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TOPIC HIGHLIGHT

2016 Gastrointestinal Endoscopy: Global view

Use of water jet instruments in gastrointestinal endoscopy

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Abstract

In recent years, water jet instruments have been used in the field of gastrointestinal endoscopy, mainly in two clinical situations: Investigation and treatment under endoscopic view. Injecting water jet into the gastrointestinal lumen is helpful for maintaining a clear endoscopic view, washing away blood or mucous in the lumen or on the surface of the tip of the endoscope. This contributes to reducing time and discomfort of examination. Water jet technology is an alternative method for dissecting soft tissue; this method does not harm the small vessels or cause mechanical or thermal damage. However, its use in clinical settings has been limited to the transmucosal injection of water into the submucosal layer that elevates the mucosa to prepare for endoscopic mucosal resection or endoscopic submucosal dissection, instead of tissue dissection, which may occur because of the continuous water jet. A preclinical study has been conducted using a pulsed water jet system as an alternative method for submucosal dissection by reducing intraoperative water consumption and maintenance of dissection capability. This review introduces recent studies pertaining to using a water jet in gastrointestinal endoscopy and discusses future prospects.

Key words: Endoscopy; Water jet; Endoscopic submucosal dissection; Endoscopic mucosal resection; Pulse

Core tip: This review provides an overview of recent clinical and preclinical studies of water jet instruments in gastrointestinal endoscopy. Water jets have been used to keep the endoscopic view clear which contributed to reduce time and discomfort of endoscopic examination, and the technology provides an alternative method for endoscopic tumor resection. However, continuous flow is used in the transmucosal injection of water into the submucosal layer for elevating the mucosa to prepare for endoscopic mucosal resection. A preclinical study has used a pulsed water jet system as an alternative method to achieve dissection of submucosal layer.

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INTRODUCTION

Incidences of colorectal cancer are increasing in the developed world; in comparison with other types of examinations such as the stool occult blood test, barium enema, and computed tomography colonography, colonoscopy enables enhanced diagnostic specificity and sensitivity[1]. The incidence of gastric cancer remains high in Asian countries, including Japan. The demand for upper gastrointestinal endoscopy has been increasing annually, especially in Asian countries[2]. It requires highly advanced techniques and a learning curve exists for digestive endoscopy[1,2]. When the endoscope first appeared, it was a struggle to maintain a clear endoscopic view. The introduction of the forceps hole into the endoscope has been useful for injecting water vigorously into the gastrointestinal lumen to keep the endoscopic view clear. Endoscopes with incorporated water jet systems have been developed and released for clinical practice and are in widespread use. Water jets have also been recently used for endoscopic treatment, *i.e.*, in endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). This review provides an overview of recent clinical and preclinical studies of water jet instrument in gastrointestinal endoscopy.

WATER JETS FOR MAINTAINING ENDOSCOPIC VIEW

Water jet instruments were initially used to facilitate endoscopic observation. During gastrointestinal endoscopy, blood, food residue, and bubbles can impede the endoscopic view. Specifically in colonoscopy, colonic cleaning with polyethylene glycol method (PEG) helps with finding small lesions[3]. However, PEG can result in a lot of bubbles forming, hindering observation as much as the feces[4]. It is necessary to wash these out to discover the minute lesions or to treat under a clear endoscopic view. During gastroendoscopy, premedication with mucolytic agents, such as pronase, N-acetylcysteine, or dimethylpolysiloxane before upper gastrointestinal endoscopy improves the mucosal visibility of the stomach[5,6]. It is still necessary to wash away the bubbles caused by saliva or mucus (Figure 1). Recently, upper gastrointestinal endoscopy using nasal endoscope has rapidly become popular, as it is less painful and causes minimum vomiting reflux[7-10]. However, problems to be solved with this technique include lower camera resolution, insufficient light intensity, and the longer duration of the procedure as compared with that of an oral endoscopy. Attempts to use fluids such as oolong tea to clean the lens surface have been reported[11]. Manual water jet pumping prolongs inspection time[12]; Takahashi *et al*[13] reported that the introduction of a water jet operated by a foot switch in the nasal gastrointestinal endoscopy reduced the average inspection time from 561 ± 123 s to 503 ± 98 s (P = 0.0002). Using a water jet to maintain a clear endoscopic view is useful for reducing time and the discomfort of examination. A water jet from an automatic lavage pump is useful to keep endoscopic view clear[14]. This is currently supplied in products from several companies. Some models of upper gastrointestinal and colonic endoscope have separate water supply and forceps holes, which make it possible to inject water during endoscopic treatment such as hemostasis, EMR, or ESD (Figure 2). Hemostatic procedure is one of the important techniques during endoscopic treatment like EMR or ESD. So water jet systems are widely used to find the bleeding point and to make a view during hemostasis.

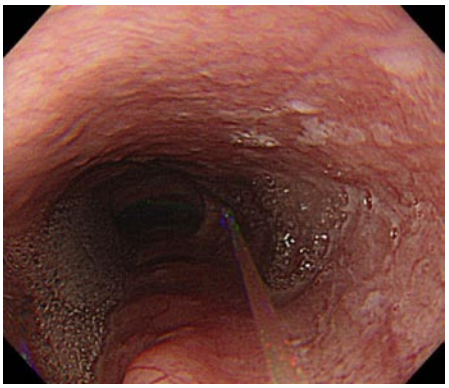

Figure 1 Endoscopic view of the esophagus shows that water jet flow washes away the bubbles caused by saliva or mucous in the esophagus.

WATER JETS AS OPERATIVE INSTRUMENTS

Water jet technology was used in liver[15] and cardiovascular[16] surgeries, as well as in neurosurgery in the late 1980s[17]. When used in liver surgery, this system reduces blood loss and parenchymal trauma better than both ultrasonic aspiration and blunt dissection[18,19]. Using the water jet instrument as a surgical device provides energy using the kinetic energy of the water flowing from a nozzle at the tip of the delivery device. This energy is transmitted to the tissue surface where it ejects particles of tissue, making an incision through the organ or tissue. Mass reduction can also be achieved using water jets[15,20]. Water jet has several features pertaining to dissection that are superior to conventional instruments, including selective tissue removal with vessel pre-

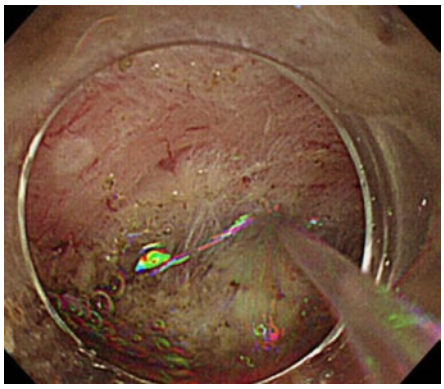

Figure 2 A water jet is useful to keep endoscopic view clear. Hemostatic procedure is one of the important techniques during endoscopic treatment like endoscopic mucosal resection or endoscopic submucosal dissection. So water jet systems are widely used to find the bleeding point and to make a view clean.

servation based on the different tensile strengths of the tissues. Water jet devices using a continuous water flow[20] allow organ dissection while preserving vessels that are > 100-200 μm in diameter[21,22]. Another notable advantage is that it helps avoid thermal damage to the surrounding parenchyma, which would otherwise be inevitable using an electric scalpel, electromagnetic, ultrasonic, and laser instruments[23,24]. However, limitations have been reported to arise from the formation of air bubbles, which obscure the operative field, and the splashing of blood fluid, which could subject surgeons and nurses to cross infection[16]. These limitations may be resolved when using the instrument in a luminal organ such as the gastrointestinal tract or in laparoscopic or thoracoscopic surgery. In addition, the development of a treatment instrument with lower water consumption would help address the limitations. Endoscopic treatment such as ESD in a narrow surgical field requires the application of highly advanced techniques by the operator. A lack of instruments that can aid this procedure preventing the risk of potential complications (thermal injury and vascular damage) is a drawback of the current ESD technique using an electric scalpel[25]. Water jet technology, which is based on a conventional, pressure-driven continuous jet[15,26] or a laser/electrically-induced pulsed pressure jet[27-29], could provide an alternative method or novel procedure for the dissection of soft tissue without impairing small-diameter vessels or causing mechanical or thermal damage during endoscopic therapy.

WATER JET INSTRUMENTS FOR ENDOSCOPIC THERAPY FOR TUMOR RESECTION

Endoscopic resection has become the standard of care for the treatment of early stage gastrointestinal tumors. EMR is performed on relatively small lesions. ESD enables the resection of large lesions in a single piece, and has low local recurrence rates[30,31]; however, operation time and the risk of complications are increased[31,32]. Various knives such as the dual knife (Olympus Medical Systems Co., Tokyo, Japan), B-knife (Zeon Medical, Tokyo, Japan), IT-knife, or Hook knife (Olympus Medical Systems Co., Tokyo, Japan) are used in ESD[33,34]; these are devised for safety and ease of use. As a preparation for safe EMR or ESD, it is useful either to inject fluids such as saline or hyaluronate or inject carbon dioxide into the submucosal layer to lift the lesion from the muscular layer[35,36]. Various water jet dissectors have been developed, such as the Flush knife (Fujifilm Medical, Tokyo, Japan), Splash needle (Pentax Co., Tokyo, Japan), HybridKnife (ERBE, Tübingen, Germany), and the ENKI-2 water-jet system (NESTIS, Lyon, France)[37-40]; these use continuous water flow to incise mucosa and inject fluid into the submucosal layer to lift the lesion. In contrast, the applying conventional pressure-driven continuous water jets endoscopically is limited to transmucosal injection of water into the submucosal layer for mucosal elevation prepare for EMR instead of tissue dissection[40,41]. This may be because of the continuous water jet. An advantage of these water jet devices is that washing of the surgical field or additional submucosal injection can be performed by flushing water through the knife without changing the instrument; this results in marked improvements pertaining to the efficiency and safety of the procedure[42]. Incision capability of these devices would be mostly due to the cooperation of water jet and electric cautery. Although Lesser *et al*[43] attempted to use a water jet dissector to cut polyp stalks clinically in the airway; the attempt to cut or dissect a submucosal layer under gastrointestinal endoscopy has been performed only in preclinical animal experiments. A continuous water jet flow of 30 kgf/cm^2 (Angiomat 3000, Liebel-Flarsheim, United States) was necessary to cut mucosa and mucosal muscle; however, injection fluid was spread in the submucosal layer in the swine stomach[44]. Kaehler *et al*[41] reported that a continuous water jet dissector, the Helix Hydro-Jet (ERBE), is capable of penetrating the mucosa and creating highly selective fluid accumulation in the submucosal layer, using a water pressure of 50-70 bar and an application angle of 20°-90°[41]. Lepilliez *et al*[45] reported a porcine gastric ESD where continuous jet dissection using a WJ medical system (Eschmann Equipment, West Sussex, England) *in vivo* was technically difficult due to the lack of visual control. Using continuous water jet also poses a potential risk of obscuring the narrow endoscopic operative view due to the large amounts of water. To date, there has been no report of continuous water flow being used to dissect the submucosal layer effectively. It has been reported that a pulsed water jet was feasible at 120 mL/min of water supply, but pulsed dissection was slower than IT knife dissection in the porcine stomach[45]. That volume of water would interfere with the endoscope view in a narrow lumen such as the esophagus or large intestine. On the other hand, Sato *et al*[46] reported that laser-induced pulsed water jet dissection in the

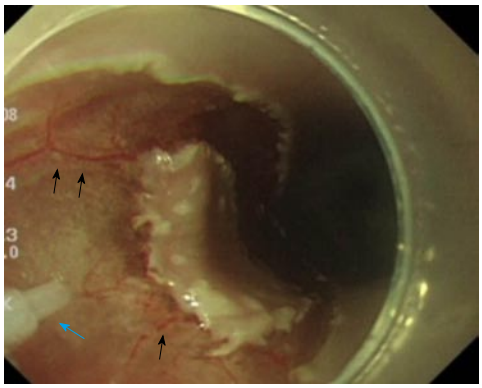

Figure 3 Preserved vessels using by pulsed water jet, which could be treated with pin-point ablation by hemostatic equipment would contribute to reliable hemostasis. Black arrows show small vessels preserved by the laser induced pulsed water jet. A blue arrow shows a nozzle of pulsed jet system.

porcine esophagus was performed safely and effectively, and the dissection rate was not different from hook knife dissection. Preservation of the vessels by water jet, which could be treated with pin-point ablation by hemostatic equipment would contribute to reliable hemostasis (Figure 3). They reported the feasibility of ESD of the esophagus with very small amounts of water (1.6 mL/min) and preserved micro-vessels. The optimal conditions for submucosal dissection are still unclear for both continuous and pulsed water jets, including the best size or shape of the nozzle, water pressure of the jet, pulse rate or volume of water supply. Since the required condition of the jet also depends on the physical properties of the tissue to be dissected[47], the conditions may vary between the esophagus, stomach, and large intestine. Further study is needed to elucidate the optimal conditions for dissection by water jet.

CONCLUSION

In gastrointestinal endoscopy, using a water jet to maintain a clear endoscopic view is useful for reducing time and the discomfort of examination; furthermore, water jets contribute to endoscopic therapy such as ESD or EMR. Using the water jet as an operative instrument is a recent development. A continuous water jet is used to lift up the mucous layer to pretreat EMR or ESD. Hybrid products combining water jet and electric scalpel have also been developed, and their results reported. It may be difficult to dissect the submucosal layer directly using continuous flow due to its nature, but use of a pulsed water jet is feasible, with a lower volume of water consumption. Although the research reported is mostly based on animal studies limited, further research is expected in the future.

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REVIEW

Diagnostic and therapeutic biomarkers in pancreaticobiliary malignancy

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) and cholangiocarcinoma (CCA) are two malignancies that carry significant morbidity and mortality. The poor prognoses of these cancers are strongly related to lack of effective screening modalities as well as few therapeutic options. In this review, we highlight novel biomarkers that have the potential to be used as diagnostic, prognostic and predictive markers. The focus of this review is biomarkers that can be evaluated on endoscopically-obtained biopsies or brush specimens in the pre-operative setting. We also provide an overview of novel serum based markers in the early diagnosis of both PDAC and CCA. In pancreatic cancer, the emphasis is placed on prognostic and theranostic markers, whereas in CCA the utility of molecular markers in diagnosis and prognosis are highlighted.

Key words: Biological markers; Pancreatic cancer; Cholangiocarcinoma; Diagnostic; Prognostic; Predictive; Brush specimens; Biopsies

Core tip: The poor prognoses of pancreatic ductal adenocarcinoma (PDAC) and cholangiocarcinoma (CCA) are strongly related to lack of effective screening modalities as well as few therapeutic options. Several novel biomarkers have been studied that have shown promise for early diagnosis and targeted therapy of these malignancies. These biomarkers provide a strong background for future clinical studies to screen for PDAC and CCA in the general population as well as to investigate molecularly targeted therapies.

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INTRODUCTION

The focus of this review will serve to summarize diagnostic, prognostic and predictive tumor markers in pancreatic cancer and cholangiocarcinoma (CCA). Despite major advances in the therapies of many solid tumors, survival in pancreatic cancer has not improved[1]. Delayed diagnosis, aggressive biology and marked chemoresistance have all contributed to this disappointing trend. Improving the sensitivity of diagnostic modalities, such as imaging or endoscopic tests and molecular markers, as well as innovation in surgical strategies and novel chemotherapeutic regimens had opened the possibility for significantly changing the status-quo. Although gemcitabine remains the back bone of chemotherapy in this disease, novel regimens have been introduced and some have demonstrated significantly better survival[2,3].

CCA arises from the neoplastic proliferation of cholangiocytes, the epithelial cells in the biliary tree[4]. It is an aggressive malignancy, characterized by early lymph node involvement and distant metastasis, with 5-year survival rates of 5%-10%[5]. The identification of new biomarkers with diagnostic, prognostic or theranostic value is especially important as resection (by surgery or combined with a liver transplant) has shown promising results and novel therapies are emerging[6]. However, the relatively low incidence of CCA, high frequency of co-existing cholestasis or cholangitis, and difficulties with obtaining adequate samples have complicated the search for accurate biomarkers.

DIAGNOSTIC SERUM MARKERS

Pancreatic cancer

Non-invasive blood-based biomarkers with high diagnostic accuracy would be ideal for the early diagnosis of pancreatic cancer. Current tumor markers [cancer antigen 19-9 (CA 19-9), carcinoembryonic antigen (CEA), *etc.*] do not have adequate accuracy. The most commonly used marker, CA 19-9, has been reported to have sensitivity and specificity rates ranging from 60%-90% and 65%-92%. Both tumor size[7], concurrent biliary or pancreatic obstruction and the presence of Lewis antigen has significant impact on CA 19-9 levels, making them even less useful as a diagnostic modality. Therefore novel molecular markers may fill an important void in non-invasive testing for early detection of pancreatic ductal adenocarcinoma (PDAC).

MicroRNAs (miRNAs) are highly stable 18-25 nucleotide single-stranded transcripts that function primarily as negative regulators of gene expression by inhibiting translation of their target messenger RNA. Emerging evidence suggests that initiation and progression of PDAC involves aberrant expression of miRNAs. Nearly 100 miRNAs are differentially expressed in pancreatic cancer. Many of these miRNAs are overexpressed and promote tumorigenesis by targeting tumor suppressor genes[8,9]. miRNAs have recently gained attention as potential diagnostic biomarkers and have been analyzed in human blood, bile, pancreatic juice, pancreatic cysts and stool. Relevant articles pertaining to miRNA and pancreatic cancer are summarized below.

Much of the research effort in this field was initially devoted to the characterization of miRNAs in pancreatic cancer. Bloomston *et al*[10] was one of the first to compare the global miRNA expression pattern of resected pancreatic cancer with healthy pancreatic tissue and chronic pancreatitis. He identified miRNAs miR-21, miR-155, miR-221 and miR-196a as key oncogenic miRNAs that correlated with aggressive tumors. In a similar fashion, miRNAs-221, -376a, -301, miR-93, -196a, -196b, -203, -205, -210, -221, -222 and -224 were found to be overexpressed in pancreatic cancer[11,12]. A supportive study by Sadakari *et al*[13] showed the relative expression levels of microRNA-21 and microRNA-155 in pancreatic juice was significantly higher when compared to chronic pancreatitis. Elevated levels of miR-196a and miR-10b were subsequently discovered in pancreatic intraepithelial neoplasia (*PanIN*) lesions suggesting these molecular compounds may be important for early carcinogenesis[14]. The prognostic significance of miRNA in pancreatic cancer was demonstrated by one study which associated elevated levels of miR-21 and miR-31 and low levels of miR-375 with poor clinical outcomes after surgical resection[15].

Circulating miRNAs in whole blood have been investigated in patients with pancreatic cancer. Whole blood miRNA analysis is an attractive screening test because of its easy clinical application and minimal patient involvement. Table 1 summarizes the largest and most recent studies to analyze the utility of novel serum-based miRNAs in the diagnosis of PDAC.

Given the overall stability of miRNA and the large abundance of hepatobiliary juice in stool, analysis for miRNA biomarker expression in feces offers another noninvasive screening option to evaluate for pancreatic cancer. Fecal miRNA expression profiling by Link *et al*[16] showed that dysregulated miRNAs can be found in stool. They report miRNAs-196a, -216a, -143 and -155 are differentially expressed in patients with PDAC when compared to controls. The purpose of this study was to evaluate the feasibility of stool miRNAs as novel biomarker for PDAC screening[17].

CCA

Acquisition of tumor tissue for histology or biomarker testing can be difficult and requires even more invasive and potentially risky procedures than diagnostic studies for PC. The most frequently used serologic markers of CCA are CA19-9 and possibly CEA. CEA has a sensitivity/specificity of 33%-84%/50%-87.8%[18-20]. CA 19-9 not only has a wide variation of sensitivity/specificity: 38%-93%/67%-98%[18-22], but can also be undetectable in 7% of the general population due to absence of the Lewis antigen[23]. Although CA 19-9 may have a role in the diagnostic algorithm, especially in

Table 1 Diagnostic serum markers for pancreatic ductal adenocarcinoma and cholangiocarcinoma

	Diagnostic markers	Countries	CCA or PDAC patients, *n*	Sensitivity (%)	Specificity (%)
Pancreatic cancer	miRNA-10b, -30c, -106b, -155, and -212[120]	United States	77	73-100	83-100
	Index 1: (miR-145, miR-150, miR-223, miR-636)	Denmark	409	Index 1: 77	Index 1: 66
	Index 2: (miR-26b, miR-34a, miR-122, miR-126, miR-145, miR-150, miR-223, miR-505, miR-636, miR-885.5p)[121]			Index 2: 80	Index 2: 82
	miR-21, miR-210, miR-155, and miR-196[122]	United States	49	64	89
CCA	CYFRA 21-1[18,24,30]	United Kingdom, Italy	30	17-76	79-95
	MMP-7[24,123,124]	Thailand, Italy	120	53-78	72.5-92
	Combo (CEA, CA 19-9, MMP-7, CYFRA 21-1)[24]	Italy	24	92	96
	Combo (CYFRA 21-1, CA 19-9)[30]	United Kingdom	6	45	96
	IL-6[35,125-127]	United States, Thailand	207	71.1-100	90-92
	SSP411[37]	China	35	90	83.3
	miR-21[128]	United States	23	95	100
	miR-150[129]	China	15	80.6	58.1
	[1]miR-192[130]	Japan	51	74	72
	MUC5AC[131,132]	Thailand	348	62.6-71	90-96.9
	Combo (AFP, CEA, CA 19-9, CA 125)[133]	China	30	90	90

All markers identified with ELISA, except for [1]Western blot. All cases of cholangiocarcinoma are histologically-proven. Control patients for CCA include those with benign liver diseases, HCC and healthy controls. Combo: Combination; PDAC: Pancreatic ductal adenocarcinoma; CCA: Cholangiocarcinoma; CYFRA 21-1: Cytokeratin 19 fragment; MMP-7: Matrix metalloproteinase-7; CEA: Carcinoembryonic antigen; CA 19-9: Cancer antigen 19-9; IL-6: Interleukin-6; SSP411: Sperm-specific protein 411; MUC5AC: Mucin 5AC; AFP: Alpha-fetoprotein; ELISA: Enzyme-linked immunosorbent assay; HCC: Hepatocellular carcinoma.

patients with primary sclerosing cholangitis (PSC) in the absence of concurrent cholangitis or pancreatitis, the low accuracy of the test limits its role in screening and early diagnosis. Thus, novel biomarkers with potential diagnostic utility have been studied (Table 1).

In malignant epithelial cells, activated proteases release cytokeratin-19 fragments (CYFRA 21-1) into the bloodstream[24]. CYFRA 21-1 levels have previously been shown to be a sensitive biomarker in non-small-cell lung cancer[25], gastric cancer[26], breast cancer[27], bladder cancer[28] and cervical carcinoma[29]. Several studies have shown elevated CYFRA 21-1 expression in CCA, but sensitivity varied depending on the cut-off value[18,24,30]. High matrix metalloproteinase-7 (MMP-7) expression has been found to be associated with cancer invasion in esophageal[31], colon[32] and pancreatic[33] cancers. The elevation of CYFRA 21-1 and MMP-7 in various malignancies can preclude their use as CCA-specific diagnostic biomarkers. Thus, combinations of serum markers can be used to improve sensitivity without compromising specificity. Using CYFRA 21-1 and MMP-7 in a multi-marker panel along with CEA and CA 19-9 demonstrated the highest diagnostic accuracy of 93.9%[24].

Interleukin-6 (IL-6) has been shown to be a growth factor for bile duct epithelium[34] and has demonstrated sensitivity as high as 100% in diagnosing CCA[35]. However, IL-6 is also elevated in many patients with hepatocellular carcinoma, benign biliary disease, and metastatic lesions, limiting its specificity[36]. This reinforces the need for more serum-based CCA-specific proteins that are not normally expressed in healthy liver tissue nor elevated in other malignancies. Sperm-specific protein 411 (SSP411) is one such protein which is elevated in the bile of CCA patients and recently found to successfully distinguish CCA from choledocholithiasis as a single serum-based biomarker[37].

miRNAs are usually stable in the circulation when bound to proteins. When miRNAs are dysregulated in cancers, they enter the circulation in free form and can be detected as potential diagnostic markers[38]. The utility of miRNAs lies in their tissue-specific patterns of expression. miRNAs commonly upregulated in other epithelial cancers (miR-192, 194 and 215 in colon, liver, pancreas and stomach cancer[39]) are not altered in CCA, while CCA-specific miRNA expression profiles exist (miR-125a, -31, and -95 are downregulated, while multiple miRNAs are upregulated as compared to nonmalignant cholangiocytes)[40,41]. The role of miRNAs in tumor invasion in CCA is supported by similar miRNA profiles between tumor tissue and adjacent non-tumor tissue as compared to normal tissue[42,43]. The most commonly overexpressed miRNA in CCA is miR-21[44-46]. However, it is also up-regulated in a variety of other cancers (gastric[47], breast[48] and colon[49]), suggesting that the most effective use of miRNAs is likely as multi-marker panels specific for CCA. MicroRNA biomarker discovery has extended from serum and plasma samples to the utilization of bile vesicles, which have demonstrated high accuracy in PSC patients[50].

The presence of circulating tumor cells (CTCs) in other solid cancers (including breast[51], prostate[52], colon[53] and pancreatic[54]) is associated with more aggressive disease and increased metastasis. Similarly,

CTCs in CCA were found to be prognostic of poor overall survival[55,56]. Using a cut-off of 2 CTCs/7.5 mL of peripheral blood, the sensitivity of CTCs for CCA diagnosis is only 17%-23%[55,56]. Despite their poor diagnostic utility, CTCs are potentially useful in detection and monitoring treatment of metastatic spread in real time.

DIAGNOSTIC BRUSH OR BIOPSY-BASED MARKERS

Pancreatic cancer

The diagnostic approach to pancreatic masses is dominated by endoscopic ultrasound-fine needle aspiration (EUS-FNA) and histologic or cytologic analysis. EUS-FNA is highly sensitive and specific for solid pancreatic lesions, with sensitivities as high as 85%-95% and specificities of 90%-95%[57].

The two areas where reliance on cytology is not supported by sufficient diagnostic accuracy are cystic neoplasms and inflammatory masses that may mask an underlying neoplasm. EUS-FNA is critical for the evaluation of pancreatic cystic lesions. It is beyond the scope and focus of this review to provide a summary of the data available on the accuracy of cyst fluid based cancer markers and molecular markers. Overall, these markers generally perform well in distinguishing mucinous type lesions from non-mucinous lesions but have thus far shown limited accuracy in identifying high-risk lesions (high grade dysplasia or carcinoma) from lower risk lesions[58-60]. Molecular analysis for DNA disruptions, Kras mutation and miRNAs has enhanced the diagnostic capability of EUS-FNA analysis of pancreatic cysts[61-64]. Similarly, molecular markers are promising in the relatively infrequent setting when a pancreatic mass is noted concurrent with inflammation (either with autoimmune pancreatitis or in the setting of chronic pancreatitis). For example, the presence of *Kras* mutations in FNA specimens has been shown to be a highly sensitive marker[65].

CCA

Despite advances in sampling techniques and visualization of the bile duct, obtaining representative tissue from the bile duct remains difficult. A single biliary stricture that occurs without associated suspicion of PSC has a different risk of being malignant than biliary strictures, even dominant strictures, identified in a patient with known PSC. Therefore, we consider the diagnostic tests used in these conditions separately.

PSC associated strictures: PSC is a chronic liver disease characterized by cholestasis, inflammation, multifocal biliary strictures and a 7%-12% lifetime risk of CCA[66,67]. A minority of CCA patients are surgical candidates and resection carries a 5-year survival rate of only 18%-32.5%[68-71]. The specialized protocol for PSC-associated CCA developed at the Mayo Clinic (neoadjuvant radio- and chemo-therapy with liver transplantation), has the highest 5-year survival rate of 79%[72]. Inclusion requires early-stage disease, thus excluding the majority of patients diagnosed by standard methods. Because the clinical presentation of CCA can mimic benign dominant biliary strictures, the major challenge lies in identifying potential biomarkers that detect early dysplasia and CCA (Table 2).

Conventional cytology has a low sensitivity due to inadequate cellular yield, but a near 100% specificity. Fluorescent *in situ* hybridization (FISH) trisomy/tetrasomy-positive results have a limited role in the detection of CCA in PSC because they were found to have a similar outcome to FISH negative patients[73]. However, polysomy has been shown to increase the sensitivity of routine cytology. There may be some reduction in specificity with FISH as PSC patients may have benign strictures that manifest with chromosomal abnormalities. The importance of sampling the biliary tree at multiple locations, regardless of the location of the dominant stricture, was demonstrated in a recent study that found that multifocal polysomy carried a greater risk of CCA diagnosis than polysomy detected at a single location[74]. Therefore, FISH should be part of the evaluation of PSC patients presenting with dominant strictures. In one retrospective study of PSC patients with polysomy on initial FISH testing but no signs of CCA, polysomy detected on repeat FISH was associated with increased incidence of CCA compared to patients with non-serial polysomy (polysomy present only on initial FISH)[75]. Repeat sampling without ongoing symptoms or signs remains an area of uncertainty but may be the most effective way to survey patients.

Kirsten rat sarcoma viral oncogene homolog (Kras) is a GTPase downstream of the epidermal growth factor receptor (EGFR) receptor that activates proteins involved in cell growth and proliferation. The high specificity of Kras analysis in biliary strictures can be useful, but the low sensitivity precludes it from diagnostic use as a sole biomarker. When used in combination with cytology, sensitivity increased to 100%[76].

Indeterminate biliary strictures: In certain series, up to a quarter of patients who undergo surgical resection for suspected CCA-related strictures turn out have benign etiology[77]. The utility of a highly sensitive modality beyond cytology or histology may therefore reduce the number of unnecessary surgeries. Thus far, assessment of polysomy by FISH has shown the greatest accuracy in brush cytology specimens. Some studies have found that the inclusion of the 9p21/p16 deletion in FISH analysis of indeterminate strictures increased the sensitivity of FISH-polysomy for pancreatobiliary tract cancers from 58% to 89% and from 70% to 76%[73,78,79].

PROGNOSTIC MARKERS

General prognostic markers, not specific to a defined

Table 2 Tissue-based diagnostic biomarkers for cholangiocarcinoma

	Diagnostic marker	Countries	Total patients, *n*	CCA patients, *n*	Sensitivity (%)	Specificity (%)
PSC-associated strictures	Brush Cytology[21,76,134-140]	United States, The Netherlands, Sweden, Norway	828	138	7-73	89-100
	FISH polysomy[21,73,136,137,140]	United States	387	89	22-50	88-100
	FISH polysomy or trisomy[21,73,136,140]	United States	373	75	60-88	57-87
	Kras[141,142]	Norway, United States	180	74	29-47	96-100
	p53[142]	Norway	48	33	31	100
	Cytology + CA19-9[135]	United States	333	44	87.5	97.3
	Cytology + DNA aneuploidy + CA19-9 + CEA[138]	Sweden	20	7	88-100	80-85
	Cytology + p53 + KRAS[76]	The Netherlands	23	10	100	79
	FISH + KRAS[141]	United States	14	14	50-68	96
Indeterminate strictures	Brush Cytology[75,78,79,136,140,143-150]	United States, Germany, France, Italy	640	199	5.8-80	92-100
	FISH Polysomy[75,78,79,136,137,140]	United States, Italy	386	165	31-80	97-100.0
	FISH Polysomy or trisomy[75,136,140]	United States	147	88	49-64	79.6-100
	Biopsy[144,145,147,150-153]	United States, Japan, France	347	65	30-88	97-100
	FNA[145,154]	United States	133	30	25-61.6	100.0
	Cytology + biopsy[144,150]	France, Austria	258	28	63-86	97-100
	Cytology + FNA + biopsy[145]	United States	133	30	47-52	100
	Cytology + KRAS[155]	Belgium	142	12	55	100

Some studies included all biliary tract cancers (cholangiocarcinoma, gallbladder, pancreatic and ampullary), but sensitivity and specificity values were similar, so data is merged. Endobiliary sampling technique for cytology and FISH: ERCP or PTC brushing; Biopsy technique: Standard forceps, mini-forceps or transpapillary biopsy. FISH: Fluorescent *in situ* hybridization; PTC: Percutaneous transhepatic cholangiography; CCA: Cholangiocarcinoma; PSC: Primary sclerosing cholangitis; p53: Tumor protein p53; KRAS: Kirsten rat sarcoma viral oncogene homolog; CEA: Carcinoembryonic antigen; CA 19-9: Cancer antigen 19-9; FNA: Fine-needle aspiration.

therapeutic regimen, can be useful in distinguishing which patients are at higher risk of a poor outcome and should therefore be managed more aggressively. Table 3 summarizes the dysregulation of certain markers in PDAC and CCA and their effect on overall survival and/or rate of metastasis.

Pancreatic cancer

Secreted protein acidic and rich in cysteine: Secreted protein acidic and rich in cysteine (SPARC) is a matricellular glycoprotein with important implications in pancreatic cancer. SPARC undergoes epigenetic silencing in pancreatic adenocarcinoma, but is often strongly expressed at the interface between the tumor and stroma by stromal fibroblasts[80]. Supporting data suggest this interaction is important for tumor progression, metastasis and protects against chemotherapeutic agents. Stromal SPARC expression is observed in all disease stages suggesting early expression is critical for tumor progression[81].

Numerous studies have identified stromal SPARC as a negative prognostic marker in pancreatic cancer[81]. Strong stromal SPARC expression in patients with well to moderately differentiated cancer who underwent surgical resection was associated with decreased overall survival when compared to patients with no SPARC expression[81,82]. Furthermore, patients with diffuse stromal SPARC expression extending beyond the peritumoral region had a significantly worse prognosis[83]. Interestingly, many report cytoplasmic SPARC expression by malignant pancreatic cells to have no prognostication value[81]. Others have revealed both stromal and cytoplasmic SPARC expression is associated with decreased overall survival in patients who were treated with gemcitabine[84]. Similarly, elevated SPARC mRNA expression in pancreatic cancer is also associated with worse patient outcome[85].

Human equilibrative nucleoside transporter 1: Human equilibrative nucleoside transporter 1 (hENT1) plays a major role in the internalization of (transportation of) gemcitabine by cancer cells. Among patients who did not receive gemcitabine in one study, hENT1 levels did not have any prognostic or predictive value[86]. Conversely, another study showed high hENT1 expression was a poor prognostic factor for early disease recurrence in the absence of gemcitabine therapy[87].

miRNAs: A large supportive study analyzing miRNA levels in PDAC revealed high expression of miR-21 and miR-31 with low expression of miR-375 were associated with poor overall survival following surgical resection[15].

CCA

miRNAs: Recent studies have been successful in establishing miRNA signatures that can discriminate between CCA and normal tissue as well as provide prognostic clues[41,88]. As various miRNA expression patterns correlate with overall survival and rate of metastasis, the identification of accurate and predictive

Table 3 Prognostic markers in pancreatic ductal adenocarcinoma and cholangiocarcinoma

	Marker	Country	Total patients, *n*	Marker positive PDAC	Type of dysregulation	Prognostic value, OS months	HR or *P* value for OS
Pancreatic cancer	SPARC	United States[81]	299	200	Up-regulated	+SPARC: 15 -SPARC: 30	1.89
		Germany[83]	58	58	Up-regulated	+SPARC: 7.6 -SPARC: 10.2	2.23
		Germany[84]	160	95	Up-regulated	+SPARC: 17.9 -SPARC: 30.2	$P = 0.006$
		Japan[85]	104	104	Up-regulated	Decreased survival	2.92
		Sweden[82]	88	68	Up-regulated	+SPARC: 11.5 -SPARC: 25.3	2.12
	Marker	Country	Total Patients, *n*	CCA patients, *n*	Type of dysregulation	Prognostic value	HR (95%CI) or *P* value for OS
CCA	[1]miR-192[130]	Japan	83	51	Up-regulated	Increased LN mets; shorter survival	2.076 (1.004-4.291) $P < 0.05$ mets
	miR-675-5p[88]	China	72	63	Up-regulated	Shorter survival	2.562 (1.295-4.929)
	miR-652-3p, miR-338-3p[88]	China	72	63	Down-regulated	Increased survival	0.477 (0.247-0.922); 0.498 (0.257-0.966)
	miR-151-3p and miR-126[156]	United States	32	32	Up-regulated and down-regulated, respectively	Increased survival	0.201 (0.043-0.928)
	[1]miR-21[46]	Thailand, China	41	32	Up-regulated	Increased LN mets; shorter survival	$P < 0.05$ OS $P = 0.037$ mets
	miR-214[157]	China	14	14	Down-regulated	Increased mets	$P < 0.05$ mets
	miR-373[90]	China	48	48	Down-regulated	Shorter survival	$P < 0.05$ OS
	Group 1: miR-21, miR-31, miR-223 Group 2: miR-122, miR-145, miR-146a, miR-200c, miR-221, and miR-222[44]	Greece	179	21	Group 1: Up-regulated Group 2: Down-regulated	None	-
	CYFRA 21-1[18,30]	United Kingdom, Japan	195	137	Up-regulated	Shorter survival	$P = 0.001$[30] $P < 0.01$[18]
	EGFR[93,94]	Japan	373	338	Up-regulated	Shorter survival	5.655 (2.72–11.74)[93] 2.67 (1.52-4.69)[94]

[1]Liver fluke-associated CCA. PDAC: Pancreatic ductal adenocarcinoma; CCA: Cholangiocarcinoma; mets: Metastases; OS: Overall survival; SPARC: Secreted protein acidic and rich in cysteine; CYFRA 21-1: Cytokeratin 19 fragment; EGFR: Epidermal growth factor receptor; LN: Lymph node.

multi-marker panels can identify patients in need of more aggressive management earlier (Table 3). However, the majority of these studies analyzed histologic samples from tumor resections, and therefore their utility from samples obtained at time of ERCP has not yet been demonstrated[44,88-92].

EGFR and CYFRA 21-1: Over-expression of EGFR[93,94] and CYFRA 21-1 values above 2.7-3 ng/mL[18,30] were each prognostic of decreased overall survival.

THERANOSTIC MARKERS

The goal of theranostic markers is to predict response to a specific therapy. In many other cancers, the role of targeted therapy has changed the approach to treatment. Various genetic mutations have been identified in PDAC and CCA (Table 4) that can be used to guide a personalized approach to therapy.

Pancreatic cancer

SPARC: One the most interesting clinical features of SPARC is its potential role as a predictive marker for response to therapy with nab-paclitaxel. Von hoff *et al*[2] identified stromal SPARC to be an important therapeutic marker in patients treated with combination nab-paclitaxel and gemcitabine chemotherapy. Specifically, patients with high SPARC expression treated with combination therapy had increased overall survival when compared to combination therapy in patients with low SPARC or absence of SPARC. This finding is thought to be due to nab-paclitaxel targeting stromal SPARC and is thought to facilitate delivery of gemcitabine by depleting tumor stroma. Contradictory results by Sinn *et al*[84] revealed high stromal SPARC expression in patients with pancreatic cancer treated solely with gemcitabine resulted in decreased overall survival. Such studies suggest the theranostic impact of SPARC is restricted to patients who receive therapy with nab-paclitaxel.

hENT1: A great deal of enthusiasm surrounds hENT1 because of its potential to remodel chemotherapy regimens in pancreatic cancer. There is overwhelming data to support its use as a first line test in pancreatic cancer. hENT1 plays a major role in the internalization

Table 4 Theranostic markers in pancreatic ductal adenocarcinoma and cholangiocarcinoma

	Marker (drug)	Countries	Patients with + marker	Staining	Median survival (mo)	HR
Pancreatic cancer	*SPARC*[2] (nab-paclitaxel/ gemcitabine)	United States	67	36	+SPARC: 17.8 -SPARC: 8.1	P = 0.0431
	hENT1 (Gemncitabine)	Canada[96]	21	Low hENT1: 12 High hENT1: 9	Low: 4 High: 13	[1]
		Italy[158]	83	Low hENT1: 27 Inter: 28 High hENT1: 26	Low: 8.5 Inter:15.7 High: 25.7	4.21
		United States[97]	91	Low hENT1: 39 High hENT1: 34	[2]	0.51
		Belgium[98]	45	Low hENT1: 26 High hENT1: 19	Low: 13.3 High: 18.7	4.31 (HR for death) P = 0.0001 (OS)
		Japan[159]	40	Low hENT1: 26 High hENT1: 14	Low: 8 High:25	P = 0.011 (OS)
		Japan[160]	55	Low hENT1: 16 High hENT1: 39	Low: 11.8 High: 24.9	3.15 (OS)
		Belgium France[86]	243	Low hENT1: 142 High hENT1: 92	[2]	0.34
		Worldwide multicenter[99]	177	Low hENT1: 118 High hENT1: 59	Low: 6.1 High: 5.2	1.147
		England[161]	176	Low hENT1: 77 High hENT1: 99	Low: 17.1 High: 26.2	0.6
	Marker	Countries	CCA patients	% mutated	Type of mutation	Potential theranostic value
CCA	EGFR[94,105,109,112]	United States, South Korea, Japan, Italy	400	1-81	G719S kinase activation	EGFR inhibitors
	VEGF[108,162]	South Korea	272	41.7-56.8	Up-regulation	Anti-VEGF therapies
	Kras[109,111,142,163-166]	United States, Germany, China, Norway, Japan	197	7.4-45	Substitution	U0126 (MEK inhibitor)
	BRAF[109,110,164,167]	United States, Germany, China	222	0-22	Activating missense	BRAF inhibitors
	ErbB2 (HER2/neu)[94,112]	South Korea, Italy	284	4-5.1	Up-regulation	Anti-ErbB2 therapies
	IDH1/2[109,114,115,168]	United States	576	10-22.3[1]	Gain of function	α-KG-mimics reverse methylation
	miR-21, miR-200b[40]; miR-29b, miR-205, miR-221[117]	United States, Japan	[1]	[1]	Up-regulated	Increased sensitivity to gemcitabine
	miR-494[92]	United States	43	[1]	Down-regulated	Up-regulation decreases tumor growth
	Panel: CDO1, DCLK1, ZSCAN18 and SFRP1[169]	Norway	39	87	Promoter methylation	Anti-methylation therapy
	Panel: CDO1, CNRIP1, SEPT9, and VIM[170]		30	85		
	SFRP1[169,171-173]	Norway, United Kingdom, South Korea, Thailand	255	59-83.6	Promoter methylation	Tumor suppression with gene therapy (RNAi)

[1]Not reported; [2]Results graphed. OS: Overall survival; PDAC: Pancreatic ductal adenocarcinoma; CCA: Cholangiocarcinoma; Kras: Kirsten rat sarcoma viral oncogene homolog; MEK: Mitogen-activated protein kinase/ERK kinase; EGFR: Epidermal growth factor receptor; ErbB2: Erythroblastosis oncogene B 2; VEGF: Vascular endothelial growth factor; CDO1: Cysteine dioxygenase type 1; DCLK1: Doublecortin-like kinase 1; ZSCAN18: Zinc finger and SCAN domain containing 18; SFRP1: Secreted frizzled-related protein 1; CNRIP1: Cannabinoid receptor interacting protein 1; SEPT9: Septin 9; VIM: Vimentin; IDH1/2: Isocitrate dehydrogenase 1/2; α-KG: Alpha-ketoglutarate.

of gemcitabine by pancreatic cancer cells[95] and is an important prognostic and predictive biomarker for gemcitabine efficacy in patients with pancreatic cancer. Its value as a biomarker is supported by an abundance of clinical studies. Acceptance of its clinical use is limited by a lack of large prospective validation studies. Supportive data is reviewed in this review.

Clinical studies have demonstrated response to gemcitabine parallels hENT1 expression. Namely, patients with tumors that test positive for hENT1 have longer median survival with gemcitabine therapy than those for whom hENT1 was absent. Spratlin *et al*[96] revealed strong hENT1 expression in patients with pancreatic adenocarcinoma was associated with a 3 fold increase

in overall survival after treatment with gemcitabine. Subsequently, a range of studies have reinforced the positive relationship observed with hENT1 expression and gemcitabine efficacy. Interestingly, this positive finding was not observed with other chemotherapy agents[97]. Additionally, several groups have reported a synergistic survival effect with hENT1 and other tumor markers including hCNT3 and deoxycitidine kinase (dCK) in subjects treated with adjuvant gemcitabine after curative resection[98].

Interestingly, Poplin *et al*[99] discovered that hENT1 expression did not predict gemcitabine sensitivity in patients with metastatic pancreatic cancer. This may be due to increased tumor heterogeneity in select patients. Acquired resistance to gemcitabine is bound to happen and may be due to altered gene expression involving important transport proteins including dCK, ribonucleotide reductase M1 (RRM1), RRM2, and hENT1[100]. Additionally, favorable single nucleotide polymorphisms (SNPs) of enzymes involved in the transportation or metabolism of gemcitabine have been identified and may be absent with an unfavorable phenotype[101,102].

Implementing pretreatment analysis for hENT1 expression is feasible, requiring a small tissue sample which can easily be obtained by EUS-FNA. Quantitative mRNA analysis of HENT1 or protein analysis with immunohistochemistry are both useful approaches that are presently limited by a lack of large validation trials.

CCA

Small-molecule inhibitors have demonstrated a good response rate in lung carcinoma harboring a mutation in the tyrosine kinase domain of the *EGFR* gene[103]. EGFR mutations can be unique to CCA[104] or identical to those in non-small cell lung cancer[105], highlighting the significance of genotyping in guiding therapy. A phase Ⅱ study of single agent erlotinib in patients with advanced biliary cancer demonstrated disease stabilization in 17%[106]. Upregulation of vascular endothelial growth factor (VEGF) is associated with an EGFR inhibitor-resistant phenotype[107]. Vandetanib, a dual inhibitor of VEGF and EGFR, has shown prolonged time to metastasis in CCA tumors that harbor both mutations[108].

Genes that function downstream of EGFR can also be important therapeutic targets. Kras is one of the most frequently mutated genes in CCA. BRAF mutations are most commonly associated with malignant melanoma, but have also been identified in up to 22% of CCAs[109,110]. Several studies suggest the potential application for targeted therapy with vemurafenib in this population, while avoiding EGFR-inhibitors[109,111]. There are no studies evaluating the response of BRAF-mutated CCA to vemurafenib therapy. However, there is an on-going phase Ⅱ "basket" study of vemurafenib in non-melanoma solid tumors harboring BRAF mutations that demonstrated stable disease at 8 wk in 4/7 CCA patients, partial response in 2/7 at 24 wk and the remaining 1/7 with disease progression (clinical trial# NCT01524978).

The small minority (4%-5%) of CCA cases that overexpress erythroblastosis oncogene B2 (ErbB2 or HER2)[94,112] may benefit from targeted anti-HER2 therapy. One case study demonstrated a dramatic regression of metastatic CCA in a HER2-positive patient who was started on trastuzumab after failing third-line chemotherapy[113].

A gain-of-function mutation in isocitrate dehydrogenase 1 (IDH1), leading to inhibition of α-ketoglutarate, has been seen in 23% of intrahepatic CCA cases[114], and a minority (0%-7%) of extrahepatic CCA tumors[114-116]. In-vivo studies have suggested that drugs mimicking α-ketoglutarate alone or in combination with inhibitors of mutant IDH1 can reverse the increased histone methylation[116]. Additionally, IDH enzymes are stable therapeutic targets because the mutation appears early in oncogenesis and is maintained throughout progression to high-grade lesions[115].

The increased expression of some miRNAs predicts a favorable response to gemcitabine treatment[40,117]. The potential of miRNAs lies not only in their theranostic utility, but also as therapeutic agents. Treatment of cholangiocytes with miR-494, which is down-regulated in CCA, induced cell-cycle arrest in tumor cells while sparing normal cells[92]. MicroRNA replacement therapy has seen success in phase Ⅰ clinical trials for ovarian[118] and hepatocellular carcinoma[119] and appears promising as a therapeutic modality in CCA.

Another benefit of these genes and miRNAs as markers is that they can be identified by mutational analysis on DNA or RNA and are commercially available.

CONCLUSION

Our review focused on PDAC- and CCA-specific biomarkers that may help in the early diagnosis of cancer or guide therapeutic decisions in the case of inoperable malignancy. The general population will benefit from a non-invasive serologic screening test with a high sensitivity, with multi-marker panels appearing advantageous. Despite the more invasive nature of tissue markers, high-risk patients would benefit from their high specificity. Additionally, the utility of predictive biomarkers will soon pave the way for individualized biliary and pancreatic cancer therapeutics.

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REVIEW

Biliary and pancreatic stenting: Devices and insertion techniques in therapeutic endoscopic retrograde cholangiopancreatography and endoscopic ultrasonography

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Abstract

Stents are tubular devices made of plastic or metal. Endoscopic stenting is the most common treatment for obstruction of the common bile duct or of the main pancreatic duct, but also employed for the treatment of bilio-pancreatic leakages, for preventing post- endoscopic retrograde cholangiopancreatography pancreatitis and to drain the gallbladder and pancreatic fluid collections. Recent progresses in techniques of stent insertion and metal stent design are represented by new, fully-covered lumen apposing metal stents. These stents are specifically designed for transmural drainage, with a saddle-shape design and bilateral flanges, to provide lumen-to-lumen anchoring, reducing the risk of migration and leakage. This review is an update of the technique of stent insertion and metal stent deployment, of the most recent data available on stent types and characteristics and the new applications for biliopancreatic stents.

Key words: Biliary stent; Pancreatic stent; Endoscopic retrograde cholangiopancreatography; Self-expandable

metal stent; Endoscopic ultrasonography

Core tip: Biliary and pancreatic stents have become one of the major advances made in therapeutic endoscopy and the endoscopic placement of these devices has a universally recognized role in the management of numerous pancreatico-biliary diseases. This review is an update of the technical considerations and available devices for biliary and pancreatic stenting.

Mangiavillano B, Pagano N, Baron TH, Arena M, Iabichino G, Consolo P, Opocher E, Luigiano C. Biliary and pancreatic stenting: Devices and insertion techniques in therapeutic endoscopic retrograde cholangiopancreatography and endoscopic ultrasonography. *World J Gastrointest Endosc* 2016; 8(3): 143-156 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i3/143.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i3.143

INTRODUCTION

In 1980 the first case of biliary stent placement for drainage of malignant obstructive jaundice was published[1]. A single-pigtail stent was fashioned using the cut end of an angiography catheter. The procedure was technically successful, but ultimately, the stent migrated upstream.

Cotton[2] reported the use of a stent made with a double-pigtail design to prevent upward migration and Huibregtse *et al*[3] described the creation of side flaps in the wall of a straight stent instead of pigtails to prevent migration.

Today a variety of plastic stents (PSs) with different designs, diameters, lengths and plastic materials have been investigated and available in the market. At the end of the 80s, some authors described the insertion of a self-expandable metal stent (SEMS) across biliary stenosis[4,5]. Early SEMS had relatively poor stent patency because of over and ingrowth of tissue. Because of their non-removability partially covered (PC) and then fully covered (FC) SEMSs were developed. Such stents are covered by a biocompatible polymer resistant to organic degradation. Despite various original articles and reviews about the types and techniques of stenting for different bilio-pancreatic disorders[6-9], the majority are focused only on one or more than one pathology or focused to pancreatic or biliary disease. The aim of our review is to emphasize the update of the technique of stent insertion and metal stent deployment, considering the most recent data available on stent types and characteristics and the new applications for bilio-pancreatic stents, both for endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasonography (EUS), considering also the gallbladder drainage and pancreatic fluid collections (PFC).

TECHNIQUES OF BILIARY AND GALLBLADDER STENTING AND TYPES OF STENTS

Plastic biliary stents

Ideally PSs should be technically easy to insert, should effectively relieve biliary obstruction, should not occlude, and should not cause injury to the bile duct or duodenal wall. Several different materials, sizes, and shapes have been used to optimize these aspects (Table 1 and Figure 1).

Plastic biliary stents are composed of polyethylene, polyurethane, polytetrafluoroethylene (Teflon) and other plastic polymers. The diameters of PSs are measured in French (Fr), corresponding to 0.33 mm, and diameters range from 5 Fr to 12 Fr.

PS with a diameter of 10 Fr require a 3.7 mm operative endoscope channel, and, when the diameter is larger ($\geqslant$ 11.5 Fr) a 4.2 mm operative channel is needed.

PSs have lengths ranging from 1 to 18 cm, and custom-made models may be requested from some manufacturers. A given stent length represents the entire length of the stent, although for some it is the distance between the end flaps. The length of a PS is generally selected to allow the shortest length possible while simultaneously ensuring adequate drainage. The length of plastic stents chosen is that which allows the ends to extent one to two cm over the proximal edge of the biliary lesion and 1 cm inside the duodenum.

Different types of PSs are commercially available. Plastic pig-tail stents are coiled at their proximal and distal extremities, or only at the distal (double pig-tail or single pig-tail, respectively). Side hole are generally placed at the coiled end. PSs may be straight or curved, with a flap on the proximal and the distal end and a side hole or with 4 flaps at both ends, without side holes (Tannenbaum stent). The role of side holes is to maintain biliary or pancreatic flow if the ends of the stent became occluded by bile or food impaction.

However, it has been hypothesized that side-holes can contribute to the formation of sludge**.** Moreover, the Tannenbaum stent (with multiple flap at its extremities but without side-holes) was designed to prevent migration. The aim of the development in biliary stenting in the recent years has been to increase the patency of the stents, improving the materials used for coating, a double-layer design, and a star-shaped stent winged stent without a central lumen. Finally, PSs are visualized radiographically, and some stents contain radiopaque markers at the proximal and/or distal ends. Introducing kits can be included in the stent package or available individually.

Biliary SEMS

The first widely used SEMS were made of stainless steel, whereas today most SEMS are made of nitinol. SEMS are available as uncovered, partially (PC-SEMS) or fully covered (FC-SEMS) (Figure 2, Tables 2 and 3). Different

Table 1 Technical characteristics of the most commonly used biliary plastic stents

Producer	Model	Diameter (Fr)	Length (cm)	Shape	Material
Boston Scientific	Advanix	7, 8.5, 10	5-18	Duodenal bend, centre bend, double pigtail	Polyethylene
ConMed	Hydroduct	7, 10, 12	4-15	Straight, angled, curved, double pigtail	Polyurethane with hydrophilic hydromer coating
Cook Endoscopy	Compass BDS	7	5, 10, 15	Double pigtail	Polyethylene
Cook Endoscopy	Cotton-Huibregtse	7, 8.5, 10, 11.5	5-18	Angled	Polyethylene
Cook Endoscopy	Cotton-Leung	7, 8.5, 10, 11.5	5-18	Curved	Polyethylene
Cook Endoscopy	Cotton-Leung Sof-Flex	7, 10	5-15	Curved	Polyethylene and polyurethane blend
Cook Endoscopy	Fusion Marathon Antireflux	10	5-12	Curved	Polyethylene with teflon sleeve
Cook Endoscopy	Soehendra-Tannenbaum	8.5, 10, 11.5	5-15	Curved	Teflon
Cook Endoscopy	Solus	10	1-15	Double pigtail	Polyethylene and polyurethane blend
Cook Endoscopy	Zimmon	5, 6, 7, 10	4, 7, 10	Double pigtail	Polyethylene
Endo-Flex	PE-Soft	7, 8.5, 10, 11.5	3-15	Bended, straight, curved, double pigtail, single pigtail	Polyethylene
Endo-Flex	PTFE-Strong	7, 8.5, 10, 11.5	5-15	Bended, straight, curved	Polytetrafluoroethylene
GI Supply	ViaDuct	7, 10	5-15	Winged straight	Polyurethane
Hobbs Medical	Biliary stent	7, 10	4-15	Curved, Double pigtail	Soft polymer blend
Indus Medical	CIBIDI	7, 10	5-15	Straight, curved, double pigtail	Polyurethane and teflon
Olympus	Double Layer	10	4-15	Duodenal bend, centre bend	Inner layer: Perfluoro; middle layer: Stainless steel; outer layer: Polyamide elastomer
Olympus	Biliary EVA	7, 8.5, 10, 12	5-18	Straight, proximal bend, centre bend, double pigtail	Ethylene vinyl acetate copolymers
Olympus	Biliary FEP	7, 8.5, 10, 12	3-15	Straight, proximal bend	Fluorinated ethylene propylene
Olympus	Biliary PE	7, 8.5, 10, 12	3-15	Straight, proximal bend, centre bend, double pigtail	Polyethylene
Pauldrach Medical	Gallengangs	7, 8.4, 10	9	Curved	Polyethylene

Figure 1 A display of different types of biliary plastic stents available.

materials contribute to the cover of the PFC-SEMS and of the FC-SEMS such as polytetrafluoroethylene, silicone and polyurethane**,** present on the exterior or interior of the SEMS.

Mechanical properties of SEMS are related to the stent design, type of wire, and covering materials. As a result of combinations of these variables, radial force and axial force were proposed as major mechanical properties that affect clinical outcomes. Radial force is well known as an expanding force, while axial force is a straightening or recovery force when SEMS are bent.

Radial force affects stent patency in that dilation of

Table 2 Technical characteristics of the most commonly used uncovered self-expandable metal stents

Producer	Model	Material	Diameter (mm)	Length (cm)	Shortening	Reconstrain	Characteristics
Boston Scientific	Wallflex®	Platinol	8, 10	4, 6, 8, 10	Yes	Yes	---
ConMed	Flexxus	Nitinol	8, 10	4, 6, 8, 10	Yes	No	Pistol delivery system
Cook Endoscopy	Zilver®	Nitinol	6, 8, 10	4, 6, 8	No	No	---
Cook Endoscopy	Evolution®	Nitinol	8, 10	4, 6, 8, 10	Yes	Yes	Pistol delivery system
Ella-CS	SX-ELLA® Nitinella Plus	Nitinol	8, 10	4, 6, 8, 10	Yes	Yes	---
Endochoice	Bonastent®	Nitinol	8, 10	4, 5, 6, 8, 10, 12	Yes	Yes	---
Endo-Flex	BIL-stent	Nitinol	10	6, 8, 10	Yes	No	---
Endo-Technik	NIT-BIL-1010®	Nitinol	10	4, 6, 8, 10	Yes	Yes	---
Leufen Medical	Aixstent® Gallengang	Nitinol	8, 10	4, 6, 8	Yes	No	---
Leufen Medical	Aixstent® Gallengang BDL - BDH	Nitinol	8, 10	4, 6, 8, 10, 12	Yes	No	The open cell design allows for Y stenting at the hilar region
Merit Endotek	Alimaxx-B®	Nitinol	8, 10	4, 6, 8	Yes	No	The open cell design allows for Y stenting at the hilar region
M.I. Tech	Hanarostent®	Nitinol	8, 10	4, 5, 6, 7, 8, 9, 10, 12	Yes	Yes	---
M.I. Tech	Hanarostent® Hilar	Nitinol	10	8	Yes	No	The large cell design allows for Y stenting at the hilar region
Micro-Tech	BD stents Classic or Platinum-Line	Nitinol	10	4, 6, 8, 10	Yes	No	---
Olympus	NIRflex	Nitinol	8, 10	4, 6, 8, 10	Yes	No	---
S and G Biotech	EGIS® Biliary DC Stent	Nitinol	8, 10, 12	4, 5, 6, 7, 8, 9, 10, 12	Yes	No	Single or double bare
TaeWoong Medical	LCD®	Nitinol	6, 8, 10	4, 5, 6, 7, 8, 9, 10, 12	Yes	No	The large cell design allows for Y stenting at the hilar region
TaeWoong Medical	Niti-S® D-type	Nitinol	6, 8, 10	4, 5, 6, 7, 8, 9, 10, 12	Yes	No	---
TaeWoong Medical	Niti-S® S-type	Nitinol	6, 8, 10	4, 5, 6, 7, 8, 9, 10, 12	Yes	No	---

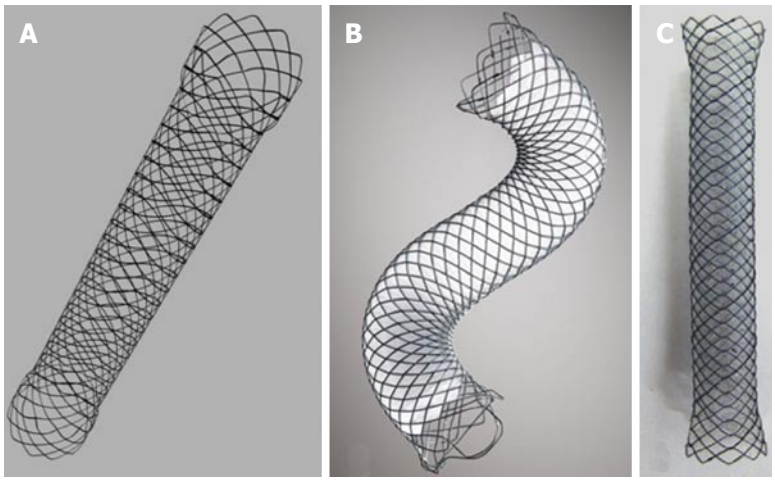

Figure 2 A display of different types of biliary self-expandable metal stents available. The Evolution (A) uncovered stent, Cook Endoscopy, the Wallflex (B) partially covered stent, Boston Scientific, and the SHC (C) fully covered stent, Hanaro MI Tech.

a biliary stricture and maintenance of luminal patency depend on the expanding force of the SEMS. Two factors in radial force exist in terms of time course. Immediate stent expansion at the time of stent deployment affects short-term outcomes, and chronic resistant force against tissue compression affects long-term outcomes. In general, the chronic resistant radial force is higher than the immediate stent expanding force because SEMS are made of a type of shape-memory alloy. This characteristic means that SEMS partially expand immediately after deployment and then gradually expand to their full extent, even though the radial force may be high. Axial force is considered to define conformability of SEMS in the bile duct and may have a greater relationship with clinical outcomes than radial force. After deployment in the bile duct, SEMS are fixed at the stricture by the tissue and axial force causes compression to the bile duct at both stent ends. As axial force increases, so does the

Table 3 Technical characteristics of the most commonly used partially and fully-covered self-expandable metal stents

Producer	Model	Material	Diameter (mm)	Length (cm)	Shortening	Reconstrain	Shape	Covering
Allium Medical	Allium BIS®	Nitinol	8, 10	6, 8, 10, 12	No	No	Straight with anchoring segment	FC in polyurethane
Boston Scientific	Wallflex®	Platinol	8, 10	4, 6, 8, 10	Yes	Yes	Two flanges	PC and FC in permalume
Cook Endoscopy	Evolution®	Nitinol	8, 10	4, 6, 8, 10	Yes	Yes	Two flanges	PC and FC in silicone
Ella-CS	SX-ELLA® Nitinella Plus	Nitinol	8, 10	4, 6, 8, 10	Yes	Yes	Two flanges	PC and FC in silicone
Endochoice	Bonastent®	Nitinol	8, 10	4, 5, 6, 8, 10, 12	Yes	Yes	Two flanges	FC in silicone
Endo-Flex	BIL-stent	Nitinol	10	6, 8	Yes	No	Straight	FC in silicone
Endo-Technik	NIT-BIL-1010®	Nitinol	10	4, 6, 8, 10	Yes	No	Straight	PC in silicone
Gore Medical	Viabil®	Nitinol	8, 10	4, 6, 8, 10	No	No	Straightwith anchoring fins	FC in PTFE with/ without drainage holes
Leufen Medical	Aixstent® Gallengang	Nitinol	8, 10	4, 6, 8	Yes	No	Two flanges	PC and FC in polyurethane
M.I. Tech	Hanarostent® BCT	Nitinol	10	4, 6, 8, 10	Yes	Yes	One flange with flaps and lasso	FC in silicone
M.I. Tech	Hanarostent® BCS	Nitinol	10	4, 6, 8, 10, 12	Yes	No	One flange and with flaps	FC in silicone
M.I. Tech	Hanarostent® BPE	Nitinol	8, 10	8, 10	Yes	No	One flange and with flaps	PC in silicone
Micro-Tech	BD stents	Nitinol	10	4, 6, 8, 10	Yes	No	Two flanges	PC and FC in silicone
S and G Biotech	EGIS® Biliary DC Stent	Nitinol	8, 10, 12	4, 5, 6, 7, 8, 9, 10, 12	Yes	No	Two flanges	PC in PTFE
TaeWoong Medical	Niti-S® S-type covered	Nitinol	6, 8, 10	4, 5, 6, 7, 8, 10, 12	Yes	No	Two flanges	FC in silicone
TaeWoong Medical	Niti-S® Kaffes	Nitinol	6, 8, 10	4, 5, 6, 7, 8	Yes	No	Tapered with long lasso	FC in silicone
TaeWoong Medical	Niti-S® Bumpy	Nitinol	6, 8, 10	4, 5, 6, 7, 8, 10, 12	Yes	No	Two flanges	FC in silicone and PTFE
TaeWoong Medical	Niti-S® Giobor	Nitinol	8, 10	8, 10	Yes	No	One flange	PC in silicone
TaeWoong Medical	Niti-S® ComVi	Nitinol	6, 8, 10	4, 5, 6, 7, 8, 10, 12	Yes	No	Straight	FC in PTFE

PC: Partially covered; FC: Fully-covered; PTFE: Polytetrafluoroethylene.

compression of the bile duct or cystic duct or pancreatic duct orifice. Clinically, this situation may cause kinking of the bile duct with resultant cholecystitis or pancreatitis. In addition, less conformability of SEMS in the bile duct leads to stent migration. In general, axial force affects clinical outcomes such as stent migration and pancreatitis more than radial force.

SEMS have lengths ranging from 4 to 12 cm and diameters from 6 to 10 mm. The stents are mounted on a delivery system accepting a wire of 0.035 diameter, and the newest models can be also used with a single operator system. The diameters of the delivery systems range between 5.0 and 10.5 Fr. The smaller the catheter the easier it is to cross the stenosis without mechanical or pneumatic dilation. The same can be said for patients with Klatskin neoplasia.

The majority of the delivery kits are resistant, avoiding kinking during insertion, allowing correct placement; the outer sheath of the kit is transparent for the visualization of the distal stent extremity during SEMS release. During stent placement, the outer sheath is gently pulled inside the operative endoscope channel to allow the release and expansion of the SEMS. Rarely, the stent is constrained by a thread that, when removed, allows SEMS expansion. Generally, SEMS can be recaptured, until 80% of their opening and all metal stents are visible fluoroscopically. The majority of SEMS have a marker at both extremities and, in some models, one at the middle. Some models of FC-SEMS have anti-migration flaps or flared ends to avoid distal or proximal migration (Figure 3).

Recently, a new type of FC-SEMS is produced with the intent to diminish proximal and distal migration (Figure 4). The Hanaro, M.I. Tech, Seoul, South Korea has an "anchoring-flap" system made of four flaps in the proximal end, flared ends and one proximal and one distal lasso for retrieval. TaeWoong produces the Bumpy®-Niti-S stent, with a membrane of silicone (distal extremity) and polytetrafluoroethylene (body of the stent). This stent has both flared ends and a string for the removal, at the distal extremity. The characteristic of this FC-SEMS are the irregular meshes; it contributes to a different radial force in every point of the stent, conferring conformability and adaptability in the lumen of the duct, preventing migration.

Technique of transpapillary biliary stenting

Before stent placement a cholangiogram is performed to confirm successful biliary cannulation and to evaluate the

Figure 3 The Viabil (A) fully covered stent, Gore Medical, and the Wallflex (B) fully covered stent, Boston Scientific.

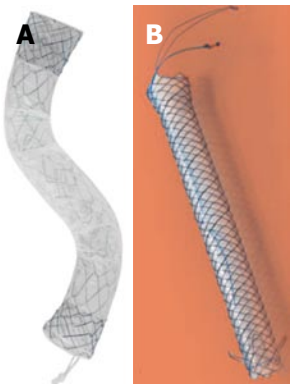

Figure 4 The Bumpy Niti-S stent (A), Taewoong Medical and The BCT stent (B), Hanaro MI Tech.

location and length of the stricture or leak[10-12].

The correct choice of PS length is often based on operator's experience. Alternatively after bile duct contrast medium injection, or using a centimeter guidewire. An alternative way to measure the length of the strictures for the choice of the stent is to gently withdrawing the catheter from the proximal to the distal end of the strictures, measuring with a ruler the centimeters of the device out of the operating channel.

Endoscopic sphincterotomy (ES) is not necessary for inserting a single PS, while is indispensable for multiple plastic stenting. If the stricture is tight, dilation with a balloon or a bougie before stenting may be useful. Balloon dilatation of strictures is usually helpful for placement of hilar PSs, particularly when bilateral stenting is attempted. Moreover, in these strictures, there is still a role for stents of smaller diameter and the tapered pigtail stent design. For example, if bilateral stenting is required in patients with hilar obstruction, it is often easier to place two 7 Fr stents initially to gradually dilate the bile duct and then replace them later with 10 Fr stents. Tapered pigtail stents are sometimes helpful to allow passage across very tight strictures.

The PS stent is loaded on a guide-catheter, over the guidewire, with the pusher-catheter. The guide-catheter and guidewire need to be made wet using a saline solution because they are hydrophilic. The entire stent insertion loaded kit is introduced inside the operative channel. When the PS is placed across the stricture, moving the endoscope in anti-clockwise rotation and with alternately moving the elevator up and down, the guide-catheter is pulled back, pushing the stent inside the CBD with the pusher-tube. When the guide-catheter is completely pulled back, the pusher-catheter can be removed from the channel.

During stent placement, maintaining the endoscope close to the Vater's papilla facilitates tent insertion because it avoids looping of the delivery system in the duodenal lumen.

If the guide-catheter is inadvertently withdrawn from the inside of the PS, it may be possible to readvance it, continuing the stent placement. When stent insertion is challenging, the "long position" of the endoscope might be useful. This position allows to the operator to then use the straightening maneuver and, maintaining the elevator in up position, insert the stent into the duct. If the PS is damaged during insertion in the bile duct it can be removed over-the-wire, by passing a dilation balloon inside the PS or by using the Soehendra retriever, leaving the wire in place, and replacing the a new PS delivery system.

A final radiographic image should be obtained to verify if contrast medium drains through the stent. For implantation of a SEMS an ES is often performed, though is not mandatory. Then, under fluoroscopic examination (for biliary strictures), the length, presence or absence of a gallbladder and the relationship of the cystic duct with the CBD is determined for the correct choice of the type of the SEMS (length, diameter and covered *vs* uncovered).

Because of a potential risk of cholecystitis, some endoscopists prefer to use uncovered SEMS in the presence of a gallbladder, to avoid the cystic duct occlusion, or to place a FCSEMS, when indicated and a small diameter plastic stent inside the cystic duct. Before their insertion into the duct, the uncovered SEMS and the FC-SEMS are generally wet with saline solution in the guidewire channel and inside the outer sheath.

The release of the SEMS is performed under X-ray control, withdrawing the outer sheath of the device, pulling down the elevator, maintaining the stent in the correct position during the release, pulling back the device as it tends to move away from the operator and proximally into the duct. Most of the stent can be recaptured until 80% of the complete release. At the end of the procedure, after metal stent release a cholangiography is required to confirm the correct position of the SEMS and flow of contrast medium flow into the duodenal lumen. If the SEMS is released too proximally, it can be withdrawn distally grasping the distal extremity, or the distal thread, with a rat-tooth forceps. If these attempts fail, a second stent can be deployed, with the distal extremity inside the proximal one of the previous stent. Contrariwise, if the SEMS is released too distally into the duodenum, it can be

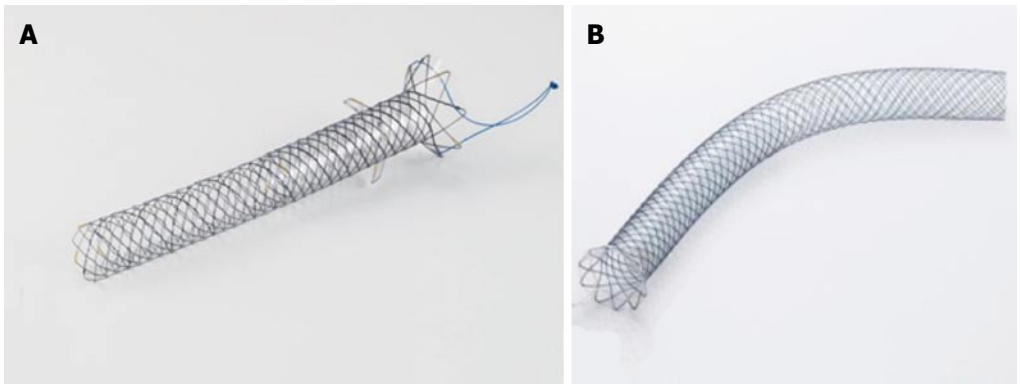

Figure 5 The BPE stent (A), Hanaro MI Tech, and the Giobor Niti-S stent (B), Taewoong Medical.

completely removed by a rat-tooth forceps or the excess stent cut using argon plasma coagulation.

Different techniques are utilized for the drainage of the hepatic hilum. Preoperative magnetic resonance cholangiopancreatography or high-resolution CT should be performed in all patients with suspected proximal biliary stenosis to delineate the anatomy before the procedure. SEMS insertion can be performed using the "side-by-side" (SBS) or the "stent-in-stent" (SIS -"Y") technique.

When SBS technique is performed, two or more guidewires are placed inside different biliary ducts to be drained. After the release of the first metal stent, the insertion of the delivery system of the second SEMS can be difficult because of the impaction of the distal ends of the first SEMS with the delivery of the second one. A way to overcome this difficulty is the insertion of a temporary plastic stent to maintain an accessory space between the first SEMS and the duct wall. In SBS technique the first lobe to drain is the left because the SEMS insertion in the right lobe is easier.

With the SIS technique, the second stent is deployed inside the meshes of the first stent. Balloon dilation of the first SEMS meshes might be helpful to facilitate positioning of the second SEMS device. Some SEMS are designed with large diameter meshes of the middle part to facilitate the deployment of the second one (Y-shaped stent).

Endoscopic ultrasound-guided biliary drainage

In recent years, EUS has evolved from a diagnostic to a therapeutic procedure, and is now increasingly used to guide biliary drainage (BD) after failed ERCP. For therapeutic EUS, the use of a linear-array endoscope with a 3.8 mm operative channel is preferable to allow the passage of large diameter accessories. There are two possible puncture routes for EUS-BD; transgastric for the intra-hepatic bile duct drainage or transduodenal (bulb) for extrahepatic bile duct drainage. During therapeutic EUS Color Doppler is mandatory, to prevent damage to interposed vessels between the endoscope and the ducts. The puncture of the duct to drain can be performed with a fine needle aspiration (FNA) needle of 19- or 22-gauge (G). The 19 G needle is generally used because the capability of support a 0.035-inch guidewire, which provides more stiffness. The 22 G needle accommodates only a 0.018-inch guidewire, which carries a greater risk of dislodgement of the guidewire during the procedure. After duct access with the EUS needle, contrast medium injection from the needle is required to perform cholangiography for the confirmation of the correct position of the needle inside the biliary tree. After that, under fluoroscopic guidance, the guidewire can be placed into the duct, advancing it inside the needle[13-16].

If the drainage is performed transmurally from the stomach, only intrahepatic ducts can be drained [hepaticogastrostomy (HPG)], and if performed from the duodenal bulb the extrahepatic bile duct are more accessible [choledochoduodenostomy (CLD)]. If the guidewire exits the papilla, the drainage can be integrated by ERCP, using the *rendezvous* technique. When the deployment of the stent is performed through the puncture route or deployed across the stricture or the ampulla in an antegrade fashion, different devices can be used for dilation of the site, such as bougie (6 or 7 Fr), pneumatic dilation balloon (4 or 6 mm) or a cystotome (8.5 Fr). Both plastic and metal stents are used for HPG or CLD although PC and FC SEMS are most often used to prevent stent migration and bile leakage. Uncovered SEMS should not be used for HPG or CLD. Recently two new SEMS have emerged specifically designed for EUS-BD (Figure 5).

The Giobor Niti-S, Taewoong, is a PC-SEMS with the inner part (intra-biliary) uncovered to prevent intrahepatic bile duct obstruction and migration, and covered in the trans and intragastric part to prevent bile leakage; it also has a single lasso for possible retrieval. The BPE, Hanaro MI Tech, is a PC-SEMS, the proximal portion, which is 15 to 55 mm in length, is uncovered for the prevention of duct obstruction, while the distal end, 35 mm in length, has a silicone cover for the prevention of bile leakage. The BPE stent and has anti-migration flaps at both extremities, for prevention of stent migration.

Technique of transpapillary gallbladder stenting

Cystic duct negotiation is the most challenging part of transpapillary gallbladder stenting. Methods to reach the cystic duct are cholangiography and fluoroscopy arm longitudinal and transversal axis rotation to allow for identification of the level of its insertion into the CBD[17,18].

Table 4 Technical characteristics of the most commonly used pancreatic plastic stents

Producer	Model	Diameter (Fr)	Length (cm)	Shape	Material
Boston scientific	Advanix	3, 4, 5, 7, 10	2-18	Straight or single pigtail with or without internal flap	Polyethylene
Cook endoscopy	Geenan Sof-Flex	5	3-12	Curved with or without internal flap	Polyethylene and polyurethane blend
Cook endoscopy	Geenan	3, 5, 7	3-15	Curved	Polyethylene
Cook endoscopy	Johlin Wedge	8.5, 10	8-22	Wedge	Polyethylene and polyurethane blend
Cook endoscopy	Zimmon	3, 5, 7	2-12	Single pigtail with or without internal flap	Polyethylene
Endo-Flex	PTFE-Strong	5, 7	3-9	Curved	Polytetrafluoroethylene
GI supply	ViaDuct	5, 7	3-12	Winged straight or single pigtail with or without internal flap	Polyurethane
Hobbs medical	Freeman Flexi-Stents	3, 4, 5, 7	2-18	Straight or single pigtail with or without internal flap	Soft polymer
Olympus	Pancreatic PE	7, 8.5, 10	3-15	Straight, S-shaped	Polyethylene

For a left-side cystic duct take-off, a flexible-tip catheter or a rotatable sphincterotome may be used, while for a right-sided take-off, a standard sphincterotome may be used because it usually bows toward the cystic duct when it takes off on the right side. A 0.035" or 0.025" guidewire (stiff or hydrophilic) is used to enter into the cystic duct orifice. The angled tip guidewires are preferable to enter and pass through the spiral valves of Heister while minimizing the risk of perforation. In difficult cannulation of the cystic duct, an inflated Fogarty balloon up to the cystic duct insertion, with an angled-tip guidewire passed alongside may be useful for its negotiation. After cystic duct negotiation, the guidewire is advanced and coiled within the gallbladder lumen and an accurate study of the course and diameter of the duct must be performed for the correct choice of the stent. The catheter is then removed and the stent placed over the wire. Double pigtail 6 to 10 Fr PSs are preferable because of their superior anchorage into the gallbladder lumen compared with straight stents. The length of the stent is chosen based upon the distance between the major duodenal papilla and the gallbladder (usually 12-15 cm long stents are used) and the stent size according to the diameter of the cystic duct and common bile duct. When 10 Fr stents are placed, an ES should be performed to minimize the risk of post-ERCP pancreatitis caused by the fulcrum effect.

EUS guided gallbladder drainage

EUS guided gallbladder drainage (EUS-GD) is performed using a large channel (3.7 or 3.8 mm) echoendoscope with fluoroscopic guidance[19-22].

The best way to visualize the gallbladder is the pre-pyloric area, in the stomach, or from the duodenal bulb. The puncture is performed in the site in which gallbladder is in contact with the bowel. The more stable the echo-endoscope position the easier the procedure. Color Doppler is mandatory, before gallbladder puncture, to avoid puncture of interposed blood vessels.

A 19 G FNA needle is usually used to obtain gallbladder access. After gallbladder puncture and removal of the stylet, cholecystography is performed by injecting contrast medium through the needle. After cholecystography, a guidewire is inserted and coiled inside the gallbladder. After the removal of the needle, the access-site can be enlarged using either a mechanical (6 or 7 Fr bougie or balloon catheters) or electrocautery (6 or 10 Fr cystotome or needle-knife) device. After dilation, the stent is advanced over the wire and into the gallbladder.

Recently, a single-step device allowing access, dilation and plastic stent placement has been developed for EUS-GD (Giovannini Needle Wire Oasis, Cook Ireland Ltd, Limerick, Ireland).

Plastic stents, standard or modified tubular covered SEMSs and lumen apposing metal stents (LAMSs) are used. Plastic stents were used for EUS-GD in early studies. However, the PSs can become occluded and may not allow complete sealing between the gallbladder and duodenal or gastric wall with a relative risk of bile leak in the abdomen.

To circumvent the limitations of plastic stents tubular FCSEMS were used for EUS-GD. Metal stents, with their high radial force and covering can reduce this risk. The larger diameters may facilitate draining of thick or necrotic debris, pus or sludge reducing the risk of stent clogging.

However when metal and plastic stents designed for ERCP are used migration remains an important risk. Recently LAMS have been developed to obtain better anchorage between the gallbladder or bile ducts and the bowel wall, reducing the risk of stent migration and bile leakage. These include the Axios stent (Boston Scientific, Natick, MA, United States) (Figure 6A) and Spaxus Niti-S stent (Taewoong Medical, Seoul, South Korea) (Figure 6B).

TECHNIQUES OF PANCREATIC DUCT AND PERI-PANCREATIC FLUID COLLECTION DRAINAGE AND TYPES OF STENTS

Pancreatic plastic stents

Pancreatic stents (Table 4 and Figure 7) are made of

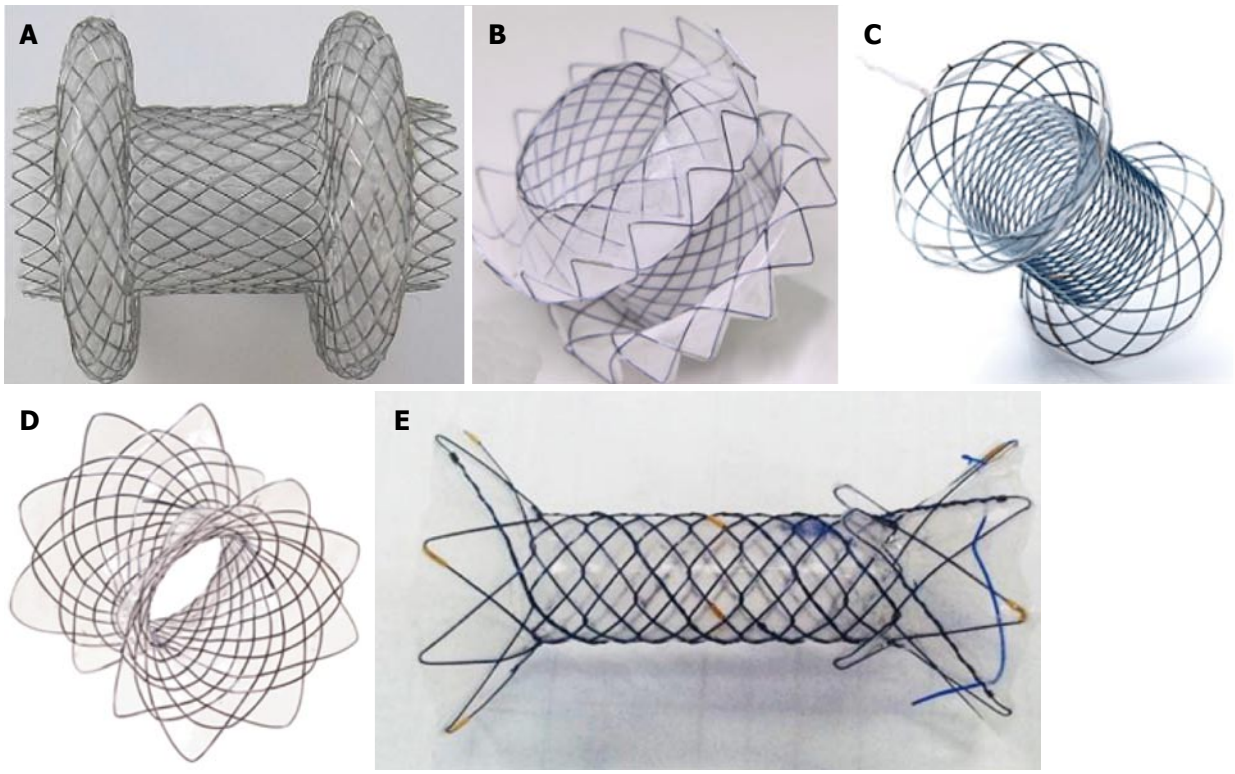

Figure 6 A display of different types of lumen apposing metal stents available: The AXIOS (A) stent, Boston Scientic, the Spaxus (B) and NAGI (C) Niti-S stents, Taewoong Medical, the Aix (D) stent, Leufen Medical, and the BCF (E) stent, Hanaro MI Tech.

polyethylene; the shape and design resemble those of biliary stents, save for the presence of side holes along the length of the stent. The side holes allow draining of pancreatic juice from side branches.

Pancreatic stents have lengths between 2 and 25 cm and diameters between 3 and 11.5 Fr. Different types of stents are now commercially available, with different shapes as straight, winged or with curved distal end or wedged proximal end. Some of these have a "J" or single pigtail shape to prevent migration into the pancreatic duct. There is also an S-shaped stent with many side holes and made in ethylene-vinyl-acetate (EVA). EVA has more flexibility compared to polyethylene.

Pancreatic stents with S-shape are made for a better adapting to the profile of the main pancreatic duct. A winged stent (Via-Duct stent, GI Supply) is made to allow pancreatic juice to flow through the wings of the stent.

Pancreatic PSs without a proximal flap are designed to allow spontaneous distal migration, when the stent are only to be used for a short time. Pancreatic PSs with a distal end pig-tail are designed for avoidance of proximal migration.

The majority of pancreatic PSs are deployed over-the-wire, only with the push-catheter, without the use of the guide-catheter, because of their small diameter. Pancreatic plastic stent with a diameter more than 8.5 Fr requires the use of a guide-catheter.

Pancreatic self-expandable metal stents

The only self-expandable stent designed for drainage of the main pancreatic duct (MPD) is the TaeWoong Bumpy® - Niti-S, that presents a non-regular cell mesh. It results in a different radial force in every part of the stent, avoiding compression of the side branches of the pancreatic duct.

However, other FC-SEMS are used off-label with good outcomes in selected situations, such as the WallFlex (Boston Scientific) and the Viabil (Gore Medical). The Viabil stent is fully covered and available with side holes designed to allow cystic duct drainage and which may allow drainage of some pancreatic duct side branches.

Technique of transpapillary pancreatic duct stenting

The pancreatic PSs placement technique is the same as used for the biliary tree. After MPD cannulation, the stent is inserted inside the duct over the wire; hydrophilic guidewire of 0.035" is used for placement of PSs from 5 to 10 Fr; 0.018" guidewires are used for 3 Fr PSs, generally reserved for cases of minor pancreatic duct stenting and temporary placement for prevention of post-ERCP pancreatitis. Pancreatic sphincterotomy is not always necessary for placement of PSs. In case of bilio-pancreatic sphincterotomy, pancreatic sphincterotomy is generally performed after biliary sphincterotomy[23].

The PSs diameter must not be greater than the maximum diameter of the pancreatic duct. Five and 7 Fr PSs are generally implanted in absence of duct dilation; 10 Fr PSs, or more than 10 Fr, are instead used when MPD stenosis with upstream duct dilation occurs. When very tight strictures are present, the placement of a PSs

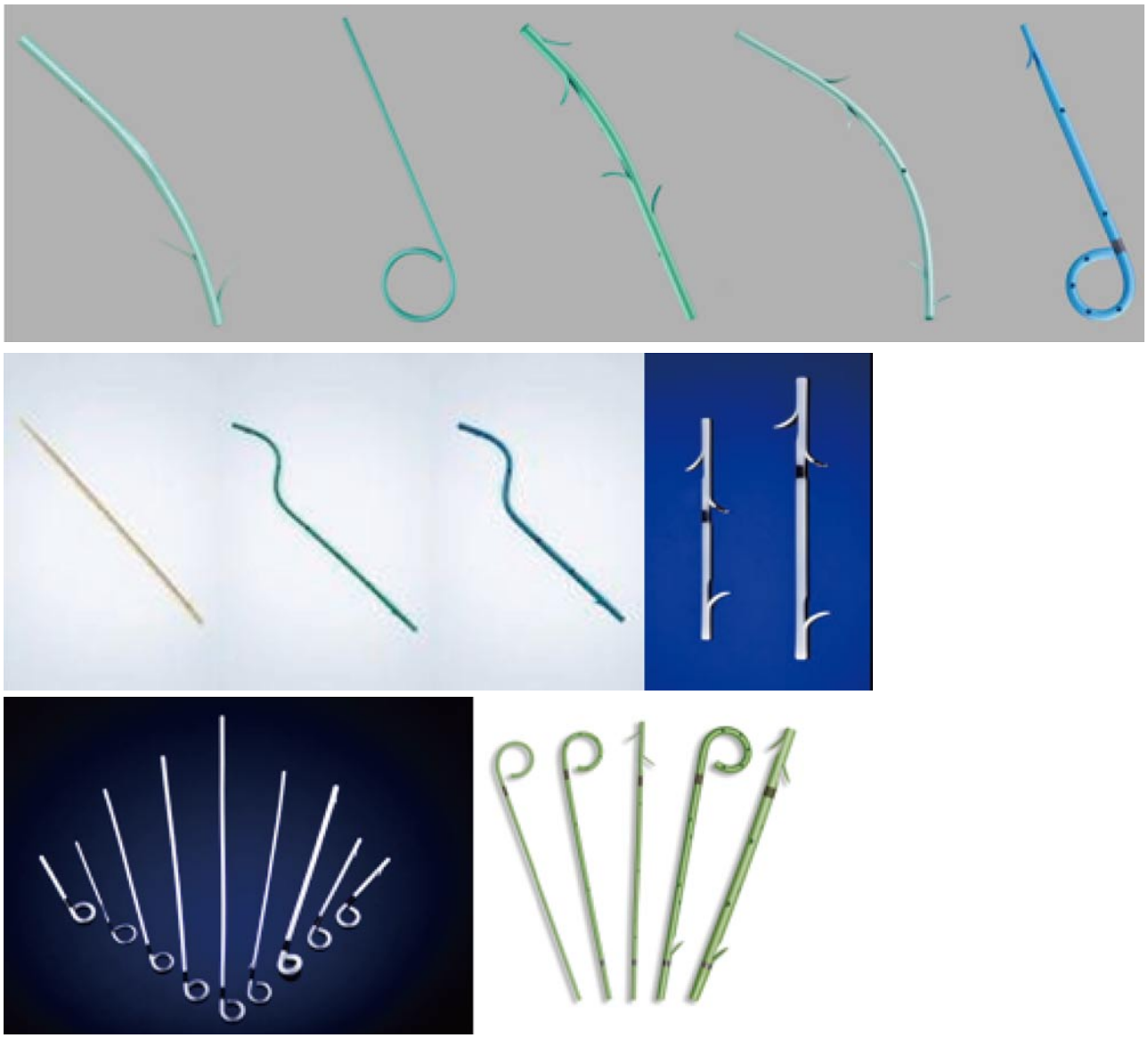

Figure 7 A display of different types of pancreatic plastic stents available.

can be challenging. In this situation balloon dilation or a bougienage dilation are often helpful to, allow stent placement.

For implantation of a SEMS a pancreatic sphincterotomy is typically performed (often also with biliary sphincterotomy). The metal stent diameter and length are determined on the basis of a combination of location of lesion (stricture or leak), ductal configuration and in cases of stricture the diameter of dilated upstream duct proximal to the lesion.

For MPD strictures dilation is typically performed before SEMS placement and the stent is deployed through the ductal lesion. The distal portion of the SEMS is left in the duodenum for prevention of proximal migration and easy removal.

EUS-guided pancreatic duct drainage

To perform EUS-guided drainage of the pancreatic duct (PDD) a large channel echoendoscope (3.7 or 3.8 mm) is required. The most common site for pancreatic duct (PD) access is the stomach (gastric body), usually the most straightforward and stable, but also transbulbar access is used (impossible in those with prior pancreatoduodenectomy)[24-28].

However, the route is selected on the basis of the pancreatic anatomical site to be treated. The aim of the drainage is to gain access the shortest way between the echoendoscope and the PD. The shorter the distance the easier the procedure, considering over-the-wire exchanges of devices. Pancreatic duct access may be performed with a 19-G FNA needle followed by either 0.035" or 0.025" guidewire placement *via* the needle or with a 22-G FNA needle that allows only the passage of an 0.018" guidewire.

After PD access, the wire is placed inside the duct, advancing it into the duodenal lumen, through the Vater's papilla, or into the jejunal lumen in presence of a pancreatico-jejunal anastomosis. During guidewire

placement and device exchanges, the use of fluoroscopy is helpful.

After guidewire placement, PD stenting can be performed in retrograde fashion, with EUS-guided PD rendezvous technique, with a side-viewing duodenoscope or with a frontal-viewing endoscope, in patients with postoperative anatomy, or in antegrade fashion, from the stomach or from the duodenal bulb, with EUS-guidance.

For antegrade stenting, dilation of the gastric wall or duodenal bulb wall and dilation of pancreatic parenchyma with a balloon is helpful before stent placement. In many cases a cystotome is used to gain access to the PD, after wire placement, creating an "electrocautery-tunnel", to allow subsequent stent deployment. During EUS-guided PDD, a plastic stent is generally preferred to a metallic one, considering the risk of leakage if uncovered SEMS are used. Finally, when PSs are used, to avoid leakage and migration, the diameter of the stent should not be less than the diameter of the dilated tract.

Endoscopic drainage of pancreatic fluid collections

Endoscopic drainage of PFCs are performed with different approaches as the trans-papillary (*i.e.*, using endoscopic retrograde pancreatography), or transmural (cystoenterostomy), or both[29-35].

For transpapillary drainage, before implantation of the stent, a major or minor papilla pancreatic sphincterotomy is typically performed. Following this, a large-bore stent is placed. When the stent is placed, its proximal part can be placed inside the PFC or, in case of leakage, across the disruption of the PD. If a stricture of the PD is present downstream to the PFC, judicious dilation by bougie or dilation balloons needs to be performed before application of the stent.

PFC drainage can be performed or through the stomach (transgastric) or through the duodenum (transduodenal). More rarely drainage is performed through the esophageal wall (transesophageal). The drainage can be undertaken with or without EUS guidance.

When non-EUS-guided techniques are performed a large channel gastroscope or duodenoscope with a 4.2-mm working channel is used.

The side-viewing endoscope is most often used because it permits better visualization of the posterior wall of the gastric body, allowing placement of large diameter accessories (deployment of 10 Fr stents) with assistance of the elevator.

The initial PFC puncture for transmural drainage is generally performed at level of visible bulging on the gastric or duodenal wall. To obtain good endoscope stability, the short position, when possible, is recommended, and the angle between the needle and the gastric/duodenal wall needs to be closer to 90°. The closer to 90° results in shorter distance to traverse.

To access a PFC with the side-viewing endoscope, diathermic puncture technique or the Seldinger technique are used. The diathermic puncture technique involves the use of a needle-knife sphincterotome (double or triple-lumen), or a 10-Fr cystotome that is a catheter with a diathermic ring and a 5-Fr inner catheter housing a low-profile, 0.38" needle knife to facilitate close apposition of the PFC to the enteral lumen. A pure cutting current is recommended and the electrocautery should be discontinued immediately upon entry of the needle into the PFC cavity to avoid thermal injury to surrounding structures.

Following this, aspiration of fluid (which can be sent for analysis) and gentle injection of contrast under fluoroscopic guidance confirm position within the cavity. The needle is exchanged for a standard catheter. After that, the guidewire is placed inside the PFC, and coiled for 2-3 times.

Following deep access with a guidewire, the catheter is exchanged for an 8 or 10 mm pneumatic balloon, to dilate the tract. After dilation, the balloon is removed and a plastic or metallic stent is deployed over the guidewire. Alternatively, a cystotome can be used for single-step drainage, avoiding balloon dilation.

When the Seldinger technique is used, a 19-G aspirating needle is used for initial puncture of the PFC. After fluid aspiration contrast is injected inside the PFC for the confirmation of the correct position of the needle. Through the needle a guidewire is passed, coiling it inside the fluid collection. Leaving the wire in place, the needle is withdrawn and a cystotome or a dilation balloon is passed over the wire. Finally the cystotome (or the dilating balloon) is removed and a stent is placed over the guidewire. Moreover balloon dilation can be performed after the creation of the fistula with the cystotome.

There are two techniques for EUS-guided drainage (EUS-GD) of PFC: The 2-step approach and the 1-step approach. For 2-step approach larger (3.7 or 3.8 mm) and smaller (2.8 or 3.2 mm) mm working channel echoendoscopes can be used.

The PFC is located and studied by EUS, identifying the best site for drainage of the collection which is closest to the transducer. Color Doppler helps to avoid puncture of interposed vessels during drainage. This site can be marked with a biopsy forceps, with a metal clip or with India ink and the echoendoscope withdrawn and replaced with a side-viewing duodenoscope to perform the drainage. Otherwise, the PFC puncture is directly performed with a 19 G needle and, after puncture, a guidewire is placed inside the collection. After wire placement, the echoendoscope can be withdrawn, leaving the guidewire in place inside the PFC, and replaced with a side-viewing endoscope over the guidewire, and the drainage can be performed using this endoscope. These exchange of endoscope approaches are now used infrequently.

With the 1-step approach the echoendoscope is used for the entire procedure. An echoendoscope with a large operative channel is required. It allows the use large diameter accessories (deployment of 10 Fr stents) with the assistance of an elevator.

The PFC puncture is usually performed using a

Table 5 Technical characteristics of the lumen apposing metal stents

Producer	Model	Internal diameter (mm)	Length (mm)	Flange diameter (mm)
Boston Scientific	Axios	10, 15	10	21, 24
Leufen Medical	Aix	10, 14	20	14/16, 18/20
M.I. Tech	Hanarostent BCF	10, 12	30, 40	25
TaeWoong Medical	Spaxus	8, 10, 16	20	25
TaeWoong Medical	Nagi	10, 12, 14, 16	10, 20, 30	22, 24, 26, 28

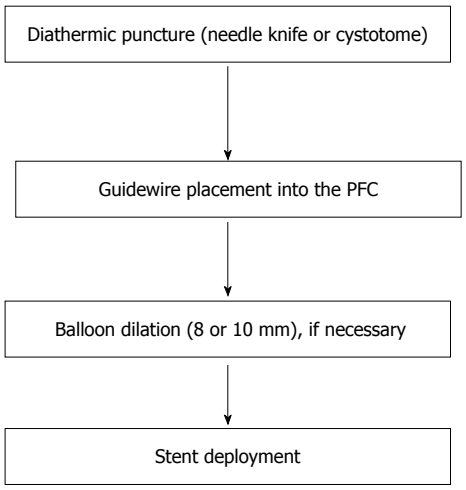

Figure 8 Traditional transluminal endoscopic drainage of pancreatic fluid collections. PFC: Pancreatic fluid collections.

19-G needle under endosonographic view. The collection contents can be aspirated for biochemical analysis, gram stain, culture and cytology. Through the lumen of the needle a 0.025" or 0.035" guidewire is advanced until it coils in the PFC which adds stabilisation of the position and access by forming anchoring extra loops in the cavity.

Fistula dilation is achieved by balloon dilatation over the guidewire, or using a cystostome and diathermy needle. Finally the stent is placed over the guidewire.

The 1-step approach PFC drainage avoids guidewire displacement during the exchange of the echoendoscope with the side-viewing endoscope. When more than one stent, or an additional naso-cystic drainage (NCD) are placed, two guidewires can be inserted inside the same catheter to avoid recannulation of the PFC. Recently, a 3-layer puncture kit, allowing synchronous placement of two guidewires has been described. This kit is composed of a 6 Fr catheter made of Teflon, inside an outer catheter of 8.5 Fr and a 22G FNA needle inside the 6 Fr catheter. Puncture of the collection is performed with a 22 G needle using electrocautery, under EUS-guidance. After puncture the 6 Fr inner catheter and the 8.5 French outer catheter are advanced inside the PFC. When the entire kit is inside the PFC, both needle and inner catheter are removed, and two guidewires can be inserted into the PFC through the outer catheter. Then, two stents, or one stent and one NCD, are placed.

After initial puncture and dilation some endoscopists described the use of the Soehendra dilator or a cystotome 10 Fr outer catheter for passage of two guidewires.

The "Navix-access-device" (Boston Scientific, Natick, MA, United States) consists of a 19-gauge trocar with a short extendable side blade. The retractable blade creates a cystoenterostomy without the use of cautery. It has an anchoring and dilating balloon (10 mm), as well as 2 guidewire ports to permit double wire advancement with the same puncture for sequential stent placement.

Traditionally, more than one plastic pigtail stent is used for PFC tansmural drainage. The fistula tract between the gastrointestinal wall and the PFC is maintained by placement of double pigtail plastic stents for preventing dislocation and migration. When 7 Fr stents are used the occlusion rates are higher. To further improve transmural drainage of PFCs, tubular FCSEMS (available for the treatment of biliary strictures) have recently been used as an alternative for the traditionally used plastic double-pigtail stents. Fully covered SEMS have larger diameters (10 mm) and placement of a single stent can provide a wide drainage opening. Furthermore, due to the larger diameter, there is a reduced risk of occlusion, especially for collections containing a significant amount of solid debris.

However, these stents are designed for drainage related to a luminal stricture and not to a transluminal route. When a bile duct stent is used for PFC drainage, protrusion of the ends of the stent both into the GI tract and inside the PFC can increase the risk of stent migration or bleeding, caused by a contact ulceration of the stent within the wall. They are not ideal in cases when the PFC is not firmly attached to the gastrointestinal wall because they do not apply any anchorage force and resultant leakage may occur.

To overcome limitations associated with the use of tubular biliary SEMS for transmural drainage, novel drainage stents have been developed.

These new lumen apposing metal stents (Table 5), are specifically designed for transmural drainage (Figure 6). These stent are fully-covered for preventing ingrowth of tissue and have large flanges at the distal ends, with a length from 10 to 40 mm. The flanges are designed to provide lumen-to-lumen anchoring and a low migration and leakage risk. The diameter of the stents, 10 and 15 mm, enable direct necrosectomy through the lumen of the stent. A flow-chart for the traditional transmural endoscopic drainage of PFC is summarized in Figure 8.

CONCLUSION

Biliary and pancreatic stents are important advancements

in therapeutic endoscopy and have revolutionized the approach to pancreaticobiliary disorders. The new designs of plastic and metal stents have allowed an increased use in a large, broad range of biliary and pancreatic benign and malignant conditions, replacing interventional radiologic approaches and surgery in most cases.

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MINIREVIEWS

Review of current and evolving clinical indications for endoscopic ultrasound

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Abstract

For the first several years after its development, endoscopic ultrasound (EUS) was primarily limited to identification of pancreatic malignancies. Since this time, the field of EUS has advanced at a tremendous speed in terms of additional clinical diagnostic and therapeutic uses. The combination of ultrasound with endoscopy provides a unique interventional modality that is a minimally invasive alternative to various surgical interventions. Given the expanding recommended indications for EUS, this article will serve to review the most common uses with supporting evidence, while also exploring innovative endeavors that may soon become common clinical practice.

Key words: Endoscopic ultrasound; Pancreatic carcinoma; Celiac plexus neurolysis; Mediastinal lymphadenopathy; Pancreatic fluid collection

Core tip: Endoscopy has presented the opportunity to improve outcomes and lessen complications in a multitude of diseases and disorders. Endoscopic ultrasound (EUS) in particular has been at the forefront in the development of novel treatment and diagnostic methods. While there have been prior articles reviewing common indications for the clinical use of EUS, the sheer volume of recent studies centered on this modality denotes an opportunity to provide an update on that information. Additionally, recent reports of using EUS with innovative techniques, such as anal dyssynergia refractory to standard therapy, warrant discussion in this forum.

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INTRODUCTION

Advancement in the clinical application and use of endoscopic ultrasound (EUS) in recent years has transformed the field of gastroenterology, with the ability to identify and manage a wide variety of disorders, even extending beyond the gastrointestinal tract (GIT). EUS combines endoscopy with intraluminal ultrasonography using a high frequency transducer to produce high-resolution ultrasound (US) images. Prior to its development in the early 1980s, external US imaging was the primary means of diagnosing clinical problems related to the biliary system. However, trans-abdominal US was limited in providing a diagnosis in 30% of cases secondary to the presence of intestinal gas obstructing views[1].

SRI international (Menlo Park, California) produced a high-resolution ultrasonic probe used in conjunction with a side-viewing endoscope with which to evaluate the ability to identify important vasculature and organs within the upper abdomen. This prototype EUS was used in a canine as the 80-mm rigid end prevented safe use in humans; it demonstrated real-time images of the aorta, spleen, gallbladder, left kidney and gastric rugae, as well as the hepatic and portal venous systems[1].

The original EUS prototype to be used in humans was developed by Olympus Opt. Company (Tokyo, Japan) using a conventional gastroscope[2]. This instrument consisted of attaching an ultrasonic probe to the rigid end of a fiberscope which transmitted at a frequency of 5 MHz to a depth of 3 cm. Strohm *et al*[2] conducted a study in which this endoscope model was used to identify organs proximal to the stomach in 18 patients. Using the aorta and vena cava as landmarks, the pancreas was identified and measured in 9 of 18 patients. The gallbladder and distal bile duct were also found on imaging in some patients, but the scope's limited mobility prevented passage through the pylorus and, thus, visualization of the duodenum. They compared the quality of these images to those obtained with conventional US, and discovered that those obtained *via* EUS appeared equivocal. This new EUS, however, provided sharper visualization of the distal common bile duct (CBD) than transabdominal US[2].

Both studies demonstrated a new means of acquiring high-resolution views of various organs and vessels that with further development could prove to be superior to transcutaneous US[1,2]. With improvement in the echoendoscope, various groups began applying this technology to advance clinical diagnoses of upper abdominal pathology. Current guidelines for the diagnostic indication of EUS produced by the American Cancer Society and American Society for Gastrointestinal Endoscopy (ASGE) include evaluation of upper gastrointestinal malignancies, mediastinal adenopathy, pancreatic lesions and cancers, and submucosal tumors[3,4]. The use of EUS has expanded beyond purely investigative uses to also become a minimally invasive means of therapeutic intervention. This article will review the primary clinical uses for EUS along with fundamental supporting study data.

Diagnostic indications

Pancreatic cancer: EUS was first evaluated for its efficacy in confirming suspected pancreatic carcinoma in the mid-1980s. These early studies revealed EUS was superior to trans-abdominal US, including differentiating pancreatitis from a pancreatic tumor and identifying ampullary and papillary tumors[4]. After multiple studies throughout the 1990s, EUS sensitivity approached beyond 90% in detecting malignant pancreatic tumors[5]. One such study from Akahoshi *et al*[6] sought to analyze the precision of EUS in earlier diagnosis of pancreatic cancer with accurate tumor staging. In this era, pancreatic cancers were identified primarily by abnormal laboratory results or abdominal US and computed tomography (CT), and thus found at very advanced stages. In the study's evaluation of 96 patients suspected of having pancreatic carcinoma based on abnormal labs or imaging and their clinical presentation, diagnosis was confirmed by post-operative histology, autopsy, or surgical exploration in non-resectable cases. They found EUS had a sensitivity of 83% in diagnosing malignant pancreatic masses less than 3 cm in size, and a sensitivity of 92% for those beyond 3 cm, with an overall specificity of 97%[6]. This high sensitivity rate was not significantly decreased by location within the pancreas; although, masses in the pancreatic body or tail were identified with a sensitivity of 100% relative to 85% for the body of the pancreas. EUS in this study revealed 64% accuracy in pancreatic tumor staging T1-T3. The main etiology for incorrect staging was those patients with masses larger than 3 cm, which limited the tissue depth penetration of the 7.5 MHz transducer[6]. These were, and remain, profound findings, as earlier diagnosis and more accurate local staging could improve patient survival. Current studies have demonstrated diagnostic sensitivity of EUS approaches 99% for malignant pancreatic tumors of 2-3 cm size which is far superior to other imaging modalities, including CT, transabdominal US, and magnetic resonance imaging (MRI)[7-9]. This is likely due to the ability to have close proximity of the endoscope transducer to the lesion of interest. Of course, EUS is not without limitations in the accuracy of diagnosing pancreatic cancer. The presence of pancreatitis, which can result in significant heterogeneous appearance of pancreatic tissue, may result in highly trained endosonographers missing an underlying pancreatic neoplasm[4,10]. As MRI techniques and equipment become more high-tech, magnetic resonance cholangiopancreatography (MRCP) has been used with increasing frequency in patients suspected of having a pancreatic malignancy. MRI has superior soft-tissue contrast compared to CT imaging, resulting in the ability to differentiate pancreatic masses[4,11]. However, as EUS affords superb visualization of the

pancreas and remains one of the most accurate means for identifying pancreatic lesions, it is considered a first-line modality for diagnosing and staging of pancreatic adenocarcinoma.

EUS is not only accurate in detecting pancreatic malignancies, but is the primary tool to rule out pancreatic cancer[8]. A large single study completed at UC Irvine by Klapman *et al*[8] determined the negative predictive value (NPV) of EUS for patients with possible cancer of the pancreas. A total 693 patients were referred for EUS due to the potential of pancreatic cancer; focus was placed on the 155 with normal pancreatic imaging on EUS. Most of this group had been referred for EUS based on abnormal CT imaging. These patients were monitored for 24 mo, at the end of which none developed malignancy of the pancreas, resulting in a 100% NPV (95%CI: 98.2-100.0)[8].

Today, EUS imaging is combined with fine-needle aspiration (FNA) to improve diagnostic accuracy of pancreatic masses. Cytological or histological confirmation of the lesion is required to determine the appropriate treatment, especially if the mass is unresectable. Retrospective reviews of EUS database information shows EUS-FNA diagnostic precision of 89% for solid pancreatic masses[9,11,12,13]. The ability to obtain samples of pancreatic lesions concerning for malignancy during real-time imaging has a direct impact on the medical management of these patients. As only a minority of patients are candidates for curative surgery at time of presentation with pancreatic carcinoma, obtaining cytological or histological diagnostic confirmation is necessary to proceed with chemotherapy[9,12,13]. Touchefu *et al*[12] examined the influence of EUS-FNA on patient management in 100 patients; intention-to-diagnose analysis revealed the FNA results directly guided treatment plans in 62 patients.

It is additionally highly recommended, and in many healthcare settings standard of care, that a cytopathologist or cytology technician be onsite to guide FNA sampling. Various studies have demonstrated the likelihood of diagnosis obtained is much improved. A large prospective multicenter study conducted in the mid-1990s evaluated 474 EUS-guided FNA diagnoses of various sites and lesions. NPV was 72% without an on-site pathologist *vs* 100% in those centers with direct pathologist assistance[4,14]. Furthermore, a retrospective study evaluating academic centers with cytopathologists on site ruled in or out a malignant diagnosis twice as often and were less likely to have unacceptable samples[14-17].

Additional supportive data for on-site cytopathology with EUS-FNA of suspicious lesions was revealed in a recent large meta-analysis by Hébert-Magee *et al*[16] reviewing 34 studies with approximately 3600 patients with solid pancreatic masses. Of those patients, a total of 2285 were found to have pancreatic adenocarcinomas. Sensitivity of FNA ranged from 0.50-1.00, with sensitivity rates notably lower in those studies without on-site cytopathology, even when correcting for sources of heterogeneity of study size and diagnostic reference standard used[16,17]. Thus, given the continued dismal survival rates for pancreatic cancer (approximately 24% survival at 1 year and 5% at 2 years) and increased chance of unresectability with late presentation, EUS-FNA biopsy can provide an earlier diagnosis and potential alternative diagnosis to decrease patient mortality. It remains superior in accurately identifying and ruling out pancreatic malignancies compared to imaging *via* CT, conventional US, and MR[8].

Mediastinal adenopathy and non small-cell lung cancer: Patients with suspected lung cancer often undergo further imaging to help with staging, as up to 26% of newly diagnosed lung cancers present with mediastinal lymph node involvement[18,19]. Imaging modalities may vary between CT, MRI, or US. A 2003 CHEST systematic database review evaluated the accuracy of mediastinal staging in CT compared to positron emission tomography (PET), MR, and EUS[19]. The analysis of EUS assessment consisted of five studies for a total of 163 patients and exhibited a pooled sensitivity of 78% (95%CI: 0.61-0.89) and specificity of 71% (95%CI: 0.56-0.82). However, PET scan demonstrated the highest accuracy in detecting malignant metastases to mediastinal nodes with sensitivity and specificity of 84% (95%CI: 0.78-0.89) and 89% (95%CI: 0.83-0.93), respectively. As EUS is often limited in its inability to image all node stations, this may partially explain its inferiority to PET imaging of the mediastinum[19]. Specifically, EUS is unable to visualize anterior upper mediastinal nodes as a result of air within the trachea obstructing US imaging[18,20].

While CT and PET detect mediastinal lymphadenopathy and suspicious masses on imaging, a lack of tissue sampling results in a presumptive diagnosis only. Thus, obtaining tissue samples is necessary to definitively confirm and stage a possible pulmonary malignancy. The American Society of Thoracic Surgery currently recognizes mediastinoscopy as the favored modality for biopsy[18]. However, the 2011 ASGE Standards of Practice state that linear echoendoscopy can perform EUS-guided FNA of the posterior and inferior mediastinum with success in obtaining specimens from nodes 5 mm in size or larger. Additionally, nodal stations 8 and 9 and posterior nodes at station 7 are accessible by EUS with a sensitivity of 90% in confirming diagnosis. This accuracy drops to 66% for station 5 nodes based on one retrospective series by Eloubeidi *et al*[21] due to logistical difficulties when inserting the biopsy needle in attempts to reach this sub-aortic locations[18]. One prospective cohort study of 104 patients with malignant posterior mediastinal lymph nodes assessed the yield and precision of EUS-FNA using pathologic confirmation *via* thoracotomy[21]. The accuracy of EUS-FNA was 97%, which was significantly increased from PET imaging alone. More invasive surgical intervention was

avoided in 57% of the patients to determine malignant spread to lymph nodes. No patients experienced major complications peri-procedurally or at 30-d follow up[21]. EUS-FNA has been recommended by Maluf-Filho *et al*[4] to detect metastasis to the posterior mediastinum in non-small-cell lung cancer (Grade A, evidence level 1). EUS-FNA of mediastinal lymphadenopathy averages a complication rate of 0.2%, compared to 1.3%-3.0% with mediastinoscopy. The American Society of Thoracic Surgery does recognize EUS-FNA as an efficient, minimally invasive alternative method to confirm and stage lung cancer involving mediastinal lymph nodes.

Choledocholithiasis, suspected: CBD stones remain a common complication related to the presence of gallstones, occurring in nearly 20% of patients with known cholelithiasis. Identifying CBD stones remains a challenge, as laboratory findings and clinical presentation is often nonspecific[22]. EUS has been studied over several years in its ability to accurately detect choledocholithiasis. Endoscopic retrograde cholangiopancreatography (ERCP) remains standard of care, as rates for successful identification of bile duct stones approaches 100%, compared with abdominal CT and US where diagnostic accuracy approximates to 50%[22,23]. ERCP is also not purely diagnostic, as it allows for CBD stone removal at time of detection; however, complication rates occur in up to 11% of patients[23,24]. Various studies performed in the 2000s evaluated EUS ability to diagnose suspected choledocholithiasis, as this could negate ERCP and its associated risks in certain patient cases. However, the data was widely variable in rates of sensitivity and sensitivity[22,23].

In order to more precisely estimate diagnostic accuracy of EUS for choledocholithiasis, Tse *et al*[22] identified 27 prospective cohort studies consisting of EUS results compared with ERCP, intraoperative cholangiogram (IOC), or surgical exploration. Included studies also had a minimum of three months follow up if initially negative EUS results with suspicion of CBD stones based on history, exam, laboratory findings, or trans-abdominal US imaging. Studies were excluded if they lacked a comparison group, demonstrated possible bias, or insufficient data. Pooled diagnostic accuracy was 98% (area under the curve). EUS decisively ruled in and ruled out CBD stones with a positive likelihood ratio (LR) of 22.41 (95%CI: 12.53-40.08) and negative LR of 0.09 (95%CI: 0.06-0.12)[22]. This impressive diagnostic ability of EUS is likely related to its high resolution down to 0.1 mm compared to ERCP or MRCP[22].

IOC is often performed during laparoscopic cholecystectomy to evaluate biliary patency. CBD stones are present in up to 15% of these patients, but the false positive rate of IOC approaches 60% in some studies[23]. Given the combination of IOC's high false positive detection of choledocholithiasis and the complication rates of ERCP, it would be ideal to have an alternative, less invasive modality of confirming CBD stones with decreased risk in patients with low suspicion for requiring stone extraction. EUS may have a potential role in a diagnostic algorithm to stratify patients proceeding to ERCP *vs* EUS initially. EUS is felt to be as sensitive and more specific than ERCP or MRCP for the diagnosis of CBD stones, especially those of smaller size (Grade A, Evidence Level 1)[4].

The use of EUS as the primary diagnostic tool, however, may be limited. While it is less invasive than ERCP resulting in lower rates of post-procedure pancreatitis, patients still require sedation. As with ERCP, EUS requires an experienced endoscopist to obtain acceptable images. Unfortunately if CBD stones are discovered on EUS imaging and require removal, these patients would require ERCP, an additional procedure.

Therapeutic indications

Pancreatic fluid collection drainage: Potential indications for intervention in pancreatic pseudocysts include abdominal pain, gastric outlet obstruction, early satiety, weight loss, jaundice, infection, or progressive enlargement[3]. Surgery has historically been accepted as the standard of care for draining pancreatic pseudocysts and walled-off pancreatic necrosis. In recent years, multiple studies examining the success of EUS-guided drainage has resulted in this becoming an established technique with comparable outcomes and significantly lower medical costs[17]. This procedure was first described in a 1992 case report by Grimm *et al*[25] with management of a pancreatic tail pseudocyst[17]. A randomized controlled trial conducted in 2009 directly compared surgical *vs* EUS-guided endoscopic pancreatic fluid collection (PFC) drainage in 40 patients[26]. A pseudocyst was defined as "a fluid collection in…pancreatic…area (with) a well-defined wall and…no solid debris or recognizable parenchymal necrosis" [26]. One-half of the patients were randomized to surgical cystogastrostomy under a single pancreatic surgeon while the other half underwent EUS with fluoroscopy. Endoscopic cystogastrostomy was achieved *via* EUS-guided 19-guage-needle access of the fluid collection with subsequent deployment of two plastic stents to allow PFC contents to drain into stomach. ERCP was performed in the experimental arm following EUS in order to identify and treat pancreatic duck leaks, if present. Traditional surgical drainage resulted in a 100% successful treatment. However, several of these patients experience postoperative complications, including recurrent pseudocyst, surgical wound infection, inability to tolerate oral intake, and pancreatic tail stricture. EUS-guided pseudocyst drainage was efficacious in 95% of patients with pseudocyst resolution by 8 wk in all 20 patients. Most importantly, these patients did not experience peri- or post-procedural complications[26]. Additional studies have since demonstrated clinical success rates of PFC drainage *via* EUS imaging approach 90% with complication rate of less than 5%[17,24,26,27]. PFC drainage under EUS guidance is a minimally

invasive procedure, resulting in a shorter hospital length of stay, lower overall healthcare costs, and feasibility in vast majority (more than 90%) of patients[24,26].

Prior to the establishment of EUS-guided PFC drainage, transmural drainage *via* esophagogastroduodenoscopy (EGD) had been accepted as a reputable technique to manage PFCs. This was attributable to data from two prospective nonrandomized trials in the early 2000s that revealed no statistical difference in treatment success or complication rates when compared with surgery[26,27]. EGD identified the location of a PFC by evaluating for a site of stomach or duodenal lumen compression. The site was punctured by a needle to allow aspiration of pseudocyst fluid and placement of double pigtail stents to allow intraluminal drainage of PFC contents[27]. Varadarajulu *et al*[27] conducted the first randomized control trial directly pitting EUS against EGD for transmural drainage of pancreatic pseudocysts in 42 patients. All patients initially underwent contrast-enhanced CT imaging to exclude those without a pseudocyst, then ERCP to assess and manage CBD stones or pancreatic duct stricture, if present. Patients were subsequently randomized to the EGD or EUS arms with treatment failures crossing over to the opposite arm. Ultimately, complete resolution of pseudocysts was achieved in 91% of the EGD arm *vs* 97% in the EUS group (10 of which crossed-over from EGD arm). Although no statistical significance was noted in improved safety with EUS, it did reveal a significantly higher technical success rate[26,27]. This is likely due to the ability of directly imaging extramural lesions.

EUS provides additional benefits over EGD beyond definitive drainage of PFCs. EUS imaging can more clearly differentiate pseudocysts from cystic neoplasms and visualize pseudocysts that spontaneously resolved, thus negating a need for PFC drainage[27]. Bleeding is one of the most common complications of endoscopic PFC drainage, occurring in up to 10% of patients. This often occurs due to the presence of gastric varices or collaterals not visible with EGD. As EUS allows real-time visualization of vasculature near a pseudocyst, one can identify a safe window for transmural puncture to achieve drainage[26,27].

Celiac plexus neurolysis: Chronic pain is a common, and at times, debilitating complication of intra-abdominal malignancies and chronic pancreatitis. It is often difficult to control with opioid analgesics, and these medications have various adverse effects. Wiersema *et al*[28] first described a technique of treating intractable pain with EUS-guided celiac plexus neurolysis (CPN) in a prospective study of 30 patients with pancreatic carcinoma or intra-abdominal metastases in 1996[17,24]. This procedure consisted of identifying the celiac trunk, as the celiac plexus is located anterolateral to this site, and injecting a local anesthetic such as bupivacaine followed by dehydrated ethanol[24,28]. Data was notable for a 79%-88% improvement in the patients' pain scores at a mean 10 wk post-procedure. Furthermore, 91% of these patients did not require increased dosages of their opioid analgesics, with nearly half using less pain medication by the last study follow up. The only complication was self-resolving diarrhea in four patients[28].

While CPN was found to provide pain relief in patients with pancreatic and intra-abdominal malignancies, Levy *et al*[29] considered whether directly injecting the celiac ganglia with a local anesthetic might result in enhanced efficacy[24]. Seventeen patients with unresectable pancreatic carcinoma and moderate to severe narcotic-dependent pain underwent EUS-guided direct celiac ganglia injections with bupivacaine and dehydrated alcohol. Immediate partial pain relief was experienced by 94% of patients. Opioid medication use decreased for 3 patients, while remaining equivalent in 13 patients. There were no major complications, suggesting this new technique for pain relief in certain patients is a safe alternative and potentially more efficacious than CPN[29].

The most recent data demonstrates substantial pain relief coupled with a reduction in narcotic dosage for patients with intra-abdominal malignancies undergoing EUS-guided CPN or celiac ganglia neurolysis (CGN). A large meta-analysis from Puli *et al*[30] in 2014 pooled data from 8 studies (approximately 300 patients) comparing EUS-CPN to analgesics in unresectable pancreatic carcinoma[24,30]. Review of data revealed EUS-guided CPN achieved pain relief in 80% of patients with bilateral celiac plexus injection. A majority of the studies again resulted in a reduction of opioid analgesic use and no major complications, thus reiterating this is a safe and effective treatment for pancreatic cancer-related pain[24,30]. Another review of 6 studies consisting of 358 patients revealed statistically significant reduction in pain at four and eight weeks and superiority in pain reduction compared to narcotic medications[24].

A multicenter randomized controlled trial by Doi *et al*[31] was the first to directly compare efficacy of EUS-guided CPN to EUS-guided CGN in reducing pain from upper abdominal malignancies. Four of the 34 patients randomized to the CGN arm crossed over to CPN due to inability to visualize the celiac ganglia. The EUS-CGN group had improved response (73.5% with decreased pain) relative to the EUS-CPN arm (45.5%), and EUS-CGN attained complete pain relief in 50% of patients compared to only 18.2% who underwent EUS-CPN[24,31].

EUS-guided CPN and CGN both inhibit the transmission of pain signals from the pancreas and abdominal viscera to the central nervous system. The celiac plexus location permits successful direct EUS visualization, and allows a method of palliation for those with unresectable pancreatic carcinoma[24,28-30]. Patients may thus require less opioid medications, which translates into fewer medication side effects of anorexia, constipation, nausea, and vomiting.

The celiac plexus is also accessible percutane-

ously when combined with CT or fluoroscopy imaging. Prior to the 1990s, this was the primary manner of performing CPN in settings of chronic abdominal pain secondary to intra-abdominal malignancies and chronic pancreatitis[24,32]. Given EUS capability to visualize vascular structures in real-time and ability to perform FNA, EUS-guided CPN using ethanol was first developed in the late 1990s[24]. To further assess this new technique, Gress *et al*[32] performed a randomized-controlled trial involving 22 patients receiving either CT-guided or EUS-guided CPN for persistent, uncontrolled abdominal pain due to chronic pancreatitis. Patients in the EUS arm had statistically significant (P = 0.02) reduced pain score. Neither group experience serious complications. Diarrhea was noted in three subjects (one from the EUS group, two from the CT arm) and attributed as a direct side effect of CPN[32]. Nine patients in the experimental group had a prior CT-guided CPN; the majority preferred the EUS technique citing less post-procedure back pain and "more completed sedation"[32]. Furthermore, the use of EUS in guiding CPN resulted in lower cost per patient relative to CT-guided CPN[24,32].

FUTURE ENDEAVORS

Anti-tumor injection therapy

Several malignancies metastasize to the liver, which often complicates treatment with intent to cure. Patients with diffuse hepatic metastases have therapy options limited to systemic chemotherapy. In the recent years, drug-eluting microbeads have been introduced as a means of delivering treatment, primarily chemotherapy), into a target tissue[24]. A relatively new study conducted by Faigel *et al*[33] evaluated the use of EUS-guided Portal Injection of Chemotherapy (EPIC) with irinotecan-containing microbeads in porcine subjects in comparison to the conventional systemic administration of irinotecan. EPIC achieved double the concentration of chemotherapy within the liver, and halved its concentration in plasma, bone marrow, and skeletal muscle, relative to what is seen with systemic irinotecan[33,34]. This new method of delivery chemotherapy to target malignant lesions of the liver has the potential of increasing the efficacy of treatment while decreased adverse effects. It may be possible to extrapolate this technique in developing alternative management strategies for primary liver malignancies, such as hepatocellular carcinoma.

Anal sphincter dyssenergia

A hypertensive anal sphincter may result in severe constipation due to defecatory dyssynergia and subsequent rectal outlet obstruction. Biofeedback therapy to correct patient contraction of the pelvic floor muscles and external anal sphincter often results in clinical improvement superior to that of laxatives alone[35]. Byrne *et al*[36] used EUS to guide injection of Botulinum toxin (Botox) into the internal anal sphincter of nine patients who had failed biofeedback therapy for anal dyssynergia. Patients underwent anal manometry prior to the procedure and again at two weeks post-injection. Within the 8-wk follow-up, 89% of these patients had improvement in their constipation. Objective findings at this time included decreased anal sphincter pressure in all patients as well as improved defecatory index with balloon expulsion. A single patient developed fecal incontinence, which was the only associated complication from this procedure. While a larger study is needed, this novel technique may prove to be a formidable therapy option for those with constipation due to a hypertensive anal sphincter with alternative treatment failure[34].

Novel peri-procedure analgesia

Traditional Chinese Medicine has included the use of electro-acupuncture for treatment of pain. Electro-acupuncture needles are placed in particular sites on the body to correlate with the specific source of pain. While endoscopic procedures such as EUS are minimally invasive, they are often uncomfortable for patients and necessitate the use of pain control and sedation with intravenous opioid analgesics and benzodiazepines, respectively. Teoh *et al*[37] hypothesized that electro-acupuncture could be used during EUS in order to decrease associated pain and the use of additional analgesics. This randomized, double-blind, sham-controlled trial applied electro-acupuncture to three acupoints related to upper abdominal pain and anxiety in 64 patients undergoing EUS. This study ended early as all patients in the electro-acupuncture group required lower doses of propofol, decreased use of patient-controlled analgesia pumps, and lower pain scores. These data points were all statistically significant[34]. As administration of sedative analgesics is not without potentially dangerous adverse events, this novel technique could lead to fewer associated complications in patients undergoing endoscopic evaluation.

CONCLUSION

EUS has continued to evolve since its conception several decades ago. It is persistently at the forefront of gastroenterological procedures in expanding its diagnostic and therapeutic use for a variety of diseases and clinical presentations. EUS often provides a marginally invasive alternative to many treatments previously requiring surgical intervention, which ultimately may result in lower healthcare costs and fewer complications in patients.

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MINIREVIEWS

Treatment of gastric outlet obstruction that results from unresectable gastric cancer: Current evidence

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Abstract

Malignant gastric outlet obstruction (GOO) is a common condition that results from locally advanced malignancies in the upper gastrointestinal tract, such as pancreatic, gastric, and other carcinomas. Two types of procedures for malignant GOO, namely, gastrojejunostomy (GJ) with laparotomy or a laparoscopic approach and endoscopic stenting (ES), are currently available. Although numerous previous reports have clarified the benefits and drawbacks of each procedure, whether GJ or ES should be used in patients with GOO that results from gastric cancer who may have a longer life expectancy than patients with other malignancies has not been determined. In this review, which focuses on gastric cancer-induced GOO, we analyzed the two systematic reviews and a meta-analysis that compared GJ and ES and outlined the current status of GOO treatment. We also provide an updated review that includes laparoscopic GJ. Various data from 13 studies in one review and 6 studies in another review were analyzed. Although the main results of the present review indicated that both GJ and ES were efficacious treatments in patients with GOO that resulted from gastric cancer, current evidence suggests that GJ may be the preferable procedure given its good performance status and improved prognosis in gastric cancer patients.

Key words: Gastric outlet obstruction; Gastrojejunostomy; Endoscopic stenting; Gastric cancer; Review

Core tip: Both gastrojejunostomy (GJ) and endoscopic stenting (ES) are effective treatments in patients with gastric outlet obstruction that results from gastric cancer. The advantages of GJ include fewer late complications and a long patency, whereas the advantages of ES include better short-term outcomes, including the length of the hospital stay. Although no large-scale randomized clinical trials have compared the safety and efficacy of the two procedures, this present literature review

indicates the superiority of GJ compared with ES given its good performance status and improved prognosis in gastric cancer patients as well as the widespread use of the less invasive laparoscopic GJ procedure.

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INTRODUCTION

Malignant gastric outlet obstruction (GOO) is a clinical symptom of advanced malignancies in the upper gastrointestinal tract, most commonly pancreatic and gastric malignancies. Other causes include lymphomas, ampullary carcinomas, biliary tract cancers, and metastases[1-3]. Associated symptoms, including nausea, vomiting, reflux, malnutrition, dehydration, and abdominal distention, reduce patient quality of life (QOL), and patients with malignant GOO often present with a poor condition and performance status (PS)[4]. Furthermore, palliative treatment is important and required for patients with unresectable primary malignancies or metastatic lesions.

Treatments for malignant GOO include gastrojejunostomy (GJ), which is traditionally adopted, and palliative endoscopic stenting (ES), which is considered less invasive with a faster improvement of oral intake compared with GJ[5]. Recently, the use of palliative ES has increased[6]. In addition, various types of stents are now available, and the procedure has been established and advocated[7-11]. However, the disadvantages of ES include a high rate of stent re-obstruction and migration as late complications, and pleural treatment is required with some frequency[2].

Many comparative trials of GJ and ES in patients with malignant GOO have been performed to evaluate the safety, feasibility, costs, and patient QOL. However, to date, the available data regarding "gastric cancer" patients with GOO who could theoretically have a longer life expectancy than patients with other malignancies are not sufficient to definitively conclude the comparative benefits and limitations of GJ and ES. In this review, we outline the current status of GJ and ES treatment for malignant GOO, especially in gastric cancer, and provide a future perspective.

STUDY STRATEGY

Data source and search strategy

An increasing number of studies regarding ES, including novel devices, has been reported during the past decade, especially in the most recent five years; thus, the outcome of GJ should be compared with recent ES. Literature searches of the electronic PubMed and Embase databases were performed. The searches were limited to articles published from January 2010 to December 2014 in English as well as human- and clinical trial-related articles to identify objective articles from January 2010 to December 2014. The following terms were utilized: "Gastric outlet obstruction", "GOO", "gastric cancer", and "gastric carcinoma". The abstracts were reviewed, and articles not related to the specific content were excluded. Duplicate references and repeated articles were also excluded. All articles considered eligible were selected, and the final selection was based on the full research papers.

Study selection

We included review articles, studies that reported randomized and controlled trials or experimental studies, and case studies. Articles were first screened and selected based on the titles. The full text was obtained for 45 articles.

MALIGNANT GOO THAT RESULTS FROM OF GASTRIC CANCER

Despite a decrease in the incidence of gastric cancer over previous decades, gastric cancer remains the fourth most common malignant disease and the second main cause of cancer-related death worldwide[12]. To date, the curative resection ratio for newly diagnosed gastric cancer is approximately 50%, and 20% to 30% of patients with gastric cancer present with stage IV disease[13,14].

Malignant GOO is a common condition among locally advanced gastric cancer patients and can lead to significant morbidity, including nausea, vomiting, abdominal pain, dehydration, malnutrition, and weight loss. Not surprisingly, these clinical symptoms have a negative impact on QOL[15]. To avoid the disastrous consequences of malignant GOO, appropriate treatment is indispensable, which enables not only an amelioration of the patient's QOL but also the commencement of chemotherapy, including essential oral agents, such as S1 or capecitabine[16]. These treatments are included in the first-line regimen for unresectable gastric cancer recommended in the Japanese gastric cancer treatment guidelines[17].

GJ is traditionally the palliative treatment of choice for patients with malignant unresectable GOO, whereas the palliative endoscopic treatment of GOO with endoluminal self-expanding metallic stents has only recently become available. Both treatments have benefits and limitations associated with prognosis; thus, it is important to determine the optimal treatment approach. Although GOO may occur with other malignancies, such as pancreatic periampullary carcinoma, lymphoma, and metastases to the duodenum of jejunum[1-3], GOO in gastric cancer should be considered separately. First,

gastric cancer has a longer life expectancy than other biological malignancies, and more chemotherapy agents have been developed for this malignancy compared with other diseases[18-20]. Second, GOO that results from gastric cancer has a reduced possibility of co-occurring with an obstruction of the bile duct compared with biliopancreatic malignancies. Several studies have reported a median overall survival of 13 mo for unresectable or recurrent gastric carcinoma[21], which is longer than pancreatic cancer (6.7-8.5 mo)[22].

Therefore, the decision regarding whether to select GJ or ES should depend on the condition and PS of patients. Furthermore, prior to any procedure, information regarding the benefits and drawbacks of GJ and ES is necessary for well-informed consent.

TREATMENTS FOR GASTRIC OUTLET OBSTRUCTION

GJ

Traditionally, GOO caused by malignancy is treated with a palliative "open" GJ (OGJ), which is surgically performed[23]. Although this modality has a favorable outcome and relieves many symptoms derived from GOO, it results in some morbidity and mortality given the poor condition of these patients[1,24]. Several recent studies have reported the effectiveness of "laparoscopic" GJ (LGJ) with regard to safety, feasibility, and invasiveness; however, its role has not been clarified[25,26]. Jeurnink *et al*[5] reported that LGJ appears to be more favorable regarding tolerable oral administration, the duration of the hospital stay, and the complication ratio compared with OGJ. However, no significant differences were identified between the two approaches[27]. Navarra *et al*[28] also published a randomized controlled trial (RCT) that compared LGJ and OGJ (n = 12 patients each). LGJ resulted in significantly less intra-operative blood loss, a shorter time to tolerating solid food intake, and a reduced rate of complications; however, no significant difference was identified in the postoperative hospital stay[28]. In contrast, older retrospective studies have reported benefits with regard to intra-operative blood loss and hospital stay as well as a high conversion rate to OGJ[29,30]. Different outcomes of LGJ have been reported, and this variation can be explained by the small sample sizes and low power. However, no clinical trials with sufficient power have demonstrated the effectiveness of LGJ compared with OGJ, and LGJ is now the preferred standard for malignant GOO treatment[31].

ES

Endoscopic treatment of GOO with endoluminal self-expanding metallic stents was first described by Topazian *et al*[6] in the early 1990s. Over the previous decade, experiences and reports of the use of ES have increased. In addition, various types of upper gastrointestinal stents have become available, and well-established ES procedures have been advocated and performed[32]. Recently, several articles have reported that patients who present with GOO with a long life expectancy should undergo ES given its safety, minimal invasiveness, and cost-effectiveness[33]. Self-expandable metallic stents (SEMSs) are the standard devices for recanalization of an obstructed digestive lumen. However, some SEMSs exhibit re-occlusion because of tumor in growth through openings between the stent wire filaments or stent migration as late major complications[34]. Covered SEMSs prevent ingrowth through the mesh wall, and they are advantageous compared with uncovered SEMSs in esophageal cancer[35]. However, in malignant colorectal obstruction, covered stents do not exhibit an advantage compared with uncovered stents due to high migration rates[36]. Several studies have also suggested that covered stents are associated with more frequent re-intervention despite approximately similar outcomes and complications in malignant GOO. Therefore, with regard to ES for GOO, the effectiveness and complications of covered and uncovered SEMSs in patients with GOO have recently been highlighted. Kim *et al*[37] reported a prospective RCT of covered *vs* uncovered stents for the palliation of GOO in gastric cancer patients and concluded that the overall stent patency did not differ between the two groups; moreover, frequent migration of the covered SEMSs offsets its advantages in the prevention of re-stenosis. Maetani *et al*[38] also reported similar results in a multicenter randomized trial in Japan, *i.e.*, no significant difference in the stent patency between triple-layered covered and uncovered metallic stents for the palliation of malignant GOO; however, the use of a triple-layered covered SEMS was associated with less frequent stent dysfunction more than 4 wk after the initial stent. Regardless of the stent configuration, covered or uncovered, the ES procedure for GOO caused by malignancy is considered safe and efficacious.

RECENT SYSTEMATIC REVIEW AND COMPARATIVE RESEARCH OF TREATMENTS FOR GOO THAT RESULTS FROM GASTRIC CANCER

Two systematic reviews

Two systematic reviews and a meta-analysis that compared GJ and ES have been published since 2010. In review 1 in 2010, Ly *et al*[27] performed a comprehensive search of the literature for the period from 1990 to 2008 using Medline, EMBASE, Google Scholar, ISI Proceedings, the Cochrane Library, and online registers of CCTs but not PubMed. This review included only clinical studies that directly compared GJ and ES for the palliative treatment of GOO, which included randomized clinical trials (RCTs) and prospective and retrospective cohort comparison studies. Thirteen studies were analyzed, including 10 retrospective cohort comparison studies[1,26,39-46], 1 prospective study[41], and 2 RCTs[25,47]. In review 2 in

Table 1 Characteristics and main results of two reviews

Review	Year	Study type			Primary tumor			Procedure		Favorable group regarding several variables			
		Retro	Pro	RCT	Stomach	Pancreas	Others	GJ	ES	Toleration of oral intake[1]	Time to oral intake[2] (d)	Hospital stay[3] (d)	Complication
1	2010	10	1	2	94 (18.3%)	240 (46.7%)	180 (35.0%)	255 (LGJ 37)	244	ES	ES (2.0 d)	ES (9.4 d)	GJ is approximately equal to ES
2	2012	0	3	3	55 (28.6%)	86 (44.8%)	51 (26.6%)	92 (LGJ 0)	74	GJ (not-RCT)	ES (2.1-5.0 d)	ES (2.5-7.0 d)	Major: GJ is approximately equal to ES Minor: ES

[1]Patients were more likely to tolerate oral intake following ES than GJ in Review 1; however, Review 2 reported the opposite results. The difference was only significant in the non-RCT group; [2]The mean time from the procedure to initiate oral intake was 7 d (Review 1) and 3.6 d (Review 2) less for ES compared with GJ; [3]The mean length of hospital stay was reduced by 12 d (Review 1) and 7.5 d (Review 2) for ES compared with GJ. Retro: Retrospective; Pro: Prospective; RCT: Randomized controlled trial; GJ: Gastrojejunostomy; ES: Endoscopic stenting; LGJ: Laparoscopic GJ.

2012, Zheng *et al*[48] searched the PubMed, Embase, Chinese Biomedical Database, and Cochrane Library for all studies between 1996 and 2010. The inclusion criteria were as follows: controlled clinical trials (CCTs) and RCTs; analyses of "both" GJ (OGJ and LGJ) and ES; any sample size; full paper; and not a duplicate report. Six studies remained in the final analysis, including three RCTs[25,47,49] and three CCTs[41,50,51]. Both reviews included the same two studies. One study was a RCT reported by Mehta *et al*[25] in 2006, and the other study was a CCT reported by Johnsson *et al*[41] in 2004.

Table 1 provides the characteristics of the comparative data and main results for GJ and ES in the two reviews with regard to the study type, primary tumor site, number of procedures, and favorable procedure group with better results regarding: (1) the number of patients who tolerated oral intake; (2) time to oral intake (days); (3) length of hospital stay (days); and (4) complications. Ninety-four (18.2%) of 514 patients and 55 (28.6%) of 192 patients with GOO that resulted from "gastric cancer" were included. Technical success was only documented in Review 2, and GJ exhibited greater technical success than ES [odds ratio (OR) = 0.10, 95%CI: 0.02-0.47, I^2 = 0%, P = 0.0039] according to a meta-analysis. However, the significant difference remained only in the non-RCT group. Nevertheless, both GJ and ES demonstrated satisfactory results regarding technical success (success rates of 99% to 100% and 8% to 100%, respectively). The ability to tolerate oral intake after palliative treatments for GOO is one of the most important endpoints and was documented as a "clinical success" in Review 2. With regard to the ability to tolerate oral intake, 11 studies included in Review 1 reported more favorable results following ES compared with GJ. Although no significant difference was identified in the two studies included in Review 2, one study reported that ES was associated with greater clinical success than GJ (P = 0.007). Regarding the time to oral intake after the palliative procedure, all reported data in both reviews indicated that ES had clear merits compared with GJ. The average time from the procedure to the initiation of oral intake was approximately 3 d less for ES compared with GJ. Several studies have evaluated the length of hospital stay and medical costs. All studies reported a significantly reduced hospital stay for patients who underwent ES compared with GJ (mean difference of 12 d). One RCT and one CCT demonstrated reduced total medical costs and hospital stay costs with ES compared with GJ. In summary, approximately all studies indicated that ES has advantages compared with GJ. However, cost should not be the main factor in decisions regarding procedures for malignant GOO patients because the costs per day for patients who consumed at least a soft diet were quite similar between both procedures. Better long-term clinical outcomes after GJ compared with ES were noted in the major prospective randomized SUSTENT study, which was included in Review 2[52].

Both reviews indicated that there are no significant differences in the major complication rates between GJ and ES (OR = 1.04, 95%CI: 0.47-2.29, P = 0.93 according to meta-analysis data in Review 1; OR = 3.76, 95%CI: 0.57-24.72, P = 0.17 in Review 2). The detailed major medical complications that result from GJ were reported as respiratory tract infections, myocardial infarction, and acute renal failure, whereas the complications of ES were procedure-related, including stent failure migration and obstruction. Although minor complications were described only in Review 2, they were less likely the result of ES compared with GJ (OR = 0.28, 95%CI: 0.10-0.83, P = 0.02). Regarding morality, both reviews indicated similar conclusions indicating no differences between the two treatments (OR = 0.58, 95%CI: 0.18-1.86, P = 0.36).

The length of survival was estimated in both reviews. Despite the inclusion of both randomized and non-RCT, no significant difference was identified between GJ and ES (mean difference 26 d; 95%CI: 69.03-16.40 d, P = 0.23 in Review 1).

Table 2 Patient demographics and main results in two reviews

Ref.	Study type	Procedure		Performance status		Comparison between GJ and ES regarding several variables				
		GJ	ES	GJ	ES	Toleration of oral intake	GOO recurrence	Time to oral intake	Hospital stay	Complication
Fiori *et al*[53]	Prospective	9 (LGJ 0)	9	NR	NR	GJ is approximately equal to ES	GJ (0%) < ES (33%)[a]	GJ (6.3 d) ES (3.1 d)	GJ (10 d) ES (4.8 d)	GJ: SSI, bleeding, ventral hernia ES: Stent dislocation, re-obstruction
No *et al*[54]	Retrospective	41 (LGJ 9)	72	0-1[1]: 68.3% 2[1]: 31.7%	0-1[1]: 59.7% 2[1]: 40.3%	GJ (95.1%) is approximately equal to ES (87.5%)	GJ (12.2%) < ES (44.4%)[a]	GJ (16 d) > ES (10 d)[a]	GJ (18 d) > ES (16 d)[3]	GJ is approximately equal to ES
Keränen *et al*[55]	Retrospective	21 (LGJ 0)	50	I-II[2]: 90.5% III-IV[2]: 9.5%	I-II[2]: 58% III-IV[2]: 42%	GJ (81%) is approximately equal to ES (88%)	GJ (9.5%) ES (24%)	GJ (4 d) > ES (1 d)[a]	GJ (8 d) > ES (3 d)[a]	GJ (10%) ES (26%)

[1]ECOG performance status; [2]WHO score; [3]Not significant; [a]$P < 0.05$. GJ: Gastrojejunostomy; ES: Endoscopic stenting; LGJ: Laparoscopic GJ; NR: Not reported; ECOG: Eastern Cooperative Oncology Group; WHO: World Health Organization.

DISCUSSION

Comparative studies between GJ and ES for malignant GOO that results from gastric cancer

One non-randomized prospective study[53] and two retrospective studies[54,55] are available regarding malignant GOO caused by limited unresectable or metastatic gastric cancer. Table 2 provides patient demographics and the main results of three studies with regard to study type, number of procedures, PS, and the favorable procedure group with better results regarding: (1) the number of patients who tolerated oral intake; (2) time to oral intake (d); (3) length of hospital stay (d); and (4) complications.

In a prospective study of 18 patients (9 OGJ and 9 ES treatment)[53], ES had more favorable results regarding the mean time to resume oral feeding (3.1 d) and mean length of hospital stay (4.8 d) compared with GJ (6.3 d and 10 d, respectively). Regarding the late results, such as the recurrence of GOO, late complications due to the procedure, overall survival, and patient satisfaction, no significant differences were identified between OGJ and ES. Recurrent symptoms of GOO were evident only in ES ($n = 3$ patients, 33%) due to stent migration and obstruction of the stent by food. Both procedures resulted in sufficient patient satisfaction.

In their retrospective study, No *et al*[54] concluded that GJ is preferable to ES for the palliation of GOO that results from gastric cancer in patients with a good PS, especially Eastern Cooperative Oncology Group (ECOG) 0 to 1. In this study, 72 ES and 41 GJ (32 OGJ and 9 LGJ) patients were compared regarding patient demographics, early outcomes and adverse events, late adverse events, patency duration, and survival. The two groups did not differ in most characteristics with the exception of sex (more men in the GJ group). The technical success rates in both groups were excellent (ES: 95.8% *vs* GJ: 97.6%); however, three technical failures were noted in the ES group. However, the time to oral intake was significantly less in the ES group compared with the GJ group (liquid diet: ES 2 d *vs* GJ 5 d, solid diet: ES 10 d *vs* GJ 16 d). Regarding adverse events, a higher rate of late adverse events was identified in the ES group compared with the GJ group (44.4% *vs* 12.2%, $P < 0.01$), whereas early adverse events were not significantly different between the two groups. The adverse events in the ES group were not significantly different according to the stent type ($P = 0.158$). Similarly, the number of re-interventions was significantly greater in the ES group compared with the GJ group (31 (43%) *vs* 4 (5.5%), respectively, $P < 0.001$). Regarding the patency duration, the median duration of both the first stent patency and total stent patency, including the patency achieved by an additional stent, was 210 d shorter in the ES group compared with the GJ group ($P = 0.001$, $P = 0.044$, respectively). The interesting finding in this previous study was the analysis according to PS (ECOG status). Patients in the GJ group exhibited significantly longer overall survival compared with the ES group, but only for ECOG 0 to 1.

Keränen *et al*[55] compared three palliative methods, including 50 ES, 26 palliative resections of the stomach (PR), and 21 GJ. All palliative surgeries were performed with laparotomy. Patients with ES presented with the poorest general condition among all groups in terms of the pre-procedure albumin level, PS, and amount of oral intake; thus, the ES group exhibited the worst survival. The main results regarding the palliation of GOO symptoms demonstrated that ES resulted in a faster improvement of oral intake, relief of GOO symptoms, and reduced hospital stay compared with GJ. The authors advocated considering how the clinical condition before treatment affects survival in malignant GOO that results from gastric cancer when determining the type of palliative procedures. Furthermore, the authors indicated that the study had several limitations. The study was non-randomized, retrospective, and

had a certain degree of defective follow-up data, which led to selection bias between the treatment groups. However, this retrospective study reported the time between ES treatment and re-obstruction; however, this information was described only in context, not in tables or figures. The median time to re-obstruction after ES was 95 d; thus, most patients had died before re-obstruction occurred. Therefore, re-obstruction of the stent is not a major problem for patients with a poor prognosis (< 3 mo), even in patients with gastric cancer and particularly in patients with pancreatic cancer or other malignancies with a worse prognosis.

In summary, the main findings of comparative studies between GJ and ES that focused on gastric cancer patients were similar to the findings of other RCTs, CCTs, and retrospective studies of patients with GOO that resulted from malignancies other than gastric carcinoma. In addition, no articles have referred to precise cost performance or compared LGJ and ES. Compared with GJ, ES is preferred for the rapid improvement of oral intake, relief of GOO symptoms, and reduced hospital stay, whereas the occurrence of late complications, such as stent obstruction or migration, is higher. The differences compared with other malignant GOOs are patient survival after GJ or ES and patient PS. The median survival durations in these three articles were 283, 189 to 293, and 50 to 241 d. Thus, the potential survival of GOO patients with gastric cancer may be increased by approximately 2 or 3 mo. Because several studies have reported that GJ is preferable for patients with a longer life expectancy[49], GJ should be selected more frequently in clinical practice for good PS patients with GOO that results from gastric cancer.

CONCLUSION

Both GJ and ES are effective treatments in patients with GOO that results from gastric cancer. GJ exhibits better long-term outcomes with regard to fewer late complications and long patency, whereas ES exhibits better short-term outcomes, including the length of the hospital stay. Although no large-scale studies or RCTs have compared the safety and efficacy of the two procedures, literature reviews suggest that GJ may be the preferable procedure because of the good PS and long prognosis of gastric cancer patients.

However, the bypass procedure is currently performed laparoscopically (LGJ), and various novel devices in the ES field can minimize stent obstruction or migration. Therefore, to determine the more preferable procedure in patients with GOO that results from gastric cancer, a prospective RCT of LGJ and ES with current devices specialized for gastric cancer patients is warranted.

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Second-look endoscopy and factors associated with delayed bleeding after endoscopic submucosal dissection

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Abstract

Endoscopic submucosal dissection (ESD) is a widely used procedure as curative treatment for superficial gastric neoplasms, including early gastric cancer without lymph node metastasis. However, ESD requires advanced endoscopic skill and there is a major concern regarding complications from bleeding. So far, extensive efforts have been made to develop strategies to reduce post-ESD bleeding. Use of proton pump inhibitors and coagulating exposed vessels on the ulcer floor after ESD are strategies known to reduce the risk of delayed bleeding. Second-look endoscopy (SLE) is also carried out to reduce delayed bleeding following ESD in many institutions. However, the incidence of bleeding still remains around 5%, and further measures are needed to reduce delayed bleeding after gastric ESD. Recently, three randomized studies indicated that routine SLE was unnecessary. Although routine SLE may not be recommended for all patients after gastric ESD, SLE might be an important tool for the prevention of the delayed bleeding in selected high-risk patients. Thus, the identification of the risk factors, such as large size of resected specimen and treatment with multiple antiplatelet medications, may help to further guide clinicians in deciding whether to perform SLE. Studies carried out on larger cohorts are necessary to clarify the efficacy of SLE after ESD in the prevention of post-ESD bleeding in potentially high-risk patients.

Key words: Endoscopic submucosal dissection; Second-look endoscopy; Early gastric cancer

Core tip: Second-look endoscopy (SLE) for selected patients might be an important tool for the prevention of delayed bleeding following endoscopic submucosal dissection (ESD). Risk factors for bleeding after ESD include large size of resected specimen and use of multiple antiplatelet agents. In addition, submucosal fibrosis and nausea might be risk factors associated with high-risk ulcer stigmata. Such risk factors require further evaluation as to whether SLE is indicated.

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INTRODUCTION

In recent years, endoscopic submucosal dissection (ESD) for superficial gastric epithelial neoplasms including early gastric cancer has been commonly used in clinical practice in Asian countries. While a snare is used in conventional endoscopic mucosal resection (EMR), various types of endoscopic surgical knives are used in ESD for the purpose of mucosal incision and submucosal dissection. Therefore, this technique enables higher en bloc resection and histologic complete resection rates in patients with larger or ulcerated tumors[1,2]. However, with ESD, concerns still exist regarding technical difficulties and a higher risk of complications, especially bleeding and perforation[1,2]. Immediate intraoperative bleeding is easily recognized at the time of the procedure and can be treated endoscopically in most cases. However, delayed bleeding, manifesting as hematemesis or melena, may occur days after the procedure, occasionally even after discharge from hospital. The reported incidence of delayed bleeding after gastric ESD varies from 5.4% to 22%[3-9]. As any delay in the recognition of such an event may result in serious cardiovascular complications, such as hypovolemic shock, prevention of delayed bleeding is an important clinical problem following ESD to address.

ESD causes large artificial ulcers, but there is no consensus regarding second-look endoscopy (SLE), and when or whether the procedure should be used. Although recent randomized studies demonstrated no benefit for the use of SLE in the prevention of post-ESD bleeding, a multicenter survey of patient management following gastric ESD demonstrated that SLE was utilized by most institutions[9]. In the present review article, the optimal perioperative management to reduce bleeding following ESD, including SLE, and the high-risk patients SLE will benefit most will be discussed.

SLE after endoscopic submucosal dissection

Delayed bleeding still occurs in approximately 5% of patients who have undergone gastric ESD, despite proton pump inhibitor (PPI) neutralization of intragastric acidity and endoscopic hemostasis through prophylactic coagulation of visible vessels at the ulcer base[3,5,10-12]. SLE is generally defined as repeat endoscopy within 24 h after the initial endoscopy and hemostatic therapy. For the management of peptic ulcer bleeding, routine SLE is not recommended following successful endoscopic hemostasis. Repeat endoscopy should be performed on patients with clinical evidence of recurrent bleeding. Hemostatic therapy should furthermore be applied to patients with higher risk stigmata of hemorrhage[13]. For the perioperative management of post-ESD bleeding, the benefit of SLE remains controversial. However, routine SLE continues to be performed in many medical centers which have inpatients-based ESD treatment setting, probably because the delayed bleeding rate overall remains at approximately 5%[9]. If high-risk ulcer stigmata after ESD are treated only using PPI without endoscopic therapy, the bleeding risk might be higher, and more serious complication may develop following discharge. Recently, the efficacy of SLE for ESD induced ulcers was evaluated in several retrospective studies and three prospective randomized trials[8,14-17] (Table 1). The results indicated that the incidence of post-ESD bleeding was not significantly affected by SLE. However, three prospective studies had several limitations that should be taken into account. Ryu *et al*[17] reported that 12 patients (16.2%) in the SLE group and 9 (11.1%) in the no SLE group experienced bleeding after ESD (P = 0.66). The delayed bleeding was defined as the presence of any symptoms or signs of bleeding such as melena or hematemesis from 2 to 28 d. This definition can include the past bleeding episode and other site bleeding, therefore, it may be the reason of higher incidence of bleeding than other studies. The number of enrolled patients was smaller than the calculated sample size, it might be under powered to assess their statistics between two groups. Kim *et al*[15] demonstrated that delayed bleeding occurred in 8 lesions (3.6%) receiving a SLE and 6 (2.8%) not receiving a SLE (P = 0.79). Delayed bleeding was defined as bleeding at 3 to 56 d requiring emergency hemostasis for bleeding on artificial ulcer sites because of hematemesis, melena, hematochezia. The sample sized was not calculated statistically in this study. Mochizuki *et al*[8] reported that post-ESD bleeding occurred in 7 patients (5.4%) with SLE and five patients with (3.8%) non-SLE (95%CI: -6.7-3.5); meeting the non-inferiority criterion (7%). Delayed bleeding was defined as hemorrhage confirmed by emergency endoscopy from the time of the completion of ESD to 28 d and showed clinical symptoms including hematemesis, melena or a decrease in hemoglobin of > 2 g/dL. The sample sized was adequately calculated for the assessment of non-inferiority of the non-SLE compared with the SLE. The limitation of three randomized controlled trial (RCT) was different definitions of delayed bleeding used. In addition, the patients taking antiplatelet or anticoagulant drug during the perioperative period were excluded in all three RCT. Is it possible to conclude that the SLE is no longer necessary following gastric ESD? Unfortunately the results remain inconclusive, as the studies so far have been performed only on relatively small cohorts.

Most delayed bleeding events have been shown to occur within the first 24 to 48 h, but remained a possibility for up to 2 wk following ESD. In many institutions, SLE was routinely carried out within 1-2 d

Table 1 Influence of second-look endoscopy on the incidence of bleeding following endoscopic submucosal dissection

Ref.	Year	*n*	Study design	Bleeding: SLE *vs* no SLE (%)	Risk factors for delayed bleeding	SLE benefit
Ryu *et al*[17]	2013	182	Prospective, single center	16.2% *vs* 11.1%	No risk factors	No
Mochizuki *et al*[8]	2014	262	Prospective, Multicenter center	5.4% *vs* 3.8%	Resected specimen size > 40 mm	No
Kim *et al*[16]	2014	437	Prospective, single center	3.6% *vs* 2.8%	Large tumor size (> 20 mm)	No
Park *et al*[14]	2015	445	Retrospective	3.0% *vs* 2.0%	Tumor in the upper-third of the stomach, resected specimen size > 40 mm	No
Kim *et al*[15]	2015	502	Retrospective	1.0% *vs* 2.5%	Large tumor size (> 15 mm)	No

SLE: Second-look endoscopy.

following ESD as a precaution against the more serious clinical outcomes for delayed bleeding[9]. The potential advantage of routine SLE is that the procedure can be used to evaluate the status of healing ulcers and to perform additional hemostasis if necessary. However, there are arguments concerning the cost/benefit of SLE for ESD ulcers as well as peptic ulcers. If a subgroup of patients at high risk for recurrent bleeding following ESD could be identified, this group potentially could derive benefit from SLE. Risk factors leading to postoperative bleeding remain controversial however because the perioperative management of gastric ESD has not been standardized. Although several factors are reported to be associated with an increased risk of delayed bleeding after ESD, none have been identified that reliably detect a high-risk population. It is therefore possible that risk factors for bleeding following ESD originate from technical parameters which are more difficult to assess objectively.

Role of proton-pump inhibitors in the prevention of bleeding events

Intraoperative bleeding is an unavoidable consequence during mucosal incision or submucosal dissections. Thus, most endoscopist never consider intraoperative bleeding as a complication except in cases requiring emergency surgery or blood transfusion, or in cases where ESD is discontinued because of bleeding[18].

One strategy to control bleeding is to regulate intragastric acidity, as intragastric pH above 5.4 facilitates blood coagulation and platelet aggregation[19]. In order to achieve this pH level, PPI is more effective than of H2RA. Previous meta-analysis result compared with PPI *vs* H2RA for the management of iatrogenic gastric ulcer after EMR or ESD showed that PPIs are more effective than H2RA[20]. Therefore, PPI infusion therapy is routinely used to prevent bleeding and promote ulcer healing following ESD in most institutions. But, recent randomized controlled studies showed conflicting results that H2RA was comparable healing rate and delayed bleeding rate[21-25].

Pre-endoscopic intravenous PPI therapy in peptic ulcer bleeding, which inhibits production of gastric acid, significantly reduces the incidence of bleeding at higher risk stigmata of hemorrhage, such as active bleeding, non-bleeding visible vessels, and adherent clots[26]. However, the effectiveness of preoperative administration of PPI in the management of artificial ulcers following ESD remains unclear. As raising intragastric pH preoperatively may lead to easy and complete endoscopic hemostasis during ESD and increases blood coagulation of iatrogenic ulcers, a randomized study has been conducted to determine the effectiveness of preoperative administration of a PPI for the prevention of bleeding. A trial of 24-h pre-administration of omeprazole increased intra-gastric pH at the time of ESD[27]. However, results demonstrated no additional benefit of a higher intra-gastric pH in the prevention of bleeding, including intraoperative and post-operative delayed bleeding following the procedure.

Because intraoperative bleeding is generally characterized as spurting or oozing, a high intra-gastric pH might not be an effective preventive measure against intraoperative bleeding. In our opinion, the occurrence of intraoperative bleeding may be related not only to measurable risk factors, such as size of resected specimen and location, but also to unquantifiable technical factors, such as electrosurgical unit settings, the type of electrosurgical knife, injection solutions, and experience of the operator[18,28]. Furthermore, this study was complicated by the fact that all patients in the study groups had been administered a regular dose of PPI for 4 wk. Thus, short course pre-operative administration of PPI might not be sufficient to produce a difference in the incidence of delayed bleeding events.

Prophylactic coagulation of visible vessel at the ulcer base following ESD

Recent guidelines for the management of peptic ulcer bleeding suggest that endoscopic therapy should be provided to patients with a non-bleeding visible vessel[13,29]. In addition, endoscopic therapy may be considered for patients with an adherent clot resistant to vigorous irrigation. Furthermore, the benefit of endoscopy may be greater for patients with clinical features associated with a higher risk of rebleeding,

Table 2 Incidence of delayed bleeding and associated risk factors after gastric endoscopic submucosal dissection

Ref.	Year	*n*	Study design	Bleeding (%)	Risk factors	Remarks
Takizawa *et al*[5]	2008	968	Retrospective	5.8% (7.1% *vs* 3.1% with PEC)	Tumor location in middle and lower regions of the stomach, PEC	PEC of visible vessels in the resected area follwing ESD may lead to a decreased bleeding rate
Chung *et al*[30]	2009	952	Retrospective	15.60%	Upper region, size of the tumor (> 40 mm), recurrent lesion, flat morphology	A significant bleeding incidence was at 0.6%
Okada *et al*[10]	2011	582	Retrospective	4.81%	Resected specimen width (⩾ 40 mm)	Mechanism of delayed bleeding may differ depending on the time elapsed between ESD and bleeding episodes
Toyokawa *et al*[11]	2012	1123	Retrospective	5.00%	Age ⩾ 80 yr, extended duration of procedure	-
Goto *et al*[9]	2012	1814	Retrospective	5.50%	No statistical parameters	Multicenter survey clarified that post-ESD management (duration of PPI use, resumption of food intake, and performance of SLE) varied among the medical centers
Koh *et al*[12]	2013	1032	Retrospective	5.30%	Size of resected specimen	The incidence of delayed bleeding in patients with two risk factors was 11.6%
Choi *et al*[3]	2014	614	Prospective observation	Early (3.7%) Late (1.9%)	(> 40 mm), use of antithrombotic drugs (only for delay bleeding) Surface erosion, high risk of stigmata during SLE, location in the middle of the stomach	Nausea and submucosal fibrosis increase the incidence of high risk of stigmata in SLE

PEC: Post-endoscopic submucosal dissection coagulation; ESD: Endoscopic submucosal dissection; PPI: Proton pump inhibitor; SLE: Second-look endoscopy.

such as older age, concurrent illness, and inpatient status at occurrence[13]. For the management of artificial ulcers generated during ESD, prophylactic coagulation of exposed visible vessels at the base of a mucosal defect following ESD was shown to lead to a reduction in the incidence of bleeding (7.1% *vs* 3.1%; $P < 0.01$)[5]. Routine coagulation of all non-bleeding visible vessels at the ulcer base is thus performed as standard practice. However, both prophylactic coagulation of all visible vessels at the ulcer bed and administration of PPIs do not completely eliminate the possibility of delayed bleeding (Table 2).

Patient-related risk factors associated with delayed bleeding

Most studies reported large resected specimen size to be an independent risk factor for delayed bleeding[10,12,30] (Table 2). Theoretically, a large lesion has a more expansive vascular network than a small lesion, which enhances the possibility of bleeding during and following ESD.

Still, risks of lesion location were variable. Intraoperative bleeding risk was reported to be higher in the upper region than in the middle and lower regions of the stomach. Arteries in the submucosal layer of the upper stomach are significantly thicker or more stubby than in other gastric sites, and the diameter of submucosal arteries is larger in the upper area than in the middle or lower stomach[5]. Therefore, the risk of intraoperative bleeding is greater in the upper stomach, and intraoperative hemostasis is more frequently necessary during removal of a lesion in this region. In contrast, a delayed bleeding risk was reported to be greater in the lower region of the stomach[5]. In other words, while intraoperative hemostasis is less frequently necessary in the middle and lower gastric regions, bleeding may still occur here later if vessels in these areas are not coagulated at the time of procedure. The occurrence of delayed bleeding might not have been due to insufficient hemostasis, but rather to insufficient coagulation during resection, because the sites where delayed bleeding occurred were different than those where immediate bleeding has been controlled endoscopically[31]. Antral peristaltic activity and bile juice reflux might also contribute to some degree.

The Forrest classification provides prognostic information regarding the risk of rebleeding, and the need for therapeutic intervention in ulcer disease. Endoscopic therapy is indicated for patients with high-risk ulcer stigmata (Forrest type Ⅰ and Ⅱa). For this reason, additional hemostasis for high-risk ulcer stigmata may decrease the chance of further bleeding and/or emergency intervention. In a prospective observation study, submucosal fibrosis [odds ratios (OR) = 3.91;

Table 3 Antiplatelet medication and the risk of delayed bleeding

Ref.	Year	*n*	Design	Method	Comparison of bleeding incidence	Comments
Lim *et al*[32]	2012	1591	Retrospective	ESD	No antiplatelet medication: 5.2% Antiplatelet withdrawal: 5.9% Antiplatelet continuation: 11.6%	Continuous administration of antiplatelet medication was not found to have an independent significant association with bleeding
Cho *et al*[33]	2012	514	Retrospective	ESD	No aspirin medication: 3.4% Aspirin withdrawal: 3.6% Aspirin continuation: 21.1%	Continuous aspirin use increases the risk of bleeding after gastric ESD
Sanomura *et al*[35]	2014	94	Retrospective	ESD	Aspirin interruption: 7.1% Aspirin continuation: 4.8%	Continued use of aspirin does not increase the risk of bleeding during or after ESD
Tounou *et al*[34]	2015	377	Retrospective	ESD	No aspirin medication: 6.1% Aspirin continuation: 14.4% Single antiplatelet: 15.5% Dual antiplatelet: 35.5%	Aspirin was not a significant risk factor for post-ESD bleeding
Ono *et al*[36]	2015	28	Prospective, observational	ESD/EMR	The study was terminated in accordance with predetermined safety criteria because 7 of 28 consecutive patients experienced major bleeding complications (25.0%)	Subanalysis of gastric ESD (23 lesions in 19 patients) confirmed that the administration of thienopyridine derivatives (P = 0.01) and multiple agents (P = 0.02) were the significant factors Continuation of aspirin alone during these endoscopic procedures may be acceptable

ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection.

95%CI: 1.92-7.94] and nausea after ESD (OR = 4.76; 95%CI: 2.39-9.43) were risk factors significantly associated with high-risk ulcers[3]. To resect submucosal fibrosis, deeper submucosal dissection is generally necessary, but superficial proper muscle damage might occur. Such manipulation of the tissue might lead to the development of ulcers with a high-risk of bleeding. Furthermore, the lesions with more submucosal vessels may require more frequent coagulation during ESD. This treatment may result in coagulation-induced gastric edema and a more intense inflammatory response, which will cause nausea. A significant amount of blood from an artificial ulcer can also induce nausea. In fact, despite additive coagulation in patients with high-risk ulcer stigmata, the rebleeding incidence on SLE was 8.6% relative to patients with low-risk stigmata. A potential explanation is that ulcers at high risk for bleeding tend to also be rich in vascularity.

Drug-related risk factors for delayed bleeding

An increasing number of patients are taking multiple antiplatelet medications or antithrombotic drugs as the incidence of cardiovascular disease rises. Antiplatelet or antithrombotic medications to prevent cardiovascular events in patients present an additional concern, as ESD is a procedure with high risk of bleeding. Most endoscopists prefer to interrupt the use of antiplatelet or antithrombotic drugs for as long as possible. In one retrospective observational study, continuous administration of antiplatelet medication was not found to be a significantly associated with bleeding[32] (OR = 1.596; 95%CI: 0.877-2.903; P = 0.126), whereas in another retrospective study, the use of aspirin by itself was associated with post-ESD bleeding[33] (OR = 4.49; 95%CI: 1.09-18.38). In the latter, the resumption specifically of clopidogrel combined with aspirin use (OR = 26.71; 95%CI: 7.09-100.53) was significantly associated with post-ESD bleeding. In recent two retrospective studies to evaluate the hemorrhagic risk of ESD in patients on antiplatelet drug, Tounou *et al*[34] demonstrated that dual antiplatelet therapy markedly increased the risk for bleeding (HR = 16.3; 95%CI: 3.4-78.2), but continuous low dose aspirin does not. Sanomura *et al*[35] also reported that continued use of low dose aspirin does not increased the risk of bleeding during or after ESD. In a recent prospective study, subanalysis of gastric ESD showed that administration of thienopyridine derivatives (P = 0.01) and multiple antiplatelet agents (P = 0.02) were significant contributing factors to bleeding[36] (Table 3), but the continuation of aspirin alone appeared to be acceptable.

In general, post-ESD bleeding in patients taking aspirin can be managed effectively without increasing long-term morbidity or mortality. However, cerebral infarction upon discontinuation of aspirin intake is a critical complication. Therefore, ASGE and ESGE and JGES guideline recommend low dose aspirin should be continued for endoscopic treatment with high bleeding risk when the risk of thromboembolism is high[37-39]. Taken together, the results indicate that if a patient has a low risk for a thromboembolic event, aspirin use should be ceased. However, if a patient has a high risk for thromboembolism, aspirin may be continued as a thromboembolic event could otherwise result in more serious consequences affecting quality of life.

CONCLUSION

Bleeding is a major potential complication both during and post-ESD. Decreased incidence of delayed bleeding

is associated with the use of anti-secretory agents, especially PPI, and prophylactic coagulation of visible vessels at the ulcer base following ESD. However, despite these therapeutic interventions, delayed bleeding still occurs in approximately 5% of patients who undergo gastric ESD. To date, SLE after ESD has been a common therapeutic strategy in order to avoid a bleeding event. The results of recent randomized studies however were unfavorable for routine SLE after gastric ESD. Although routine SLE for all patients after gastric ESD might be unnecessary, SLE may be an important tool in the treatment of a subgroup of patients at risk for bleeding or high-risk ulcer stigmata. Well-known potential risk factors of delayed bleeding are large size of resected specimen and treatment with multiple antiplatelet agents. Submucosal fibrosis and nausea after ESD might be associated with high-risk ulcer stigmata. Thus, these factors can be considered as indications for the use of SLE following ESD. To establish the optimal perioperative strategies for safe ESD, well-designed prospective studies should be conducted in the future to more clearly identify at risk patients.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Safety of immediate endoscopic sphincterotomy in acute suppurative cholangitis caused by choledocholithiasis

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Author contributions: Ito T and Sai JK contributed equally to this work; Ito T collected and analyzed the data, and drafted the manuscript; Sai JK provided analytical oversight and designed and supervised the study; Watanabe S and Shiina S revised the manuscript for the important intellectual content; Okubo H, Saito H, Ishii S, Kanazawa R and Tomishima K participated in collecting the data; all authors have read and approved the final version to be published.

Institutional review board statement: This study was approved by the Institutional Review Board of Juntendo University.

Informed consent statement: Written informed consent for the procedures and treatment was obtained from patients or their next of kin in accordance with normal clinical practice.

Conflict-of-interest statement: No conflict of interests.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at (jinkans@juntendo.ac.jp). Consent for data sharing was not obtained from the participants but the presented data are anonymized and risk of identification is low.

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Abstract

AIM: To examine the safety of immediate endoscopic sphincterotomy (EST) in patients with acute suppurative cholangitis (ASC) caused by choledocholithiasis, as compared with elective EST.

METHODS: Patients with ASC due to choledocholithiasis were allocated to two groups: Those who underwent EST immediately and those who underwent EBD followed by EST 1 wk later because they were under anticoagulant therapy, had a coagulopathy (international normalized ratio > 1.3, partial thromboplastin time greater than twice that of control), or had a platelet count < 50000 × $10^3/\mu L$. One of four trainees [200-400 cases of endoscopic retrograde cholangiopancreatography (ERCP)] supervised by a specialist (> 10000 cases of ERCP) performed the procedures. The success and complication rates associated with EST in each group were examined.

RESULTS: Of the 87 patients with ASC, 59 were in the immediate EST group and 28 in the elective EST group. EST was successful in all patients in both groups. There were no complications associated with EST in either group of patients, although white blood cell count, C-reactive

protein, total bilirubin, and serum concentrations of liver enzymes just before EST were significantly higher in the immediate EST group than in the elective EST group.

CONCLUSION: Immediate EST can be as safe as elective EST for patients with ASC associated with choledocholithiasis provided they are not under anticoagulant therapy, or do not have a coagulopathy or a platelet count < 50000 × 10^3/μL. Moreover, the procedure was safely performed by a trainee under the supervision of an experienced specialist.

Key words: Acute cholangitis; Complications; Endoscopic sphincterotomy

Core tip: Immediate endoscopic sphincterotomy (EST) can be as safe as elective EST for patients with acute suppurative cholangitis associated with choledocholithiasis, because there were no complications associated with EST in either group of patients, although white blood cell count, C-reactive protein, total bilirubin, and serum concentrations of liver enzymes just before EST were significantly higher in the immediate EST group (n = 59) than in the elective EST group (n = 28). Moreover, the procedure was safely performed by a trainee under the supervision of an experienced specialist.

Ito T, Sai JK, Okubo H, Saito H, Ishii S, Kanazawa R, Tomishima K, Watanabe S, Shiina S. Safety of immediate endoscopic sphincterotomy in acute suppurative cholangitis caused by choledocholithiasis. *World J Gastrointest Endosc* 2016; 8(3): 180-185 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i3/180.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i3.180

INTRODUCTION

Acute suppurative cholangitis (ASC) is a life-threatening condition that requires prompt treatment[1,2]. At present, endoscopic biliary drainage (EBD), including endoscopic nasobiliary drainage (ENBD) and endoscopic retrograde biliary drainage (ERBD), followed by elective endoscopic sphincterotomy (EST) is the established mode of treatment for ASC, with a high success rate and low morbidity and mortality[3-7]. However, the validity of immediate EST with stone extraction is uncertain.

In the present study, we examined the success and complication rates of immediate EST for patients with ASC associated with bile duct stones and compared them with those of elective EST.

MATERIALS AND METHODS

Patient characteristics

Between January 2009 and February 2013, patients with acute cholangitis, suspected of having ASC due to choledocholithiasis were enrolled for the present study. The diagnosis of acute cholangitis was based on clinical evidence of both infection (fever, chills, leukocytosis, or abdominal pain) and biliary obstruction (clinical jaundice or hyperbilirubinemia), and patients with any of the following at admission were suspected of having ASC requiring emergency endoscopic retrograde cholangiopancreatography (ERCP): (1) fever (temperature > 39 ℃); (2) septicemic shock (systolic blood pressure < 90 mmHg); (3) increasing abdominal pain with clinical evidence of peritoneal inflammation (right upper quadrant pain with guarding on palpation); or (4) an impaired level of consciousness on admission. In the present study, ASC was defined based on the evidence of purulent bile. Therefore, patients were included in the current study after bile duct access was gained, the cholangiogram confirmed the presence of bile duct stones, and bile aspiration through the catheter showed the presence of purulent bile on ERCP. Exclusion criteria were prior sphincterotomy, concomitant pancreatic or biliary malignancies, and coexisting intrahepatic stones. Patients who died within 6 h after admission were also excluded.

Patients were allocated to two groups: Immediate EST with stone extraction, and EBD followed by elective EST 1 wk later because they were under anticoagulant therapy, had a coagulopathy (international normalized ratio > 1.3, partial thromboplastin time greater than twice that of control), or had a platelet count < 50000 × 10^3/μL.

Complete blood count, serum electrolytes, clotting profile, and biochemical tests of liver function were monitored daily. Blood pressure, pulse rate, and body temperature were monitored every 4 h. All patients were administered antibiotics intravenously and underwent abdominal CT before ERCP.

Written informed consent for the procedures and treatment was obtained from patients or their next of kin in accordance with normal clinical practice. This study was approved by the Institutional Review Board of Juntendo University.

Endoscopic procedure

ERCP was performed using a side-viewing duodenoscope (JF-240, JF-260V, TJF-260; Olympus, Tokyo, Japan). Electrocautery was administered using a 120-watt endocut current (ERBE International, Erlangen, Germany). One of four trainees (200-400 cases of ERCP) supervised by a specialist (>10000 cases of ERCP) performed the procedures. If the trainee could not cannulate the bile duct within 3 min, the specialist did it, and then the trainee was in charge again after deep bile duct cannulation was attained in both groups. All the subjects in the present study started to receive drip infusion of protease inhibitors prior to EST to prevent the occurrence of pancreatitis. Following preparation with pharyngeal anesthesia and intravenous injection of midazolam (0.06 mg/kg), ERCP was performed. After deep cannulation into the bile duct, bile was aspirated to

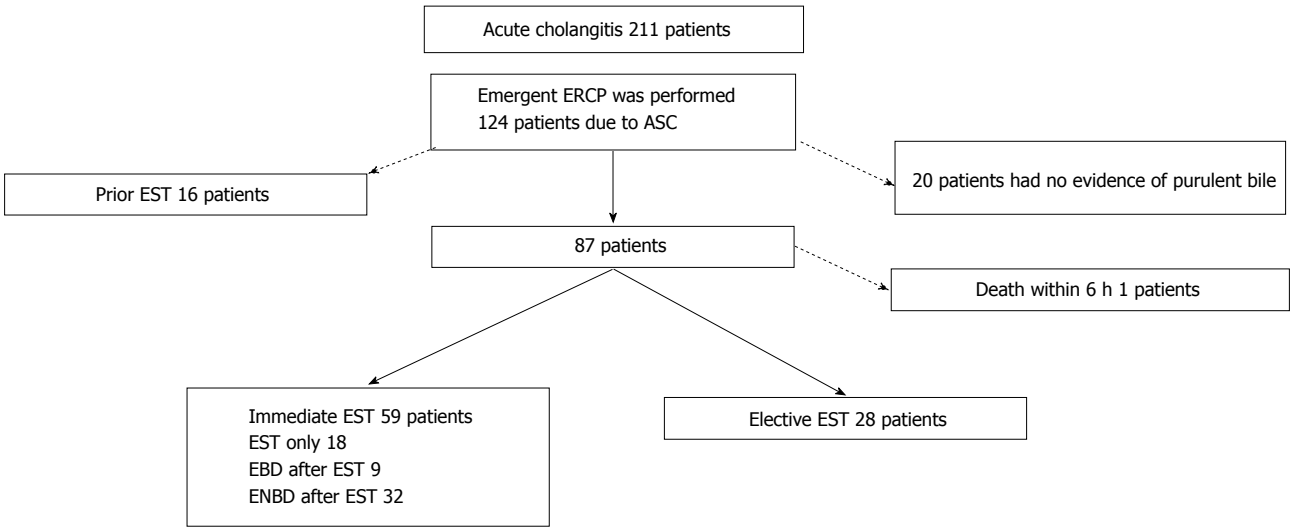

Figure 1 Patient inclusion flow chart. EBD: Endoscopic biliary drainage; ENBD: Endoscopic nasobiliary drainage; EST: Endoscopic sphincterotomy; ASC: Acute suppurative cholangitis; ERCP: Endoscopic retrograde cholangiopancreatography.

reduce intrabiliary pressure, and low-osmolar nonionic contrast medium was carefully injected to confirm the etiology of cholangitis. After the cholangiogram confirmed the presence of bile duct stones and bile aspiration through the catheter showed the presence of purulent bile, EST or EBD including ENBD and ERBD was performed.

EST was performed with a 30 mm pull-type sphincterotome (Clever Cut 3; KD-V41M, Olympus) under the guidewire. For ENBD, a 6F nasobiliary tube (Gadelius, Tokyo) was inserted in the bile duct. For ERBD, a 7F double pig type plastic endoprosthesis (Wilson-Cook Medical Inc., Winston-Salem, NC) was placed across the papilla. For patients in the immediate EST group, stone removal by retrieval balloon catheter was tried at first ERCP, and EBD (ERBD or ENBD) was performed if the patient had or was suspected of having remnant stones. In the elective EST group, EST was performed 1 wk after EBD for stone removal. After ERCP, all the patients were kept under strict observation.

Procedure-related pancreatitis was defined as abdominal pain, with at least a 3-fold elevation of serum amylase more than 24 h after the procedure. Continuation of preexisting acute pancreatitis was not included as a complication. Hemorrhage was considered clinically significant only if there was clinical evidence of bleeding, such as melena or hematemesis, with an associated decrease of at least 2 g per deciliter of the hemoglobin concentration, or the need for a blood transfusion. Bleeding that was controlled during the procedure without hemodynamic instability or transfusion was not considered a complication[8].

The clinical characteristics of both groups of patients were compared. The primary endpoints of the study were the success and complication rates of immediate EST compared with elective EST. Secondary endpoints were the period for normalization of body temperature, leukocytosis, and C-reactive protein (CRP) leading to discharge from hospital in both groups of patients.

Statistical analysis

Statistical analyses were performed using SPSS version 17.0 for Windows. Data are presented as the mean ± SD and were compared using paired *t*-test. Mann-Whitney *U* test was used for comparing continuous data with skewed distribution in the two groups. A χ^2 test with Yate's correction was used to analyze gender. Statistical significance was defined as a *P*-value < 0.05 (two tailed). The statistical methods of this study were reviewed by Jin Kan Sai from Juntendo University.

RESULTS

A total of 211 patients were hospitalized for acute cholangitis during the study period, and 124 of them underwent emergency ERCP within 24 h after admission. Sixteen patients were excluded because of prior sphincterotomy.

Thus, 88 had bile duct stones associated with the evidence of purulent bile and were diagnosed as having ASC. Among them, 27 had anticoagulant therapy, and 2 had a coagulopathy with a platelet count < 50000 × $10^3/\mu L$; one of these two patients died within 6 h after successful EBD because of uncontrolled sepsis and multiorgan failure and was excluded from the study. Therefore, there were 59 in the immediate EST group and 28 in the elective EST group (Figure 1). Patient characteristics and demographic data of the patients on admission are shown in Table 1. Patients were significantly older and PT (%) was significantly lower in the elective EST group. Peritonism and pre-existing pancreatitis were more frequent in the immediate EST group. All procedures of EBD were successful, but one patient in the elective EST group had pancreatitis associated with EBD. Demographic data of the two groups just before immediate and elective EST (1 wk after EBD) are shown in Table 2. Compared

Table 1 Characteristics of patients undergoing emergency endoscopic retrograde cholangiopancreatography

	Immediate EST group (n = 59)	Elective EST group (n = 28)	P value
Sex (M:F)	31:28	13:15	0.59
Age (mean ± SD, range)	68.76 ± 14.58	78.82 ± 9.07	0.0001
Clinical presentation, n (%)			
Peritonism	51 (86)	19 (68)	0.04
Fever	28 (47)	15 (54)	0.59
Hypotension	1 (1.6)	1 (3.5)	0.54
Altered sensorium	1 (1.6)	0 (0)	0.67
Pre-existing pancreatitis (%)	15 (25)	1 (3.5)	0.01
WBC	10959 ± 5857	10025 ± 4110	0.39
Plt	20.4 ± 8.0	18.5 ± 6.3	0.26
PT (%)	86.7 ± 15.8	72.7 ± 22.2	0.009
CRP	5.32 ± 5.59	7.84 ± 6.76	0.069
T-Bil	4.09 ± 2.8	3.9 ± 2.5	0.76
AST	253.3 ± 215.2	262.3 ± 370.3	0.90
ALT	243.5 ± 182	262.3 ± 278.7	0.83
γGTP	458.6 ± 326.7	453.4 ± 233.6	0.82
ALP	760.1 ± 404.9	826.3 ± 608.4	0.60

CRP: C-reactive protein; EST: Endoscopic sphincterotomy; WBC: White blood cells; Plt: Blood platelet; T-Bil: Serum total bilirubin; AST: Aspartate aminotransferase; ALT: Glutamic-pyruvic transaminase; ALP: Alkalinephosphatase; γGTP: Serum gamma gamma glutamyl transpeptidase.

Table 2 Demographic data of patients before endoscopic sphincterotomy

	Immediate EST group	Elective EST group	P value
WBC	10959 ± 5857	6521 ± 2274	0.0002
Plt	20.4 ± 8.0	32.6 ± 42.2	0.03
PT (%)	86.7 ± 15.8	82.9 ± 14.1	0.23
CRP	5.32 ± 5.59	1.82 ± 1.65	0.0017
T-Bil	4.09 ± 2.8	1.4 ± 1.0	< 0.0001
AST	253.3 ± 215.2	50.6 ± 53.5	< 0.0001
ALT	243.5 ± 182	66.9 ± 55.3	< 0.0001
γGTP	458.6 ± 326.7	254.3 ± 230.3	< 0.0001
ALP	760.1 ± 404.9	494.5 ± 241.7	< 0.0001

CRP: C-reactive protein; EST: Endoscopic sphincterotomy; WBC: White blood cells; Plt: Blood platelet; T-Bil: Serum total bilirubin; AST: Aspartate aminotransferase; ALT: Glutamic-pyruvic transaminase; ALP: Alkaline-phosphatase; γGTP: Serum gamma gamma glutamyl transpeptidase.

with the elective EST group, white blood cell count, CRP, total bilirubin, and serum concentrations of liver enzymes before EST were significantly higher in the immediate EST group, while the platelet count was significantly lower.

All EST procedures were successful, and there were no complications such as pancreatitis, bleeding (hemorrhage), or perforation in the two groups, although trainees achieved deep cannulation of the bile duct in 31 (35.6%) of them. Deterioration of pre-existing pancreatitis and cholangitis as a direct result of ERCP is difficult to assess; however, all indicators, including daily serum levels of amylase, liver enzymes, white blood cell count, and CRP, improved after the procedure (data not shown). In the immediate EST group complete stone extraction was achieved at once in 30.5% (18/59) of the patients while 69.5% (41/59) were suspected of having remnant stones and required EBD. Time for normalization of CRP and discharge was significantly shorter in patients who underwent immediate EST and the stones were extracted at once, although the period for normalization of body temperature and leukocytosis was not significantly different between the two groups (Table 3).

DISCUSSION

ASC requires early drainage of the biliary system to reduce the incidence of septic complications[1,2]. The endoscopic techniques used for biliary drainage include EST with stone extraction, and EBD, either ENBD or ERBD. EBD is an established mode of treatment for ASC, with a high success rate and low morbidity and mortality[3-7]. Lin *et al*[9] reported a 100% success rate and no mortality with ENBD in 40 patients with acute cholangitis. Leung *et al*[1] treated 105 patients with acute cholangitis by ERBD, with a success rate of 97% and mortality of 4.7%. EBD can be performed easily, quickly, and safely at the endoscopy, avoiding the risk of bleeding in patients with coagulopathy.

On the other hand, EST with stone extraction is another mode of biliary drainage in ASC with an associated mortality rate of 4.7%-7.6%, although EST related complications, such as bleeding, retroduodenal perforation, and acute pancreatitis, may occur in 6%-12% of cases[1,10-12]. The complications associated with EST are most undesirable in acutely ill patients. Moreover, EST cannot be performed in patients with coagulopathy. Therefore, most endoscopists currently prefer EBD to EST as the first treatment for ASC.

In the present study, immediate and elective EST was performed by one of four trainees supervised by one experienced specialist, and there were no complications associated with EST in either group. Therefore we think

Table 3 Outcome of patients subjected to endoscopic retrograde cholangiopancreatography

		Elective EST group (n = 28)	P value
Immediate EST group (n = 59)			
Normalization of body temperature	1.37 ± 1.86	1.68 ± 2.83	0.6
Normalization of WBC	2.19 ± 2.87	1.39 ± 1.13	0.06
Normalization of CRP	9.12 ± 7.73	13.75 ± 9.32	0.017
Time to discharge	16.79 ± 11.89	21.75 ± 14.1	0.09
Immediate EST with stone extraction group (n = 18)			
Normalization of body temperature	1.61 ± 0.98	1.68 ± 2.83	0.92
Normalization of WBC	1.78 ± 0.9	1.39 ± 1.13	0.53
Normalization of CRP	7.0 ± 5.7	13.75 ± 9.32	0.008
Time to discharge	13.2 ± 7.5	21.75 ± 14.1	0.02

CRP: C-reactive protein; EST: Endoscopic sphincterotomy; WBC: White blood cells.

that EST can be safely performed in patients with ASC by trainees supported by an experienced specialist, although it is undoubtedly that the frequency of post-EST complications is closely related to endoscopic techniques, case volume, skill, and training[13]. Furthermore, despite EBD was conducted as the initial treatment in order to perform EST safely in the elective EST group, in the present study, immediate EST did not increase the risk of post-EST complications provided the patient was not under anticoagulant therapy, or do not have a coagulopathy or a platelet count < 50000 × 10^3/μL, despite patients in the immediate EST group were in worse general conditions than those in the elective EST group at the time of EST. The immediate EST group patients were significantly younger and the occurrence of post-EST complication was not significantly higher than that in older patients of the elective EST group, although Ueki *et al*[7] reported that younger patients with moderate acute cholangitis due to choledocholithiasis were likely to experience post-EST pancreatitis and hemorrhage. However, we do not have a clear explanation as to why no complication associated with EST was encountered in these groups of patients, although we suspect that with a larger sample size, complications would occur.

In this study complete stone extraction was achieved in 30.5% (18/59) of patients in the immediate EST group, and 69.5% (41/59) of them suspected of having remnant stones required EBD. Hui *et al*[4] reported that when endoscopic sphincterotomy is performed with biliary stent insertion in patients with severe acute cholangitis, the procedure is prolonged and the patient is exposed to the risks associated with endoscopic sphincterotomy. However, immediate EST followed by EBD was not associated with an increased frequency of complications in the present study.

Hospitalization of immediate EST patients with stone extraction at once was significantly shorter than that of elective EST patients, and the validity of immediate EST followed by stone extraction was definitive in this aspect for patients with ASC caused by choledocholithiasis. Our results were in line with those of Jang *et al*[14] who reported that hospitalization of patients with moderate cholangitis subjected to EBD plus EST as the initial treatment (emergency EST) was significantly shorter than that of those who palliatively underwent EST after EBD.

The present study has several limitations. First, patients with anticoagulant therapy, coagulopathy, or platelet count < 50000 × 10^3/μL were included in the EBD group because they were at high risk for post-EST bleeding. This may have resulted in selection bias. Second, time for the procedure, the volume of contrast, and number of injections made into the bile duct were not monitored. Third, in a review by Freeman *et al*[15], suspected sphincter Oddi dysfunction (SOD), history of post-ERCP pancreatitis (PEP), and absence of chronic pancreatitis on the pancreatogram were identified as independent patient-related risk factors for PEP. Moreover, significant procedure-related risk factors were the number of pancreatic duct injections, and difficult or failed cannulation. And we did not examine those factors in the present study, although it is noteworthy that pancreatography was not intended to be performed in the present study. Fourth, this study was done by very experienced endoscopists, limiting to generalize the trial findings. Finally, the present study was not a randomized study, although such trials would be of great interest.

In conclusion, the present study indicated that immediate EST may be equally safe and effective compared with elective EST, and can be definitive for patients with ASC caused by choledocholithiasis provided they are not under anticoagulant therapy, or do not have a coagulopathy or a platelet count < 50000 × 10^3/μL. Furthermore, EST can be safely performed by a trainee supervised by an experienced specialist even in patients with ASC.

COMMENTS

Background

Acute suppurative cholangitis (ASC) is a life-threatening condition that requires prompt treatment. At present, endoscopic biliary drainage (EBD), including endoscopic nasobiliary drainage and endoscopic retrograde biliary drainage, followed by elective endoscopic sphincterotomy (EST) is the established mode of treatment for ASC, with a high success rate and low morbidity and mortality.

However, the validity of immediate EST with stone extraction is uncertain.

Research frontiers

To examine the safety of immediate EST in patients with ASC caused by choledocholithiasis, as compared with elective EST.

Innovations and breakthroughs

Patients with ASC due to choledocholithiasis were allocated to two groups: Those who underwent EST immediately and those who underwent EBD electively followed by EST 1 wk later. There were no complications associated with EST in either group of patients, although white blood cell count, C-reactive protein, total bilirubin, and serum concentrations of liver enzymes just before EST were significantly higher in the immediate EST group than in the elective EST group.

Applications

The paper may interest readers in particular because immediate EST can be as safe as elective EST for patients with acute suppurative cholangitis associated with choledocholithiasis.

Peer-review

This manuscript "Safety of immediate endoscopic sphincterotomy in acute suppurative cholangitis caused by choledocholithiasis" is very interesting.

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ORIGINAL ARTICLE

Retrospective Study

Percutaneous endoscopic gastrostomy under steady pressure automatically controlled endoscopy: First clinical series

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Author contributions: Imaeda H and Nakajima K planed the study design; Hosoe N and Kashiwagi K advised the study design, data analyst and enrollment of patients; Nakahara M, Zushi S, Kato M and Matsumoto Y enrolled the patients; Kimura K and Nakamura R were the endoscopist; Wada N, Tsujii M, Yahagi N, Hibi T, Kanai T, Takehara T and Ogata H supervised the study.

Institutional review board statement: The study protocol was approved by the institutional review board at our institutions.

Informed consent statement: Written informed consent was obtained from all the patients.

Conflict-of-interest statement: The authors disclosed no financial relationships relevant to this study.

Data sharing statement: No additional data are available.

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Abstract

AIM: To elucidate the safety of percutaneous endoscopic gastrostomy (PEG) under steady pressure automatically controlled endoscopy (SPACE) using carbon dioxide (CO_2).

METHODS: Nine patients underwent PEG with a modified introducer method under conscious sedation. A T-tube was attached to the channel of an endoscope connected to an automatic surgical insufflator. The stomach was inflated under the SPACE system. The intragastric pressure was kept between 4-8 mmHg with a flow of CO_2 at 35 L/min. Median procedure time, intragastric pressure, median systolic blood pressure, partial pressure of CO_2, abdominal girth before and immediately after PEG, and free gas and small intestinal gas on abdominal X-ray before and after PEG were recorded.

RESULTS: PEG was completed under stable pneumostomach in all patients, with a median procedural time of 22 min. Median intragastric pressure was 6.9 mmHg and median arterial CO_2 pressure before and after PEG was 42.1 and 45.5 Torr (NS). The median abdominal girth before and after PEG was 68.1 and 69.6 cm (NS). A mild free gas image after PEG was observed in two patients, and faint abdominal gas in the downstream bowel was documented in two patients.

CONCLUSION: SPACE might enable standardized pneumostomach and modified introducer procedure of PEG.

Key words: Percutaneous endoscopic gastrostomy; Steady pressure automatically controlled endoscopy; Carbon dioxide

Core tip: We report the safety of percutaneous endoscopic gastrostomy (PEG) under steady pressure automatically controlled endoscopy (SPACE) using carbon dioxide (CO_2). Nine patients underwent PEG with a modified introducer method under conscious sedation. The stomach was inflated under the SPACE system. PEG was completed under stable pneumostomach in all patients. Median arterial CO_2 pressure before and after PEG was 42.1 and 45.5 Torr (NS). The median abdominal girth before and after PEG was 68.1 and 69.6 cm (NS). A mild free gas image after PEG was observed in two patients. SPACE might enabled standardized pneumostomach which leads to easier and safer PEG procedures.

Imaeda H, Nakajima K, Hosoe N, Nakahara M, Zushi S, Kato M, Kashiwagi K, Matsumoto Y, Kimura K, Nakamura R, Wada N, Tsujii M, Yahagi N, Hibi T, Kanai T, Takehara T, Ogata H. Percutaneous endoscopic gastrostomy under steady pressure automatically controlled endoscopy: First clinical series. *World J Gastrointest Endosc* 2016; 8(3): 186-191 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i3/186.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i3.186

INTRODUCTION

Percutaneous endoscopic gastrostomy (PEG) has been widely accepted for external feeding since Gauderer *et al*[1] first reported it in 1980. A conventional on-demand insufflation using atmospheric air through the endoscope has been a gold standard in performing PEG, not only for optimal visualization but also for maintaining pneumostomach to keep puncture sites on the gastric/abdominal walls stabilized. Abdominal distension and pneumoperitoneum often occur after PEG[2-7]. Carbon dioxide (CO_2) insufflation has been initially reported for colonoscopic electrosurgical polypectomy in the field of gastrointestinal (GI) endoscopy[8]. CO_2 is now increasingly being used instead of atmospheric air in GI endoscopic procedures since CO_2 is rapidly absorbed *via* the gut lining. Total colonoscopy[9-13], endoscopic retrograde cholangiopanreatography[14-17], peroral cholangioscopy[18], double-balloon enteroscopy[19], PEG[20], gastric and colonic endoscopic submucosal dissection (ESD)[21-25], and upper GI intragastric endoscopy during laparoscopic surgery under CO_2 insufflation[26] have been reported to be safe and more comfortable compared with air insufflation.

GI endoscopy has been performed under on-demand insufflation by endoscopists through the endoscope itself in a manual manner without pressure monitoring. This practice has been justified because the gastrointestinal tract allows migration of excessive gas into the upstream/downstream bowel. Excessive air supply may result in gaseous regurgitation, vomiting, and abdominal bloating. Steady pressure automatically controlled endoscopy (SPACE) using CO_2, developed by Nakajima *et al*[27,28], Kato *et al*[29] and Yamada *et al*[30] is expected to improve and standardize endoscopic visualization and working space in the GI lumen. Although SPACE has been reported to shorten procedural time and improve the safety of endoscopic intervention[28-30], CO_2 narcosis is of concern during PEG under sedation, since patients usually suffer from respiratory disease and/or consciousness disturbance. The SPACE system consists of a standard commercially available endoscope overtube (Top Co., Ltd., Tokyo, Japan) and a newly developed detachable leak-proof device with an anti-reflux valve and a Luer lock connection (Leak Cutter, Top)[28,29]. A commercially available automatic surgical insufflator is then connected to the system. Esophageal ESD under SPACE has been reported to be feasible and safe[28,29]. Recently, gastric ESD under SPACE has been also reported to be feasible and safe in an preclinical study[30].

The aim of this study is to elucidate the safety of PEG under the SPACE system. To our knowledge, this is the first clinical study regarding application of SPACE technology in PEG.

MATERIALS AND METHODS

Ten patients undergoing treatment at our institutions were enrolled in the study. Patients who had CO_2 retention due to chronic obstructive pulmonary dysfunction were excluded. One of the ten enrolled patients was excluded because he withdrew his consent after informed consent

Table 1 Clinical characteristic of patients

Clinical characteristics	Data
Male/female	6/3
Mean age	78 (61–89)
Comorbid disease	
Parkinson's disease	4
Cerebrovascular disease	1
Amyotrophic lateral sclerosis	1
Necrotizing fasciitis	1
Disuse syndrome	1
Laryngeal cancer	1

was obtained. Therefore, a total of nine patients, six males and three females, underwent PEG under SPACE. The mean age of patients was 78 years (ranging from 61 to 89). Four patients had Parkinson's disease, one had cerebrovascular disease, one had amyotrophic lateral sclerosis, one had necrotizing fasciitis, one had disuse syndrome, and one had laryngeal cancer (Table 1).

PEG was performed under conscious sedation using intravenous injection of 35 mg pethidine chloride and 0.1-0.2 mg of flunitrazepam or 1-2 mg of midazolam and oxygen inhalation. A T-tube with two junctions (MD-807, Olympus Medical Systems Co. Ltd., Tokyo, Japan) was connected directly to the channel of the flexible gastroscope (GIF-H260, Olympus Medical Systems Co. Ltd., Tokyo, Japan) (Figure 1). One of the junctions was connected to a commercially available automatic surgical insufflator (UHI-3, Olympus Medical Systems Co. Ltd., Tokyo, Japan) that feeds 35 L of CO_2 per minute into the stomach through the channel (Figure 2). The intragastric pressure was kept between 4-8 mmHg. PEG was performed using a modified introducer procedure and a dedicated kit (Direct Ideal PEG kit, Olympus Medical Systems Co. Ltd., Tokyo, Japan). The gastroscope was inserted from the mouth to the esophagus under conventional manual air insufflation. After insertion into the stomach, conventional manual air insufflation was switched to the SPACE system. First, percutaneous gastropexy was conducted at two sites while the stomach was inflated under the SPACE system through the endoscope channel. Second, after puncture using an indwelling needle was performed between the two gastropexy sites, a guide-wire was replaced with the needle. Third, the PEG site was dilated by the dilator through the guide-wire. When the dilator was withdrawn, the CO_2 supply was temporarily stopped, the PEG tube was inserted through the guide-wire, and the CO_2 supply was restarted and checked to ensure it had been located correctly.

Data such as mean procedure time, intragastric pressure, mean systolic blood pressure, partial pressure of CO_2 ($PaCO_2$), abdominal circumference before and soon after PEG, and change of free gas and small intestinal gas on abdominal X-ray before and immediately after PEG were obtained and prospectively recorded in the database.

Figure 1 T-tube attached to the endoscopic channel.

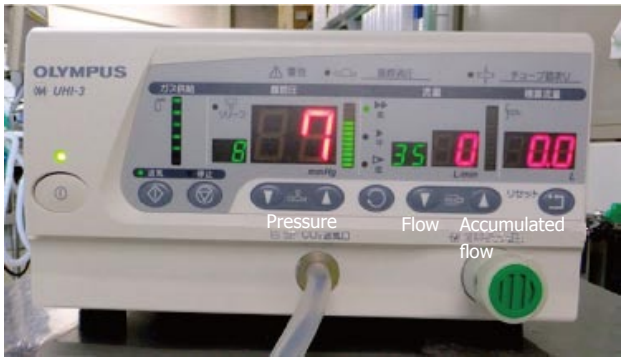

Figure 2 Automatic surgical insufflator connected to the T-tube.

The study protocol was in accordance with the tenets of the revised Declaration of Helsinki (1989) and was approved by the institutional review board at our institutions. Written informed consent was obtained from all the patients.

Statistical analysis

Statistical analysis was performed by Fischer's test using SPSS software, version 17 (SPSS Inc., Chicago, IL). For therapeutic performance, sensitivity, specificity, and accuracy are presented as percentages with 95%CIs. All probability values calculated in this analysis were sided, and $P < 0.05$ was considered significant.

RESULTS

The median procedural time was 22 min (14-38 min) (Table 2). It was possible to maintain a good endoscopic visualization and a sufficient pneumostomach to keep puncture sites stabilized during PEG, which was completed easily in all 9 patients. Visualization after intentional suction was regained more quickly than with conventional endoscopy (Video 1). PEG was established exactly in the scheduled puncture sites. Median intragastric pressure was kept at 6.9 mmHg as preset (5-8 mmHg). Median O_2 inhalation was 1.7 L/min (0-3). Median systolic blood pressure before and immediately after PEG was 129.3 mmHg (101-158 mmHg) and 120.6 mmHg (90-145

Table 2 Results of percutaneous endoscopic gastrostomy under steady pressure automatically controlled endoscopy

Clinical outcomes		*P* value
Median procedural time (min)	22 (14-38)	
Median intragastric pressure (mmHg)	6.9 (5-8)	
Median systolic pressure		
Before PEG (mmHg)	129.3 (101-158)	
Soon after PEG (mmHg)	120.6 (90-145)	0.33
Median $PaCO_2$		
Before PEG (Torr)	42.1 (35.2-45.7)	
Soon after PEG (Torr)	45.5 (41.0-54.6)	0.10
Median abdominal girth		
Before PEG (cm)	68.1 (58-85)	
Soon after PEG (cm)	69.6 (60-86)	0.38
Mild free gas after PEG (*n*)	2	
Mild increase of small intestinal gas after PEG (*n*)	2	

PEG: Percutaneous endoscopic gastrostomy.

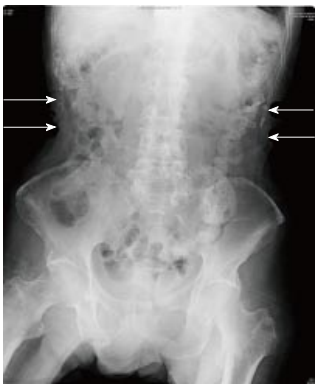

Figure 3 Free air (indicated by arrows) in abdominal X-ray after percutaneous endoscopic gastrostomy under steady pressure automatically controlled endoscopy.

mmHg). There was no significant difference in these data (P = 0.33). Median $PaCO_2$ before and after PEG was 42.1 Torr (35.2-45.7 Torr) and 45.5 Torr (41.0-54.6 Torr). There was a tendency to an elevated median $PaCO_2$ after PEG compared with prior values (P = 0.10); however no CO_2 narcosis was encountered in the series.

The median abdominal girth before and immediately after PEG was 68.1 cm (58-85 cm) and 69.6 cm (60-86 cm), and there was no significant difference (P = 0.38). Mild free gas was observed postoperatively in two patients, and small intestinal gas was slightly increased in two patients (Figure 3). All these were subclinical, and no other serious adverse events were encountered in any patients.

DISCUSSION

Several endoscopic procedures under CO_2 insufflation have been reported to be safe and more comfortable compared with air insufflation because CO_2 is absorbed rapidly *via* the gut lining. CO_2 insufflation during PEG reduces risk of pneumoperitonium and bloating[8-25]. Technically, it is a key point to maintain pneumostomach stabilized during PEG so that PEG can be fashioned in the scheduled puncture sites.

In our study, although $PaCO_2$ was subclinically elevated during and after the procedure, there were no adverse events associated with CO_2 insufflation. The insufflation is mandatory in PEG for maintaining a pneumostomach to keep puncture sites stabilized. Nishiwaki *et al*[20] reported that PEG under CO_2 insufflation compared with air insufflation was safer and more comfortable because of the lower incidence of pneumoperitoneum, less distension of the small bowel, and no adverse events. Our present data first showed that PEG is safely fashioned under SPACE.

Nakajima *et al*[27] reported that a steady-pressure pneumostomach was successfully created and maintained for 100 min on average without clamping the downstream bowel in laparoscopic intragastric surgery (LIGS). The stomach was insufflated with a UHI-3 surgical insufflation unit connected to a transgastric port at an intragastric pressure of 6-8 mmHg. No adverse events were noted during LIGS, and no postoperative abdominal distention was observed. Nakajima *et al*[28] have also reported esophageal ESD under SPACE using a standard endoscopic overtube and a detachable leak-proof valve with a luer-lock connection in an animal model. Moreover, Kato *et al*[29] reported on the feasibility and safety of esophageal ESD under SPACE in a clinical study, and Yamada *et al*[30] reported on the feasibility and safety of gastric ESD under SPACE in an animal model. In SPACE, endoscopic visualization is automatically obtained once the insufflation pressure and flow rate are set. Visualization after suction is automatically regained more quickly than with conventional endoscopy. The flow capacity of current surgical insufflators is higher than that of manual endoscopic insufflators and is considered responsible for the rapid regaining. UHI-3 can supply 35 L of CO_2 per minute and these flow rates are significantly higher than those of actual endoscopic flow with manual CO_2 insufflation (1.4 L/min). The insufflation process is automatic in SPACE. Air/water button manipulation is no longer necessary, leaving the endoscopist free to focus on the intervention itself. SPACE can prevent excessive CO_2 supply, which may result in gaseous regurgitation, vomiting, and abdominal bloating[30].

In this study, CO_2 was successfully supplied through the endoscopic channel using a T-tube without an overtube. The intragastric pressure was kept from 5 to 8 mmHg throughout the procedure. PEG under SPACE had no negative effects such as vomiting or abdominal bloating and no impact on vital signs. Mild postprocedural free gas was observed in two patients and abdominal gas was slightly increased in another two patients. There were, however, no adverse events in any patients. Even if CO_2 is leaked into the abdominal cavity through the PEG site, CO_2 can be absorbed quickly *via* the peritoneal lining and abdominal distention will be resolved immediately. Nishiwaki *et al*[20] reported that pneumoperitoneum was

not observed in the CO_2 insufflation group. In our study, pneumoperitoneum might have occurred because of the leakage of remnant air in the stomach. Nishiwaki *et al*[20] performed a pull method of the PEG procedure, while in our study, a modified introducer method was performed. After the dilator was withdrawn, the PEG tube was inserted during the modified introducer method, and it was possible that intragastric gas (air) might have leaked into the abdominal cavity at this time. Thus we hypothesized that postprocedural pneumoperitoneum might be caused by the difference of the PEG procedure. Yamada *et al*[30] reported the potential safety of pneumoperitoneum under SPACE, because intra-gastric pressure was regulated within the preset pressure range to prevent excessive transmural insufflation. Nakajima *et al*[28] have reported that the migration of CO_2 over the proximal jejunum does not occur because of a pinch-cock phenomenon and intestinal surface tension. In this pinch-cock phenomenon, the distended upstream bowel (stomach and duodenum) acts as a cock that compresses the downstream bowel, resulting in the prevention of massive gas migration. The surface tension in the collapsed gut lumen may work as another pressure barrier. The insufflated gas volume was sufficiently low in each SPACE, suggesting no major gas migration into the downstream bowel during SPACE. In fact, CO_2 outflow stopped automatically whenever the stomach was insufflated.

Although conscious sedation is necessary during PEG procedure, most patients who undergo PEG have cerebrovascular diseases and aspiration pneumonia, which means they are at high risk for developing respiratory dysfunction. CO_2 narcosis might develop in patients with chronic pulmonary diseases, so they were excluded from this study. There was a tendency to an elevated $PaCO_2$ median after PEG compared with before PEG, but CO_2 narcosis did not occur in any cases. This elevation might be caused by PEG under SPACE, but it could also be caused by the administration of sedative drugs that suppress the respiratory function.

There were several limitations in this study. First, as this was a pilot study, the sample size was very small. We need to accumulate more clinical data such as a randomized controlled trial between PEG under conventional manual air or CO_2 insufflation and that under SPACE system in near future. There was a tendency to an elevated median $PaCO_2$ after PEG compared with previous values, indicating that a randomized controlled trial to compare PEG under SPACE and under manual air insufflation is necessary. We examined $PaCO_2$ only twice: once before and once after PEG. Ideally we should examine the course of PCO_2 during PEG using the monitor of transcutaneous measurement of PCO_2. Most patients cannot complain of abdominal pain or distention because of comorbid diseases such as cerebrovascular disease, so the complaints of all patients cannot be detected. We have to examine the gas volume in the small intestine and the pneumoperitoneum in the abdominal X-ray and/or CT scan. The channel is free during a modified introducer procedure of PEG, therefore, the SPACE system is available during PEG procedure. The introduction of snares or forceps through the channel affects the SPACE system.

In conclusion, PEG under SPACE might be feasible and safe. SPACE might enable standardized pneumostomach which leads to easier and safer PEG procedures.

COMMENTS

Background

"On-demand" insufflation using atmospheric air has been a gold standard in performing percutaneous endoscopic gastrostomy (PEG), not only for optimal visualization but also for maintaining pneumostomach to keep puncture sites stabilized. However, excessive air insufflation may result in gaseous regurgitation, vomiting, and abdominal bloating.

Research frontiers

PEG under steady pressure automatically controlled endoscopy (SPACE) using carbon dioxide (CO_2) has not been reported.

Innovations and breakthroughs

PEG under SPACE was feasible and safe.

Applications

SPACE enables standardized pneumostomach which leads to easier and safer PEG procedures.

Peer-review

The authors evaluated the safety of PEG under SPACE using CO_2. PEG was completed under stable pneumostomach in all nine patients. Further clinical trials in a randomized controlled study between PEG under conventional manual air or CO_2 insufflation and that under SPACE system will be necessary.

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CASE REPORT

Endoscopic ultrasound-guided ethanol ablation of pancreatic neuroendocrine tumours: A case study and literature review

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Author contributions: Armellini E performed the endoscopic procedures; Ballarè M, Pallio S and Occhipinti P collected and analyzed the data; Armellini E and Crinò SF wrote the paper and contributed equally to this manuscript.

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Abstract

Here we offer a review of the literature regarding endoscopic ultrasound-guided ethanol ablation for pancreatic neuroendocrine tumours and describe the case of a cystic tumour completely ablated after a multisession procedure. A total of 35 PubMed indexed cases of treated functioning and non-functioning pancreatic neuroendocrine tumours resulted from our search, 29 of which are well-documented and summarised. Endoscopic ultrasound-guided ethanol ablation appears as a local, minimally invasive treatment of pancreatic neuroendocrine tumours, suitable for selected patients. This technique appears feasible, relatively safe and efficient, especially when applied to symptom relief in functioning tumours, aiming at loss of endocrine secretion. For non-functioning tumours, where the goal is complete tissue ablation, eus guided ethanol ablation can provide good results for patients who are unfit for surgery or for those who refuse surgical resection. Its role in "fit for surgery" patients requires assessment through further studies.

Key words: Endoscopic ultrasound; Pancreatic neuroendocrine tumour; Endoscopic ultrasound-guided injection; Ethanol; Tumour ablation

Core tip: We report a complete review of the literature about endoscopic ultrasound-guided ethanol ablation for pancreatic neuroendocrine tumours. The case of a cystic tumour completely ablated after a multisession procedure is described. On long term follow-up a durable

remission of the tumour was obtained; a complete image gallery showing the pre and post-treatment appearance is available. The technical aspects, clinical success and complication rates related to this kind of procedures are described.

Armellini E, Crinò SF, Ballarè M, Pallio S, Occhipinti P. Endoscopic ultrasound-guided ethanol ablation of pancreatic neuroendocrine tumours: A case study and literature review. *World J Gastrointest Endosc* 2016; 8(3): 192-197 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i3/192.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i3.192

INTRODUCTION

In recent years the improvement of diagnostic and therapeutic technologies has led to less invasive treatments in any field of medicine with a shift from surgery to imaging guided treatments.

Endoscopic ultrasonography (EUS) has demonstrated excellent diagnostic accuracy for bilio-pancreatic district diseases and high safety and precision when applied for operative purposes. Along the years this peculiarity has made of EUS an optimal technique for imaging and cytological diagnosis, as well as for execution of more advanced procedures (*i.e.*, drainages and local treatments).

The current management of T1 and T2 pancreatic neuroendocrine tumours (pNETs) is somewhat similar to that of most pancreatic tumours (surgical resection), with a considerable economic burden and post-operative complications. However we are dealing with a pathology that offers a better prognosis and that is potentially responsive to local treatments[1,2].

Neuroendocrine tumours arise from cells present in the diffuse endocrine system and can be found throughout the body. They are most commonly located in the gastrointestinal tract and lung but are also found in the pancreas[3]. The 2010 World Health Organization (WHO) classification divides the pNETs in three grades (G1, G2 and G3) on the basis of Ki-67 nuclear antigen expression (< 2%; 2%-20% and > 20%) and mitotic rate (< 2; 2-20 and > 20). Biopsy is most commonly used to assess the grade of the tumour. According to the TNM, the tumour is classified as T1a (< 1 cm), T1b (1-2 cm) and T2 (larger than 2 cm); T3 and T4 are locally advanced tumours (Table 1).

Tumour grading and tumour stage are the main prognostic factors of pNETs. Well and moderately differentiated have a significantly better survival compared to poorly differentiated neuroendocrine carcinomas.

pNETs are also classified as functioning and non-functioning depending on the secretion of specific hormones. Functioning tumours are commonly associated with a specific hormonal syndrome directly related to a hormone secreted by the neoplasm such as insulinomas with ipoglicemia, gastrinomas with Zollinger–Ellison or carcinoid syndrome. Most non-functioning tumours occur in the head of the pancreas and produce mass effect symptoms. When small, they are usually incidentally discovered due to the incremental use of high-level diagnostic imaging.

Table 1 World Health Organization classification of pancreatic neuroendocrine tumors

Grade	Ki-67 index (%)	Mitotic count/10 HPF
G1	≤ 2	< 2
G2	3-20	2-20
G3	> 20	> 20
TNM	Size (cm)	Muscularis propria invasion
T1a	< 1	–
T1b	1-2	–
T2	> 2	+

Accordingly to the WHO classification 2010, the higher grade is assumed if the Ki-67 index and mitotic count differ; in the WHO 2010 TNM, the tumor is classified as T2 if it is larger than 2 cm in diameter or if it invades the muscularis propria. T3 and T4 tumors are locally aggressive tumors. WHO: World Health Organization; HPF: High-power field.

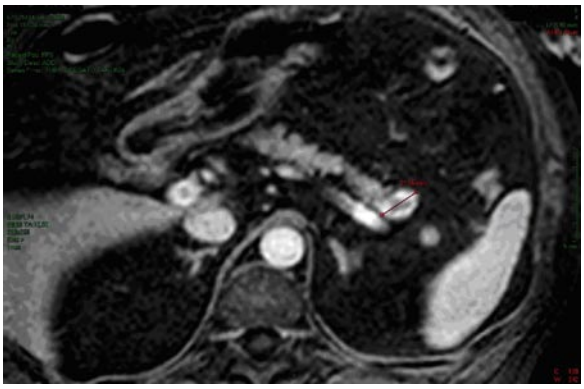

Figure 1 Abdominal magnetic resonance imaging demonstrating a round, well-demarcated nodule of the pancreatic tail. The 22 mm lesion (calipers) shows highly vascularised peripheral tissue.

EUS is the optimal diagnostic modality and can provide a biopsy specimen for histological confirmation and differentiation grade. The EUS image is usually of a solid, ipoechoic, round and smooth nodule, sometimes with a cystic central component (bull's eye appearance).

To date, the management of pancreatic sporadic, small (< 2 cm), asymptomatic, low-grade (G1) NETs suggests a "wait and see" strategy. Surgical resection of non-functioning pNETs is actually recommended for large (> 2 cm) or G2-G3 lesions[4]. For patients unfit for surgery due to high-risk comorbidity or for those who refuse resection, the EUS-guided ethanol ablation has been reported in a few cases[5] as a local and minimally invasive therapy.

CASE REPORT

A 58-year-old man with essential hypertension and recent onset of glucose intolerance was referred for a

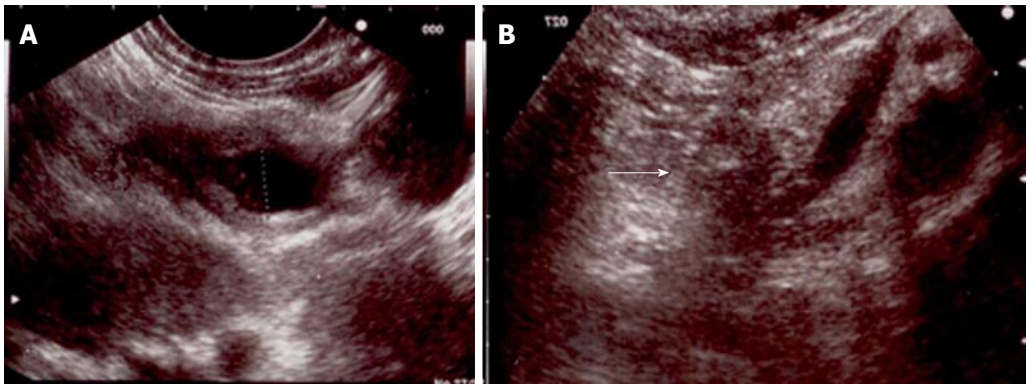

Figure 2 Endoscopic ultrasound appearances before (A) and after (B) treatment (white arrow).

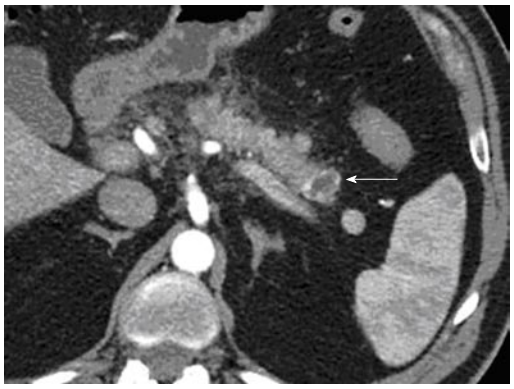

Figure 3 Computed tomography scan showing thin residual hypervascular tissue (white arrow) two months after the first treatment.

transabdominal ultrasonography (US). Other laboratory test results including levels of carcinoembryonic antigen and carbohydrate antigen were all within normal ranges. The US session diagnosed a focal lesion on the pancreatic tail. An abdominal magnetic resonance image showed a 22 mm nodule with peripheral hypervascularization (Figure 1), and EUS confirmed a "bull's-eye" appearance nodule with peripheral hypervascular pattern *via* power Doppler and a central cystic component. The EUS-guided FNA of the lesion confirmed the diagnosis of pNET. The Ki67 proliferative index was > 5% to yield a G2 grade. However, because the patient adamantly refused surgical resection, we decided to ablate the lesion *via* EUS-guided ethanol injection.

After aspiration of the cystic component, a mean volume of 1.7 mL of 95% ethanol per session was injected into the tumour and re-aspirated using a 25-gauge needle (Echo-tip ultra, Cook, Limerick, Ireland) through a linear array echoendoscope (Figure 2). Three treatment sessions over six months were performed to ablate the nodule (Figure 3).

The hospitalization time was 2 d for each session. The patient experienced mild pancreatitis in 2 out of 3 sessions - that resolved with standard-of-care. No major or late complications were observed. After 24 mo, we achieved a durable and complete remission of the tumour as shown by CT and EUS morphological imaging (Figure 4).

DISCUSSION

Most diagnosed pNETs are non-functioning tumours (90.8%); the remaining 9% are malignant functioning tumours such as gastrinomas (4.2%), insulinomas (2.5%), glucagonomas (1.6%), and VIPomas (0.9%). Although commonly perceived to be indolent tumours, they exhibit a broad range of growth rates, malignant potential, and overall prognosis. Most patients with pNETs (60%-70%) present with metastatic disease at diagnosis. Following surgical resection, the 5-year cumulative survival for pNETs other than insulinomas is roughly 65% with a 10-year survival of 45%[6].

Patients with incidental diagnosis of pNETs with a tumour size < 2 cm and low-grade (G1) dysplasia have a 5-year overall survival of 100% with a minimal risk of recurrence[6]. In this setting, a "wait and see" policy is recommended.

On the contrary, surgical resection is the standard treatment for functioning and non-functioning G2-G3 pNETs. However, this is associated with a high risk of complications. Even when performed in high-volume centres, typical pancreatic resections (pancreaticoduodenectomy or distal pancreatectomy) have a mortality rate of about 5% with complications ranging from 40% to 50%[7]. This is particularly common in the elderly or patients with comorbidities. Typical pancreatic resections are also associated with a high incidence of exocrine and endocrine insufficiency.

In an attempt to reduce complications and pancreatic impairment, new parenchyma-sparing resection techniques such as enucleation and middle pancreatectomy (resection of the central part of the gland) have been applied to small tumours[8]. Although pancreatic head tumour enucleation resulted in decreased operative time and length of hospitalization, the 5-year survival and overall morbidity and mortality were comparable to standard surgical resection even for small pNETs[9]. To date, no alternative treatment has been standardized for patients unfit for surgery or for those who refuse

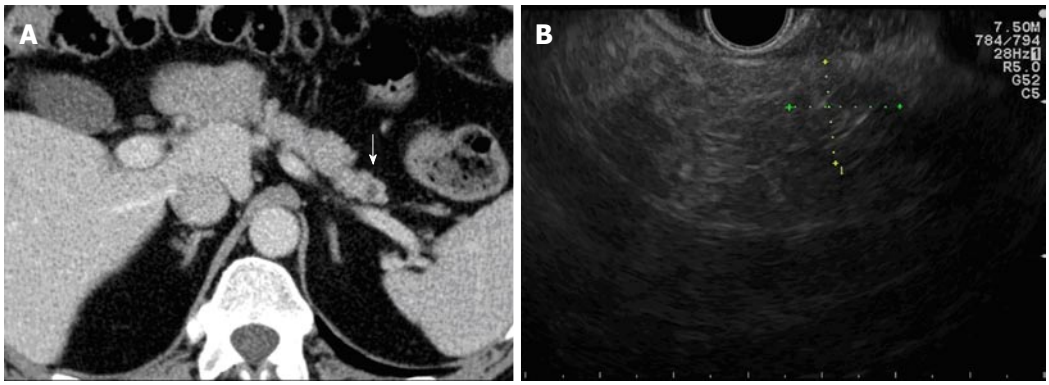

Figure 4 Twenty-four months follow-up. A: Computed tomography scan showing absence of hypervascular tissue around a small hypodense area (white arrow); B: Endoscopic ultrasound scan of the pancreatic tail demonstrating poorly defined hyperechoic tissue (fibrosis) with posterior shadow (caliper).

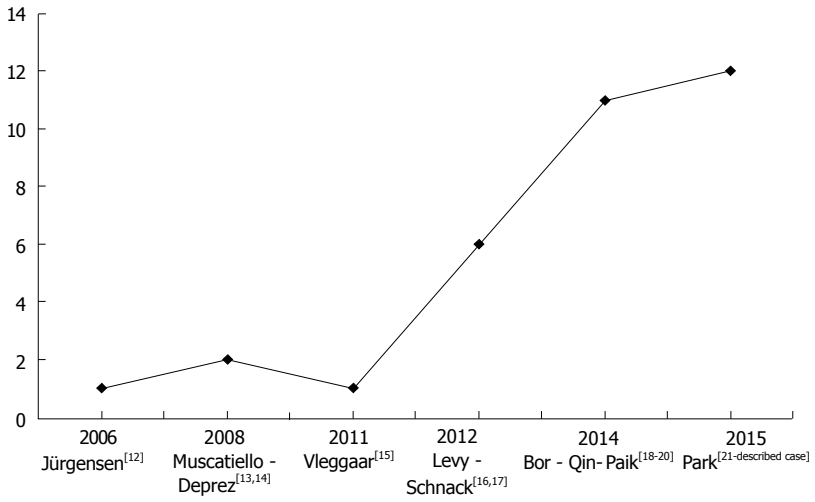

Figure 5 Reported endoscopic ultrasound-guided ethanol ablation procedures over time. Literature review showed a progressive increase of performed procedures from 2006 to 2015. Cases described in abstract form by Paik *et al*[20] were not included in the final results analysis.

resection.

In the recent decades, EUS has evolved into a useful therapeutic tool for treating a broad range of tumours. EUS-guided injection has been applied both as a pancreatic cancer treatment aimed at controlling pain through nerve blockade as well as a solid tumour therapy for the introduction of brachytherapy seeds and viral vectors or as a tool for ablation therapy[10,11]. The pNET EUS-guided ethanol ablation is a new, less invasive therapeutic option although it remains rare.

A PubMed literature review showed 26 patients affected by small pNETs (maximum diameter of 21 mm) who underwent EUS-guided ethanol ablation[12-21] including 19 functioning and 10 non-functioning tumours (Table 2). The number of patients treated by this tecnique progressively increased from 2006 to 2015 (Figure 5).

Conscious sedation is generally reported during the procedure. A mean hospitalization time of 2 d/session is usually necessary even in the absence of complications.

Technical success is reported in 100% of cases; a 22 or 25 gauge needle was generally used to inject a small volume of ethanol with a range between 0.2 and 8 mL per session. The choice of ethanol volume is a function of tumour size. For small ($\leqslant$ 20 mm) tumours, Qin *et al*[19] suggested that the volume be calculated as follows. For round tumours, the volume of ethanol corresponds to half the tumour size; for oval or irregular tumours, the volume of ethanol is (major axis + minor axis of the tumour)/2. A 1.0 mL syringe should be used for precise injection.

In terms of therapeutic outcomes, differentiation of functioning and non-functioning tumours seems to be very important. For small functioning symptomatic G1 tumours, the aim of the ablation is the symptom relief. For non-functioning tumours, the treatment goal is complete ablation of the lesion as confirmed by imaging.

Including the case here described, this technique achieved clinical success (complete symptom resolution) in 100% of 19 functioning tumours with a mean follow-up of 13.6 mo (range 2-38). Ethanol ablation is less effective for non-functioning tumours with a reported success (complete radiological ablation) of 70% (7/10 tumours were ablated, one lost to follow-up) with a mean follow-up of 13.4 mo (range 3-24) (Table 2). The reason is unclear but it might be due to a "debulking" effect in functioning ones, resulting in loss of endocrine

Table 2 Patient demographic information and baseline characteristics of the tumours

No. of patients[1]	27
Age, yr	
Mean (range)	59 (27-89)
Sex, male/female	10-17
No. of tumors	30
Functioning	19
Non functioning	11
Type of functioning tumor	
Insulinoma	18
Vipoma	1
Diameter, mm	
Mean (range)	12.5 (5-22)

[1]Including described case.

Table 3 Procedural outcomes

No. of treatment session per tumor	
Mean (range)	1.43 (1-3)
Alcohol volume, mL	
Mean (range)	1.83 (0.18-8)
Technical success, *n* (%)	30/30 (100)
Clinical success[1], *n* (%)	
Functioning	19/19 (100)
Non functioning[2]	7/10 (70)
Adverse events[3], *n* (%)	11 (25.5)
Early (within one week), *n* (%)	9 (21)
Pancreatic necrotic lesion	1 (2.3)
Mild pancreatitis	7 (16.2)
Abdominal pain	1 (2.3)
Late, *n* (%)	2 (4.6)
Hematoma and ulceration of the duodenal wall	1 (2.3)
Main pancreatic duct stricture	1 (2.3)
Follow-up, mo	
Mean (range)	13.4 (2-38)

[1]Clinical success: Symptom resolution for functioning tumours and radiological ablation for non-functioning tumour; [2]One non functioning tumor was lost to follow-up; [3]Adverse events percentage is intended in relation to procedure number.

secretion, although with persistent viable tissue, or to a more aggressive histological grading of non-functioning tumours. Unfortunately, lesion grading was not available in most of the reviewed cases.

Few early complications (within one week) are reported: 7 mild pancreatitis cases were observed (16.2%) out of 43 procedures. One (2.3%) major early complication was described[13]: A pancreatic necrotic lesion that was likely caused by ethanol effusion. It was managed by laparoscopic necrosectomy.

Two (4.6%) late complications occurred: One hematoma and ulceration of the duodenal wall[14] and main pancreatic duct stricture[21]. These were managed by endoscopic retrograde cholangiopancreatography and stent placement (Table 3).

In our case, we achieved a diagnosis of a non-functioning pNET with moderate dysplasia, grade (G2), established on the basis of biopsy (Ki67 > 5%) in a 58-year-old male who refused surgery. We decided to ablate based both on the grading and the age of the patient. Moreover it is worth noting that FNA cytology may underestimate the staging based on surgical specimens. Physicians should be very cautious in using FNA specimens to classify a tumour as low-grade[22]. Consequently our treatment aimed at the complete ablation of the lesion while sparing the pancreatic parenchyma. The nodule we treated had a cystic central component, which has not yet been described in the literature for pNET EUS-guidance ablation. A tecnique similar to that described for cystic neoplasm ablation (ethanol injection and reaspiration) was used.

In conclusion, based on our case study and literature review, we find that this technique is feasible, relatively safe and efficient when applied to symptom relief in functioning tumours. However, the long-term outcomes remain unknown. For non-functioning tumours, it can provide good results for patients unfit for surgery or for those who refuse surgical resection. Its role in "fit for surgery" patients is still undefined and larger comparative studies with long-term follow-up are needed to assess its role.

COMMENTS

Case characteristics

The authors describe a procedure of eus guided ethanol ablation along three sessions for a cystic pancreatic neuroendocrine tumours (pNET).

Clinical diagnosis

Incidental focal lesion of the pancreatic tail with endoscopic ultrasound (EUS) "bull's eye appearance" and peripheral hypervascularization, suspicious for neuroendocrine tumour.

Differential diagnosis

Other focal lesions of the pancreas.

Laboratory diagnosis

No lab abnormality including levels of carcinoembryonic antigen and carbohydrate antigen, but recent onset of glucose intolerance.

Imaging diagnosis

Abdominal ultrasound, endoscopic ultrasound, magnetic resonance, EUS guided FNA.

Pathological diagnosis

Neuroendocrine tumor, G2, Ki67 proliferative index > 5%.

Treatment

The authors treated the patient by EUS-guided ethanol injection along three sessions.

Related reports

For patients unfit for surgery due to high-risk comorbidity or for those who refuse resection EUS-guided ethanol ablation has been reported in a few cases.

Term explanation

pNETS: Pancreatic neuroendocrine tumours; EUS: Endoscopic ultrasound.

Experiences and lessons

The authors find that EUS guided ethanol ablation is relatively safe and efficient

for the treatment of pNETs in patients unfit for surgery or for those who refuse surgical resection. Its role in "fit for surgery" patients is still undefined.

Peer-review

A well written paper having a clear endpoint and objectives. The review of the literature is complete and presented in an attractive way.

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