C and Alkaddour A collected the data; Vega KJ, and Munoz JC reviewed the data for completeness and revised the manuscript for intellectual content; Vega KJ performed the statistical analysis; McGaw C, Alkaddour A, Vega KJ and Munoz JC approved the final version for submission.

Institutional review board statement: This study was approved by the University of Florida Health Science Center-Jacksonville Institutional Review Board (IRB).

Informed consent statement: This study was retrospective, using previously collected endoscopic and hospital data, which did not require a specific informed consent other than each patient agreeing to treatment with written consent at the time of procedure.

Conflict-of-interest statement: No conflict of interest exists for all authors.

Data sharing statement: No additional data are available.

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Abstract

AIM: To evaluate if differences exist between self-expanding esophageal metal stents (SEMS) and self-expanding esophageal plastic stents (SEPS) when used for benign or malignant esophageal disorders with regard to safety, efficacy, clinical outcomes, placement ease and cost.

METHODS: A retrospective analysis was performed to evaluate outcome in patients having SEPS/SEMS placed for malignant or benign esophageal conditions from January 2005 to April 2012. Inclusion criteria was completed SEMS/SEPS placement. Outcomes assessed included technical success of and time required for stent placement, procedure-related complications, need for repeat intervention, hospital stay, mortality and costs.

RESULTS: Forty-three patients underwent stent placement for either benign/malignant esophageal

disease during the study period. Thirty patients had SEMS (25 male, mean age 59.6 years old) and 13 patients had SEPS (10 male, mean age 61.7 years old). Placement outcome as well as complication rate (SEPS 23.1%, SEMS 25.2%) and in-hospital mortality (SEPS 7.7%, SEMS 6.7%) after placement did not differ between stent types. Migration was the most frequent complication reported occurring equally between types (SEPS 66.7%, SEMS 57.1%). SEPS was less costly than SEMS, decreasing institutional cost by $255/stent.

CONCLUSION: SEPS and SEMS have similar outcomes when used for benign or malignant esophageal conditions. However, SEPS use results in decreased costs without impacting care.

Key words: Esophageal; Stent; Benign; Malignant; Complication; Placement; Cost

Core tip: Self-expanding esophageal metal stents (SEMS) are preferable to self-expanding esophageal plastic stents (SEPS) for treatment of malignant or benign esophageal conditions, due to decreased technical difficulties. Comparative studies between stent types evaluating differences between SEMS and SEPS for these conditions with regard to safety, efficacy, clinical outcomes, placement ease and cost are lacking. Retrospective analysis indicated placement outcome, complication rate, most frequent complication and in-hospital mortality after placement was equivalent between stent types. SEPS was less costly than SEMS. SEPS and SEMS have similar outcomes when used for malignant/benign esophageal conditions but SEPS results in decreased costs without impacting care.

McGaw C, Alkaddour A, Vega KJ, Munoz JC. Stent type used does not impact complication rate or placement time but can decrease treatment cost for benign and malignant esophageal lesions. *World J Gastrointest Endosc* 2016; 8(7): 338-343 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i7/338.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i7.338

INTRODUCTION

Placement of an esophageal stent is a minimally invasive procedure regularly used in both malignant and benign disease. Since the initial description in 1976, treatment using esophageal stents has advanced into a commonly accepted therapeutic technique for malignant esophageal strictures, fistulas and other complications[1-3]. The aim of esophageal stenting is to restore luminal patency and thereby nutritional intake, improving patient quality of life[2,4,5]. In addition, esophageal stent use has expanded to various inoperable malignancies localized in the esophagus, gastroesophageal junction and cardia as well as benign conditions including benign refractory strictures, anastomotic leaks, perforations, and trachea-esophageal fistulas[2-7].

Presently, the two most common types of self-expandable esophageal stents are the self-expandable esophageal plastic stent (SEPS), made from durable polymers and multiple self-expandable esophageal metal stent (SEMS), made from metal alloy compounds (Table 1)[3,7]. SEMS are considered preferable to SEPS for treatment of malignant or benign esophageal conditions, due to decreased technical difficulties at or following placement[8,9]. However, comparative studies of between stent types used for either benign or malignant esophageal conditions are limited with inconsistent results reported regarding technical outcome and migration[10-12]. The aim of the present investigation was to evaluate if differences exist between SEMS and SEPS placed for benign or malignant esophageal disorders with regard to safety, efficacy, clinical outcomes, placement ease and cost.

MATERIALS AND METHODS

A retrospective analysis was performed at the University of Florida Health Science Center-Jacksonville to evaluate the outcomes of patients undergoing endoscopic SEPS placement compared to endoscopic SEMS placement for malignant or benign esophageal conditions. Inclusion criteria were the following: Endoscopic esophageal stent placement between January 1, 2005 to April 30, 2012, presence of adenocarcinoma or squamous cell carcinoma of the esophagus, recurrent fistula caused by malignant tumor, benign esophageal strictures, and esophageal perforation or leak. Exclusion criteria were tumor above 2 cm from the upper esophageal sphincter. Clinical data obtained and assessed included technical success of stent placement, procedure-related complications, need for subsequent re-intervention, hospital stay, and mortality. Demographic and clinical data were collected from the local electronic medical record. Stent type selected for use was based on endoscopist and referring physician preference. Stent length was determined according to the size and localization of the tumor. All endoscopic treatments occurred under conscious sedation, monitored anesthesia, or general anesthesia. Initial evaluation occurred using standard esophagogastroduodenoscopy (EGD). If dilation was required, this was performed by means of fluoroscopic guidance prior to stent placement. Proximal and distal ends of the lesion to be stented was determined during EGD and hemoclips were used as markers to delineate both ends. A 0.35 mm tracer metro direct wire or Savary guide wire was used to assist placement. All stents used in the present investigation were from Boston Scientific, Marlborough, MA. The SEMS used was WallFlex fully covered with an institutional cost of $2650 and patient insurance cost of $4500. The SEPS used was Polyflex with an institutional cost of $2395 and patient insurance cost of $4090. All SEMS were placed under dual vision (fluoroscopy and endoscopy) while

Table 1 Currently available stents in the United States

Stent	Manufacturer	Material	Diameter body/flare (mm)	Length (cm)	Covering
Alimaxx-E	Alveolus	Nitinol	18/22	7/10/12	FC with antimigration struts
Esophageal Z-stent	Cook	Stainless steel	18/25	8/10/12/14	PC
Evolution	Cook	Nitinol	20/25	8/10/12.5/15	PC
Flamingo Wallstent	Boston Scientific	Stainless steel	20/30	12/14	PC
Gianturco-Z	Cook	Stainless steel	18/25	8/10/12/14	FC
Niti-S	Taewong Medical	Nitinol	16/20	8/10/12/14	FC
			18/23		
			20/25		
Niti-S; double layered	Taewong Medical	Nitinol	18/26	9/12/15	FC with additional uncovered outer nitinol wires
Niti-S; single layered	Taewong Medical	Nitinol	18/26	9/12/15	FC
Polyflex	Boston Scientific	Polyester	16/20	9/12/15	FC
			18/23		
			21/28		
SX-ELLA	Ella-CS	Nitinol	20/25	8.5/11/13.5/15	FC with antimigration ring
Ultraflex	Boston Scientific	Nitinol	18/23	10/12/15	PC
			23/28		
Wallflex	Boston Scientific	Nitinol	18/23	10/12/15	PC/FC
			23/28		

Adapted with permission from Curr Gastroenterol Rep 2013; 15: 319. PC: Partially covered; FC: Fully covered.

Table 2 Overall demographics in patients having self-expanding esophageal metal stents/self-expanding esophageal plastic stents placed for malignant or benign esophageal conditions from January 2005 to April 2012

	Overall (n = 43)	nHw (n = 25)	AA (n = 15)	Other (n = 3)
Mean age (yr)	60.2	57.7	60.4	80[1]
% male	85.1	80	80	100

[1]Compared to nHw (P < 0.01) and AA (P < 0.03). nHw: Non-Hispanic White; AA: African American.

SEPS were placed under fluoroscopy vision only due to the delivery system. Appropriate placement of the SEPS was confirmed by direct visualization using EGD to verify positioning. A contrast esophagogram was performed postoperatively at the discretion of the endoscopist. This study was approved by the University of Florida Health Science Center-Jacksonville Institutional Review Board.

Statistical analysis

Continuous data were described as mean ± SD and compared using two sided student t tests. Categorical data were presented as numbers or percentages and analyzed using appropriate χ^2 testing. Results were analyzed in relation to stent type placed (SEMS or SEPS). A P value of less than 0.05 was considered statistically significant. Data analysis was performed using the GraphPad Prism statistical analysis program (Kenneth J Vega, version 6, La Jolla, CA).

RESULTS

Patient characteristics

Forty-three patients underwent stent placement for either benign (8 patients) or malignant (35 patients) esophageal disease during the study period. Patients with benign esophageal disease had the following diagnosis: 3 with esophageal fistulas, 2 with extrinsic compression and 1 each with esophageal stricture, perforation or iatrogenic tear. Of the 35 patients with malignant esophageal disease, 14 patients had squamous cell carcinoma, 16 patients had adenocarcinoma and 5 patients had mixed malignant histology. Mean patient age of the overall group was 60.2 years (SD 13.5 years) and 81.4% were male (Table 2). Ethnicity was distributed as follows, 25 non-Hispanic Whites (nHw), 15 African Americans (AA) and 3 from other groups (2 Asian Americans and 1 Hispanic American). Compared to both nHw and AA, the other group was older [80 (other) *vs* 57.7 (nHw), P < 0.01 or 60.4 (AA) years, P < 0.03]. No significant difference was seen in the number of males in each ethnic group.

Stent groups

SEMS were placed in 30 patients and SEPS used in 13 patients. Patient characteristics of both stent groups are seen in Table 3. Mean age, percentage of male patients and ethnic distribution was equivalent in the SEMS and SEPS groups (Table 3). Both stent groups also were similar with regard to esophageal lesion location, percentage of malignant esophageal lesions and comorbid diseases (Table 3).

Stent placement, outcome and cost

Successful stent placement occurred in all SEMS and SEPS patients. No patient in either stent group required more than 1 stent initially. Table 4 illustrates placement and outcome comparisons between SEMS and SEPS. Dilation was more frequent in the SEPS group compared to SEMS (P = 0.023). No significant difference was seen between stent groups in initial placement time, complication rate, time to first complication, in hospital mortality, repeat intervention required frequency, length

Table 3 Patient characteristics based on stent type placed

	SEMS (n = 30)	SEPS (n = 13)	P value
Mean age (yr ± SD)	59.6 ± 14.87	61.7 ± 9.95	0.645
% male	83.3%	76.9%	0.681
Race/ethnicity, n (%)	AA: 9 (30%)	AA: 6 (46%)	0.704
	nHw: 18 (60%)	nHw: 7 (54%)	
	Other: 3 (10%)	Other: 0	
Malignant esophageal lesion, n (%)	25 (83.3%)	10 (76.9%)	0.681
Esophageal lesion location, n (%)	Upper third: 0	Upper third: 1 (7.7%)	0.15
	Middle third: 9 (30%)	Middle third: 6 (46.2%)	
	Lower third: 21 (70%)	Lower third: 6 (46.2%)	
Comorbid diseases, n (%)	HTN: 16 (53.3%)	HTN: 6 (46.2%)	0.747
	CAD: 7 (23.3%)	CAD: 2 (15.4%)	0.699
	COPD: 5 (16.7%)	COPD: 1 (7.7%)	0.649
	DM: 11 (36.7%)	DM: 3 (23.1%)	0.491

SEMS: Self-expanding esophageal metal stents; SEPS: Self-expanding esophageal plastic stents; nHw: Non-Hispanic White; AA: African American; HTN: Hypertension; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; DM: Diabetes mellitus.

Table 4 Placement and outcome comparisons between self-expanding esophageal metal stents and self-expanding esophageal plastic stents

	SEMS (n = 30)	SEPS (n = 13)	P value
Initial placement procedure time (min, mean ± SD)	33.17 ± 16.88	35.85 ± 27.39	0.696
Dilation required prior to stent placement	0	23%	0.023
Complications, n (%)	7 (23%)	3 (23%)	1
Time to first complication (n)	< 30 d: 6	< 30 d: 2	1
	> 30 d: 1	> 30 d: 1	
In-hospital mortality (%)	7%	8%	1
Re-intervention required (%)	20%	23%	1
30 d survival after procedure (%)	95%	80%	0.251
Length of stay (d, mean ± SD)	11.47 ± 12.78	12.15 ± 16.21	0.883

SEMS: Self-expanding esophageal metal stents; SEPS: Self-expanding esophageal plastic stents.

of stay and 30 d survival (Table 4). Stent migration was the most frequent complication, occurring in 4 SEMS and 2 SEPS patients. Interestingly, SEMS resulted in increased costs than SEPS with an average cost savings of $255-410 for each SEPS used instead of SEMS for hospital and patient insurance cost, respectively.

DISCUSSION

SEMS are considered preferable to SEPS for treatment of malignant or benign esophageal conditions, due to decreased technical difficulties[8,9]. However, comparative studies between stent types are limited[10-12]. The present study was designed to assess whether if differences exist between SEMS and SEPS use for benign or malignant esophageal disorders with regard to safety, efficacy, clinical outcomes, placement ease and cost. The results indicate SEPS and SEMS are equivalent when used for benign or malignant esophageal conditions with regard to initial placement time, complication frequency, time to initial complication, in-hospital mortality, repeat intervention need, 30 d post procedure survival and length of hospital stay. In addition, SEPS use results in decreased costs without impacting care for either benign of malignant esophageal conditions.

The current investigation is the first to compare use of SEMS and SEPS on a combined population of benign and malignant conditions of the esophagus. All stents were placed successfully which is consistent with previous literature evaluating stent placement in exclusive subsets of either benign or malignant esophageal disease (98%-100%)[10-12]. Comparison of procedure time required for initial SEMS and SEPS placement was only performed by 1 group previously[10]. Conio *et al*[10] found initial SEPS placement was significantly longer than SEMS by a median of 12 min. However, no difference was seen between mean initial placement procedure time based on stent type in the present study. Moreover, no significant difference was present regarding lesion type stented in the SEMS and SEPS groups removing a potential confounder for initial placement time and suggesting equivalent placement ease in all cases in spite of different delivery systems used.

Complication rates following SEMS and SEPS were equal in both stent groups. Interestingly, the rate observed (23% for both SEMS and SEPS) was less than the reported in the literature (46%-48%)[10-12]. The main complication seen was stent migration in both stent groups which is consistent with the majority of studies

evaluating stent type for either benign or malignant esophageal lesions[11,12]. However, no difference was seen between SEMS and SEPS in frequency of migration. Of note, earlier data has been inconclusive with regard to migration rates with one study suggesting fully covered stents (either metal or plastic) are more likely to migrate while another indicated SEPS migrated more frequently[10,12]. Only one patient had recurrent dysphagia following stent placement (received SEMS) which was treated conservatively. Furthermore, no difference was observed in re-intervention requirement, in-hospital mortality, length of initial hospital stay and 30 d survival between SEMS and SEPS groups.

Health care costs remain a significant concern in the United States in spite of the Affordable Care Act of 2010[13]. In addition, placement of esophageal stents decrease costs for both benign and malignant esophageal conditions[14]. The present study indicated that if using SEPS in contrast to SEMS for either benign or malignant conditions reduced cost between $255-410 per SEPS used. Moreover, as outcome was not affected by stent type used in our investigation, significant cost savings could be achieved with SEPS use only for esophageal conditions requiring endoscopic intervention.

Of note, a third, less commonly used self-expandable esophageal stent, the biodegradable (BD) - stent, has been developed as an alternative to SEPS. Currently available BD stent designs are the ELLA-BD stent (ELLA-CS, Hradec Kralove, Czech Republic), which is composed of polydioxanone, a surgical suture material and the poly-L-lactic acid (PLLA)-BD stent (Marui Textile Machinery, Osaka, Japan), which consists of knitted PLLA monofilament. These stents can be degraded by hydrolysis, which is accelerated at low ambient pH. Generally, BD stents begin to degrade after 4 to 5 wk following placement and dissolve completely after a period of 2 to 3 mo. The major strength of BD stent over SEMS or SEPS is that it does not require removal, even after migration, as it is dissolved by gastric acid, thus avoiding further procedures and potential morbidity[15].

We are aware of the limitations of the present investigation. The primarily limitation is the retrospective design. In addition, our study had a small sample size for SEPS patients. Nevertheless, the majority of previously published studies have included small samples of SEPS patients as well. Furthermore, classification of stents used according to degree covered (fully or partially) may have had an impact in the results but given the small number of subjects, this was not performed. Finally, selection bias could impacted the results observed as stent type selected for insertion was dependent on the endoscopist performing the procedure.

In conclusion, SEPS should be considered as a treatment option for any esophageal indication, benign or malignant, with no increase in complications and equivalent efficacy to SEMS. In addition, SEPS use appears cost effective for management of esophageal lesions requiring restoration of luminal patency compared to SEMS. Performance of prospective clinical trials comparing SEMS and SEPS should be implemented to validate these findings. Furthermore, investigations comparing esophageal stents should occur and include biodegradable stents as well as longitudinal evaluations of biodegradable stents with an increased *in vivo* half-life, to assess longer term stent patency, mitigate stent-related complications, and whether the need for repeat interventions is required.

COMMENTS

Background

Self-expanding esophageal metal stents (SEMS) are preferable to self-expanding esophageal plastic stents (SEPS) for treatment of malignant or benign esophageal conditions, due to decreased technical difficulties. Comparative studies between stent types evaluating differences between SEMS and SEPS for these conditions with regard to safety, efficacy, clinical outcomes, placement ease and cost are lacking.

Research frontiers

To evaluate if differences exist between SEMS and SEPS placed for benign or malignant esophageal disorders with regard to safety, efficacy, clinical outcomes, placement ease and cost.

Innovations and breakthroughs

Stent placement outcome, complication rate, most frequent complication and in-hospital mortality after placement was equivalent between stent types. SEPS was less costly than SEMS. SEPS and SEMS have similar outcomes when used for malignant/benign esophageal conditions but SEPS results in decreased costs without impacting care.

Applications

SEPS should be considered as a treatment option for any esophageal indication, benign or malignant, with no increase in complications and equivalent efficacy to SEMS. In addition, SEPS use appears cost effective for management of esophageal lesions requiring restoration of luminal patency compared to SEMS.

Terminology

SEPS are made from durable polymers and SEMS are made from metal alloy compounds.

Peer-review

Both SEMS and SEPS are considered useful for treatment of malignant or benign esophageal conditions. However, few comparative studies between stent types have been reported. The study compared the safety, efficacy, clinical outcomes, placement ease and cost between SEMS and SEPS for benign or malignant esophageal disorders and found SEPS is cheaper. This may be helpful for clinical doctors in choosing stent types.

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ORIGINAL ARTICLE

Retrospective Study

What is the impact of capsule endoscopy in the long term period?

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Author contributions: Akyuz F evaluated the recorded capsule endoscopy images; Ormeci A and Akyuz F collected the clinical data and wrote the manuscript, with contributions from Gokturk S, Pinarbasi B, Soyer OM, Evirgen S, Akyuz U and was responsible for the design of the study and collected the clinical data; Passage opening was evaluated with computerized tomography from Ormeci T; Akyuz F and Baran B performed the statistical analyses; Karaca C, Demir K, Kaymakoglu S and Besisik F participated in the design and coordination of the study; all authors read and approved the final manuscript.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Istanbul University, Istanbul Medical Faculty.

Informed consent statement: All patients provided written consent to undergo capsule endoscopy. All data are anonymized and there were no prospective interventions.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at filizakyuz@hotmail.com.

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Abstract

AIM: To assess the clinical impact of capsule endoscopy (CE) in the long-term follow-up period in patients with obscure gastrointestinal bleeding (OGIB).

METHODS: One hundred and forty-one patients who applied CE for OGIB between 2009 and 2012 were retrospectively analyzed, and this cohort was then questioned prospectively. Demographic data of the patients were determined *via* the presence of comorbid diseases, use of non-steroidal anti-inflammatory drugs anticoagulant-antiaggregant agents, previous diagnostic tests for bleeding episodes, CE findings, laboratory tests and outcomes.

RESULTS: CE was performed on 141 patients because

of OGIB. The capsule was retained in the upper gastrointestinal (GI) system in two of the patients, thus video monitoring was not achieved. There were 139 patients [62% male, median age: 72 years (range: 13-93 years) and a median follow-up duration: 32 mo (range: 6-82 mo)]. The overall diagnostic yield of CE was 84.9%. Rebleeding was determined in 40.3% (56/139) of the patients. The rebleeding rates of patients with positive and negative capsule results at the end of the follow-up were 46.6% (55/118) and 4.8% (1/21), respectively. In the multivariate analysis, usage of NSAIDs, anticoagulant-antiaggregant therapies (OR = 5.8; 95%CI: 1.86-18.27) and vascular ectasia (OR = 6.02; 95%CI: 2.568-14.146) in CE were detected as independent predictors of rebleeding. In the univariate analysis, advanced age, comorbidity, and overt bleeding were detected as predictors of rebleeding.

CONCLUSION: CE is a reliable method in the diagnosis of obscure GI bleeding. Negative CE correlated with a significantly lower rebleeding risk in the long-term follow-up period.

Key words: Capsule endoscopy; Small bowel; Obscure gastrointestinal bleeding; Rebleeding

Core tip: This study determines the results of using capsule endoscopy in obscure gastrointestinal bleeding in long-term. Our main aim was to describe the long-term clinical impact of capsule endoscopy during follow-up period. Positive capsule endoscopy results correlated with higher rebleeding rates. Independent predictors of rebleeding were detected to be usage of non-steroidal anti-inflammatory drugs, anticoagulant/antiaggregant therapy and vascular ectasia.

Ormeci A, Akyuz F, Baran B, Gokturk S, Ormeci T, Pinarbasi B, Soyer OM, Evirgen S, Akyuz U, Karaca C, Demir K, Kaymakoglu S, Besisik F. What is the impact of capsule endoscopy in the long term period? *World J Gastrointest Endosc* 2016; 8(7): 344-348 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i7/344.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i7.344

INTRODUCTION

Obscure gastrointestinal bleeding (OGIB) is a frequent problem in the daily gastroenterology practice that represents nearly 5% of all gastrointestinal (GI) hemorrhages[1-3]. The most extensive location of OGIB is small bowel, where it is usually far beyond the range of a standard endoscopic examination. Therefore, capsule endoscopy (CE) is the preferred technique to assess patients with OGIB[4-6]. The high specificity and sensitivity of CE in OGIB cases and increased diagnostic value of this method was shown in several previously published studies. Even though diagnostic value of CE is the focus point of most studies, in the literature there is not enough data about the long-term results of using CE and its effectiveness in predicting and assessment of rebleeding risks. In this study, our main aim was to determine the long-term clinical impact of capsule endoscopy during follow-up period.

MATERIALS AND METHODS

Patients

The data obtained from the patients presented to gastroenterology department and referred to endoscopy unit with OGIB from January 2009 to December 2012 was analyzed in a retrospective design. This cohort was then questioned prospectively.

Before the CE procedure, all of the patients were applied colonoscopy and upper GI endoscopy (GIE) in our endoscopy unit. The collected data from the patients included their demographics, previous intake of anticoagulant/antiaggregant therapy, non-steroidal anti-inflammatory drugs (NSAIDs), present comorbidities, their previous diagnostic test results [upper GIE, colonoscopy, radiological studies of small bowel, computerized tomography (CT) imaging], CE findings and follow-up data.

Before the CE procedure, the passage opening was evaluated using CT. CE was not undertaken in patients who had strictures or obstructions.

The study was done after the patients were informed about this study and the patients' written informed consents were taken according to Helsinki Declaration. The study was obtained from local ethics committee.

CE procedure

CE procedures were performed on an outpatient basis without hospitalization. Pillcam SB2 (Given Imaging, Yoqneam, Israel) was used for the procedure. Patients' bowel preparation was done using 4 L polyethylene glycol solution one day before the procedure. The patients swallowed the capsules (Pillcam SB2) in the outpatient clinic. Fluid intake was permitted 2 h and eating was allowed 4 h after the initial administration of capsules. Patients were instructed to check their stool for the ejection of capsule and to notify the endoscopy unit if it was not ejected. Failure of the capsule ejection in more than 2 wk was defined as capsule retention in the GI tract. One gastroenterologist (F-A) with extensive experience in small bowel endoscopy evaluated the recorded CE images.

Follow-up

Charts were used to gather full follow-up information including OGIB recurrence and CE complications. Each patient was called and reevaluated for the follow-up results. The period between the initial CE and last recorded follow-up appointment was defined as follow-up period. Overt bleeding or the decrease in Hb levels >

Table 1 Capsule endoscopy findings in patients with obscure gastrointestinal bleeding

Findings	*n* (%)
Positive findings in CE	118 (84.9)
Normal	21 (15.1)
Angiodysplasia	27 (19.42)
Polypoid lesion	25 (17.98)
Ulcer	25 (17.98)
Erosions	22 (15.82)
Malign lesions	7 (5.12)
Active bleeding	4 (2.87)
Portal hypertensive enteropathy	2 (1.43)
Mucosal bleeding	2 (1.43)
Arteriovenous malformation	2 (1.43)
Diverticulum	1 (0.71)
Parasite infection	1 (0.71)

CE: Capsule endoscopy.

Table 2 Evalution of rebleeding according to the demographic data *n* (%)

		Rebleeding (+)	Rebleeding (-)	*P*
Age, *n* (%)	< 70 yr	32 (32)	68 (68)	[1]0.001[b]
	> 70 yr	24 (61.5)	15 (38.5)	
Comorbidity		33 (66)	17 (34)	[2]0.001[b]
OGIB				
Overt		42 (48.8)	44 (51.2)	[2]0.015[a]
Occult		14 (26.4)	39 (73.6)	
Vasculary lesion		31 (72.1)	12 (27.9)	[2]0.001[b]
Positive capsule result		55 (46.6)	63 (53.4)	[2]0.001[b]
NSAIDs-anticoagulant antiaggregant therapy		19 (73.1)	7 (26.9)	[2]0.001[b]

[1]Pearson Ki-kare test; [2]Yates' Continuity Correction test. [a]$P < 0.05$; [b]$P < 0.01$. OGIB: Obscure gastrointestinal bleeding; NSAIDs: Non-steroidal anti-inflammatory drugs.

2 g/dL were considered as "rebleeding".

Statistical analysis

Statistical analysis was performed using Number Cruncher Statistical System 2007 with Power Analysis and Sample Size 2008 statistical software. The data was analyzed by definitive methods (mean, standard deviation, median, minimum, maximum, frequency, ratio,) together with Pearson's χ^2 test, Fisher-Freeman-Halton test, Yates's Continuity Correction test. In the determination of multivariate effects of the variables on rebleeding, Stepwise logistic regression analysis was used. Significance levels were determined as $P < 0.01$ and $P < 0.05$.

RESULTS

CE was performed on 141 patients with OGIB. The capsule was retained in the upper GI tract in two patients thus video monitoring was not achieved. The first patient was diagnosed as having achalasia after CE, and the second had gastric diabetic gastroparesis by further investigation. A total of 139 patients (62% male) who applied CE had available follow-up data. Median age of patients was 72 years (13-93) and median follow-up duration was 32 mo (6-82 mo). In 112 of the 139 (80.6%) patients, capsule transit time to caecum was within the recording time. Spontaneous elimination of the capsule within 2 wk was seen in 133 (95.4%) patients. Capsule retention was found in 6 patients (4.6%). The overt obscure bleeding rate was 61.9% ($n = 86$), whereas the rate for occult obscure bleeding was 38.1% ($n = 53$). Comorbidities were detected in 35.5% ($n = 50$) of the patients. NSAIDs, anticoagulant-antiaggregant drugs were used at a rate of 18.9% ($n = 26$). CE was positive in 118 (84.9%) patients (Table 1).

Long-term outcome of CE

Rebleeding was seen in 40.3% of the patients (26.4% occult and 48.8% overt bleeding, $P = 0.015$). The rebleeding rate was 46.6% (55/118) in patients with positive CE and 4.8% (1/21) with negative CE results at the end of follow-up period. Evaluation of rebleeding in relation with the demographic data is shown in Table 2. Both univariate and multivariate analyses were performed to find out the factors related with a higher risk of rebleeding. When we evaluated the effects of comorbidity, age, overt presentation, NSAIDs-anticoagulant-antiaggregant therapy and vascular lesion on rebleeding by stepwise logistic regression analysis, the OR for the effect of NSAIDs-anticoagulant-antiaggregant therapy on rebleeding was 5.8 (95%CI: 1.86-18.27), and 6.027 (95%CI: 2.56-14.14) for vascular lesions. Although, OR was 2.274 (95%CI: 0.86-5.98) for comorbidities, it was not statistically significant. The association analysis is detailed in Table 3. One patient who had diverticulosis coli and negative CE died because of bleeding at 46 mo. The specificity of the CE was found to be 95.2% and positive predictive value was 98.2% in the prediction of rebleeding. Treatment was applied to 29 patients (51.7%): Surgery ($n = 4$), argon plasma coagulation ($n = 11$), transcatheter aortic valve implantation (TAVI) (the reason of the bleeding was aortic stenosis so to treat that TAVI procedure was applied) ($n = 2$), hormonal therapy ($n = 2$), reason based treatment (NSAIDs, anticoagulant, antiplatelet, antiaggregant drugs withdrawal) ($n = 10$). Seven patients died at the end of the follow-up and six of them died because of a rebleeding episode.

DISCUSSION

For the diagnosis of OGIB, capsule endoscopy is a useful imaging technique. Therefore, it is accepted as a gold standard method and should be the first step in the management of patients with OGIB[7]. The number of studies about the results of CE in long-term is limited[8-10]. In this study, we assessed the impact of CE in the long-term period (median: 32 mo) in patients with OGIB. The diagnostic yield of CE was 84.9%. Rebleeding was determined in 40.3% (56/139) in patients with OGIB. Specificity of CE was 95.2% and positive predictive value for rebleeding was 98.2%. Previous studies in the

Table 3 Risk factors for rebleeding (univariate-multivariate analysis)

	Univariate			Multivariate		
	OR	95%CI	*P*	OR	95%CI	*P*
Comorbidity	5.176	2.442-10.972	0.001[b]	2.274	0.864-5.986	0.096
Age	3.400	1.574-7.342	0.001[b]	1.735	0.595-5.057	0.313
Overt OGIB	2.659	1.265-5.589	0.015[a]	1.222	0.490-3.048	0.667
NSAIDs-anticoagulant-antiagregant therapy	5.575	2.153-14.438	0.001[b]	5.843	1.868-18.275	0.002[b]
Vascular lesion	6.458	2.852-14.625	0.001[b]	6.027	2.568-14.146	0.001[b]
Positive CE results	17.460	2.269-134.371	0.001[b]	-	-	-

[a]$P < 0.05$; [b]$P < 0.01$. OGIB: Obscure gastrointestinal bleeding; NSAIDs: Non-steroidal anti-inflammatory drugs; CE: Capsule endoscopy.

Table 4 Rebleeding rates in different studies

Ref.	Total number of case	Follow-up duration (mo)	Rebleeding rates after negative CE (%)
Lai *et al*[11]	49	12	6
Macdonald *et al*[12]	49	17	11
Park *et al*[13]	51	32	36
Delvaux *et al*[14]	44	12	0
Iwamoto *et al*[16]	78	6	4
Lorenceau-Savale *et al*[17]	35	12	0
Koh *et al*[18]	51	23	23

CE: Capsule endoscopy.

literature reported lower bleeding ratios in patients with negative CE results in comparison with positive[11-13]. Delvaux *et al*[14]'s study on 44 patients in one-year follow-up period reported that the negative predictive values was 100% in patients with negative CE and the positive predictive values of CE were 94.4% in patients with positive CE results. Arakawa *et al*[15] also reported that none of their patients who had a normal CE had rebleeding. As compatible with the literature, only one patient has a rebleed who had a normal CE in our group. The follow-up time is important for patients who have negative CE. In our study, the mean follow-up duration for patients was 46 ± 21 mo (range: 6-82 mo). The rebleeding rate is variable in the literature (0%-36%, Table 4)[11-14,16-18]. However, the main restriction of these studies is the small group of patients and their relatively short follow-up periods. Rahmi *et al*[19] showed that overt OGIB at presentation was a risk factor for rebleeding. We also found that the rebleeding ratio was higher in overt obscure bleeding when compared with occult obscure bleeding (48.8% *vs* 26.4%, $P = 0.015$). Vascular lesions were more susceptible to rebleeding when it was compared with the others (72.1% *vs* 27.9%, $P = 0.001$). These results also confirm the results of previous studies[20,21]. In present study, NSAIDs-anticoagulant-antiaggregant therapy (OR = 5.8; 95%CI: 1.86-18.27) and vascular ectasia (OR= 6.02; 95%CI: 2.568-14.146) were detected as an independent risk factors for rebleeding in the multivariate analysis. In univariate analysis; advanced age, comorbidity, overt bleeding, were also detected as a predictors of rebleeding. Therefore, anticoagulant/antiaggregant/NSAIDs users, and vascular lesions in CE should be follow-up carefully because of the high rebleeding rate. Our long-term follow-up results were compatible with the short-term follow-up results in the literature[20-23].

In conclusion, CE is a reliable method in the diagnosis of obscure GI bleeding. Negative CE correlated with a significantly lower rebleeding risk in the long-term follow-up period.

COMMENTS

Background

Obscure gastrointestinal bleeding (OGIB) is a frequent problem in the daily gastroenterology practice that represents nearly 5% of all gastrointestinal (GI) hemorrhages. The most extensive location of OGIB is small bowel, where it is usually far beyond the range of a standard endoscopic examination. Therefore, capsule endoscopy (CE) is the preferred technique to assess patients with OGIB. The high specificity and sensitivity of CE in OGIB cases and increased diagnostic value of this method was shown in several previously published studies. Even though diagnostic value of CE is the focus point of most studies, in the literature there is not enough data about the long-term results of using CE and its effectiveness in predicting and assessment of rebleeding risks.

Research frontiers

Diagnosis of OGIB is mostly dependent on CE. However, there is not enough data about the long-term outcomes of patients with OGIB who applied CE.

Innovations and breakthroughs

The authors evaluated 139 patients with OGIB diagnosed by CE in a long-term follow-up study. Several risk factors for rebleeding were detected. Negative CE correlated with a significantly lower rebleeding rate.

Applications

CE is a safe, well-tolerated and powerful diagnostic tool which may also provide prognostic implications.

Terminology

OGIB usually originates from small bowel and is not detected by both

esophagogastroduedonoscopy and colonoscopy. CE is a device with a tiny camera. Following the administration of the capsule, the camera within the capsule can obtain pictures of GI tract and gut as it passes through the GI system of the patient. The images obtained are transferred into an external disk using wireless technology and those images are later reviewed by the gastroenterologist.

Peer-review

It is an important novel study on CE for diagnosis of obscure GI bleeding and rebleeding rates on long term basis.

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ORIGINAL ARTICLE

Retrospective Study

Risk factors for postoperative bleeding after gastric endoscopic submucosal dissection in patients under antithrombotics

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Author contributions: Shindo Y collected and analyzed the data, and drafted the manuscript; Matsumoto S provided analytical oversight and designed and supervised the study; Miyatani H, Yoshida Y and Mashima H revised the manuscript for important intellectual content; all authors have read and approved the final version to be published.

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Conflict-of-interest statement: The authors declare that there are no conflicts of interest.

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Abstract

AIM: To evaluate the risk factors for postoperative bleeding after gastric endoscopic submucosal dissection (ESD) based on the latest guidelines.

METHODS: A total of 262 gastric neoplasms were treated by ESD at our center during a 2-year period from October 2012. We analyzed the data of these cases retrospectively to identify the risk factors for post-ESD bleeding.

RESULTS: Of the 48 (18.3%) cases on antithrombotic treatment, 10 were still receiving antiplatelet drugs perioperatively, 13 were on heparin replacement after oral anticoagulant withdrawal, and the antithrombotic therapy was discontinued perioperatively in 25 cases. Postoperative bleeding occurred in 23 cases (8.8%). The postoperative bleeding rate in the heparin replacement group was 61.5%, significantly higher than that in the non-antithrombotic therapy group (6.1%). Univariate analysis identified history of antithrombotic drug use, heparin replacement, hemodialysis, cardiovascular disease, diabetes mellitus, elevated prothrombin time-international normalized ratio, and low hemoglobin level on admission as risk factors for post ESD bleeding. Multivariate analysis identified only heparin replacement (OR = 13.7, 95%CI: 1.2-151.3, P = 0.0329) as a significant risk factor for post-ESD bleeding.

CONCLUSION: Continued administration of antiplatelet agents, based on the guidelines, was not a risk factor for postoperative bleeding after gastric ESD; however, heparin replacement, which is recommended after withdrawal of oral anticoagulants, was identified as a significant risk factor.

Key words: Postoperative bleeding; Antithrombotic treatment; Gastric neoplasms; Endoscopic submucosal dissection

Core tip: There are few data on the risk factors for postoperative bleeding after gastric endoscopic submucosal dissection (ESD) in patients continued on antithrombotic treatment during the perioperative period. This study was aimed to evaluate the risk factors for postoperative bleeding after gastric ESD in patients continued or not continued on antithrombotic treatment. Univariate analysis showed that an antithrombotic agent user, especially heparin replacement was significantly associated with risk factors for postoperative bleeding. Multivariate analysis identified heparin replacement as the independent risk factor for post ESD bleeding. Therefore, patients with heparin replacement should be carefully observed after gastric ESD.

Shindo Y, Matsumoto S, Miyatani H, Yoshida Y, Mashima H. Risk factors for postoperative bleeding after gastric endoscopic submucosal dissection in patients under antithrombotics. *World J Gastrointest Endosc* 2016; 8(7): 349-356 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i7/349.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i7.349

INTRODUCTION

Early gastric cancer is defined as a tumor confined to the mucosa or submucosa, irrespective of the presence/absence of lymph node metastasis[1]. Endoscopic submucosal dissection (ESD) is a widely used procedure now for early gastric cancers and gastric adenomas[2,3]. The major complications of this procedure are perforation and postoperative bleeding. Postoperative bleeding after gastric ESD is reported to occur in 4.8%-9.4% of patients not receiving antithrombotic agents/patients in whom these drugs are discontinued during the perioperative period[4-9]. While several factors (large resected tumor size[6,8], advanced age of the patient, long procedure time[10,11], patient under dialysis, and ulcerative lesions[12,13]) have been suggested as risk factors for postoperative bleeding after gastric ESD, no consensus has been reached yet with regard to the precise risk factors for postoperative bleeding after gastric ESD.

Recently, the incidence of gastric cancer has been increasing, owing to the increasing lifespan of the general population[14]. The number of patients suffering from gastric cancer and taking antithrombotic agents is also growing as a result of the increasing prevalence of ischemic heart disease, cerebrovascular disease, and other arteriosclerotic diseases. The previous guidelines published by the Japan Gastroenterological Endoscopy Society (JGES) focused primarily on the prevention of hemorrhage after gastrointestinal endoscopy associated with continuation of antithrombotic therapy in the perioperative period, without considering the risk of thrombosis associated with withdrawal of the therapy[15]. The new edition of the JGES guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment was published in July 2012. The new guidelines include discussions of the risk of gastroenterological hemorrhage associated with continuation of antithrombotic therapy, as well as of the risk of thromboembolism associated with discontinuation of antithrombotic therapy[16]. There are few data on the risk factors for postoperative bleeding after gastric ESD in patients continued on antithrombotic treatment during the perioperative period.

We have been performing ESD for gastric neoplasms based on the new guidelines since October 2012. This study was aimed at evaluating the risk factors for postoperative bleeding after gastric ESD in patients continued or not continued on antithrombotic treatment.

MATERIALS AND METHODS

Patients

The subjects were 283 cases who underwent ESD for gastric neoplasms at Saitama Medical Center from October 2012 to September 2014. Of these cases, 21 cases were excluded from this retrospective study for the following reasons: Multiple lesions were removed on the same day (19 cases), and the procedure could not be completed (2 cases).

Patient characteristics

We retrospectively reviewed the patient's medical records and collected the following data: Age, sex, hemoglobin level, prothrombin time-international normalized ratio (PT-INR), comorbidities (hypertension, diabetes mellitus, cardiovascular disease, hemodialysis, or liver cirrhosis), the Charlson comorbidity index[17,18], and details about any antithrombotic therapy. Patients taking antithrombotic agents were classified into three groups based on the guidelines: A group in which the antithrombotic therapy was discontinued, a group in which antiplatelet drug therapy was continued (including replacement of thienopyridine with aspirin or cilostazol)[16], and a group in which oral anticoagulant treatment was replaced by heparin. We used continuous infusion of unfractionated heparin for heparin replacement. The start dose of unfractionated heparin was 10000 to 15000 units. Check activated partial thromboplastin time during continuous infusion; adjust to target of 1.5 to 2 times the upper limit of control. We stopped continuous heparin infusion four to six hours

before procedure.

ESD procedure

ESD was performed using the conventional single-channel endoscope (GIF-Q260J, or -H260Z; Olympus, Tokyo, Japan) and a high-frequency electrical generator (VIO 300D; Erbe, Tubingen, Germany) by 15 endoscopists. An expert endoscopist was defined as one who had the experience of performing more than 50 gastric ESDs. After marking dots circumferentially on the surrounding normal mucosa 5-10 mm away from the lesion demarcation line, a mixture of 10% glycerin and 0.4% sodium hyaluronate solution (Mucoup; Johnson and Johnson, Tokyo, Japan) containing indigo carmine and 0.01% epinephrine was injected submucosally. A circumferential incision was performed using the Dual knife (KD-650L; Olympus, Tokyo, Japan) or Flush knife (DK2618JN20; Fujinon, Tokyo, Japan). After the circumferential incision was completed, the submucosa was dissected using the Dual knife, Flush knife, or IT2 knife (KD-611L; Olympus, Tokyo, Japan). Hemostatic forceps (FD-410LR; Olympus, Tokyo, Japan) were used to control the bleeding during and after the procedure. A second-look endoscopy was performed routinely the following weekday, and preventive coagulation of visible vessels was performed[19]. A proton pump inhibitor, that is, omeprazole 20 mg, was administrated intravenously twice a day starting on the day of the ESD until the day before the start of a soft diet. Then, oral administration of esomeprazole 20 mg was started and continued for 8 wk after the ESD.

Lesion characteristics and curability

All lesions were pathologically examined on the basis of the Japanese Classification of Gastric Carcinoma[1]. The macroscopic type was classified as the protruded type, flat type, or depressed type. The size of the tumor and the resected area were measured on the specimen. The location of the tumor was classified as the upper third, middle third, or lower third of the stomach. The depth of the tumor invasion was classified as pT1a (up to the mucosa) or pT1b (up to the submucosa). Invasion of the submucosal layer (SM) was divided into SM1 (less than 0.5 mm from the muscularis mucosae) and SM2 (more than 0.5 mm submucosal invasion). The tumor differentiation grade was based on the most dominant differentiation grade, and the tumors were classified as adenoma, differentiated cancer (including well-differentiated, moderately differentiated, tubular, and papillary adenocarcinoma), or undifferentiated cancer (poorly differentiated adenocarcinoma and signet-ring cell carcinoma).

En bloc resection was defined as resection in a single piece. Complete resection was defined as *en bloc* resection of a tumor with a negative horizontal margin and vertical margin. Curative resection was defined as follows: *En bloc* resection, tumor size $\leqslant$ 2 cm, differentiated-type tumor, pT1a, ulceration (Ul)-negative, no lymphovascular infiltration [ly(-), v(-)], negative horizontal margin (HM0), and negative vertical margin (VM0). The expanded indications of curative resection were as follows: *En bloc* resection, ly(-), v(-), HM0, and VM0, as well as: (1) tumor size $\geqslant$ 2 cm, differentiated-type tumor, pT1a, Ul(-); (2) tumor size $\leqslant$ 3 cm, differentiated-type tumor, pT1a, Ul(+); (3) tumor size $\leqslant$ 2 cm, undifferentiated-type tumor, pT1a, Ul(-); and (4) tumor size $\leqslant$ 3 cm, differentiated-type tumor, pT1b (SM1)[20,21]. All other lesions were classified as non-curative resection.

Adverse events

Postoperative bleeding was defined as bleeding events, including hematemesis and/or melena, after the procedure requiring endoscopic hemostasis, or a decrease of the hemoglobin level by more than 2 mg/dL as compared to the preoperative hemoglobin level.

Statistical analysis

Data are expressed as mean ± SD or as percentages. Statistical analysis was carried out using student's *t*-test or Fisher's exact test. Factors identified as significant by the univariate analysis ($P < 0.15$) were entered into a multivariate logistic regression analysis model. All data analyses were carried out using the StatView software (version 5.0; SAS Institute Inc., Cary, North Carolina, United States). Differences with *P* values of less than 0.05 were considered as denoting significance. The statistical methods of this study were reviewed by Dr. Satohiro Matsumoto from the Department of Gastroenterology, Jichi Medical University, Saitama Medical Center, Saitama, Japan.

RESULTS

The overall clinicopathological profiles of the 262 gastric neoplasms in 250 patients are shown in Table 1. Twelve patients had received treatment for 2 lesions occurring metachronously during the investigation period, and were counted twice. The mean age of the patients was 71 ± 8 years (range 32-87) (M:F = 190:72). Of the 262 cases, 48 (18.3%) had a history of receiving antithrombotic therapy for cardiovascular diseases. The details of the antithrombotic therapy were as follows: Aspirin 28 cases, clopidogrel 6 cases, ticlopidine 1 case, cilostazol 4 cases, and warfarin 14 cases. Perioperative management of the antithrombotic therapy was as follows: The antithrombotic drugs were discontinued in 25 cases, the antiplatelet agents were continued in 10 cases, and oral anticoagulant treatment was replaced by heparin in 13 cases (most of the patients who were under warfarin treatment received heparin replacement, except one patient who had past history of paroxysmal atrial fibrillation).

The mean tumor size was 15.9 ± 10.9 mm (range, 2-85 mm). The gastric tumors were mainly located in the lower third and in the lesser curvature of the stomach. The *en bloc* resection rate was 98.8% (259 cases) and the curative resection rate was 66.8%

Table 1 Overall clinicopathological profiles of 262 gastric neoplasms in 250 patients

Patients background factors	
Age (yr, mean ± SD) (range)	71 ± 8 (32-87)
Sex (male/female)	190/72
Antithrombotic agent user	48 (18.3%)
Detail	
Aspirin	28
Clopidogrel	6
Ticlopidine	1
Cilostazol	4
Warfarin	14
Heparin replacement (withdrawal warfarin)	13
Hemodialysis	6 (2.3%)
Hypertension	130 (49.6%)
Diabetes mellitus	54 (20.6%)
Cardiovascular disease	48 (18.3%)
Resected lesion factors	
Curability (curative/expanding indications curative/non-curative)	175/57/30
Macroscopic type (depressed/flat/protruded)	151/101/10
Location (upper third/middle third/lower third)	38/73/151
Circumference (anterior wall, greater curvature, lesser curvature, posterior wall)	38/52/124/48
Tumor size (mm, mean ± SD) (range)	15.9 ± 10.9 (2-85)
Differentiation (adenoma/differentiated cancer/undifferentiated cancer)	34/216/12
Depth (M:SM1:SM2)	236/12/14
Ulcer findings positive	16 (6.1%)
Lymphovascular infiltration positive	18 (6.9%)
Horizontal or vertical margin positive	8 (3.1%)
Perioperative factors	
En bloc resection	259 (98.8%)
Operator (beginner/expert)	97/165
Operation time (min, mean ± SD) (range)	81.5 ± 50.9 (16-307)
Resected size (mm, mean ± SD) (range)	36.1 ± 11.6 (12-88)
Perforation	2 (0.8%)
Postoperative bleeding	23 (8.8%)
Blood transfusion (%)	7 (2.7%)

SM: Submucosal layer.

(175 cases). The curative resection rate according to the expanded indications was 21.8% (57 cases). The non-curative resection rate was 11.5% (30 cases). Postoperative bleeding occurred in 23 cases (8.8%). Perforation during ESD occurred in 2 cases. No events of thromboembolism occurred with discontinuation of the antithrombotic therapy. Among the 23 patients who had postoperative bleeding, 6 (26.1%) needed blood transfusion. One patient needed blood transfusion due to underlying anemic disease.

Univariate analysis carried out to determine the risk factors for postoperative bleeding identified antithrombotic agent user (P = 0.0011), heparin replacement (P < 0.0001), hemodialysis (P = 0.0321), diabetes mellitus (P = 0.0435), cardiovascular disease (P = 0.0069), PT-INR (P < 0.0001), and the hemoglobin level on admission (P < 0.0153) as risk factors for postoperative bleeding (Table 2).

The postoperative bleeding rates in the group in which the antithrombotic therapy was discontinued and the group in which the antiplatelet agents were continued were 0% (0/25) and 20% (2/10), respectively. These rates were not significantly different from the rate in the non-antithrombotic therapy group (6.1%, 13/201). On the other hand, the postoperative bleeding rate in the heparin replacement group was 61.5% (8/13), which was significantly higher than the rate in the non-antithrombotic group (6.1%) (P < 0.0001) (Figure 1).

Multivariate analysis identified heparin replacement (OR = 13.7; 95%CI: 1.2-151.3, P = 0.0329) as the only significant risk factor for post ESD bleeding. It appeared that the tumor location in the lower third of the stomach may be related to postoperative bleeding; however, the difference in the bleeding rate was not statistically significant (OR = 2.9, 95%CI: 0.92-8.94, P = 0.0697) (Table 3).

DISCUSSION

We investigated risk factors for postoperative bleeding in patients undergoing gastric ESD based on the new guidelines published by the JGES[16]. The postoperative bleeding rate in the group not under anti-thrombotic therapy was 6.1% (13/214), which was consistent with previous reports (4.81%-9.4%)[4-9]. Antithrombotic agents were used in 18.3% of the cases (48/262), and the postoperative bleeding rate increased in the following order, depending on the perioperative management of antithrombotic therapy: Group in which the antithrombotic therapy was discontinued (0%, 0/25), group in

Table 2 Univariate analysis of postoperative bleeding

	Present (n = 23)	Absent (n = 239)	P value
Patients background factors			
Age (yr, mean ± SD) (range)	73 ± 7 (58-82)	71 ± 8 (32-87)	0.4304
Sex (male/female)	7/16	174/65	0.7397
Antithrombotic agent user	10 (43.5%)	38 (15.9%)	0.0011[1]
Category of antithrombotic treatment (non-antithrombotic therapy/discontinuation of antithrombotic agents/continuation of antiplatelet agents/heparin replacement)	13/0/2/8	201/25/8/5	< 0.0001[1]
Hemodialysis	2 (8.7%)	4 (1.7%)	0.0321[1]
Hypertension	10 (43.5%)	120 (50.2%)	0.5375
Diabetes mellitus	1 (4.3%)	53 (22.1%)	0.0435[1]
Cardiovascular disease	9 (39.1%)	39 (16.3%)	0.0069[1]
PT-INR (mean ± SD) (range)	1.2 ± 0.5 (0.9-2.1)	0.9 ± 0.1 (0.9-2.0)	< 0.0001[1]
Charlson comorbidity index (mean ± SD) (range)	3.5 ± 1.2 (1-6)	3.2 ± 1.3 (0-8)	0.2674
Hemoglobin levels on admission (g/dL, mean ± SD) (range)	12.5 ± 1.3 (9.6-14.4)	13.3 ± 1.5 (7.8-17.1)	0.0153[1]
Resected lesion factors			
Curability (curative/expanding indications curative/non-curative)	19/3/1	156/54/29	0.2305
Macroscopic type (depressed/flat/protruded)	11/11/1	140/90/9	0.6058
Location (upper third/middle third/lower third)	2/3/18	36/70/133	0.0907
Circumference (anterior wall, greater curvature, lesser curvature, posterior wall)	3/4/11/5	35/48/113/43	0.9645
Tumor size (≥ 21 mm)	3 (13.0%)	51 (21.3%)	0.3476
Differentiation (adenoma/differentiated cancer/undifferentiated cancer)	3/2/18	31/198/10	0.6108
Depth (M:SM1:SM2)	22/0/1	214/12/13	0.525
Ulcer findings positive	0 (0%)	16 (6.7%)	0.2003
Lymphovascular infiltration positive	1 (4.3%)	17 (7.1%)	0.6166
Horizontal or vertical margin positive	1 (4.3%)	7 (2.9%)	0.7204
Tumor size (mm, mean ± SD)	17.3 ± 16.1 (6-85)	15.7 ± 10.3 (2-70)	0.5147
Perioperative factors			
Operator (beginner/expert)	9/14	88/151	0.8265
Resected size (mm, mean ± SD) (range)	38.9 ± 12.8 (25-88)	35.8 ± 11.5 (12-85)	0.5147
Perforation (%)	1 (4.3%)	1 (0.4%)	0.1286
Operation time (min, mean ± SD) (range)	87.4 ± 63.5 (31-260)	80.9 ± 49.6 (16-307)	0.5608

[1]Significantly different. SM: Submucosal layer; PT-INR: Prothrombin time-international normalized ratio.

Table 3 Multivariate analysis of postoperative bleeding

Risk factors	Odds ratio	95%CI	P value
Cardiovascular disease	1.1	0.09-13.2	0.931
Diabetes mellitus	0.2	0.02-1.8	0.156
Hemodialysis	3.3	0.17-65.1	0.434
Heparin replacement	13.7	1.2-151.3	0.033[1]
Location lower third	2.9	0.9-8.9	0.07

[1]Significantly different.

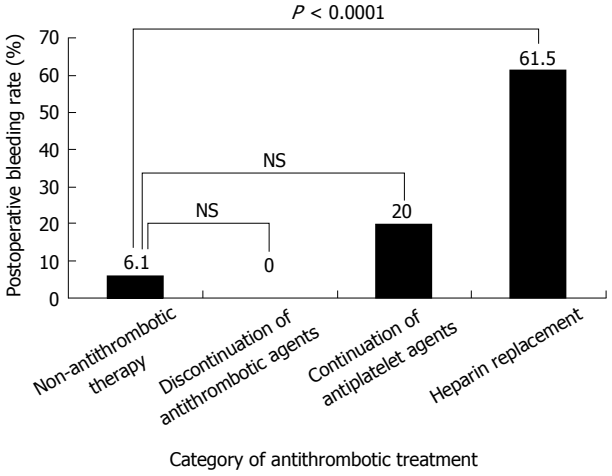

Figure 1 Comparison of the postoperative bleeding rate after gastric endoscopic submucosal dissection according to category of antithrombotic treatment. NS: Not significant.

which antiplatelet agents were continued (20%, 2/10), and the group which received heparin replacement (61.5%, 8/13).

While one previous report suggests that antiplatelet drugs do not increase the risk of postoperative bleeding after ESD[22], there are several reports contending that antiplatelet drugs increase the risk of postoperative bleeding[23-25]. On the other hand, withdrawal of antithrombotic therapy has been reported to increase the risk of development of thromboembolic events[22].

Although there is no mention about ESD, the 2009 guidelines published by the American Society for Gastrointestinal Endoscopy (ASGE) recommend continuation of aspirin in endoscopy candidates at a high risk of thrombosis. And in patients taking thienopyridines, ASGE recommends substitution of the thienopyridine with aspirin for 7-10 d[26]. The 2011 guidelines of the European Society of gastrointestinal Endoscopy also recommend continuation of aspirin in patients at a high risk of thrombosis. However, the risk of bleeding doubles when the lesions are removed by ESD rather than by endoscopic mucosal resection. Discontinuation of all antiplatelet agents, including aspirin, is recommended, provided that the patient is not at a high risk for thrombotic events[27]. The new JGES guidelines suggest

that withdrawal of aspirin monotherapy is not required in patients who would be at a high risk of thromboembolic events following withdrawal of the drug. Aspirin can be withdrawn for 3 to 5 d in patients who are low-risk candidates for thromboembolism. Thienopyridines should be discontinued for 5 to 7 d, and substitution with aspirin or cilostazol should be considered[16]. In our study, the postoperative bleeding rate in the patient group that was continued on antiplatelet drug therapy during the perioperative period was 20%, which is not significantly higher than the reported rate in patients not on antithrombotic drug therapy.

On the other hand, the JGES guidelines recommend heparin replacement after oral anticoagulant agent withdrawal for patients who need to be continued on anticoagulant therapy. Such patients should be treated as high-risk patients, because once thromboembolic complications have occurred, they are often serious[16]. In this study, 13 of the 14 patients who were on oral anticoagulant therapy received heparin replacement. Although the sample size in this study was small, the postoperative bleeding rate in the heparin replacement group was significantly higher (61.3%, 8/13) as compared with that in the patient group not on antithrombotic drug therapy (6.1%, 13/201). Thus, heparin replacement was identified as an independent, significant risk factor for postoperative bleeding after gastric ESD by both univariate analysis and multivariate analysis. Four of the 6 patients who required blood transfusion after gastric ESD were from the heparin replacement group (data not shown). This suggests that heparin replacement is associated with a significant increase in the risk of massive bleeding as compared to the other groups once postoperative bleeding occurred. There are few reports of investigation of the safety of heparin replacement after withdrawal of anticoagulant therapy in patients undergoing gastric ESD; however, all report high postoperative bleeding rates (23.8%-37.5%)[24,28]. In our study, the postoperative bleeding rate was much higher (61.3%, 8/13) than that reported in previous studies. According to Yoshio *et al*[28] reported that in the heparin replacement group, postoperative bleeding occurred in 2 of 8 cases with tumors in the upper third of the stomach, 5 of 9 cases with tumors in the middle third, and 2 of 7 cases with tumors in the lower third of the stomach. The corresponding values in our study were 2/3, 0/0 and 6/10. Thus, the tumor location might have some influence on the postoperative bleeding rate; however, investigation including a larger number of cases would be required.

Recently, several new oral anticoagulants (NOACs) have been introduced. The NOACs show prompt effects and have shorter half-lives than warfarin[29,30]. Therefore, in patients on anticoagulant therapy scheduled for gastric ESD, it may be better to substitute warfarin with NOACs rather than with heparin. Tsuji et al. reported that use of polyglycolic acid sheets and fibrin glue decreased the risk of bleeding after gastric ESD[31]. This technique, as well as preventive coagulation of visible vessels[19], should be considered to prevent postoperative bleeding in high-risk patients, such as those receiving heparin replacement.

Our investigation had some limitations, as follows: The study was a retrospective study from a single center, and the sample size was small. Detailed prospective investigations are necessary in the future.

In regard to the risks associated with gastric ESD in patients on antithrombotic therapy, continuation of antiplatelet drugs, based on the guidelines, during the perioperative period was not associated with an elevated risk of postoperative bleeding after gastric ESD; the heparin replacement after oral anticoagulant agent withdrawal for patients should be considered carefully for postoperative bleeding after gastric ESD.

COMMENTS

Background

The latest guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment, published in July 2012 by the Japan Gastroenterological Endoscopy Society, include discussions of postoperative bleeding associated with continuation of antithrombotic therapy, as well as of the risk of thromboembolism associated with withdrawal of antithrombotic treatment.

Research frontiers

The new guidelines include discussions of the risk of gastroenterological hemorrhage associated with continuation of antithrombotic therapy, as well as of the risk of thromboembolism associated with discontinuation of antithrombotic therapy. There are few data on the risk factors for postoperative bleeding after gastric endoscopic submucosal dissection (ESD) in patients continued on antithrombotic treatment during the perioperative period.

Innovations and breakthroughs

The postoperative bleeding rate in the heparin replacement group was 61.5%, significantly higher than that in the non-antithrombotic therapy group (6.1%). Multivariate analysis identified only heparin replacement as a significant risk factor for post-ESD bleeding.

Applications

The heparin replacement after oral anticoagulant agent withdrawal for patients should be considered carefully for postoperative bleeding after gastric ESD.

Terminology

Polyglycolic acid is an absorbent suture reinforcement material, which expected for the prevention of post-ESD bleeding in patients with a high risk of bleeding undergoing gastric ESD.

Peer-review

This study was well written and presented. ESD is a novel technique. Endoscopists have to accept the need for advanced endoscopic techniques for performing this technique. Anti-coagulants and anti-platelet agents are widely used to prevent thromboembolic disease.

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