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Contents

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REVIEW

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

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Abstract

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

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

retrograde cholagiopancreatography; Pancreatic cystic neoplasm; Pancreatic endocrine tumours

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

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INTRODUCTION

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

Locally advanced pancreatic cancer

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

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

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

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

Pancreatic neuroendocrine tumours

Pancreatic neuroendocrine tumours (PNETs) are usually

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

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

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

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

Pancreatic cystic lesions

Pancreatic cystic lesions (PCLs) are extremely common,

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

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

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

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

RADIOFREQUENCY ABLATION

Physical and biological considerations

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

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

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

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

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

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

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

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

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

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

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

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

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

Previous applications

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

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

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

Pancreatic applications

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CRYO-THERM ABLATION

Previous applications

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

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

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

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

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

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

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

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

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

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

Pancreatic applications

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

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

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

ALCOHOL/CHEMO ABLATION

Previous applications

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

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

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

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

Pancreatic applications

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

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

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

An initial study[72] on 14 patients found that complete resolution of pancreatic cystic tumours was achieved in 11 out of 14 patients followed for more than 6 mo. After treatment, minor complications were observed in one patient (including hyperamylasemia and abdominal pain). The same authors reported the results of 10 patients with septated cysts[73]. They observed a 60% rate of complete radiological cyst resolution, proving that the presence of septations within the cyst is not an absolute contraindication to injection therapy. The same group published a subsequent study in 2011 involving a larger population (n = 52)[74], reporting a complete resolution in 62% of the patients without any major complications.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CONCLUSION

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

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

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

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MINIREVIEWS

Overdiagnosis of gastric cancer by endoscopic screening

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Abstract

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

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

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

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INTRODUCTION

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

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

BASIC CONCEPT OF OVERDIAGNOSIS

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

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

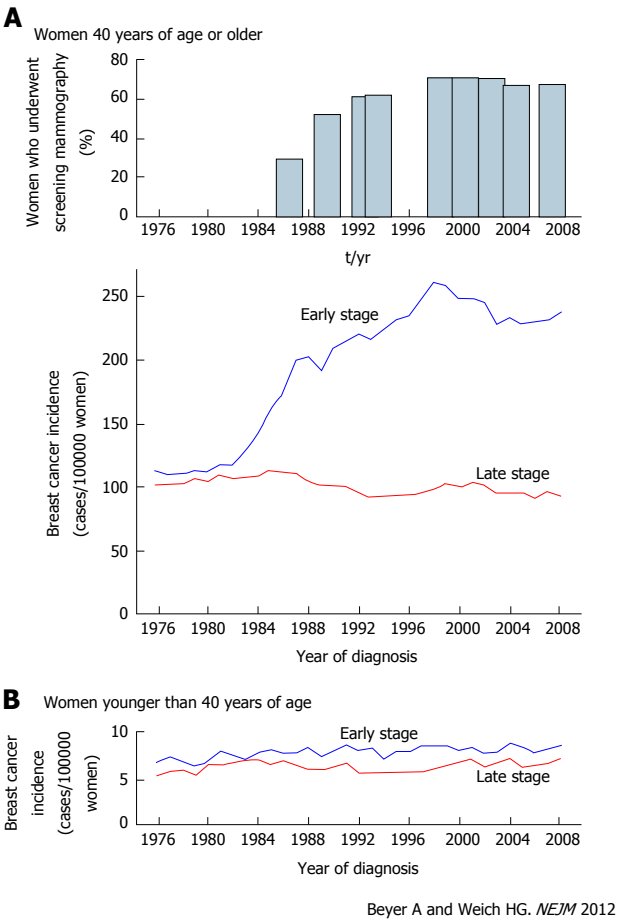
In Figure 1B, breast cancer incidence flattened in women younger than 40 years of age because they did not have any opportunity to have mammographic screening. These trends of breast cancer in women aged 40 years and over suggested that the detected early stage cancer included cases of overdiagnosis.

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

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

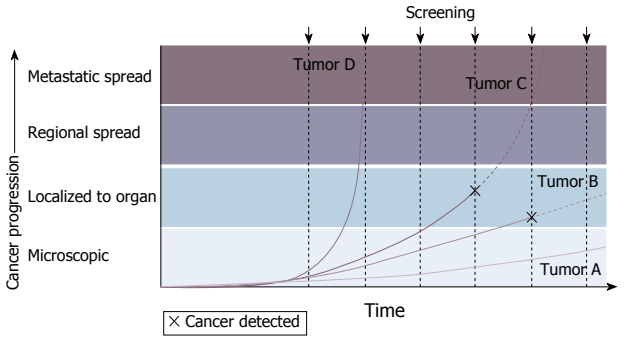
ESTIMATION OF OVERDIAGNOSIS

Overdiagnosis has been estimated from randomized



Beyer A and Weich HG. *NEJM* 2012

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



Essernanl *et al*. *JAMA* 2009

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

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

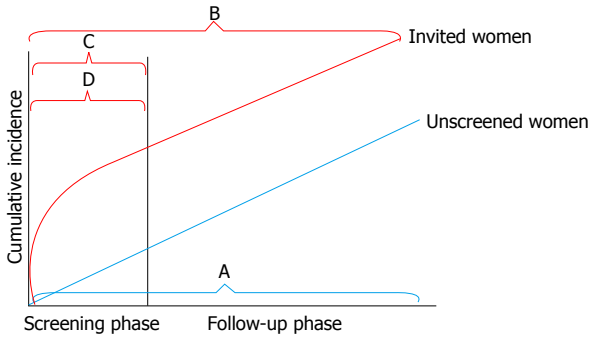
The frequency of overdiagnosis was previously estimated on the basis of RCTs without the provision of mammographic screening at the end of the screening phases. In the Independent United Kingdom Panel on Breast Cancer Screening, the overdiagnosis rate was calculated from the Canadian and Malmo studies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

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

OVERDIAGNOSIS OF GASTRIC CANCER BY ENDOSCOPIC SCREENING

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

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



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

Marmot MG Br J Cancer 2013

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

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

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

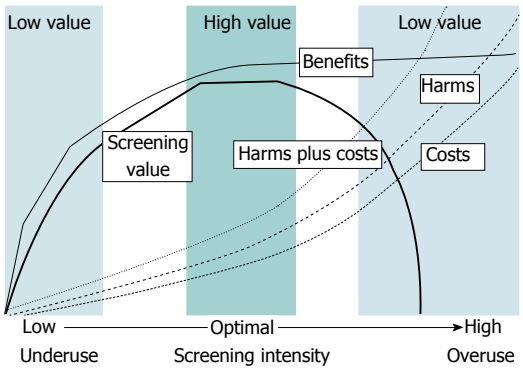
Available from Hamashima *et al*[18], 2006. O: Observed number; E: Expected number; CT: Computed tomography; PSA: Prostate specific antigen.

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

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

Available from Hamashima *et al*[23], 2013.

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



Harris RP. *Ann intem Med* 2015

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

STRATEGIES FOR MANAGEMENT OF OVERDIAGNOSIS

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

CONCLUSION

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

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ORIGINAL ARTICLE

Retrospective Cohort Study

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

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Abstract

AIM

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

METHODS

Pathology and endoscopy databases at an academic

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

RESULTS

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

CONCLUSION

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

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

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

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INTRODUCTION

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

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

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

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

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

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

MATERIALS AND METHODS

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

Pathology and endoscopy databases were reviewed to identify patients with and without gastric IM. Patients who had pathology-confirmed gastric IM from 2005-2011 were extracted from a dedicated pathology database. Using an endoscopic billing database, a control group of patients was established by reviewing 300 consecutive patients who had undergone EGD with biopsies (186 patients had gastric biopsies) from March to June 2011, from which 171 patients were identified who had gastric biopsies without gastric IM. The rate of gastric IM in this control group of patients was 5%, which we have previously reported[31]. All upper endoscopies were performed by experienced gastrointestinal endoscopists, and all pathological diagnoses included in this study were made by academic pathologists at our institution. Diagnosis of gastric IM was made histologically on H and E-stained slides. Diagnosis of *H. pylori* infection was made histologically using immunohistochemical stains.

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

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

RESULTS

Patients and demographics

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

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

Table 1 Patient characteristics and their associations with gastric intestinal metaplasia

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

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

Table 2 Association among indications and gastric intestinal metaplasia

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

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

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

Indication for endoscopy

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

Endoscopic findings

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

Endoscopic findings of a gastric mass [OR 8.84 (1.88, ∞), $P = 0.005$] and atrophic gastritis [OR 2.05 (1.00, 4.58), $P = 0.051$] were significantly associated with finding gastric IM on histopathology by multivariate analysis. The endoscopic appearance of duodenal polyps [OR 4.21 (0.81, ∞), $P = 0.081$] trended towards an increased association with finding gastric IM on biopsies. On multivariate analysis, the esophageal abnormalities of an esophageal mass [OR 0.04 (0.01, 0.16), $P < 0.001$], esophagitis [OR 0.49 (0.26, 0.91), $P = 0.023$], and Barrett's esophagus [OR 0.56 (0.26, 1.21), $P = 0.134$] were found to inversely correlate with finding gastric IM on histopathology.

Histopathological diagnoses

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

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

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

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

IM: Intestinal metaplasia.

Table 4 Association among histopathological biopsy results and gastric intestinal metaplasia

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

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

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

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

DISCUSSION

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

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

0.027].

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

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

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

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

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

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

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

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

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

COMMENTS

Background

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

Research frontiers

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

Innovations and breakthroughs

In Western nations and populations, the epidemiological risk of gastric IM has been largely ignored given the lower prevalence of gastric cancer, as compared to Asian, South American, and Eastern European populations. However, data are re-emerging that demonstrate that gastric IM can be an important problem in Western populations. In the present study, gastric IM was associated with a statistically significant six-fold increased odds ratio of finding gastric cancer. Being mindful of clinical demographic factors and findings on endoscopic evaluation of the stomach can assist in determining which patients might benefit from screening gastric biopsies. Proper diagnosis of gastric IM might also identify a patient population that might benefit from surveillance endoscopy.

Applications

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

Terminology

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

Peer-review

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

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ORIGINAL ARTICLE

Retrospective Study

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

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Abstract

AIM

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

METHODS

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

RESULTS

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

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

CONCLUSION

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

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

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

Harada H, Suehiro S, Murakami D, Nakahara R, Shimizu T, Katsuyama Y, Miyama Y, Hayasaka K, Tounou S. Endoscopic submucosal dissection for small submucosal tumors of the rectum compared with endoscopic submucosal resection with a ligation device. *World J Gastrointest Endosc* 2017; 9(2): 70-76 Available from: URL: http://www.wjgnet.com/1948-5190/full/v9/i2/70.htm DOI: http://dx.doi.org/10.4253/wjge.v9.i2.70

INTRODUCTION

Submucosal tumors (SMTs) consist of neoplastic lesions covered by normal overlying mucosa. SMTs with an intramural origin include carcinoid tumors, leiomyoma, lipoma, lymphoma, and gastrointestinal stromal tumors (GISTs). Rectal SMTs are relatively rare and are occasionally detected by screening colonoscopy without any symptoms. Rectal carcinoid tumors smaller than 10 mm in diameter are candidates for local excision (*e.g.,* by endoscopic resection or transanal endoscopic microsurgery). As previous studies of endoscopic resection for rectal carcinoid tumors have reported, conventional endoscopic resection, such as polypectomy or endoscopic mucosal resection (EMR), is associated with involvement of the resection margin that necessitates further intervention[1-3]. On the other hand, endoscopic submucosal resection with a ligation device (ESMR-L) or endoscopic submucosal dissection (ESD) achieves a high rate of complete resection for rectal carcinoid tumors without involvement of the resection margin[4-12]. Complete resection rates have been reported as ranging from 93.3% to 100% for ESMR-L[4-9] and from 80.6% to 100% for ESD[8-16]. Although both endoscopic procedures are excellent treatments for carcinoid tumors, ESD takes longer to perform and has a longer hospitalization period[8-10]. However, an advantage of ESD is that the submucosal layer beneath the tumors can be directly visualized during submucosal dissection[17].

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

MATERIALS AND METHODS

Patients

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

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

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

ESMR-L procedure

The ESMR-L procedure was performed with the use of a single-channel endoscope (GIF-Q260J; Olympus, Tokyo, Japan) with an attached a band-ligation device (pneumo-activate EVL device; Sumitomo Bakelite, Tokyo, Japan). The procedure was performed as follows (Figure

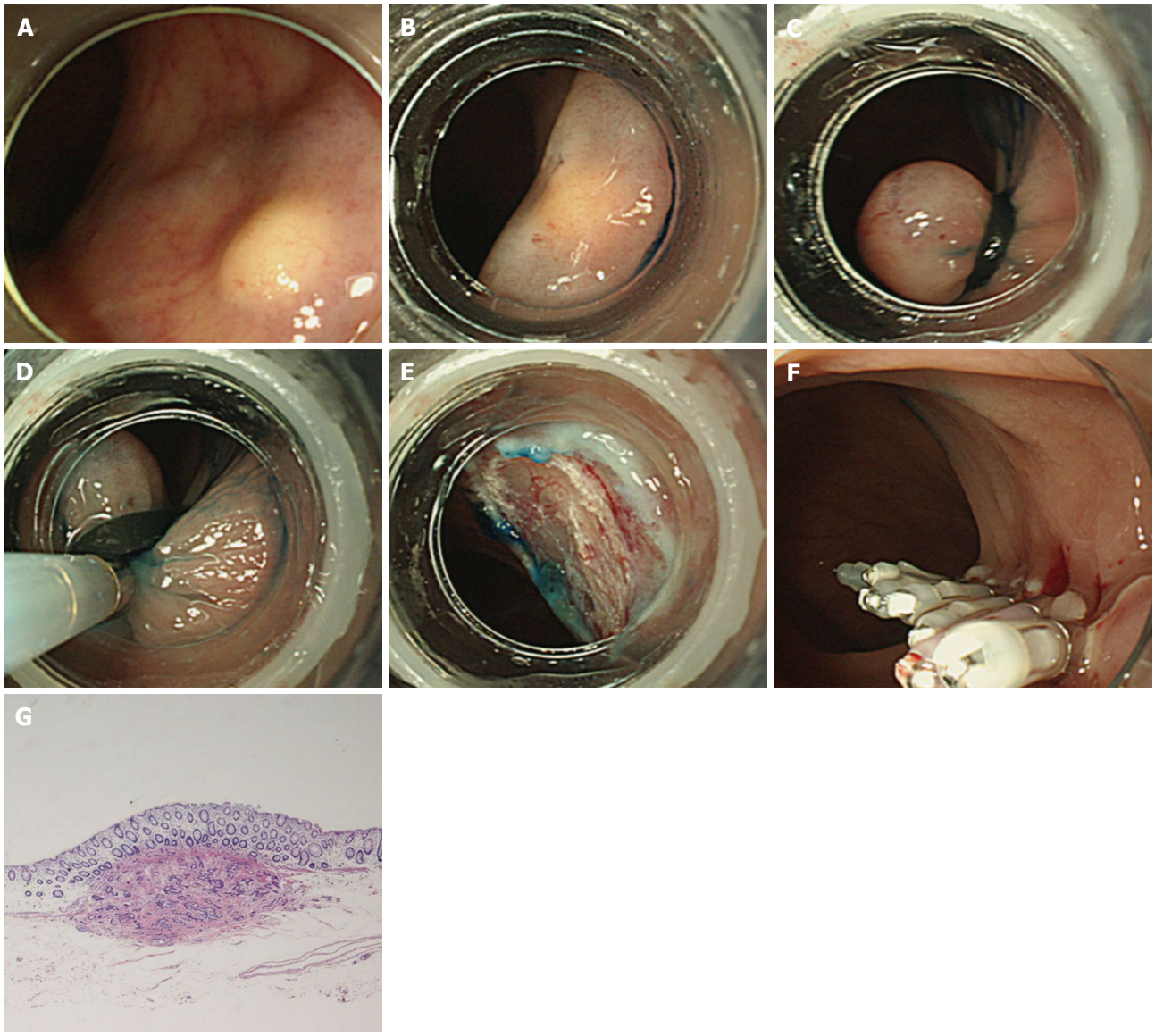

Figure 1 Endoscopic submucosal resection with a ligation device. A: Endoscopic view of a carcinoid tumor in the rectum; B: Submucosal injection beneath the tumor with glycerin solution; C: An elastic band was deployed, and then pseudopolyp was created; D: Snare resection was performed beneath the elastic band; E: An artificial ulcer was observed; F: Endoscopic plication was performed with the use of metal endoclips; G: Histopathological examination showed *en bloc* resection of the carcinoid tumor.

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

ESD procedure

The ESD procedure was performed with the use of a single-channel endoscope (GIF-Q240; Olympus, Tokyo, Japan). The procedure was performed as follows (Figure 2). After submucosal injection with sodium hyaluronate was performed, a hemicircumferential mucosal incision was made from the anal side with the use of a FlushKnife BT (DK2618JB; Fujifilm, Tokyo, Japan). Next, a pocket of the submucosa was created to allow the endoscope to enter the submucosal layer while the submucosa was being dissected. In order to keep sufficient margin between the bottom of the tumor and the cutting margin, the submucosal dissection was performed just above the muscular layer using an Endocut I current (effect 2, cut duration 3, cut interval 2), which was generated by using a VIO300D. During the submucosal dissection, precoagulation was performed on visible vessels by using hemostatic forceps (FD-230U or FD-410LR; Olympus, Tokyo, Japan). After the submucosal dissection was performed beyond the tumor, the intact mucosa was cut by the electrosurgical knife. Finally, endoscopic plication was performed with the use of metal endoclips. For both of ESMR-L and ESD, the procedure time was defined as

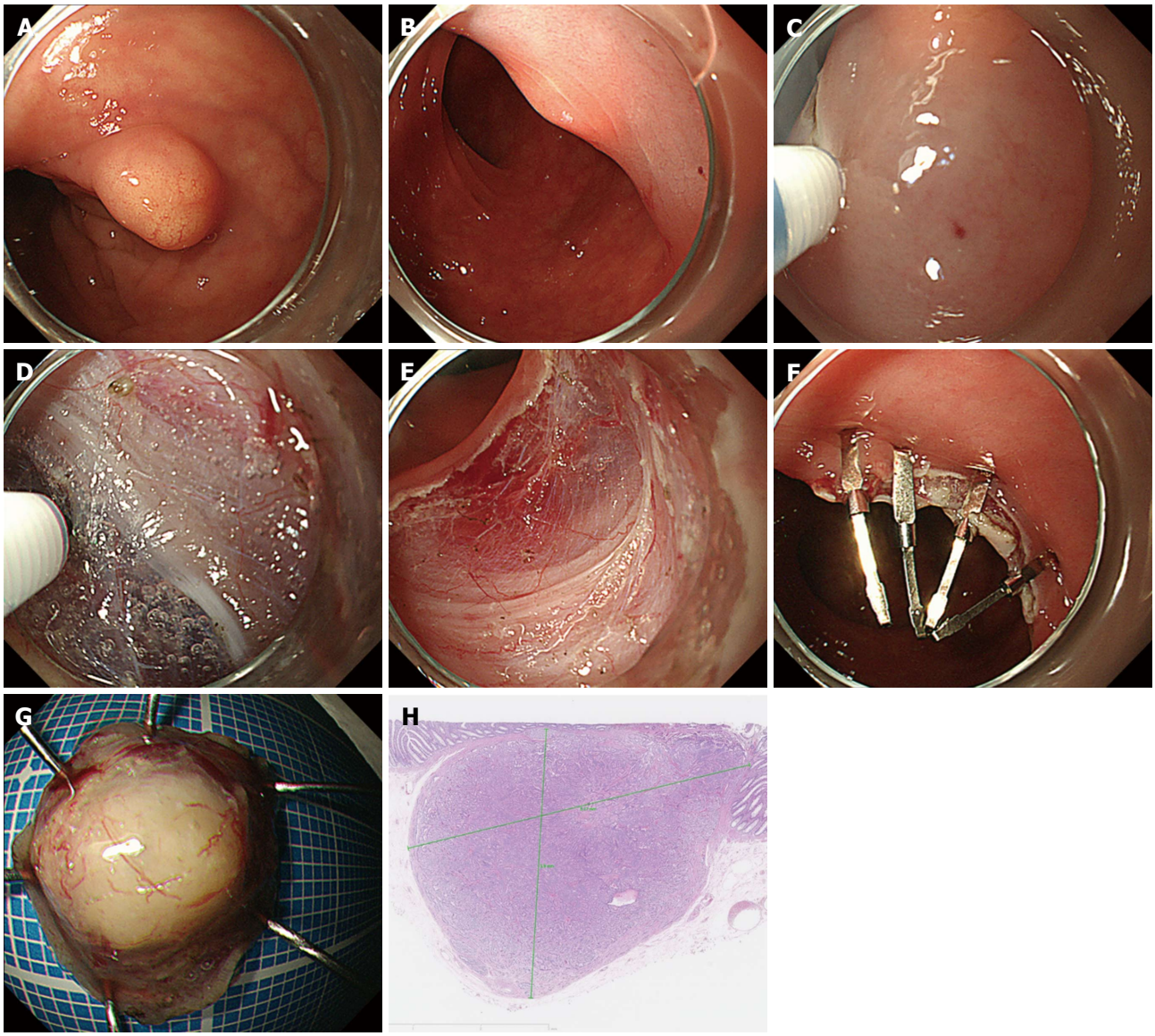

Figure 2 Endoscopic submucosal dissection. A: Endoscopic view of a carcinoid tumor in the rectum; B: Submucosal injection beneath the tumor with sodium hyaluronate; C: A hemicircumferential incision was performed with the use of the electrosurgical knife; D: A submucosal pocket was created during ESD. Submucosal dissection was performed just above the muscular layer; E: An artificial ulcer was observed; F: Endoscopic plication was performed with the use of metal endoclips; G: The specimen resected by ESD; H: Histopathological examination showed *en bloc* resection of the carcinoid tumor. ESD: Endoscopic submucosal dissection.

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

Histological evaluation

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

Complications

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

Follow-up

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

Statistical analysis

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

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

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

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

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

RESULTS

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

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

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

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

The mean length of the procedure was significantly greater in the ESD group than in the ESMR-L group (14.7 ± 6.4 min *vs* 5.4 ± 1.7 min, $P < 0.05$). The mean length of the hospitalization was also significantly greater in the ESD group than in the ESMR-L group (3.7 ± 0.9 d *vs* 2.8 ± 1.5 d, $P < 0.05$). Postoperative bleeding occurred in one patient with carcinoid tumor in the ESMR-L group after discharge from the hospital. The bleeding was successfully managed with emergency endoscopic hemostasis. There were no complications in the ESD group.

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

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

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

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

DISCUSSION

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

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

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

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

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

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

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

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

COMMENTS

Background

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

Research frontiers

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

Innovations and breakthroughs

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

Applications

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

Terminology

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

Peer-review

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

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ORIGINAL ARTICLE

Clinical Trials Study

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

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Author contributions: Sakai Y, Tsuyuguchi T and Yokosuka O were responsible for study design and manuscript preparation; Sakai Y wrote the paper; Hirata N, Nakaji S, Shimura K, Nishikawa T, Fujimoto T, Hamano T and Nishino T were responsible for data collection.

Institutional review board statement: This study was conducted under our ethical committee.

Informed consent statement: All the treatment procedures were performed after obtaing the informed consent in writing from the patients.

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Data sharing statement: I share data in the group of us.

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Abstract

AIM

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

METHODS

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

RESULTS

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

CONCLUSION

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

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

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

Sakai Y, Tsuyuguchi T, Hirata N, Nakaji S, Shimura K, Nishikawa T, Fujimoto T, Hamano T, Nishino T, Yokosuka O. Clinical utility of 0.025-inch guidewire VisiGlide2™ in the endoscopic retrograde cholangiopancreatography-related procedures. *World J Gastrointest Endosc* 2017; 9(2): 77-84 Available from: URL: http://www.wjgnet.com/1948-5190/full/v9/i2/77.htm DOI: http://dx.doi.org/10.4253/wjge.v9.i2.77

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP)-related procedures have played a very important role for diagnosis/treatment of biliary and pancreatic disease. In ERCP-related procedures, it is needless to say that the guidewire (GW) is essential in performing the procedure safely, and elevating the accomplishment rate of the procedure. There are the GWs of various diameters, but the GW which has been used as the first choice was of 0.035 inches considering the stability of procedure[1-12]. The 0.025-inch GW is thin and excellent in breaking through the stenosis and selecting the branch but problematic in visibility and rigidity, which has not been used as the first choice[1-12]. It has been used in the case in which it was impossible to break through the stenosis even by using 0.035-inch GW, and in particular, peroral cholangioscopy (POCS) and placement of metallic stent (MS) have generally been conducted with 0.035-inch GW because of the problem of rigidity[8-12]. Previously, after 0.025-inch GW was used for breaking through the stenosis, GW was switched to 0.035 inch GW to stabilize the procedure, and the procedure was re-started. However, together with advancement of the endoscope, GW was improved, and it has become possible to use VisiGlide™ with excellent visibility and sufficient rigidity in spite of the external diameter of 0.025-inch in the clinical setting. As a result, we have treated a number of patients in whom ERCP-related procedure can be accomplished using only this GW. However, there remained still problems that GW must be changed due to seeking failure in some patients, and GW perforation comparatively frequently occurs[13]. After that, it has become possible to use VisiGlide2™ remodeled from VisiGlide™ in the clinical setting (Figure 1)[14]. VisiGlide2™ has excellent endoscopic visibility (Figure 2), and also has improved fluoroscopic visibility of GW using 2 radiopaque chips similarly to VisiGlide™ (Figure 3). Although it has thinness of 0.025-inch (0.63 mm), its special processing method ensures rigidity equivalent to that of 0.035 inch (0.89 mm) (Figure 4). It is the GW that was devised to reduce GW perforation, the accidental symptom observed in use of VisiGlide™, by making the tip flexible. The torque device for 0.025-inch GW VisiGlide™ was compliant to 0.035 inch previously, whereas that for 0.025-inch GW VisiGlide2™ has become compliant to 0.025-inch, thus torque transmissibility was improved.

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

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

MATERIALS AND METHODS

All the patients with biliary and pancreatic diseases, who were decided to undergo ERCP in 5 institutions participating in this clinical study in a month of December 2014, were included. A 0.025-inch GW (VisiGlide2: Olympus Corp. Japan straight type or angle type) was used. For cannulation, catheters PR-104Q, PR110Q-1,

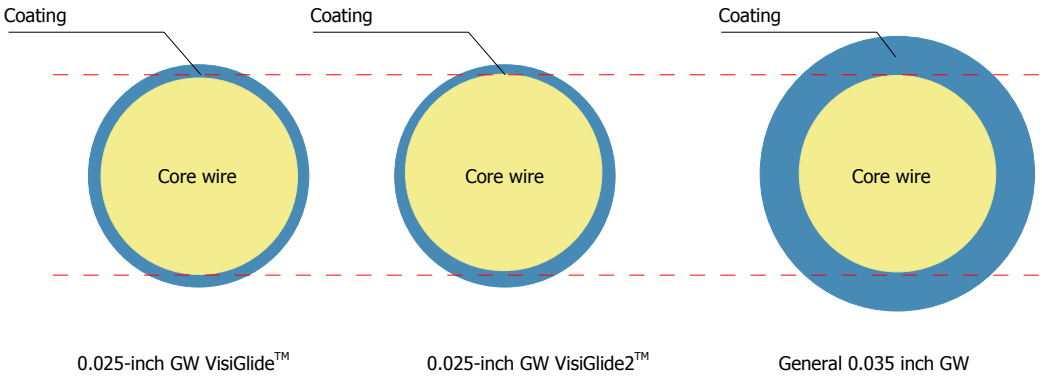

Figure 2 Comparison between 0.025-inch guidewire VisiGlide2™, 0.025-inch guidewire VisiGlide™, and 0.035 inch guidewire. Although it has thinness of 0.025-inch (0.63 mm), its special processing method ensures rigidity equivalent to that of 0.035 inch (0.89 mm). GW: Guidewire.

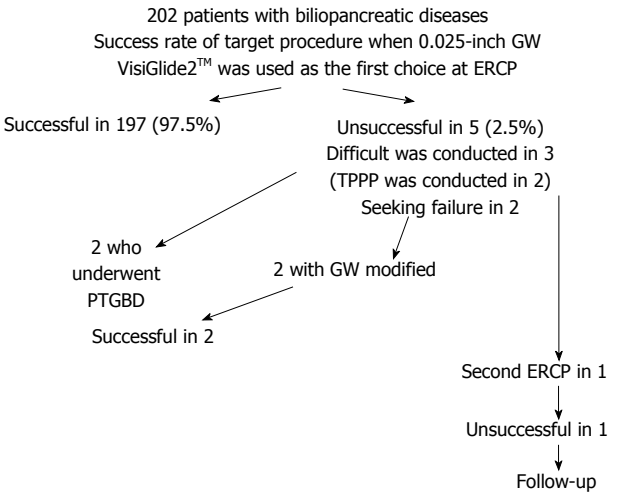

Figure 3 Result of use of 0.025-inch guidewire VisiGlide2™ in the endoscopic retrograde cholangiopancreatography as the first choice. ERCP: Endoscopic retrograde cholangiopancreatography; TPPP: Transpancreatic precut papillotomy; PTGBD: Percutaneous transhepatic gallbladder drainage; GW: Guidewire.

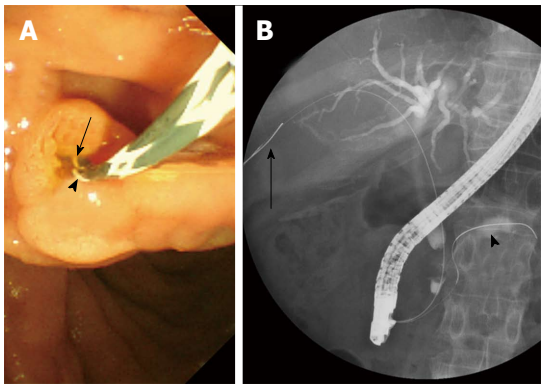

Figure 4 Although it has thinness of 0.025-inch (0.63 mm), its special processing method ensures rigidity equivalent to that of 0.035 inch (0.89 mm). A: 0.025-inch guidewire (GW) VisiGlide2™ placed in the bile duct (arrow)/pancreatic duct (arrow head). The visibility is good under endoscopy; B: 0.025-inch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

PR-233Q and Clever-Cut3V (Olympus Corp. Japan) were used. The endoscopes used were JF200, JF240, JF260V, and TJF260V (Olympus Corp. Japan). Prospective data collected in multicenter study were compared with those obtained from multicenter prospective study of 0.025-inch GW VisiGlide™ which we have already reported[13]. Patients treated using VisiGlide2™are shown. There were 202 patients including 122 males and 80 females, and the age was 72.9 (36 to 98) years old on average. The ERCP was conducted aiming at bile duct in 190 patients and pancreatic duct in 12 patients. There were 80 patients undergoing ERCP for the first time and 122 patients on whom papillary treatment has already been implemented. The case in which 0.025-inch guidewire VisiGlide2™ was used as a versatile GW and the scheduled procedure could be accomplished only with VisiGlide2™ at the ERCP was considered as the success of procedure, and the success rate and the incidence of accidental symptom were examined. Patients with difficulty in selective biliary cannulation were defined as patients who are considered by an investigator to be difficult cases for biliary cannulation after over 10 min performing papilla cannulation through the frontal view. If such patients were observed, the following procedures were used to achieve biliary cannulation at the investigator's discretion: Needle knife precut papillotomy starting at orifice, transpancreatic precut papillotomy and pancreatic duct guidewire indwelling method. For patients with moderate or severe cholangitis, urgent ERCP was performed according to the Tokyo Guideline[15]. Iatrogenic morbidity was assessed according to the criteria of Cotton *et al*[16]. The observation period was 30 d after the procedure and any coincidental events noted during the period were considered as early coincidental events. All the treatment procedures were performed after obtaining the informed consent in writing from the patients. Assessment of this GW was performed based on approval of ethical committee of each institution, and registered at UMIN Clinical Trial Registry (UMIN0000016042-VIP2 study).

Statistical analysis

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

Table 1 Patients' background and disease background

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

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

Table 2 Accomplishment rate of procedure and procedural time

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

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

RESULTS

Comparisons of patient background and disease background are shown (Table 1). There was no significant difference between VisiGlide2™ and VisiGlide™ in the patient background. The accomplishment rate of procedure only with VisiGlide2™ was 97.5% (197/202). The procedural time was 23.930 ± 16.207 (4-65) min. Use of VisiGlide2™ enabled significantly to elevate accomplishment rate of procedure and shorten procedural time compared with VisiGlide™ ($P < 0.05$) (Table 2). Of patients who failed accomplishment of the procedure, GW was changed in 2 patients. Of 2 patients, the procedure was successful in 1 patient using Radifocus™ (RF-GS25263 TERUMO Japan), and the procedure was also successful in 1 patient using Navipro™ (Boston Scientific Corp. Natick, MA). Three patients had difficulty in selective bile duct insertion and 2 were acute cholecystitis patients to whom percutaneous transhepatic gallbladder drainage was inserted. One patient was clinically suspicious spontaneous passage of bile duct stone, and underwent unsuccessfully second ERCP, and followed-up. The final success rate of ERCP was 98.5% (199/202) (Figure 5). Among the patients succeeded in insertion into the bile duct and not undergoing papillary treatment, 74 patients underwent papillary treatment. The papillary treatment was successful in all the 74 patients conducted, the success rate of 100% (74/74) (Table 3). After papillary treatment, we underwent the procedure of purpose. The success rate was 99.4% (331/333) (Table 4). Accidental symptoms were observed at 3.0% (6/202). Bleeding, pancreatitis and perforation were observed at 1.0% (2/202), 1.5% (3/202) and 0.5% (1/202), respectively. Although there was no significant difference in accidental symptoms between VisiGlide2™ and VisiGlide™, GW perforation, which was observed in 2.1% (4/194) when

Table 3 Papillary treatment

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

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

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

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

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

Table 5 Results of incidence of accidental symptoms

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

NS: Not significant.

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

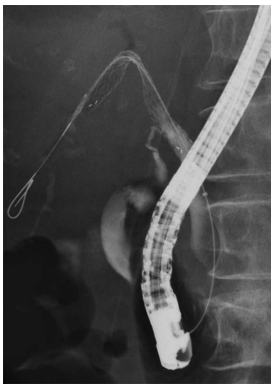

Figure 5 Placement of metallic stent using 0.025-inch guidewire VisiGlide2™. It was possible to break through the stenosis, to induce delivery and to place stents only with this guidewire.

DISCUSSION

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

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

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

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

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

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

COMMENTS

Background

In endoscopic retrograde cholangiopancreatography (ERCP)-related procedures, it is needless to say that the guidewire (GW) is essential in performing the procedure safely, and elevating the accomplishment rate of the procedure. The authors decided to examine the accomplishment rate of procedures and the incidence of accidental symptoms in the use of 0.025-inch GW VisiGlide2™ as the first-choice universal GW in the ERCP-related procedures without selecting patients in a multicenter prospective study.

Research frontiers

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

Innovations and breakthroughs

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

Applications

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

Terminology

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

Peer-review

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

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CASE REPORT

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

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Abstract

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

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

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

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

Heinrich H, Gubler C, Valli PV. Over-the-scope-clip closure of long lasting gastrocutaneous fistula after percutaneous endoscopic gastrostomy tube removal in immunocompromised patients: A single center case series. *World J Gastrointest Endosc* 2017; 9(2): 85-90 Available from: URL: http://www.wjgnet.com/1948-5190/full/v9/i2/85.htm DOI: http://dx.doi.org/10.4253/wjge.v9.i2.85

INTRODUCTION

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

Non-healing gastrocutaneous fistula (GCF) is a rare complication after removal of percutaneous endoscopic gastrostomy (PEG) tubes and can be treated surgically or endoscopically[11]. Clip application, suture, gluing, banding[12] and coagulation techniques have been described as endoscopic therapeutic options[13-17]. Nevertheless, OTSC® application is emerging as a simple and safe endoscopic treatment for persistent GCF.

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

CASE REPORT

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

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

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

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

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

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

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

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

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

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

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

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

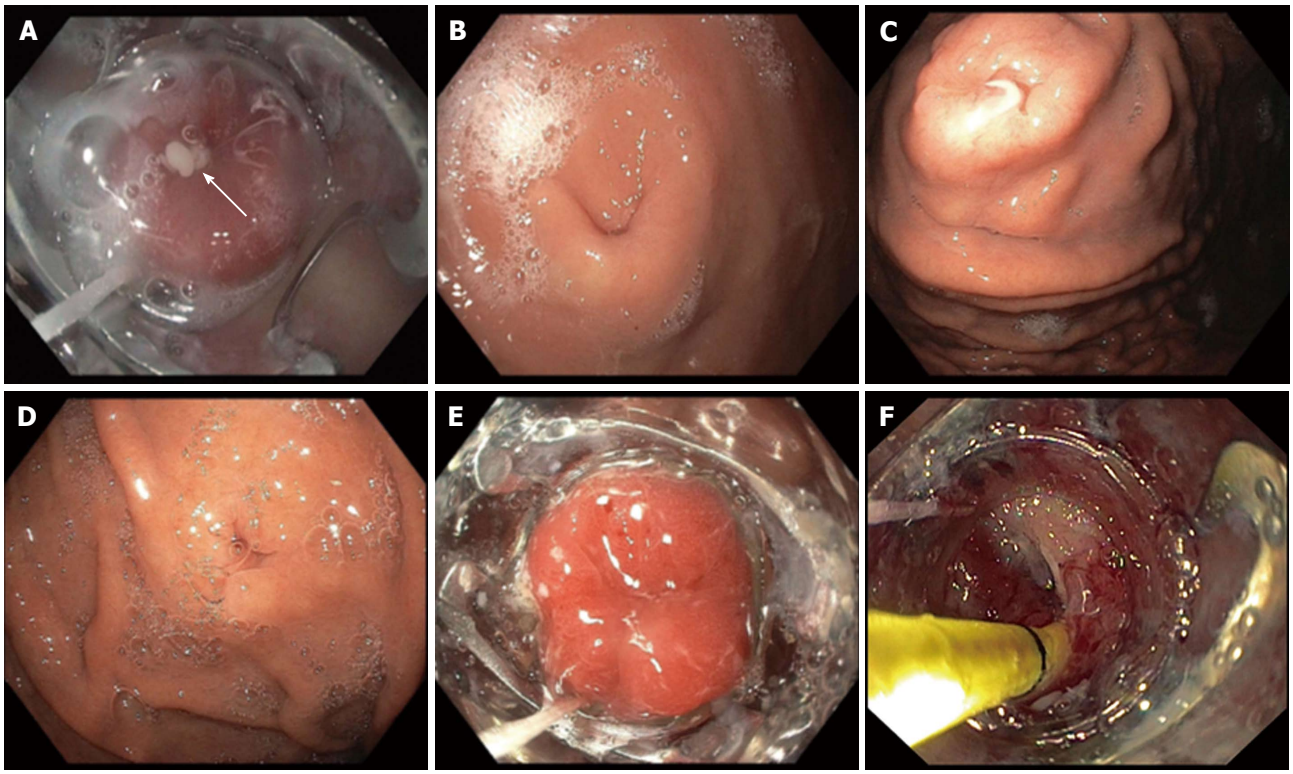

Figure 1 Upon suction during over-the-scope-clips placement, pus drained through the fistula towards the endoscope. A: Patient 1, arrow indicates pus; B: Patient 2; C: Patient 3; D: Patient 4; E: Patient 4, fistula after OTSC deployment; F: Patient 5, alignment of OTSC using a guide wire. OTSC: Over-the-scope-clip.

DISCUSSION

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

Portal hypertension with tense ascites is known

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

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

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

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

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

COMMENTS

Case characteristics

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

Research frontiers

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

Innovations and applications

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

Terminology

OTSC application for GCF closure after PEG Tube removal.

Peer-review

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

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CASE REPORT

Successful endoscopic fragmentation of large hardened fecaloma using jumbo forceps

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Abstract

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

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

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

Matsuo Y, Yasuda H, Nakano H, Hattori M, Ozawa M, Sato Y, Ikeda Y, Ozawa SI, Yamashita M, Yamamoto H, Itoh F. Successful endoscopic fragmentation of large hardened fecaloma using jumbo forceps. *World J Gastrointest Endosc* 2017; 9(2): 91-94 Available from: URL: http://www.wjgnet.com/1948-5190/full/v9/i2/91.htm DOI: http://dx.doi.org/10.4253/wjge.v9.i2.91

INTRODUCTION

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

CASE REPORT

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

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

As the fecaloma was huge and actually occupied the colonic lumen, endoscopic extraction was attempted without laxatives because it was thought that the oral administration of laxatives, such as polyethylene glycol, might cause an intestinal obstruction. The surface of the fecaloma was hard, large and slippery, and fragmentation was not possible despite the use of biopsy forceps (Radial Jaw 4 Biopsy Forceps Standard Capacity, Boston Scientific, United States), an injection needle for endoscopic treatment (Impact Flow, Top, Japan), a needle knife (KD-10Q-1-A, Olympus, Japan), and a snare for endoscopic mucosal resection (EMR) (Snare Master, Olympus, Japan). Consequently, the surface of the fecaloma was shaved using jumbo forceps (Radial Jaw 4 Jumbo Cold Polypectomy Forceps, Boston Scientific, Japan) with about ten passes, which scraped the surface and made it possible to advance the forceps into the fecaloma. The same procedure was then repeated several hundred times, aiming for the center of the fecaloma and resulting in gradual fragmentation (Figure 3). A total of 6 h over 2 d were required to break the fecaloma into fragments of a size that could pass through the anus. We used the midazolam as a sedative and the pentazocine as an analgesic. Midazolam was administered intravenously according to the degree of affliction and administered 5 mg per time of the procedure. Pentazocine was administered 15 mg per each procedure. The fecaloma was then eliminated using laxatives (Figure 4).

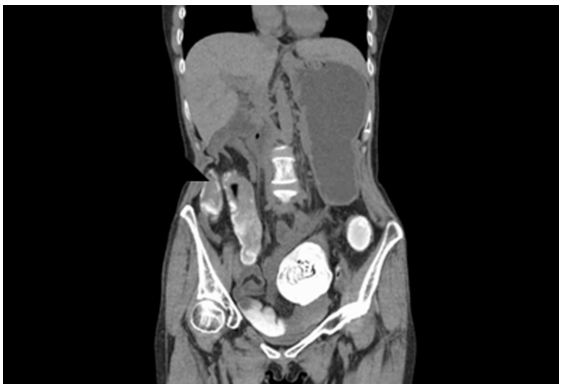

Figure 1 Abdominal computed tomography-scan demonstrating 7 cm fecaloma in the transverse colon.

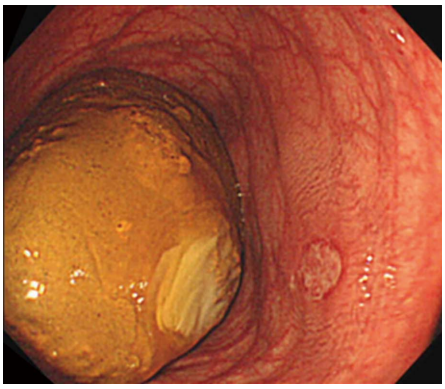

Figure 2 Lower gastrointestinal endoscopy revealed dilated colonic lumen and brown fecaloma in the transverse colon. There is 2 cm ulcer near the fecaloma.

DISCUSSION

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

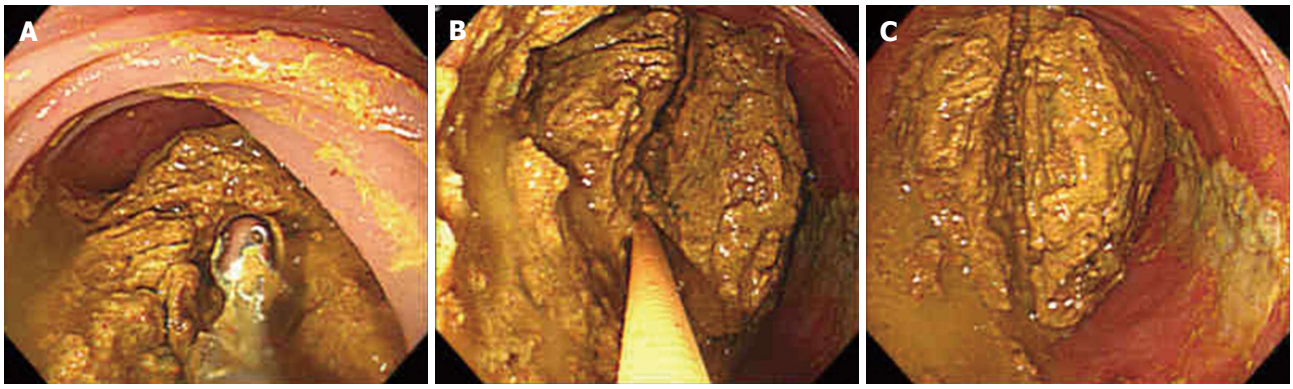

Figure 3 Same procedure was then repeated several hundred times, aiming for the center of the fecaloma and resulting in gradual fragmentation. A: Jumbo forceps scrape off the surface of hardened fecaloma; B: Jumbo forceps split the fecaloma; C: Fecaloma is separated into two blocks by biting the jumbo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

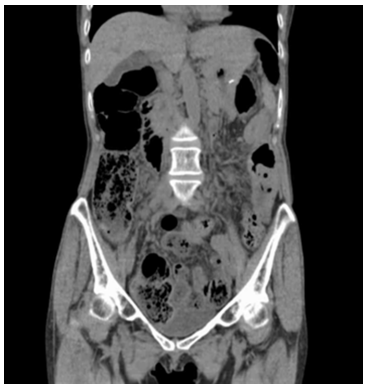

Figure 4 Abdominal computed tomography reveal the disappearance of the fecaloma.

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

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

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

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

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

In summary, Jumbo forceps might be a useful device

for fragmenting hardened fecalomas.

COMMENTS

Case characteristics

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

Clinical diagnosis

Queasiness and peri-umbilical abdominal pain.

Differential diagnosis

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

Laboratory diagnosis

All labs were within normal limits.

Imaging diagnosis

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

Treatment

Endoscopic jumbo forceps break the fecaloma by repeated biting.

Related reports

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

Term explanation

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

Experiences and lessons

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

Peer-review

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

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CASE REPORT

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

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Abstract

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

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

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

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

Wei Y, Gong JF, Zhu WM. Endoscopic closure instead of surgery to close an ileal pouch fistula with the over-the-scope clip system. *World J Gastrointest Endosc* 2017; 9(2): 95-98 Available from: URL: http://www.wjgnet.com/1948-5190/full/v9/i2/95.htm DOI: http://dx.doi.org/10.4253/wjge.v9.i2.95

INTRODUCTION

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

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

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

CASE REPORT

A 26-year-old male patient was admitted to our hospital due to fever and severe bloody diarrhea. Endoscopy revealed acute ulcerative colitis with a Mayo score of 12. He failed to respond to intravenous corticosteroid therapy, and toxic megacolon appeared. He underwent a total laparoscopic restorative proctocolectomy with IPAA (with a loop ileostomy). After surgery, the patient recovered without complications and was discharged 10 d after the operation. Six weeks later, he was readmitted to our department for ileostomy reversal. Prior to the operation, pouch endoscopy, antegrade Gastrografin enema, and an abdominal computed tomography scan did not reveal an abnormality. A stapled side-to-side ileostomy reversal was performed, and he was discharged 3 d after the operation. One month after the final operation, he developed a high fever again (39.9 ℃) with stool leaking from the right lower abdominal trocar site. Colonoscopy and a Gastrografin enema confirmed there was a fistula on the tip of the "J" Pouch (Figures 1 and 2). He was treated with percutaneous drainage, total parenteral nutrition (TPN) and bowel rest. Signs of intra-abdominal sepsis were controlled after 4 wk of therapy. However, there was persistent feculent discharge from the fistula tract. The patient was comprehensively informed about the endoscopic procedure.

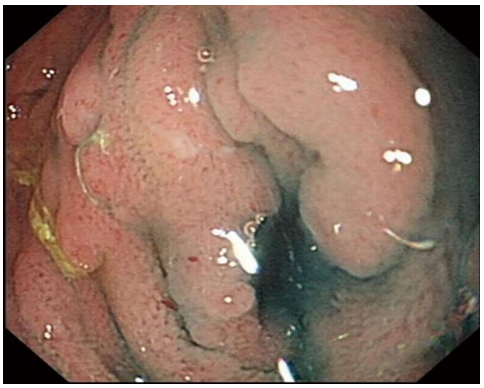

Figure 1 Methylene blue was injected *via* the trocar site and flooded the enteric cavity to reveal a leak in the pouch.

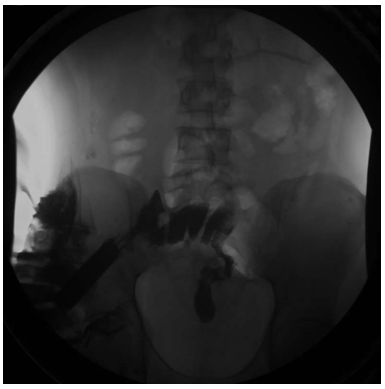

Figure 2 Urografin was injected *via* the sinus, and the pouch was visualized to confirm a fistula on the top of the "J" pouch.

DISCUSSION

Alternatives, such as surgical treatment, were also

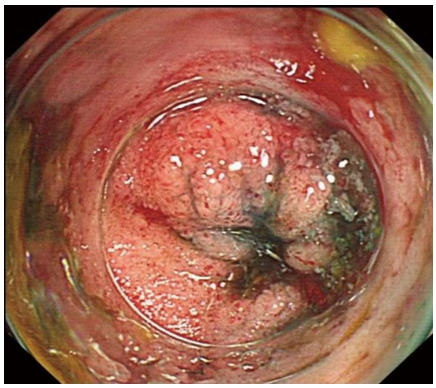

Figure 3 Fistula was closed by the over-the-scope clip system.

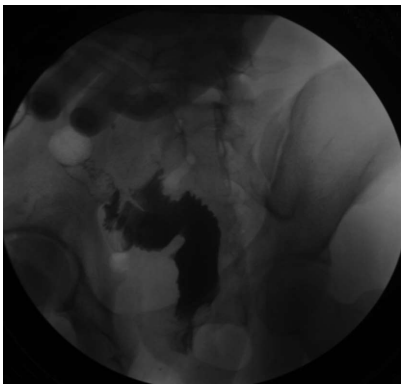

Figure 4 Gastrografin enema confirmed the fistula was closed.

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

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

ACKNOWLEDGMENTS

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COMMENTS

Case characteristics

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

Clinical diagnosis

Intestinal fistula.

Differential diagnosis

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

Laboratory diagnosis

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

Imaging diagnosis

Leaks from the tip of the J-pouch.

Pathological diagnosis

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

Treatment

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

Related reports

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

Term explanation

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

Experience and lessons

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

Peer-review

The paper is well written.

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CASE REPORT

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

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Abstract

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

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

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

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

Shi S, Fu K, Dong XQ, Hao YJ, Li SL. Combination of concurrent endoscopic submucosal dissection and modified peroral endoscopic myotomy for an achalasia patient with synchronous early esophageal neoplasms. *World J Gastrointest Endosc* 2017; 9(2): 99-104 Available from: URL: http://www.wjgnet.com/1948-5190/full/v9/i2/99.htm DOI: http://dx.doi.org/10.4253/wjge.v9.i2.99

INTRODUCTION

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

CASE REPORT

Before POEM, the patient was scored as Eckardt score 6 and Grade Ⅱ. Chest computed tomography showed an obviously dilated esophageal cavity with large amount fluid retention in the lumen. The cardiac muscle layer was significantly thickened (Figure 1). Esophagogastroduodenoscopy also revealed significantly expanded esophageal lumen and remarkable fluid retention. After pumping the liquid and washing the lumen repeatedly, all of esophagus mucosa appeared edematous and turbid white. A reddish lesion (1.5 cm × 1.0 cm) was detected at 24 cm from the incisor. The lesion was identified as type Ⅳ of intra-epithelial papillary capillary loops (IPCLs) according to Inoue's classification by narrow-band imaging with magnification and background colorization was also seen. Biopsy histopathology showed normal tissue with inflammation. Another lesion (1.0 cm × 0.8 cm) was detected at 32 cm and identified as IPCLs type Ⅴ1, and the biopsy histopathology showed high-grade intraepithelial neoplasia. The third lesion (1.0 cm × 1.5 cm) was found at 34 cm disclosed type Ⅳ-Ⅴ1 IPCLs, and analysis of the biopsy revealed low-grade intraepithelial neoplasia. The neoplastic lesions were located in the anterior wall of the esophagus. The esophageal lumen below 30 cm was distorted and dilated. The cardia was tightly closed and the resistance was significant (Figure 2). According to the endoscope and pathology funding, the patient was diagnosed with Sigmoid-type achalasia combined with neoplastic lesions.

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

DISCUSSION

Esophageal achalasia is caused by esophageal neuromuscular dysfunction associated with lack of peristalsis of the esophagus, high pressure of lower esophageal sphincter and weakening response to the swallowing relaxation. Esophageal retention of foods and fluids,

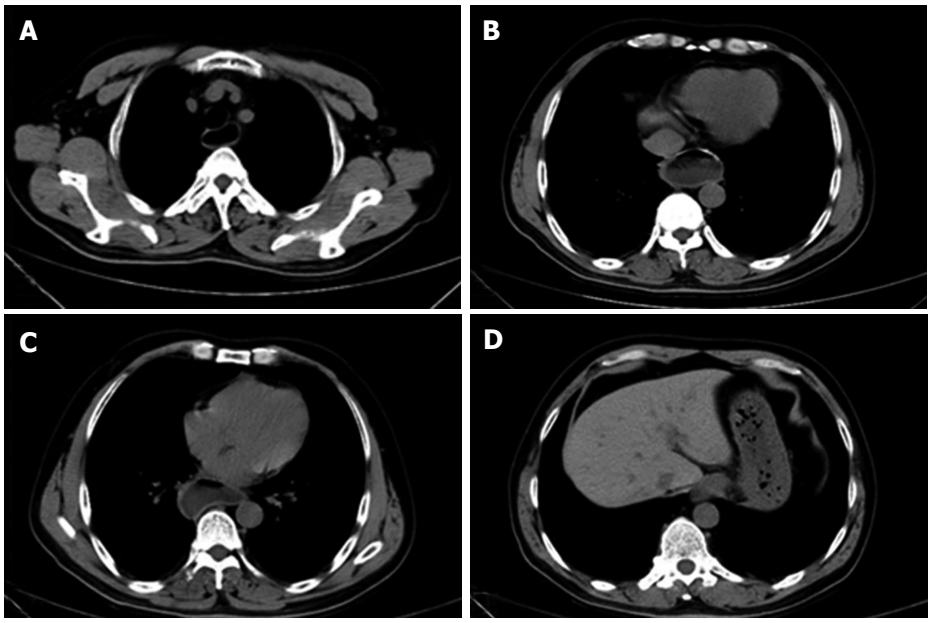

Figure 1 Chest computed tomography examination showed that the esophageal cavity was obviously expanded (A-C); large amount of fluid retention was seen in the lumen (D). The cardiac muscle layer was significantly thickened.

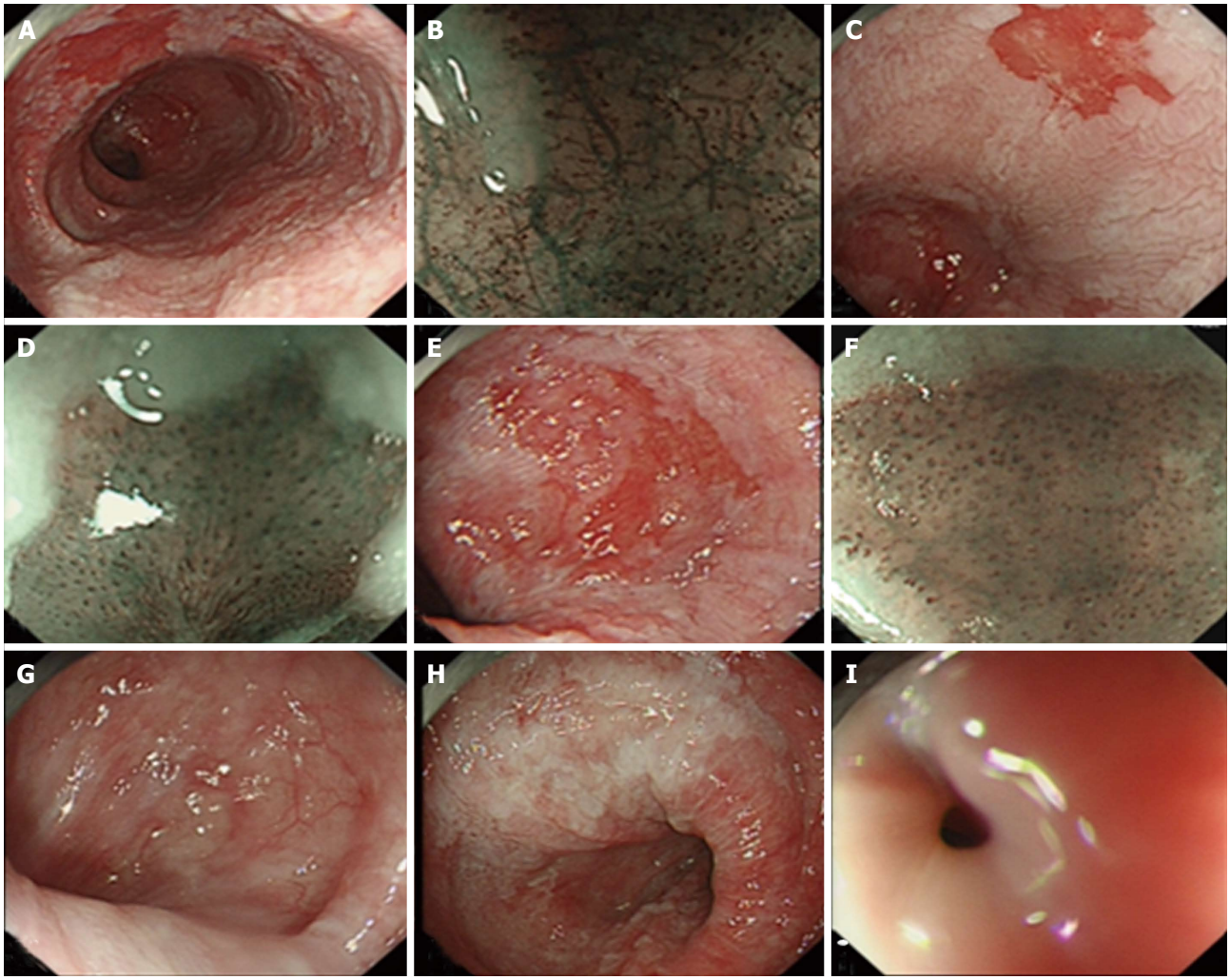

Figure 2 Cardia was tightly closed and the resistance. A, B: Lesion at 24 cm from the incisor and Narrow-band imaging (NBI) with magnification revealed type Ⅳ intra-epithelial papillary capillary loops (IPCLs) according to Inoue's classification; C, D: Another lesion at 32 cm, IPCLs were type Ⅴ1; E,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

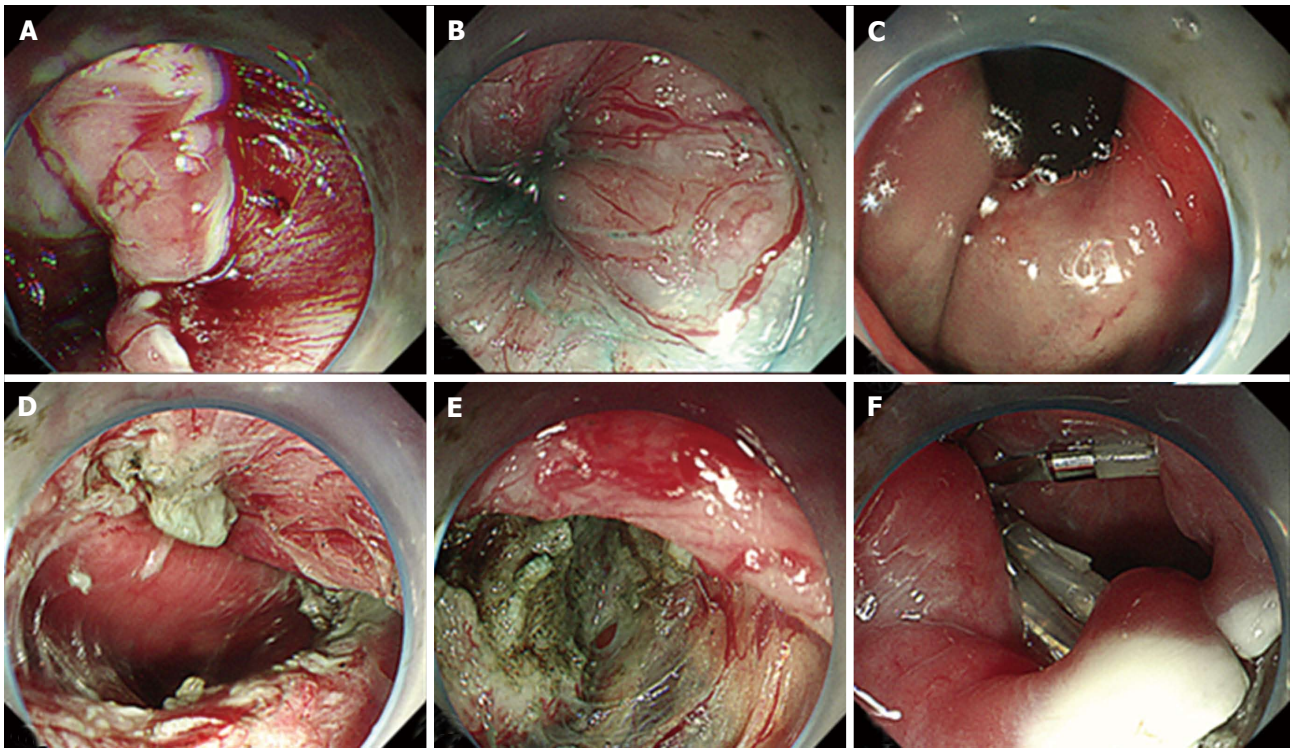

Figure 3 Peroral endoscopic myotomy procedure. A: A 2-cm longitudinal incision was made into the mucosa after injection of natural saline with indigo carmine and epinephrine; B: A submucosal tunnel from the esophagus to the gastric cardia was created using a Dual knife; C: The submucosal tunnel was completed;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

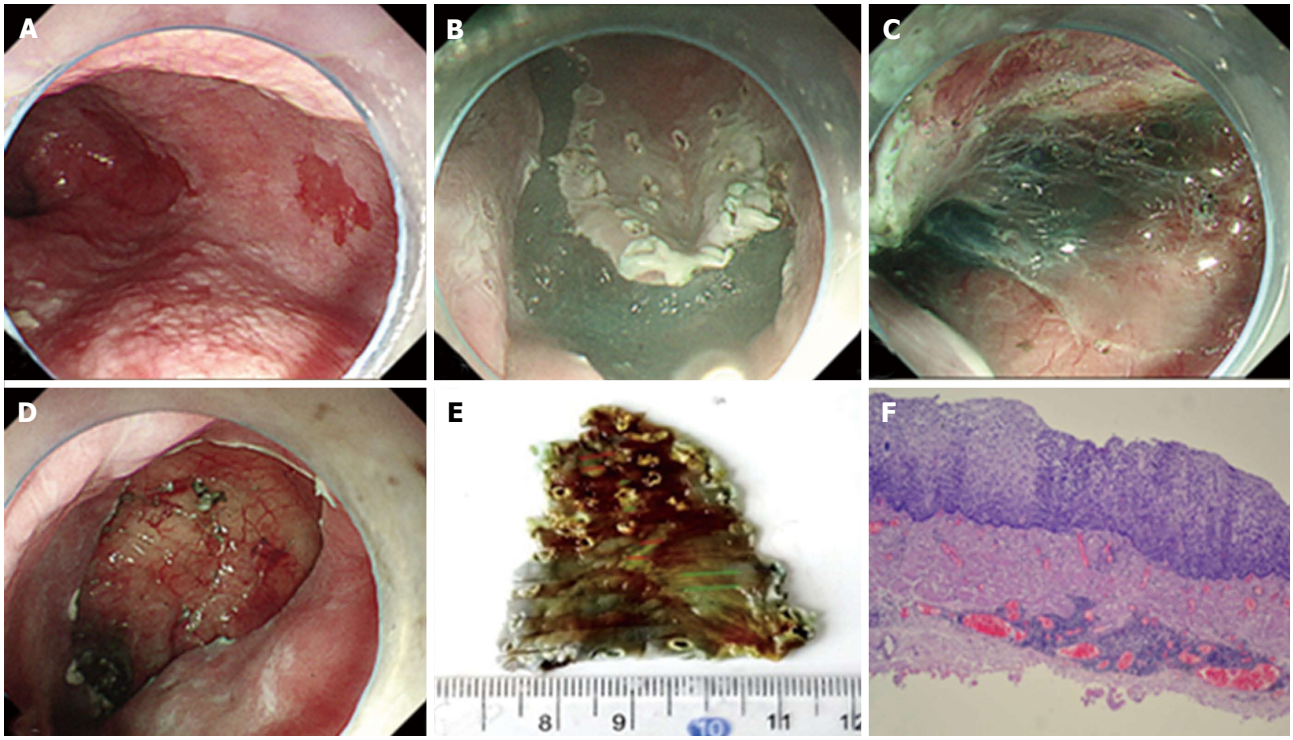

Figure 4 Endoscopic submucosal dissection procedure and pathological examination. A-D: Marking around the lesion using Dual knife; submucosal injection of 10 mL saline with 0.3% indigo carmine and 1:100000 epinephrine; cutting open the mucosa; the submucosa was stripped and the lesion was completely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

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

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

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

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

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

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

COMMENTS

Case characteristics

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

Clinical diagnosis

Esophageal achalasia, early esophageal neoplasms.

Differential diagnosis

Carcinoma of gastric cardia, reflux esophagitis, angina pectoris.

Laboratory diagnosis

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

Imaging diagnosis

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

Pathological diagnosis

High-grade intraepithelial neoplasia.

Treatment

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

Experiences and lessons

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

Peer-review

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

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