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MINIREVIEWS

Confocal endomicroscopy and cyst fluid molecular analysis: Comprehensive evaluation of pancreatic cysts

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Abstract

Increases in the quality as well as utilization of cross-sectional imaging have led to rising diagnoses of pancreatic cystic lesions (PCL). Accurate presurgical diagnosis enables appropriate triage of PCLs. Unfortunately, current diagnostic approaches have sub-optimal accuracy and may lead to unnecessary surgical resections or missed diagnoses of advanced neoplasia. Additionally, early detection represents an opportunity for intervention to prevent the progression to pancreatic adenocarcinoma. Our aim for this review is to systematically review the current literature on confocal endomicroscopy and molecular biomarkers in the evaluation of PCLs. Confocal laser endomicroscopy is a novel technology that allows for real-time *in vivo* microscopic imaging with multiple clinical trials identifying characteristic endomicroscopy findings of various pancreatic cystic lesions. DNA-based molecular markers have also emerged as another diagnostic modality as the pattern of genetic alternations present in cyst fluid can provide both diagnostic and prognostic data. We propose that both techniques can be utilized to improve patient outcomes.

Key words: Pancreas; Pancreatic cyst; Pancreatic adenocarcinoma; Confocal endomicroscopy; Next generation sequencing; Molecular marker

Core tip: Current diagnostic guidelines for the evaluation of pancreatic cystic lesions have suboptimal accuracy and may lead to unnecessary surgical resections or missed diagnoses of advanced neoplasia. We propose that two new diagnostic technologies, confocal laser endomicroscopy and DNA-based molecular markers, may be used synergistically to improve diagnostic accuracy. In this review, we summarize the current literature regarding these two techniques.

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INTRODUCTION

Increases in the quality as well as utilization of cross-sectional imaging have led to rising diagnoses of pancreatic cystic lesions (PCL) with a reported incidence ranging from 2.4%-19.6%[1-3]. Unfortunately, current diagnostic approaches have suboptimal accuracy and may lead to unnecessary surgical resections or missed diagnoses of advanced neoplasia[4]. Accurate pre-surgical diagnosis enables appropriate triage of PCLs, allowing for surveillance of lower-risk lesions and surgical resection of high-risk lesions. Additionally, early detection represents an opportunity for intervention to prevent the progression to pancreatic adenocarcinoma. Our aim for this review is to summarize the current literature on confocal endomicroscopy and molecular biomarkers in the evaluation of PCLs. We propose that both techniques can be complementary to improve patient outcomes.

CURRENT KNOWLEDGE

Pancreatic cysts can be divided into mucinous cysts [intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasm (MCN)], non-mucinous cystic neoplasms [serous cystadenoma (SCA), pseudocysts], cystic neuroendocrine tumors (cystic-NETs), and solid pseudopapillary neoplasm (SPN)[5]. Each of these lesions have unique characteristics and malignancy potential requiring different management strategies.

The current standard of care in the evaluation of PCLs utilizes a multimodality approach, including clinical and radiographic assessment, Endoscopic ultrasound (EUS)-guided fine needle aspiration (EUS-FNA), cyst fluid analysis (*i.e.,* tumor markers such as CEA), and cytology. Despite these techniques, the pre-surgical differentiation of PCLs remains challenging with continued need for improved diagnostic accuracy. A landmark prospective study comparing cyst fluid CEA, cytology, and EUS showed that that cyst fluid CEA > 192 ng/mL had a diagnostic accuracy of 79.2%, cytology had a diagnostic accuracy of 58.7%, and EUS morphology had a diagnostic accuracy of 50.9%[6]. However, a more recent, larger multicenter retrospective study showed that a CEA cutoff of 192 ng/mL for the diagnosis of mucinous cysts resulted in a sensitivity of only 61%[7].

In an effort to improve diagnostic accuracy, multiple guidelines have been developed over the past decade to assist in the management of PCLs, including the International Consensus Guidelines (Sendai 2006, Fukuoka 2012, and 2017 revision of the Fukuoka guidelines) and the American Gastroenterological Association (AGA) 2015 guidelines[8-10]. The 2006 Sendai guidelines recommended surgical resection of any suspected MCN, main duct IPMN, or mixed duct IPMN. Additional criteria for surgical resection included: clinical symptoms, dilated pancreatic duct ($\geqslant$ 6 mm), intracystic mural nodules, or positive cytology[8]. While the Sendai guidelines have a sensitivity approaching 100%, specificity is limited, ranging from 23%-31%[11,12]. In 2012, stricter surgical criteria were developed for the revised Fukuoka guidelines for IPMN and MCN including: pancreatic duct $\geqslant$ 10 mm, presence of an enhancing solid component, obstructive jaundice with a pancreatic cyst[9]. Although the Fukuoka guidelines were more specific compared to the Sendai guidelines, sensitivity was decreased. In a retrospective analysis, the updated Fukuoka (2012) guidelines were not superior to the Sendai guidelines for detection of invasive carcinoma or high-grade dysplasia[13].

Given these limitations, the AGA introduced guidelines in 2015 for the management of all asymptomatic neoplastic pancreatic cysts, whereas neither the Sendai nor the Fukuoka guidelines address the management of non-mucinous cysts. Compared to the Fukuoka guidelines, the AGA guidelines have a higher threshold for both endoscopic evaluation and surgical resection. EUS-FNA was recommended if 2 high-risk features were present, including size $\geqslant$ 3 cm, a dilated main pancreatic duct, or associated solid component. Surgical resection was recommended if a cyst had both a solid component and a dilated pancreatic duct and/or concerning features on EUS-FNA[10]. In a retrospective study of 225 patients who underwent EUS-FNA for pancreatic cysts, applying the AGA criteria detected advanced neoplasia with 62% sensitivity, 79% specificity, 57% positive predictive value, and 82% negative predictive value. Unfortunately, 45% of IPMNs with adenocarcinoma or high-grade dysplasia were missed[14].

In 2017, the International Consensus Group released updated guidelines regarding the prediction of invasive carcinoma and high-grade dysplasia, as well as the surveillance and post-operative follow-up of IPMNs. In the revised guidelines, increased serum CA19-9 and cyst growth rate greater than 5 mm in diameter over 2 years were added as "worrisome features" for BD-IPMN. These limitations show that current guidelines are suboptimal to accurately diagnose PCLs and additional imaging and molecular biomarkers are necessary to improve diagnostic accuracy of these increasingly

Table 1 Summary of major trials investigating role of endoscopic ultrasound guided needle based confocal laser endomicroscopy in the diagnosis of pancreatic cystic lesions

Study	Study outcome	Patients (*n*)	Surgery	Sensitivity	Specificity	Accuracy
Inspect[15]	Neoplastic cyst	66	14 (21.2%)	59	100	71
Detect[23]	Mucinous cyst	30	2 (6%)	80	100	89
Contact-1[19]	SCA	31	7 (22.5%)	69	100	87
Contact-2[17]	Mucinous cyst	33	9 (27.3%)	91	95	94
Index[24]	Mucinous cyst	30	22 (73.3%)	88	100	93

SCA: Serous cystadenoma.

prevalent lesions. EUS-guided needle-based confocal laser endomicroscopy (nCLE) and pancreatic cyst fluid molecular markers are promising new diagnostic modalities to aid in diagnosis and management of PCLs.

Imaging biomarkers for the evaluation of pancreatic cystic lesions

CLE is a novel technology that allows for real-time *in vivo* microscopic imaging. The CLE probe can be inserted through a 19-gauge FNA needle for real-time microscopic examination of the pancreatic cyst epithelium during EUS.

Multiple clinical trials have identified characteristic nCLE findings of various pancreatic cystic lesions (Table 1). For IPMN and MCN, characteristic findings include finger-like papillae and a single or layers of band-like epithelium, respectively[15-17]. *In vivo* and *ex vivo* nCLE findings for IPMN have been validated compared to surgical pathology as gold standard[18]. The finding of a "superficial vascular network" or "fern pattern" is highly specific for SCA[19,20]. Pseudocysts contain bright particles, corresponding to inflammatory cells, against a dark background due to the lack of a true cyst wall[17]. Cystic neuroendocrine tumors demonstrate high cellularity demonstrating trabeculae or cords of cells separated by fibrous bands[18]. More rare cystic lesions, such as those lined by squamous epithelium (lymphoepithelial cysts) have been characterized in case reports[21,22].

The INSPECT study was a pilot to assess the feasibility of nCLE in differentiating mucinous PCLs and establish safety[15]. The DETECT study's aim was to identify the feasibility, safety, diagnostic yield of cystoscopy and nCLE to diagnose PCLs using the consensus criteria developed for the INSPECT trial. The patients included in the study had clinical diagnoses of IPMN, MCN, pseudocyst, lymphoepithelial cyst, and retention cyst. The diagnosis of IPMN was supported by the identification of finger-like papillae[23]. The CONTACT-1 trial enrolled 31 patients with solitary pancreatic cystic lesions who underwent EUS-nCLE. The nCLE finding of a superficial vascular network, which correlated microscopically to a dense and subepithelial capillary vascularization, was only seen in SCA[19]. The CONTACT-2 study identified new nCLE criteria for MCN (epithelial bands), pancreatic pseudocysts (field of bright particles), and cystic neuroendocrine neoplasm (black cell clusters with white fibrous areas), which correlated with histologic features[17]. The INDEX trial validated the previously described nCLE findings in *ex vivo* CLE of resected PCLs; demonstrated substantial interobserver agreement for mucinous PCLs among nCLE-naïve observers; and established an "almost perfect" interobserver agreement and intraobserver reliability among external blinded observers for the detection of mucinous PCLs[24]. Based on the above studies and our experience, we have suggested an algorithm for evaluation of a PCL utilizing EUS-nCLE (Figure 1).

Pancreatic cyst fluid molecular biomarkers

Over the last decade, DNA-based molecular testing has emerged as a potent diagnostic modality for the assessment of PCLs. Analyzing the DNA present in the cyst fluid for the pattern of genetic alterations can provide both diagnostic and prognostic data regarding likelihood of progression to pancreatic adenocarcinoma[25,26].

There are three main components of molecular analysis: DNA quantity and quality, oncogenic mutations, loss of heterozygosity (LOH) of tumor suppressor genes. DNA quantity is determined by spectrophotometric analysis. By exposing the DNA sample to ultraviolet light, a photo-detector can be used to determine the quantity of nucleic acid in the sample. The concentration of DNA can be determined using the optical density ratio at a certain wavelength (260 of 280) light after extracting DNA from fluid. In a study of 113 patients with pancreatic cysts, elevated amounts of cyst fluid DNA were associated with malignancy[27]. Loss of heterozygosity results in loss of the entire gene and the surrounding chromosomal region. The detection of LOH by using microsatellite markers closely linked to key tumor suppressor genes correlates with gene inactivation and mutation, resulting in loss of tumor suppressor activity and development of malignancy[28].

Prior studies evaluating DNA testing of PCL fluid were limited by insensitive detection strategies (conventional

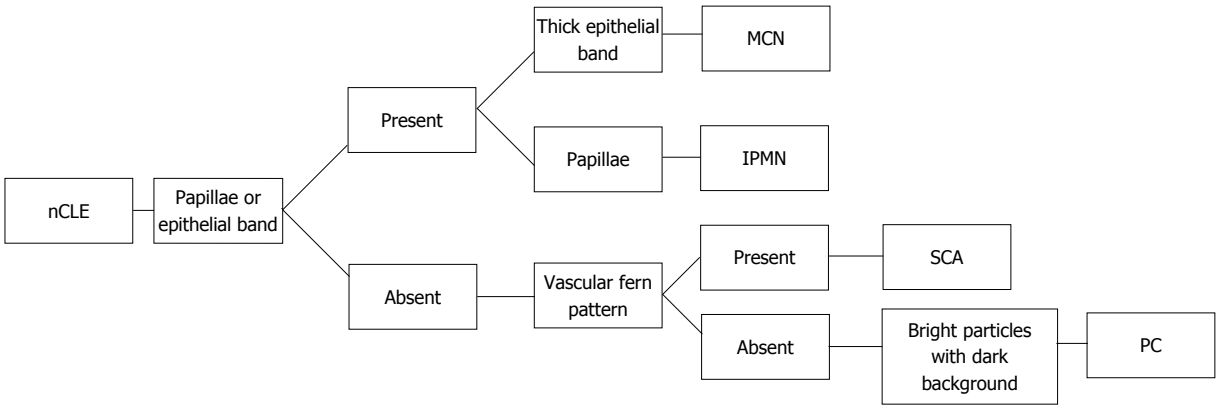

Figure 1 Algorithm for endoscopic ultrasound-guided needle-based confocal laser endomicroscopy imaging biomarker analysis for the evaluation of pancreatic cystic lesions. nCLE: Needle-based confocal laser endomicroscopy; IPMN: Intraductal papillary mucinous neoplasm; MCN: Mucinous cystic neoplasm; SCA: Serous cystadenoma; PC: Pseudocyst.

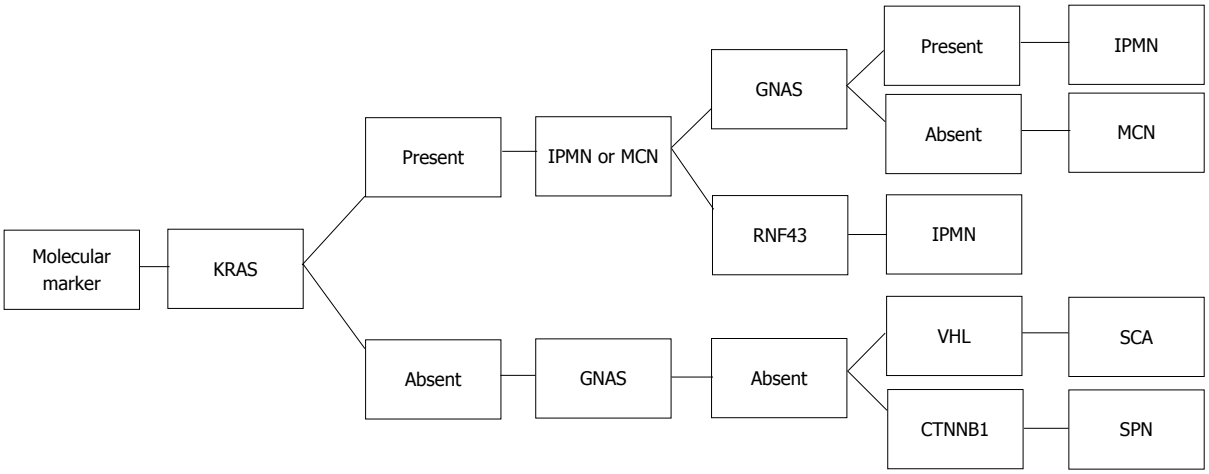

Figure 2 Proposed algorithm for cyst fluid molecular biomarker for the evaluation of pancreatic cystic lesions. IPMN: Intraductal papillary mucinous neoplasm; MCN: Mucinous cystic neoplasm; SPN: Solid pseudopapillary neoplasm; SCA: Serous cystadenoma.

Sanger sequencing). The use of next-generation sequencing (NGS) has revealed specific molecular markers that aid in the diagnosis of mucinous cysts as well as detection of advanced neoplasia. NGS refers to DNA sequencing technologies that allow sequencing of numerous small fragments of DNA in parallel, which are then pieced together by mapping individual reads to the reference genome. This allows rapid sequencing of entire genomes compared to conventional Sanger sequencing. Whole exome and targeted sequencing studies of PCL fluid have revealed certain mutational profiles of major cyst subtypes as well as markers of advanced neoplasia (high-grade dysplasia/pancreatic adenocarcinoma).

More widespread utilization of NGS is limited by suboptimal identification of specific PCL types, including MCN (low sensitivity) and cystic neuroendocrine tumor (lack of DNA) as well as poor sensitivity for detection of the *VHL* gene (as seen in SCAs) requiring Sanger sequencing[8,29]. A proposed algorithm for evaluation of PCLs based on cyst fluid molecular markers is shown in Figure 2.

KRAS mutations are seen in both IPMN and MCN, although less sensitive for detection of MCN[30]. GNAS mutations are found in IPMN but not MCN[25,31]. RNF43 mutations occur in 14%-38% of IPMNs[25,31]. VHL gene mutations have been identified in SCA but not in other pancreatic cystic lesions[25,29]. CTNNB1 gene mutations are the most commonly seen alteration in SPN[25].

Integration of imaging and molecular biomarkers for the evaluation of PCLs

EUS guided evaluation of PCLs permits integrated evaluation with imaging (nCLE) and molecular (cyst fluid) biomarkers. Table 2 and Figure 3 summarize the key imaging and molecular biomarkers for different types of PCLs.

Types of pancreatic cystic lesions

Intra-ductal papillary mucinous neoplasm: IPMNs are epithelial neoplasms that produce mucin. They are classified based on involvement of the main pancreatic duct: main duct IPMN (MD-IPMN), branch duct IPMN (BD-IPMN), mixed (both main and branch duct) IPMN.

Table 2 Summary of imaging (endoscopic ultrasound-needle-based confocal laser endomicroscopy) and molecular (cyst-fluid) biomarkers characteristic of different types of pancreatic cystic lesions

	IPMN	MCN	SCA	SPN	PC	NEN
Imaging biomarker						
nCLE patterns	Finger-like Papillae[17,24]	Epithelial bands (single or multiple)[17]	Fern pattern or superficial vascular network[17,19]	Not well defined	Bright particles against dark background[17]	Trabecular pattern[17]
	Rope ladder or branched type vascularity[49]	Rope ladder or branched type vascularity[49]				
Molecular biomarker						
Cyst fluid molecular analysis	KRAS, GNAS, RNF43 positive[25,31,34]	KRAS, RNF43 positive, GNAS negative[25,31]	VHL positive[29]	CTNNB1 positive[25]	Negative	Not well characterized
Cysts with advanced neoplasia	TP53, SMAD4, PIK3CA, PTEN, CKDN2A positive[35,38,37]	TP53, SMAD4, PIK3CA, PTEN, CKDN2A positive[31]				
	p16, p53 positive[37]					

nCLE: Needle-based confocal laser endomicroscopy; IPMN: Intraductal papillary mucinous neoplasm; MCN: Mucinous cystic neoplasm; SCA: Serous cystadenoma; SPN: Solid pseudopapillary neoplasm; PC: Pseudocyst; NEN: Neuroendocrine neoplasm; Advanced neoplasia: Presence of high-grade dysplasia and/or adenocarcinoma.

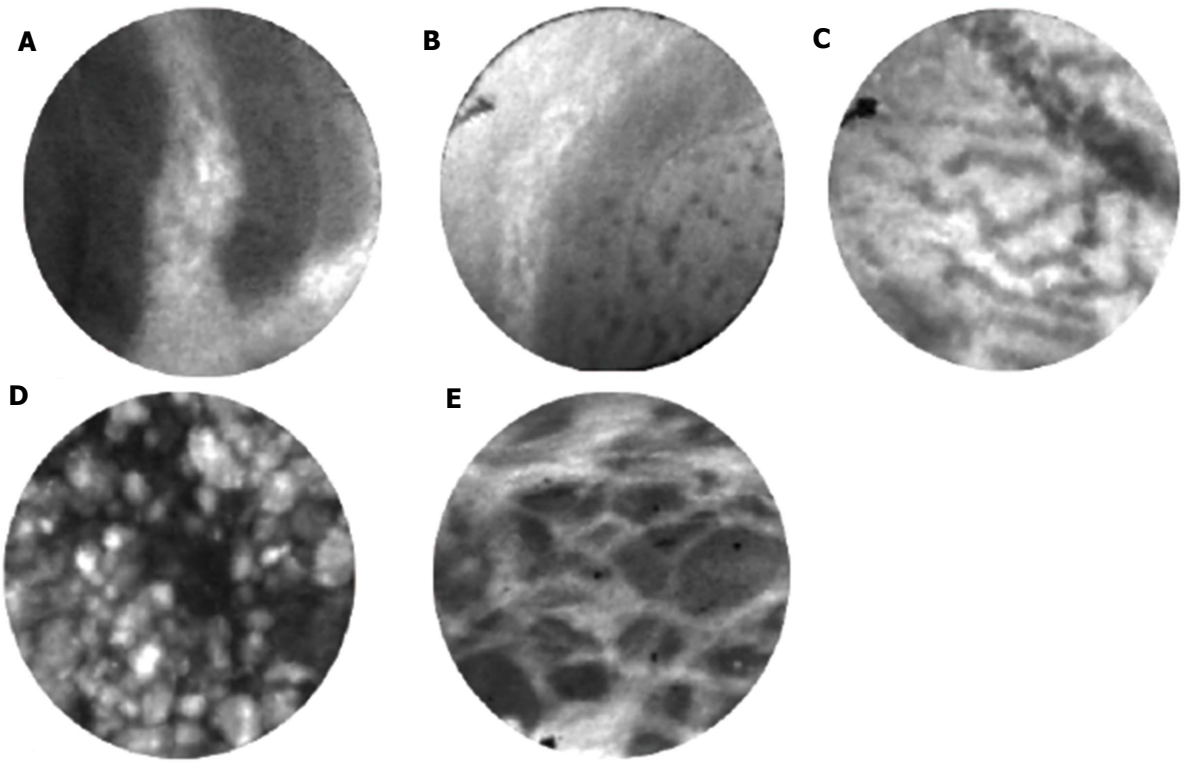

Figure 3 Confocal endomicroscopy findings of various types of pancreatic cystic lesions. A: Papillae of intraductal papillary mucinous neoplasm; B: Epithelial bands of mucinous cystic neoplasm; C: Fern pattern of serous cystadenoma; D: Bright particles against a dark background of pseudocyst; E: Trabecular pattern of neuroendocrine neoplasm.

MD-IPMN is characterized by either segmental or diffuse dilation of the main pancreatic duct greater than 5 mm without other causes of obstruction. BD-IPMN is characterized by cyst diameter greater than 5 mm that communicates with the main pancreatic duct. Mixed-IPMN meets criteria for both MD-IPMN and BD-

IPMN. MD-IPMN and mixed IPMN are associated with significantly higher incidence of malignancy compared to BD-IPMN (60% *vs* 25%)[9,32]. They are also classified into gastric, intestinal, pancreaticobiliary, oncocytic subtypes[33].

Patterns of papillae or epithelial bands on nCLE have high correlation with mucinous cysts[15,17]. The epithelial bands typically seen in MCNs do not have papillary morphology. On the other hand, IPMNs have complete papillae[24]. Analysis of performance of nCLE criteria for IPMN showed an accuracy 90%, sensitivity 80%, specificity 92%, positive predictive value 67%, and 96% negative predictive value[17].

The oncogenic KRAS and GNAS mutations have been extensively studied in IPMNs. The KRAS mutation is seen in 80% of IPMNs while 65% of IPMNs have mutations in the GNAS oncogene[34]. KRAS mutations are associated with branch duct location[30], while GNAS mutations are associated with main duct location[29]. KRAS and GNAS are considered early events in the progression to PDAC and mutations in either KRAS or GNAS are seen in over 96% of IPMNs[29].

In addition, inactivating mutations of the tumor suppressor gene RNF43 occur in 14%-38% of IPMNs[25,31]. Additional molecular markers present in IPMNs include p16 (lost earlier compared to p53), SMAD4, p53, and TP53[35-38].

IPMNs with advanced neoplasia may have TP53, PIK3CA, PTEN, and/or AKT1 mutations[36,39-43]. A prospective single center study showed that a combination of KRAS/GNAS mutations and changes in TP53/PIK3CA/PTEN had 78% sensitivity and 97% specificity for advanced neoplasia[44]. Studies combining DNA quantity, KRAS mutations, and LOH mutations have shown variable sensitivities: 50%[45] *vs* 83%[46]. An additional study found that both KRAS and LOH was present in 50% of carcinoma or high grade dysplasia compared to 8% of premalignant IPMNs, indicating the progression of neoplasia may correlate with accumulation of genetic disturbances[38].

Mucinous cystic neoplasm: Like IPMNs, MCNs are also mucin-producing epithelial neoplasms. Typically they are located in the body or tail of the pancreas and are not associated with the main pancreatic duct[47]. They are more commonly seen in women and typically occur between the ages of 30 to 50 years of age[34]. Microscopically, MCNs are composed of columnar mucinous epithelium and characteristic dense ovarian-type stroma, which express hormone receptors.

During EUS-nCLE, MCNs typically demonstrate single or layers of epithelial bands rather than papillae[17]. In a minority of patients, some MCN show evidence of chronic inflammation with bright fluorescent inflammatory cells[24].

Similar to IPMNs, the most common mutation in MCNs is the *KRAS* gene. The prevalence of KRAS mutations increases with the degree of dysplasia: 26% in low-grade MCNs but 89% in advanced neoplasia[25]. Mutations or deletions in TP53, PIK3CA, PTE, CDKN2A, SMAD4 are associated with advanced neoplasia in MCN[31]. Unlike IPMNs, the GNAS mutation is not seen in MCNs[25,31].

Although the KRAS mutation is seen in both IPMN and MCN, it is much less sensitive for detection of MCN (sensitivity of 14%) than IPMN[30]. Other genetic alterations in MCNs include *KRAS*, *TP53*, and *SMAD4*. Additional associations with *PIK3CA*, *PTEN*, and *CKDN2A* have also been published[25,31,40].

Serous cystadenoma

Serous cystadenomas are benign cystic neoplasms that are more common in women[48]. A large retrospective, multinational study of over 2600 patients diagnosed with serous cystic neoplasms showed minimal risk of clinically relevant symptoms over a three-year follow up period. Given their lack of malignant potential, surgical management is only needed if they are symptomatic (causing pancreatitis or jaundice)[48].

A report from the CONTACT study identified a superficial vascular network (subepithelial vessels uniformly distributed in the cyst wall) or fern pattern as a characteristic of SCA[19,49]. The presence of this pattern is highly specific for SCA. On the other hand, sensitivity for diagnosis of SCA is low in the absence of this pattern (69% to 75%)[17,19].

VHL gene mutations have been identified in SCA cyst fluid[29] but not in IPMN, MCN, or SPN[25]. However, VHL mutations are also seen in pancreatic neuroendocrine tumors and are not specific to SCAs. TP53 and PIK3CA have been rarely described. KRAS, GNAS, and RNF43 mutations, which can be seen in mucinous cysts, have not been identified[25,29].

Solid pseudopapillary neoplasm

Solid pseudopapillary neoplasms are typically well-defined solitary lesions often found in younger women[50]. Microscopically, they are composed of poorly cohesive cells forming a mixed pattern of solid, pseudopapillary, and hemorrhagic cystic structures[34]. They do not communicate with the main pancreatic duct and contain myxoid stroma on cytology[47].

The nCLE findings of solid pseudopapillary neoplasms are not well defined due to their rarity.

Mutations of the B-catenin gene (CTNNB1) are the most commonly seen alteration in SPN[25]. This results in cytoplasmic and nuclear accumulation of B-catenin. VHL, GNAS, RNF43 mutations have not been identified in these cysts[25,29]. Therefore, the presence of CTNNB1 in the absence of KRAS, GNAS, and RNF43 mutations is confirmatory for diagnosing SPNs[25].

Pancreatic pseudocyst

Pancreatic pseudocysts are an encapsulated collections of fluid with a well-defined inflammatory wall with minimal or no necrosis[51]. They are histologically composed of fibro-inflammatory tissue surrounding necrotic

adipocytes without epithelial lining. No vasculature is seen because pseudocysts do not have an epithelium. On nCLE, this is characterized by bright inflammatory cells against a dark background[17]. As pseudocysts are not neoplastic, molecular markers related to malignancy are not found.

Cystic neuroendocrine neoplasms

Microscopically, cystic neuroendocrine neoplasms are characterized by a neoplastic monomorphic cell proliferation with variations in cellular architecture. Characteristic nCLE appearance of pancreatic neuroendocrine tumors have been described[21]. Endomicroscopy demonstrates dark, irregular clusters or trabeculae of compact cells (neoplastic cells) surrounded by gray tissue (fibrovascular stroma)[17]. Neuroendocrine neoplasms have not been well characterized on molecular studies and further research is needed.

CONCLUSION

This review summarizes the current status of new technologies for the evaluation of PCLs including confocal endomicroscopy and molecular markers. Both EUS-nCLE and cyst fluid molecular analysis of PCLs represent promising new modalities to improve the diagnostic evaluation of PCLs by supplementing the standard evaluation of pancreatic cysts which includes imaging (MRI, CT) and endoscopy (EUS). Given the limitations of current diagnostic algorithms, these imaging and molecular biomarkers can increase diagnostic accuracy and improve management of PCLs. Prospective multicenter studies are needed to determine how to integrate nCLE and molecular analysis into existing management protocols and clinical practice. In clinical practice, these technologies may especially be applied in the setting of cases with diagnostic uncertainty in order to improve accuracy and allow for appropriate risk stratification. Expertise in these technologies may not be widespread and referral to centers with experience may be necessary.

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MINIREVIEWS

Imaging of gall bladder by endoscopic ultrasound

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Abstract

Endoscopic ultrasonography (EUS) is considered a superior investigation when compared to conventional ultrasonography for imaging gall bladder (GB) lesions as it can provide high-resolution images of small lesions with higher ultrasound frequencies. Examination of GB is frequently the primary indication of EUS imaging. Imaging during EUS may not remain restricted to one station and multi-station imaging may provide useful information. This review describes the techniques of imaging of GB by linear EUS from three different stations. The basic difference of imaging between the three stations is that effective imaging from station 1 is done above the neck of GB, from station 2 at the level of the neck of GB and from station 3 below the level of the neck of GB.

Key words: Gallbladder; Gallbladder cancer; Gallstones; Biliary sludge; Antrum; Duodenal bulb; Endoscopic ultrasound

Core tip: Endoscopic ultrasonography (EUS) is superior investigation than ultrasonography for imaging gall bladder (GB). Different techniques of imaging of GB by EUS have been described by different authors but a standard technique has not been specifically described. We herein discuss the techniques of imaging of GB by linear EUS from three different stations.

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Table 1 Imaging of gall bladder from three stations

Station	Home base structure	Main position where gall bladder is seen	Part of biliary tract seen on clockwise rotation	Part of biliary tract seen on anti-clockwise rotation
Station - 1: OG junction	Joining of right branch of portal vein with left branch of portal vein	Beyond the curving part of portal vein between 6-8 o'clock position	Upper 1/3rd of CBD	Neck of Gall Bladder, Fundus
Station - 2: Antrum of stomach/ duodenal bulb	Portal vein, superior mesenteric vein	Between 2-4 o'clock position	Lower 1/3rd of CBD	Upper 1/3rd of CBD, neck of Gall Bladder and Fundus, left and right hepatic duct union
Station - 3: Descending duodenum	Superior mesenteric vein	Between 9-11 o'clock position	Pancreatic duct	Middle and upper 1/3rd of CBD, neck of gall bladder and fundus, left and right hepatic duct union

CBD: Common bile duct.

INTRODUCTION

Imaging modalities used in evaluating gall bladder (GB) diseases include transabdominal ultrasonography (USG), endoscopic ultrasonography (EUS), computerized tomography, and magnetic resonance imaging[1,2]. Although USG is considered the gold standard for GB imaging, in view of providing high resolution images; EUS has been found to be better than USG for GB lesions imaging[3-6]. Different techniques of imaging by EUS have been described by different authors for GB imaging but a standardized technique has not been mentioned[7-10]. In view of close proximity of GB to the duodenum, usually EUS imaging is restricted to duodenum[11]. Usually, endosonographers performs GB imaging from multiple stations and the initial station of imaging differs among different endosonographers[12,13]. The present review elaborates the various methods of GB imaging by linear EUS.

APPLIED ANATOMY OF GB

The GB lies on the visceral surface of the liver. The non-peritoneal upper surface of the GB is attached by connective tissue to a shallow fossa on the liver located between the right lobe and the quadrate lobe. The GB has three segments: The fundus, the body, and the left segment which is the infundibulum or neck. The fundus projects beyond the inferior margin of the liver, is covered completely in peritoneum and is in contact with the anterior abdominal wall. The body tapers towards the neck, which lies in the porta hepatis. The neck or infundibulum is hook-shaped and may show a pouch like dilation toward the right (Hartmann's pouch). The neck turns sharply downward as it becomes continuous with the cystic duct. The mucous membrane of the cystic duct is raised up into a spiral fold that consists of five to ten irregular turns; it is continuous with a similar fold in the neck of the GB.

TECHNIQUES OF IMAGING

The images included in this review were obtained utilizing the linear echoendoscope EG-3830 UT (Pentax, Tokyo, Japan), along with a Hitachi Avius processor (Hitachi, Tokyo, Japan). The EUS image orientation on screen was as follows: Monitor's right side corresponds to the cranial and left to the caudal end of the patient. Rotation of the echo endoscope is the most crucial aspect to GB imaging. Majority of the movements are performed in a straight position of the echo endoscope, except during EUS imaging from first part of duodenum when the scope is in a J-shaped position. Proper right/left knobs movements along with in/out movement of the echo endoscope are utilized for adequate contact with the gastrointestinal wall for proper EUS imaging.

STATIONS OF IMAGING

EUS of the GB can be done from the fundus of stomach, duodenal bulb, descending duodenum and antrum. The imaging from duodenal bulb and antrum are almost similar in appearance hence the description is restricted to three stations (Figure 1 and Table 1): (1) the fundus of stomach; (2) duodenal bulb and antrum; and (3) descending duodenum.

Imaging from fundus of stomach/esophagogastric junction

The GB lies on the far side of screen between 6 to 9 o'clock position. Movements near esophagogastric junction (40 cm) should be performed under direct vision to avoid the possibility of perforation. Initially, segment 2 and 3 portal vein tributaries are identified within the left lobe of liver. A clockwise rotation follows the tributaries which form the left branch of portal vein (PV). Further clockwise rotation traces the left branch of PV towards the liver hilum where it is joined by the right branch of PV. After the union the supraduodenal part of PV is seen as a curving vessel going from 9/11 o'clock position to 4/6 o'clock position (Figure 2). The common bile duct (CBD) and GB are seen in the area beyond the curving part of PV in the left lower quadrant of screen (Figure 3). Initially, the CBD and neck of GB are identified just beyond the PV (Figure 4). Imaging of remaining part of GB can be done by following GB down from the fundic part of stomach. This follow down of GB is possible due to EUS probe movement along

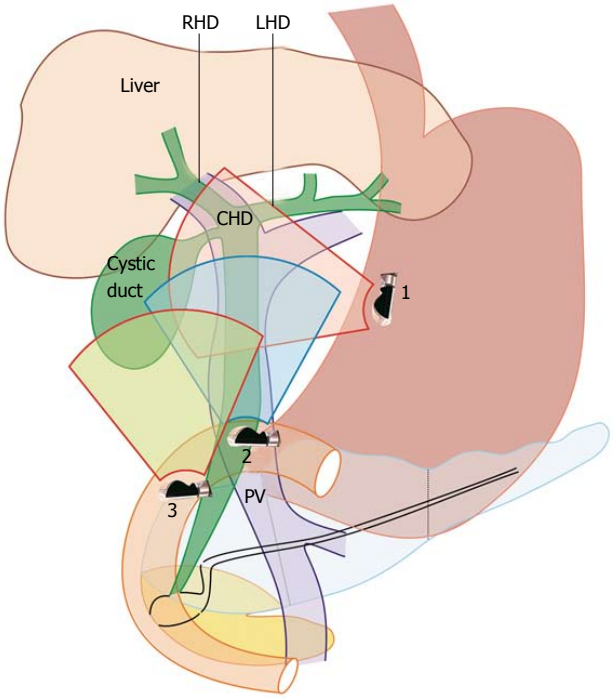

Figure 1 Station 1 shows the gall bladder at around 6 o'clock position; station 2 shows the gall bladder at around 3 o'clock position; and station 3 shows the gall bladder at around 9 o'clock position. RHD: Right hepatic duct; LHD: Left hepatic duct; CHD: Common hepatic duct; PV: Portal vein.

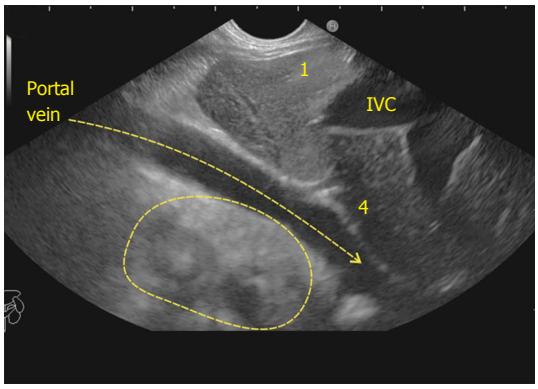

Figure 2 The supraduodenal part of portal vein is seen as a curving vessel going from 5/6 o'clock position to 9/10 o'clock position. The yellow arrow points to the curving part of portal vein. The area marked with yellow outline shows the area in which the CBD and Gall Bladder can be seen. 1: Segment 1; 4: Segment 4; IVC: Inferior vena cava; CBD: Common bile duct.

the lesser curvature along with combination of three smooth movements: (1) Pushing around 25 to 30 cm; (2) 90 degree clockwise rotation; and (3) up movement of up/down knob on echo endoscope for about 90 degree. This combination of movements allows smooth pathway of EUS transducer along the lesser curvature and follows down the GB from neck towards the fundus of GB.

Imaging from antrum and duodenal bulb

The GB lies close to the probe between 2 to 4 o'clock position. The imaging from the antrum is sometimes

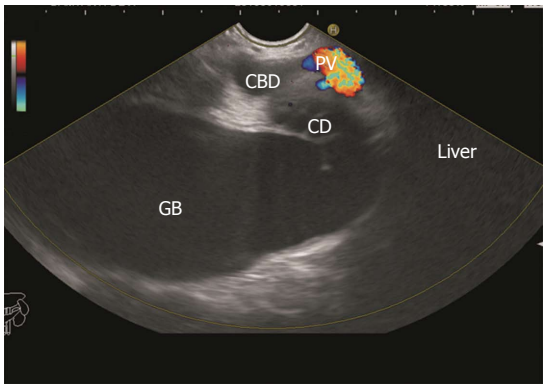

Figure 3 The upper part of common bile duct is first identified beyond the curving part of portal vein. With slight rotation of the scope the cystic duct and gall bladder can be traced in the area beyond the portal vein between 5 o'clock position to 10 o'clock position. CBD: Common bile duct; GB: Gall bladder.

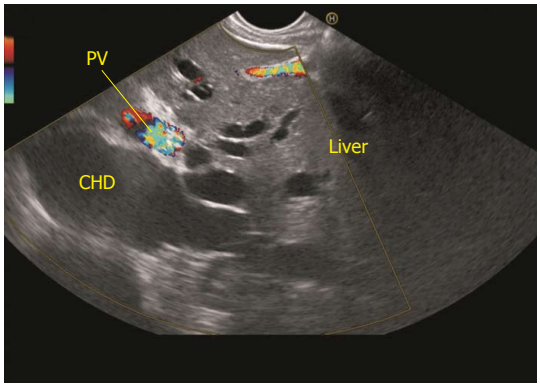

Figure 4 The dilated ducts of segment 2 and 3 can be followed to formation of left hepatic duct. The left hepatic duct joins the right hepatic duct to form common hepatic duct. The common hepatic duct (CHD) lies beyond the supraduodenal part of portal vein. PV: Portal vein.

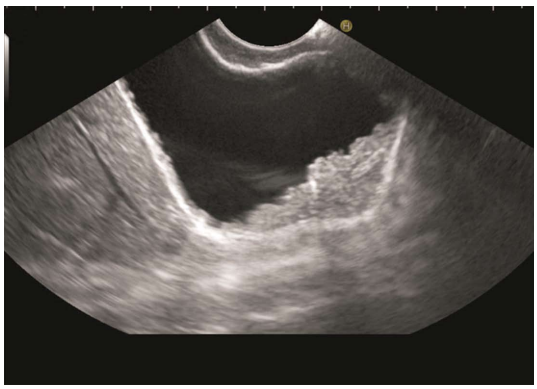

Figure 5 The gall bladder imaging is done from duodenal bulb. The layers of GB can be seen. The irregular polypoidal mass occupying the lumen is due to adenomyomatosis of GB. GB: Gall bladder.

best done by pushing the echo endoscope from the body of stomach towards the pylorus with a hyperinflated balloon (Figure 5). The imaging from duodenum can be done without a balloon by passing the scope beyond the pylorus and pushing it into the duodenal bulb apex. The contact with the superior and anterior duodenal

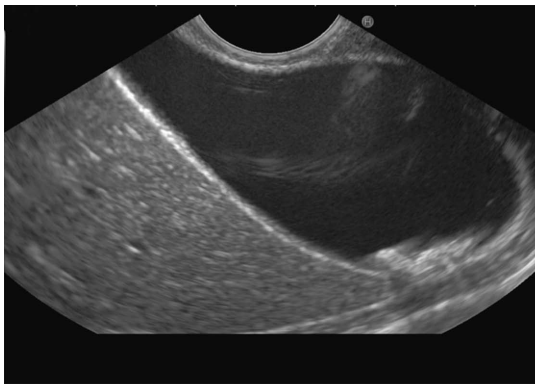

Figure 6 Gall bladder imaging from the duodenal bulb. The stones are present in the lumen of GB. The neck of the Gall Bladder is present at 11 o'clock position and the fundus is present at 3 o'clock position. GB: Gall bladder.

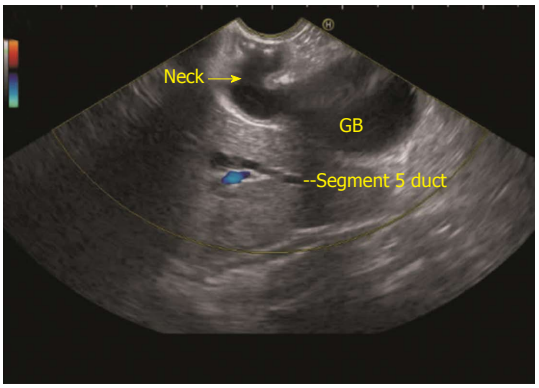

Figure 9 The neck of the gall bladder is present just below the probe and the fundus is present at 3 o'clock position. The segment 5 duct is seen beyond the GB. GB: Gall bladder.

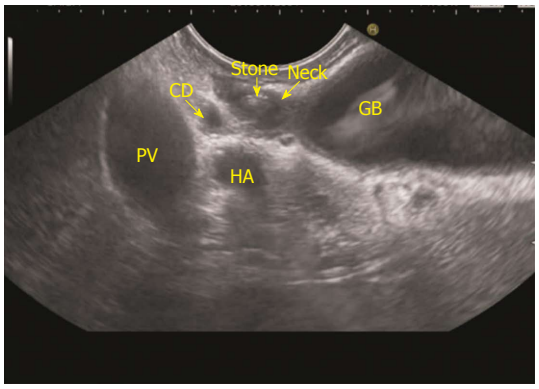

Figure 7 A stone is seen in the neck of gall bladder. These stones can be missed by routine abdominal ultrasound. The neck of the gall bladder is present just below the probe and the fundus is present at 3 o'clock position. PV: Portal vein; GB: Gall bladder.

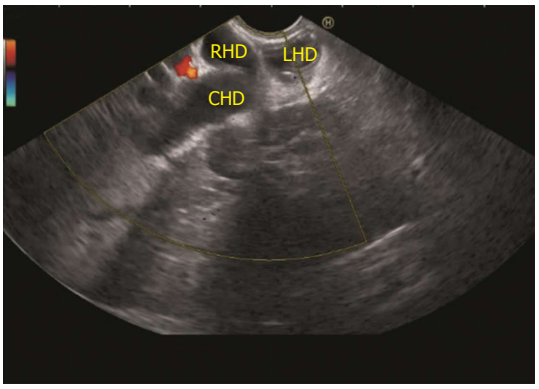

Figure 10 Once the gall bladder imaging is done from duodenal bulb an anticlockwise rotation can trace the common bile duct towards the hilum of liver. The CHD is seen to be dividing into right and left hepatic duct. RHD: Right hepatic duct; LHD: Left hepatic duct; CHD: Common hepatic duct.

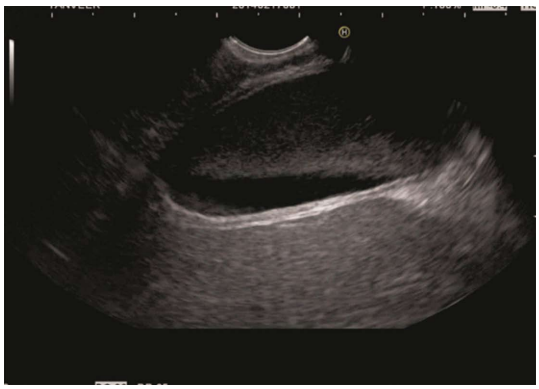

Figure 8 The segment 5 of liver is seen beyond the gall bladder. A layer of gall bladder (GB) sludge is seen in the lumen of GB.

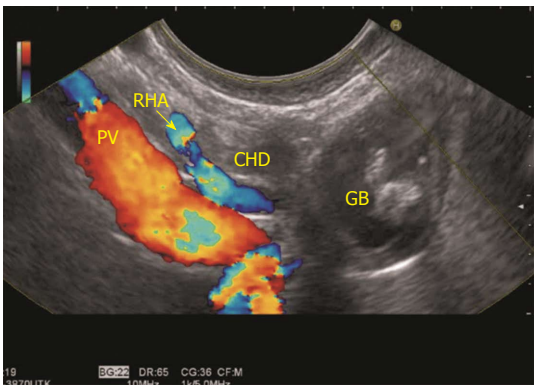

Figure 11 The imaging is done from duodenal bulb and the portal vein is identified going from 5 o'clock position to 10 o'clock position in a long axis. The CHD is identified between the probe and portal vein. The CHD is followed up by anticlockwise rotation and the remnant of gall bladder is seen in continuity with CHD. CHD: Common hepatic duct; GB: Gall bladder; PV: Portal vein.

wall is established after sucking the air out of the lumen of duodenum, by turning in an anticlockwise direction and by moving the up and down knobs generally in a downward direction (Figures 6-10). Home base position is identified with adequate rotation and minor adjustments of both knobs, where the portal vein is seen on the far side of the screen in a long axis (Figure 11). Clockwise rotation follows the CBD towards the papilla and anticlockwise rotation makes the scanning towards the liver hilum, the upper part of CBD, the cystic duct and GB (Figures 7-9). The CBD and GB are seen in the area between the probe and portal vein and

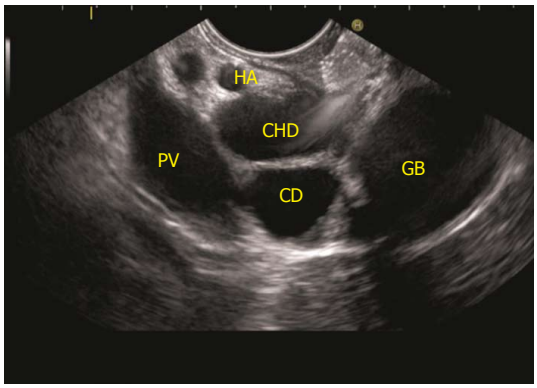

Figure 12 The imaging is done from duodenal bulb and the portal vein is identified going from 5 o'clock position to 10 o'clock position in a long axis. The CHD is identified between the probe and portal vein. The CHD is followed up by anticlockwise rotation and the continuity into cystic duct and gall bladder is seen. CHD: Common hepatic duct; PV: Portal vein; GB: Gall bladder.

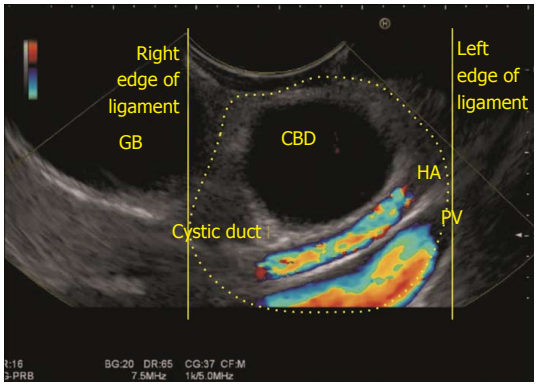

Figure 13 The gall bladder imaging is done from descending duodenum with up deflection and anti-clockwise rotation. The hepatoduodenal ligament is identified as a bean shaped structure between the probe and liver (shown in dotted yellow area). The CBD can be traced along the cystic duct and the gall bladder which lies outside the right edge of hepatoduodenal ligament. CBD: Common bile duct; GB: Gall bladder.

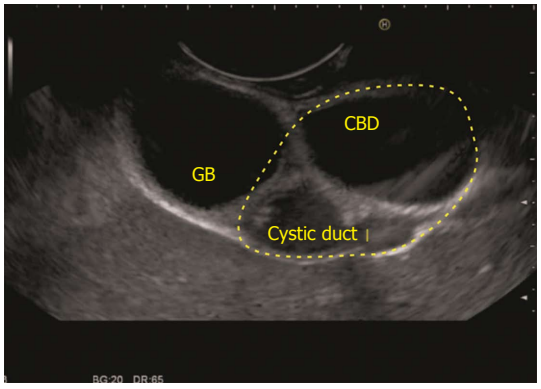

Figure 14 The gall bladder imaging is done from descending duodenum. The hepatoduodenal ligament is identified between the probe and liver (shown in dotted yellow area). The CBD, the cystic duct and the gall bladder are visualized on the under surface of liver. CBD: Common bile duct; GB: Gall bladder.

higher up between the probe and liver (Figure 12).

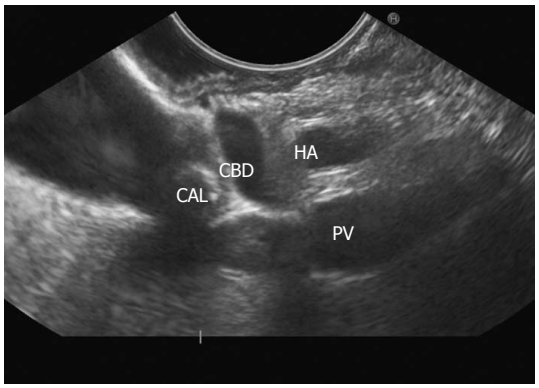

Figure 15 The gall bladder imaging is done from descending duodenum with up deflection and anti-clockwise rotation. The CBD can be traced and a stone is seen in the Cystic duct. The distended gall bladder is also visualized. PV: Portal vein; CBD: Common bile duct.

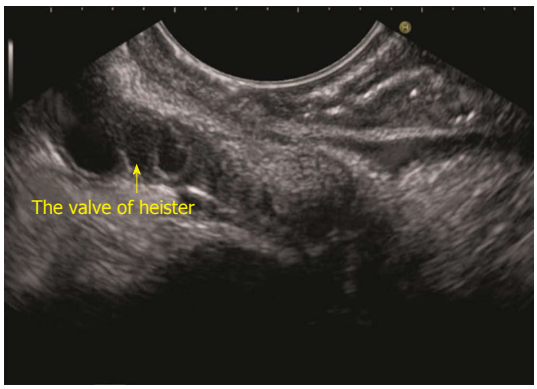

Figure 16 The gall bladder imaging is done from descending duodenum with up deflection and anti-clockwise rotation. The tortuous cystic duct with a spiral valve of Heister is seen.

Imaging from descending duodenum

The GB lies close to the probe between 8 to 11 o'clock position. Imaging from descending duodenum requires the entry into 2nd part of duodenum followed by shortening of scope. After entry, multiple times pushing the scope in/out is required to place the echo endoscope into the descending duodenum (3rd part of duodenum). By combining three movements, *i.e.*, slow withdrawal up to the duodenal bulb, clockwise/anticlockwise torque and upward movement of the up/down knobs in third part of duodenum, there is better visualization of lower one third of CBD. The combination of three movements should be done with a main emphasis on anticlockwise rotation. During this rotation the superior mesenteric vein can be followed all the way towards the hilum where the portal vein is seen in a rounded axis within the hepatoduodenal ligament. The anechoic bile duct can be identified and followed all the way to the liver hilum (Figures 13-15). The continuity of CBD can be seen with the cystic duct and GB. Sometimes the valve of heister can be visualized within the cystic duct (Figure 16).

CONCLUSION

The techniques described in the present paper are likely to provide the images as discussed in most of the cases and from majority of the stations. However, the reproducibility of the images may be compromised in the duodenal bulb due to the variability of the scope position and due to the balloon use. The basic concept of GB imaging by linear EUS is simple: Station 1 shows the GB at around 6 o'clock position, station 2 shows the GB at around 3 o'clock position and station 3 shows the GB at around 9 o'clock position. The difference between the three imaging is that effective imaging in station 1 lies above the neck of GB, in station 2 lies at the level of the neck of GB and station 3 lies below the level of the neck of GB. These techniques will be useful for evaluation of different kind of pathologies of GB by EUS[14-22].

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ORIGINAL ARTICLE

Retrospective Cohort Study

New 14-mm diameter Niti-S biliary uncovered metal stent for unresectable distal biliary malignant obstruction

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Abstract

AIM

To investigate whether an uncovered self-expandable metal stent (UCSEMS) with a large diameter could prevent recurrent biliary obstruction (RBO).

METHODS

Thirty-eight patients with malignant biliary obstruction underwent treatment with an UCSEMS with a 14-mm diameter (Niti-S 14). Retrospectively, we evaluated technical and functional success rate, RBO rate, time to RBO, survival time, and adverse events in these patients.

RESULTS

Stent placement success and functional success were

achieved in all patients. Two patients (5.3%) had RBO due to tumor ingrowth or overgrowth. The median time to RBO was 190 (range, 164-215) d. The median survival time was 120 (range, 18-502) d. The 6-mo non-RBO rate was 91%. Other adverse events other than RBO occurred as follows: Acute cholecystitis, post-ERCP pancreatitis, hemobilia, and fever without exacerbation of liver injury, and liver abscess in 4 (10.3%), 3 (7.9%), 2 (5.3%), 1 (2.6%), and 1 (2.6%), respectively. Migration of the stents was not observed.

CONCLUSION

Niti-S 14 is considered to be a preferable metal stent because of a low rate of RBO with no migration.

Key words: Metal stent; Malignant biliary obstruction; Pancreatic cancer; Migration; Pancreatitis; Bile duct cancer; Overgrowth; Recurrent biliary obstruction; Ingrowth; Adverse event

Core tip: Our manuscript reports on 38 patients with unresectable distal malignant biliary obstruction (MBO) treated with a newly developed 14-mm diameter Niti-S biliary uncovered metal stent. The results could show the stent is preferable for the palliate treatment of unresectable distal MBO because of a low rate of recurrent biliary obstruction, no migration, a low rate of other complications, and a high success rate of placement.

Kikuyama M, Shirane N, Kawaguchi S, Terada S, Mukai T, Sugimoto K. New 14-mm diameter Niti-S biliary uncovered metal stent for unresectable distal biliary malignant obstruction. *World J Gastrointest Endosc* 2018; 10(1): 16-22 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i1/16.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i1.16

INTRODUCTION

Endoscopic transpapillary biliary stent placement is an established procedure for relieving jaundice and treating cholangitis in patients with malignant biliary obstruction (MBO). The treatment can contribute to the improvement of quality of life and prognosis of patients with unresectable MBO. A plastic tube stent had been widely used as the first generation of stent treatment for MBO[1], although it had the issue of being easily occluded due to its small diameter of 7 to 11 Fr.

In the last decade of the 20th century, a self-expandable metal stent (SEMS) with a wider diameter of 8 to 10 mm without being covered, *i.e.*, an uncovered SEMS (UCSEMS), was developed with recognition for its efficacy in relieving jaundice with long term patency[2-5]. However, stent occlusion due to tumor ingrowth and food impaction was frequently experienced and thus requires a solution.

A covered SEMS (CSEMS) was produced to prevent tumor in growth through the stent mesh. The advantage of the CSEMS was long-term patency because the membrane could prevent tumor in growth[6]; however, this stent type could not perfectly avoid occlusion as sludge or food impaction was encountered, or stent migration easily occurred[7-9]. It was hypothesized that the larger stent diameter could contribute to maintaining a longer patency with supportive evidence by some reports[10-12]. Recently, a CSEMS with a 12-mm diameter, SUPREMO 12, was developed and verified this hypothesis[13]. However, easy migration of CSEMS remained an issue despite the larger diameter[13].

To prevent migration, an UCSEMS is preferable[6,14,15] to a CEMS, because the uncovered mesh of the stent is embedded in the bile duct wall and makes the stent keep still. However, occlusion due to tumor in growth remains unresolved for treatment by an UCSEMS. If an UCSEMS stent had a larger diameter, it could be expected to keep the bile flow despite tumor ingrowth and maintain a longer patency and a UCSEMS with a large diameter of 14 mm, Niti-S 14 (Taewoong Medical CO., Ltd., Seoul, South Korea), was developed. Herein, the efficacy and safety of the Niti-S 14 for MBO was evaluated.

MATERIALS AND METHODS

Study design

We retrospectively evaluated the efficacy and safety of Niti-S 14, placed transpapillarily for consecutive and unresectable MBO from April 2014 to May 2016 in the following 3 institutions; Shizuoka General Hospital, Gifu Municipal Hospital, and Hamamatsu University Hospital. The outcome measures were rate of technical and functional achievement, rate of recurrent biliary obstruction (RBO)[16], time to RBO (TRBO)[16], survival time, and stent-related adverse events. Diagnosis of MBO was established by laboratory data, imaging findings, and histopathological examinations. Stage of the disease was determined by the findings of computed tomography or endoscopic ultrasonography.

Patients

Thirty-eight patients with MBO of the middle to lower part of the extrahepatic bile duct and expectance of survival for longer than 2 mo underwent treatment for MBO by Niti-S 14 placement (Table 1). Twenty-one males and 17 females were included with median age of 70 (range, 52-90) years. All patients had fair activity of daily living (ECOG-PS grade 0-2). Those with post-gastrectomy state (Billroth Ⅱ or Roux-en-Y reconstruction) were excluded from candidates for this treatment. Causes of obstruction of the extrahepatic bile duct were pancreatic cancer, bile duct cancer, and metastatic lymphadenopathy in 36, 1, and 1 patients, respectively. Thirty-seven patients belonged to the clinical stage Ⅳ of the UICC TNM classification, and

Table 1 Patient characteristics

	n = 38
Men/women	21/17
Age (yr)	70 (52-90)
PS (0/1/2)	8/21/9
Diagnosis	
Pancreatic cancer	36
Bile duct cancer	1
Metastatic nodes	1
Clinical stage Ⅲ/Ⅳ	1/37
Tumor size (mm)	33 (13-70)
Length of the biliary stricture (mm)	27 (10-60)
Maximum diameter of the proximal bile duct (mm)	13.5 (7-20)

PS: Performance status.

Table 2 Results of stent placement

	n (%)
Technical success	38 (100)
Functional success	38 (100)
Selected stent length (60/80 mm)	14/24 (36.8/63.2)
Endoscopic sphincterotomy	20 (52.6)
Previous drainage (RBD/NBD)	9/2 (23.7/5.3)
Replacement for CSEMS	5 (13.2)

RBD: Retrograde biliary drainage; NBD: Naso-biliary drainage; CSEMS: Covered self-expandable metal stent.

the remaining one patient was stage Ⅲ. The median tumor size was 33 (range, 13-70) mm and the median length of the biliary stricture was 27 (range, 10-60) mm. The median diameter of the proximal bile duct was 13.5 (range, 7-20) mm.

Niti-S 14

Niti-S 14 is a newly developed UCSEMS with braided structure made from nitinol, and a large diameter of 14 mm with a length of 60 or 80 mm (Figure 1). The outer diameter of the delivery sheath was 9 Fr. A 0.035-inch guide-wire can be used for introducing the stent into the bile duct.

Stent placement

In all patients, Niti-S 14 was placed through the duodenum major papilla during endoscopic retrograde cholangiopancreatography. A 60- or 80-mm stent length was selected according to the length of the stricture. The distal end of the stent was placed in the duodenum (Figure 2). Endoscopic sphincterotomy (EST) was performed at the discretion of the operator, mainly to avoid post-ERCP pancreatitis. The stricture was not dilated by a balloon before stent placement. Niti-S 14 was used as the primary treatment for MBO in principal.

Following-up and adverse events definition

Clinical signs and symptoms and biochemical parameters of liver function and inflammation (aspartate transaminase, alanine transaminase, alkaline phosphatase, gamma glutamyl transpeptidase, total and direct bilirubin, and C-reactive protein levels) were evaluated at least monthly. Complications were defined according to the Tokyo Criteria 2014[14]. According to these criteria, RBO was defined as occlusion or symptomatic migration, and TRBO was the interval between stent placement and RBO, which was calculated instead of patency. The definition of post-ERCP pancreatitis (PEP) was new or worsened abdominal pain with serum amylase ⩾ threefold the upper limit of normal, measured > 24 h after the procedure. Acute cholecystitis was diagnosed when a fever > 38 ℃ or right upper abdominal pain occurred with supportive imaging studies.

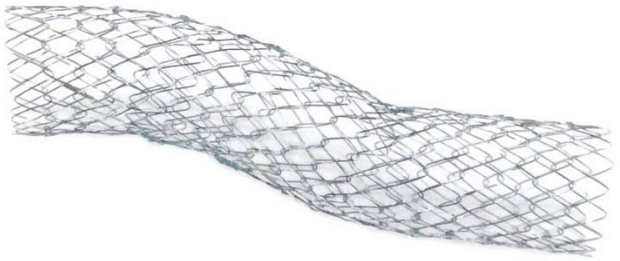

Figure 1 Niti-S 14 appearance with a braided structure made from nitinol, and a large diameter of 14 mm with a length of 60 or 80 mm.

Statistical analysis

Stent patency duration and survival time were estimated by the Kaplan-Meier method. Continuous variables were analyzed using one-way analysis of variance, and categorical and binary variables were analyzed using Fisher's exact test. All statistical tests were two-tailed and assessed at a 0.05 probability level. All analyses were performed using SPSS software, version 18.0 (SPSS Inc., Chicago, Illinois, United States).

RESULTS

Technical and functional achievement

In all patients, stent placement was successful (technical success rate = 100%) (Table 2). Stents with a length of 60 mm and 80 mm were selected for and placed in 14 and 24 patients, respectively. EST was performed before placement in 20 patients (52.6%) because the orifice of the major papilla was small with incomplete obstruction of the main pancreatic duct by pancreatic head cancer in 18 and without pancreatic head cancer in 2. In all patients, total bilirubin level deceased and normalized within 14 d and functional success (defined as 50% decrease in or normalization of the bilirubin level within 14 d of stent placement[14]) was achieved (functional success rate = 100%). Stent placement was performed after relieving jaundice by retrograde biliary drainage and naso-biliary drainage (NBD) in 9 (23.7%) and 2 (5.3%) patients, respectively, and for replacing a previously placed CSEMS with smaller diameter due to cholangitis in 5 (13.2%).

Table 3 Retrograde biliary drainage, time to retrograde biliary drainage, and survival time

	n (%)
RBO	2 (5.3)
Tumor ingrowth	1 (2.6)
Tumor overgrowth	1 (2.6)
Median TRBO (d)	190 (164-215)
Non-obstruction rates of 3, 6, 12 mo (%)	100, 91, 78
Median survival time (d)	120 (18-502)

RBO: Recurrent biliary obstruction; TRBO: Time to recurrent biliary obstruction.

Table 4 Complications other than recurrent biliary obstruction

Complications	11/38 (28.9%)	Time to event (d)
Acute cholecystitis	4 (10.3)	3, 32, 217, 487
PEP	3 (7.9)	1 (each)
Hemorrhage	2 (5.3)	92, 119
Fever without exacerbation of liver injury	1 (2.6)	1
Liver abscess	1 (2.6)	17

PEP: Post-ERCP pancreatitis; ERCP: Endoscopic retrograde cholangiopancreatography.

RBO, TRBO, and survival time

Two patients (5.3%) experienced RBO due to tumor ingrowth and overgrowth just above the upper end of the stent (Table 3). Jaundice with liver injury was recognized on 164 d and 215 d in two patients. The median TRBO was 190 (range, 164-215) d. RBO was treated by placing a CSEMS endoscopically across the obstructed biliary portion through the previously placed Niti-S 14. In the patient with tumor overgrowth, the Niti-S 14 was patent on endoscopic retrograde cholangiography, and endoscopic observation revealed coverage of the inside wall of the stent by a hyperplastic mucosal tissue (Figure 3).

The non-obstruction rates of 3, 6 and 12 mo were 100%, 91% and 78%, respectively (Figure 4). The median survival time was 120 (range, 18-502) d (Figure 5).

Adverse events

Adverse events occurred in 11 patients (28.9%). RBO was recognized in two patients (5.3%) in the manner of tumor ingrowth and tumor overgrowth as described above. Adverse events other than RBO occurred as follows (Table 4): Acute cholecystitis, PEP, hemobilia, fever without exacerbation of liver injury, and liver abscess in 4 (10.3%), 3 (7.9%), 2 (5.3%), 1 (2.6%) and 1 (2.6%), respectively. Stent migration was not observed. Bile duct perforation was not experienced despite of the large diameter of 14 mm. Acute cholecystitis occurred on day 3, 32, 217 and 487 after stent placement in four respective patients and the inflamed and swollen gallbladder was punctured percutaneously without placing a percutaneous drainage tube with the infected bile aspirated from the gallbladder. PEP

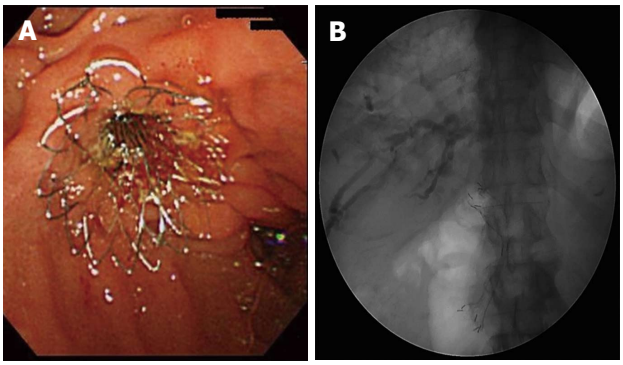

Figure 2 Stent placement of Niti-S 14 after sphincterotomy in pancreatic cancer. A: Endoscopic view; B: Picture of endoscopic retrograde pancreatocholangiography.

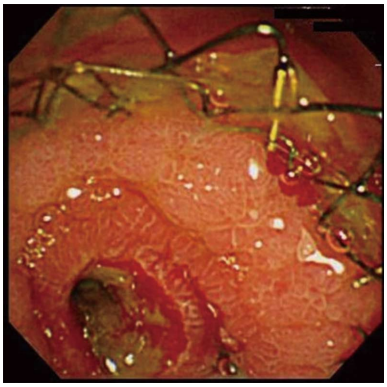

Figure 3 Endoscopic view of the duodenal major papilla after Niti-S 14 placement. The bile duct cavity is maintained despite bile duct mucosa or tumor growth into the stent.

was diagnosed within the day after placement but was mild and treated by conservative ways. In 2 patients, hemobilia was recognized by examining the cause of hematemesis on day 92 in one and 119 in the other, and a fully covered EMS (WallFlex stent, 10 mm × 60 mm, Boston Scientific Corp, Natick, Mass, United States) was placed inside the 14-mm Niti-S with achievement of hemostat. In patients with cholangitis due to migration of a previously placed CSEMS, we swapped the previously placed stent to the Niti-S 14 in 5 patients. Among them, one patient had persistent high fever after replacement without cholecystitis despite the relief of hepatobiliary dysfunction; the patient was treated by antibiotic administration for 10 d. One patient experienced liver abscess, which was diagnosed on day 17 because of high fever, and was treated by percutaneous puncture with drainage tube placement. However, the patient died the next day due to septic shock with abscess rupture toward the peritoneal cavity.

DISCUSSION

The ideal stent is free from occlusion, migration, and other adverse events. Especially, occlusion and

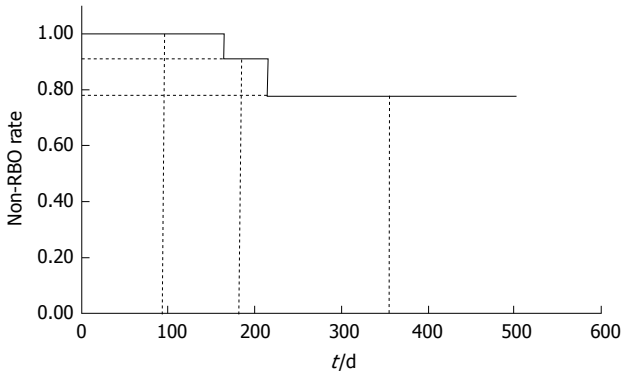

Figure 4 Kaplan-Meier analysis of stent patency. The non-RBO rates of 3, 6 and 12 mo were 100%, 91% and 78%, respectively. RBO: Recurrent biliary obstruction.

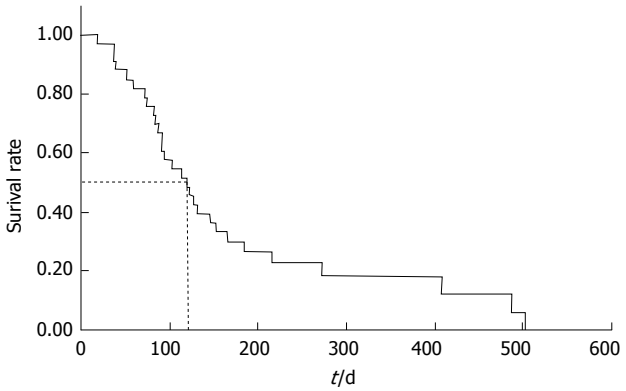

Figure 5 Kaplan-Meier analysis of survival. The median survival time was 120 d.

migration are major problems for treating MBO by SEMS. To resolve these complications, the 14-mm Niti-S™ biliary uncovered-stent (Niti-S 14) was developed, which was characterized by an uncovered feature and a large diameter of 14 mm. On development, the diameter of 14 mm was expected to be large enough to prevent occlusion despite tumor ingrowth. In this study, the results support the superiority of the Niti-S 14 with a low RBO rate, lack of migration, low rates of other complications, and a high technical success rate.

Low RBO rate

Stent occlusion was recognized in just 2 patients (5.3%) with Niti-S 14, and the 6-mo stent patency was 91%. Previous reports described stent occlusion rates of 18%-38% using conventional types of UCSEMS with a diameter of 10 mm[5,6,15,16]. If our result of 5.3% in Niti-S 14 is comparable with that of previous reports, it is because of low incidence of tumor ingrowth. In patients with Niti-S 14, endoscopic observation of the stent showed mucosa or tumor tissue growth into the inside of the stent, which is the same finding observed with the conventional type of UCSEMS, while the stent was not occluded because the large 14-mm diameter could maintain the stent cavity. On the other hand, tumor overgrowth was recognized in one patient. The length of the stent might be insufficient to prevent bile duct obstruction due to overgrowth in patients with a large tumor, and tumor overgrowth resulting from RBO could be resolved by a longer Niti-S 14.

In CSEMS, stent occlusion by tumor ingrowth is rarely experienced, while tumor overgrowth, food impaction, and migration were relatively common causes of stent occlusion, with reported occlusion rates of 14%-23% in a fully-covered SEMS[6,15], 5.8%-29% in a partially covered SEMS[16,17], and 26% in SUPREMO 12[13]. In comparing our result with those of previous reports on CSEMS, an RBO rate of 5.3% was preferable.

Six-month stent patency was also evaluated previously, and reported to be 78%-90%, 70%-94%, 63%-91%, and 50% in a conventional type of UCSEMS[5,6,15,16], fully-covered SEMSs[6,18,19], partially-covered SEMS[16,17], and SUPREMO 12[13], respectively. Our result of 91% using Niti-S 14 was comparable or superior to that of these previous studies.

No migration

Niti-S 14 is an uncovered, which is a characteristic that prevents migration. A lack of migration also contributes to low RBO rate. RBO in patients with CSEMS placement was frequently due to stent migration in previous reports[13,16,20]; this complication was also observed if a partially-covered SEMS was used[20]. To prevent migration, selecting a UCSEMS may be desirable, and the other issue of tumor ingrowth should be resolved. As mentioned above, the large diameter of 14 mm could provide a solution for this problem.

Low other adverse event rates

Acute cholecystitis and PEP are relatively common adverse events after placing an SEMS with rates of 0%-10% and 0%-8%, respectively, in previous reports[6,15-23], and were experienced in 10.3% and 7.9% of patients with Niti-S 14, respectively. Despite the large diameter of the stent, the incidences were almost equal to those of previous reports. After placing Niti-S 14, EST was performed in 18 patients with pancreatic head cancer or without pancreatic head cancer in 2 for the purpose of preventing PEP, because the main pancreatic duct was not completely obstructed by the tumor and the orifice of the major papilla was small. As a result, PEP occurred in 5% of patients with EST and 11% of those without EST. In patients with EST, the incidence of PEP tended to be low, but it was not statistically significant. Those results suggest that the large diameter of a stent is not responsible for PEP and EST does not contribute to preventing PEP. Our result of performing EST to prevent PEP does not contradict the previous report describing that EST does not effectively act to prevent PEP in patients undergoing stent placement[24]. It is suggested that several factors besides obstructing a pancreatic duct orifice by a stent are responsible for PEP.

High technical success rate

We succeeded placement of SEMS in all patients using Niti-S 14. Despite the large diameter of the stent, the delivery system of Niti-S 14 is thin (9 Fr) and soft. The characteristics of the Niti-S 14 delivery system could provide an optimal effect for endoscopic introduction of the delivery system into the bile duct through the duodenal papilla.

Although these preferable results were obtained in placing Niti-S 14, our study showed that patients undergoing Niti-S 14 placement had a shorter survival time of 113 (range, 18-502) d compared with those of previous reports[14,15,20]. In Niti-S 14, almost all patients had pancreatic cancer and the levels of CA19-9 tended to be higher. This tendency might lead to shorter survival, because, as it is widely known, pancreatic cancer has a poor prognosis and high CA19-9 levels indicate advanced tumor progression[25]. On the other hand, it cannot be denied that the larger diameter were responsible for shorter survival time. The problem of the shorter survival time should be resolved by further randomized control studies comparing Niti-S 14 with other types of stent. Another problem regarding the shorter survival time is this shorter observation time might lead to an apparent low rate of RBO.

In our study, persistent high fever was observed after replacing the CSEMS for Niti-S 14 because of cholangitis due to RBO from migration. Acute cholecystitis was not recognized in the patient. We speculate that this complication might be induced by an enwrapped infected bile duct epithelium, probably with micro-abscess. Moreover, we experienced one patient die on day 18 due to liver abscess in Niti-S 14. The abscess was large at diagnosis, and the possibility that the abscess had already developed by the time of stent placement was presumed.

In conclusion, Niti-S 14 is considered to be a preferable SEMS because of a low rate of RBO, no migration, a low rate of other complications, and a high success rate. However, this study is limited because of the small number of patients and the retrospective evaluation. Further prospective, multicenter, international double-blind controlled studies, comparing different type of stents (*e.g.*, UCSEMS *vs* partially covered SEMS) are necessary, in order to standardize the best drainage policy.

ARTICLE HIGHLIGHTS

Background

Recurrent biliary obstruction (RBO) due to tumor ingrowth or migration remains to be resolved in endoscopic transpapillary biliary stent placement for malignant biliary obstruction (MBO).

Research frontiers

It was expected that an uncovered self-expandable metal stent with a large diameter could prevent RBO.

Innovations and breakthroughs

Niti-S 14 is a large bore and uncovered metal stent, but is safe for treatment for MBO and considered to be a preferable SEMS because of a low rate of RBO with no migration.

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ORIGINAL ARTICLE

Retrospective Study

Post-endoscopic procedure satisfaction scores: Can we improve?

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Author contributions: Steinberg JM, Kallus SJ and Mattar MC designed the study and obtained IRB approval; Munjal A, Steinberg JM, Kallus SJ and Mossaad A performed majority of the data collection; Munjal A and Steinberg JM wrote the manuscript; Kallus SJ, Mattar MC and Haddad NG were involved in the editing of the manuscript.

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Conflict-of-interest statement: There are no conflicts of interest to disclose for all of the authors of this manuscript.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at Ankita.munjal@gunet.georgetown.edu. Consent was not obtained but the presented data are anonymized and risk of identification is low.

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Abstract

AIM

To organize post-procedure satisfaction data into a useful reference and analyze patient-centered parameters to find trends that influence patient satisfaction.

METHODS

A robust database of two cohorts of outpatients that underwent an endoscopic procedure at Georgetown University Hospital at two separate three-month intervals ranging from November 2012 to January 2013 and November 2015 to January 2016 was compiled. Time of year was identical to control for weather/seasonal issues that may have contributed to the

patient experience. The variables recorded included age, sex, body mass index (BMI), type of procedure, indication for procedure, time of the procedure, length of the procedure, type of prep used, endoscopist, satisfactory score, and comments/reasons for score. For continuous variables, differences in averages were tested by two sample *t*-test, Wilcoxon rank sum test, and ANOVA as appropriate. For categorical variables, differences in proportions between two groups were tested by χ^2 test. Correlation test and linear regression analyses were conducted to examine relationships between length of procedure and continuous predictors. A *P* value < 0.05 used to indicate statistically significant relationship.

RESULTS

The primary outcome of this study was to assess if telephone outreach after an endoscopic intervention was a satisfactory method of obtaining post-procedure satisfaction scores from patients at a tertiary care center. With the addition of post-procedure calls, instilled in January 2014, the response rate was 40.5% (508/1256 patients) from a prior completion rate of 3.4% (31/918) with the mail out survey initially. There was a statistically significant improved response rate pre and post intervention with *P* < 0001. The secondary outcome of this study was to assess if we could use predictive analytics to identify independent predictors of procedure length, such as gender, age, type of procedure, time of procedure, or BMI. The combined pre and post intervention data was used in order to optimize the power to identify independent predictors of procedure length. The total number of patient's data analyzed was 2174. There was no statistically significant difference in procedure length between males and females with *P* value 0.5282. However, there was a small (1 min), but statistically significant difference (*P* = 0.0185) in procedure length based on the time of day the procedure took place, with afternoon procedures having a longer duration than morning procedures. The type of procedure was an independent predictor of procedure length as demonstrated with *P* value < 0.0001. There is a statistically significant correlation between age and procedure length, although it is only a weak relationship with a correlation coefficient < 0.3. Contrary to patient age, BMI did not have a statistically significant correlation with procedure length (*P* = 0.9993), which was also confirmed by linear regression analysis.

CONCLUSION

Our study proves calling patients after endoscopy improves post-procedure satisfaction response rates and changing procedural time allotment based on patient characteristics would not change endoscopic workflow.

Key words: Survey; Quality improvement; Patient satisfaction

Core tip: We analyzed the post-endoscopy survey system that had been implemented and largely ignored in the past in order to understand where we are succeeding and failing in our endoscopy suite in regards to the overall patient experience. We also looked at patient-centered parameters that could influence procedure length, which is a common surrogate for satisfaction, to reflect on current practices and allow for process improvements in order to optimize the patient experience in our endoscopy suite.

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INTRODUCTION

According to the recently published article, Quality Indicators Common to All GI Endoscopic Procedures[1], a key post-procedure quality measure should include factors that can improve with endoscopy. It is recognized that patient satisfaction is an important outcome measure as it pertains to both the patient and the endoscopy unit. Poor experiences in the endoscopy unit may lead to non-compliance with endoscopic screening and/or monitoring[2]. Quality measures are put in place so that there is constant oversight and evaluation of the process, guaranteeing continued improvement. A commonly used survey known as the modified Group Health Association of America patient satisfaction survey (mGHAA-9) focuses on key points throughout the patient's experience, including, waiting time, manners of the staff and doctor, doctor skills and explanation of the procedure[3]. Currently, the mGHAA-9 is not in use at Georgetown University Hospital; rather, every patient that has an outpatient procedure receives a follow-up call asking him/her to rank the experience on a scale of 1-3. This formal post-procedural call system was implemented in January 2014 and is carried out by our administrative personnel. This data is filed in the electronic medical record and has been largely ignored to date.

The purpose of this study is to organize the post-procedure satisfaction data into a useful and minable reference in order to understand our successes and failures in our endoscopy suite. Furthermore, by looking at various patient-centered parameters such as age, sex, body mass index (BMI) and procedural parameters including length of procedure, type of procedure, and the time of day a procedure is performed, we intended to find trends in these factors that might influence the overall outcome. Statistical analysis of this information will allow for reflection on current practices and lead to process improvements in order to optimize the patient experience in our endoscopy suite at Georgetown Univer-

Table 1 Comparison of response rate between pre and post intervention

Characteristics	Pre intervention, *n* = 918	Post intervention, *n* = 1256	*P* value
Response rate (satisfaction score)	31 (3.4%)	508 (40.5%)	< 0.0001

Table 2 Examining gender and time of procedure as independent predictors of procedure length

				Time of procedure		
	Female, *n* = 1162	Male, *n* = 1012	*P* value	AM, *n* = 1089	PM, *n* = 1084	*P* value
Procedure length	20.6 ± 12.1	20.9 ± 12.6	0.5282	20.1 ± 11.8	21.3 ± 12.8	0.0185

sity Hospital, and perhaps help to construct a universal protocol that could be adopted by other institutions nationwide that would enhance the patient experience.

MATERIALS AND METHODS

Our investigators compiled a robust database of two cohorts of outpatients that underwent an endoscopic procedure ranging from EGDs, colonoscopies, flexible sigmoidoscopy, ileoscopy, single and double balloon enteroscopies, ERCPs and endoscopic ultrasound at Georgetown University Hospital at two separate three-month intervals. The first was between November 1st 2012 and January 31st 2013, and the second was from November 1st 2015 through January 31st 2016. Those months were chosen, as they were the most up to date in regards to available survey data at the start of the study. The time of year remained identical to control for possible weather/seasonal issues that may have contributed to the patient experience. Patients' charts were then reviewed with all personal health information being de-identified. The variables recorded included: Patient age, sex, BMI, type of procedure, indication for procedure, time of day the procedure took place, length of procedure, type of prep used (if any), endoscopist, satisfaction score, and comments/reasons for score (if recorded). It should be noted that our institution adopted a post-procedure call survey system in January 2014 to obtain patient feedback and satisfaction scores. Prior to January 2014, the method for attaining patient satisfaction information was *via* a letter that was mailed to the patient's home.

Our primary outcome was to assess improvement in response rates from a mailed out survey *via* the postal service to telephone outreach to assess post-procedure satisfaction scores. The secondary analysis, and more informative aspect of the study, was to see if the use of predictive analytics could identify independent predictors of procedure length, which could then be focused on to optimize patient experience in the endoscopy unit at this tertiary care facility.

Statistical analysis

Means and standard deviations for continuous variables and frequencies and percentages for categorical variables are respectively provided in the following tables below. For the continuous variables, differences in the averages between two groups were tested by two sample *t*-test and Wilcoxon rank sum test as appropriate. ANOVA was used to examine differences in the averages between three or more groups. For categorical variables, differences in proportions between two groups were tested by χ^2 test. Correlation test and linear regression analyses were conducted to examine the relationship between length of procedure and continuous predictors. A *P* value < 0.05 was used to determine a statistically significant relationship.

RESULTS

The primary outcome of this study was to assess if telephone outreach after an endoscopic intervention was a satisfactory method of obtaining post-procedure satisfaction scores from patients at a tertiary care center. With the addition of post-procedure calls, instilled in January 2014, the response rate increased to 40.5% (508/1256 patients). Prior to the calls, the documented post-procedure satisfaction survey completion rate *via* mailed out surveys was 3.4% (31/918). With the implementation of the phone call survey, we are able to show a statistically significant improved response rate pre and post intervention (Table 1).

The secondary outcome of this study was to assess if we could use predictive analytics to identify independent predictors of procedure length, such as gender, age, type of procedure, time of procedure, or BMI. The combined pre and post intervention data was used in order to optimize the power of the study to identify independent predictors of procedure length which is often used as a surrogate for patient satisfaction and can allow for changes to the work flow within the endoscopy suite to better suit their needs. The total number of patient's data analyzed was 2174. Table 2 examines independent predictors including gender as well as timing of the procedure, particularly morning *vs* afternoon. In regards to gender, there was no statistically significant difference in procedure length between males and females. However, there was a small, 1-min, but statistically significant difference in procedure length based on the time of day the procedure took place, with afternoon procedures having

Table 3 Comparing procedure type with length of procedure

	Procedure							
	Colonoscopy, *n* = 981	EGD, *n* = 714	EUS, *n* = 301	ERCP, *n* = 116	Enteroscopy, *n* = 36	Flex sig, *n* = 20	Ileoscopy, *n* = 6	*P* value
Procedure length	22.1 ± 10.1	18.6 ± 13.1	17.4 ± 10.7	23.0 ± 12.7	49.2 ± 19.3	14.8 ± 9.7	18.8 ± 15.2	< 0.0001

EUS: Endoscopic ultrasonography; ERCP: Endoscopic retrograde cholangiopancreatography

Table 4 Mean age, body mass index, and procedure length

Variable	*n*	Mean	Std Dev
Age	2174	57.97286	15.84377
Body mass index	2030	27.18420	7.01924
Length of procedure	2174	20.71665	12.31821

a longer duration than morning procedures.

As would be expected, the type of procedure was an independent predictor of procedure length as demonstrated in Table 3. The final two variables that were analyzed to assess if they were independent predictors of procedure length were age and BMI. Table 4 shows the relationship between mean age and BMI and length of procedure for the combined pre and post intervention group. The average age of patients in the study was 58 years old and average procedure length was 20.7 min. The average BMI of the patient population was 27. Table 5 looks at the strength of the relationship between age and BMI and procedure length. While there is a statistically significant correlation between age and procedure length, it is a weak relationship being defined as correlation coefficients < 0.3 as weak, correlation coefficient > 0.3 but < 0.5 as moderate, correlation coefficient > 0.5 but < 0.7 as strong, correlation coefficient > 0.7 as a perfect correlation. Contrary to patient age, BMI did not have a statistically significant correlation with procedure length (*P* value 0.9993). Linear regression analysis also confirmed no statistically significant relationship between BMI and procedure length (data not shown).

Figure 1 is a FitPlot of the relationship between age and procedure length. As is shown by the positive slope in the graph, there is a statistically significant relationship, albeit small. Using a linear regression analysis, the relationship between age and procedure length was confirmed (data not shown), and it can be concluded that for every year increase in age, there is a 0.06-min (3.6 s) increase in length of procedure.

DISCUSSION

In this retrospective study analyzing patient satisfaction following an endoscopic procedure at a tertiary care center, a number of statistically significant findings were observed. Most importantly, our research demonstrates that following the January 2014 implementation of a formal post-endoscopic telephone call to patients, patient response dramatically increased from a response rate of 40.5% compared to 3.4% initially with the mailed out survey. This finding highlights the importance of provider-initiated follow-up in obtaining patient feedback. Implementing this phone call system as a means of direct communication with patients at other locations who do not currently utilize such a process could potentially increase response rates in patient feedback, as was seen in our center so that endoscopy centers, same day surgery centers, or entire hospital systems can better meet the needs of their patients. As our phone communication requires live callers from our endoscopy center, a future study to investigate whether the use of an automated system would similarly result in increased patient response rates, would be of particular interest for optimum resource management. Ultimately, a reporting system that approaches 100% response rate should be achieved. Even with the strides made in the implementation of post-procedure telephone calls, we still fall far short of our goal of 100% response rate. This may require patient's filling out surveys prior to discharge from the endoscopy suite, *vs* scheduling early, post-procedure follow-up visits where this data can be obtained, *vs* email or text message response systems. Future studies on how best to meet the needs of our ever-changing population are needed to identify the best practices.

Similar studies by Rasool *et al*[4], Trujillo-Benavides *et al*[5] and Qureshi *et al*[6] using the modified GHAA-9 questionnaire showed patient satisfaction rates of close to 90%. Waiting times for the appointment, waiting time before the procedure, and inadequate explanations were identified as the most common reasons leading to patient dissatisfaction. Interestingly, in a study performed by Del Río *et al*[7], a one question survey was administered at the end of the procedure rating the overall performance and then the modified GHAA-9 questionnaire was used 3 wk later. The results of both the questionnaires did not adequately correlate, which may influence survey practices in order to improve patient satisfaction in the future as the one question post-endoscopic question survey is a common practice in many universities including here at Georgetown University. It is possible that this is related to post-procedural complications that may occur after the patient has left the endoscopy suite and is therefore not reflected in the initial survey. Salmon *et al*[8] created a 31-item questionnaire to evaluate satisfaction in colonoscopy. However, this was not an easily used method for survey using telephone interviews per Del

Table 5 Strength of relationship between age or body mass index and procedure length

	Pearson correlation coefficients, n = 2174	
	Age	Length of procedure
Age	1.00000	0.07781
		0.0003
Length of procedure	0.07781	1.00000
	BMI	Length of procedure
	0.0003	
BMI	1.00000	-0.00002
		0.9993
Length of procedure	-0.00002	1.00000
	0.9993	

BMI: Body mass index.

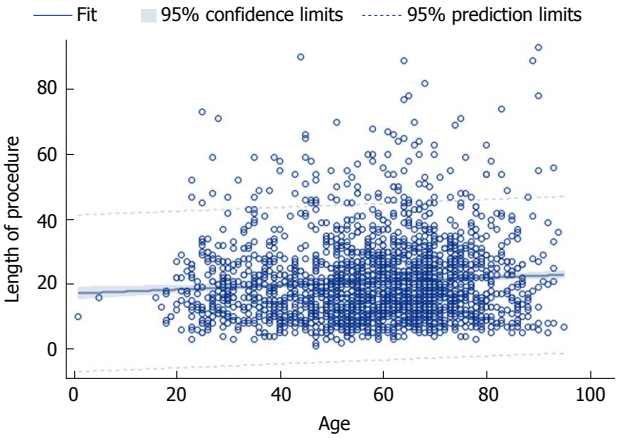

Figure 1 Fit Plot of the relationship between age and procedure length.

Río *et al*[7]. It is important to also note that our study included all endoscopic procedures ranging from EGDs to balloon enteroscopies and colonoscopies, which have significant differences in invasiveness and length of procedure and may lead to variances in patient satisfaction. Feedback that is provided with such questionnaires is important in leading to improvement in endoscopy practices in the future as it identifies patients' thoughts and concerns.

Further analysis in our study focused on whether there were any independent variables that predicted shorter length of procedure, which was used as a surrogate outcome for patient satisfaction. Many factors have been associated with procedure length including age[9,10,11], sex[9,10,12], BMI[9,10,13], quality of bowel preparation[9,11], history of prior hysterectomy[12,14], diverticulosis[10], constipation[10,11], fellow involvement[15], lower endoscopist annual case volume[9,16], and two-person method[17] although many of these studies have had conflicting results[18]. A few studies have shown that patients with a lower BMI are more likely to have an incomplete colonoscopy or longer insertion time, which may be directly correlated to the amount of visceral fat although our study revealed no correlation[9,10,13]. Other factors such as the endoscopist's skill level, instrument used, coordination of the team, and anesthesia administered are also linked to procedure length[19,20,21] and may be confounding factors that lead to conflicting results in prior studies. In a study performed by Hsu *et al*[17], it was shown that female sex, poor quality of bowel preparation, smaller waist circumference and older age were predictors of a longer cecal intubation time. The differences in sexes are thought to be secondary to women having longer colons and less visceral fat, which predisposes them to loop formation[9,16,22]. In our study, we were not able to show any such difference between sexes. Of particular interest is the finding that procedure length increased with patient age, with statistical analysis showing that for every year increase in age, there is a 0.06-min (3.6 s) increase in length of procedure. This was ultimately determined to be a weak relationship after further statistical analysis in our study, Anderson *et al*[10], Kim *et al*[11] and Hsu *et al*[17]. Also found that older age was associated with increased procedure length. It has been reported that the length of the colon increases with age causing increased compliance and decreased elasticity likely contributing to this association[23]. When scheduling time slots for endoscopic procedures, it would then be unreasonable to allot more dedicated procedure time for older patients as compared to younger patients given this small difference in procedure time. Not surprisingly, procedure type was an independent predictor of procedure length as is a direct reflection of the invasiveness of the procedure. Timing of the procedure, in particular morning *vs* afternoon, also showed a statistically significant difference in regards to procedure length. There was a one-min increase in procedure length for procedures completed in the afternoon. It can be postulated that this is related to physician fatigue or overall delays that may occur in the workflow of the endoscopy suite that translates into delays as the day goes on. By tailoring endoscopic services to our patients, ideally this would improve workflow while simultaneously enhancing the patient experience.

Limitations in this study include analyzing data at only one endoscopic center in a retrospective fashion. As our center is a university affiliated tertiary referral center in a major metropolitan area, perhaps our findings would not be entirely generalizable or extrapolated to other smaller, community institutions or private practices in rural areas. As our post-endoscopic satisfaction survey telephone calls depended on our institution's administrative personnel, there is also a possibility for systems errors in accurate documentation in the EMR. Furthermore, if an attempt was made in contacting a patient post-procedurally was unsuccessful, it typically was recorded as such in the EMR. Unfortunately, there were some records that were missing entirely, and therefore, make it unclear if any attempt was made to call the patient. One variable that was not considered was cost of procedure and patient insurance. Health care disparities often drive patients' experiences in the health care system, and perhaps looking further into

this topic within our own institution would prove to be an influential factor in patient satisfaction.

In conclusion, our study proves that calling patients after they undergo endoscopy can drastically improve post-procedure satisfaction response rates (3.4% increased to 40.5%). However, the ideal method of obtaining post-procedure satisfaction responses has yet to be implemented in our endoscopy suite. The secondary aim of this study, to identify independent variables that directly affect length of procedure, found statistical significance for patient age, but interestingly, did not find patient's BMI to influence length of procedure. We can conclude based on our data that changing the scheduling or time allotted for procedures based on age or weight would not drastically change the flow in the endoscopy suite.

ARTICLE HIGHLIGHTS

Research Background

Patient satisfaction is an important outcome measure for both the patient and endoscopy unit. Poor experiences may lead to non-compliance with endoscopic screening and/or monitoring. Quality measures are instated to ensure oversight and evaluation of processes guaranteeing continued improvement. A commonly used survey known as the modified Group Health Association of America patient satisfaction survey (mGHAA-9) focuses on key points throughout the patient's experience, including, waiting time, manners of the staff and doctor, doctor skills and explanation of the procedure[3]. Currently, the mGHAA-9 is not in use at Georgetown University Hospital; rather, every patient that has an outpatient procedure receives a follow up call asking him/her to rank the experience on a scale of 1-3. This formal post procedural call system was implemented in January 2014 and is carried out by our administrative personnel. This data is filed in the electronic medical record and has been largely ignored to date.

Research motivation

The purpose of this study is to organize the post-procedure satisfaction data into a useful reference as well as analyze various patient-centered parameters to find trends that might influence the overall outcome and lead to process improvements in order to optimize the patient experience. Our primary outcome was to assess improvement in response rates from a mailed out survey *via* the postal service to telephone outreach to assess post-procedure satisfaction scores. The secondary analysis, and more informative aspect of the study, was to see if the use of predictive analytics could identify independent predictors of procedure length, which could then be focused on to optimize patient experience in the endoscopy unit at this tertiary care facility.

Research objectives

Our primary outcome was to assess improvement in response rates from a mailed out survey *via* the postal service to telephone outreach to assess post-procedure satisfaction scores. The secondary analysis, and more informative aspect of the study, was to see if the use of predictive analytics could identify independent predictors of procedure length, which could then be focused on to optimize patient experience in the endoscopy unit at this tertiary care facility. Statistical analysis of this information will allow for reflection on current practices and lead to process improvements in order to optimize the patient experience in our endoscopy suite at Georgetown University Hospital, and perhaps help to construct a universal protocol that could be adopted by other institutions nationwide that would enhance patient experience.

Research methods

A database of two cohorts of outpatients that underwent endoscopic procedures at Georgetown University Hospital was compiled. Several patient-related and procedure-related variables were recorded. For continuous and categorical variables, differences in averages were tested by two sample *t*-test, Wilcoxon rank sum test, ANOVA and χ^2 test as appropriate. Correlation test and linear regression analyses were also conducted to examine relationships between length of procedure and continuous predictors.

Research results

With the addition of post-procedure calls, instilled in January 2014, the response rate was 40.5%. Prior to the calls, the documented post procedure satisfaction survey completion rate was 3.4%. There was a statistically significant improved response rate pre and post intervention. Upon analysis of patient-related variables, there was also a statistically significant relationship that was seen between age and procedure length. Our study proves that calling patients after they undergo endoscopy can drastically improve post procedure satisfaction response rates. However, the ideal method of obtaining post procedure satisfaction responses has yet to be implemented. The secondary aim of this study, to identify independent variables that directly affect length of procedure, which is often a surrogate for patient satisfaction, found statistical significance for patient age, but not body mass index (BMI).

Research conclusions

Our research demonstrates that following the January 2014 implementation of a formal post-endoscopic telephone call to patients, patient response dramatically increased (satisfaction survey response rate of 40.5% compared to 3.4%). This finding highlights the importance of provider-initiated follow-up in obtaining patient feedback. Implementing this phone call system as a means of direct communication with patients at other locations who do not currently utilize such a process could potentially increase response rates in patient feedback, as was seen in our center so that endoscopy centers, same day surgery centers, or entire hospital systems can better meet the needs of their patients. As our phone communication requires live callers from our endoscopy center, a future study to investigate whether the use of an automated system would similarly result in increased patient response rates, would be of particular interest for optimum resource management. Ultimately, a reporting system that approaches 100% response rate should be achieved. Even with the strides made in the implementation of post procedure telephone calls, we still fall far short of our goal of 100% response rate. This may require patient's filling out surveys prior to discharge from the endoscopy suite, *vs* scheduling early, post procedure follow-up visits where this data can be obtained, *vs* email or text message response systems. Future studies on how best to meet the needs of our ever-changing population are needed to identify best practices. The secondary aim of this study, to identify independent variables that directly affect length of procedure, which is often a surrogate for patient satisfaction, found statistical significance for patient age, time of the day of the procedure and type of procedure, but not BMI or sex. We can conclude based on our data that changing the scheduling or time allotted for procedures based on these characteristics would not drastically change the flow in the endoscopy suite.

Research perspectives

The research is able to show that following the January 2014 implementation of a formal post-endoscopic telephone call to patients, patient response improves dramatically. This finding highlights the importance of provider-initiated follow-up in obtaining patient feedback. Implementing this phone call system as a means of direct communication with patients at other locations who do not currently utilize such a process could potentially increase response rates in patient feedback, as was seen in our center so that endoscopy centers, same day surgery centers, or entire hospital systems can better meet the needs of their patients. As our phone communication requires live callers from our endoscopy center, a future study to investigate whether the use of an automated system would similarly result in increased patient response rates, would be of particular interest for optimum resource management. Ultimately, a reporting system that approaches 100% response rate should be achieved. Even with the strides made in the implementation of post-procedure telephone calls, we still fall far short of our goal of 100% response rate. This may require patient's filling out surveys prior to discharge from the endoscopy suite, *vs* scheduling early, post-procedure follow-up visits where this data can be obtained, *vs* email or text message response systems which should be studies in a prospective fashion. Future studies on how best to meet the needs of our ever-changing population are needed to identify the best practices. Limitations in this study also include analyzing data at only one endoscopic center in a retrospective fashion. As our center is a university affiliated tertiary referral center in a major metropolitan

area, perhaps our findings would not be entirely generalizable or extrapolated to other smaller, community institutions or private practices in rural areas and should be studied in those settings in a similar fashion as ours.

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ORIGINAL ARTICLE

Retrospective Study

Case series on multimodal endoscopic therapy for gastric antral vascular ectasia, a tertiary center experience

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Abstract

AIM

To study and describe patients who underwent treatment for gastric antral vascular ectasia (GAVE) with different endoscopic treatment modalities.

METHODS

We reviewed patients with GAVE who underwent treat-

ment at University of Alabama at Birmingham between March 1, 2012 and December 31, 2016. Included patients had an endoscopic diagnosis of GAVE with associated upper gastrointestinal bleeding or iron deficiency anemia.

RESULTS

Seven out of 15 patients had classic watermelon description for GAVE, 1/15 with diffuse/honeycomb pattern and 6/15 with nodular GAVE per EGD description. Seven out of 15 patients required multimodal treatment. Four out of six of patients with endoscopically nodular GAVE required multimodal therapy. Overall, mean pre- and post-treatment hemoglobin (Hb) values were 8.2 ± 0.8 g/dL and 9.7 ± 1.6 g/dL, respectively ($P \leqslant 0.05$). Mean number of packed red blood cells transfusions before and after treatment was 3.8 ± 4.3 and 1.2 ± 1.7 ($P \leqslant 0.05$), respectively.

CONCLUSION

Patients with nodular variant GAVE required multimodal approach more frequently than non-nodular variants. Patients responded well to multimodal therapy and saw decrease in transfusion rates and increase in Hb concentrations. Our findings suggest a multimodal approach may be beneficial in nodular variant GAVE.

Key words: Gastric antral vascular ectasia; Upper GI bleed; Radiofrequency ablation; Endoscopic band ligation; Argon plasma coagulation

Core tip: Over the past several years, treatment for gastric antral vascular ectasia (GAVE) has continued to evolve and the number of available treatments has continued to increase. However, the optimal treatment of GAVE is currently unknown and there currently aren't any studies comparing every modality. However, it is becoming apparent that patients with severe, diffuse or refractory disease require multimodal therapy. Our case series not only shows that but also that patients specifically with nodular variant GAVE require and respond well to multimodal therapy.

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INTRODUCTION

First described in 1953 by Rider *et al*[1], gastric antral vascular ectasia (GAVE) is now a well-recognized cause of chronic upper gastrointestinal bleeding (UGIB) accounting for 4% of non-variceal UGIB[2] and an important cause of chronic iron deficiency anemia. Endoscopically, GAVE can appear as organized red spots emanating radially from the pylorus (watermelon stomach), arranged in a diffuse manner (honeycomb stomach), or as nodules[3]. Histologically, GAVE appears as ectatic mucosal capillaries with fibrin thrombi, spindle cell formation and fibrohyalanosis[4]. Immunohistochemical staining for CD61, a platelet marker, further confirms a diagnosis of GAVE[5]. GAVE has been associated with cirrhosis, chronic kidney disease, diabetes mellitus, autoimmune diseases, hypothyroidism, bone marrow transplant and left ventricular assist devices[6-8]. Over the past two decades, many therapeutic options have been implemented for treatment of GAVE including surgical, medical and endoscopic therapies. Data is emerging on the resolution of GAVE following liver transplant in cirrhotics[9]. Endoscopic therapies have rapidly become the mainstays of first line therapy namely with argon plasma coagulation (APC) as the most common modality and more recently with radiofrequency ablation (RFA) using Halo^{90} catheter[9] and endoscopic band ligation (EBL) both of which have been shown to be safe and effective for GAVE treatment[10,11]. The latter two have been utilized in treatment of severe, diffuse, APC refractory GAVE[10,21]. Furthermore, there has been the advent of BARR χ Through The Scope technique (Covidien, TTS-1100) for RFA, which posits some advantages over the traditional Halo^{90} system. Despite these advances, the best therapeutic approach has yet to be defined. This case series describes patients who underwent treatment for GAVE with TTS-RFA alone or part of a multimodal approach incorporating other methods such as APC and EBL (Figure 1). We believe that the multimodal approach may be appropriate for certain subsets of patients, namely patients with severe nodular GAVE.

MATERIALS AND METHODS

We reviewed patients with GAVE who underwent treatment at University of Alabama at Birmingham (UAB) between March 1, 2012 and December 31, 2016. Included patients had an endoscopic diagnosis of GAVE with associated UGIB or iron deficiency anemia. Medical history including demographic data and chronic medical conditions associated with GAVE were collected. Patients receiving transfusions for other issues outside of GAVE (*i.e.,* for surgeries) were excluded.

Outcomes

The primary outcomes measured included number of packed red blood cells (pRBC) transfusions required and hemoglobin (Hb) concentrations 6 mo prior to and after initiation of treatment, either with TTS-RFA alone or multimodal therapy. In case of patients in the multimodal group, the same variables were collected 6 mo before and after initiation of an alternative modality (APC, EBL or TTS-RFA). Secondary outcome measures included adverse events, post-treatment adverse events, and number of hospitalizations at University of

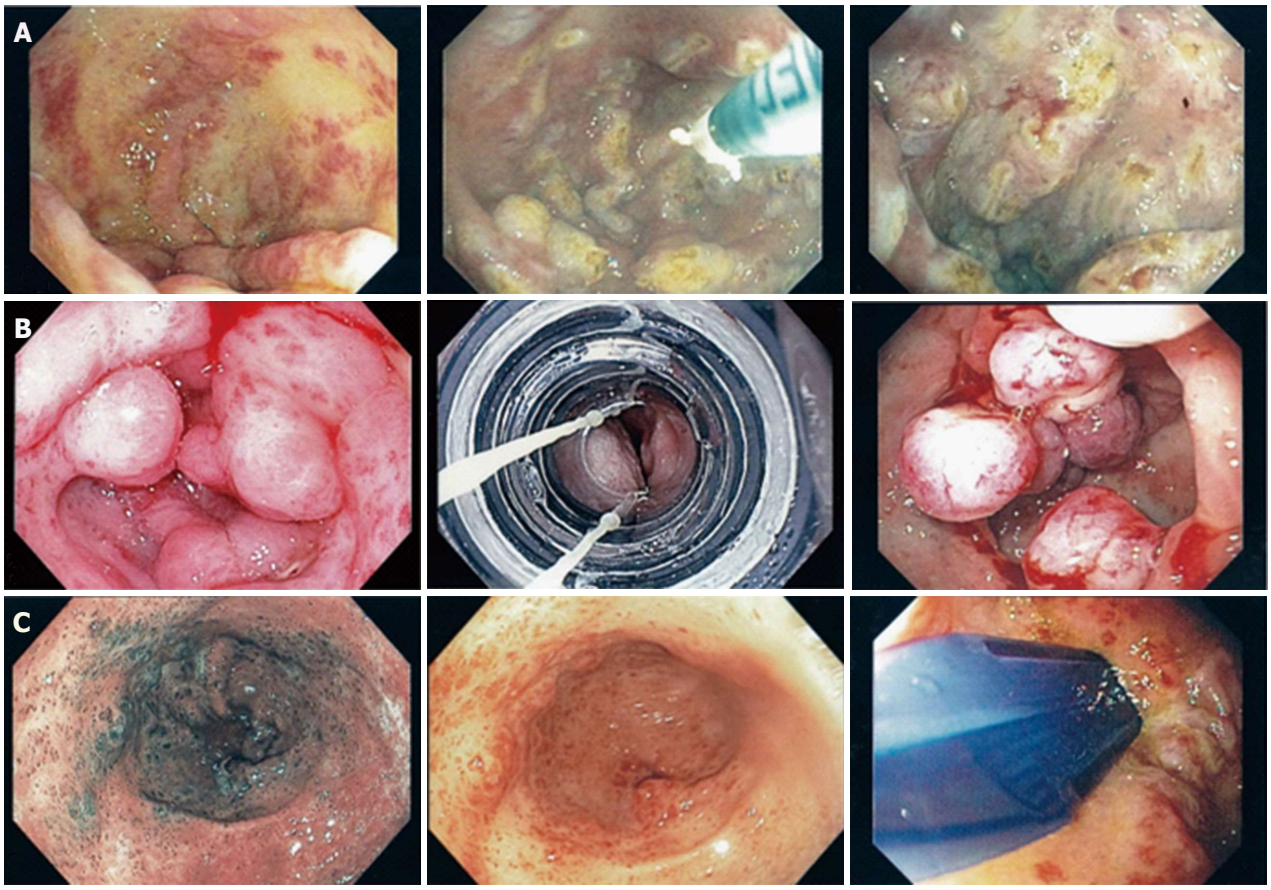

Figure 1 Argon plasma coagulation (A), endoscopic band ligation (B) and TTS- radiofrequency ablation (C).

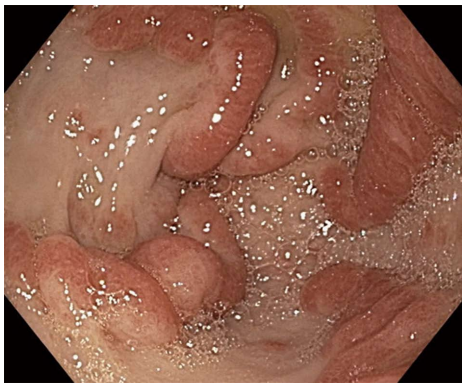

Figure 2 White light endoscopy.

Alabama (UAB).

Technique

Informed consent was obtained from all patients prior to the procedure. All antiplatelet/anticoagulant therapy was discontinued prior to the procedure. High-resolution endoscopy was performed using white light endoscopy (Figure 2) as well as narrow band imaging. Focal ablation was performed using TTS-RFA catheter. The catheter, consisting of 15.7 mm × 7.5 mm transparent electrode array, was passed through the 2.8 mm working channel of the endoscope. The electrode was the placed in opposition of the GAVE lesions and two consecutive pulses of energy at settings 12-15 J/cm^2, 40 W/cm^2 were delivered. Circumferential ablation of antral lesions was achieved using the external rotatory function of the catheter (Video 1). Repeat endoscopies and RFA was performed at intervals of 6-8 wk until all lesions appeared healed.

Statistical analysis

Frequencies (%) were used for categorical variables. For continuous variables, mean ± SD was used. Non-parametric, matched pairs, two-tailed Wilcoxon signed rank tests were used to assess differences in pRBC transfusions before and after treatment. Paired T test was used to compare pre and post treatment Hb concentrations. All the analysis were conducted with SAS 9.4 (Cary, NC, United States) and $P < 0.05$ was considered statistically significant.

RESULTS

Fifteen patients were included in this case series Table 1 describes the demographics. The mean patient age was 62.9 ± 8.7 (range 46-79). Seven out of 15 were women (47%). Included patients underwent a mean of 2.7 ± 1.8 TTS-RFA sessions. TTS-RFA was performed in all patients without adverse events. In addition to TTS-RFA, 7/15 (47%) patients required multimodal

Table 1 Patient demographics, medical history and gastric antral vascular ectasia characteristics

Patient	Age	Sex	Race	GAVE associated conditions	Description	Biopsy confirmed?	ASA	On anticoagulation?	Sedation used	MELD-Na
1	65	F	W	Cirrhosis	Watermelon	N	3	No	MAC	15
2	58	M	W	Cirrhosis	Watermelon	N	3	Yes	MAC	17
3	75	F	B	LVAD	Watermelon	Y	4	No	MAC	n/a
4	55	M	W	Cirrhosis, DM	Nodular	N	3	No	MAC	15
5	79	F	W	Hypothyroidism	Watermelon	Y	3	No	MAC	n/a
6	65	F	W	Cirrhosis	Nodular	Y	3	No	MAC	11
7	70	F	B	Hypothyroidism	Watermelon	Y	2	No	MAC	n/a
8	53	M	W	Cirrhosis	Watermelon	N	3	No	MAC	26
9	70	M	W	DM	Diffuse	N	4	Yes	MAC	n/a
10	46	F	W	CKD	Nodular	Y	3	No	MAC	n/a
11	60	M	W	DM	Watermelon	N	4	No	MAC	n/a
12	68	F	W	Cirrhosis, DM	Watermelon	N	3	No	MAC	18
13	59	M	W	Cirrhosis, DM	Nodular	N	2	No	MAC	14
14	62	M	W	Cirrhosis, DM, LVAD	Nodular	N	4	Yes	MAC	25
15	58	M	W	Cirrhosis, DM	Nodular	Y	3	No	MAC	23

GAVE: Gastric antral vascular ectasia; F: Female; M: Male; LVAD: Left ventricular assist device; DM: Diabetes mellitus; CKD: Chronic kidney disease; Y: Yes; N: No; ASA: American Society of Anesthesiologists score; MAC: Monitored Anesthesia Care; MELD-Na: Model for end-stage liver disease–with sodium.

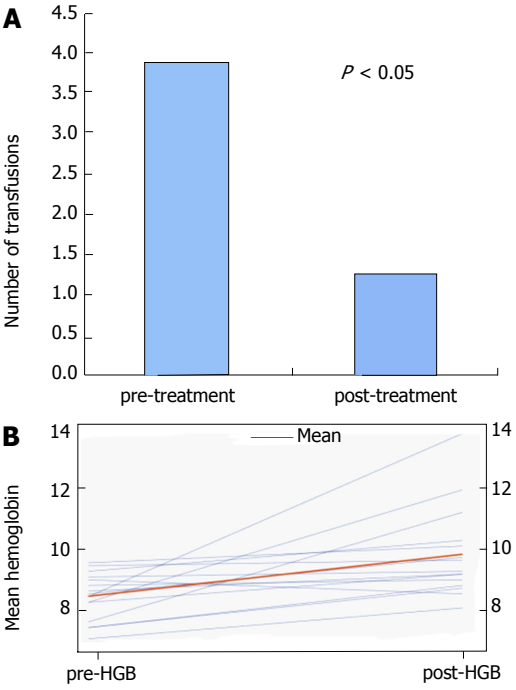

Figure 3 Number of transfusions (A) and mean hemoglobin (B) in 6-mo period pre- and post-treatment for gastric antral vascular ectasia. HGB: Hemoglobin.

approach with APC and/or EBL as well. Average amount of hospitalizations prior to first intervention was 1.4 ± 1.3 and average after initial intervention was 1.1 ± 1.4 ($P > 0.05$). Average time between initial intervention and second intervention was 2.35 ± 2.27 mo. Overall, mean pre- and post-treatment Hb values were 8.2 ± 0.8 g/dL and 9.7 ± 1.6 g/dL, respectively ($P \leqslant 0.05$) (Figure 3A). Mean number of pRBC transfusions before and after treatment was 3.8 ± 4.3 and 1.2 ± 1.7 ($P \leqslant 0.05$), respectively (Figure 3B).

In patients who were primarily treated with TTS-RFA (patients 1-8, $n = 8$), mean number of sessions was 2.8 ± 1.5. Mean number of transfusions was reduced from 3.0 ± 2.7 to 1.2 ± 1.9 ($P > 0.05$). Mean Hb increased from 8.3 ± 1.0 g/dL to 9.9 ± 1.2 g/dL ($P > 0.05$). In patients who required multimodal therapy (patients 9-15, $n = 7$), mean number of TTS-RFA, APC and EBL sessions was 2.9 ± 2.0, 2.9 ± 3.1 and 1.6 ± 2.2, respectively. The mean number of transfusions decreased from 4.9 ± 5.7 to 1.3 ± 1.7 ($P > 0.05$) and the mean Hb increased from 8.1 ± 0.7 g/dL to 9.5 ± 2.1 g/dL ($P > 0.05$). Overall, 8 out of 15 patients were weaned off transfusions (53%) entirely at 6-mo follow-up (Figure 4) and 13/15 saw a decrease in requirements (87%). Only one out of the 15 saw an increase in requirements, while 2 had no change in requirements.

Seven out of 15 patients had classic watermelon description for GAVE, 1/15 with diffuse/honeycomb pattern and 6/15 with nodular GAVE per EGD description. Four out of six of patients with endoscopically nodular GAVE required multimodal therapy. Of the 7 patients requiring multimodal therapy, 4 (57%) had nodular GAVE. Three of these four patients were completely weaned off transfusions in the post-treatment period.

DISCUSSION

GAVE is an important cause of chronic anemia[7]. Though, often asymptomatic and an incidental finding, it can lead to chronic transfusion dependence. Over the past several years, treatment for GAVE has continued to evolve as the number of available effective therapeutic interventions has increased. These included: YAG laser, APC, EBL, cryotherapy and surgical anterectomy (Figure 5)[10,13-15]. APC is most commonly used but has been associated with sepsis, post-APC bleeding, gastric outlet

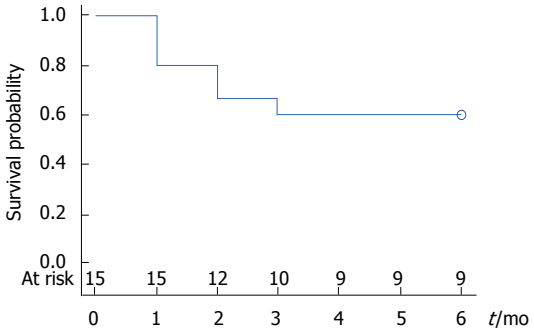

Figure 4 Transfusion free survival curve.

obstruction and increased incidence of hyperplastic polyps[16-18]. Recently, the BARR x Halo^{90} system (Covidien, Sunnyvale, CA, United States), which mounts on to the tip of the standard endoscope, has been successfully used for treatment of GAVE[19,20]. Given the fixed positioning of the electrode, the Halo^{90} catheter requires removal of the endoscope for rotation of the electrode for exact apposition to the mucosa. Repeated intubations are cumbersome and can increase the risk of adverse events, including gastroesophageal junction laceration[21].

The newly introduced TTS-RFA is an improvement over the Halo^{90} system as it enables the endoscopist to reach all areas of the antrum by internally rotating the catheter without having to remove the endoscope. While it does have a reduced ablative area (1.2 cm^2)[22], it delivers up to 120 pulses per session compared to 80 pulses delivered by the Halo^{90} systems. While TTS-RFA is an effective treatment for GAVE, it may not be sufficient to some subgroups of patients.

EBL has lately been demonstrated as a good alternative to APC especially in refractory cases of GAVE and has been found to have a similar safety profile and per Zepeda's randomized controlled time performed better than APC[11,24].

The optimal treatment for GAVE is still unknown and currently there are no studies comparing every modality. However, it is becoming more apparent that patients with more severe, diffuse or refractory GAVE would benefit from multimodal therapy[11,18].

From our review, our numbers indicate that patients undergoing single modality treatment with TTS-RFA and multimodality treatment had overall increase in mean Hb concentrations and decreased transfusion requirements in the 6 mo following treatment.

Interesting, of the 6 patients described as having nodular GAVE, 4 required multimodal therapy suggesting perhaps the multimodal approach should be applied to this newly described variant. Outcomes were favorable with multimodal approach in this group showing increased Hb and decreased transfusion requirements. Increased Hb concentrations and subsequent decreased transfusion requirements together decrease patient costs with fewer hospitalizations related to anemia and

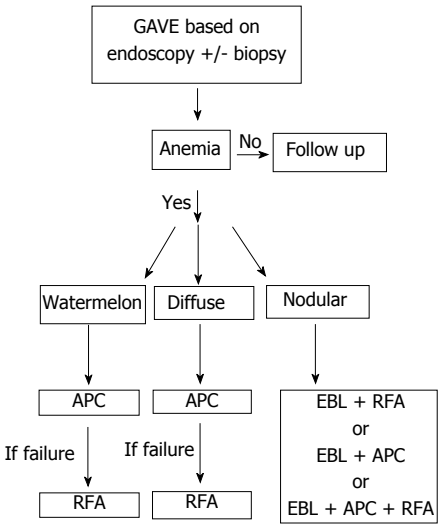

Figure 5 Suggested flow chart for treatment algorithm. GAVE: Gastric antral vascular ectasia; APC: Argon plasma coagulation; RFA: Radiofrequency ablation; EBL: Endoscopic band ligation. Can consider radiofrequency ablation as first line therapy as well for watermelon and diffuse type.

outpatient costs. We did not see a statistically significant decrease in hospitalizations in our case series and this may be due to a myriad of factors including the fact that hospitalizations may be due to another of patients' comorbidities. Also, it is difficult to attain data on number of hospitalizations outside of our facility.

There are several limitations to the conclusions that can be drawn from this study that need to be addressed. First, this is a small, single center, single operator, retrospective study. Second, GAVE was not confirmed on biopsy on all patients. Third, this study is observational and cannot ascertain if any one therapy is superior over other modalities as study design was not to compare modalities. Lastly, patients were followed for a period of 6 mo after the initiation of treatment While the data is promising, it is not clear if GAVE lesions recur or if patients have worsening anemia after our follow-up period of 6 mo.

In conclusion, patients with nodular variant GAVE required multimodal approach more frequently than non-nodular variants. Patients responded well to multimodal therapy and saw decrease in transfusion rates and increase in Hb concentrations. Our findings suggest a multimodal approach may be beneficial in nodular variant GAVE.

ARTICLE HIGHLIGHTS

Research background

At present, optimal treatment of gastric antral vascular ectasia (GAVE) is unknown but it is apparent that severe cases require multimodal therapy. The newly discovered nodular variant, from our study, appears to more often require multimodal therapy.

Research motivation

GAVE is an important cause of chronic anemia and can lead to chronic blood transfusion dependence. Having effective treatment is an important for patient

quality of life.

Research objectives

Main objectives were to study patients presenting with GAVE and chronic anemia and following outcomes based on type of GAVE as well as type of intervention.

Research methods

We reviewed patients with GAVE who underwent treatment at University of Alabama at Birmingham. Included patients had an endoscopic diagnosis of GAVE with associated upper gastrointestinal bleeding or iron deficiency anemia. Medical history including demographic data and chronic medical conditions associated with GAVE were collected. Patients receiving transfusions for other issues outside of GAVE (*i.e.,* for surgeries) were excluded.

Research results

Seven out of 15 patients had classic watermelon description for GAVE, 1/15 with diffuse/honeycomb pattern and 6/15 with nodular GAVE per EGD description. Seven out of 15 patients required multimodal treatment. Four out of six of patients with endoscopically nodular GAVE required multimodal therapy. Overall, mean pre- and post-treatment hemoglobin (Hb) values were 8.2 ± 0.8 g/dL and 9.7 ± 1.6 g/dL, respectively ($P \leqslant 0.05$). Mean number of pRBC transfusions before and after treatment was 3.8 ± 4.3 and 1.2 ± 1.7 ($P \leqslant 0.05$), respectively.

Research conclusions

Patients who received TTS-radiofrequency ablation and patient with multimodal therapy, both had decrease in transfusion requirements and improvement in mean Hb. Our study found that patients with nodular variant GAVE tended to require multimodal therapy more frequently. We believe patients with nodular variant GAVE would benefit from a multimodal approach.

Research perspectives

Lessons learned from this study include importance of larger study population. Future directions include involving larger patient pool and possibly attempting a prospective approach based on suggested algorithm.

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ORIGINAL ARTICLE

Retrospective Study

Mediastinal node staging by positron emission tomography-computed tomography and selective endoscopic ultrasound with fine needle aspiration for patients with upper gastrointestinal cancer: Results from a regional centre

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Abstract

AIM

To investigate the impact of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and positron

emission tomography-computed tomography (PET-CT) in the nodal staging of upper gastrointestinal (GI) cancer in a tertiary referral centre.

METHODS

We performed a retrospective review of prospectively recorded data held on all patients with a diagnosis of upper GI cancer made between January 2009 and December 2015. Only those patients who had both a PET-CT and EUS with FNA sampling of a mediastinal node distant from the primary tumour were included. Using a positive EUS-FNA result as the gold standard for lymph node involvement, the sensitivity, specificity, positive and negative predictive values (PPV and NPV) and accuracy of PET-CT in the staging of mediastinal lymph nodes were calculated. The impact on therapeutic strategy of adding EUS-FNA to PET-CT was assessed.

RESULTS

One hundred and twenty one patients were included. Sixty nine patients had a diagnosis of oesophageal adenocarcinoma (Thirty one of whom were junctional), forty eight had oesophageal squamous cell carcinoma and four had gastric adenocarcinoma. The FNA results were inadequate in eleven cases and the PET-CT findings were indeterminate in two cases, therefore thirteen patients (10.7%) were excluded from further analysis. There was concordance between PET-CT and EUS-FNA findings in seventy one of the remaining one hundred and eight patients (65.7%). The sensitivity, specificity, PPV and NPV values of PET-CT were 92.5%, 50%, 52.1% and 91.9% respectively. There was discordance between PET-CT and EUS-FNA findings in thirty seven out of one hundred and eight patients (34.3%). MDT discussion led to a radical treatment pathway in twenty seven of these cases, after the final tumour stage was altered as a direct consequence of the EUS-FNA findings. Of these patients, fourteen (51.9%) experienced clinical remission of a median of nine months (range three to forty two months).

CONCLUSION

EUS-FNA leads to altered staging of upper GI cancer, resulting in more patients receiving radical treatment that would have been the case using PET-CT staging alone.

Key words: Endoscopic ultrasound; Oesophago-gastric cancer staging; Oesophageal cancer; Positron emission tomography-computed tomography; Mediastinal nodes

Core tip: We have found that positron emission tomography-computed tomography (PET-CT) in the setting of upper gastrointestinal cancer has a high sensitivity and negative predictive value, but has poor specificity and positive predictive value for the detection of malignant mediastinal lymph nodes. This could lead to many patients being over-staged by PET-CT alone. The use of endoscopic ultrasound-guided fine-needle aspiration of mediastinal nodes results in more patients being offered radical therapy.

Harrington C, Smith L, Bisland J, López González E, Jamieson N, Paterson S, Stanley AJ. Mediastinal node staging by positron emission tomography-computed tomography and selective endoscopic ultrasound with fine needle aspiration for patients with upper gastrointestinal cancer: Results from a regional centre. *World J Gastrointest Endosc* 2018; 10(1): 37-44 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i1/37.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i1.37

INTRODUCTION

The optimal management of oesophageal or oesophago-gastric junctional cancer relies on accurate staging to ensure that patients are directed towards the most appropriate treatment pathway for their stage of disease. Surgical resection for patients with localised disease offers the best outcomes with five year survival rates of 17%-47%[1-3]. It is particularly important to ensure that the nodal staging is as accurate as possible in these patients so that patients with incurable disease avoid radical surgical or oncological therapy but are offered a palliative approach. It is equally important that potentially curable patients are not incorrectly thought to have incurable disease.

Several imaging modalities are available and when used in combination, provide the most accurate staging in upper gastrointestinal (GI) cancer. The 2011 United Kingdom joint medical, surgical and oncology guideline advised that positron emission tomography-computed tomography (PET-CT) imaging should be used in combination with standard computed tomography (CT) and upper GI endoscopic ultrasound (EUS) in the assessment and staging of oesophageal and oesophago-gastric junctional cancer[4]. However in the era of relatively widespread use of PET-CT in this setting, the exact role of EUS remains unclear[5].

EUS has proven accuracy in both the assessment of tumour depth (T staging) and the extent of local nodal involvement (N stage) for patients with oesophageal and oesophago-gastric junctional cancer[6-8]. Standard EUS nodal imaging criteria suggestive of malignant lymphadenopathy include node size, border, shape and echogenicity. However, in practice, malignant lymph nodes rarely exhibit all of these characteristics and even with all four characteristics suggestive of malignancy, accuracy is sub-optimal[9-11]. To address this issue, other imaging techniques including tissue elastography and strain ratio have been used to help differentiate between benign and malignant mediastinal lymph nodes in upper GI cancer[12-15]. However tissue acquisition by EUS-FNA remains the optimal way to assess a (non-peritumoural) node for malignant involvement.

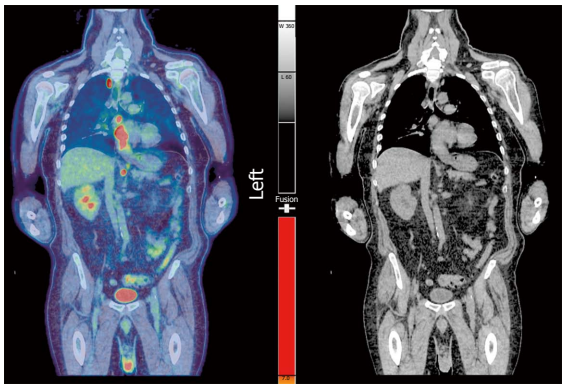

Figure 1 Positron emission tomography-computed tomography image. Positron emission tomography (PET)-computed tomography image of PET positive lower oesophageal tumour with uptake in the primary tumour and also in high paratracheal and coeliac nodes.

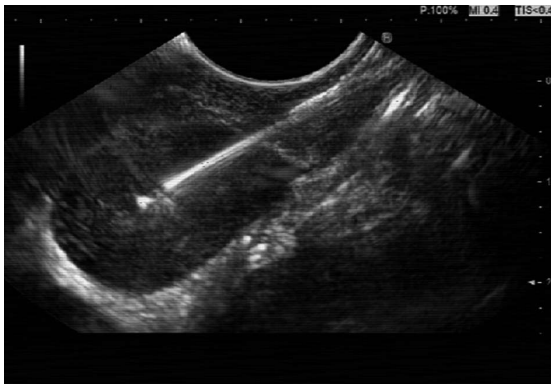

Figure 2 Endoscopic ultrasound-guided fine-needle aspiration image. Endoscopic ultrasound-guided fine-needle aspiration of a high mediastinal node in upper Gastrointestinal cancer.

PET-CT imaging has been shown to be more accurate than PET alone in loco-regional nodal staging of oesophageal cancer[16]. PET-CT is also superior to both PET and CT alone in the detection of distant metastases[17,18]. It also has the potential to alter the staging and management of 12%-18% of patients[19,20]. However, it is well recognised that non-malignant processes such as inflammation can result in false positive findings which will affect the specificity of PET-CT in this setting. The false positive rate of PET-CT has been quoted as between 1.5% and 7.5% in upper GI cancer[21-24]. It has also been suggested that this may be an underestimate as positive findings are not always evaluated further[25]. However some studies have reported excellent specificity figures for PET-CT in this setting[26-32].

The aim of this study was to analyse the results and concordance of PET-CT and EUS-FNA in the staging of mediastinal lymph nodes in one tertiary referral centre, and to assess the impact of EUS-FNA on deciding the final therapeutic pathway.

MATERIALS AND METHODS

Patients

This was a retrospective single centre study. Glasgow Royal Infirmary is a regional tertiary referral centre for EUS staging of upper GI cancer. Using a prospectively collected database, we reviewed the electronically held case records of all patients with a diagnosis of oesophago-gastric cancer who underwent PET-CT and EUS-FNA of at least one mediastinal lymph node between the 1st January 2009 and 31st December 2015. For each identified patient, we reviewed the PET-CT radiology report, the EUS-FNA procedure report and cytology report in addition to the final agreed therapeutic pathway after the conclusive multi-disciplinary team meeting.

Cases were described as PET-CT positive if mediastinal lymph node(s) demonstrated mild, moderate or high FDG uptake on imaging as described in the radiology report. PET-CT negative cases were those cases that demonstrated no uptake in any mediastinal lymph nodes. PET-CT indeterminate cases were those who demonstrated minimal FDG uptake and were excluded from further analysis.

Following PET-CT imaging, all of our patients proceeded to have EUS-FNA within (a maximum of) 4 wk, but within 10-14 d for the vast majority. After MDT discussion, mediastinal nodes of concern distant from the primary tumour were targeted for FNA sampling (Figures 1 and 2).

EUS-FNA positive cases were defined as those whose cytology reports confirmed the presence of malignant cells in the sampled lymph node consistent with origin from their primary upper GI cancer. EUS-FNA negative cases were defined as those reported by the cytologist to show no evidence of malignant cells, together with benign lymphocytes consistent with lymph node sampling indicating an adequate specimen. Samples that did not meet either of these criteria were deemed to be insufficient for diagnosis and were excluded from further analysis.

Using a positive EUS-FNA result as the gold standard for lymph node involvement, we calculated the sensitivity, specificity, positive and negative predictive values (PPV and NPV) and accuracy of PET-CT in the staging of mediastinal lymph nodes. We also reviewed the final tumour stage and patient outcomes to determine the influence that EUS-FNA had in the cases where there was discordance between the PET-CT and EUS-FNA findings.

Instruments and technique

Staging EUS was undertaken by one of three experienced endosonographers (SP, NJ, AJS) using a Pentax linear ± radial echoendoscope, attached to a Hitachi EUB-8500 ultrasound processor. Standard EUS grey-scale images of suspicious lymph nodes were obtained and conventional characteristics of nodal size, shape, distinction of border and density were recorded.

Table 1 Patient characteristics

	n = 121
Gender, *n* (%)	
Male	91 (75.2)
Female	30 (24.8)
Primary diagnosis, *n* (%)	
Oesophageal adenocarcinoma	38 (31.4)
Oesophago-gastric junctional adenocarcinoma	31 (25.6)
Oesophageal squamous cell carcinoma	48 (39.7)
Gastric adenocarcinoma	4 (3.3)
Excluded patients	13
EUS-FNA inadequate	11
PET-CT indeterminate	2

EUS-FNA: Endoscopic ultrasound-guided fine-needle aspiration; PET-CT: Positron emission tomography-computed tomography.

EUS-FNA was performed using a Cook™ 22 gauge needle (Figure 2). A minimum of three samples were obtained by standard technique, stored in cytolite then sent to the laboratory for later cytological analysis by specialist pathologists.

Statistical analysis

A cytological report describing evidence or absence of malignancy in a sample consistent with lymph node sampling was used as the gold standard for analysis. We were then able to calculate the concordance of results between EUS-FNA and PET-CT. We also calculated the sensitivity, specificity, PPV and NPV of PET-CT in the identification of malignant mediastinal lymph nodes in patients with upper GI cancer.

RESULTS

One hundred and twenty one patients were identified in the study period (Table 1). Ninety one (75.2%) were male and thirty (24.8%) were female. The FNA sample was described as inadequate for analysis by the cytologist in eleven cases (8.9%) and the PET-CT findings were indeterminate in two cases (1.7%). These thirteen cases were excluded from further analysis. For the remaining one hundred and eight patients, sixty two had a histological diagnosis of adenocarcinoma (Thirty had oesophageal, twenty eight had junctional and four had gastric adenocarcinoma) and forty six had oesophageal squamous cell carcinoma. Of all these patients, thirty seven were positive on both PET-CT and EUS-FNA and thirty four were negative on both PET-CT and EUS-FNA, giving an overall concordance of 65.7%. The sensitivity, specificity, PPV and NPV results of PET-CT were 92.5%, 50%, 52.1% and 91.9% respectively.

Thirty four (31.5%) patients had positive PET-CT findings but negative EUS-FNA cytology and three (2.8%) patients had negative PET-CT findings and positive EUS-FNA cytology (Table 2). There were therefore thirty seven patients with discordant findings. The final treatment decision was unknown in five patients due to the majority of their management being undertaken at another health board, having been referred to our unit for EUS. For the remaining thirty two patients with discordant results, MDT discussion led to a radical treatment pathway in twenty seven, after the final tumour stage was altered as a consequence of the EUS-FNA findings. In all but one case this was due to downgrading of tumour stage as a result of a negative EUS-FNA in the setting of a positive PET-CT, however in one case the final tumour stage was upgraded due to a positive EUS-FNA but negative PET-CT result. Five patients were directed to a palliative management strategy (Table 3).

Table 2 Breakdown of results of positron emission tomography-computed tomography and endoscopic ultrasound-guided fine-needle aspiration

	PET-CT positive	PET-CT negative
EUS-FNA positive	37 (34.3%)	3 (2.8%)
EUS-FNA negative	34 (31.5%)	34 (31.5%)

EUS-FNA: Endoscopic ultrasound-guided fine-needle aspiration; PET-CT: Positron emission tomography-computed tomography.

When all one hundred and eight cases were taken into consideration, EUS-FNA led directly to an alteration in clinical stage and subsequent clinical management in twenty seven (25%) patients.

In the group of twenty seven patients with discordant results who received radical treatment, six (22.2%) had progression of their disease whilst receiving treatment. Eleven developed progressive disease after completion of treatment at a median of nine months (range three to forty two months). Four patients remained in clinical remission post completion of radical treatment, although one of these patients died from urinary sepsis two years after completion of therapy. The median duration of clinical remission for the fifteen patients (55.6%) who experienced this was nine months (range three to forty two months).

One patient initially accepted radical treatment but refused further treatment after one cycle of neo-adjuvant chemotherapy. One other patient was not fit to have surgical resection after completing neo-adjuvant chemotherapy due to deterioration of other medical comorbidities rather than disease progression. The follow-up records after radical treatment were not available in four patients (Table 4).

We also analysed the data on the basis of histological subtype. For the forty six cases with oesophageal squamous cell carcinoma, nineteen were positive on both PET-CT and EUS-FNA and fourteen were negative on both investigations, resulting in a concordance of 71.7%. In the sixty two cases with adenocarcinoma (which includes oesophageal, junctional and gastric adenocarcinoma), eighteen were positive on both PET-CT and EUS-FNA and twenty were negative on both

Table 3 Multidisciplinary team decision in discordant cases

	n = 37
Radical treatment	27
Palliative care	5
Unknown	5

investigations, resulting in a concordance of 61.3%.

DISCUSSION

Upper GI cancer is a significant public health issue, accounting for 4% of cancers diagnosed in the United Kingdom. The most recent Cancer Research United Kingdom statistics from 2014 report an age standardised incidence of oesophageal cancer of 15.2 per 100000. The corresponding figure for gastric cancer was 11.4 per 100000 population, giving an overall incidence of upper GI cancer of 26.6 per 100000 population[33,34]. In recent years, there has been an increase in the use of PET-CT for clinical staging[5]. Its role in this setting however is controversial[21-25]. We devised this study to assess the impact of EUS-FNA in conjunction with PET-CT in the staging of patients with upper GI cancer.

We have found that PET-CT has 92.5% sensitivity for the detection of metastatic mediastinal lymphadenopathy in the setting of upper GI cancer. However, this is offset by poor specificity at 50%, leading to false-positive mediastinal nodes and the danger of over-staging upper GI cancer with PET-CT. Therefore EUS-FNA appears to have a critical role in confirming whether suspicious nodes identified on PET-CT have malignant involvement, in order to optimise staging of this disease. We feel that this is the most significant and clinically relevant finding of this study. The addition of EUS-FNA to PET-CT appears to lead to more accurate staging with the result of more patients being offered potentially curative treatment. After MDT discussion, EUS-FNA led to altered tumour stage and subsequent clinical management in 25% patients.

Our findings contrast with several previous studies which reported lower sensitivity but higher specificity rates for the detection of malignant mediastinal lymph nodes by PET-CT[26-32]. The interpretation of a positive mediastinal lymph node on PET-CT imaging in these studies seems to have been the same as our interpretation in that any FDG uptake beyond background level was considered significant. The reasons for our different findings remain unclear and require further study.

We looked in detail at the subgroup of 34 patients who had PET-CT positive, EUS-FNA negative nodes. Perhaps unexpectedly, we found that the majority (*n* = 22) of these patients demonstrated moderate or high (rather than just mild) uptake. The reasons for this finding are unclear, but do not suggest over-interpretation of low PET avidity.

Table 4 Outcomes after radical treatment in discordant group

Radical treatment	*n* = 27
Disease progression after completion of treatment	11
Disease progression whilst receiving treatment	6
Clinical remission after completion of treatment	3
Death from other cause whilst in remission	1
Consent for radical treatment withdrawn	1
Had neo-adjuvant chemo but not fit for surgery	1
Unknown	4

Perhaps unexpectedly, we found three cases that had PET-CT negative but EUS-FNA positive nodes. All of these cases had adenocarcinoma; two were junctional and one case had oesophageal adenocarcinoma. Interestingly, we found that one of these cases displayed conventional EUS appearances of malignancy despite negative PET-CT appearances.

Upon analysis of our findings specifically in the context of histological subtype, we found that the concordance rate between PET-CT and EUS-FNA was 71.7% in those with oesophageal squamous cell carcinoma compared to 61.3% in those with adenocarcinoma. A recent paper which evaluated the extent of FDG uptake by malignant lymph nodes in the context of lung cancer found no significant difference on the basis of histological subtype (Which included adenocarcinoma and squamous cell carcinoma)[35]. We could not find any similar study which addresses this issue in the context of upper GI cancer. This is an area that requires further study.

Our study has several limitations. Firstly, this was a study which required us to access notes and electronic data retrospectively, albeit from a prospectively collected database. For some patients, all of the clinical information was not available because they received their follow-up care outside our tertiary referral centre, where the central staging investigations, including EUS and PET-CT, were performed. Secondly, the interpretation of mediastinal nodal involvement and designation of patients as either PET-CT positive or negative was a subjective judgement based on the radiological report rather than the maximum standardised uptake valves (SUVmax), which was only available in a minority of these reports. We agree that such data would be useful for future studies. Thirdly, the duration of follow-up was variable for each patient, although the minimum follow-up for all patients was 6 mo. This relatively short period of follow-up for some patients means that it is difficult to compare longer term survival outcomes with those reported in other studies. Finally, we accept that PET-CT and EUS-FNA are indirect ways of assessing for malignant involvement of mediastinal lymph nodes in the setting of upper GI cancer and that the most certain way to do this is by surgical resection. Unfortunately however, only a minority of our cases proceeded to surgical resection whereas they all had PET-CT followed by targeted mediastinal node sampling by EUS-FNA.

The lack of surgical findings is a weakness of our study but it is reflective of our experience within our tertiary referral centre within the study period.

In conclusion and in the context of widespread use of PET-CT, we suggest that EUS-FNA remains an important diagnostic tool to optimise mediastinal nodal staging in upper GI cancer. Use of this modality ensures that patients are not potentially overstaged by PET-CT, and allows them to be directed to the appropriate therapeutic pathway after MDT discussion.

ARTICLE HIGHLIGHTS

Research background

Upper GI cancer accounts for 4% of cancers diagnosed in the United Kingdom and as such is a significant public health issue. Surgical resection of the primary tumour and any involved lymph nodes results in the best outcomes. For this to be possible however, the surgical team must be confident that the disease is localised. Accurate pre-operative tumour staging is therefore paramount before any decisions regarding treatment are undertaken. In keeping with other organ systems, tumour staging of the upper digestive tract follows the TNM (Tumour, Node, Metastasis) system. The nodal staging of upper GI cancer has been an area of controversy. The 2011 United Kingdom joint medical, surgical and oncology guideline advised that positron emission tomography-computed tomography (PET-CT) imaging should be used in combination with standard computed tomography (CT) and upper GI endoscopic ultrasound (EUS) in the assessment and staging of oesophageal and oesophago-gastric junctional cancer. However in the era of relatively widespread use of PET-CT in this setting, the exact role of EUS remains unclear.

Research motivation

Several studies have assessed the role of PET-CT in the nodal staging of upper GI cancer. Most studies agree that PET-CT has high levels of sensitivity in the detection of malignant mediastinal lymph nodes. However, it is well documented that non-malignant processes such as inflammation can result in false positive findings which will adversely affect the specificity of PET-CT in this setting. The false positive rate of PET-CT has been quoted as between 1.5% and 7.5% in upper GI cancer. It has also been suggested that this may be an underestimate as positive findings are not always evaluated further. We performed this study to evaluate the performance of PET-CT in this setting within our centre and to compare this with the findings from other centres.

Research objectives

The first objective of this project was to evaluate the sensitivity, specificity, positive predictive value and negative predictive value of PET-CT in the detection of malignant mediastinal lymph nodes in the setting of upper GI cancer within the authors' tertiary referral centre. The second objective was to evaluate the impact on subsequent therapeutic strategy that the addition of EUS-FNA had in these patients.

Research methods

The authors performed a retrospective review of prospectively recorded data held on all patients with a diagnosis of upper gastrointestinal (GI) cancer made between January 2009 and December 2015. Only those patients who had both a PET-CT and EUS with FNA sampling of a mediastinal node distant from the primary tumour were included.

Research results

The authors found that EUS-FNA leads to altered staging of upper GI cancer, resulting in more patients receiving radical treatment that would have been the case using PET-CT staging alone. The authors found that EUS-FNA resulted in altered tumour staging and subsequent management in 25% of cases included in this study. The authors were also interested to find that the rate of concordance of PET-CT and EUS-FNA findings was dependent on the tumour histological subtype. There was a 71.7% rate of concordance in cases with squamous cell carcinoma compared with 61.3% concordance in cases with adenocarcinoma. The reasons for this are unclear and this is therefore an area that requires further study.

Research conclusions

The authors suggest that EUS-FNA remains an important diagnostic tool to optimise mediastinal nodal staging in upper GI cancer. Use of this modality ensures that patients are not potentially overstaged by PET-CT, and allows them to be directed to the appropriate therapeutic pathway after MDT discussion. Therefore EUS-FNA appears to have a critical role in confirming whether suspicious nodes identified on PET-CT have malignant involvement, in order to optimise staging of this disease. The authors feel that this is the most significant and clinically relevant finding of this study.

Research perspectives

The authors' findings contrast with several previous studies which reported lower sensitivity but higher specificity rates for the detection of malignant mediastinal lymph nodes by PET-CT. The interpretation of a positive mediastinal lymph node on PET-CT imaging in these studies seems to have been the same as our interpretation in that any FDG uptake beyond background level was considered significant. The reasons for our different findings remain unclear and require further study. The authors also found that the rate of concordance between PET-CT and EUS-FNA findings was greater in patients with squamous cell carcinoma than in those with adenocarcinoma (71.7% and 61.3% respectively). The authors could not find any study which addresses this area in the context of upper GI cancer specifically. This is therefore an area that requires further study.

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ORIGINAL ARTICLE

Retrospective Study

Management of endoscopic biliary stenting for choledocholithiasis: Evaluation of stent-exchange intervals

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Abstract

AIM

To evaluate the best management of plastic stents in patients with choledocholithiasis who were unfit for endoscopic stone removal or surgery.

METHODS

Between April 2007 and September 2017, 87 patients (median age 83.7 years) with symptomatic choledocholithiasis were treated with insertion of 7-Fr plastic stents because complete endoscopic stone retrieval was difficult, and their general condition was not suitable for surgery. Seventy of these patients agreed to regular stent management and stent exchange was carried out at every 6 mo (Group A, n = 35) or every 12 mo (Group B, n = 35). The remaining 17 patients did not accept regular stent exchange, and stents were replaced when clinical symptoms appeared (Group C). We evaluated the frequency of biliary complication and stent patency rate during follow-up periods.

RESULTS

The patency rate of biliary plastic stents was 91.4% at 6 mo (Group A) and 88.6% at 12 mo (Group B), respectively. Acute cholangitis occurred in 2.9% of Group A patients and in 8.6% of Group B patients. In Group C, median stent patency was 16.3 mo, and stent exchange was carried out in 70.6% of cases because of acute cholangitis or obstructive jaundice. Although a high incidence of acute cholangitis occurred, there was no biliary-related mortality.

CONCLUSION

Plastic stent exchange at 12-mo intervals is considered

a safe procedure for patients with choledocholithiasis. Long-term biliary stenting increases biliary complications, but it can be an acceptable option for select patients who are medically unfit for further invasive procedures.

Key words: Acute cholangitis; Endoscopic retrograde cholangiopancreatography; Stent exchange; Plastic stent; Biliary stenting

Core tip: Adequate management of plastic stents for choledocholithiasis was evaluated. Stent exchange was carried out at every 6 mo (Group A), every 12 mo (Group B) or on demand (Group C). The stent patency rates were 91.4% for Group A and 88.6% for Group B, respectively. In Group C, median stent patency was 16.3 mo, and stent exchange was required in 70.6% of patients. There was no biliary-related mortality. Although 12 mo is considered a safe interval for plastic stent exchange, long-term biliary stenting can be an acceptable option for selected patients who are medically unfit for further invasive procedures.

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INTRODUCTION

Endoscopic biliary sphincterotomy with stone removal is the gold standard for the treatment of choledocholithiasis. In the case of difficult biliary stones, various approaches such as mechanical lithotripsy, electrohydraulic lithotripsy, laser lithotripsy, and extracorporeal shock wave lithotripsy have been used for stone extraction[1]. Although most common bile duct stones can be treated successfully by conventional endoscopic procedures, in cases where endoscopic stone removal has failed, surgery must be considered as a next step. However, in elderly patients with serious comorbidities and higher surgical risks, plastic stent placement could be an alternative treatment to surgery. In these cases, the principal aim of biliary stenting is to avoid acute cholangitis, which can progress to sepsis.

With the progressive increase in the elderly population, endoscopic biliary stenting is widely used as a safe approach for the management of choledocholithiasis[2]. However, there are complications, such as stent occlusion and migration[3,4], after stent implantation. The longer the stents are in place, the more likely stent-related complications such as obstructive jaundice and acute cholangitis are to happen. According to a previous report[5], the mean complication rate was 22.4% (0%-64%), and the biliary-related mortality rate was 3.5% (0%-21.1%) after plastic stent replacement. Although the optimal time for biliary plastic stent exchange has not yet been established, a standard type of polyethylene stent patency is approximately 3 mo[6]. Therefore, 3-6-mo intervals for plastic stent exchange have commonly been recommended. However, it is difficult for elderly patients with numerous comorbidities to follow the recommendation for further biliary stent exchange in such a short period. In the present study, we evaluated the adequate intervals for biliary stent exchange as a treatment for patients with choledocholithiasis.

MATERIALS AND METHODS

Study design

Only patients with difficulty of complete endoscopic stone retrieval by conventional endoscopic lithotripsy were eligible for participation in this study. These patients had multiple large stones and/or difficult anatomy after abdominal surgery. From Aril 2008 to September 2017, 87 patients (37 male/50 female; median age 83.7 years) with symptomatic choledocholithiasis who were not suitable for repeated endoscopic lithotripsy and for surgical procedures because of multiple comorbidities were treated with the insertion of 7-Fr biliary plastic stents. Among these, 70 patients received regular stent exchange at every 6 mo (Group A, n = 35) or every 12 mo (Group B, n = 35). They were divided into odd (Group A) and even numbers (Group B) taken from their medical chart. The remaining 17 patients did not accept the recommendation of regular stent exchange (Group C). In this group, we simply observed their conditions until any biliary-related symptom appeared, and stent exchange was carried out only when the onset of a clinical suspicion of stent blockage (*i.e.*, acute cholangitis or obstructive jaundice). After obtaining ethical approval from the Institutional Review Board of our institution, we conducted a retrospective review of medical records of patients. The main outcomes were the stent patency rate and frequency of stent-related complications, especially acute cholangitis. The diagnosis of all patients was based on symptoms, blood tests and imaging modalities. Acute cholangitis was diagnosed according to The Tokyo Consensus Meeting criteria[7].

Endoscopic procedure

Before performing ERCP, informed consent was obtained from each patient and/or caregiver. All endoscopic procedures were performed under moderate sedation by giving intravenous injections of midazolam and pethidine hydrochloride. All patients underwent continuous monitoring by electrocardiogram and pulse

oximetry and received 2 L/min of oxygen through a nasal cannula throughout the endoscopic procedure. The straight type of plastic biliary stents (7 Fr diameter, Boston Scientific Japan) were routinely used for biliary drainage. The length of the stent was routinely 7 cm, but it varied depending on the patients' anatomic characteristics. After plastic stent were inserted, all patients and/or their caregivers received oral and written instructions about further biliary stent management.

Statistical analysis

Various parameters were compared between Group A and Group B. Continuous variables with normal distributions were compared by two-sample *t*-test. Mann-Whitney *U* test was used for the comparison of continuous variables with skewed distributions. The χ^2 test or Fisher's exact test was used for categorical variables as appropriate. *P*-values of 0.05 or less were considered statistically significant. All statistical analyses were performed using the EZR[8] (Saitama Medical Center, Jichi Medical University, Saitama, Japan, version 1.32), which is a graphical user interface for R (the R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander that was designed to add statistical functions frequently used in biostatistics.

RESULTS

In this study, 87 patients with a high surgical risk, for whom it was not possible to completely remove biliary stones using conventional endoscopic lithotripsy, were included. Characteristics of Groups A and B are shown in Table 1. There were no significant differences between the two groups in age, sex, frequency of periampullary diverticulum, reasons for endoscopic stone removal failure, and median follow-up period. Stent patency in Groups A and B is shown in Table 2. Plastic stents were changed at scheduled intervals in 91.4% (32 of 35) of patients in Group A and 88.6% (31 of 35) of patients in Group B. In Group A, stents were changed prior to schedule (6 mo) in 3 cases because of stent occlusion (n = 1) or migration (n = 2), while 4 cases required stent exchange prior to schedule (12 mo) in Group B, due to stent occlusion (n = 3) or migration (n = 1). Acute cholangitis occurred in 2.9% of patients in Group A and 8.6% of patients in Group B.

Characteristics of Group C (stent exchange on demand) are summarized in Table 3. During the follow-up periods, plastic stent exchange was carried out in 70.6% (12 of 17) of patients in this group because of stent-related biliary complications (Table 4). Indications for stent exchange were acute cholangitis (35.3%, n = 6), obstructive jaundice (23.5%, n = 4) or liver dysfunction (11.8%, n = 2). The median stent exchange interval was 16.3 mo (interquartile range 12.7-21.2 mo).

Sphincterotomy was undergone by 83.9% (73 of 87) of patients before the insertion of the biliary stent. In the remaining patients, sphincterotomy was not carried out because of the presence of a large periampullary diverticulum (n = 11) or continuous anticoagulant therapy (n = 3). All 10 cases with acute cholangitis in this study improved with antibiotics and prompt biliary stent exchange. Although 1 case of acute cholangitis progressed into septic shock, the patient recovered within 7 d. There was no mortality related to biliary complication.

DISCUSSION

Endoscopic biliary lithotripsy has been established as a gold standard for the treatment of choledocholithiasis. However, complete stone clearance is not feasible in some cases. Multiple large stones, stone impaction, and difficult anatomy after abdominal surgery are significant predictors for failure of endoscopic lithotripsy. If endoscopic stone removal attempts have failed, surgical procedures such as sphincteroplasty and/or choledochoduodenostomy are required. However, elderly patients with multiple comorbidities tend to be poor candidates for invasive surgery. In these cases, to avoid the onset of biliary complication, especially acute cholangitis, biliary stenting could be an alternative option.

The principal aim of this study is how to manage biliary stents in patients with choledocholithiasis for whom previous endoscopic lithotripsy had failed and who were medically unfit for surgery. According to previous studies[4,6,9], plastic stents should be exchanged within 3-6 mo to prevent later complications, such as acute cholangitis. Di Giorgia *et al*[9] evaluated 78 patients with biliary stenting for choledocholithiasis. They compared two groups as follows: Scheduled stent exchange *vs* stent exchange on demand. They suggested that the best way to prevent acute cholangitis was to change the plastic stent every 3 mo. Although plastic stent exchange within 3-6 mo is commonly advocated, it is too difficult for elderly patients with numerous comorbidities to undergo an ERCP in such a short period. In the present study, we attempted to define the best intervals for stent exchange for choledocholithiasis and planned plastic stent exchange at every 6 mo (Group A) or every 12 mo (Group B). Stent exchange prior to schedule was required in 8.6% of patients in Group A and 11.4% of patients in Group B. Li *et al*[10] evaluated 50 patients with biliary stenting for choledocholithiasis and reported that stent patency rates were 94% at 6 mo, 79% at 12 mo, and 58% at 24 mo. Slattery *et al*[11] analyzed stent patency rates of 201 patients with choledocholithiasis, and their results were 93.5% at 6 mo and 81.9% at 24 mo. Our results are similar to those of these reports. High stent patency rates at 12 mo in our study suggest that short-term plastic stent exchange is not always necessary.

Table 1 Characteristics of patients who underwent regular stent exchange, *n* (%)

	Group A (*n* = 35)	Group B (*n* = 35)	*P* value
Stent-exchange schedule	6 mo	12 mo	
Age, yr	82.9 (77-87)	84.4 (76-89)	NS
Sex, male/female	15/20	16/19	NS
Periampullary diverticulum	7 (20.0)	8 (22.9)	NS
Sphincterotomy	30 (85.7)	29 (82.9)	NS
Post-ERCP pancreatitis	1 (2.9)	1 (2.9)	NS
Reason for endoscopic stone removal failure			
No. of stones	16 (45.7)	14 (40.0)	NS
Size of stones	17 (48.6)	18 (51.4)	NS
Anatomical difficulty	2 (5.7)	3 (8.6)	NS
Follow-up periods, mo	27.3 (12-40)	26.5 (14-37)	NS

Continuous variables are expressed as median (interquartile range). Categorical variables are expressed as numbers. ERCP: Endoscopic retrograde cholangiopancreatography; NS: Not significant.

Table 2 Stent patency of patients who underwent regular stent exchange, *n* (%)

	Group A (*n* = 35)	Group B (*n* = 35)	*P* value
Stent-exchange schedule	6 mo	12 mo	
Stent patency at scheduled time	32 (91.4)	31 (88.6)	NS
Stent exchange prior to schedule	3 (8.6)	4 (11.4)	NS
Details of stent troubles			
Stent occlusion	1 (2.9)	3 (8.6)	< 0.05
Stent migration	2 (5.7)	1 (2.9)	NS
Acute cholangitis	1 (2.9)	3 (8.6)	< 0.05
Biliary-related mortality	0	0	NA

NS: Not significant; NA: Not available.

Table 3 Characteristics of patients who underwent stent exchange on demand, *n* (%)

Group C (*n* = 17)	
Age, yr	84.1 (76-90)
Sex, male/female	6/11
Periampullary diverticulum	4 (23.5)
Sphincterotomy	14 (82.3)
Post-ERCP pancreatitis	0
Reasons for endoscopic stone removal failure	
No. of stones	9 (52.9)
Size of stones	6 (35.3)
Anatomical difficulty	2 (11.8)
Reasons for rejecting scheduled stent exchange	
Cardiovascular diseases	4 (23.5)
Stroke sequelae	4 (23.5)
Age factors	3 (17.6)
Dementia	3 (17.6)
Malignancy	3 (17.6)
Follow-up periods, mo	24.8 (14-32)

Continuous variables are expressed as median (interquartile range). Categorical variables are expressed as numbers. ERCP: Endoscopic retrograde cholangiopancreatography.

Table 4 Stent patency of patients who underwent stent exchange on demand, *n* (%)

Group C (*n* = 17)	
Stent-exchange cases	12 (70.6)
Indication for stent exchange	
Acute cholangitis	6 (35.3)
Obstructive jaundice	4 (23.5)
Liver dysfunction	2 (11.8)
Details of stent troubles	
Stent occlusion	10 (58.8)
Stent migration	2 (11.8)
Duration of stent patency	16.3 (12.7-21.2)
Biliary-related mortality	0

Continuous variables are expressed as median (interquartile range).

Patients were instructed regarding the possible complications of delayed stent replacement and the necessity of regular stent exchange, but some patients or their caregivers did not accept the recommendation. In this study, 17 patients refused regular stent exchange (Group C) because of their serious conditions.

High incidence of acute cholangitis (35.3%) was seen in Group C. Sepsis due to acute cholangitis was seen in 23.5% (4 of 17) of patients in Group C, but all cases recovered with prompt stent exchange and antibiotics. There have been several studies regarding long-term biliary stenting for choledocholithiasis[5,10-13]. Ang *et al*[5] evaluated 83 patients with choledocholithiasis treated with long-term biliary stenting and found biliary complication in 34% of patients and acute cholangitis in 24% of patients. Bergman *et al*[12] analyzed 58 patients with choledocholithiasis and permanent biliary stenting; acute cholangitis was seen in 36% of patients, and the mortality rate related to biliary complication

was 16%. Pisello *et al*[13] reported on 30 patients with choledocholithiasis and long-term biliary stenting; late complications occurred in 34% of patients, and the mortality rate related to biliary complication was 6.6%. Slattery *et al*[11] reported on 201 patients with long-term biliary stenting for choledocholithiasis. According to their report, the frequencies of acute cholangitis (2.9%) and obstructive jaundice (8%) were significantly lower, and median stent patency (59.6 mo) was significantly longer than in other reports. They insisted that their superior stent patency was attributable to adequate sphincterotomy at the initial stent placement and attempts for partial duct clearance in all cases.

In the present study, rates of acute cholangitis in Group A (2.9%) and B (8.6%) were lower than we had estimated. When stents were exchanged at scheduled intervals, sludge occluded the stent lumen or adhered to the stent in 12 cases in Group A and 16 cases in Group B. However, most of these cases showed no signs of biliary obstruction. In these situations, bile duct patency is maintained by the bile drain mechanism around the stent. Moreover, even if the plastic stent becomes occluded, a clogged stent would have the potential to keep common bile duct stones from impacting. In the present study, we used plastic stents with a 7Fr diameter. We believe that stent diameter is not relevant to stent patency if adequate sphincterotomy was carried out. Regarding the migration of plastic stents, it was seen in only 5.7% (5 of 87) of patients. This might be because biliary stones stabilized the plastic stent inside the common bile duct and prevented stent migration.

According to previous studies[14-17], the size of biliary stones decreases after plastic stent placement, and long-term stenting offers the possibility of complete stone elimination. In contrast, it has also been reported that long-standing biliary stents consequentially increase the risk of formation of biliary stones. The sphincter of Oddi functions as a mechanical barrier preventing the regurgitation of duodenal contents into bile duct. Therefore, lost sphincter of Oddi function results in bacterial growth in the bile duct by ascending infection and results in formation of brown pigment stones[18-20]. Sohn *et al*[21] reported that most cases of acute cholangitis after long-term biliary stenting occurred due to the development of brown pigment biliary stones. They suggested that biliary stents themselves could serve as the nidus for stone formation and development. In the present study, stone clearance was obtained in 5 patients (14.3%) from Group A and in 4 patients (11.4%) from Group B after repeated stent exchange. The mean period for stone clearance was 659 days in Group A and 718 d in Group B. However, significant stone growth also appeared in 2 patients (5.7%) in Group B and 3 patients (17.6%) in Group C (these data are not shown in the table). Our clinical data suggest that biliary stenting for choledocholithiasis could assist in subsequent biliary stone clearance, although it could also be related to stone formation and development, depending on the situation.

In this study, poor surgical candidates who underwent endoscopic biliary stenting showed low frequency of acute cholangitis and superior stent patency at 12 mo after stent implantation. In a progressively aging society, 1 year should be considered as an appropriate interval for plastic stent exchange in the treatment of choledocholithiasis. Although long-term biliary stenting increases the risk of biliary complication, it could also be an acceptable strategy for patients with limitations who are clinically unfit for invasive procedures. In this study, a small sample size may be one of the problems to support our definite conclusion. In addition, our study is retrospective evaluation, so it may be difficult to exclude any bias completely. Superior stent patency rate which are observed in this study may not hold true because of these limitations. Further studies with a large number of patients under prospective design will be required to confirm our results.

ARTICLE HIGHLIGHTS

Research background

In elderly patients with serious comorbidities, endoscopic biliary stenting is widely used as a safe approach for the management of choledocholithiasis. Although short intervals for plastic stent exchange have commonly been recommended to avoid acute cholangitis, it is difficult for elderly patients with numerous comorbidities to accept biliary stent exchange in such a short period. We evaluated the safe interval of endoscopic biliary stent exchange for choledocholithiasis.

Research motivation

There has been limited data on the outcome of long-term biliary stenting for choledocholithiasis. In order to reduce the unnecessary medical procedures for high-risk patients, the optimal time for biliary stent exchange has to be established.

Research objectives

The principal aim of this study is an evaluation of the adequate intervals for biliary stent exchange as a treatment for patients with choledocholithiasis. This research will contribute to the management of endoscopic biliary stenting for choledocholithiasis of high-risk patients.

Research methods

Patients with symptomatic choledocholithiasis were treated with biliary plastic stents because complete endoscopic stone retrieval was difficult. Stent exchange was carried out at every 6 mo or every 12 mo. In the patients who didn't accept the recommendation of regular stent exchange, biliary stents were replaced when clinical symptoms appeared. The authors evaluated the frequency of biliary complication and stent patency rate during follow-up periods.

Research results

Regarding the stent patency rate, there is no significant difference between the 6 mo stent exchange group and the 12 mo stent exchange group. Although a high incidence of acute cholangitis occurred in the on demand stent exchange group, there was no biliary-related mortality.

Research conclusion

Although exchanges of plastic stent in short intervals have been recommended to avoid acute cholangitis, this study concluded that 12 mo is considered a safe interval for plastic stent exchange in choledocholithiasis. Long-term biliary stenting longer than 12 mo can also be an acceptable option for selected patients who are medically unfit for further invasive procedures, but we have

to observe these cases carefully because of the high frequency of acute cholangitis.

Research perspectives

The authors' research findings contribute to the discussion about safe interval for plastic stent exchange in choledocholithiasis. The study design is retrospective and sample size is small, so further clinical trials in a large population under prospective design will be valuable.

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ORIGINAL ARTICLE

Prospective Study

Bacterial presence on flexible endoscopes *vs* time since disinfection

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Informed consent statement: All patients provided written consent prior to the performed procedure; all data was anonymized prior to analysis.

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Data sharing statement: Complete dataset is available from the first author by e-mail at mallett4@myumanitoba.ca. No additional data is available.

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Abstract

AIM

To correlate the length of endoscope hang time and number of bacteria cultured prior to use.

METHODS

Prospectively, we cultured specimens from 19 gastroscopes, 24 colonoscopes and 5 side viewing duodenoscopes during the period of 2011 to 2015. A total of 164 results had complete data denoting date of cleansing, number of days stored and culture results. All scopes underwent initial cleaning in the endoscopy suite utilizing tap water, and then manually cleaned and flushed. High level disinfection was achieved with a Medivator© DSD (Medivator Inc., United States) automated endoscope reprocessor following manufacturer instructions, with Glutacide® (Pharmax Limited, Canada), a 2% glutaraldehyde solution. After disinfection, all scopes were stored in dust free, unfiltered commercial cabinets for up to 7 d. Prior to use, all scopes were sampled and

plated on sheep blood agar for 48 h; the colony count was obtained from each plate. The length of endoscope hang time and bacterial load was analyzed utilizing unpaired *t*-tests. The overall percentage of positive and negative cultures for each type of endoscope was also calculated.

RESULTS

All culture results were within the acceptable range (less than 200 cfu/mL). One colonoscope cultured 80 cfu/mL after hanging for 1 d, which was the highest count. ERCP scopes cultured at most 10 cfu, this occurred after 2 and 7 d, and gastroscopes cultured 50 cfu/mL at most, at 1 d. Most cultures were negative for growth, irrespective of the length of hang time. Furthermore, all scopes, with the exception of one colonoscope which had two positive cultures (each of 10 cfu/mL), had at most one positive culture. There was no significant difference in the number of bacteria cultured after 1 d compared to 7 d when all scopes were combined (day 2: P = 0.515; day 3: P = identical; day 4: P = 0.071; day 5: P = 0.470; day 6: P = 0.584; day 7: P = 0.575). There was also no significant difference in the number of bacteria cultured after 1 day compared to 7 d for gastroscopes (day 2: P = 0.895; day 3: P = identical; day 4: P = identical; day 5: P = 0.893; day 6: P = identical; day 7: P = 0.756), colonoscopes (day 2: P = 0.489; day 4: P = 0.493; day 5: P = 0.324; day 6: P = 0.526; day 7: P = identical), or ERCP scopes (day 2: P = identical; day 7: P = 0.685).

CONCLUSION

There is no correlation between hang time and bacterial load. Endoscopes do not need to be reprocessed if reused within a period of 7 d.

Key words: Bacteria; Endoscopy; Processing; Hang time; Colonoscopy; Endoscopic retrograde cholangiopancreatography; Gastroscopy

Core tip: Several cases of transmission of antibiotic resistant microbes have recently been reported, most notably carbapenem-resistant *Enterobacteriaceae*. However, according to our research, there does not appear to be a correlation between the number of days that an endoscope has been hanging and the bacterial load. Therefore, reprocessing of endoscopes is unnecessary prior to use, if they undergo cleaning according to guidelines, maintained in a ventilated, dust-free cabinet between use and the period of hang time does not exceed 7 d.

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INTRODUCTION

The use of flexible endoscopes is instrumental in the diagnosis and management of gastrointestinal and hepatobiliary disease. Due to the invasive nature of these procedures they carry a risk of infection, either by bacteria within the individuals' gastrointestinal tract or through bacteria contaminating the endoscope[1,2]. Endoscopes are defined as "semi critical" devices as per the Spaulding classification of medical devices; in order to minimize the risk of inoculating patients with microbes from a previous patient, they must undergo high level disinfection between patients[1].

Previous guidelines established by several international societies, including the European Society of Gastrointestinal Endoscopy, suggested that in addition to high level disinfection after use, endoscopes should be reprocessed the day of procedure prior to use[3,4]. However, these guidelines were based on very limited research and data[5]. This extra reprocessing of endoscopes is extremely expensive for facilities and leads to extra wear and damage to the equipment (both processing machines and endoscopes)[6]. A study conducted at our institution examined the necessity of the aforementioned guidelines, and established that endoscopes could be stored up to 7 d prior to use without the need for reprocessing when maintained in a ventilated, dust free cabinet[7]. Thus, our institution has been following these guidelines for the past few years. Similarly, a limited study conducted in Czechoslovakia identified that colonoscopes and duodenoscopes, if properly disinfected and stored, did not require reprocessing for up to 5 d[8].

Several cases of transmission of antibiotic resistant microbes have been documented recently, most notably carbapenem-resistant *Enterobacteriaceae*, in the United States *via* endoscopy[9]. One of the most concerning aspects of these recent cases is that no breaches in reprocessing of the endoscopes was identified[9]. The aim of this study was to verify a previous study conducted at our institution, correlating endoscope hang time and bacterial load prior to use, as well as to evaluate our procedures in light of the recent cases of transmission of bacteria between patients.

MATERIALS AND METHODS

During the period of 2011 to 2015, we prospectively sampled specimens from nineteen gastroscopes, twenty-four colonoscopes, and five side viewing duodenoscopes, available in our institution. Each week during that time frame, two scopes were sampled on a rotating basis, accounting for a total of 327 samples. Only 164 results could be obtained which had complete data including date of cleansing, number of days stored and culture results.

Prior to removal from the endoscopy suite, all scopes are flushed with tap water and then the outer surface

is wiped clean with tap water. Endoscopes were initially manually brushed to remove debris from the ports. For the duodenoscopes and the colonoscopes, the suction cylinder (to distal end and suction connector end) and instrument channel ports were manually brushed a total of three times and then flushed with at least 500 cc while submersed in detergent. With respect to ERCP scopes, the elevator recess, in both the up and down position, suction cylinder and instrument channel port were manually flushed three times each. In addition, for the ERCP scopes, the elevator wire and forceps elevator (in the up and down position) were manually cleaned three times. The elevator recess was flushed with a 30 mL water/detergent mixture in the up and down position. Using an automated flushing pump all scopes were flushed with a water/detergent mixture for 1 min and 15 s and then with air for 30 s; during flushing of ERCP scopes, the elevator mechanism was moved up and down.

The endoscopes then underwent high level disinfection using a Medivator© DSD (Medivator Inc., United States) automated endoscope reprocessor (AER). High level disinfection was achieved utilizing Glutacide® (Pharmax Limited, Canada), a 2% glutaraldehyde solution that can be utilized for 30 d. The AER cycle consists of a 1-min flush with reverse osmosis water, followed by a 5-min detergent disinfection and a 20-min detergent soak. Next, the scopes undergo two rinses with reverse osmosis water (4:10 min and 3 min each), then a 1-min rinse with 70% alcohol. Finally, they undergo a 5-min air dry and a 5-min manual air dry (utilizing filtered medical, non-heated air), of the suction channel, air/water channel and dials. All endoscopes are then stored in dust free, unfiltered, roll top commercial cabinets manufactured by Olympus. The cabinets were wiped clean by staff health care aides monthly, as well as, on an as needed basis.

Samples for culture were obtained using a protocol, developed at our institution, in accordance with those developed by the Endoscopy Working Group as part of the Manitoba Advisory Committee on Infectious Diseases[10]. The endoscopes were all sampled after a period of hang time, as described below. Sampling of the endoscopes was undertaken outside the reprocessing room, within the health care aide room, within a designated area. The distal end of the endoscope is held inside a sterile specimen container, 10 mL of sterile water is drawn up, and 5 mL is flushed through the biopsy channel. An endoscopy brush is then dipped into sterile water and passed through the biopsy channel until it emerges out the distal end, it's then pulled back up the channel and pushed through once more until it emerges 2 cm into the sterile container. Scissors are then cleaned with an alcohol pad and used to cut off 2 cm of the brush into the sterile container. Finally, the remaining 5 mL of sterile water are passed through the biopsy channel and collected in the sterile container. Prior to plating, the water containing the cleaning brush was vortexed, to ensure a representative sample was obtained. A 100 μL aliquot of the samples were placed on a sheep blood agar plate, spread with a glass rod until absorbed by the media. Plates were then incubated at 35 ℃ for 48 h. The colony count was obtained after 48hours and was then equated to colony forming units per milliliter. It should be noted that ERCP scopes were cultured with the elevator in the down position.

Hang time was determined by calculating the total number of days between cleaning and microbiological sampling. Guidelines at our facility dictate that any samples greater than 200 cfu/mL (cut-off for acceptable microbial levels for potable water) are deemed as an unacceptable level of bioburden and the scope would be removed from use to be reprocessed[10]. The data was evaluated using an unpaired *t*-test with Minitab statistical software©, comparing the number of colony forming units cultured on each type of endoscope after 1 d of hang time compared to subsequent days (up to day 7). Overall, the percentage of negative cultures (*i.e.*, no growth) and positive cultures, for each type of endoscope was also calculated. The statistical methods in the manuscript were reviewed and approved by all authors with the help of the quality improvement specialist affiliated with the Brandon Reginal Health Centre.

RESULTS

All positive culture results were less than 200 cfu/mL, and thus no endoscopes required additional reprocessing or quarantine. It should be noted that samples which were excluded from our study, due to missing data and inability to calculate hang time, all had culture results within the acceptable limit. A colonoscope cultured the highest bacterial load at 80 cfu/mL, with a hang time of 1 d. The highest bacterial load for ERCP scopes was 10 cfu/mL, this occurred at hang times 2 and 7 d. The highest count for gastroscopes was 50 cfu/mL after a hang time of 1 d. Most cultures, regardless of hang time, were negative for growth (Figures 1-3). Only one endoscope had more than one positive culture, one colonoscope had two positive cultures (of 4 obtained), each of 10 cfu/mL.

There was no significant difference at the 95% confidence interval, in the number of bacteria cultured after 1 d compared to 7 d when grouping all scopes (Table 1). At the 95%CI no statistical differences were observed, in culture results after 1 d of hang time compared to subsequent days for each scope type (Table 1).

DISCUSSION

The percentage of negative cultures is similar for both day 1 and day 7 of storage for each type of endoscope, suggesting that storage of endoscopes for 7 d is safe, and that the risk of patient transmission is relatively

Table 1 Comparison of number of bacteria cultured from the different types of endoscopes sampled from day 1-7, *P*-values from the unpaired *t*-test performed with a 95%CI

	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
All Scopes (Day 1: $n = 82$)	$P = 0.515$ ($n = 18$)	P = identical ($n = 3$)	$P = 0.071$ ($n = 18$)	$P = 0.470$ ($n = 15$)	$P = 0.584$ ($n = 7$)	$P = 0.575$ ($n = 21$)
Gastroscopes (Day 1: $n = 34$)	$P = 0.895$ ($n = 4$)	P = identical ($n = 3$)	P = identical ($n = 12$)	$P = 0.893$ ($n = 8$)	P = identical ($n = 2$)	$P = 0.756$ ($n = 10$)
Colonoscopes (Day 1: $n = 46$)	$P = 0.489$ ($n = 10$)	No data ($n = 0$)	$P = 0.493$ ($n = 5$)	$P = 0.324$ ($n = 7$)	$P = 0.526$ ($n = 4$)	P = identical ($n = 5$)
ERCP Scopes (Day 1: $n = 2$)	P = identical ($n = 4$)	No data ($n = 0$)	Insufficient data ($n = 1$)	No data ($n = 0$)	No data ($n = 0$)	$P = 0.685$ ($n = 6$)

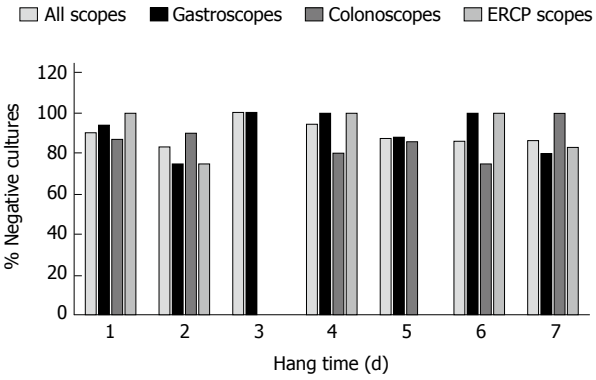

Figure 1 Percentage of negative cultures obtained for all endoscopes throughout the test period. The large percentage of negative cultures is consistent from 1 to 7 d of hang time and between the different types of scopes. ERCP: Endoscopic retrograde cholangiopancreatography.

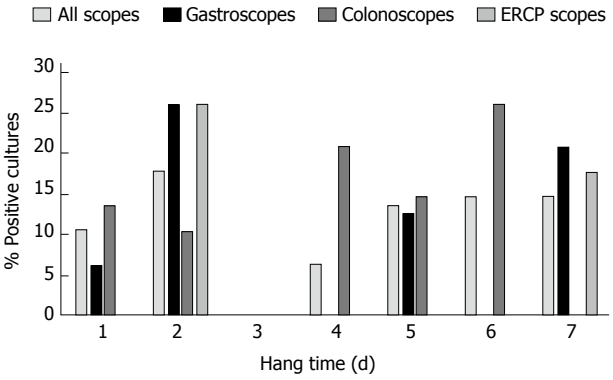

Figure 2 Percentage of positive cultures obtained for all endoscopes throughout the test period. ERCP: Endoscopic retrograde cholangiopancreatography.

low. This correlates with the previous findings of the study conducted at our institution[7].

Furthermore, all culture results were less than 200 cfu/mL, the acceptable limit for potable water, and thus were within the guidelines for use in endoscopy[10]. It is also of note that the highest bacterial load was cultured from a colonoscope, and the lowest was from an ERCP scope. This is despite the fact that ERCP scopes have a large number of moving parts, which are more likely to harbour bacteria[11]. Overall, it appears that proper disinfection and storage of endoscopes makes reprocessing prior to use unnecessary within a period of 7 d. Interim guidelines produced by the Centers for Disease Control and Prevention have suggested that cultures obtained after processing should possess less than 10 cfu[12]. All samples obtained in our study were

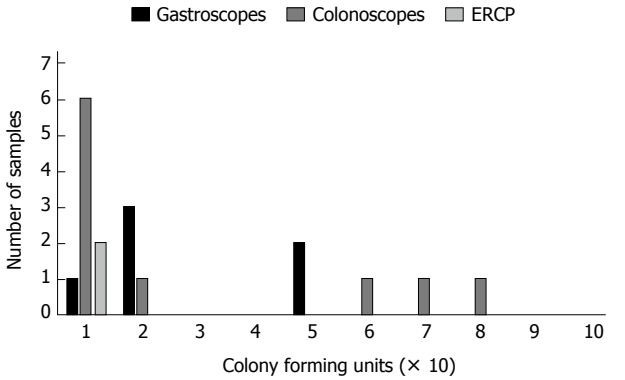

Figure 3 Number of positive culture samples at each level of colony forming units for each endoscope type, where the number of negative cultures for gastroscopes was 67 ($n = 73$), for colonoscopes 67 ($n = 78$) and endoscopic retrograde cholangiopancreatography scopes was 12 ($n = 14$). ERCP: Endoscopic retrograde cholangiopancreatography.

less than this new limit, however our centre should adjust our guidelines to fit these new suggestions.

Limitations

One limitation to this study is the relatively small sample size, especially with regards to ERCP scopes, as a statistical difference may not have been detected utilizing the *t*-test even if it existed. Furthermore, the type of bacteria cultured was not assessed in this study and therefore in future studies, it would be important to assess which bacteria are able to withstand the disinfection process. It has been suggested that sterilization of endoscopes may be required for prevention of transmission of certain species of bacteria rather than disinfection[13]. Lastly, not all bacteria are amenable to culture using the medium employed in this study. Moving forward, our institution will be assessing the use of different culture media in comparison to the commonly used sheep blood agar, including reasoner's 2A agar which may identify water stressed or damaged organisms[14]. For future studies, it may be valuable to initially plate a 0.5 mL sample onto MacConkey media to allow for rapid screening for organisms which may lead to patient harms[15].

In conclusion, there is no clear correlation between the duration of hang time of an endoscope and bacterial load. This further supports the previous study conducted at our institution indicating that there is not a need to reprocess endoscopes prior to use if they are properly disinfected, and properly stored for up to 7 d[7]. It is important to stress that proper cleansing of endoscopes be carried out immediately after use, according to

manufacturer suggestions. Further work in this area should focus on assessing the type of bacteria cultured in order to determine the true risk to the patient, as well as determining methods to further decrease the risk of transmission of antibiotic resistant organisms. Lastly, new research should assess whether a limit of 200 cfu/mL is appropriate or if transmission of virulent organisms can occur below this limit.

ARTICLE HIGHLIGHTS

Background

Due to the nature of endoscopy, all endoscopes must undergo high level disinfection after use. Previously, guidelines suggested that endoscopes be reprocessed prior to use, regardless of the hang time. These guidelines led to excessive wear on the instruments, and were quite costly for institutions. A previous study conducted at our institution suggested that endoscopes could be stored for up to 7 d prior to requiring reprocessing. The aim of this study was to determine if there was a correlation between the hang time and bacterial load on endoscopes.

Research frontiers

There have recently been several documented cases of transmission of antibiotic resistant organisms, specifically carbapenem-resistant *Enterobacteriaceae via* endoscopy. This has led to increased interest in the bacterial contamination on endoscopes after thorough disinfection.

Innovations and breakthroughs

The study demonstrates that endoscopes can be stored for a period of up to 7 d without significant levels of bacterial contamination, there does not appear to be a correlation between hang time and bacterial load. There does not appear to be a need for reprocessing of endoscopes prior to use if disinfected and stored properly. This is contrary to previous society guidelines which suggested disinfection prior to use.

Applications

Endoscopes if disinfected and stored properly can be stored for up to 7 d without requiring reprocessing prior to use.

Terminology

Hang time refers to the number of days an endoscope was stored, from disinfection to microbiological evaluation.

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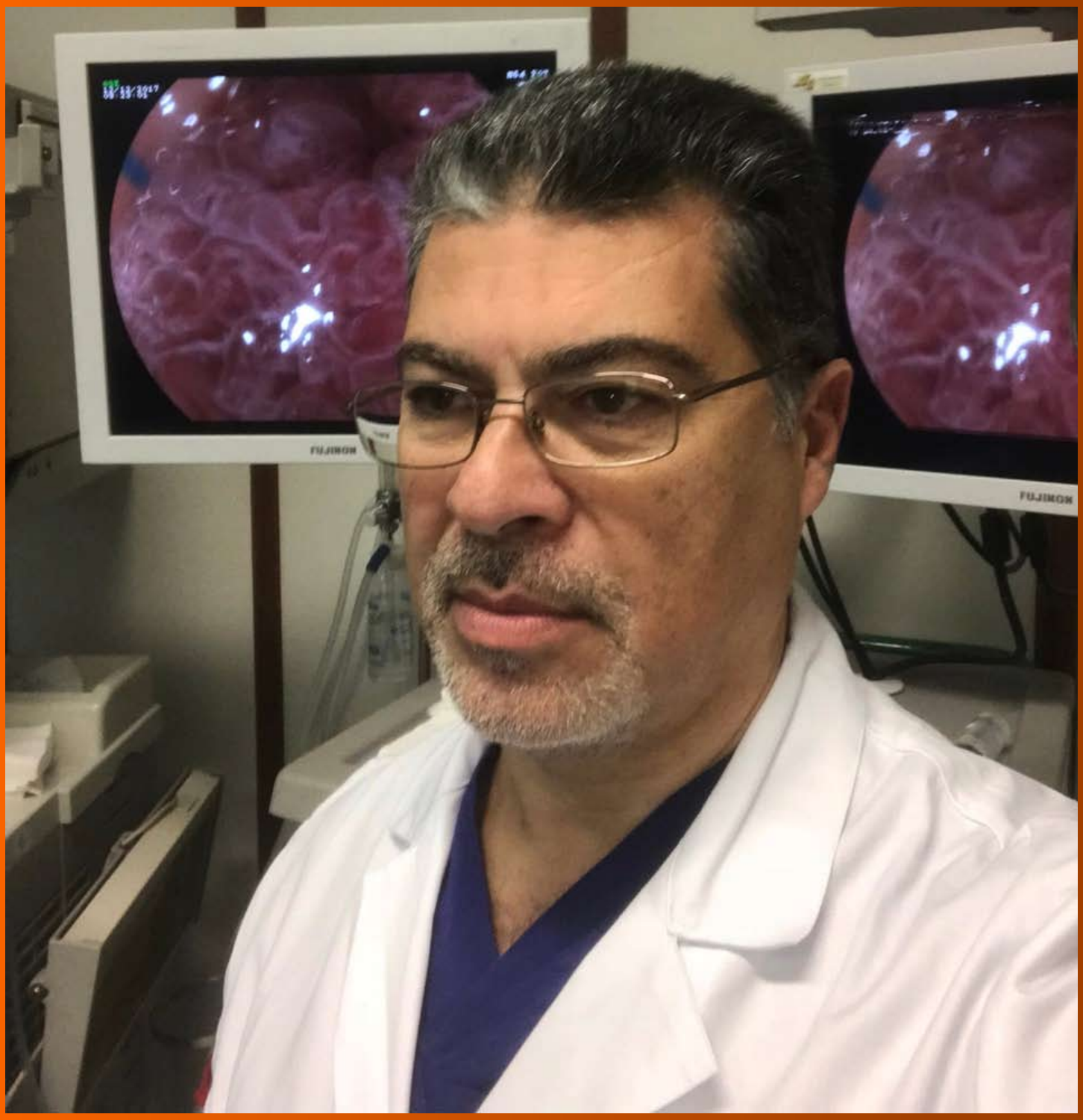

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REVIEW

Utility of endoscopic ultrasound and endoscopy in diagnosis and management of hepatocellular carcinoma and its complications: What does endoscopic ultrasonography offer above and beyond conventional cross-sectional imaging?

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Abstract

Hepatocellular carcinoma constitutes over 90% of the primary liver tumors, the rest being cholangiocarcinoma. It has an insidious presentation, which is responsible for the delayed presentation. Hence, the management strategy relies on screening to diagnose it an early stage for curative resection and/or treatment with local ablative techniques or chemotherapy. However, even with different screening programs, more than 60% of

tumors are still detected at an advanced stage, leading to an unchanged mortality rate, thereby implying a room for improvement in the screening and diagnostic process. In the last few years, there has been evolution of utility of endoscopy, specifically endoscopic ultrasonography along with Fine needle aspiration, for this purpose, which we comprehensively review in this article.

Key words: Hepatocellular carcinoma; Liver; Cancer; Fine needle aspiration; Endoscopy; Endoscopic ultrasound; Endoscopic ultrasonography; Staging; Management; Treatment

Core tip: Hepatocellular carcinoma (HCC) constitutes the commonest primary liver cancer, and if diagnosed at an early stage, has better prognosis. Of late, there has been evolution of utility of endoscopic techniques, specifically endoscopic ultrasonography (EUS) with fine needle aspiration, for this purpose. EUS is superior over computed tomography in detecting hepatic lesions smaller than 1cm, and also allows FNA for accurate histopathological diagnosis. This strategy is particularly useful for indeterminate nodules, with non-specific imaging characteristics. Role of EUS in diagnosis and management of HCC are the focus of this article. In addition, other endoscopic techniques, including esophagogastroduodenoscopy and endoscopic retrograde cholangio-pancreatography, are of immense use in management of complications of HCC, which are also briefly discussed in this review.

Girotra M, Soota K, Dhaliwal AS, Abraham RR, Garcia-Saenz-de-Sicilia M, Tharian B. Utility of endoscopic ultrasound and endoscopy in diagnosis and management of hepatocellular carcinoma and its complications: What does endoscopic ultrasonography offer above and beyond conventional cross-sectional imaging? *World J Gastrointest Endosc* 2018; 10(2): 56-68 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i2/56.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i2.56

INTRODUCTION

Hepatocellular carcinoma (HCC) constitutes the most common primary liver cancer. It is the fifth most frequent cancer and the second commonest cause of cancer related death worldwide[1], the occurrence of which is more in men and increases with age. Over 75% of HCC in the United States is due to hepatitis C and B viral infections. Successful management strategy relies on screening with the help of imaging techniques to diagnose it at an early stage for curative resection and/or treatment with local ablative techniques or chemotherapy. Tumors diagnosed at an early stage have a better prognosis with a five-year survival rate up to 80%[2]. However, more than 60% of tumors are still detected at an advanced stage, thereby implying that there is a room for improvement in the screening and diagnostic process[3]. In the last few years, there have been few studies evaluating the utility of endoscopy, and specifically endoscopic ultrasonography (EUS) along with fine needle aspiration (FNA), for this purpose, which we attempt to review in this article.

Utility of EUS and endoscopy in diagnosis and staging of HCC

Diagnosis of HCC is often difficult and usually occurs late in the course of chronic liver disease because of absence of any pathognomonic signs or symptoms[4]. Even with the current screening strategies, vast majority of cases of HCC are diagnosed at an advanced stage and hence palliative treatments are the only available options[5,6]. Current guidelines for diagnosis of HCC involve frequent monitoring of liver nodules < 1 cm with abdominal ultrasound and advanced imaging for nodules > 1 cm. Imaging options include liver ultrasound (US), computed tomography (CT), or magnetic resonance imaging (MRI) scans[7,8]. Barcelona convention of HCC experts agreed on non-invasive establishment of a radiological diagnosis requiring a > 2 cm focal hepatic lesion in cirrhotic patient confirmed by 2 different imaging techniques. However, for lesions < 2 cm, histological confirmation was deemed necessary[9,10] (Figure 1). The American Association for Study of liver Disease guidelines recommend biopsy of lesions under 2 cm only if there is no pathognomonic imaging (wash out) and an alfa-feto protein (AFP) below 200 ng/mL. This is where EUS may be potentially used safely and effectively to obtain cytology or histology from the lesion, even in patients with cirrhosis.

Traditional esophagogastroduodenoscopy is useful prior to EUS in evaluating the grade of esophageal or gastric varices if any, as lot of these patients have HCC complicating cirrhosis. EUS combines two different investigations-endoscopy and ultrasound-into one, to acquire images from the digestive tract and surrounding organs. Considering its proximity to the surrounding organs, it is more accurate than traditional US. EUS further combined with fine needle aspiration (FNA) or fine needle biopsy (FNB) offers further evaluation of a suspected lesion often with rapid on-site evaluation (ROSE). Currently, it is mostly used for diagnosis and staging of pancreatic cancer and for staging of esophageal cancer[11,12]. However, over the last decade, there have been efforts to define role of EUS in evaluation of liver lesions-particularly metastatic lesions and HCC[13-14], which forms the focus of our discussion.

EUS and EUS-FNA vs other imaging techniques (US, CT and MRI)

The superiority of EUS over CT in detecting hepatic lesions smaller than 1cm was demonstrated as early as 1999[14]. Imaging with CT scans and MRI may have a high miss rate in the diagnosis of HCC. Several studies have reported a sensitivity of 60%-68% with CT scans,

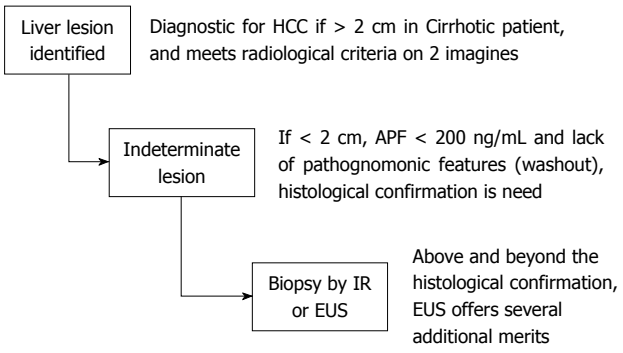

Figure 1 Diagnostic algorithm discussing role of endoscopic ultrasonography (EUS), and potential merits. Potential advantages of EUS in the management algorithm (1) Stratification of indeterminate nodules, especially in high-risk patients, with negative imaging characteristics, which may eventually change the management[14]; (2) In detection and characterization of smaller lesions < 2 cm[14,19,113]; (3) If a lesion is found by EUS, cytology / histology can be obtained in the same session rather than performing another procedure at later time[19]; (4) Assessment of portal vein invasion, spread to other vasculature and lymph nodes[26,118]; (5) The ability to sample enlarged regional lymph nodes for preoperative staging[118]; (6) Therapeutic roles: tumor ablation by intratumoral injection of absolute alcohol, radiofrequency probes, fiducial placement for stereotactic radiotherapy, brachytherapy using radioactive seeds and EUS guided biliary drainage[121]. EUS: Endoscopic ultrasonography.

based on the type of study and the technique of CT scan, for diagnosis of HCC[15,16]. Awad *et al*[17] studied the role of EUS in pre-operative evaluation of HCC, compared it with CT and found EUS to be a feasible investigation for the purpose examined. EUS diagnosed hepatic lesions between 0.3-14 cm, detected new/additional lesions in 28% of patients (all lesions < 0.5 cm), could more reliably detect smaller lesions and successfully differentiated hemangiomas among lesions which appeared suspicious for HCC on CT. In this study, EUS led to change of management in around 67% of patients. In the study by DeWitt *et al*[18], EUS diagnosed malignancy in over 40% with previously negative traditional imaging, having an impact on management in 84% either by making new diagnoses or by upstaging thus avoiding un-necessary surgery. Singh *et al*[19] conducted a prospective study to compare the accuracy of EUS and EUS-FNA with CT for detection of HCC. They found that for diagnosis of HCC, EUS had a sensitivity of 100% as compared to 71% for CT although the specificity and positive predictive values were much lower (25% *vs* 67% and 60% *vs* 71%, respectively)[19]. However, when combined with FNA, EUS had accuracy of 94% in comparison to 69% with CT scan[19]. EUS was able to detect significantly more lesions in the left lobe of the liver, sample hilar nodes (non-feasible by traditional imaging methods)[20] and characterize lesions that were too small and indeterminate for HCC on a CT scan. They proposed a diagnostic algorithm for evaluating high-risk patients with negative imaging. Choudhary *et al*[21] in their prospective study of over 50 patients showed that EUS-FNA of lymph nodes detected in patients with HCC confirmed metastasis and hence precluded transplantation in over a third of the patient cohort.

MRI with angiography has been shown to be better than CT for diagnosis of HCC, the benefit being mostly for detection of nodules between 10-20 mm[22,23]. At present, it is considered the gold standard for staging of HCC prior to surgery[22,24]. The accuracy of EUS alone for accurate diagnosis of liver lesions may only be 65%, but it increases to ~ 94% when combined with FNA which is similar to that of MRI[19]. However, in the same study EUS was found to detect a significantly higher number of nodular lesions than MRI (P = 0.04)[19]. In addition, few other reports have also supported the use of FNA to identify lesions missed by CT scan[25-27], which may be of clinical significance only if their size is over 1 cm, in which case, biopsy could be accomplished at the time of EUS.

Lai *et al*[25], Storch *et al*[26] and Michael *et al*[27], independently demonstrated the safety of EUS-FNA to diagnose HCC as the cause of portal vein thrombosis. In all three reports, CT scan showed portal vein thrombosis without any definite hepatic mass, but FNA of the thrombus was used to diagnose malignant HCC, thus proving it to be a tumor thrombus rather than a bland one, thereby changing the management. In addition to the role of EUS to provide tissue diagnosis, it also provides better visualization of the portal vein and the FNA needle also has to travel a short distance only[28,29]. Doppler ability of EUS helps choose an avascular trajectory for the needle.

Data on utility of EUS in primary diagnosis of hepatic lesions and HCC is limited (Figure 2). One of the earliest studies looking at role of EUS in liver lesions was conducted by Nguyen *et al*[14] who prospectively evaluated the livers of 574 patients with history or suspicion of malignancy with EUS. Hepatic lesions were found in 14 patients, only 3 of who had a lesion previously detected by CT scan. Moreover, amongst these 14 patients, while 7 carried a diagnosis of malignancy, the other 50% received the initial diagnosis with help of EUS-FNA. Since this study did not include any patients with primary HCC, its results cannot be fully extrapolated to HCC patients. Similar studies were conducted by DeWitt *et al*[18] in 2003, Prasad *et al*[30] in 2004 and Crowe *et al*[31] in 2006, underscoring the benefits of EUS and EUS-FNA in diagnosis of liver metastasis (Figure 3). More recently, Fujii-Lau *et al*[32] proposed EUS-derived criteria for distinguishing benign from malignant metastatic solid hepatic masses, but are not specific for HCC. The authors suggested using 7 EUS features, which had fair-moderate inter-observer agreement among expert endosonographers, and yielded an area under the receiver-operating curve (AUC) of 0.92, and overall positive predictive value of 88%.

Previous studies have upheld that diagnosis of HCC is highly dependent on size of the lesion. For lesions < 2 cm, accurate diagnosis requires presence of histologic confirmation, which is currently achieved using CT-guided percutaneous route[33]. EUS with FNA/FNB is an alternate strategy. In their prospective study of 17

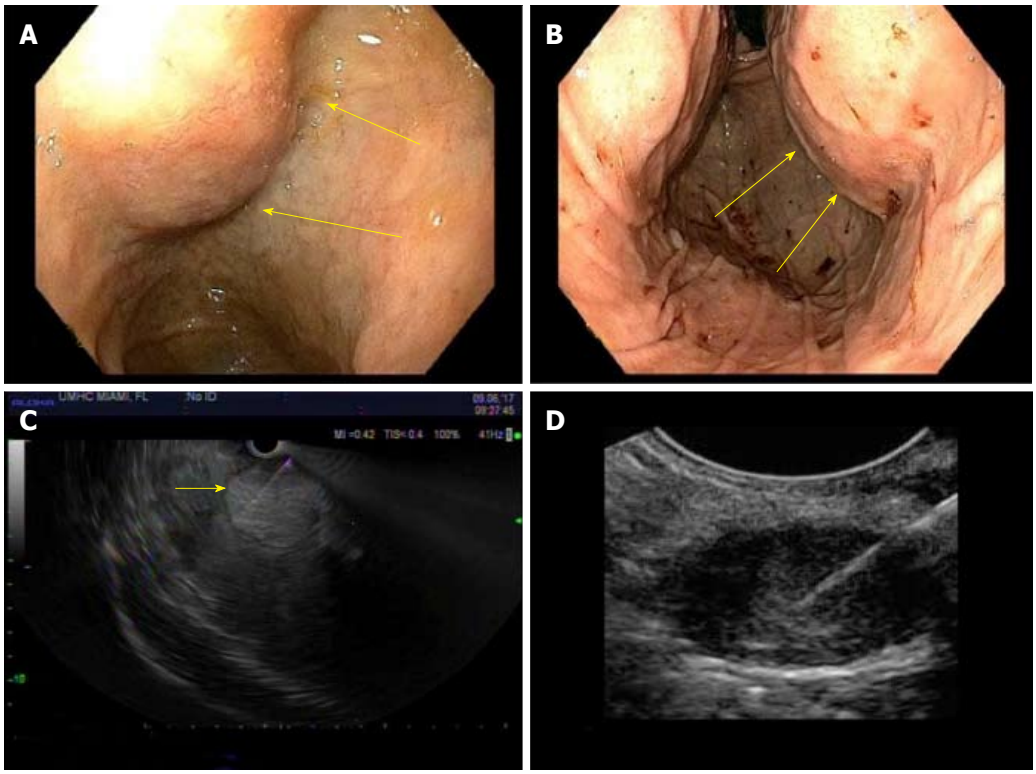

Figure 2 Endoscopic ultrasonography (EUS) diagnosis of primary liver tumors. A and B: Indentations seen in the duodenal bulb and stomach, from large lesions in the right and left lobes of the liver; C: On EUS, the entire liver tissue was seen replaced by numerous hyperechoic lesions of medium size, causing hepatomegaly and hence indentations. Fine needle aspiration (FNA) of a prominent and accessible hyperechoic lesion obtained, which was diagnostic of neuroendocrine tumor; D: In another patient, EUS-FNA of solitary hypoechoic liver lesion obtained, which diagnosed hepatocellular carcinoma.

patients (10 with malignancy), Singh *et al*[19] found 5 lesions < 2 cm, of which three were diagnosed to be malignant using EUS-FNA and the rest two were benign with the smallest lesion to undergo FNA being 4 mm in size. In cirrhosis, hyperintense non-dysplastic nodules are commonly seen on MRI, which may be indistinguishable from dysplastic lesions[34]. This happens more frequently in cases of smaller lesions, which makes it even more difficult to evaluate[35]. Smaller lesions are difficult to characterize by either CT or traditional US as HCC can present with hypoechoic, hyperechoic or isoechoic lesions. Targeted EUS-FNA can be performed on these lesions to obtain histologic confirmation. A multi-centric study reported EUS-FNA to diagnose malignancy in 89% patients, after traditional US guided FNA was non-diagnostic[36]. It is also well known that presence of dysplastic nodules in liver is a major risk factor for development of HCC, especially in presence of HBsAg and anti-hepatitis C virus antibodies[37-39].

Use of endoscopy for staging of HCC

There exist various staging systems for HCC, including American joint committee on Cancer (AJCC) TNM (which does not incorporate hepatic function and reserve, which are major determinants of outcome), Cancer of the Liver Italian Program (CLIP) score, Japanese Staging System and Japan Integrated Staging (JIS) score (which includes TNM + Child-Pugh score), GRoupe d'Etude et de Traitement du Carcinoma Hépatocellulaire (GRETCH) system (which includes serum AFP + liver function parameters and portal vein thrombosis) and Chinese University Prognostic Index (CUPI) (combines conventional TNM + serum AFP + liver function parameters). The Barcelona Clinic Liver Cancer (BCLC) staging system is a comprehensive scheme using variables related to tumor size, number of nodules, liver functional status, physical status, and cancer-related symptoms, and links the five stages described with a treatment algorithm. The purpose of BCLC was to stratify patients into treatment groups according to the extent of the disease and the predicted prognosis[40]. The consensus statement of the American Hepato-Pancreato-Biliary Association, updated in 2010, recommends the use of the TNM system to predict outcomes following resection or liver transplantation and the BCLC scheme for patients with advanced HCC who are not candidates for surgery[41]. Since we know that EUS/EUS-FNA may detect smaller liver tumors more effectively than available imaging, sample the lymph nodes and metastatic lesions, we hypothesize that EUS/EUS-FNA may play a strong role in the diagnosis of indeterminate lesions.

Utility of EUS and endoscopy in general management of a patient with HCC

In addition to EUS improving staging and diagnostic yield of HCC, other endoscopic modalities might play a

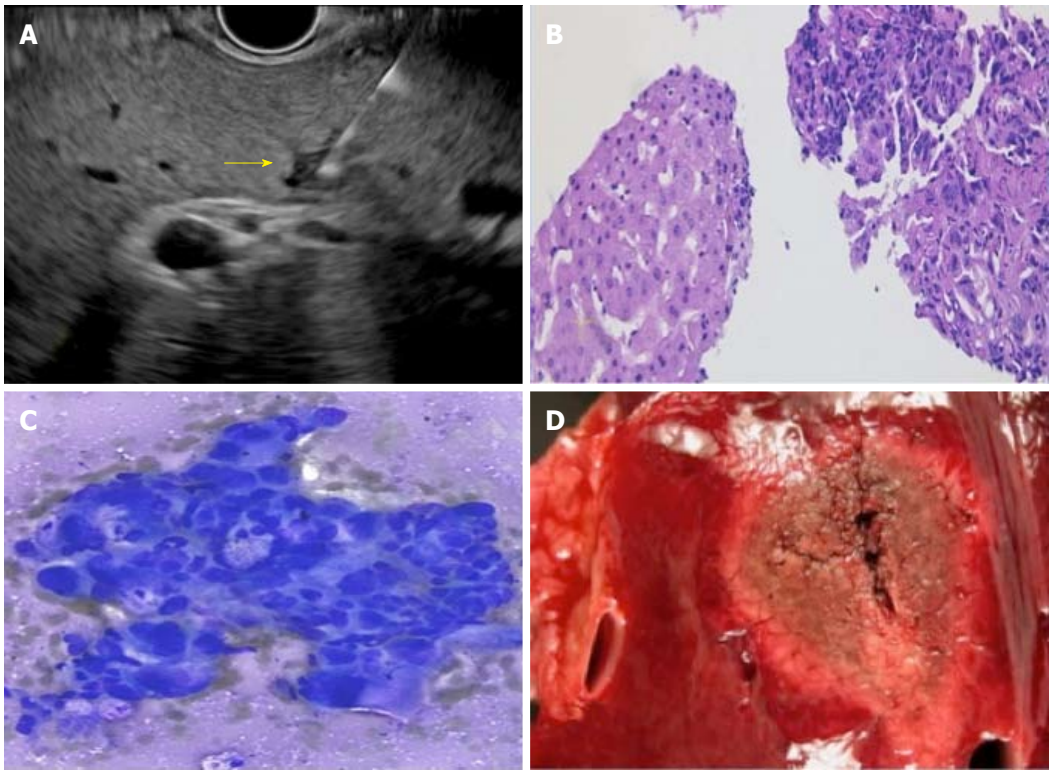

Figure 3 Endoscopic ultrasonography diagnosis of secondary liver lesions. A: Fine needle aspiration performed on small hypoechoic lesion in the liver; B and C: Pathology suggested pancreatic metastatic lesion; D: Partial hepatectomy performed for a solitary metastatic lesion.

role in comprehensive management of these patients. HCC develops on a background of cirrhotic liver in most circumstances; hence all the clinical manifestations of a cirrhotic liver may be seen, ranging from splenomegaly, ascites, and jaundice to formation of varices and variceal bleeding due to portal hypertension (PHT). Esophageal varices are treated with band ligation and rarely with sclerotherapy. However gastric varices may be managed either with endoscopic injection of cyanoacrylate glue or EUS guided coil embolization and glue injection[42]. EUS could also be used to confirm obliteration of the varices, perforators and peri/paraesophageal varices presence of which might predict recurrence[43]. Along with this, occult gastrointestinal bleeding (OGIB) can also be observed in patients with HCC either due to small bowel varices, portal hypertensive enteropathy, metastasis or mucosal erosions which are observed with a higher frequency in patients with HCC[44]. These can be diagnosed with capsule endoscopy (CE) and managed with deep enteroscopy (spiral, single or double balloon). Kunizaki *et al*[45] described a case where a patient with metastatic HCC developed OGIB secondary to a small bowel metastatic lesion diagnosed with double balloon enteroscopy (DBE).

Endoscopic palliation of obstructive jaundice in HCC

Jaundice occurs infrequently in HCC, and only 1%-12% of patients manifest with obstructive jaundice as the initial complaint[46]. Cholestasis occurs due to bile duct occlusion, which may be from benign causes (blood clots, pus, or sludge), malignant causes (primary intra-biliary malignant tumors, HCC with invasion to bile ducts, or metastatic cancer with bile duct invasion) or combination or progressive terminal liver failure (advanced underlying cirrhosis). Furthermore, trans-catheter arterial chemoembolization (TACE) can also increase probability of tumor thrombi obstructing the biliary tree[47]. The ominous features indicative of malignant obstruction are high level of serum AFP, history of cholangitis with dilation of intrahepatic bile duct, aggravating jaundice and rapidly deteriorating liver function[46].

Various endoscopic techniques find utility in such scenarios. Choledochoscopy and bile duct brush cytology are useful endoscopic techniques in differentiating obstruction due to intraluminal mass, infiltrating ductal lesions or extrinsic compression[48-49]. Besides technical difficulties in accessing the bile duct with tumor fragments or protrusion and possible strictures, endoscopic biliary drainage (EBD) is frequently debated because of the short survival of these patients. EBD, achieved *via* bilio-nasal and bilio-duodenal drainage, could be considered for palliation in these patients with obstructive jaundice caused by tumor fragments and/or protruding into the CBD lumen. Endoscopic retrograde cholangiography (ERC) may be diagnostic as well as therapeutic in such cases as it can relieve jaundice *via* biliary stenting[50]. In terms of choice of stent, metal stent is preferred for palliation of malignant biliary obstruction due to larger lumen ensuring patency over longer period of time[51-54]. Plastic stents would be more cost effective if the life expectancy is under 3 mo. Cho

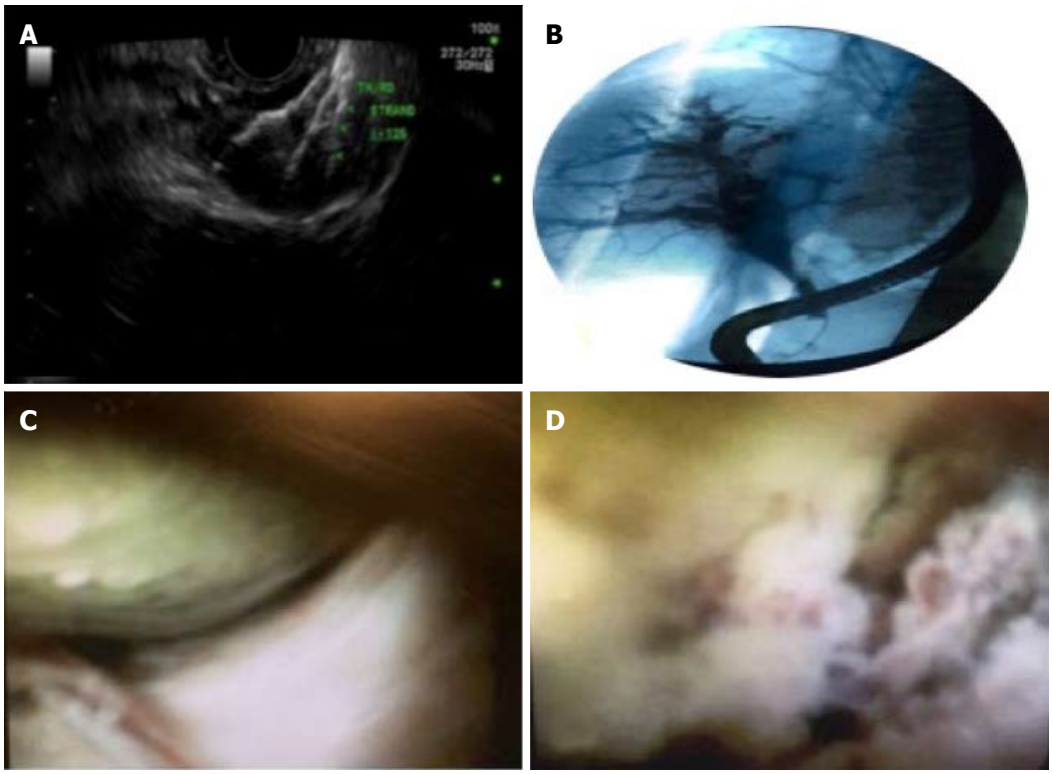

Figure 4 Other novel uses of endoscopic ultrasonography and cholangioscopy in hepatocellular carcinoma diagnosis and management. A: HCC EUS guided Brachytherapy: Radioactive seeds loaded and deployed with endoscopic ultrasound, similar to fiducial placement, as an alternative to transarterial chemoembolization therapy; B, C and D: Patient with choledochal cyst, found to have ectopic HCC, diagnosed with digital cholangioscopy and biopsies[122].

et al[55] evaluated the effects of biliary drainage on clinical outcomes in patients with obstructive jaundice secondary to HCC. They observed that patients with bilirubin >13 mg/dL and Child-Turcotte-Pugh class C did not have effective biliary drainage, which correlated with decreased mean survival time in such patients[55]. Choi *et al*[56] also showed that presence of portal vein thrombosis is also correlated with ineffective drainage of the biliary tree along with the above-mentioned factors. A recent study also advocated that while there was no statistical difference in rate of successful drainage with ERC compared to percutaneous cholangiography (PTC), ERC had longer duration of drainage patency, thus the first choice for palliative biliary drainage[57]. More recently, EUS guided biliary drainage is increasingly being used when endoscopic retrograde cholangiopancreatography fails[58]. Thus, the combination of palliative endoscopic methods may relieve jaundice, ensure a good quality of life and possibly prolong survival of this type of HCC patients.

Utility of EUS and endoscopy in treatment of HCC

HCC tends to stay within the liver, with late occurrence of distant metastases. Hence, early diagnosis and an effective local therapy can have a great impact on the course of the disease and outcome. Curative liver resection and orthotopic liver transplant (OLT) are the best modalities of treatment, however, only 10%-50% of patients get to them due to impaired liver function and the delay in diagnosis[59]. For these reasons, local therapy to treat such subset of patients has garnered a lot of interest, with the modalities including radiofrequency ablation (RFA), microwave ablation (MWA), percutaneous ethanol injection (PEI), transarterial chemoembolization (TACE), radioembolization (TARE), cryoablation, brachytherapy, stereotactic radiotherapy (Figure 4), systemic and molecularly targeted therapies (Sorafenib).

Local ablation (using RFA or PEI) is the standard of care for BCLC stage 0-A not suitable for surgery. This can be administered by various routes including laparoscopy, percutaneous route or endoscopy. The latter is still mostly at experimental stage, though there has been progress made over the years. Before the advent of RFA, PEI was the most widely accepted, minimally invasive method for treating such patients. However, RFA has been proven to be a very safe procedure with a reported mortality rate of less than 1% and a complication rate of 3%-7%[60-61]. It is utilized in patients who do not meet the criteria for surgical resection of the tumor or OLT, and has been studied in patients with HCC $\leqslant$ 4 cm[62]. Recent meta-analysis suggests that overall and disease-free survival rates continue to improve with RFA, despite an increase in the size and numbers of tumors treated[63]. RFA has been shown to be more efficacious with higher tissue necrosis rate, decreased local recurrence and higher cancer free survival rates, than other local ablative techniques like PEI[61,64-66]. These facts have been demonstrated

in studies evaluating RFA over a long period of time, which make RFA one of the established treatments for local and small HCC at present[67-71]. However, it is associated with more complications than PEI, especially when RFA is performed on a lesion in proximity to a large vessel or another visceral organ, and may lead to bleeding, hemothorax or gastric perforation[54,72]. RFA can be delivered by either a percutaneous, endoscopic or surgical approach, latter being most invasive[73]. Percutaneous approach is less invasive but is more often associated with tumor seeding[74-75]. On the other hand, open surgical approach is highly invasive with an increased rate of complications. RFA using thoracoscopy or laparoscopy is associated with less blood loss, post-operative complications and duration of surgery while delivering similar success rates for treatment of HCC as open RFA[76-78]. It can also be combined with other local therapies for HCC like TACE which is better than RFA alone[79,80]. With these merits, it's the first line treatment for small sized HCCs that are not suitable for surgical resection and can act as a bridging therapy before liver transplantation. EUS-guided Nd: YAG laser ablation of caudate lobe HCC and EUS-guided ethanol ablation of deep HCC closer to IVC have also been reported[81-82]. Nakaji *et al*[83] showed that twelve patients with early stage HCC of the caudate lobe, who underwent EUS guided ethanol injection, had overall survival rates of 91.7%, 75% and 53% at 1, 2 and 3 years respectively. Recurrence was seen in 2 cases after 3 and 9 mo respectively[83]. Laser ablation *via* percutaneous route has been shown to be useful[84,85]. Di Matteo *et al*[81] successfully delivered Nd:YAG laser ablation *via* EUS in a patient with HCC to obtain encouraging results. Hybrid approach may be an alternative to consider, using percutaneous ablation for deep seated, while endoscopic ablation for superficial HCC[86]. Another example of successful hybrid technique was laparoscopic RFA while cooling bile ducts *via* endoscopic nasobiliary drainage tube, to prevent bile duct injury, to manage HCC located adjacent to the Glisson's capsule in the hilar region in two patients[87]. Conceptually, EUS may also have similar use, especially for easily accessible lesions.

Among patients with large multifocal HCC or noncurative (inoperable/non-ablatable) tumor characteristics, TACE is used as first-line, especially for BCLC stage B multinodular asymptomatic tumors without vascular invasion or extra-hepatic spread. This technique involves the injection into the arteries feeding the tumor, a mixture of a chemotherapeutic agent (doxorubicin, cisplatin, mitomycin, and epirubicin) and embolic material, to potentially obtain higher intra-tumoral drug concentrations compared with intravenous therapy, with occlusion of the blood vessel causing infarction and necrosis, thus causing shrinkage. In future, EUS guided intra-tumoral administration of chemotherapy may be considered. Artifon *et al*[88] utilized EUS to deliver intra-arterial chemotherapy for liver metastases in colon cancer patients. The authors reported a statistically significant decrease in the median hospital stay after such a procedure, while maintaining the safety profile and response rates. This technology is still in a nascent phase.

Microwave ablation (MWA) is a newer loco-regional therapy for HCC, especially in patients who are not candidates for surgical resection. Currently, RFA is the most popular loco-regional therapeutic modality throughout the world, but has significant limitations including higher complication rates, especially in HCC lesions located close to the gallbladder, liver capsule, and diaphragm, or near large vessels, which may be associated with incomplete ablation due to the "heat-sink" effect[89-91]. These situations may render at least 10%-25% of patients with HCC ineligible for RFA[89]. In such difficult to treat tumors, MWA can be offered as an alternative ablation strategy, since it provides a homogeneous and more predictable ablation zone[92-94]. MWA also offers improved efficacy for perivascular tumors, since the faster heating and higher temperatures provided by microwave energy allow heat-sink effect reduction[93,95]. Shibata *et al*[96] demonstrated statistically comparable local control rates of 89% for MWA as compared to 96% for RFA in a randomized study. The survival benefit remains similar in both the techniques with fewer complications associated with MWA as compared to RFA. Shi *et al*[97] reported MWA to be as effective as surgical resection for solitary HCC ≤ 3 cm. The overall 1-, 3-, and 5-year survival rates were 94%, 70%, 52% for the MWA group and 94%, 72%, 60% for the resection group[97].

Transarterial radioembolization (TARE) delivers microspheres impregnated with the radioisotope yttrium-90 (Y90, 90Y) through the hepatic vasculature directly to the target tumor, thus allowing for safe administration of high radiation doses to the tumor burden. This strategy is usually utilized in patients with unresectable HCC, deemed not to be good candidates for TACE, or those with failed prior TACE procedures[98]. TARE is delivered in a lobar fashion, rather than segmental fashion as is TACE, and can target more lesions at the same time. Thus, most of the patients undergoing TARE have much more advanced disease, as compared to those undergoing TACE. Currently, two Y90 products are commercially available: TheraSphere_ glass microspheres (BTG, Canada) and SIR-Spheres_resin microspheres (Sirtex Medical, Woburn, MA, United States). Salem *et al*[99] showed a trend towards a higher response rate for patients who underwent TARE as compared to TACE (49% *vs* 36%, respectively, P = 0.104). Also, time-to-progression was longer following TARE than TACE (13.3 mo *vs* 8.4 mo, respectively, P = 0.046), although median survival times were not statistically different[99]. TARE is associated with fewer side effects, and is considered as an outpatient procedure, as opposed to TACE, which typically requires post-procedure hospitalization. TARE may also be used in patients with portal vein thrombosis and has been shown to downstage patients outside of transplant criteria from UNOS stage T3 to T2, helping them under-

go transplant[100,101].

Contrast-enhanced ultrasound (CE-US) has been demonstrated to have superiority over CE-CT for detection of residual tumors after TACE[102]. With improved imaging technique with EUS, availability of contrast-enhanced option in EUS and its inherent ability to detect smaller lesions, contrast-enhanced EUS (CE-EUS) is emerging as a newer technique to assess the treatment effects of TACE on HCC in the caudate lobe of the liver[103], previously difficult to assess with CE-US.

Treatment of complications

Treatment of HCC by local therapies can result in several serious complications, which may be managed endoscopically. TACE can lead to formation of biliary stricture, variceal bleeding, bile leak and hepatoduodenal fistulae; all of which have been reported to be managed endoscopically[104-107]. A hepatoduodenal fistula is a rare complication, which ideally should be resected surgically. Recently, endoscopic closure of the fistula using histoacryl injection has been described in a case report[104]. Similarly, use of RFA has been associated with the formation of biliocutaneous fistula that can be managed endoscopically[105] and infected biloma drained *via* trans-gastric route[108]. RFA can also lead biliary stricture, which can further lead to sepsis and liver failure. This can be prevented by "cooling" the bile ducts using endoscopic nasobiliary drainage (ENBD) tube, during RFA[106]. Bile leak following TACE for HCC has been successfully managed with choledochoscope-assisted fibrin glue[107].

EUS guided portal vein interventions in HCC: EUS based portal vein interventions are emerging as newer diagnostic and therapeutic techniques in HCC. EUS-FNA can be used to differentiate between a bland *vs* tumor thrombus in the portal vein, which can help us in the correct staging of HCC. The approach for this technique is trans-duodenal (25 gauge needle) which has been shown to cause less sampling errors, thus leading to fewer false positive or negative results, as compared to trans-hepatic approach with US/CT. This technique has also shown to cause less biliary and vascular injury as well. EUS-FNA has also been shown in several case reports in diagnosing tumor thrombus in the portal vein from HCC without visualization of any hepatic mass on the imaging[25-27].

There are few experimental animal studies being performed to assess the efficacy of EUS-guided portal vein chemotherapy injections in anaesthetized pig models. The advantage of this technique will be a higher hepatic and lower systemic chemotherapy drug levels. Thus, it is hypothesized that it may lead to lower systemic toxicities in patients with diffuse liver metastasis[109]. In another animal model, selective PV embolization has been demonstrated for causing the contralateral hypertrophy of the liver lobe. This helps in resection in hepatic malignancies without compromising the liver function[110]. Further human studies are needed to validate the therapeutic benefits of EUS guided portal vein interventions suggested by these animal studies.

Limitations and adverse events related to EUS

In spite of the zeal generated by these studies, like every technique, EUS also comes with its share of controversies and limitations[111,112]. The major criticism is that large-scale studies and randomized controlled trials evaluating the role of EUS in the management of HCC are still lacking. In addition, it may also be associated with multiple technical problems like difficulty to visualize and sample right lobe lesions that need a transduodenal approach[14]. Although sensitivity is high in reported cases, EUS may also miss smaller lesions, especially if farther from the probe, which may also pose challenges when attempting to perform FNA. While lesions in peri-hepatic region, hilum, caudate lobe, left lobe and part of right lobe in proximity to the falciform ligament (Liver segments 1, 2, 3 and 4) may be easy to evaluate with EUS, the remainder of the right lobe (segments 5-8) may pose a technical challenge. There are no studies yet to evaluate which hepatic segments are consistently seen by EUS. Furthermore, not only does EUS add to the overall cost of the work-up, it also involves a long and complex learning curve for the operator, which is yet another Understand factor in this conundrum. This limits its availability and accessibility.

An additional debate in the utility of EUS-FNA for evaluation of liver cancers is the potential for tumor seeding along the needle track and peritoneal spillage, which are known to occur with the more traditional radiologic approach. This has already been reported in pancreatic cancer; but in liver biopsy the increased vascularity of the tumor and the distance between the gut wall and the liver capsule theoretically increases the risk[113]. EUS-guided tissue acquisition is not feasible if an avascular trajectory cannot be obtained when viewed under Doppler. Moreover, pneumobilia, calcification, metal stents, fatty infiltration and fibrosis could interfere with the image quality. Furthermore, HCC being a much more vascular tumor than pancreatic cancer, further augments the potential risk of tumor spillage. However, needle tracking has been observed in less than 2% of cases of percutaneous biopsy and is more common in lesions > 2 cm[114,115], although, analogous data for EUS-FNA is lacking. Complications are more in those individuals with moderate ascites and decompensated liver disease. Though intravenous contrast is not used unlike traditional cross sectional imaging, newer technology like power doppler, tissue harmonic imaging, real time elastography and contrast enhanced imaging offer promise in differentiating various lesions.

Due to the mechanical properties of large echoendoscope, with longer fixed segment at the tip, coupled with learning curve of therapeutic endoscopists, the adverse events with EUS are greater than standard upper or lower endoscopic procedures, perforation being the most feared. Esophageal perforation was noted in 8 of almost 85000 diagnostic EUS in Germany[116], and 16

of almost 44000 EUS in United States[117], half of which were by endosonographers during early learning phase. Duodenal perforation is more common, accounting for 6 of 10 GI perforations reported in a prospective United States registry of almost 14000 EUS[118]. Overall mortality with EUS is reported around 0.02%[118], and another study attributed 73% of all EUS-related mortalities (13/18) to duodenal tears with retroperitoneal perforations[119]. Cognizance of these occurrences is essential for therapeutic endoscopist attempting any of the above-discussed EUS maneuvers. For liver lesions in particular, the overall rate of complications was noted to be approximately 1% in a multi-centric international survey, including biliary sepsis (0.6%), local bleeding (0.6%), fever (1.2%) and pain (1.2%)[36].

CONCLUSION

In summary, we have reviewed the current literature on the utility of endoscopic techniques, with a special focus on EUS, in management of HCC, especially as an adjunct to traditional imaging. The current HCC staging systems and diagnostic guidelines do not yet utilize EUS, as most of the literature on its use is either from retrospective studies or small prospective analysis, without any dedicated randomized controlled trials. However, we have presented the data on the increasing role of EUS in the diagnosis of indeterminate and small lesions, and highlighted the settings where lesions can be better visualized with EUS for diagnosis and treatment. If incorporated on a more regular basis, EUS/EUS-FNA can potentially further help in the accurate staging of HCC, thereby impacting management strategies in selected patients, especially with indeterminate nodules. Other endoscopic modalities find their potential role in the treatment of HCC itself and management of complications as result of current approved treatments. This is an evolving field, and we anticipate greater use of endoscopy in these scenarios with further progression of research in this field, leading to improved clinical care.

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CASE REPORT

Gastric and enteric anisakiasis successfully treated with Gastrografin therapy: A case report

Hiroki Fujikawa, Toshio Kuwai, Toshiki Yamaguchi, Ryoichi Miura, Yuki Sumida, Takeshi Takasago, Yuki Miyasako, Tomoyuki Nishimura, Sumio Iio, Hiroki Imagawa, Atsushi Yamaguchi, Hirotaka Kouno, Hiroshi Kohno

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Author contributions: Kuwai T assessed the patients; Fujikawa H and Yamaguchi T wrote the manuscript; Nishimura T and Iio S assisted in performing the diagnostic tests; Miura R, Sumida Y, Takasago T, and Miyasako Y interpreted the data; Imagawa H, Yamaguchi A, Kouno H, and Kohno H critically reviewed the manuscript.

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Abstract

We report a case of a 59-year-old woman who was diagnosed with gastric and small intestinal anisakiasis, which was successfully treated with endoscopic extraction and Gastrografin therapy. She was admitted to our hospital with epigastric pain and vomiting one day after eating raw fish. She exhibited tenderness in the epigastrium without obvious rebound tenderness or guarding. Computed tomography (CT) demonstrated segmental edema of the intestinal wall with proximal dilatation and a small number of ascites. Because enteric anisakiasis was suspected based on the patient's history of recent raw fish consumption and abdominal CT, we performed gastroscopy and confirmed that nine *Anisakis* larvae were attached to the gastric mucosa. All of the *Anisakis* larvae were extracted *via* endoscopy, and the patient was diagnosed with gastric and enteric anisakiasis. Additionally, in the hospital, we performed ileography twice using Gastrografin, which led to shortened hospital stay. Based on the clinical results of this case, we suggest that Gastrografin therapy is a

safe, convenient, and useful method to extract enteric *Anisakis* larvae.

Key words: Enteric anisakiasis; Gastrografin; Ileus; Endoscopic extraction; *Anisakis* larvae

Core tip: Enteric anisakiasis is difficult to diagnose due to a lack of definitive criteria, and there is currently no curative treatment. This case report describes two important clinical suggestions: (1) Abdominal computed tomography (CT) is useful for the diagnosis of enteric anisakiasis; and (2) Gastrografin administration is a safe, convenient, and useful therapy. In the case of intestinal anisakiasis, CT scan showed submucosal edema of the intestine with proximal dilatation and ascites. We performed ileography using Gastrografin to extract enteric *Anisakis* larvae after placing an ileus tube, which led to shortened hospital stay.

Fujikawa H, Kuwai T, Yamaguchi T, Miura R, Sumida Y, Takasago T, Miyasako Y, Nishimura T, Iio S, Imagawa H, Yamaguchi A, Kouno H, Kohno H. Gastric and enteric anisakiasis successfully treated with Gastrografin therapy: A case report. *World J Gastrointest Endosc* 2018; 10(3): 69-73 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i3/69.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i3.69

INTRODUCTION

Anisakiasis is a human disease caused by the accidental ingestion of larval nematodes belonging to the Anisakidae family[1]. Anisakiasis usually occurs in the stomach, and can easily be diagnosed *via* gastroscopy and treated with endoscopic extraction. On the other hand, enteric anisakiasis is relatively rare. The clinical characteristics of enteric anisakiasis mainly consist of colicky or diffuse abdominal pain, nausea, vomiting, ascites, and peritonitis. In addition, because intestinal obstruction and ileus have been observed[2], patients are often misdiagnosed as having acute appendicitis or terminal ileitis[1]. However, enteric anisakiasis can generally be treated with conservative therapy such as analgesic drugs, because the larvae die within approximately one week in the human body. Thus, there is currently no curative treatment for enteric anisakiasis. This case report describes a patient with gastric and enteric anisakiasis who was successfully treated with endoscopic extraction and Gastrografin therapy.

CASE REPORT

A 59-year-old Japanese woman was suffering from epigastric pain and vomiting since the evening and was brought to our hospital. She had eaten sliced raw horse mackerel and salmon at lunch. She was conscious, her blood pressure was 120/70 mmHg, her pulse was 75 beats/min, and her body temperature was 37.3 ℃. Her medical history was significant for appendectomy. On physical examination, she exhibited tenderness in the epigastrium without obvious rebound tenderness or guarding. Her bowel sounds were slightly decreased. Laboratory examinations showed only increased C-reactive protein (19.7 mg/dL) and were otherwise unremarkable. Abdominal x-ray revealed a nonspecific gas pattern. Abdominal computed tomography (CT) demonstrated segmental edema of the intestinal wall with dilated bowel and a small number of ascites (Figure 1). Small intestinal anisakiasis was suspected based on the patient's recent raw fish consumption and abdominal CT images; therefore, we performed gastroscopy to place an ileus tube. We confirmed that nine *Anisakis* larvae were attached to the gastric mucosa and performed direct endoscopic removal of all of the *Anisakis* larvae with a biopsy forceps (Figure 2). Therefore, she was diagnosed with gastric and enteric anisakiasis and we administered Gastrografin after placing an ileus tube. Ileography, using Gastrografin, on postoperative day 4 revealed that there was no small intestinal obstruction (Figure 3), and this was followed by clinical improvement. The patient was discharged 11 d after the procedure.

DISCUSSION

The course of this patient provides two important clinical suggestions: (1) Abdominal CT is useful for the diagnosis of enteric anisakiasis; and (2) Gastrografin administration therapy is a safe, convenient, and useful method to extract enteric *Anisakis* larvae.

First, abdominal CT is useful for the diagnosis of enteric anisakiasis. Anisakiasis commonly involves the stomach and rarely involves the intestine. According to Ishikura *et al*[3], gastric anisakiasis accounted for 95.6% of cases, enteric anisakiasis for 4.1% of cases, and other sites for 0.3% of cases However, as diagnosis *via* gastroscopy is relatively easy, the incidence of enteric anisakiasis is much lower due to a lack of definitive diagnosis criteria[4]. Consequently, it is considered that the true number of enteric anisakiasis cases is probably greater than has been reported[5]. For this type of infection, ultrasonography[5,6] and CT[7] have been useful for establishing a diagnosis. Intestinal anisakiasis shows marked submucosal edema of the intestine without showing complete intraluminal occlusion, ascites, or fluid collection in the distal segment of the constricted small intestine on CT[7]; these points were confirmed for this case.

Second, Gastrografin administration therapy is a safe, convenient, and useful method to extract enteric *Anisakis* larvae. In several reported cases, scattering Gastrografin over the lesion was useful for patients with gastric anisakiasis[8]; however, the effect on enteric anisakiasis is unclear. Regardless, it is known that Gastrografin therapy is effective for tapeworm

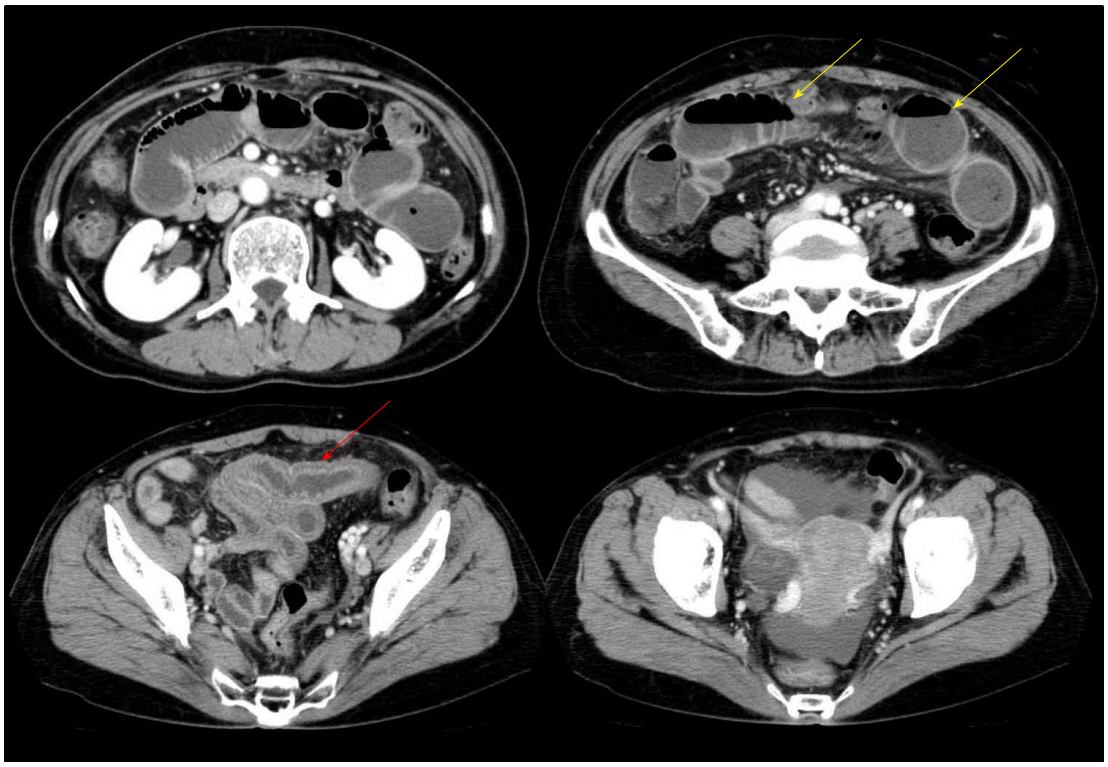

Figure 1 Abdominal computed tomography showing segmental edema of the intestinal wall (red arrow) with proximal dilatation (yellow arrow) and a small number of ascites.

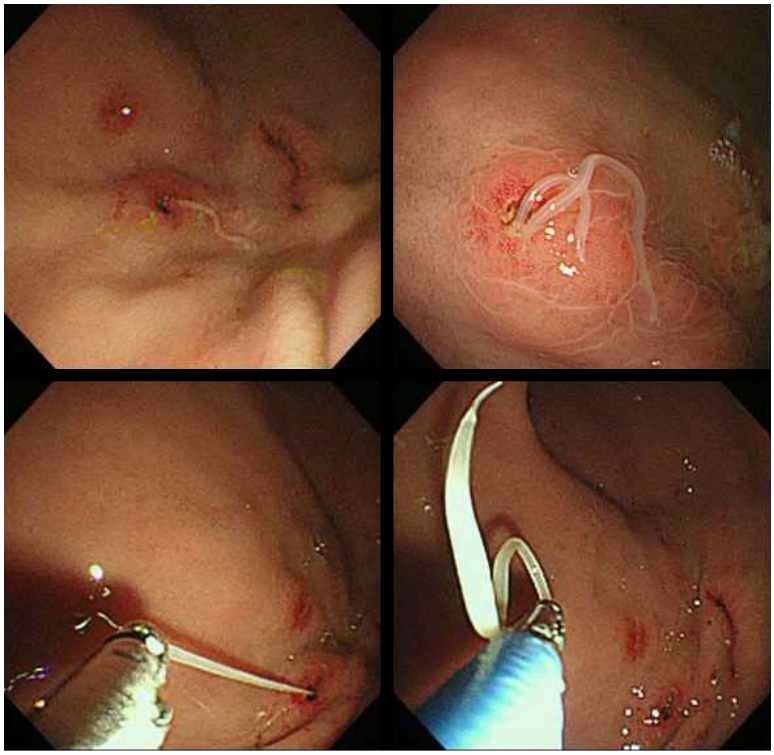

Figure 2 *Anisakis* larvae that are attached to the gastric mucosa can be removed using a biopsy forceps.

infections such as *Taenia saginata* in the intestinal tract[9]. Gastrografin is a 76% solution of diatrizoate, a water-soluble contrast medium, and a three-iodine compound. It contains 66% meglumine salt solution and 10% sodium salt solution. It is a hypertonic solution with a specific gravity of 1.416-1.420, pH 6.0-7.7, iodine content of 370 mg/mL, and osmotic pressure of 1900 mOsmol/L[10]. Because of its high osmotic pressure,

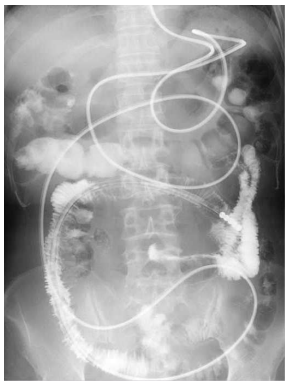

Figure 3 Ileography using gastrografin. It did not reveal small intestine obstruction.

when Gastrografin is used for patients with upper gastrointestinal symptoms, diarrhea is often a result, and it seems that extraction of *Anisakis* larvae is the result of this purgative effect.

Since *Anisakis* larvae die over time, enteric anisakiasis is generally alleviated through conservative therapy. For example, Amano *et al*[11] suggested that retrieving *Anisakis* larvae through endoscopic extraction using double-balloon enteroscopy *via* the anal approach is useful for treating enteric anisakiasis. However, double-balloon enteroscopy still requires a high-level of expertise and is not routinely performed. Using an antiallergic drug such as Stronger Neo-Minophagen C and steroids is useful; however, it is just one of many conservative therapies and is not a radical treatment[12,13]. Kasuya *et al*[14] examined the killing effect of foods such as *Perilla frutescens* viridis *Makino*, *Zingiber officinale*, *Wasabia japonica*, *Allium sativum*, and ethanol to find the most effective form of prophylaxis, and confirmed that these foods were effective in stopping the motion of worms *in vitro*. However, these foods would need to be consumed in too high of a volume to be practical as an effective prophylaxis. Thus, of the available known treatment options, Gastrografin administration is the most convenient and useful therapy.

In conclusion, based on this case, abdominal CT is useful for the diagnosis of enteric anisakiasis, and Gastrografin administration therapy is useful for the extraction of enteric *Anisakis* larvae. Because most patients with intestinal anisakiasis cause intestinal obstruction and ileus, an ileus tube is indwelled. Our Gastrografin administration therapy is only two times of ileography using Gastrografin after placing an ileus tube, which is less in burdens on a patient. However more studies are necessary to confirm our results.

ARTICLE HIGHLIGHTS

Case characteristics

A 59-year-old Japanese woman who had eaten sliced raw horse mackerel and salmon at lunch presented with epigastric pain and vomiting since the evening.

Clinical diagnosis

Tenderness in the epigastrium without obvious rebound tenderness or guarding.

Differential diagnosis

Acute abdomen including digestive disorders and gynecological disorders, acute coronary syndromes, urinary system diseases.

Laboratory diagnosis

All labs were within normal limits, except for increased C-reactive protein (19.7 mg/dL).

Imaging diagnosis

Computed tomography (CT) scan demonstrated segmental edema of the intestinal wall with dilated bowel and a small number of ascites, and endoscopy revealed that nine *Anisakis* larvae were attached to the gastric mucosa.

Treatment

Direct endoscopic removal of all of the *Anisakis* larvae in the stomach with a biopsy forceps and Gastrografin administration for enteric anisakiasis.

Experiences and lessons

Abdominal CT is useful for the diagnosis of enteric anisakiasis and Gastrografin administration therapy is useful for the extraction of enteric *Anisakis* larvae.

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ORIGINAL ARTICLE

Retrospective Study

Impact of the timing of capsule endoscopy in overt obscure gastrointestinal bleeding on yield and rebleeding rate - is sooner than 14 d advisable?

Catarina Gomes, Rolando Pinho, Adélia Rodrigues, Ana Ponte, Joana Silva, Jaime Pereira Rodrigues, Mafalda Sousa, João Carlos Silva, João Carvalho

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Author contributions: Gomes C and Pinho R designed the study, performed the research, analyzed the data and wrote the paper; Rodrigues A, Ponte A, Silva J, Rodrigues JP, Sousa M, Silva JC and Carvalho J performed the research and analyzed the data.

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Abstract

AIM

To evaluate the impact of the timing of capsule endoscopy (CE) in overt-obscure gastrointestinal bleeding (OGIB).

METHODS

Retrospective, single-center study, including patients submitted to CE in the setting of overt-OGIB between January 2005 and August 2017. Patients were divided into 3 groups according to the timing of CE (≤ 48 h; 48 h-14 d; ≥ 14 d). The diagnostic and therapeutic yield (DY and TY), the rebleeding rate and the time to rebleed were calculated and compared between groups. The outcomes of patients in whom CE was performed before (≤ 48 h) and after 48 h (> 48 h), and before (< 14 d) and after 14 d (≥ 14 d), were also

compared.

RESULTS

One hundred and fifteen patients underwent CE for overt-OGIB. The DY was 80%, TY-46.1% and rebleeding rate - 32.2%. At 1 year 17.8% of the patients had rebled. 33.9% of the patients performed CE in the first 48 h, 30.4% between 48h-14d and 35.7% after 14 d. The DY was similar between the 3 groups (P = 0.37). In the $\leqslant$ 48 h group, the TY was the highest (66.7% *vs* 40% *vs* 31.7%, P = 0.005) and the rebleeding rate was the lowest (15.4% *vs* 34.3% *vs* 46.3% P = 0.007). The time to rebleed was longer in the $\leqslant$ 48 h group when compared to the > 48 h groups (P = 0.03).

CONCLUSION

Performing CE within 48 h from overt-OGIB is associated to a higher TY and a lower rebleeding rate and longer time to rebleed.

Key words: Overt-obscure gastrointestinal bleeding; Capsule endoscopy; Timing; Diagnosis; Therapeutic; Rebleeding

Core tip: An early diagnosis with capsule endoscopy (CE) in overt-obscure gastrointestinal bleeding (OGIB) patients can lead to an appropriate specific intervention, better long term-outcomes and reduce unnecessary medical costs. In this paper we evaluated the impact of the timing of CE in these patients. ESGE recommends performing CE as soon as possible after the bleeding episode, optimally within 14 d. We found that in spite of a similar diagnostic yield, performing CE within 48 h is associated with greater therapeutic yield, less rebleeding episodes, and a longer rebleeding-free time. This suggests that a more timely approach in the evaluation of overt-OGIB than the 14 d recommendation is advisable.

Gomes C, Pinho R, Rodrigues A, Ponte A, Silva J, Rodrigues JP, Sousa M, Silva JC, Carvalho J. Impact of the timing of capsule endoscopy in overt obscure gastrointestinal bleeding on yield and rebleeding rate - is sooner than 14 d advisable? *World J Gastrointest Endosc* 2018; 10(4): 74-82 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i4/74.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i4.74

INTRODUCTION

Obscure gastrointestinal bleeding (OGIB) is defined as recurrent acute or chronic bleeding of unknown origin that persists or recurs despite negative findings from bidirectional endoscopy[1]. OGIB accounts for approximately 5% of all cases of gastrointestinal bleeding and is usually due to a lesion in the small bowel (SB)[2]. OGIB can be classified as overt or occult. Overt-OGIB refers to recurrent or persistent visible bleeding (hematochezia, melena or hematemesis) and occult-OGIB is defined as recurrent or persistent iron-deficiency anemia and/or positive fecal occult blood[1].

Since the introduction of Capsule Endoscopy (CE) in 2000[3], SB visualization became possible with this safe and non-invasive method. Its advent has resulted in a paradigm shift in the management of patients with OGIB[1]. OGIB is the main indication for both the performance of CE and device-assisted enteroscopy[2,4]. The European Society of Gastrointestinal Endoscopy (ESGE) recommends CE as the first-line investigation in patients with OGIB, and in overt presentations, their recommendation is to perform CE as soon as possible after the bleeding episode, optimally within 14 d[2]. CE has been shown to have a high diagnostic yield (DY) in OGIB and is significantly more sensitive when compared to other alternative diagnostic radiographic and endoscopic methods[5-7].

Patients with overt-OGIB are more likely to present a significant lesion, which is associated with recurrent bleeding[8-11]. An early definitive diagnosis in these patients can lead to an appropriate specific intervention, better outcomes and reduce unnecessary medical costs[11,12].

Using CE early in the course of overt-OGIB seems to be attractive, because of the higher DY, and even if no lesion is found, at least, it has the potential to localize the source of the bleeding[12-15]. However, the data is limited and the optimal timing for CE in overt-OGIB remains unclear[1,16].

The aim of this study is to evaluate the impact of the timing of CE in overt-OGIB in the DY, therapeutic yield (TY), rebleeding rate and time to rebleed, mainly when CE is performed within the first 48 h.

MATERIALS AND METHODS

Patient and data collection

A cohort of patients with overt-OGIB who underwent CE after bidirectional endoscopy at Centro Hospital Vila Nova de Gaia from January 2005 to August 2017 was evaluated. Patients were follow-up until October 2017.

Patient clinical information was retrospectively collected from electronic medical records, including demographic characteristics (gender, age); comorbidities (cardiovascular, renal, hepatic disease, tumor, previous abdominal surgeries); medical therapy [anticoagulants, antiplatelet and nonsteroidal anti-inflammatory drugs (NSAID's)]; hemoglobin (Hg) at admission, international normalized ratio (INR) at admission, and number of units of packed red blood cells (RBC) transfused prior to CE.

Capsule endoscopy

The Given® Video Capsule and Mirocam® Video Capsule systems were used in this study. CE studies were carried out according to our unit's protocol, which includes an overnight fast without prior bowel

preparation, suspension of iron supplements 8 d before the procedure and a liquid diet in the last dinner. Written informed consent was obtained from all patients. Patients were allowed to have an oral light diet 4 h after CE ingestion. Patients in whom CE was Mirocam®, were evaluated 1 h and 2 h after CE ingestion. Removal of the recorder 12 h after CE ingestion or earlier if real-time viewing confirms that the device has already reached the colon. A prokinetic agent (metoclopramide 10 mg) was administered when the capsule was found in the stomach.

Overt-OGIB (melena or hematochezia) was subdivided into ongoing-overt-OGIB (bleeding during the procedure, at the time of CE) and previous-overt-OGIB (bleeding in the past but not during the procedure).

The period between overt-OGIB and CE was divided into 3 groups: Within 48 h (≤ 48 h); between 48 h and 14 d (48 h-14 d); and after 14 d (≥ 14 d). The outcomes of patients whose CE was performed before (≤ 48 h) and after 48 h (> 48 h), and before (< 14 d) and after 14 d (≥ 14 d), were also compared.

CE cleansing was evaluated according to the scale Brotz *et al* [17-18]. Cleansing was considered appropriate when graduated as excellent, good or fair.

CE findings were classified as positive and negative findings. Positive findings included bleeding without visible lesions, angiodysplasia, varices, hemangioma, ulcer, erosion, eroded polyps, diverticulum with bleeding stigmata, small-bowel tumor, or extra-small-bowel causes that could explain the bleeding (extra-SB cause of bleeding). Bleeding was subdivided into recent or active. The diagnostic yield was defined as the proportion of CE with positive findings to the total number of CE.

Treatment for OGIB was divided into medical, endoscopic, radiological or surgical. The therapeutic yield was defined as the proportion of patients performing one of the above mentioned treatments to the total number of patients.

The occurrence and time to rebleeding episodes, as well as the mortality, were also evaluated. Rebleeding episodes were defined as evidence of melena or hematochezia, a drop in hemoglobin of 2 g/dL or more from baseline, or the need for transfusion[19-21].

Statistical analysis

Data was analyzed using SPSS version 23.0. Descriptive statistics were used to describe the patient's demographic features, clinical characteristics and type of endoscopic findings. Categorical variables were presented as percentages and numeric variables as means. Results are expressed as percentages or means standard deviation (SD) for continuous variables.

The χ^2 test was used to compare non-continuous variables. The *t*-test and ANOVA test were used to compare continuous variables. The Kaplan-Meier test was used to calculate the time to rebleed. The Log-Rank test was used to compare the time to rebleed between groups. A $P < 0.05$ was considered to be statistically significant.

RESULTS

A total of 115 patients underwent CE for overt-OGIB. Patient characteristics are shown in Table 1. The mean age was 65.1 years (SD ± 14.6) and 51.3% percent (*n* = 59) were female. The mean delay between overt-OGIB and CE was 48.9 d (SD ± 161.5).

Most patients were referred for melena (54.8%, *n* = 63), while 45.2% (*n* = 52) were referred for hematochezia. On-going-overt-OGIB was present in 53.9 % (*n* = 62). In 67.8% of the patients, CE was performed during hospitalization. The two systems of capsule endoscopy (Given® and Mirocam®) were compared. Only the presence of on-going OGIB and the CE performance in the inpatient setting were significant higher with the Mirocam® system ($P < 0.05$) (Table 2).

CE findings are presented in Table 3. The CE reached the cecum in 90.4% of all examinations (*n* = 104) and in 75.7% the cleansing was considered appropriate (*n* = 87). Almost all patients had positive findings (81.8%, *n* = 94). The most frequent findings were vascular lesions-29.6% (angiodysplasia 26.1%, varices 0.9% and hemangioma 2.6%); ulcers/erosions-16.4% (10.4%/6%); diverticula 1.7% and mass lesions-13.1%: tumors 9.6% (adenocarcinoma, neuroendocrine tumours, GIST, carcinoid tumours and subepitelial lesions) and polyps 3.5%. Blood in the GI tract was observed in 41.7% of the patients, and was divided into active (73%) and inactive bleeding (27%).

The DY was 80% (*n* = 92), TY 46.1% (*n* = 53), rebleeding rate 32.2% (*n* = 37), and the global mortality 24.3% (*n* = 28) (Table 4). At 1 year the rebleeding rate was 17.8%, at 2 years 24.1%, at 3 years 33.9%, at 4 years 30.8% and at 5 years 52.6% (Table 4 and Figure 1).

The treatment was conservative in 53.9% of the patients (*n* = 62), endoscopic in 26.1% (*n* = 30), surgical in 16.5% (*n* = 19), radiological in 2.6% (*n* = 3) and one of the patients performed endoscopic therapy (APC for the treatment of angiodysplasia) and was subsequently submitted to surgical treatment of a GIST (gastrointestinal stromal tumor) (found in the same enteroscopy) (0.9%) (Table 5).

Per group analysis

≤ 48 h *vs* 48 h-14 d *vs* ≥ 14 d: Capsule endoscopy was performed in the first 48 h in 33.9% of the patients (*n* = 39), between 48 h-14 d in 30.4% (*n* = 35) and after 14 d in 35.7% (*n* = 41) (Table 1).

The mean age was not significantly different between groups ($P = 0.23$). Regarding the baseline characteristics and comorbidity status, only the presence of renal disease was more prevalent in the ≥ 14 d group ($P = 0.04$) (Table 1).

On-going overt-OGIB was present in all patients in the ≤ 48 h group, and all of them were still hospitalized when CE was performed (Table 1). These data were

Table 1 Patient characteristics *n* (%)

No. of patients (*n* = 115)	All	⩽ 48 h (*n* = 39, 33.9)	48 h-14 d (*n* = 35, 30.4)	⩾ 14 d (*n* = 41, 35.7)	*P* value[1]
Time to CE after OOGIB, mean ± SD, d	48.9 ± 161.5				
Age, mean ± SD, yr	65.1 ± 14.6	63 ± 14.2	63.9 ± 15.9	68.2 ± 13.6	0.234
Female sex	59 (51.3)	18 (46.2)	20 (57.1)	21 (51.2)	0.64
Comorbidities					
Cardiovascular disease	61 (53)	20 (51.3)	16 (45.7)	25 (61)	0.40
Renal disease	20 (17.4)	2 (5.1)	8 (22.9)	10 (24.4)	0.045
Hepatic disease	8 (7)	3 (7.7)	2 (5.7)	3 (7.3)	0.940
Tumour	7 (6.1)	2 (5.1)	2 (5.7)	3 (7.3)	0.91
Previous abdominal surgeries	27 (23.5)	10 (25.6)	8 (22.9)	9 (22)	0.92
Drugs					
Anti-platelet drugs	49 (42.6)	17 (43.6)	13 (37.1)	19 (46.3)	0.71
Anticoagulation	25 (21.7)	8 (20.5)	9 (25.7)	8 (19.5)	0.79
NSAIDs	10 (8.7)	4 (10.3)	2 (5.7)	4 (9.8)	0.75
Melena	63 (54.8)	18 (46.2)	21 (60)	24 (58.5)	0.41
Hematochezia	52 (45.2)	21 (53.8)	14 (40)	17 (41.5)	0.41
On-going OOGIB	62 (53.9)	39 (100)	17 (48.6)	6 (14.6)	< 0.001
Hg at admission, mean ± SD, g/dL	8.91 ± 6.24	8.51 ± 2.65	8.26 ± 2.32	9.93 ± 9.88	0.12
INR at admission, mean ± SD	1.61 ± 1.18	1.57 ± 1.00	1.83 ± 1.65	1.47 ± 0.77	0.08
Packed RBC transfusions, mean ± SD, units	1.41 ± 1.31	1.41 ± 1.37	1.51 ± 1.20	1.29 ± 1.36	0.29
Inpatient	78 (67.8)	39 (100)	31 (88.6)	8 (19.5)	< 0.001

[1]ANOVA, χ^2 test, as appropriate; *P* value of 0.05 indicating statistical significance. CE: Capsule endoscopy; SD: Standard deviations; NSAIDs: Nonsteroidal anti-inflammatory drug; OOGIB: Overt-obscure gastrointestinal bleeding; Hg: Hemoglobin; INR: International normalized ratio; RBC: Red blood cells.

Table 2 Patient characteristics according to the system of capsule endoscopy used *n* (%)

No. of patients (*n* = 115)	All	Given® (*n* = 32, 27.8)	Mirocam® (*n* = 83, 72.2)	*P* value[1]
Time to CE after OOGIB, mean ± SD, d	48.9 ± 161.5	51 ± 119.1	48.1 ± 175.8	0.93
Age, mean ± SD, yr	65.1 ± 14.6	60.8 ± 16.9	66.8 ± 13.3	0.08
Female sex	59 (51.3)	18 (56.2)	41 (49.4)	0.51
Comorbidities				
Cardiovascular disease	61 (53)	15 (46.9)	46 (55.4)	0.41
Renal disease	20 (17.4)	3 (9)	17 (20.5)	0.16
Hepatic disease	8 (7)	2 (6)	6 (7)	0.85
Tumour	7 (6.1)	1 (3)	6 (7)	0.41
Previous abdominal surgeries	27 (23.5)	5 (16)	22 (26.5)	0.22
Drugs				
Anti-platelet drugs	49 (42.6)	12 (37.5)	37 (44.6)	0.49
Anticoagulation	25 (21.7)	7 (21.9)	18 (21.7)	0.98
NSAIDs	10 (8.7)	4 (12.5)	6 (7)	0.37
Melena	63 (54.8)	21 (65.6)	42 (50.6)	0.15
Hematochezia	52 (45.2)	11 (34.4)	41 (49.4)	0.15
On-going OOGIB	62 (53.9)	7 (21.9)	55 (66.3)	< 0.001
Hg at admission, mean ± SD, g/dL	8.91 ± 6.24	8.94 ± 2.77	8.94 ± 7.14	0.99
INR at admission, mean ± SD	1.61 ± 1.18	1.55 ± 0.81	1.64 ± 1.29	0.72
Packed RBC transfusions, mean ± SD, units	1.41 ± 1.31	1.28 ± 1.42	1.45 ± 1.27	0.55
Inpatient	78 (67.8)	18 (56.2)	60 (72.3)	0.01
Timing of CE				
⩽ 48 h	39 (33.9)	4 (12.5)	35 (42.2)	0.009
48 h-14 d	35 (30.4)	14 (43.75)	21 (25.3)	
⩾ 14 d	41 (35.7)	14 (43.75)	27 (32.5)	

[1]*t*-test: χ^2 test, as appropriate; *P* value of 0.05 indicating statistical significance. CE: Capsule endoscopy; SD: Standard deviations; NSAIDs: Nonsteroidal anti-inflammatory drug; OOGIB: Overt-obscure gastrointestinal bleeding; Hg: Hemoglobin; INR: International normalized ratio; RBC: Red blood cells.

significantly different from the other groups (100% *vs* 48.6% *vs* 14.6%, $P < 0.001$ and 100% *vs* 88.6% *vs* 19.5%, $P < 0.001$, respectively).

The Mirocam® system was performed more often in the first 48 h ($P < 0.05$), compared to the Given® system (42.2% *vs* 12.5%, $P = 0.009$) (Table 2).

The total of positive findings in CE did not appear to differ between groups ($P = 0.3$), however active bleeding tends to be more prevalent in the ⩽ 48 h group (43.6% *vs* 28.6% *vs* 19.5%, $P = 0.06$) (Table 3).

The DY and mortality rate were similar between the 3 groups ($P = 0.37$ and $P = 0.78$, respectively). Conversely, the TY was significantly higher (66.7% *vs* 40% *vs* 31.7%, $P = 0.005$) and the rebleeding rate

Table 3 Capsule endoscopy findings in all patients and between ⩽ 48 h, 48 h-14 d and ⩾ 14 d group *n* (%)

	All (*n* = 115)	⩽ 48 h (*n* = 39)	48 h-14 d (*n* = 35)	⩾ 14 d (*n* = 41)	*P* value[1]
Total enteroscopy	104 (90.4)	33 (84.6)	32 (91.4)	39 (95.1)	0.27
Appropriate cleansing	87 (75.7)	21 (53.8)	31 (88.6)	35 (85.4)	0.00
Positive Findings	94 (81.8)	33 (84.3)	31 (88.6)	31 (75.6)	0.30
Angiodysplasia	30 (26.1)	6 (15.4)	11 (31.4)	13 (31.7)	
Varices	1 (0.9)	0	1 (2.9)	0	
Hemangioma	3 (2.6)	1 (2.6)	1 (2.9)	1 (2.4)	
Ulcers	12 (10.4)	3 (7.7)	5 (14.3)	4 (9,8)	
Erosions	7 (6)	1 (2.6)	1 (2.9)	5 (12.2)	
Tumours	11 (9.6)	2 (5.1)	7 (20)	2 (4.9)	
Polyps	4 (3.5)	1 (2.6)	2 (5.7)	1 (2.4)	
Diverticula	2 (1.7)	1 (2.6)	0	1 (2.4)	
Extra-SB cause	2 (1.7)	2 (5.1)	0	0	
Bleeding	48 (41.7)	23 (59)	15 (42.9)	10 (24.4)	0.007
Inactive bleeding	13 (11.3)	6 (15.4)	5 (14.3)	2 (4.9)	0.27
Active bleeding	35 (30.4)	17 (43.6)	10 (28.6)	8 (19.5)	0.06

[1]χ^2 test; *P* value of 0.05 indicating statistical significance. CE: Capsule endoscopy.

Table 4 Capsule endoscopy outcomes in all patients, and between ⩽ 48 h, 48h-14 d and ⩾ 14 d groups *n* (%)

Outcome	All (*n* = 115)	⩽ 48 h (*n* = 39)	48 h-14 d (*n* = 35)	⩾ 14 d (*n* = 41)	*P* value[1]	*P*[1] (⩽ 48 h *vs* 48 h-14 d)
DY	92 (80)	32 (82.1)	30 (85.7)	30 (73.2)	0.37	0.67
TY	53 (46.1)	26 (66.7)	14 (40)	13 (31.7)	0.005	0.02
RR	37 (32.2)	6 (15.4)	12 (34.3)	19 (46.3)	0.007	0.06
Time to rebleed, yr	1 yr, 17.8	1 yr, 11.8	1 yr, 20.1	1 yr, 21.9		
	2 yr, 24.1	2 yr, 11.8	2 yr, 30.7	2 yr, 31.4		
	3 yr, 33.9	3 yr, 18.5	3 yr, 37	3 yr, 46.9		
	4 yr, 30.8	4 yr, 18.5	4 yr, 44	4 yr, 58.2		
	5 yr, 52.6	5 yr, 60	5 yr, 53.4	5 yr, 64.2		
Mortality	28 (24.3)	9 (23.1)	10 (28.6)	9 (22)	0.78	0.59

[1]χ^2 test; *P* value of 0.05 indicating statistical significance. DY: Diagnostic yield; TY: Therapeutic yield; RR: Rebleeding rate.

Table 5 Type of treatment between ⩽ 48 h, 48 h-14 d and ⩾ 14 d groups *n* (%)

Type of treatment	All (*n* = 115)	⩽ 48 h (*n* = 39)	48 h-14 d (*n* = 35)	⩾ 14 d (*n* = 41)	*P* value[1]
Conservative	62 (53.9)	13 (33.3)	21 (60)	28 (68.3)	0.005
Endoscopic	30 (26.1)	14 (35.9)	6 (17.1)	10 (24.4)	0.18
Surgical	19 (16.5)	9 (23.1)	7 (20)	3 (7.3)	0.13
Radiological	3 (2.6)	2 (5.1)	1 (2.9)	0	0.353
Endoscopic + Surgical	1 (0.9)	1 (2.6)	0	0	0.37

[1]χ^2 test; *P* value of 0.05 indicating statistical significance.

lower (15.4% *vs* 34.3% *vs* 46.3% *P* = 0.007) in the ⩽ 48 h group (Table 4). Conservative treatment was the only type of treatment that differed between groups, being higher when CE was performed after 14 d (33.3% *vs* 60% *vs* 68.3%, *P* = 0.005) (Table 5).

Time to rebleed was not significantly different between groups (*P* = 0.055) (Figure 2A).

⩽ 48 h *vs* 48 h-14 d: In spite of a similar DY and mortality rate (*P* = 0.67 and 0.59, respectively), the TY was significantly higher (66.7% *vs* 40%, *P* = 0.02) and the rebleeding rate tended to be inferior (15.4% *vs* 34.3%, *P* = 0.06) in the ⩽ 48 h group. The time to rebleed was not significantly different (*P* = 0.15) (Table 4 and Figure 2B).

⩽ 48 h *vs* > 48 h: The DY and mortality were similar between the 2 groups (*P* = 0.69 and *P* = 0.82, respectively). However, the TY was higher (66.7% *vs* 35.5%, *P* = 0.002) and rebleeding episodes were less frequent (15.4% *vs* 43%, *P* = 0.004) in the ⩽ 48 h group. The time to rebleed was also significantly longer (*P* = 0.03) (Figure 2C and Table 6).

< 14 d *vs* ⩾ 14 d: The DY and mortality were also similar between these 2 groups (*P* = 0.17 and 0.66, respectively). However in the < 14 d group, the TY was higher and the rebleeding rate lower (54% *vs* 31.7%, *P*

Table 6 Outcomes between ⩽ 48 h and > 48 h groups and < 14 d and ⩾ 14 d groups

Outcome	⩽ 48 h	> 48 h	P^1 (⩽ 48 h *vs* > 48h)	< 14 d	⩾ 14 d	P^1 (< 14 d *vs* ⩾ 14 d)
DY	32 (82.1)	60 (78.9)	0.69	62 (83.8)	30 (73.2)	0.17
TY	26 (66.7)	27 (35.5)	0.002	40 (54.1)	13 (31.7)	0.02
RR	6 (15.4)	31 (43)	0.004	18 (25)	19 (46.3)	0.008
Time to re-bleed, yr	1 yr, 11.8	1 yr, 1		1 yr, 15.6	1 yr, 21.9	
	2 yr, 11.8	2 yr, 31.1		2 yr, 20.4	2 yr, 31.4	
	3 yr, 18.5	3 yr, 42.6		3 yr, 26.8	3 yr, 46.9	
	4 yr, 18.5	4 yr, 52		4 yr, 30.6	4 yr, 58.2	
	5 yr, 60	5 yr, 59.7		5 yr, 38.3	5 yr, 64.2	
Mortality	9 (23.1)	19 (25)	0.82	19 (25.7)	9 (22)	0.66

[1]χ^2 test; *P* value of 0.05 indicating statistical significance. DY: Diagnostic yield; TY: Therapeutic yield; RR: Re-bleeding rate.

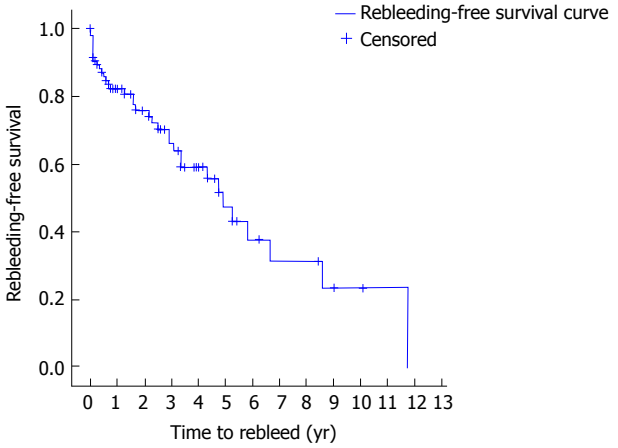

Figure 1 Kaplan–Meier curve in all patients, analysis of the % patients that had rebled the time.

= 0.02; 25% *vs* 46.3%, *P* = 0.008, respectively). The time to rebleed was also significantly longer in the < 14 d group (*P* = 0.047) (Figure 2D and Table 6).

DISCUSSION

In our study, the timing of CE in the setting of overt-OGIB influenced several outcomes. The earlier performance of CE was associated with a higher TY, lower rebleeding rates and longer rebleeding-free time.

Some series reported that performing CE within 24-72 h from the onset of overt-OGIB, results in a DY higher than 60%[12,14,15]. Lecleire *et al*[14] analyzed the performance of emergency CE (within 24-48 h) in severe overt-OGIB and found that specific diagnostic and therapeutic procedures were undertaken in 78% of the patients. Apostolopoulos *et al*[12] enrolled patients with mild-to-moderate overt-OGIB that performed urgent CE (within 48 h) and reported a DY of 91.9%. So it seems that independently of the severity of bleeding, CE performed as soon as possible in overt-OGIB is associated with good outcomes.

On-going overt-OGIB has been associated with a higher number of positive CE findings in other studies[13,22-24]. In our study on-going overt-OGIB was present in the totality of patients in the ⩽ 48 h group and declined progressively in the remaining groups.

Patient characteristics in both systems were analyzed. The presence of on-going OGIB and CE in the inpatient setting were significantly higher with the Mirocam® system (*P* < 0.05). When comparing the two systems according to the timing of CE performance, the Mirocam® system was more often used in the first 48 h, which can be associated to the presence of on-going bleeding. This can be explained by the fact that the Given® system was used in the beginning of the series and at that time there was not so much evidence about the use of urgent CE in the setting of a bleeding event.

When comparing different groups according to the timing of CE, previous studies have shown that the earlier the capsule study is started, the greater the DY achieved[13,16,25-30]. Several studies evaluating the timing from overt-OGIB to CE, such as 48-72 h[16,25,27], 1 wk[28], 10 d[29], 15 d[30] have already been reported, demonstrating that the DY was always superior whenever CE was performed earlier. In our study, that association was not found, since independently from the timing of CE, the DY was similar between all periods examined (*P* > 0.05). Then again, the ⩽ 48 h group of CE had a tendency to detect active bleeding more often than the others groups (*P* = 0.06).

The main purpose of small bowel evaluation is to guide a subsequent therapeutic intervention, usually endoscopically[4,20,21,31]. In this sense, the TY is a better surrogate in the evaluation of the best timing of CE. In the present study, the TY was higher when CE was performed earlier, as it has been described in previous studies[13,16,26,27]. Yamada *et al*[26] found that the proportion of interventions were significantly higher in 1st and 2nd quartiles of time between CE and overt-OGIB (*P* = 0.048). Singh *et al*[27] enrolled patients with overt-OGIB in 2 groups (CE performed before and after 3 d), and found that the TY was higher in the first group (*P* = 0.046). More recently, Kim *et al*[16] showed that specific therapeutic interventions were performed in 26.7% of the patients in the ⩽ 48 h group, a higher rate compared to the > 48 h group (*P* = 0.028). On the other hand, several studies demonstrate that the yield of therapeutic endoscopy in the setting of overt-OGIB is also higher the sooner it is performed[11].

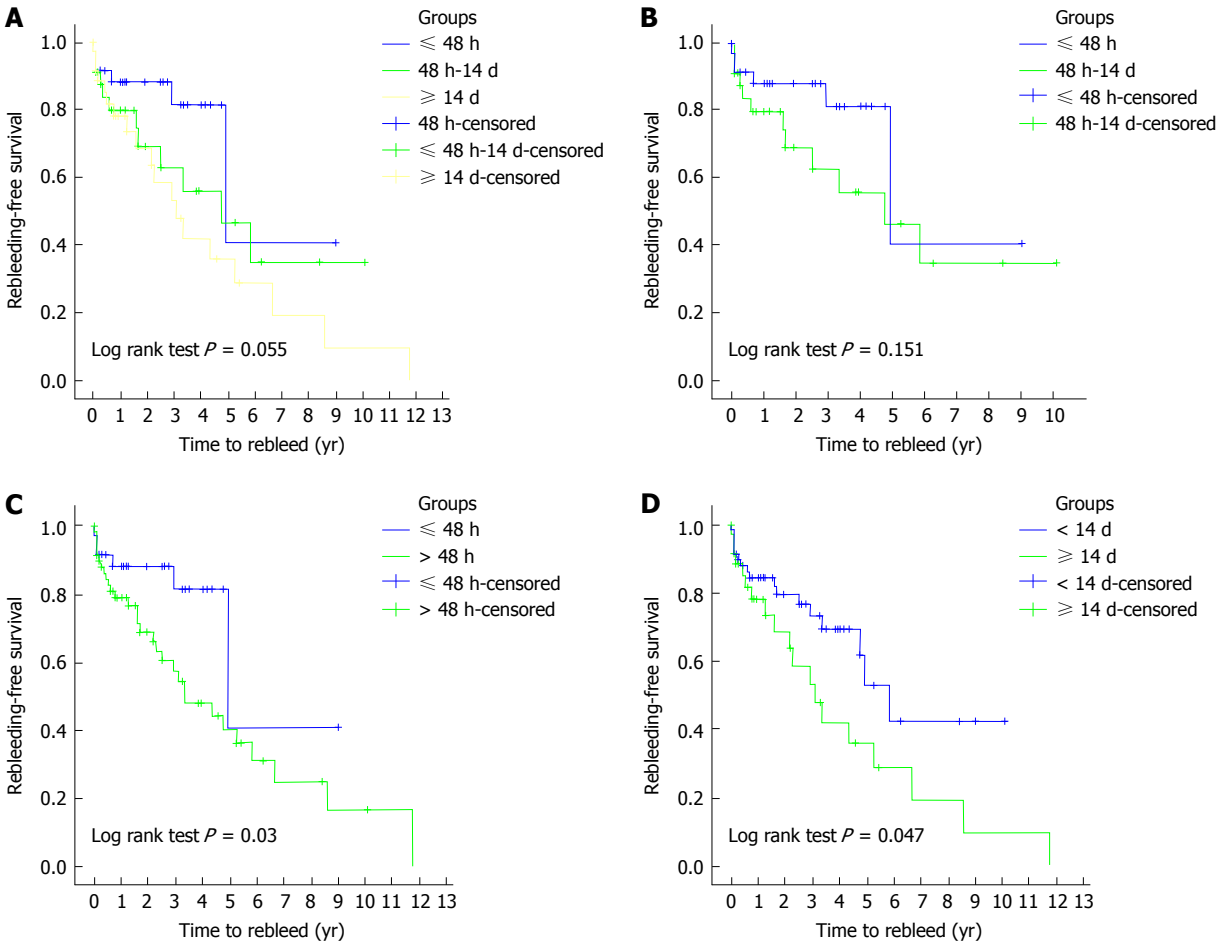

Figure 2 Kaplan–Meier curves according to the time of capsule endoscopy performance after overt-OGIB. A: The rebleeding risk in the ≤ 48 h group was 11.8% and 18.5% at 1 and 3 yr, in the 48 h-14 d group was 20.1% and 37% at 1 and 3 yr, and in the ≥ 14 d group was 21.9% and 46.9% at 1 and 3 years. The rebleeding risk was not significantly different between groups (P = 0.055); B: The rebleeding risk in the ≤ 48 h groups was 11.8% and 18.5% at 1 and 3 yr, compared with 20.1% and 37% at 1 and 3 yr in the 48 h-14 d group (P = 0.151); C: The rebleeding risk in the ≤ 48 h groups was 11.8% and 18.5% at 1 and 3 yr, compared with 21% and 42.6% at 1 and 3 yr in the > 48 h group. The rebleeding risk was significantly different between groups (P = 0.03); D: The rebleeding risk in the ≤ 48 h group was 15.6% and 26.8% at 1 and 3 yr, compared with 21.9% and 46.9% at 1 and 3 yr in the ≥ 14 d group. The rebleeding risk was significantly different between groups (P = 0.047).

The rebleeding rate was not systematically evaluated in other studies. In the study from Apostolopoulos *et al*[12] a rebleeding rate of 15.6% at 1 year was found in patients who performed CE in the first 48 h, a similar result to the 15.4% found in the present study in the same subset of patients (≤ 48 h). Furthermore, the present study demonstrated that this rebleeding rate was lower (P = 0.007) than the rebleeding rate of other patients subsets (48 h-14 d, > 14d).

The current recommendation of the ESGE guidelines on capsule endoscopy is to perform CE within 14 d from the bleeding event[2], but according to our study and to the studies described above, the therapeutic intervention is higher when CE is performed within 48 h.

Therefore, in the present study, the conservative approach was higher in the ≥ 14 d group and in this same group the rebleeding rate was also superior. This can be explained by the fact that when CE is done later in the course of the bleeding event, an effective therapeutic intervention to control bleeding is less often employed, which could lead to recurrent bleeding. The presence of renal disease was more prevalent in the ≥ 14 d group (P = 0.04), and usually this has been associated with greater risk of gastrointestinal bleeding, which could influence the outcomes[19,32].

When performance of CE before and after 48 h and before and after 14 d was compared, a shorter rebleeding-free time was found in groups > 48 h and ≥ 14 d (P = 0.03 and P = 0.047, respectively). Once again, these results suggest that performing CE as soon as possible can influence the long-term outcomes.

In conclusion, performing CE within 48 h from the onset of overt-OGIB is associated with a higher therapeutic yield, a lower rebleeding rate and a longer rebleeding-free time. These findings may prompt to a more timely approach in the evaluation of overt-OGIB than the current 14 d-time frame recommendation.

The present study has some limitations. First, it has a retrospective design with a small number of patients that has not the sufficient power to change the current recommendations. Therefore a prospective assessment of the timing of CE for this indication is warranted to

confirm these findings. Second, the presence of renal disease was different between the groups, which can bias the results, mainly the rebleeding rate.

ARTICLE HIGHLIGHTS

Research background

An early diagnosis with capsule endoscopy in overt-obscure gastrointestinal bleeding patients can lead to an appropriate specific intervention, better long term-outcomes and reduce unnecessary medical costs. European Society of Gastrointestinal Endoscopy recommends performing capsule endoscopy as soon as possible after the bleeding episode, optimally within 14 d. In this paper we evaluated the impact of the timing of capsule endoscopy in these patients, focusing in an earlier evaluation.

Research motivation

As an earlier diagnosis could lead to an earlier and more effective therapy, the authors ought to evaluate the impact of an earlier capsule evaluation on the therapeutic yield and the rebleeding rate.

Research objectives

To evaluate how the timing of capsule endoscopy (CE) in overt-obscure gastrointestinal bleeding (OGIB) could change management of overt-OGIB and future outcomes.

Research methods

The diagnostic and therapeutic yield (DY and TY) rebleeding rate, time to rebleed and mortality were calculated and compared according to the timing of capsule endoscopy ($\leqslant$ 48 h; 48 h-14 d and $\geqslant$ 14 d).

Research results

Despite a similar diagnostic yield, performing capsule endoscopy within 48 h is associated with greater therapeutic yield, less rebleeding episodes, and a longer rebleeding-free time. This suggests that a more timely approach than the 14 d recommendation in the evaluation of overt-OGIB should be considered.

Research conclusions

Performing CE within 48 h from the onset of overt-OGIB is associated with a higher therapeutic yield, a lower rebleeding rate and a longer rebleeding-free time. It raises the question that performing CE sooner than 14 d could be advisable.

Research perspectives

Our study has a retrospective design with a small number of patients, so a prospective assessment of this timing of CE in overt-OGIB in a larger population is warranted to confirm these findings and change recommendations.

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ORIGINAL ARTICLE

Retrospective Study

Severity of gastric mucosal atrophy affects the healing speed of post-endoscopic submucosal dissection ulcers

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Abstract

AIM

To investigate factors associated with the healing of endoscopic submucosal dissection (ESD)-induced ulcers.

METHODS

We enrolled 132 patients with gastric tumors scheduled for ESD. Following ESD, patients were treated with daily lansoprazole 30 mg or vonoprazan 20 mg. Ulcer size was endoscopically measured on the day after ESD and at 4 and 8 wk. The gastric mucosa was endoscopically graded according to the Kyoto gastritis scoring system. We assessed the number of patients with and without a 90% reduction in ulcer area at 4 wk post-ESD and scar formation at 8 wk, and looked for risk factors for slower healing.

RESULTS

The mean size of gastric tumors and post-ESD ulcers was 17.4 ± 12.1 mm and 32.9 ± 13.0 mm. The mean

reduction rates in ulcer area were 90.4% ± 0.8% at 4 wk and 99.8% ± 0.1% at 8 wk. The reduction rate was associated with the Kyoto grade of gastric atrophy at 4 wk (A0: 97.9% ± 0.6%, A1: 93.4% ± 4.1%, and A2: 89.7% ± 1.0%, respectively). In multivariate analysis, the factor predicting 90% reduction at 4 wk was gastric atrophy (Odds ratio: 5.678, 95%CI: 1.190-27.085, P = 0.029).

CONCLUSION

The healing speed of post-ESD ulcers was associated with the degree of gastric mucosal atrophy, and *Helicobacter pylori* eradication therapy is required to perform at younger age.

Key words: *Helicobacter pylori*; Gastric mucosal/AB; Endoscopic submucosal dissection; Gastric ulcer

Core tip: It is important to investigate factors influencing the healing speed of endoscopic submucosal dissection (ESD)-induced ulcers to prevent gastrointestinal bleeding. Although previous studies have looked at many factors related to ESD-induced ulcer healing, such as location of the tumor, submucosal fibrosis, initial ulcer size, diabetes, and method of gastric acid suppression, this report showed that the severity of gastric atrophy is possible factor to affect speed of ESD-induced ulcer healing. Therefore, *Helicobacter pylori* (*H. pylori*) eradication therapy is required to perform at younger age before progression of gastric mucosal atrophy to prevent development of *H. pylori*-related diseases and bleeding from ESD-induced ulcer.

Otsuka T, Sugimoto M, Ban H, Nakata T, Murata M, Nishida A, Inatomi O, Bamba S, Andoh A. Severity of gastric mucosal atrophy affects the healing speed of post-endoscopic submucosal dissection ulcers. *World J Gastrointest Endosc* 2018; 10(5): 83-92 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i5/83.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i5.83

INTRODUCTION

The efficacies of endoscopic submucosal dissection (ESD) and surgical gastrectomy for early-stage gastric cancer are generally similar[1]. ESD, being less invasive, is the first-line treatment for early-stage gastric cancer. ESD allows en bloc resection and is associated with a lower recurrence rate than endoscopic mucosal resection (EMR)[2,3].

Gastrointestinal bleeding from ESD-induced ulceration is a common complication[4-7]. Factors associated with an increased risk of post-ESD gastrointestinal bleeding include the size, location, and histology of the gastric cancer; kinds of gastric acid suppressant; patient use of dialysis; and long procedure time[4-7]. The risk of bleeding is reduced by endoscopic coagulation of exposed vessels at the base of ESD-induced ulcers and potent acid inhibition over the first 24 h post-treatment[4-7]. When ESD is performed for gastric cancer, proton pump inhibitors (PPIs) are used to treat ESD-induced ulcers[7]. However, PPIs may not suppress gastric acid secretion over 24 h, especially at night. Administration is required over several days to maximize gastric acid inhibition. More recently, interindividual genetic variations (*e.g.*, CYP2C19 genotype)[8,9] have been linked to different metabolism rates of PPIs. Vonoprazan, a potassium-competitive acid blocker (P-CAB) with more potent and sustained acid inhibition than PPIs, has been approved in Japan[10-12]. Although vonoprazan inhibits gastric H^+/K^+-ATPase similarly to PPIs, its mechanism of acid inhibition involves inhibition of H^+, K^+-ATPase by binding reversibly and competitively with K^+[13]. It remains unclear whether vonoprazan is associated with improved ulcer healing speed and prevention of post-ESD bleeding, due to the low statistical power of the most recent studies[5,14].

Previous studies have looked at many factors related to ESD-induced ulcer healing, such as location of the tumor[15], submucosal fibrosis[16], initial ulcer size[17,18], diabetes[18], coagulation abnormality[18], electrocoagulation during ESD[18], and method of gastric acid suppression[19].

Concurrent *Helicobacter pylori* (*H. pylori*) infection has been found to influence the speed of peptic ulcer healing[20,21]. However, it is unclear whether current *H. pylori* infection and eradication therapy affect the healing of ESD-induced ulcers[22,23]. In addition, there may be an association with the severity of gastritis/gastric atrophy and post-ESD ulcer healing[23,24].

Rapid healing of ESD-induced ulcers is key to the prevention of delayed bleeding. We investigated factors that might be associated with healing of post-ESD ulcers, including *H. pylori* status, profile of the gastric tumor, kinds of acid inhibitory drugs, and severity of gastritis (*e.g.*, gastric atrophy and intestinal metaplasia).

MATERIALS AND METHODS

Patients

We enrolled 132 Japanese patients who underwent ESD for clinical early-stage gastric cancer and adenoma between March 2013 and October 2016 at our institution. Approval for the study protocol was given in advance by the Institutional Review Board of the Shiga University of Medicine Science (Number 27-36). This trial was registered in the University Hospital Medical Information Network, UMIN000018188.

ESD was performed if cases met the following criteria of early-stage gastric cancer and gastric adenoma according to the Union for International Cancer Control/American Joint Committee on Cancer stages: (1) Intramucosal intestinal-type neoplasm without ulceration, regardless of tumor size; (2) intramucosal

intestinal-type cancer with ulceration, ≤ 3 cm; (3) intestinal-type cancer invading the submucosa < 500 μm from the muscularis mucosa, ≤ 3 cm in size; and (4) intramucosal diffuse-type cancer without ulceration, ≤ 2 cm. Exclusion criteria were patients with advanced-stage gastric cancer, patients who refuse follow-up endoscopy at both 4 and 8 wk after ESD treatment and patients with lack of informed consent.

Although severity of anemia and oxygenation were expected to affect the healing speed of ESD-induced ulcer, there were no patients with severe anemia of less than 10 g/mL or hypoxemia.

Study protocol

For this study, we enrolled patients who had undergone ESD for resection of gastric tumor and provided blood samples for an anti-*H. pylori* IgG serological testing and *CYP2C19* genotyping. The endoscopic severity of gastritis was characterized by the Kyoto classification[25]. According to the Kyoto classification of gastritis, patients are scored according to atrophy (None: A0, atrophic patterns with a margin between the non-atrophic fundic mucosa and atrophic mucosa located in the lesser curvature of the stomach: A1, and atrophic patterns, whose margin does not cross the lesser curvature: A2), intestinal metaplasia (none: IM0, within antrum: IM1, and up to corpus: IM2), hypertrophy of gastric folds (negative: H0, positive: H1), and diffuse redness (negative: DR0, mild: DR1, severe: DR2)[25].

ESD was performed with a single-channel magnifying endoscope (GIF-H290Z or GIF-H260Z; Olympus, Tokyo, Japan). We used a fixed-length disc-tipped knife (Dual knife®, KD-650L/Q; Olympus, Tokyo, Japan) or an insulated-tip diathermic knife (IT knife 2®, KD-611L, Olympus, Tokyo, Japan) and applied electric current using an electrosurgical generator (VIO300D®; ERBE Elektromedizin GmbH, Tubingen, Germany). Visible vessels were heat-coagulated using hemostatic forceps (FD-412LR®; Olympus, Tokyo, Japan). After ESD, 73.5% of patients were dosed with lansoprazole 30 mg and 26.5% were dosed with vonoprazan 20 mg (Table 1) for 8 wk.

The major and minor axes of ESD-induced ulcers were endoscopically measured the day after ESD by measurement forceps (M2-4K®; Olympus Corporation, Tokyo, Japan), and at 4 and 8 wk post-ESD.

H. pylori infection

Infection status of *H. pylori* was evaluated based on findings from two tests: an anti-*H. pylori* IgG serological test (E plate Eiken *H. pylori* antibody®; Eiken Chemical Co. Ltd., Tochigi, Japan) and a rapid urease test (Helicocheck®; Otsuka Co., Tokyo, Japan). When either test was positive, the patient was diagnosed as positive for *H. pylori* infection.

CYP2C19 genotyping

Genomic DNA was extracted from the blood (DNA Extract All Reagents®, Applied Biosystems, Foster City CA, United States). Subsequently, genotyping was performed using a single-nucleotide polymorphism (SNP) genotyping assay (TaqMan®, Applied Biosystems) in a real-time polymerase chain reaction (PCR) system (Step One Plus®, Applied Biosystems). Genotyping for identifying the *CYP2C19* wild-type gene and two mutated alleles, *CYP2C19 *2* (rs4244285, A/G) and **3* (rs-4986893, G/A) were performed to classify each subject as belonging to one of the following four genotype groups: extensive metabolizers (EMs, * 1/ * 1), intermediate metabolizers (IMs; * 1/ * 2 or * 1/ * 3), or poor metabolizers (PMs; * 2/ * 2, * 2/ * 3 or * 3/ * 3).

Statistical analysis

Age, ESD procedure time and ESD-induced ulcer area are expressed as mean ± SD. The healing rates of ulcers were calculated as (1-ulcer area/ulcer area just after ESD) × 100 (%) and are expressed as mean ± SD. Statistical differences in these parameters among CYP2C19 genotypes; between *H. pylori* infection statuses; among degrees of atrophy, intestinal metaplasia, and diffuse redness according to the Kyoto classification; and among tumor locations were determined using one-way ANOVA with Scheffé multiple comparison and Fisher's exact tests. All *P* values are two-sided, and $P < 0.05$ was considered statistically significant. Calculations were performed using commercial software (SPSS version 20, IBM Inc; Armonk NY, United States).

RESULTS

ESD and ESD-induced ulcers

The mean procedure time was 76.4 ± 56.7 min and the mean resected ESD-induced ulcer area was 671.9 ± 720.9 mm^2 at Day 1. Procedure time for lesions in the lower third of the stomach (47.5 ± 3.2 min) was significantly shorter than those for the middle and upper thirds [*vs* middle (85.7 ± 6.6 min), $P = 0.001$, *vs* upper (131.3 ± 17.9 min), $P < 0.001$, respectively]. The initial ulcer area in the lower third (456.4 ± 265.2 mm^2) was significantly smaller than that of the middle third (822.0 ± 922.2 mm^2, $P = 0.008$).

After ESD, mean ESD-induced ulcer areas at 4 and 8 wk were 71.3 ± 135.6 mm^2 and 2.8 ± 15.6 mm^2, respectively, and mean healing rates were 90.4% ± 0.8% at 4 wk and 99.8% ± 0.1% at 8 wk (Figures 1A and 2A). At 8 wk, mean healing rate in the *H. pylori*-positive group (99.7% ± 0.1%) was significantly lower than that in the negative group (99.9% ± 0.0%, $P = 0.035$). There were no significant differences between mean healing rates for lansoprazole and vonoprazan treatment at 4 and 8 wk (Figures 1B and C, 2B and C).

Healing rate was associated with the severity of gastric atrophy at 4 wk (A0: 97.9% ± 0.6%, A1: 93.4% ± 4.1%, and A2: 89.7% ± 1.0%, respectively).

In patients with severe gastric atrophy, the healing

Table 1 Characteristics of enrolled patients with gastric tumor

Parameter	
Number	132
Age (yr)	71.0 ± 8.6
Gender (male/female)	100/32 (75.8%/34.2%)
H. pylori status (positive/negative)	68/64 (51.5%/48.5%)
Anti-coagulant administration (+/-)	22/110 (16.7%/83.3%)
Acid suppressant post-ESD (lansoprazole/vonoprazan)	97/35 (73.5%/26.5%)
CYP2C19 genotype (EM/IM/PM)	40/51/22 (35.4%/45.1%/19.5%)
Endoscopic background of gastric mucosa	
Atrophy (Kyoto A0+A1/Kyoto A2)	20/112 (15.2%/84.8%)
Intestinal metaplasia (none + mild/severe)	72/55 (56.7%/43.3%)
Diffuse redness (none/mild/severe)	65/62 (51.2%/48.8%)
Tumor	
Types (adenoma/cancer)	16/116 (12.1%/87.9%)
Depth (mucosa/submucosa)	118/14 (89.4%/10.6%)
Location of tumors (upper/middle/lower third)	15/67/50 (11.4%/50.8%/37.8%)
ESD	
Mean procedure time (min)	76.4 ± 56.7
Mean resected ulcer area (mm^2)	671.9 ± 720.9
ESD-induced ulcer area	
Reduction at 4 wk	90.4% ± 10.7%
Mean ulcer area at 4 wk (mm^2)	71.3 ± 135.6
Reduction at 8 wk	99.8% ± 0.6%
Mean ulcer area at 8 wk (mm^2)	2.8 ± 15.6

EM: Extensive metabolizer of *CYP2C19*; ESD: Endoscopic submucosal dissection; IM: Intermediate metabolizer of *CYP2C19*; PM: Poor metabolizer of *CYP2C19*.

rate was significantly lower than that in patients with mild or no atrophy (A0 + A1) ($P < 0.001$ and $P = 0.010$) (Figures 1D and 2E). In addition, at 4 wk, the mean healing rate in the lower third (92.8% ± 1.2%) was significantly delayed compared to the upper two-thirds (83.7% ± 5.3%, $P = 0.013$) (Figure 1E and 2F). After 8 wk, ESD-induced ulcers were scarred in 85.7% (12/14) in the upper third, 89.2% (58/65) of the middle third, and 83.3% (40/48) of the lower third ($P = 0.657$) of the stomach. There was no significant association of healing rates at 4 wk with CYP2C19 genotypes (Figure 2D).

Factors affecting ESD-induced ulcer healing

We investigated the healing rate of ESD-induced ulcers by setting up over 90% of ESD-induced ulcer area at 4 wk and 100% at 8 wk. ESD-induced ulcers with ⩾ 90% healing at 4 wk were associated with absence of atrophy ($P = 0.010$), depth of gastric tumor ($P = 0.004$), and procedure time $P = 0.026$) (Table 2). The mean procedure time in the ⩾ 90% healing group was significantly shorter than that in the < 90% healing group (65.6 ± 41.1 min *vs* 89.7 ± 64.0 min, $P = 0.026$). The prevalence of patients with open-type atrophic gastritis in the ⩾ 90% healing group was 78.0% (64/82), which was significantly lower than that in the < 90% healing group (96.0%, 43/45, $P = 0.01$).

In achievement of scar formation at 8 wk, the rates were associated with gender ($P = 0.021$) and age ($P = 0.047$), but not gastritis or tumor-related factors (Table 2).

In the univariate analysis to identify possible factors related to achievement of 90% healing at 4 wk, healing was associated with gastric atrophy (OR = 6.047, 95%CI: 1.334-27.403, $P = 0.019$), procedure time (OR = 1.009, 95%CI: 1.002-1.017, $P = 0.018$) and initial ESD-induced ulcer size (OR = 0.001, 95%CI: 1.000-1.001, $P = 0.032$) (Table 3). At 8 wk, gender and initial ESD-induced ulcer size significantly correlated with the achievement of scarring at 8 wk ($P = 0.021$ and $P = 0.013$, respectively) (Table 3).

In the multivariate analysis including gender, *H. pylori* infection, endoscopic severity of atrophy, tumor location, mean procedure time, and mean initial ESD-induced ulcer size, the factor associated with 90% healing at 4 wk was gastric atrophy (OR = 5.678, 95%CI: 1.190-27.085, $P = 0.029$) (Table 4). The factors associated with scarring at 8 wk were gender (female, OR = 4.438, 95%CI: 1.253-15.724, $P = 0.021$) and initial ESD-induced ulcer size (1.001, 1.000-1.002, $P = 0.023$) (Table 4).

ESD-related adverse events

Two patients (1.5%) experienced delayed bleeding with tarry stool and only one patient received transfusion treatment after ESD treatment. Although the prevalence of patients received anti-coagulants was 16.7% and no cases with hematologically abnormal coagulation ability were observed (Table 1), intake of aspirin of non-steroidal anti-inflammatory drug did not increase incidence of gastric bleeding after ESD. There were no other major ESD-related adverse events.

DISCUSSION

The healing speed of ESD-induced ulcers may be a

Table 2 Characteristics of patients who achieved early healing of artificial ulcer area after endoscopic submucosal dissection

Characteristic	Reduction rate over 90% at 4 wk			Reduction rate 100% at 8 wk		
	Achieved (n = 82)	Not achieved (n = 45)	P value	Achieved (n = 110)	Not achieved (n = 16)	P value
Age (yr)	70.9 ± 9.3	71.2 ± 7.3	0.831	70.4 ± 8.9	74.1 ± 6.2	0.047
Gender (male/female)	62/20 (75.6%/24.4%)	33/12 (73.3%/26.7%)	0.777	86/24 (78.2%/21.8%)	8/8 (50.0%/50.0%)	**0.021**
H. pylori (positive/negative)	42/40 (51.2%/48.8%)	24/21 (53.3%/46.7%)	0.82	54/56 (49.1%/50.9%)	12/4 (75.0%/25.0%)	0.053
Anti-coagulants	13 (15.9%)	8 (17.8%)	0.78	16 (14.5%)	4 (25.0%)	0.231
PPI or PCAB (post-ESD)	60/22 (73.2%/26.8%)	32/13 (71.1%/28.9%)	0.804	82/28 (74.5%/25.5%)	14/2 (87.5%/12.5%)	0.210
CYP2C19 type (EM/IM/PM)	27/28/15 (38.6/40/21.4)	12/20/7 (30.8/51.3/17.9)	0.522	35/39/19 (37.6/41.9/20.5)	4/9/1 (28.6%/64.3%/7.1%)	0.249
Gastric mucosa						
Trophy (Kyoto A0+A1/Kyoto A2)	18/64 (22.0%/78.0%)	2/43 (4.0%/96.0%)	0.01	19/91 (17.3%/82.7%)	1/15 (6.3%/93.7%)	0.233
Metaplasia (none-mild/severe)	51/31 (62.2/37.8)	21/24 (46.7/53.3)	0.091	64/46 (58.2/41.8)	8/8 (50.0/50.0)	0.537
Diffuse redness (none-mild/severe)	44/38 (53.7/46.3)	21/24 (46.7/53.3)	0.451	60/50 (54.5/45.5)	7/9 (43.8/56.2)	0.419
Tumor						
Depth (mucosa/submucosa)	78/4 (95.1/4.9)	35/10 (77.8/22.2)	0.004	101/9 (91.8 /8.2)	15/1 (93.8/6.2)	0.629
Location (upper/middle/lower third)	7/39/36/ (8.5/47.6/43.9)	7/26/12 (15.6/57.8/26.6)	0.124	12/58/40 (10.9/52.7/36.4)	2/7/7 (12.4/43.8/43.8)	0.797
ESD						
Mean procedure time (min)	65.6 ± 41.1	89.7 ± 64.0	0.026	73.9 ± 52.3	76.1 ± 41.4	0.872
Mean resected ulcer area (mm^2)	544.7 ± 387.1	809.8 ± 849.8	0.053	567.3 ± 435.2	1178.5 ± 1520.1	0.130

EM: Extensive metabolizer; ESD: Endoscopic submucosal dissection; IM: Intermediate metabolizer; PCAB: Potassium competitive acid blocker; PM: Poor metabolizer; PPI: Proton pump inhibitor; *H. pylori*: *Helicobacter pylori*.

Table 3 Univariate analysis of factors preventing healing of ulcers after endoscopic submucosal dissection

Variable	Reduction rate over 90% at 4 wk		Reduction rate 100% at 8 wk	
	Not achieved (n = 45)	P value	Not achieved (n = 16)	P value
Age (yr)	1.004 (0.963-1.048)	0.841	1.058 (0.987-1.135)	0.113
Gender (female *vs* male)	1.127 (0.491-2.588)	0.777	3.583 (1.218-10.545)	0.021
Helicobacter pylori	1.088 (0.525-2.255)	0.820	3.111 (0.945-10.244)	0.053
Lansoprazole *vs* vonoprazan	1.108 (0.493-2.488)	0.804	0.418 (0.089-1.956)	0.210
Anti-coagulants	1.148 (0.436-3.018)	0.780	1.958 (0.561-6.832)	0.231
CYP2C19 type (EM *vs* IM/PM)	1.084 (0.635-1.850)	0.768	0.921 (0.420-2.020)	0.838
Atrophy (Kyoto A0+A1 *vs* Kyoto A2)	6.047 (1.334-27.403)	0.010	3.132 (0.390-25.163)	0.233
Tumor located in upper and middle third (*vs* lower third)	0.465 (0.211-1.026)	0.055	1.361 (0.471-3.934)	0.568
Mean procedure time (min)	1.009 (1.002-1.017)	0.018	1.001 (0.991-1.011)	0.871
Mean resected ulcer area (mm^2)	1.001 (1.000-1.001)	0.032	1.001 (1.000-1.001)	0.013

EM: Extensive metabolizer; IM: Intermediate metabolizer; PM: Poor metabolizer.

Table 4 Multivariate analysis of factors preventing healing of ulcers after endoscopic submucosal dissection

Variable	Reduction rate over 90% at 4 wk		Reduction rate 100% at 8 wk	
	Not achieved (n = 45)	P value	Not achieved (n = 16)	P value
Gender (male *vs* female)	1.833 (0.715-4.698)	0.207	4.438 (1.253-15.724)	0.021
Helicobacter pylori	1.012 (0.463-2.213)	0.976	3.340 (0.866-12.885)	0.080
Atrophy (Kyoto A0+A1 *vs* Kyoto A2)	5.678 (1.190-27.085)	0.029	2.764 (0.309-24.711)	0.363
Tumor located in upper and middle third (*vs* lower third)	0.698 (0.283-1.724)	0.436	1.848 (0.493-6.933)	0.362
Mean procedure time (min)	1.007 (0.997-1.017)	0.194	0.998 (0.982-1.015)	0.850
Mean resected ulcer area (mm^2)	1.000 (1.000-1.001)	0.443	1.001 (1.000-1.002)	0.023

key factor in preventing ESD-related bleeding. In this study, we investigated possible risk factors associated with healing of ESD-induced ulcers and found that of all possible factors, severe gastric atrophy at 4 wk post-ESD and initial ulcer size at 8 wk were independent risk factors in multivariate analysis. However, we found no significant association of healing of ESD-induced ulcers and tumor location[15], initial ulcer size[17,18], coagulation abnormality[18], electrocoagulation during ESD[18], or kind of gastric acid suppressant[19]. Because the healing rate of ESD-induced ulcers was affected by tumor size, post-ESD ulcer size and severity of gastritis (*e.g.*, gastric atrophy), attention should be paid to the incidence of complications (*i.e.*, bleeding and perforation) in patients with severe gastric atrophy and a large size of gastric tumor.

In this study, we focused on the influence of the severity of gastric atrophy on the healing rate of ESD-

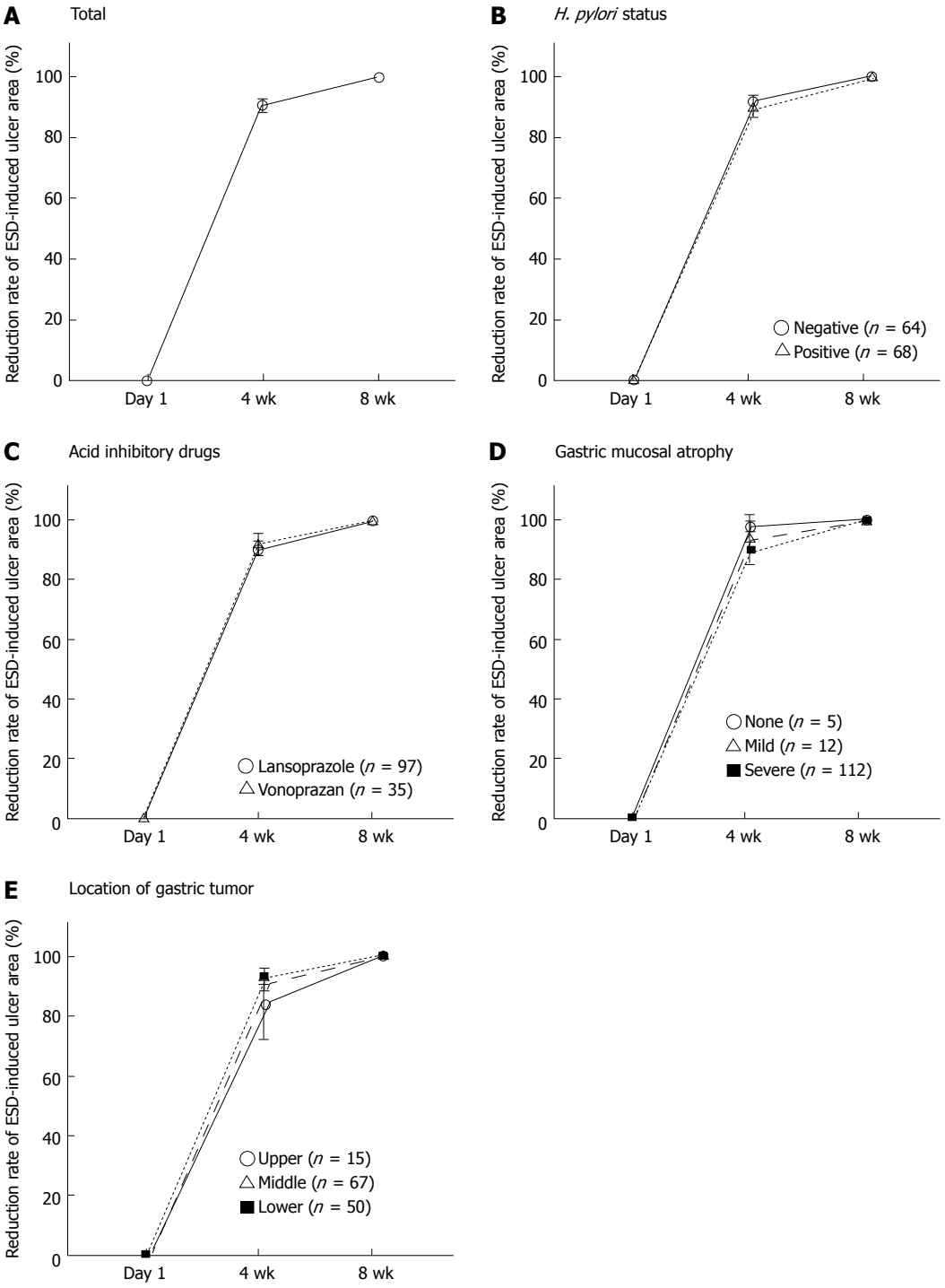

Figure 1 After endoscopic submucosal dissection endoscopic submucosal dissection, mean endoscopic submucosal dissection-induced ulcer areas at 4 and 8 wk in all patients (A), between *Helicobacter pylori*-positive patients and *Helicobacter pylori*-negative patients (B), between lansoprazole and vonoprazan (C), among patients with no atrophy, mild atrophy and severe atrophy (D), and among different locations of tumor (E). ESD: endoscopic submucosal dissection; *H. pylori*: *Helicobacter pylori*.

induced ulcers. Previously, Fujiwara *et al*[24] reported improved healing at 8 wk post-ESD for patients with severe atrophic gastritis when treated concomitantly with a PPI and rebamipide. In this study, at 4 wk after ESD, we revealed that severe gastric atrophy, especially of the A2 type according to the Kyoto classification, slowed healing speed. Kakushima *et al*[23] failed to show a significant association between the severity of gastric atrophy and ESD-induced ulcer healing with administration with omeprazole and sucralfate for 8 wk post-ESD; our study also did not demonstrate significant differences at 8 wk post-ESD. At 8 wk, mean reduction rates were 99.8% ± 0.1% and ESD-induced ulcers were scarred in 83.3% (110/132). We therefore hypothesize that the severity of gastric atrophy may influence healing of ESD-induced ulcers at 4 wk, but not at 8 wk.

Intestinal metaplasia is often observed in patients

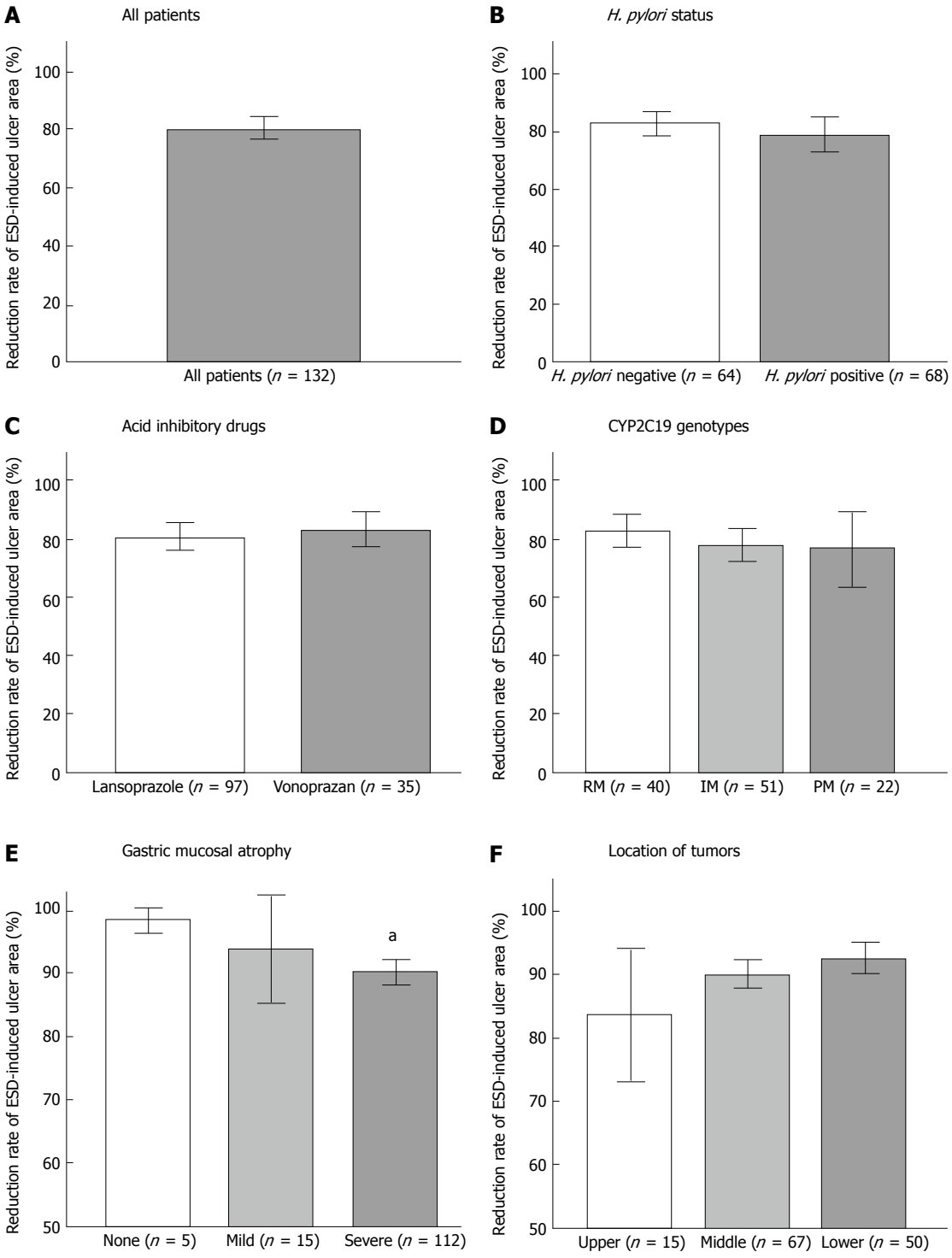

Figure 2 After endoscopic submucosal dissection, mean reduction rate of endoscopic submucosal dissection-induced ulcer area at 4 wk in all patients (A), between *Helicobacter pylori*-positive and *Helicobacter pylori*-negative patients (B), between lansoprazole and vonoprazan (C), among CYP2C19 genotypes (EM, IM and PM) (D), among non-atrophy, mild atrophy and severe atrophy (E), and among different locations of tumor (lower third, middle third and upper third) (F). *H. pylori*: *Helicobacter pylori*.

with severe gastric atrophy and is a well-known risk factor for gastric cancer, similar to severe gastric atrophy alone. The prevalence of intestinal metaplasia in *H. pylori*-positive patients is 57% in Japanese aged approximately 70 years[26]. Although we saw no significant association between the severity of intestinal metaplasia and ulcer healing speed in this study, Chen *et al*[27] reported that patients with intestinal metaplasia had a higher healing rate of gastric ulcers than those without intestinal metaplasia, suggesting that patients with severe gastric atrophy accompanied by intestinal metaplasia should be considered as likely candidates for ESD-related complication, due to delayed ulcer healing.

In general, peptic ulcer healing has been correlated with intragastric pH[28], *H. pylori* infection[20], gastric motility[29], microcirculation in gastric mucosa[30-32],

gastric mucosal levels of growth factors[33,34] and prostaglandins (PGs)[35]. The aggressive factors induced gastric mucosal injury resulting in loss of mucosal barrier can be quickly healed if adequate supply of PGE_2, epidermal growth factor and tumor growth factor (TGF) α takes place. Although it is unclear whether peptic ulcers and ESD-induced ulcers share a similar healing mechanism, because severity of gastric mucosal atrophy reduced microcirculation in gastric mucosa and gastric mucosal levels of prostaglandin and growth factors, resulted that advanced gastric atrophy perturbs the process of ulcer healing in the presence of these above factors.

Association with intragastric pH and speed of post-ESD ulcer healing

Vonoprazan has a longer half-life (7.7 h) than PPIs, due to its slow dissociation from H^+/K^+-ATPase[36]. In addition, vonoprazan inhibits H^+/K^+-ATPase activity with 400-fold greater potency than lansoprazole at pH 6.6[37]. Therefore, use of vonoprazan for treatment of ESD-induced ulcers is expected to confer an advantage over the conventional regimen with a PPI. This is despite the finding of Kagawa *et al*[5], who reported that the rates of ESD-related ulcer healing were 96.0% ± 6.7% at 6 wk with vonoprazan and 94.7% ± 11.6% at 8 wk with PPI, despite the fact the post-ESD bleeding incidence in the vonoprazan group (1.3%) was less than that in the PPI group (10.0%, $P = 0.01$). In a prospective randomized controlled trial, the rate of scar formation attained with vonoprazan at 8 wk was significantly higher than that for esomeprazole (94.9% *vs* 78.0%, $P = 0.049$), and in a multivariate analysis, only vonoprazan was correlated with scar formation (OR = 6.33; 95%CI: 1.21-33.20)[14]. However, although we have two kinds of clinical pathways scheduled to use lansoprazole or vonoprazan after ESD treatment for gastric tumors and investigated to analyze the healing speed of ulcer after ESD by use of only the two kinds of acid inhibitory drugs, lansoprazole and vonoprazan, there was no significant difference between vonoprazan and lansoprazole at 4 wk and 8 wk after ESD in this study. Given that one factor associated with healing of ESD-induced ulcers at 8 wk in multivariate analysis was initial ulcer size, this discrepancy may be due to differences in the size of lesions. Although potent acid inhibition is required to heal ESD-induced ulcers, a 90% reduction in ESD-induced ulcers was achieved at 28 d, irrespective of acid inhibitors. It is important to investigate whether the kind of acid inhibitor influences the speed of artificial ulcer reduction in an earlier phase (*i.e.*, within 2 wk).

Limitations

Several limitations of this study warrant mention. First, the sample size is not large. Second, we did not gather data regarding the reduction rate at 2 wk post-ESD. In this study, most ESD-induced ulcers had already healed by 4 wk post-ESD, which means evaluation at an earlier phase is required. Third, although we investigated the influence of CYP2C19 genotype, which impacts the pharmacodynamics of PPI, on the healing of ulcers, we did not clarify whether the CYP3A4/5 genotype, which is related to vonoprazan-dependent pharmacodynamics, influenced healing[38]. Forth, although minerals (*e.g.*, Zn) and vitamins (*e.g.*, Vitamin C) may affect the healing speed of ulcer after ESD, unfortunately, we have no data of minerals and vitamins in all patients[39,40].

In conclusions, we conducted a study to investigate factors influencing the healing speed of ESD-induced ulcers. Healing speed was affected by the severity of gastric atrophy, but not by *H. pylori* status, kinds of acid inhibitory drugs, or CYP2C19 genotype. These results suggest that eradication of *H. pylori* can be carried out at any time in terms of ulcer healing and that PPI or vonoprazan treatment for ESD-induced ulcers can be administrated at the standard dose irrespective of CYP2C19 genotype.

ARTICLE HIGHLIGHTS

Research background

The endoscopic submucosal dissection (ESD) for early-stage gastric cancer is first-line therapy in Japan, because of en bloc resection and a lower local recurrence rate of gastric cancer. However, bleeding from ESD-induced ulcer is a major complication of ESD treatment. When ESD is performed for gastric cancer, PPIs or vonoprazan are used to treat ESD-induced ulcers in Japan. It remains unclear whether vonoprazan with more potent and sustained acid inhibition than PPIs, *H. pylori* infection and characteristics of gastric mucosa (*e.g.*, inflammation and atrophy) are associated with improved ulcer healing speed and prevention of post-ESD bleeding. Rapid healing of ESD-induced ulcers is key to the prevention of delayed bleeding.

Research motivation

Of many possible factors related to ESD-induced ulcer healing, such as location of the tumor, submucosal fibrosis, initial ulcer size, diabetes, coagulation abnormality, electrocoagulation during ESD, and method of gastric acid suppression, it is unclear whether above parameters actually affect the healing of ESD-induced ulcers and the incidence of gastrointestinal bleeding after ESD treatment. Especially, there was no report investigated with the healing speed of ulcer after ESD and characteristics of gastric mucosa (*e.g.*, inflammation and atrophy).

Research objectives

The main objective was to clarify factors that might be associated with healing of post-ESD ulcers and bleeding, including *H. pylori* status, profile of the gastric tumor, kinds of acid inhibitory drugs, and severity of gastritis including of gastric atrophy and intestinal metaplasia.

Research methods

We retrospectively enrolled 132 patients with gastric tumors scheduled for ESD, irrespective to *H. pylori* infection. Following ESD, patients were treated with daily lansoprazole 30 mg or vonoprazan 20 mg for 8 wk. Ulcer size was endoscopically measured on the day after ESD and at 4 and 8 wk. The gastric mucosa was endoscopically graded according to the Kyoto gastritis scoring system. We assessed the number of patients with and without a 90% reduction in ulcer area at 4 wk post-ESD and scar formation at 8 wk, and looked for risk factors for slower healing.

Research results

After ESD, mean healing rates of ESD-related ulcer were 90.4% ± 0.8% at 4 wk and 99.8% ± 0.1% at 8 wk. The reduction rate was associated with the Kyoto grade of gastric mucosal atrophy at 4 wk and ESD-induced ulcers with ⩾ 90% healing at 4 wk were associated with absence of atrophy, depth of

gastric tumor, and procedure time. In the univariate analysis to identify possible factors related to achievement of 90% healing at 4 wk, healing was associated with gastric atrophy, procedure time and initial ESD-induced ulcer size. In the multivariate analysis, the factor associated with 90% healing at 4 wk was gastric mucosal atrophy (OR = 5.678, 95%CI: 1.190-27.085, *P* = 0.029).

Research conclusions

The healing speed of ESD-induced ulcers was affected by the severity of gastric atrophy, but not by *H. pylori* status, kinds of acid inhibitory drugs, or CYP2C19 genotype. Patients with severe gastric atrophy accompanied by intestinal metaplasia should be considered as likely candidates for ESD-related complication, due to delayed ulcer healing. Therefore, *H. pylori* eradication therapy is required to perform at younger age before progression of gastric mucosal atrophy to prevent development of *H. pylori*-related diseases and bleeding from ESD-induced ulcer.

Research perspectives

Eradication of *H. pylori* can be carried out at any time in terms of ulcer healing and that PPI or vonoprazan treatment for ESD-induced ulcers can be administrated at the standard dose irrespective of CYP2C19 genotype. However, because this is a preliminary small study, further study is required to plan whether the healing speed of ESD-induced ulcers was affected by the severity of gastric atrophy in prospective multicenter study. In addition, we will clarify the potential mechanism about association with the healing of ESD-induced ulcer and severity of gastric atrophy as further study.

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ORIGINAL ARTICLE

Observational Study

Endoscopic ultrasound-guided drainage of pancreatic walled-off necrosis using self-expanding metal stents without fluoroscopy

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Author contributions: Braden B and Dietrich CF contributed to study conception and design, performed the interventions and data acquisition; Braden B, Koutsoumpas A, Silva MA, Soonawalla Z and Dietrich CF contributed to data acquisition, data analysis and interpretation, editing, reviewing and final approval of article.

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Abstract

AIM

To investigate whether endoscopic ultrasound (EUS)-guided insertion of fully covered self-expandable metal stents in walled-off pancreatic necrosis (WOPN) is feasible without fluoroscopy.

METHODS

Patients with symptomatic pancreatic WOPN undergoing EUS-guided transmural drainage using self-expandable and fully covered self expanding metal stents (FCSEMS) were included. The EUS visibility of each step involved in the transmural stent insertion was assessed by the

operators as "visible" or "not visible": (1) Access to the cyst by needle or cystotome; (2) insertion of a guide wire; (3) introducing of the diathermy and delivery system; (4) opening of the distal flange; and (5) slow withdrawal of the delivery system until contact of distal flange to cavity wall. Technical success was defined as correct positioning of the FCSEMS without the need of fluoroscopy.

RESULTS

In total, 27 consecutive patients with symptomatic WOPN referred for EUS-guided drainage were included. In 2 patients large traversing arteries within the cavity were detected by color Doppler, therefore the insertion of FCSEMS was not attempted. In all other patients (92.6%) EUS-guided transgastric stent insertion was technically successful without fluoroscopy. All steps of the procedure could be clearly visualized by EUS. Nine patients required endoscopic necrosectomy through the FCSEMS. Adverse events were two readmissions with fever and one self-limiting bleeding; there was no procedure-related mortality.

CONCLUSION

The good endosonographic visibility of the FCSEMS delivery system throughout the procedure allows safe EUS-guided insertion without fluoroscopy making it available as bedside intervention for critically ill patients.

Key words: Necrotizing pancreatitis; Peripancreatic fluid collection; Therapeutic endoscopic ultrasound; Transmural drainage; Acute pancreatitis

Core tip: The use of self-expanding and lumen-apposing metal stents for the drainage of walled-off necrosis has revolutionised the treatment options and outcome of this disease. Conventionally, these stents are placed by endoscopic ultrasound-guidance but under fluoroscopic control. We could demonstrate that all steps of the stent insertion are visible endosonographically which allows safe and controlled stent placement. Without the need for fluoroscopy and consequent radiation protection regulations, this procedure becomes available in the endoscopy unit and at the bedside of critically ill patients.

Braden B, Koutsoumpas A, Silva MA, Soonawalla Z, Dietrich CF. Endoscopic ultrasound-guided drainage of pancreatic walled-off necrosis using self-expanding metal stents without fluoroscopy. *World J Gastrointest Endosc* 2018; 10(5): 93-98 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i5/93.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i5.93

INTRODUCTION

Endoscopic management by endoscopic ultrasound (EUS)-guided drainage and endoscopic necrosectomy has become the preferred treatment of walled-off pancreatic necrosis (WOPN) after necrotizing pancreatitis as it is minimally invasive and has lower morbidity compared to surgery[1,2]. Pancreatic pseudocysts can be relatively easily drained by insertion of plastic stents but the drainage of WOPN requires large caliber drainage or multi-stenting to empty the necrotic debris and often the remaining necrotic material has to be extracted by endoscopic necrosectomy[3-5]. The use of conventional plastic stents has limitations when treating WOPN because their narrow lumen is often prematurely occluded by necrotic debris[3].

The development of large caliber, specially designed lumen apposing fully covered self-expanding metal stents (FCSEMS) has provided new options for the drainage of peripancreatic fluid collections and improved clinical outcome[4-7].

Previously Rana *et al*[8] demonstrated that transmural drainage of non-bulging WOPN using plastic stents and nasocystic drains can be safely and effectively achieved non-fluoroscopically by endoscopic ultrasound guidance. The EUS-visibility during EUS-guided placement of metal stents has not been studied previously. However, the avoidance of radiation exposure and fluoroscopy would improve the availability of this outcome changing procedure for critically ill patients as it could be performed at the bedside.

Therefore, in this two-center, single arm study we investigated whether the transmural insertion of FCSEMS for large caliber drainage of WOPN is safely possible by EUS guidance only, avoiding fluoroscopy. For this purpose, we aimed to assess the EUS-visibility of all procedural steps that are required for EUS-guided transmural insertion of FCSEMS.

MATERIALS AND METHODS

From May 2014 we started a prospectively maintained database to audit clinical outcome of EUS-guided therapy of pancreatic fluid collections. EUS-guided transmural drainage of walled-off necrosis by FCSEMS insertion performed between May 2014 and August 2017 were analysed. Participating centers were the John Radcliffe Hospital in Oxford, United Kingdom and the Caritas Hospital in Bad Mergentheim, Germany.

The observational nature of the study was established with the respective Health Research Authority and Trust R and D department. The study was therefore registered locally in accordance with Trust clinical governance guidelines. All authors had access to the study data and had reviewed and approved the final manuscript.

Patients underwent EUS-guided FCSEMS insertion only if computed tomography or MRCP had confirmed WOPN based on the revised Atlanta classification[9] and the patients were symptomatic due to gastric outlet obstruction or biliary obstruction, or ongoing infection and fever despite intravenous antibiotic therapy. EUS-guided transluminal drainage of the pancreatic collection

was performed at least four weeks after onset of pancreatitis to allow for sufficient demarcation of the necrotic tissue. Patients were informed in detail about the risks and benefits of the endoscopic treatment and surgical and endoscopic alternatives. Informed consent was obtained from all patients before the endoscopic procedure.

Using a linear scanning therapeutic echoendoscope (EG 3870 Pentax Inc., Tokyo, Japan) EUS-guided drainage was performed in the endoscopy unit under endotracheal intubation and monitoring by an anaesthetic team. Doppler guidance was used to avoid intervening blood vessels and the optimal site for transmural access was selected giving the closest distance between necrotic fluid collection and the gastroduodenal lumen. Transmural access into the WOPN was achieved using a cystotome (Cook Endoscopy, Winston-Salem, NC, United States) or directly the Hot Axios™ electrocautery system (Xlumena Inc., Mountain View, CA, United States).

A 0.035-inch guidewire was advanced under EUS-guidance and coiled at least twice into the cavity to stabilize the position. The new tract was enlarged using the diathermy of the cystotome or the Axios™ electrocautery system before the stent delivery system (Axios™ or NAGI™ stent, TaeWoong Medical, Gyeonggi-do, South Korea) was introduced over the guidewire. For correct positioning, the opening of the distal flange in the cavity and slow withdrawal of the entire delivery system until the distal flange was in contact with the wall was controlled by EUS while the opening of the proximal flange was then observed endoscopically.

The EUS visibility of each step involved in the transmural stent insertion was assessed by the operators as "visible" or "not visible": (1) Access to the cyst by needle or cystotome; (2) insertion of a guide wire; (3) introducing of the diathermy and delivery system; (4) opening of the distal flange; and (5) slow withdrawal until contact of distal flange to cavity wall.

Final correct position of the FCSEMS was confirmed endoscopically when the liquid content of the WOPN emptied through the stent into the gastric lumen. Fluoroscopy was not used at any time during the procedure.

As clinically indicated, endoscopic necrosectomy was performed through the large diameter metal stent[10]. When the collection had shrunk to less than 4 cm on ultrasound or computed tomography after at least 6 wk follow-up the metal stent was endoscopically removed. Additional pigtail plastic stents were not inserted during this study, neither through the FCSEMS to prevent stent migration nor after removal of the FCSEMS.

Further imaging after stent removal was reviewed to assess recurrence of pancreatic collections.

Primary outcome of this study was the technical feasibility of EUS-guided FCSEMS placement without fluoroscopy and the EUS visibility of the different steps during stent insertion. Technical success was defined as correct positioning of the transmural FCEMS without using fluoroscopy during the procedure. Secondary outcome parameters included adverse events and clinical outcome.

Statistical analysis

Continuous variables were reported in median and interquartile range. Categorical variables were described as frequencies. The technical success of EUS-guided stent insertion was reported according to intention-to-treat-analysis. Procedure-related adverse events are given as per-protocol.

RESULTS

From the prospective database, 27 consecutive patients with symptomatic walled-off necrosis after necrotizing pancreatitis were identified who were referred for EUS-guided insertion of FCSEMS to drain the fluid content and necrotic debris. Patient demographics and indications for endoscopic intervention are given in Table 1.

Technical feasibility

In 2 patients large diameter traversing arteries within the cavity were detected by Doppler during the orientating EUS, therefore the insertion of FCSEMS was not attempted to avoid possible erosion of the vessels by the stent edges with reducing collection size. In one patient a plastic stent was inserted instead, the other suffered a spontaneous haemorrhage into the necrotic cavity a week later and was found to have a necrotic tumour at surgery.

In all other patients, the EUS-guided insertion of the FCSEMS was technically successful achieving correct stent positioning without any fluoroscopy (92.6%) (Table 2).

EUS visibility

(1) Access to the cyst by needle or cystotome could be endosonographically visualized in all 25 patients; (2) insertion of a guide wire could be monitored on EUS in all patients, however, the visibility of the entire coiling of the wire was limited in 6 patients with large amounts of debris within the cavity (> 30%); (3) introduction of the diathermy and delivery system was clearly seen, both in all NAGI™ as well as all Hot Axios™ stents. The diathermy produces artefacts on EUS during transmural transition but the caliber difference between guidewire and diathermy/delivery system is clearly visible within the fluid filled cavity; (4) opening of the distal flange could be clearly observed using all stents; and (5) the slow withdrawal of the opened distal flange until reaching contact to the cavity wall could be continuously monitored with both stent types in all patients (Figure 1).

Adverse events and clinical outcome

In nine patients, endoscopic necrosectomy through the large diameter metal stent became necessary due to incomplete clearance of debris or stent occlusion by obstructing necrotic tissue and/or infection.

Overall procedure-related adverse events occurred in 3 of 25 patients (12.0%); one patient developed self-

Table 1 Patient demographics and baseline characteristics of 27 patients with walled-off necrosis after necrotizing pancreatitis

Characteristic	Value
Sex, male/female	21/6
Median age (interquartile range), yr	54 (45-63)
Median size of walled-off pancreatic necrosis (interquartile range), cm	14 (12-16)
Cause of pancreatitis	
Alcohol induced	9
Biliary	17
Idiopathic	1
Main indication	
Gastric outlet obstruction	15
Biliary obstruction	3
Infection/fever despite antibiotic therapy	9

Table 2 Performance characteristics of non-fluoroscopic endoscopic ultrasound-guided fully covered self expanding metal stents insertion in patients with walled-off necrosis

Characteristic	Patients, *n* = 27
Technical success	25 (92.6%)
Type of stent	
Axios™	8
NAGI™	17
Stent diameter, mm	
12	2
14	11
15	10
16	2
Transduodenal/transgastric/ transoesophageal approach	1/24/0
Adverse events	4 (in 3 patients)
Stent migration	1 (after WOPN resolved)
Self-limiting bleeding	1
Perforation/Pneumoperitoneum	0
Readmission with fever	2

FCSEMS: Fully covered self-expanding metal stent; WOPN: Walled-off pancreatic necrosis.

limiting bleeding, two patients were readmitted with fever and a blocked stent and subsequently underwent endoscopic necrosectomy. In one of the readmitted patients the stent migrated spontaneously after 4 wk but the WOPN had already resolved. There was no procedure-related mortality (Table 2).

After 8 wk the WOPN had resolved in all but one patient (96.0%) to a diameter of less than 4 cm. The patient with persistent WOPN had deep extensions of the inflammatory cavity into the retrocolic gutter requiring additional percutaneous drainage.

There were no adverse events at the time of stent removal. From the 24 patients with successful resolution of the WOPN, 20 had further imaging (ultrasound, CT or MRCP) after six months. None had reoccurrence of pancreatic collections indicating disconnected pancreatic tail syndrome. Four patients did not have follow-up of more than 8 wk available as they had been discharged back to the referring hospitals.

DISCUSSION

The endoscopic management of WOPN has been simplified by technical advances in EUS and the development of specially designed, dumbbell-shaped, fully covered large caliber stents which can be placed endoscopically in a few or even only one step[5,11-13]. In contrast to plastic stents, the radial expansive forces of FCSEMS and the lumen-apposing design avoid leakage of fluid along the newly created transmural tract. The wide flanges should prevent dislodgment and migration.

Usually, FCSEMS are placed under EUS-guidance with fluoroscopic control of guidewire insertion, tract enlargement and stent deployment. In these series, we could show that all the steps required for endoscopic transmural insertion of FCSEMS into a WOPN can be visualized and safely monitored by EUS without the need for fluoroscopy. Although we used different stents due to availability and preference in the different centres, the EUS visibility of both types during all steps of the procedure was excellent: The cystotome access, the insertion of the guidewire, the transmural advancing of the diathermy and delivery system, the opening of the distal flange and the correct positioning by withdrawal to the wall of the WOPN could be controlled and displayed by EUS in all patients.

On the other hand, the endosonographic visibility of access needle, guide-wire, cystotome and stent delivery system might depend on the debris content within the WOPN. None of the WOPNs in this series had debris of more than 50% but we only very rarely see WOPN with debris filling more than 50% of the cavity.

Fluoroscopy has not been applied in any of the transgastric stent insertions in this study. It might be argued that the availability of fluoroscopy is important should adverse events occur during the procedure. However, the most common complications related to EUS-guided transluminal stent insertion into pancreatic collections can be managed endoscopically or recognized endosonographically as well. In case of massive bleeding it might be helpful to inflate a balloon within the stent to achieve tamponade. Stent dislocation or incorrect positioning is recognized endoscopically and usually requires repeating the procedure.

Recently, an intra-channel release technique has been described for the hot axios stent which also enables a fluoroless placement[14]. However, it remains unclear whether fluoroscopy has been used additionally in these cases and the visibility of the deployment steps has not been reported. Another retrospective recent study reports on 25 selected patients in whom EUS-guided stent insertion was safely performed without fluoroscopy[15].

The strength of our study is the fact that we included consecutive patients and systematically assessed the visibility of all procedure steps. Another advantage is that we tested the EUS-visibility of two types of stents, a lumen apposing and another FCSEMs, the most commonly inserted metal stents for the purpose of

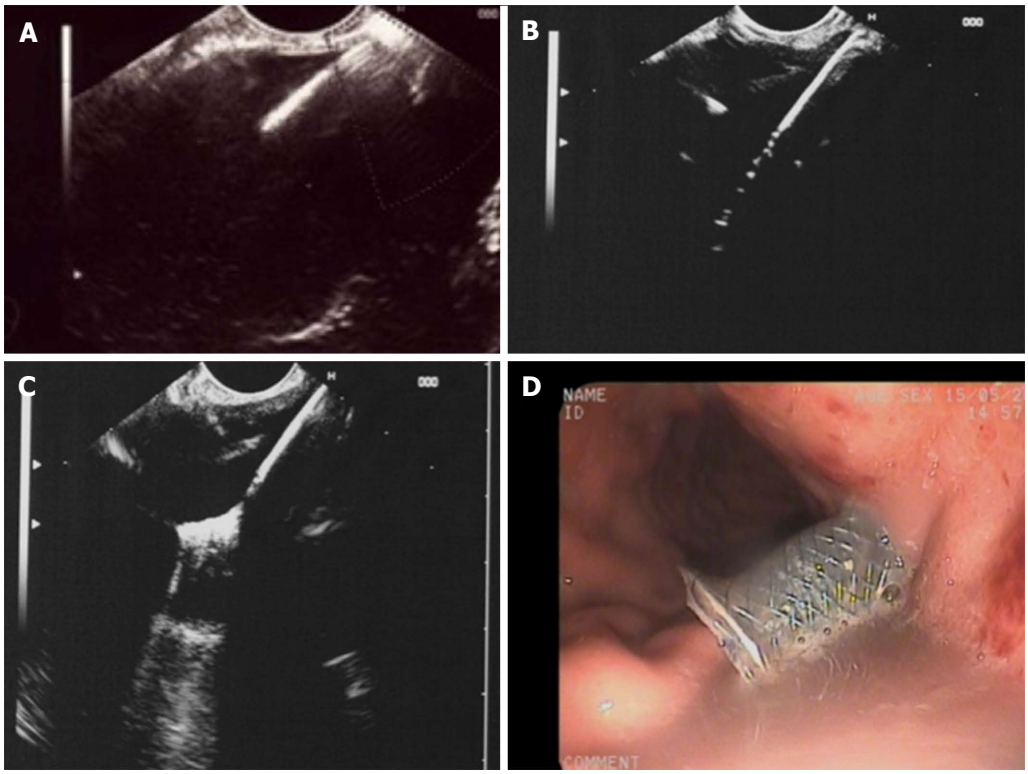

Figure 1 Endoscopic ultrasound-guided transgastric insertion of a fully covered self-expanding metal stent into a walled-off necrosis. A: Transmural access using the the cystotome; B: Insertion and coiling of the guidewire into the cavity; C: Opening of the distal flange; D: Endoscopic confirmation of correct positioning.

WOPN drainage.

In nine patients endoscopic necrosectomy to extract obstructing necrotic material from the stent was required. The large diameter of the stents allows the direct endoscopic access and the anchoring flanges prevent stent dislodgment during the endoscopic debridement of the necrotic cavity.

For 20 patients imaging follow-up after 6 mo was available. None of these patients had signs of re-occurrence of a peripancreatic collection after removal of the FCSEMS as would be expected in case of dis-connected pancreatic tail syndrome. The large diameter of the newly created track between pancreatic cavity and gastric lumen by the FCSEMS might facilitate persistence of a pancreaticogastric fistula if the pancreatic tail cannot drain *via* the papilla.

Our study has some limitations. The endoscopists evaluated the visibility of the different procedure steps themselves during the intervention. The procedures were not recorded and images were not evaluated by a second person. Also, we are tertiary centers practicing advanced endoscopic ultrasound procedures and our results may not be replicated in other centers. However, we believe that patients with complex WOPN should be treated in expert centers with multidisciplinary teams and expertise in pancreatic surgery. In addition, our study was not randomized or controlled and the sample size was relatively small. Ideally, a larger randomized study with a control arm using EUS and fluoroscopic imaging should be conducted.

In conclusion, all procedural steps during EUS-guided insertion of FCSEMS are well visualized by EUS. Non-fluoroscopic EUS-guided transmural insertion of FCSEMS for drainage of WOPN is feasible and appears to be safe and effective. Without the need for fluoroscopy and radiation exposure, EUS-guided drainage of WOPN with insertion of FCSEMS can become a bedside intervention for critically ill patients.

ARTICLE HIGHLIGHTS

Research background

Transluminal placement of specially designed fully covered self-expandable and lumen-apposing metal stents (FCSEMS) has improved the management and clinical outcome of walled-off pancreatic necrosis (WOPN). Most often this procedure is performed under fluoroscopy after EUS-guided access.

Research motivation

Without the need for fluoroscopy EUS-guided drainage using large diameter metal stents would also become available in endoscopy units and at the bedside of critically ill patients. This procedure is often crucial for the management of patients with complex pancreatic necrosis.

Research objectives

The principal aim of this study is to assess the feasibility and safety of fluoroless, purely EUS-guided insertion of self-expandable and lumen-apposing stents for the drainage of walled-off pancreatic necrosis.

Research methods

In 27 consecutive patients, we investigated the EUS-visibility of all procedural steps required to insert a fully covered self-expandable metal stent as transluminal drainage of walled-off pancreatic necrosis. EUS-visibility, technical

success, outcome and adverse events were analysed.

Research results

All procedural steps could be visualised by EUS alone. Fluoroscopy was avoided in all patients undergoing transmural stent placement. EUS-guided insertion of the FCSEMS was technically successful achieving correct stent positioning in 92.6%.

Research conclusions

Non-fluoroscopic EUS-guided transmural insertion of FCSEMS for drainage of WOPN is feasible and appears to be safe and effective.

Research perspectives

Large multi-center studies and prospective registries would provide more information on the use of EUS-guided WOPN drainage as bedside intervention, its safety and long-term outcome, the best time intervals when to remove the metal stents.

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ORIGINAL ARTICLE

Prospective Study

Different options of endosonography-guided biliary drainage after endoscopic retrograde cholangio-pancreatography failure

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Author contributions: Ardengh JC performed the procedures; Lopes CV designed the study and wrote the manuscript; Kemp R and dos Santos JS provided the collection of all human material.

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Abstract

AIM

To investigate the success rates of endosonography (EUS)-guided biliary drainage (EUS-BD) techniques after endoscopic retrograde cholangiopancreatography (ERCP) failure for management of biliary obstruction.

METHODS

From Feb/2010 to Dec/2016, ERCP was performed in 3538 patients, 24 of whom (0.68%) suffered failure to cannulate the biliary tree. All of these patients were initially submitted to EUS-guided rendez-vous (EUS-RV) by means of a transhepatic approach. In case of failure, the next approach was an EUS-guided anterograde stent insertion (EUS-ASI) or an EUS-guided hepaticogastrostomy (EUS-HG). If a transhepatic approach was not possible or a guidewire could not be passed through the papilla, EUS-guided choledochoduodenostomy (EUS-CD) was performed.

RESULTS

Patients were submitted to EUS-RV (7), EUS-ASI (5), EUS-HG (6), and EUS-CD (6). Success rates did not differ among the various EUS-BD techniques. Overall,

technical and clinical success rates were 83.3% and 75%, respectively. Technical success for each technique was, 71.4%, 100%, 83.3%, and 83.3%, respectively (P = 0.81). Complications occurred in 3 (12.5%) patients. All of these cases were managed conservatively, but one patient died after rescue percutaneous transhepatic biliary drainage (PTBD).

CONCLUSION

The choice of a particular EUS-BD technique should be based on patient's anatomy and on whether the guidewire could be passed through the duodenal papilla.

Key words: Cholestasis; Drainage; Endosonography; Interventional procedures; Jaundice; Neoplasms

Core tip: Endosonography-guided biliary drainage is an effective alternative in the failure of endoscopic retrograde cholangiopancreatography, with the potential to provide the least invasive and the lowest risk therapeutic modality for biliary drainage when compared to percutaneous transhepatic biliary drainage or surgery. For this procedure, access to the biliary tree can be obtained by transhepatic or transduodenal approaches. However, the transhepatic approach offers a good acoustic window for puncture of the biliary tree, a straight and easier to work with position of the echoendoscope, a better positioning of the guidewire, and a lower chance of bleeding or choleperitoneum.

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INTRODUCTION

Traditionally, endoscopic retrograde cholangiopancreatography (ERCP) is the standard approach to biliary drainage[1,2]. However, the procedure fails in up to 10% of patients, especially owing to anatomic variations, malignant duodenal obstructions and previous surgeries[3,4]. For these cases, percutaneous transhepatic biliary drainage (PTBD) or surgery has been used, despite the high morbidity and not negligible mortality caused by these procedures[5,6].

More recently, endosonography-guided biliary drainage (EUS-BD) has emerged as an effective alternative, with the potential to provide the least invasive and lowest risk therapeutic modality for biliary access and drainage[7,8]. A recent meta-analysis has reported technical and clinical success of 90% and 94%, respectively[9].

We aimed to evaluate the role of different EUS-BD techniques in case of ERCP failure, and to propose a systematic routine for EUS-BD according to the feasible access routes to the biliary tree.

MATERIALS AND METHODS

Study design

This was a retrospective study with prospective data collection about the role of EUS-BD conducted at two tertiary-referral centers. Between February 2010 and December 2016, 3528 ERCPs were performed at these centers. Eligible cases included patients older than 18 years with unresectable biliopancreatic neoplasia, and patients with benign conditions referred to EUS-BD when access to the biliary tree and internal biliary drainage by ERCP were not possible. ERCP failure was considered when biliary cannulation could not be achieved even after advanced techniques (cannulation in addition to a pancreatic guidewire or stent, needle-knife access papillotomy over a pancreatic stent, cannulation through a duodenal stent, and back-loading of the duodenoscope over a duodenal guidewire to pass a luminal stricture). Exclusion criteria were an international normalized ratio (INR) > 1.5 or platelet count < 50000/μL, ascites around the puncture area, absence of an adequate acoustic window for hepatic or choledochal puncture, total gastrectomy, and patient refusal. After EUS-BD, four follow-up visits were scheduled for each patient during the first 90 d, or until their death. The study was approved by the Institutional Review Board (Approval No. 2.191.319), and all patients gave written informed consent for ERCP and EUS-BD before enrollment.

Technical aspects

All EUS-BD procedures were performed by the same experienced endoscopist with Fujinon (FujiFilm Corporation, Nishiazabu 2-chome Minato, Ku, Tokyo) duodenoscopes (ED-530XT) and curvilinear array echoendoscopes (EG530UT2) coupled to SU-7000 or SU-8000 ultrasound units. The sequential EUS-BD procedures proposed for all patients were as follows: first, transhepatic puncture with a 19 gauge aspiration needle (EUSN-19 T, Cook, Winston Sallen, NC, United States) was tried. The EUS-RV technique was successful when the guidewire could be passed through the papilla and seized in the second portion of the duodenum. In case of papillary benign disease or absence of duodenal stenosis, retrograde treatment with a duodenoscope or echoendoscope was performed. An anterograde approach was attempted when tumoral duodenal infiltration or duodenal stenosis did not allow the capture of the guidewire in the duodenum. If the anterograde approach failed, Endosonography-guided hepatogastrostomy (EUS-HG) was the next alternative. In case of failure of the intrahepatic puncture due

to unfavorable anatomy, cirrhosis or difficulty in maintaining the adequate position of the guidewire, patients were submitted to endosonography-guided choledocoduodenostomy (EUS-CD). If all approaches for EUS-BD were unsuccessful, patients were submitted to PTBD. Duodenal self-expandable metallic stents (SEMS) were used in all stenoses obstructing access to the papilla.

The procedures were always performed with the patient in the left lateral decubitus position, under deep sedation with the assistance of an anesthesiologist. After the procedure, patients were monitored for two hours, and intravenous antibiotics (ciprofloxacin and metronidazole) were given for 7 d.

Routine for EUS-BD approaches

Endosonography-guided rendez-vous: When the duodenoscope could reach the major papilla, EUS-RV was tried and a curvilinear echoendoscope was used to obtain biliary access. The tip of the echoendoscope was positioned in the gastric fundus to access the intrahepatic bile duct. A 19 gauge EUS aspiration needle was used to puncture the bile duct close to the hepatic hilum, and to insert a large-caliber guidewire to deploy the stent. After fluoroscopic confirmation of the needle inside the bile duct, the guidewire was inserted through the obstruction and passed to the duodenum. Once the guidewire crossed the papilla, the guidewire was retrieved with a biopsy forceps or snare. Next, a metal stent was deployed by means of the over-the-wire technique[10].

Endosonography-guided anterograde stent insertion: In the presence of neoplastic duodenal stenosis, when the guidewire could not be seized in the duodenum, the stent was placed in an anterograde way. Access to the intrahepatic bile duct was obtained using a 19 gauge aspiration needle. Once puncture of the bile duct was confirmed by fluoroscopy, the guidewire was inserted through the duodenal major papilla and positioned in the second portion of the duodenum. At this point, a SEMS was inserted through the gastric wall across the papilla.

Endosonography-guided hepatogastrostomy: EUS-HG was tried after failure of the EUS-RV and EUS-anterograde stent insertion (EUS-ASI) techniques, in those cases whose hepatic puncture was successful but the guidewire could not be passed through the papilla. The dilated intrahepatic bile duct was punctured, and the guidewire was placed through the stenosis. The tract was dilated with a 6 Fr cystostome, and a fully covered metal stent was deployed, with care taken to leave more than 3 cm of the stent in the gastric lumen to avoid food obstruction.

Endosonography-guided Choledocoduodenostomy: In patients for whom a transhepatic approach was not feasible, EUS-CD was performed with the identification of the extrahepatic bile duct from the duodenal bulb. Once the insertion of the guidewire into the bile duct was confirmed by cholangiography, the tract was dilated with a 6 Fr cystostome, and a fully covered self-expandable metal stent was inserted.

Technical and clinical success

Technical success was defined as adequate positioning of the stent as shown by endoscopic and fluoroscopic images. Clinical success was defined as a decrease of at least 50% in serum total bilirubin levels.

Statistical analysis

A linear model was adjusted for the calculation of the technical success prevalence ratios, generalized by Poisson distribution and by the linking logarithmic function using the Proc Genmod of SAS 9.3 software (SAS Institute Inc., Cary NC, United States) to determine whether the different approaches had any impact on efficacy, compared to the EUS-RV technique ($P > 0.05$).

RESULTS

Patient demographics and technical aspects

During the study period, it was not possible to cannulate the biliary tree in 24 of 3528 (0.68%) patients submitted to ERCP. Thirteen men and 11 women with a mean age of 67.8 years old were included in the study. The most common symptom was jaundice in 96% of the patients, followed by abdominal pain and acute biliary pancreatitis in 21% and 8.3% of cases, respectively. The demographics, reasons for ERCP failure, indications for EUS-BD, as well as technical and clinical success are listed in Table 1.

Endosonography-guided rendez-vous

The EUS-guided transhepatic approach was tried in all patients (Figure 1). In 18/24 (75%) cases, puncture of the bile duct was possible, but the passage of the guidewire through the papilla occurred only in 12 (50%) cases. The guidewire could be recovered in 5/7 cases, and the passage of the stent was performed by means of an EUS-RV technique (Figure 2). The complication rate for these cases was 28% (2/7), consisting of an intracavitary hemorrhage and a choleperitoneum, both managed conservatively. In 5 other cases the guidewire could not be recovered in the duodenum owing to duodenal stenosis (3) or papillary infiltration (2). For these cases, an EUS-ASI technique was the next option. In 6 other cases, the guidewire did not cross the papilla, and was positioned in the proximal common bile duct (4), and in the right lobe (1) and left lobe of the liver (1). For these cases, an EUS-HG was the next alternative. The remaining 6 patients for whom transhepatic approaches were not possible underwent EUS-CD.

EUS-guided anterograde stent insertion

Even after passage of the guidewire in the second

Table 1 Demographics and treatment success of patients submitted to endosonography-guided biliary drainage due to endoscopic retrograde cholangiopancreatography failure

	EUS-BD	EUS-RV	EUS-ASI	EUS-HG	EUS-CD
***n* (%)**	**24 (100)**	**7 (29)**	**5 (21)**	**6 (25)**	**6 (25)**
Sex (M/F)	13/11	5/2	1/4	4/2	3/3
Age (range), yr	67.8 (42-91)	67.7 (42-84)	60.8 (42-70)	68.2 (50-81)	73.5 (52-91)
Reasons for ERCP failure (*n*)	-	-	-	-	-
Malignant duodenal stenosis	8	2	3	2	1
Malignant papillary infiltration	7	1	2	1	3
Impossibility of access to the common bile duct or intrahepatic duct	7	2	0	3	2
Giant duodenal diverticulum	1	1	0	0	0
Billroth Ⅱ gastrectomy without access to the duodenal papilla	1	1	0	0	0
Indications for EUS-BD	-	-	-	-	-
Malignant	20	3	5	6	6
Pancreatic cancer	13	3	4	2	4
Liver metastases of colon cancer	4	0	0	3	1
Cholangiocarcinoma	1	0	0	1	0
Duodenal lymphoma	1	0	1	0	0
Papillary cancer	1	0	0	0	1
Benign	4	4	0	0	0
Common bile duct stones	2	2	0	0	0
Biliary necrotizing acute pancreatitis	1	1	0	0	0
Recurrent acute pancreatitis due to sphincter of Oddi dysfunction	1	1	0	0	0
Technical success *n* (%)	20 (83.3)	5 (71.4)	5 (100)	5 (83.3)	5 (83.3)
Clinical success (%)	18 (75)	4 (57.1)	5 (100)	4 (66.7)	5 (83.3)
Complications (%)	3 (12.5)	2 (28.5)	0 (0)	1 (16.7)	0 (0)

EUS-BD: Endosonography-guided biliary drainage; EUS-RV: Endosonography-guided rendez-vous; EUS-ASI: Endosonography-guided anterograde stent insertion; EUS-HG: Endosonography-guided hepaticogastrostomy; EUS-CD: Endosonography-guided choledochoduodenostomy.

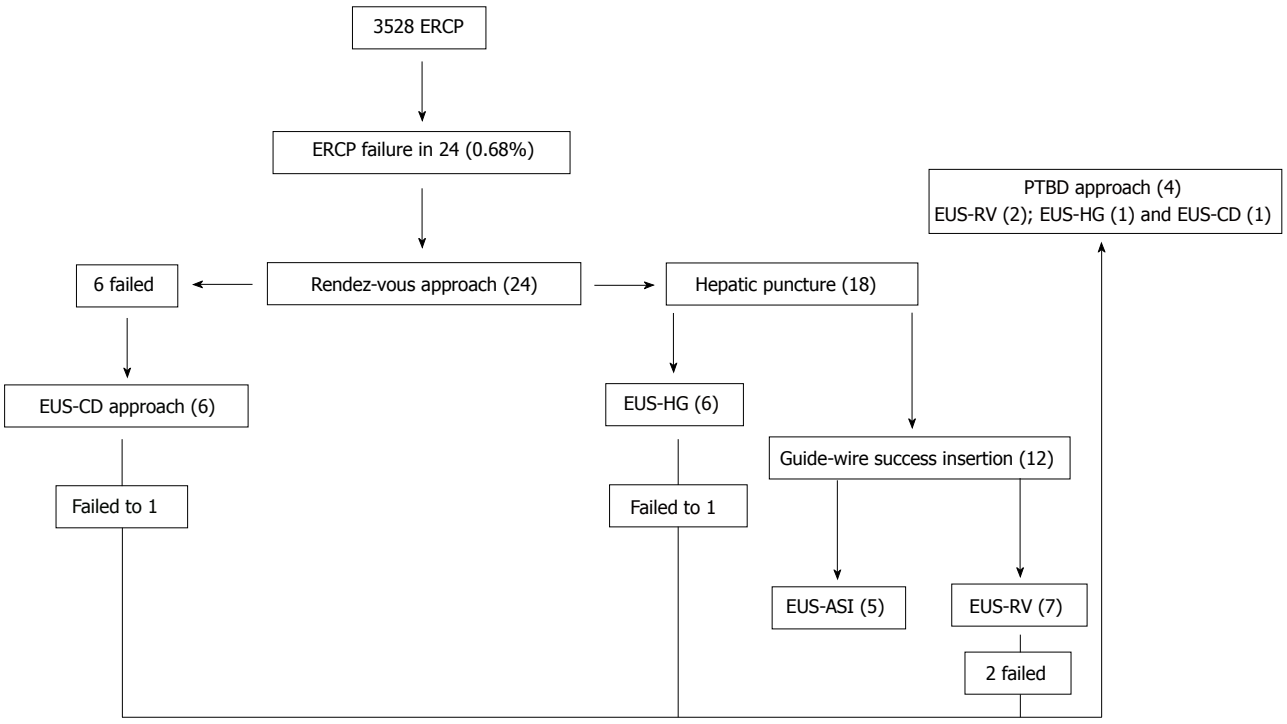

Figure 1 The systematic endosonography-guided biliary drainage approach for endoscopic retrograde cholangiopancreatography failure. PTBD: Percutaneous transhepatic biliary drainage; EUS-CD: Endosonography-guided choledochoduodenostomy; EUS-HG: Endosonography-guided hepaticogastrostomy; EUS-ASI: Endosonography-guided anterograde stent insertion; EUS-RV: Endosonography-guided rendez-vous.

duodenal portion, the recovery of the guidewire was not possible in 5 patients due to malignant duodenal stenosis (3) or papillary infiltration (2). For these cases, anterograde deployment of the biliary SEMS was performed (Figure 3). After passage of the biliary SEMS, a duodenal SEMS was delivered in 3 patients

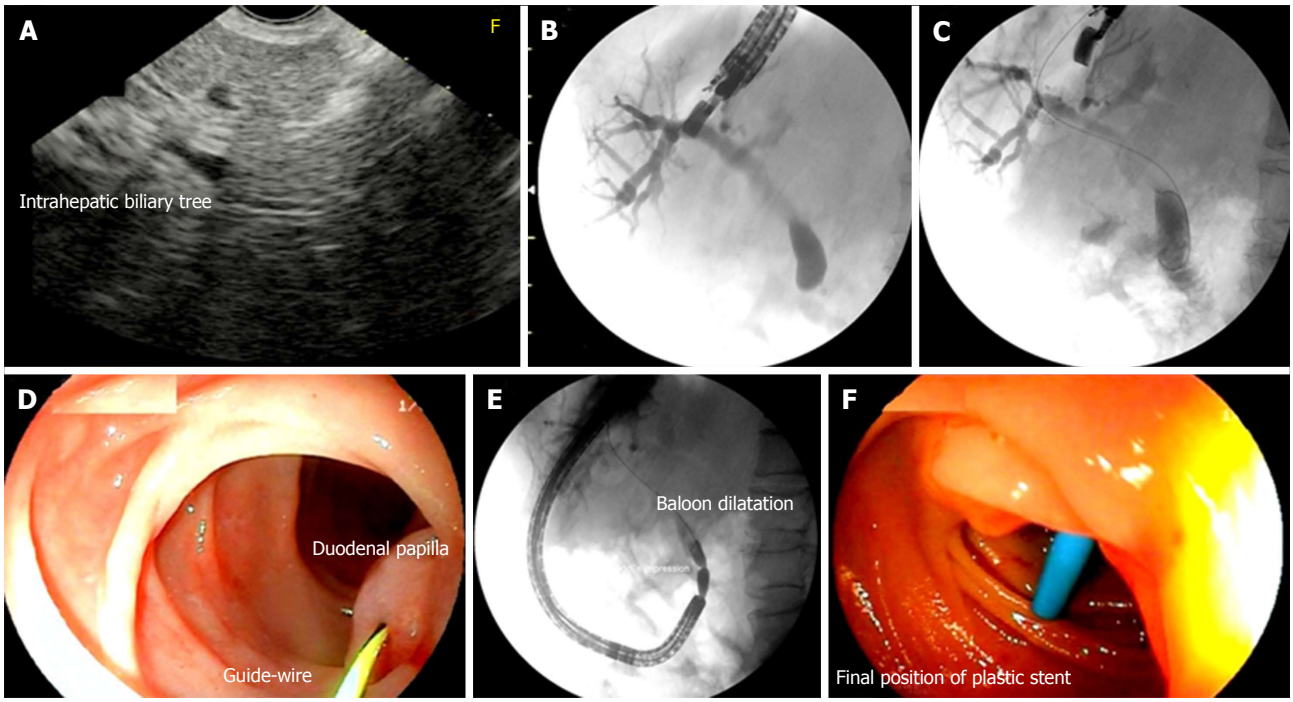

Figure 2 Patient with acute pancreatitis after cholecystectomy and Billroth Ⅱ gastrectomy. Endosonography (EUS)-guided rendez-vous technique. A: EUS image with dilation of the intrahepatic biliary duct; B: EUS-guided cholangiography; C: Insertion of the guidewire across the duodenal papilla and positioning in the duodenum; D: Capture of the guidewire with a frontal view endoscope; E: Balloon dilatation of the duodenal papilla; F: Insertion of a 10 Fr plastic stent.

with neoplastic duodenal stenosis. The overall technical success was 100%.

Endosonography-guided hepatogastrostomy

EUS-HG through transhepatic puncture was tried in 6 patients in whom the guidewire was positioned in the common bile duct (4), right lobe (1) and left lobe of the liver (1) (Figure 4). In 5/6 (83.3%) cases, an uneventful passage of the biliary SEMS was possible. For a single patient with recurrent liver metastasis from colon cancer after hepatectomy, the introduction of the transhepatic guidewire was impossible. The technical success rate was 83.3%, with one patient developing a pneumoperitoneum after the procedure.

Endosonography-guided choledochoduodenostomy

The insertion of the biliary stent through the duodenal puncture was tried in 6 patients as a rescue EUS-guided procedure for biliary drainage (Figure 5). All of these cases presented malignancies (Table 1). The correct positioning of the guidewire was achieved in 5/6 (83.3%), and one case was referred to PTBD. There was no complication.

Technical and clinical success

The overall technical success for EUS-BD was 83.3% (20/24). There was no significant difference among the various techniques (P = 0.81). Prior to EUS-BD, the mean levels of serum total and direct bilirubin were 13.3 mg/dL (5-29.9) and 9.1 (3-20.4) mg/dL, respectively. Ten days after EUS-BD, the mean levels were 2.3 (1.3-33) mg/dL, and 1.7 (0.6-22) mg/dL, respectively. The overall clinical success of EUS-BD was 75%.

Complications

Three (12.5%) complications occurred in patients submitted to EUS-BD: a pneumoperitoneum, a choleperitoneum, and an intracavitary liver hemorrhage. All of them were a consequence of the liver puncture in the hilum and were treated conservatively (Table 1). The patient with liver hemorrhage died three days after the PTBD due to acute respiratory and renal failure.

DISCUSSION

In our experience, an alternative to ERCP failure for biliary drainage was necessary in 0.68% of the cases, a finding similar to the rate of 0.62% in the experience of Holt *et al*[11]. Elderly people with malignant biliary obstruction are the most common candidates for the procedure[11], which was the case in our study, with patients at a median age of 68 years and with malignancies representing 83% of the cases. Endosonography-guided biliary drainage has been an alternative therapy to PTBD and surgery in ERCP failure[8,12]. PTBD, despite its satisfactory results, has a complication rate of about 30%, and surgery, although regarded as the definitive treatment for biliary drainage, is associated with high morbidity and mortality, especially for cases with terminal neoplastic disease[11,13,14].

Overall, the therapeutic success of EUS-BD ranges

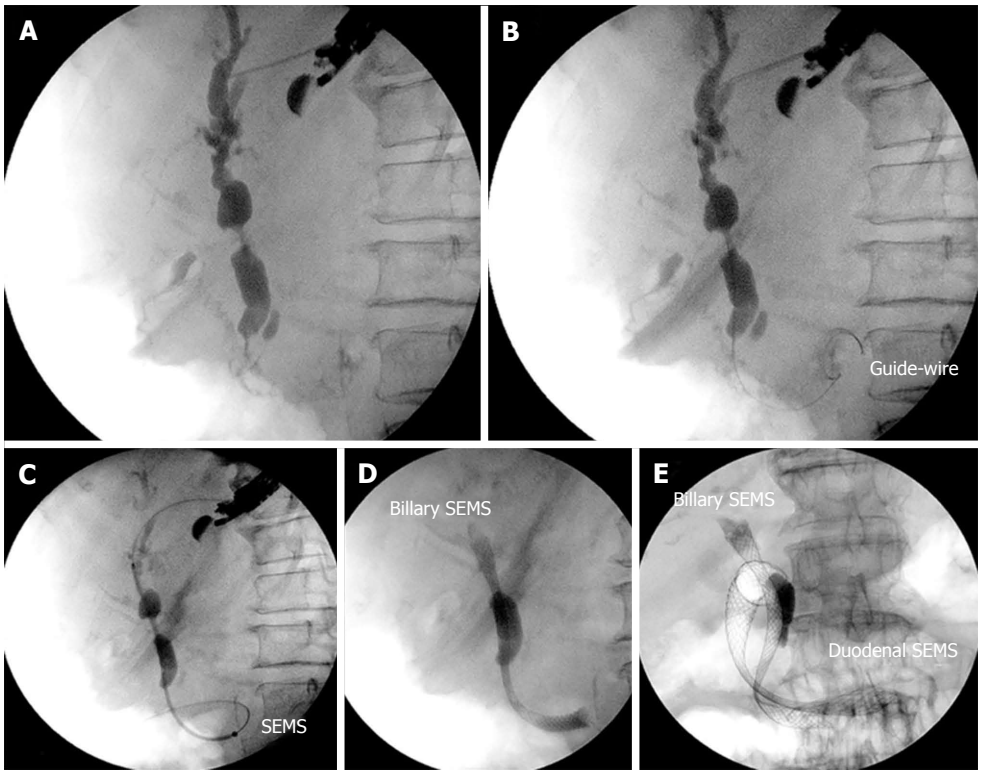

Figure 3 Patient with duodenal stenosis due to a pancreatic carcinoma. A: Endosonography (EUS)-guided cholangiography; B: Insertion of the guidewire through the duodenal major papilla and positioning in the duodenum; C: Anterograde insertion of the self-expandable metallic stents (SEMS) through the gastric wall across the duodenal major papilla and its positioning in the duodenum; D: Deployment of the SEMS; E: Insertion of the duodenal SEMS. SEMS: Self-expandable metallic stents.

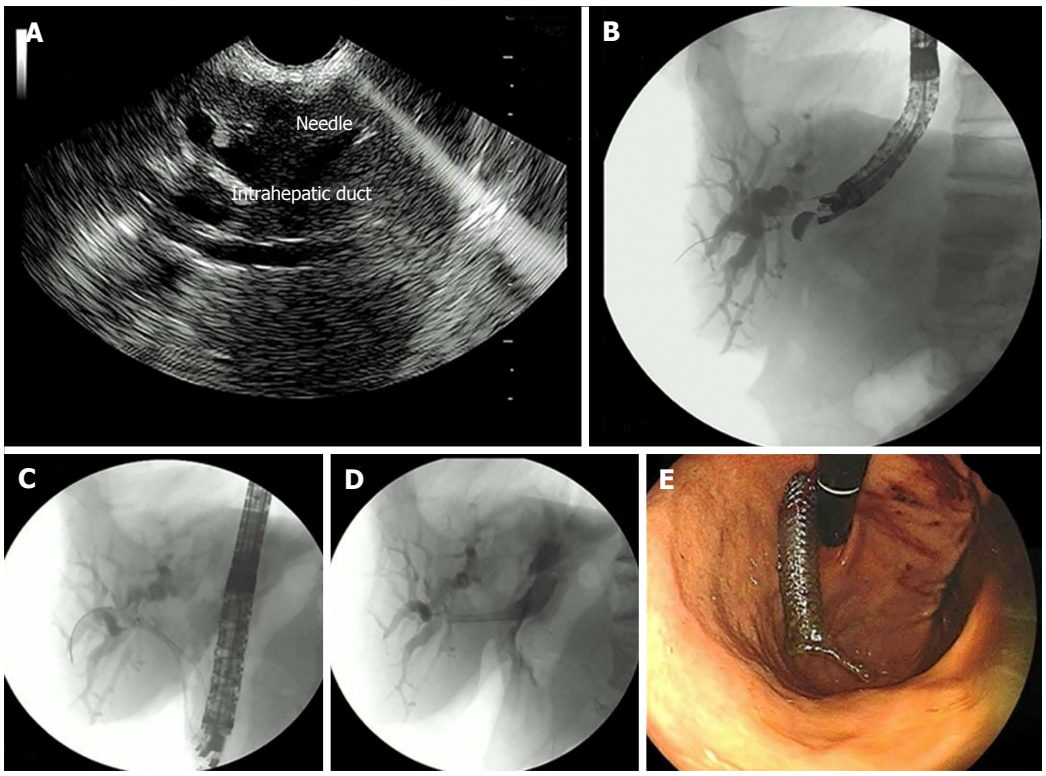

Figure 4 Endosonography-guided hepatogastrostomy. A: Endosonography (EUS) puncture of the dilated biliary intrahepatic duct; B: EUS-guided cholangiography; C and D: Deployment and positioning of the biliary self-expandable metallic stents (SEMS); E: Endoscopic view of the SEMS through the gastric wall.

from 73% to 100%[15-19]. However, there is no consensus about the best EUS-BD technique[9]. Regarding

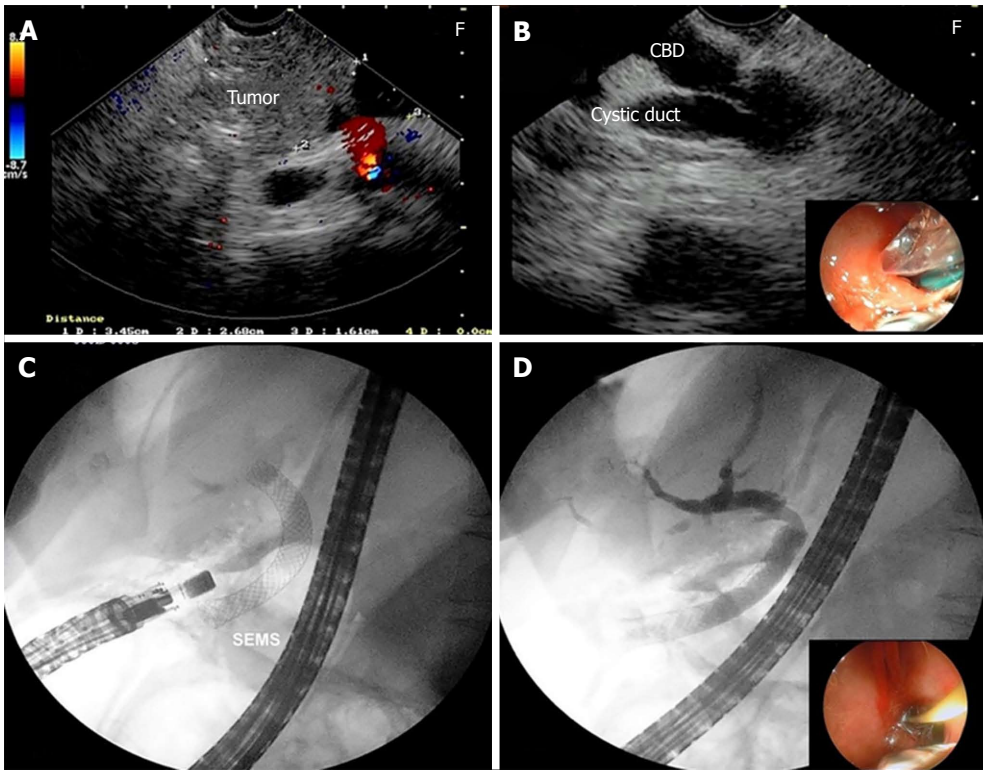

Figure 5 Endosonography-guided choledochoduodenostomy. A: Endosonography (EUS) image of the pancreatic carcinoma; B: Puncture of the common bile duct through the duodenum with a 19 gauge aspiration needle; C: Insertion of the self-expandable metallic stents after balloon dilation of the fistula; D: EUS-guided cholangiography through the choledochoduodenostomy.

particular EUS-BD techniques, there is a scarcity of comparative studies. Ogura *et al*[20] compared EUS-HG and EUS-CD for patients with jaundice and duodenal obstruction. Patients submitted to the transhepatic approach exhibited a longer patency of the biliary stent than those submitted to the transduodenal approach. In addition, the EUS-CD technique revealed a higher rate of complications, especially reflux cholangitis (OR = 10.285; 95%CI: 1.686-62.733; P = 0.012). Artifon *et al*[21] also evaluated the two techniques in a randomized clinical trial. There was no significant difference in effectiveness or safety between the two procedures. Technical and clinical success, as well as complications rates were 96%, 91%, and 20% for EUS-HG, respectively, and 91%, 77% and 12.5% for EUS-CD, respectively.

In an attempt to demonstrate the value of EUS-RV as the initial therapeutic option for biliary drainage in ERCP failure, Iwashita *et al*[22] performed the procedure using the transduodenal approach and using the transhepatic approach after failure of the transcholedochal approach. The authors concluded that EUS-RV is an effective and safe procedure, as also observed in our own experience. However, in contrast to the cited study, we began EUS-BD by the transhepatic approach, leaving the transduodenal approach only for the rescue option in the failure of the transhepatic approach.

In our experience, the transhepatic approach allows us to choose among three EUS-BD techniques according to the recovery or not of the guidewire, *i.e.*, the EUS-RV, EUS-ASI and EUS-HG techniques. Our group has adopted a systematic EUS-BD routine starting with the transhepatic access to initially perform the EUS-RV or EUS-ASI technique. This approach offers a good acoustic window for puncture of the biliary tree, a straight and easier to work position of the echoendoscope, a better positioning of the guidewire, and a lower chance of bleeding or choleperitoneum, with both complications amenable to tamponade by the liver parenchyma[19,23]. In our study, beginning with the transhepatic approach, the overall technical success was 83%, and the clinical success (intention-to-treat) was 75%, similar to literature results[23]. On the other hand, the transduodenal approach permits an easier execution of only the EUS-CD or, although more laborious and time-consuming, the EUS-RV. In the failure of this approach, the transhepatic approach should be the rescue therapy.

Nevertheless, despite the good results of EUS-BD when using the transhepatic approach, the literature still mentions some concern about the risk of complications with the intrahepatic access[18,20,24]. The needle must traverse the peritoneal cavity, a procedure that might increase the risk of pneumo- and choleperitoneum. This complication occurred in one of our patients and was managed conservatively. Another issue is the movement of the stomach and liver during breathing

and peristalsis, which might induce stent migration, trauma to the bilioenteric tract, and bile leakage. Finally, small-caliber intrahepatic ducts may not accommodate wider 8-mm to 10-mm metal stents, possibly predisposing to pneumoperitoneum and bile leakage due to incomplete sealing of the bilioenteric fistula[25,26]. For this reason, our goal during EUS-BD by means of the transhepatic approach is to obtain an intrahepatic duct of larger caliber as close as possible to the hepatic hilum.

In all of our cases in which the guidewire could not be reached in the duodenum due to stenosis or papillary infiltration, EUS-ASI succeeded without complications. The good performance and low complications rate of the EUS-ASI technique has been demonstrated in the literature[27].

On the other hand, if the patient has only a dilated biliary tree where the hepatic puncture is feasible but the guidewire could not reach the papilla, EUS-HG should be the next option. The greatest limitation in patients undergoing EUS-HG is the access to the right intrahepatic biliary tract and the progression of the guidewire to the common bile duct or its passage through the duodenal papilla. However, many authors justify selective drainage of the left intrahepatic biliary tract compared to the extrahepatic approach[7,28,29]. Both approaches have been shown to be effective and to involve low complications rates[21,26].

Nonetheless, EUS-BD by transhepatic approach may not be possible in some cases, depending on the patient anatomy[19,30]. We observed EUS-RV failure due to the impossibility of puncturing the liver or the inability to maintain the stability of the guidewire, and the difficulty to seize the guidewire in the duodenal lumen. In such cases, an extrahepatic approach must be adopted. The transcholedochal approach has the benefit of being feasible in patients whose papilla cannot be reached and has the advantage of being close to the duodenum[7,31,32]. In the current study, the technical success rates were the same (83.3%) for EUS-HG and EUS-CD, in agreement with published series[20,21]. Except for a pneumoperitoneum in the intrahepatic group, no difference in major complications was found between EUS-HG and EUS-CD (16.6% *vs* 0%; $P = 0.81$).

As a whole, EUS-BD is a safer technique than PTBD and surgery, with complication rates ranging from 10% to 20%, although the severity of most cases is mild to moderate[10,13]. Our complication rate also agreed with that reported in other studies[10,13]. Three of our cases developed complications, representing an overall rate of 12.5%. All of these cases were managed conservatively, but a patient with intracavitary bleeding was submitted immediately to PTBD after EUS-BD failure, and died three days later.

Despite the small number of our patients, this study did not demonstrate any significant difference in technical success or complication rates among different techniques of EUS-BD, in agreement with other studies[19,23].

In summary, a rational algorithm for EUS-BD in case of obstructive biliary diseases and ERCP failure might begin with the transhepatic approach, followed by particular EUS-BD techniques based on the patient's anatomy and feasibility to recover the guidewire.

ARTICLE HIGHLIGHTS

Research background

Endoscopic retrograde cholangiopancreatography (ERCP) is the standard approach to biliary drainage, and, in the failure of the procedure, percutaneous transhepatic biliary drainage or surgery must be used. However, endosonography can guarantee the least invasive and lowest risk treatment for biliary drainage of these cases. This study presents the results of different techniques for endosonography-guided biliary drainage in case of ERCP failure.

Research motivation

In case of ERCP failure, patients must be submitted to surgery or percutaneous transhepatic biliary drainage at different places in the hospital and with a long delay in treatment, conditions which can increase the morbidity and risks for the patient. Endosonography-guided biliary drainage can be performed immediately after ERCP failure, decreasing the time and risk of definitive treatment of the patient.

Research objectives

The main objectives of the study were to evaluate the success rates of endosonography (EUS)-guided biliary drainage techniques after ERCP failure for the management of biliary obstruction, and to propose a rational approach based on the access to the biliary tree and feasibility to recover the guidewire.

Research methods

In our experience, an alternative to ERCP failure for biliary drainage was necessary in 24 of 3538 (0.68%) cases. Elderly people with malignant biliary obstruction were the most common candidates for the procedure. The sequential endosonography-guided biliary drainage (EUS-BD) procedures proposed for all patients were transhepatic puncture in order to perform the EUS-guided rendez-vous technique. An anterograde approach was attempted when the capture of the guidewire in the duodenum was not possible. If the anterograde approach failed, EUS-guided Hepatogastrostomy was the next alternative. In case of failure of the intrahepatic puncture, patients were submitted to EUS-guided choledochoduodenostomy (EUS-CD).

Research results

Patients were submitted to EUS-guided rendez-vous (7), EUS-guided anterograde stent insertion (5), EUS-guided hepaticogastrostomy (6), and EUS-CD (6). Success rates did not differ among the various EUS-BD technique. Overall, technical and clinical success rates were 83.3% and 75%, respectively. The technical success for each technique was 71.4%, 100%, 83.3%, and 83.3%, respectively ($P = 0.81$). Complications occurred in 3 (12.5%) patients. All of these cases were managed conservatively, but one patient died after a rescue percutaneous transhepatic biliary drainage. Regarding particular EUS-BD techniques, there is a scarcity of comparative studies, and a consensus about the best technique has not been established.

Research conclusions

A rational approach to EUS-guided biliary drainage in case of obstructive biliary disease and ERCP failure should begin with the transhepatic approach, followed by particular EUS-guided biliary drainage techniques based on the patient's anatomy and feasibility to recover the guidewire in the duodenum.

Research perspectives

EUS-guided biliary drainage should be included in the therapeutic arsenal for the management of malignant biliary obstruction in case of ERCP failure, and should be the choice rather than surgery or percutaneous transhepatic biliary drainage.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Is there a difference in adenoma detection rates between gastroenterologists and surgeons?

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Abstract

AIM

To compare the adenoma detection rate (ADR) between gastroenterologists and colorectal surgeons at Box Hill Hospital, Melbourne, Australia.

METHODS

A total of 300 colonoscopies performed by gastroenterologists and colorectal surgeons at Box Hill Hospital were retrospectively reviewed from May 2016 to June 2017. Exclusion criteria were: Patients ⩽ 50 years old, colonoscopies with failure of caecal intubation, patients who previously had colon cancer and/or a colonic rese-

ction, history of polyposis syndromes or inflammatory bowel disease, or a colonoscopy within the last 10 years. Patient demographics, indications, symptoms and procedural-related outcomes were measured.

RESULTS

The ADR was not significantly different between gastroenterologists and colorectal surgeons (34% *vs* 34.67%; P = 0.90). The adjusted odds ratio correcting for gender, age, 1st degree relative with colorectal cancer, previous colonoscopy, trainee involvement and caecal or terminal ileum intubation rate was 1.19 (0.69-2.05).

CONCLUSION

Both specialties at our institution exceed benchmark standards suggested by published Australian and American guidelines. An association between endoscopist specialty and ADR was not observed.

Key words: Colorectal surgery; Gastroenterologists; Surgeons; Adenoma; Colonoscopy; General surgery

Core tip: Our study concludes that there is no association between specialty (gastroenterology and colorectal surgeons) and proficiency in colonoscopy, using adenoma detection rate as a quality indicator. The adenoma detection rate in both specialties at our institution exceed benchmark standards suggested by published Australian and American guidelines, reflecting the high standards of care and efficacy of the common training pathway for both specialties.

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INTRODUCTION

Colorectal cancer (CRC) poses a significant health burden in Australia. In 2018, it is estimated to become the second most commonly diagnosed cancer with an incidence of 17004 new cases[1]. Colonoscopy is the gold standard screening tool for CRC, allowing for the detection and removal of precursor lesions. To ensure high standards for colonoscopy in Australia, gastroenterologists and colorectal surgeons are required to complete similar training requirements under the Gastroenterological Society of Australia (GESA).

ADR is the primary quality measure in colonoscopy, having been proven to accurately predict effective CRC prevention. It is defined as the proportion of screening colonoscopies that detect at least one histologically confirmed colorectal adenoma. Meeting the standard ADR is crucial in reducing CRC incidence and minimising CRC-related mortality[2]. The performances of gastroenterologists and colorectal surgeons in colonoscopy have been compared in the literature, with varied results. Several studies have demonstrated that gastroenterologists are more effective than non-gastroenterologists at preventing CRC by colonoscopy whilst other studies have showed no difference between the two specialties[3-6].

Comparing the ADR between gastroenterologists and colorectal surgeons in Australia is of significant interest. Although both specialties have similar training requirements, they remain completely separate specialties. This study aims to compare the ADR between gastroenterologists and colorectal surgeons at a single centre in Melbourne, Australia.

MATERIALS AND METHODS

Study design

Consecutive patients undergoing colonoscopies by gastroenterologists and colorectal surgeons were identified from the endoscopy database at Box Hill hospital (Melbourne, Australia) between May 2016 and June 2017. Exclusion criteria included patients aged 50 and younger, colonoscopies with failure of caecal intubation, previous CRC and/or a colonic resection, history of polyposis syndromes or inflammatory bowel disease, or a colonoscopy within the last 10 years.

Excluding such patients was for ease of comparison of our results with guidelines published by the Gastroenterological Society of Australia (GESA), American Society for Gastrointestinal Endoscopy(AGSE) and American College of Gastroenterology (ACG) discussed in detail below. These guidelines were specific to patients ⩾ 50 years old of "average-risk", and patients with previous pathologies would not lie within this bracket. Exclusion of cases with failure of caecal intubation ensured that proficiency was strictly based on the ability to detect adenomas, and ADR was not affected by pre-existing patient-related factors impacting caecal intubation (*e.g.*, poor bowel preparation, obstructing/stenosing lesion, significant looping, redundant colon). Rex *et al*[7] also recommends that failed caecal intubation due to poor bowel preparation, severe colitis or known stricture or polyp for treatment, need not be counted in determining caecal intubation rates when assessing effectiveness of colonoscopy.

Information regarding cases was obtained from the electronic medical record system. All participating endoscopists were either certified by the GESA or supervised by an endoscopist certified by the GESA[1].

The study was approved by the Office of Research and Ethics at Eastern Health.

Data collection

Data were collected by two investigators and included patient demographics, indication for colonoscopy (screening versus non-screening), trainee involvement, and

Table 1 Patient and procedure-related characteristics in colonoscopies performed by gastroenterologists and colorectal surgeons

	Gastroenterologists (n = 150)	Colorectal surgeons (n = 150)	P-value
Female (%)	50.67	52	0.817
Patient age (mean, yr)	66.59	67.18	0.61
1st degree relative with CRC (%)	6.67	10	0.296
1st colonoscopy (%)	98	89.33	0.002
Trainee involved (%)	12	36.67	< 0.0001
Caecal intubation rate (%)	100	100	-
TI intubation rate (%)	70	36	< 0.0001

CRC: Colorectal cancer.

caecal and terminal ileum (TI) intubation rate. Screening colonoscopies were those performed for a positive faecal occult blood test in the absence of any other indications. Indications for non-screening colonoscopies included investigation of symptoms, 1st degree relative with CRC, abnormal imaging and iron deficiency anaemia. Colonoscopies performed for symptoms included abdominal pain, bloating, change in bowel habits, macroscopic per rectal bleeding, loss of weight, anorexia, anal symptoms such as pruritus or pain, and symptomatic anaemia such as syncope or shortness of breath. It was recorded if an adenoma was detected when at least one polyp was removed during the colonoscopy.

Trainees were registered surgical or gastroenterology trainees, under The Royal College of Surgeons or The Royal College of Physicians, who have not attained certification by the GESA. When trainees were involved, they performed the colonoscopy with direct supervision by consultants, who only intervened when there was difficulty traversing a part of the colon. Caecal intubation was recorded if reported or on viewing photo documentation of caecal landmarks such as the triradiate fold, ileocaecal valve and appendiceal orifice. TI intubation was recorded if reported.

The primary outcome was adenoma detection rate (ADR), the definition of which was extended to include colonoscopies for all indications. Secondary outcomes included polypectomy rate, polyp detection rate, tumour detection rate, hyperplastic polyp detection and adenocarcinoma detection rate.

Statistical analysis

Comparative statistics were performed using Student's t test and Pearson's Chi-squared analysis. Separate analyses of ADRs by gender, indication and age were performed to control for different patient populations. Multivariate logistic regression was performed to control for patient-level confounders (gender, age, 1st degree relative with CRC, 1st colonoscopy, trainee involvement, caecal or TI intubation). Associations were quantified by odds ratios and 95% confidence intervals (CI). A significant P-value was defined as < 0.05. All analyses were conducted using Stata IC Version 15.

RESULTS

Patient characteristics

A total of 300 colonoscopies performed at Box Hill Hospital were found to have met inclusion criteria (Figure 1). 150 colonoscopes performed by 16 gastroenterologists and 150 colonoscopes performed by 8 colorectal surgeons were obtained from May 2016 to June 2017.

Baseline demographics are summarised in Table 1. Gastroenterologists were more likely to perform colonoscopies on patients who had never had a colonoscopy (98.0% *vs* 89.33%, P = 0.002) and were more likely to intubate the TI (70.00% *vs* 36.00%, P = 0.000), whereas colorectal surgeons had a higher trainee involvement rate (12.00% *vs* 36.67%, P = 0.0001).

In both specialties, the majority of colonoscopies were indicated for non-screening purposes-84.67% and 86.67% of colonoscopies performed by gastroenterologists and colorectal surgeons respectively.

Primary and secondary outcomes

There were no significant differences identified between gastroenterologists and colorectal surgeons for ADR (34.00 *vs* 34.67, P = 0.903), hyperplastic polyp detection rate (14.00 *vs* 8.67, P = 0.145), polyp detection rate (51.33 *vs* 46.00, P = 0.355), tumour detection rate (2.00 *vs* 4.67, P = 0.198), adenocarcinoma detection rate (2.67 *vs* 4.00, P = 0.520) and polypectomy rate (51.33 *vs* 46.00, P = 0.3555).

Separate analyses of adenoma-detection rate

We analysed ADR according to gender, indication and age for each specialty (Table 2). While controlling for various population groups, no statistically significant difference was detected between specialties.

Within each speciality, ADR was higher in males compared to females. There was also a peak in ADR for colonoscopies performed in those 70 to 84 years of age. ADR was higher in the screening colonoscopies compared to non-screening in gastroenterologists, but the opposite was observed for colorectal surgeons. Only the differences in ADR between genders (41.89 *vs* 26.32, P = 0.440) and between indications (52.17 *vs* 30.71, P = 0.046) within gastroenterologists were statistically significant.

Results of multivariate logistic regression

The logistic regression results with ADR are demonstrated in Table 3. The odds ratio for ADR with surgeons as compared to gastroenterologists, adjusted for sex, age, 1st degree relative with CRC, previous colonoscopy, tr-

Table 2 Adenoma detection rate for gastroenterologists and colorectal surgeons, by patient sex, indication and age-group

	Adenoma detection rate (%)		
	Gastroenterologists	Colorectal surgeons	*P*-value
Gender			
Male	41.89	38.89	0.712
Female	26.32	30.77	0.541
P-value	0.044	0.297	
Indication			
Screening	52.17	30	0.142
Non-screening	30.71	35.38	0.426
P-value	0.046	0.638	
Age group			
50-54	31.58	26.32	0.721
55-59	31.82	33.33	0.91
60-64	33.33	28.57	0.724
65-69	20.83	33.33	0.362
70-74	38.46	47.83	0.509
75-79	56.25	36.84	0.251
80-84	37.5	38.46	0.965
85-89	28.57	30	0.949
90-94	0	0	-
P-value	0.606	0.89	

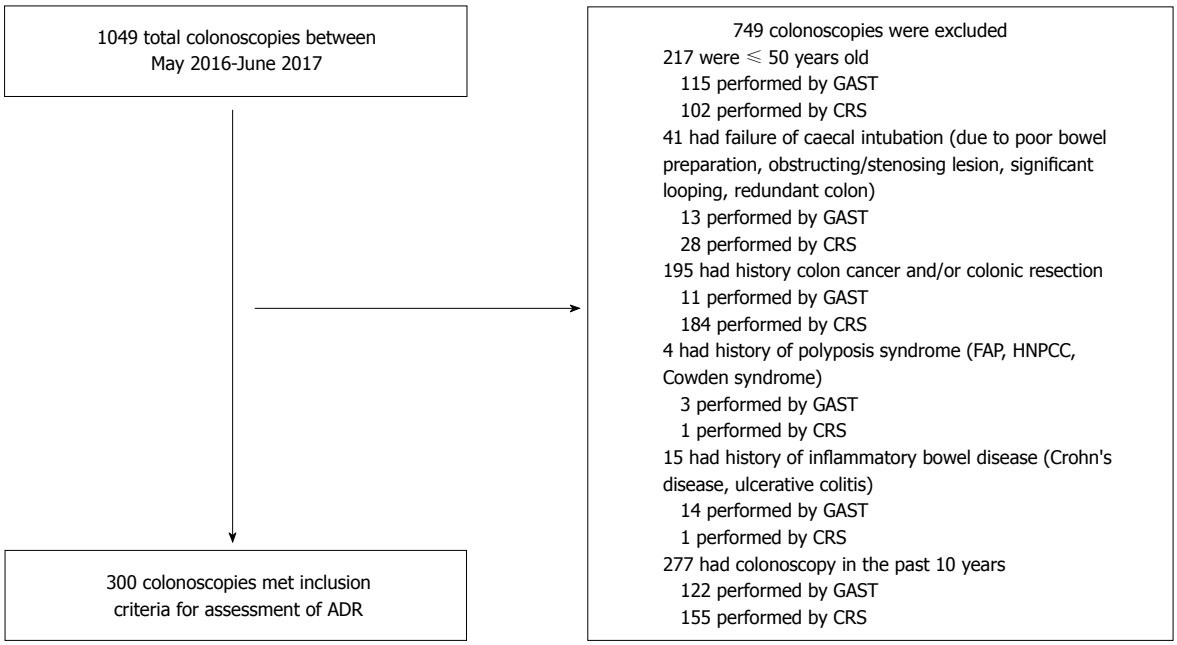

Figure 1 Colonoscopies performed by gastroenterologists and colorectal surgeons at Box Hill Hospital. GAST: Gastroenterologists; CRS: Colorectal surgeons; FAP: Familial polyposis syndrome; HNPCC: Hereditary nonpolyposis colorectal cancer; CRC: Colorectal cancer; ADR: Adenoma detection rate.

ainee involvement and caecal or TI intubation rate was 1.19 (95%CI: 0.69-2.05). A significant difference in ADR was not demonstrated even after adjusting for potential confounders.

DISCUSSION

This is the first study in Australia to compare the ADR between gastroenterologists and colorectal surgeons. In our institution, we found no significant difference in the ADR between the two specialities.

It is important to monitor ADR performance in order to optimise CRC prevention. Corley *et al*[2] found that each 1% increase in ADR predicted a 3% decrease in the risk of cancer. Similarly, Kaminski *et al*[8] found that an increased ADR was associated with a reduced risk of CRC and death. Low ADRs not only reflect the failure of detecting precancerous lesions at colonoscopy, but also result in an inappropriately increased length of time to the next colonoscopy, thereby increasing the risk of interval cancers[9].

Our findings parallel other studies that found no significant differences for ADRs between specialties. Ollington *et al*[3] compared the ADR between gastr-

Table 3 Odds ratio estimates for adenoma detection rate from logistic regression models

Variable	Odds ratio (95%CI)
Endoscopist level Specialty[1] (SURC/GAST)	1.19 (0.69-2.05)
Patient level Gender[2] (F/M)	0.57 (0.34-0.93)
Age	1.02 (0.99-1.04)
1st degree relative with CRC (N/Y)	1.21 (0.48-3.11)
1st colonoscopy (N/Y)	0.89 (0.32-2.54)
Trainee involvement (N/Y)	1.44 (0.78-2.65)
Caecal intubation (N/Y)	1
Terminal ileum intubation (N/Y)	0.89 (0.53-1.49)

[1]The reference category is gastroenterologists; [2]The reference category is males. CRC: Colorectal cancer.

oenterologists and colorectal surgeons in California. 180 and 119 colonoscopies were performed by 8 gastroenterologists and 16 colorectal surgeons respectively. No significant difference was detected between both specialties (33% gastroenterologists *vs* 29% colorectal surgeons; $P = 0.38$). Bhangu *et al*[4] prospectively reviewed 10, 026 colonoscopies performed by physicians (general physicians or gastroenterologists) and surgeons (general or colorectal), from a United Kingdom hospital endoscopy service. After adjusting for age, sex and indication, it concluded that accreditation and procedural volume, but not endoscopic specialty, were predictors of ADR. Most recently, a study by Kozbial *et al*[10] analysing 59901 screening colonoscopies performed in Austria concluded that there was no significant difference in ADRs in relation to specialty or setting.

In contrast, 3 studies demonstrated higher ADRs in gastroenterologists compared to non-gastroenterologists. Pox *et al*[11] performed a prospective cross-sectional study on 2821392 colonoscopies in Germany for individuals 55 years and older. He reported ADRs of 25.1% and 22.3% for gastroenterologists and non-gastroenterologists (internists and colorectal surgeons) respectively (adjusted OR 1.18; 95%CI: 1.16-1.21). Though this is a statistically significant result, its clinical significance is arguable and the colonoscopies analysed were indicated for screening purposes only. De jonge *et al*[12] found that surgeons were 80% less likely to find an adenoma as compared to gastroenterologists (OR 0.2; 95%CI: 0.1-0.6). However, there was not an equal representation of specialties, with surgeons representing 1% of endoscopists. Additionally, a lower caecal intubation rate was found in surgeons and internists as compared to gastroenterologists (after adjusting for poor bowel preparation, severe colitis and an intervention as an indication), which could have accounted for the significant difference in ADR. Leyden *et al*[13] assessed colonoscopies performed by gastroenterologists and surgical trainees and reported ADRs of 14% and 9% respectively ($P = 0.0065$). Given the low ADRs in this study, the results may not be an accurate representation of each specialty.

There is evidence in the literature postulating the superior performance of gastroenterologists in colonoscopies, utilising other outcome measures such as incidence of post-colonoscopy CRC[14,15], mortality secondary to CRC[5] and polypectomy rate[6,16]. However, most results were reported against non-gastroenterologists and not colorectal surgeons[5,6,14,15]. The difference reported was not significant[15] or if significant, was usually small and may not be clinically significant[16].

Both specialties at our institution exceed the recertification criteria set by the GESA, *i.e.*, an ADR of at least 25% in patients 50 years or older, having intact colons, with no findings of acute IBD, and with intubation to the caecum or terminal ileum. They also exceed benchmark standards suggested by the ASGE and ACG. As of 2015, ADR targets of 30% in men and 20% in women over the age of 50 are endorsed[9]. In our study, gastroenterologists demonstrated ADRs of 41.89% and 26.32% in males and females over the age of 50 while colorectal surgeons demonstrated ADRs of 38.89% and 30.77% in males and females over the age of 50.

Although the differences in the ADR between both specialties were not significant in our study, a higher ADR in colorectal surgeons was observed with a higher trainee involvement. This finding is mirrored by Qayed *et al*[17], who observed a significantly greater ADR with trainee participation than without, and attributed this to the presence of an additional observer and more focused examination behind each colonic fold during withdrawal of the colonoscope due to active supervision. Although this association was not statistically analysed for in our study, greater trainee involvement may increase ADRs, and may be implemented to increase ADRs.

Quality of colonoscopy is a pertinent issue. The National Bowel Cancer Screening program in Australia has plans of expansion, offering free screening FOBT, followed by colonoscopy if FOBT positive, to Australians aged 50 to 74 years old biannually by 2020. Our study reflects that high standards are upheld in colonoscopy, regardless of specialty.

Ways to improve ADR has been explored due to large variations in ADRs in the literature[18]. Interventions targeting endoscopist performance have varied effects

on ADRs. Performance report cards could be used to improve ADR, especially among physicians with low ADR < 25%[19]. Video recording led to the increase in inspection time and quality, however its impact on ADR was equivocal[20]. In contrast, a multi-intervention program involving personalised feedback and financial penalties, showed no significant improvements in ADR[21].

Interventions directed at withdrawal time have been looked into. Recording or lengthening the withdrawal time was not associated with improvement of adenoma or polyp detection rates[22-24]. However, ADR improved significantly when implementation of a targeted 8-min withdrawal time with the use of an audible timer was combined with inspection training. This highlights the potential of continuous feedback in improving ADRs instead of addressing withdrawal time in isolation[25,26]. A repeat examination or increased observation time at the right side of the colon has been shown to increase ADR. Hence greater time could be spent examining the proximal colon, especially since small lesions located there are more frequently associated with advanced neoplasia[27,28].

Utilising technological adjuncts to augment ADRs have been explored[29,30]. High definition imaging and selective application of dyes are not useful in increasing ADRs[29,31]. Widespread use of dyes increase the detection of small flat adenomas but are time consuming[32]. Evidence around electronic highlighting of flat lesions are still lacking[33]. The use of full-spectrum colonoscopy, with a panoramic 330 degree view of the colon, has not been shown to be superior to standard colonoscopy with regards to ADR through a meta-analysis of eight randomised controlled trials[34]. Despite this, narrow band imaging has been demonstrated to be effective in endoscopic predictions of histology, reducing costs and avoiding risks associated with polypectomy[29].

The use of attachable add-on devices which increase exposure of mucosa has been introduced. Cap cuff-assisted colonoscopy has been tested, with 4 randomised studies demonstrating gains of 3%-9% in ADR, albeit carrying risks of mucosal erosions and lower ileal intubation rates[35-38]. Another novel idea is the use of behind-folds visualising colonoscopy technologies. Through the review of 3 randomised tandem studies, Brand *et al*[39] found that it reduced miss rates for 1 to 9 mm adenomas. However, the validity of this in reducing incidence of CRC and death has yet to be determined. Despite uncertainty surrounding efficacy, such devices show promise and could be used with discretion in daily practice[30].

The use of pre-operative simethicone has been shown to increase ADR. Simethicone is an anti-foaming agent which reduces the surface tension of bubbles, thereby reducing the need for intraoperative flushing which could reduce visualisation of the colon due to fluid accumulation. It has also been shown to reduce air accumulation and abdominal bloating, thereby improving patient compliance to bowel preparation[40,41].

Our study had limitations, such as its retrospective nature. Hence, several information was not able to be obtained. Withdrawal time was not recorded, hence no insight could be provided regarding withdrawal time and increased ADR. However as mentioned previously, evidence shows that isolated increase in withdrawal time does not increase ADR and hence its inclusion in analysis would not provide much insight. The level of consultant participation in colonoscopy when a trainee was involved, the level of experience armed by each trainee at the time of colonoscopy as well as the actual number of trainees involved were not recorded. Hence, an accurate association between trainee involvement and ADR could not be established. However, this is not the main aim of our study and this could be explored in further future studies. Despite these limitations, we applied strict exclusion criteria and all colonoscopies in this study were performed under similar conditions and with mandatory compliance to quality guidelines at an institutional and national level. Multivariate analysis controlling for age and gender was implemented as studies have shown that ADR is affected by these factors[11,18].

A larger sample size may have increased the power of the study and allowed the differences to reach statistical significance, but the clinical significance of such small differences come into question. Moreover, the sample size required to attain statistical significance would not be feasible for retrospective review. Finally, our study was performed at a single centre and a sample of colonoscopies during a certain time period were used to ascertain ADRs for both specialties. Therefore, this may not be a true representation of all gastroenterologists and colorectal surgeons across Australia.

In conclusion, both gastroenterologists and colorectal surgeons at our institution exceed benchmark standards suggested by the GESA, ASGE and ACG. An association between endoscopist specialty and ADR was not observed, even after controlling for patient-level factors. Our study reassures clinicians and patients that high standards are upheld in colonoscopy, regardless of specialty.

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer (CRC) poses a significant health burden in Australia. In 2017, it is estimated to become the second most commonly diagnosed cancer with an incidence of 16682 new cases. Colonoscopy is the gold standard screening tool for CRC, with the adenoma detection rate (ADR) as the primary quality measure. ADR is defined as the proportion of screening colonoscopies that detect at least one histologically confirmed colorectal adenoma. Meeting the standard ADR is crucial in reducing CRC incidence and minimising CRC-related mortality. The performances of gastroenterologists and colorectal surgeons in colonoscopy have been compared in the literature, with varied results.

Research motivation

Quality of colonoscopy is a pertinent issue, with the expansion of the National Bowel Cancer Screening program, offering free screening to Australians aged

50 to 74 years old every two years by 2020. ADR has been established as an important measure of endoscopist proficiency. At present, no study has compared the ADR between gastroenterologists and colorectal surgeons in Australia. Although both specialties have similar training requirements, they remain completely separate specialties. This study aims to compare the ADR between gastroenterologists and colorectal surgeons, and hence reflect the standards of colonoscopy of both specialties in Australia. This would propel higher quality research to be undertaken regarding ways to increase ADR in colonoscopy and hence ensure more effective prevention of CRC.

Research objectives

This study aims to compare the ADR between gastroenterologists and colorectal surgeons at a single centre in Melbourne, Australia.

Research methods

A total of 300 colonoscopies performed by gastroenterologists and colorectal surgeons at Box Hill Hospital were retrospectively reviewed from May 2016 to June 2017. Exclusion criteria were: Patients ≤ 50 years old, colonoscopies with failure of caecal intubation, patients who previously had colon cancer and/or a colonic resection, history of polyposis syndromes or inflammatory bowel disease, or a colonoscopy within the last 10 years. Patient demographics, indications, symptoms and procedural-related outcomes were measured.

Research results

The ADR was not significantly different between gastroenterologists and colorectal surgeons (34% *vs* 34.67%, P = 0.90). The adjusted odds ratio correcting for gender, age, 1st degree relative with colorectal cancer, previous colonoscopy, trainee involvement and caecal or terminal ileum intubation rate was 1.19 (0.69-2.05).

Research conclusions

Both gastroenterologists and colorectal surgeons at our institution exceed benchmark standards suggested by the GESA, ASGE and ACG. An association between endoscopist specialty and ADR was not observed, even after controlling for patient-level factors. Our study reassures clinicians and patients that high standards are upheld in colonoscopy, regardless of specialty. Ways to improve ADR has been explored, such as interventions targeted at endoscopists performance, increasing withdrawal time or observation time, technological adjuncts or add-on devices and the use of simethicone. Currently, there is a lack of high quality evidence that demonstrates increase in ADR with each of these interventions to support their routine use in colonoscopy. Despite this uncertainty, technological adjuncts such as narrow band imaging and cap cuff-assisted colonoscopy may be used with discretion in daily practice. Greater time spent examining the proximal colon could be considered.

Research perspectives

The ADR in both specialties exceed benchmark standards reflecting the high standards of education and training in Australia. Higher quality evidence investigating patient and endoscopist-specific factors that increase ADR is warranted.

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CASE REPORT

Off label use of lumen-apposing metal stent for persistent gastro-jejunal anastomotic stricture

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Author contributions: Mansoor MS, Tejada J and Yoon E designed the report; Mansoor MS, Parsa NA and Hida S performed the literature review; Mansoor MS, Tejada J and Hida S wrote the manuscript.

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Abstract

We are reporting a novel "off-label" use of lumen apposing metal stent (LAMS) for management of refractory gastro-jejunal (GJ) anastomotic stricture after Roux-en-y gastric bypass (RYGB). With increasing prevalence of obesity, bariatric surgery is performed more frequently than ever. RYGB is one of the most commonly performed bariatric procedures. GJ anastomotic stricture is a late complication of this procedure. Our patient, seven years after RYGB developed GJ anastomotic ulcer and subsequently a stricture not amendable to repeated pneumatic dilations. Instead of using the conventional fully covered self-expanding metal stent (fcSEMS) we deployed the relatively new LAMS keeping in mind its novel dumbbell shaped design. Our patient's symptoms were controlled successfully and she remained asymptomatic on follow-up. Despite initial approval for pancreatic pseudocyst drainage, LAMS has been used with increased frequency at various locations within gastrointestinal tract including GJ anastomotic strictures. Future randomized control trials are warranted to compare the efficacy of fcSEMS to LAMS.

Key words: Gastro-jejunal anastomotic stricture; Lumen apposing metal stent; Dysphagia; Roux-en-Y gastric bypass

Core tip: Gastro-jejunal (GJ) anastomotic stricture is a common late complication of Roux-en-y gastric bypass.

Pneumatic dilation is the first line treatment for these strictures and fully covered self-expanding metal stent (fcSEMS) can be used as an alternative. In this case report we represent the successful off-label placement of lumen apposing metal stent instead of fcSEMS for GJ anastomotic stricture.

Mansoor MS, Tejada J, Parsa NA, Yoon E, Hida S. Off label use of lumen-apposing metal stent for persistent gastro-jejunal anastomotic stricture. *World J Gastrointest Endosc* 2018; 10(6): 117-120 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i6/117.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i6.117

INTRODUCTION

Worldwide obesity has tripled since 1975. The number of bariatric surgeries performed each year in united states has been increasing steadily with approximately 196000 surgeries performed in the year 2015[1]. Roux-en-y gastric bypass (RYGB) is the second most common bariatric surgery performed after sleeve gastrectomy. One of the late complications of this procedure is gastro-jejunal (GJ) anastomotic stricture[2]. Initially this is typically managed safely with pneumatic dilation[3]. Alternatives to dilation include needle-knife incisional therapy, local steroid injection and fully covered self-expanding metal stent (fcSEMS). The fcSEMS has a high rate of adverse events including stent migration and recurrence of strictures after removal of stent[4]. Lumen apposing metal stent (LAMS) was initially used for draining pancreatic fluid collections/cystogastrostomy though recently has been used in various locations throughout the gastrointestinal tract due to its novel dumbbell shaped design. In this case report we present a case of GJ anastomotic stricture successfully managed with LAMS after failure of serial balloon dilations and steroid injections. LAMS was preferred over fcSEMS to avoid the high rate of complications.

CASE REPORT

A 42-year-old female with history of RYGB performed seven years ago, complicated by GJ anastomotic ulcer three years ago was seen in follow-up for symptomatic GJ anastomotic stricture. She reported weakness, fatigue and a 50-pound weight loss over the past year due to her inability to tolerate both solids and liquids orally. Her BMI was 18.79 and she did not have any medical comorbidities including no obstructive sleep apnea or hypertension. Patient's GJ anastomotic ulcer healed two years ago after starting a hydrogen-potassium ATPase inhibitor and she reduced her smoking from one pack per day to three cigarettes per day. For her persistent GJ anastomotic stricture she underwent through-the-scope (TTS) dilation twice this year and twice in the year before with triamcinolone injected in the stricture on her second dilation. These measures provided only temporary relief of her symptoms. On her last esophagogastroduodenoscopy (EGD), she had persistent GJ stricture and no gastro-gastric fistula. Her *Helicobacter pylori* status was negative on multiple occasions on stool antigen testing and on microscopic examination of obtained tissue samples during EGD. We performed a repeat EGD on which the GJ anastomosis was characterized by severe stenosis (2 mm opening) (Figure 1). A LAMS (Axios stent 15 mm x 10 mm; Boston Scientific, Marlborough, MA, United States) was placed into the anastomotic stricture (Figures 2-4). A wire-guided TTS balloon dilator (CRE; Boston Scientific, Marlborough, MA, United States) was passed over a guidewire (Hydra Jagwire 0.035 cm x 260 cm; Boston Scientific, Marlborough, MA, United States) through the LAMS. Dilation with 10 mm-11 mm-12 mm anastomotic balloon dilators was performed and held inflated for 2 min under fluoroscopic guidance. Our patient did not develop any immediate or delayed stent-related adverse events. Patient's symptoms improved remarkably after the procedure, she had gained 5 pounds and was asymptomatic on three-month follow-up. We aim to remove the stent after a total of six months for maximum effect.

DISCUSSION

RYGB is associated with both early and late adverse events. The early adverse events include staple/suture leak, postoperative hemorrhage and bowel obstruction. Late adverse events include but are not limited to marginal ulceration, fistula formation, nutritional deficiencies, difficulty performing endoscopic retrograde cholangiopancreatography (ERCP) and anastomotic stricture. The rate of GJ anastomotic stricture ranges between 2.9% to 23% after RYGB[5-7]. Factors that are implicated in development of this adverse events include anastomotic dehiscence, local ischemia, tension at anastomosis, healing capacity of patient, non-adherence to recommended nutrition and the technique used to create the anastomosis[4,8,9]. This condition is more common in patients with laparoscopic RYGB compared to an open approach[6]. Patients can present anywhere from a couple of weeks to months post-operatively with progressively worsening dysphagia, nausea, vomiting, gastroesophageal reflux and epigastric pain[8]. GJ anastomotic stricture can be identified through various radiographic studies though EGD should be performed if suspected.

Pneumatic dilation is the first line therapy for GJ anastomotic strictures and has shown good results though in some cases serial dilations may be required[6,9-11]. Carrodeguas *et al*[12] reported a mean of two dilatory sessions required to achieve an anastomotic diameter of 10 mm to 16.5 mm for 94 patients with GJ anastomotic stricture identified through retrospective analysis. Rate of perforation in this study was reported as 2.1%. Alternatives to pneumatic dilation include needle-knife

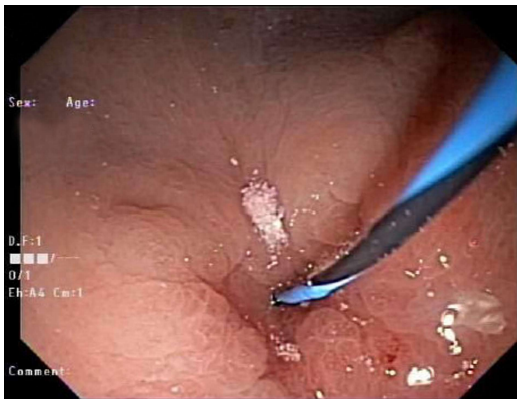

Figure 1 Gastro-jejunal anastomotic stricture with 2 mm opening.

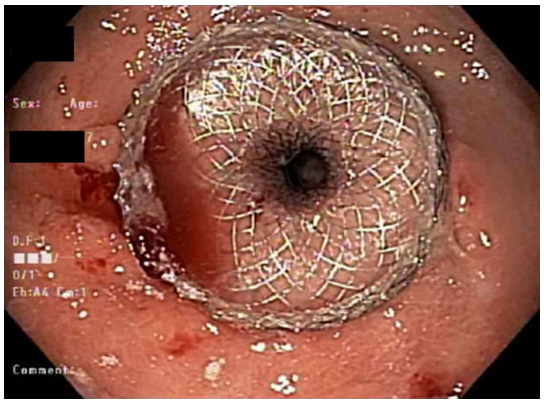

Figure 2 Axios stent placed in gastro-jejunal anastomotic stricture.

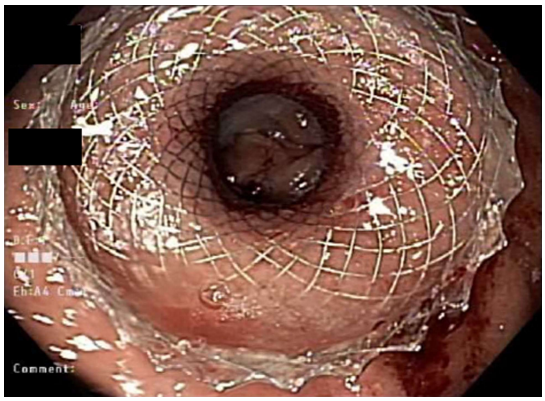

Figure 3 Dilated gastro-jejunal anastomotic stricture with visible jejunal lumen.

incisional therapy[13] and fcSEMS. The fcSEMS are not ideal due to the high rate of adverse events including intolerance, stent migration and recurrence of symptoms after stent removal[14]. LAMS were originally FDA approved for draining pancreatic fluid collections[15] but case reports/series of off-label use have been recently published with promising results. Gastrointestinal strictures/stenosis where LAMS has been successfully used include benign esophageal stricture, benign gastric outlet obstruction[16], malignant duodenal stricture, colorectal anastomotic stricture[17] and GJ anastomotic

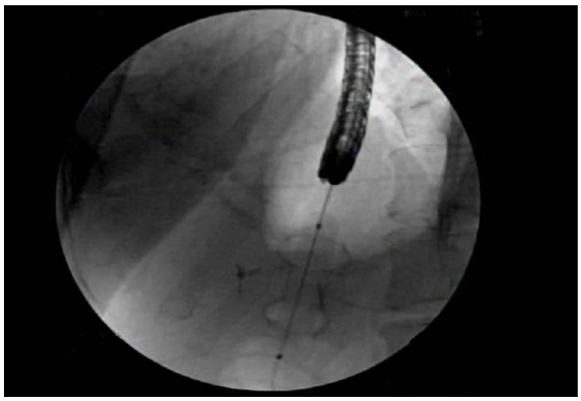

Figure 4 Confirmation of lumen apposing metal stent with fluoroscopic guidance.

stricture[18]. Bazerbachi *et al*[19] published a multi-center retrospective analysis of 49 patients who underwent 56 LAMS placement procedures for benign gastrointestinal luminal strictures, 77.6% of these patients had anastomotic strictures with 34.7% (17/49) being gastro-jejunal. 36.4% LAMS placed at anastomotic strictures required re-intervention and rate of migration for upper gastrointestinal strictures was 11.1%.

In our case we describe an off-label use of LAMS for GJ anastomotic stricture as a result of RYGB. LAMS was utilized here due to stricture caused by ulceration induced stenosis and not purely "anastomotic stricture", there was fibrosis from multiple prior dilation attempts. In contrast to conventional fcSEMS, the LAMS is shorter, smaller and its novel dumbbell shape design prevents leakage and migration due to 24 mm anchoring flanges. The stent is deployed with or without fluoroscopic guidance and this is a TTS device. Using conventional stents such as fcSEMS have a higher chance of migration despite using clip fasteners with higher rate of adverse events including ulceration and perforation. The inflation of CRE balloon inside Axios stent causes shortening as with fcSEMS, however due to novel dumbbell design the risk of migration while dilating the stricture through LAMS is very low. The manufacturer recommendation on LAMS duration for cystogastrostomy is four weeks. For off-label use commonly chosen duration is three months[16,17], we intend to keep it in for six months for maximal effect and to prevent stricture recurrence/stent replacement.

Recently published literature has suggested safety and efficacy of LAMS for management of GJ anastomotic strictures and this stent provides us with an alternative to fcSEMS. In our case LAMS was successful in controlling patient's symptoms without any adverse events. Future randomized controlled trials are warranted to compare the safety, efficacy and cost effectiveness of more expensive LAMS to conventional fcSEMS.

ARTICLE HIGHLIGHTS

Case characteristics

Our patient's main reported symptoms were weakness, fatigue and a 50-pound

weight loss.

Clinical diagnosis
On esophagogastroduodenoscopy (EGD) patient was found to have a gastro-jejunal (GJ) anastomotic stricture.

Differential diagnosis
A careful endoscopic evaluation is necessary to exclude alternative diagnosis such as marginal ulcer and gastro-gastric fistula which can present with similar symptoms.

Laboratory diagnosis
Main laboratory testing for GJ anastomotic stricture involves checking for *Helicobacter Pylori* through hydrogen breath test, serology, stool antigen test or microscopic examination of obtained tissue during EGD.

Imaging diagnosis
No imaging techniques were used in diagnosis and management of this case though an upper gastrointestinal series can be performed to diagnosis GJ anastomotic stricture/stenosis.

Pathological diagnosis
No *Helicobacter pylori* organisms were found on microscopic examination of specimens obtained during EGD.

Treatment
Lumen apposing metal stent (LAMS) was deployed in GJ anastomotic stricture during EGD while patient was continued on daily proton pump inhibitor orally.

Term explanation
The term "Hydrogen-potassium ATPase inhibitor" mentioned in this case report is more commonly known as "proton pump inhibitor".

Experiences and lessons
The newer LAMS is a safe and effective option for management of GJ anastomotic stricture and provides us with an alternative to fully covered self-expanding metal stent.

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CASE REPORT

Gastric endoscopic submucosal dissection *via* gastrostoma before the second operation for esophageal perforation: A case report

Takuma Sasaki, Masaya Uesato, Takumi Ohta, Kentarou Murakami, Akira Nakano, Hisahiro Matsubara

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Author contributions: Sasaki T and Uesato M wrote the manuscript; Sasaki T, Uesato M, Ohta T, Murakami K and Nakano A diagnosed and treated the patient; all authors discussed the results and commented on the manuscript.

Informed consent statement: The patient involved in this study gave his written informed consent authorizing the use and disclosure of his protected health information.

Conflict-of-interest statement: The authors state that they have no conflicts of interest regarding this case report.

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Abstract

A 69-year-old man with advanced esophageal cancer and 2 early gastric cancers received chemoradiotherapy and was scheduled to undergo subtotal esophagectomy after gastric endoscopic submucosal dissection (ESD). However, left lower esophageal perforation induced by vomiting suddenly occurred, and he urgently underwent esophago-proximal gastrectomy and gastrostomy without reconstruction. The resected specimen showed a complete response of pretreatment for the esophageal cancer and radical resection of one gastric cancer. Radical resection of the other gastric lesion was necessary before reconstruction. The fistula of gastrostoma was gradually dilated from 6.7 to 9.3 mm in order to pass the endoscope. At nine months after emergent operation, gastric ESD was performed *via* only the gastrostoma. A hemoclip with thread was attached to the specimen, and the thread was pulled out of the gastrostoma. The specimen was able to be removed *en bloc*, resulting in radical resection. Gastric tube reconstruction through the posterior sternal route was performed at six months after the ESD. He has not developed recurrence of the esophageal or gastric cancer in the two years since the emergent operation.

Key words: Gastric cancer; Endoscopic submucosal dissection; Gastrostomy; Gastrostoma

Core tip: Gastric endoscopic submucosal dissection (ESD), which is a useful and minimally invasive procedure for early gastric cancer, is usually performed through the mouth. This patient's stomach had a gastrostoma that was not connected to the mouth after surgery for esophageal perforation. The fistula of the gastrostoma was dilated in order to pass the endoscope. ESD for the early gastric cancer was performed *via* the gastrostoma. The specimen was able to be removed *en bloc*, and the residual stomach was able to be used for reconstruction. We herein report a unique gastric ESD technique using a gastrostoma.

Sasaki T, Uesato M, Ohta T, Murakami K, Nakano A, Matsubara H. Gastric endoscopic submucosal dissection *via* gastrostoma before the second operation for esophageal perforation: A case report. *World J Gastrointest Endosc* 2018; 10(6): 121-124 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i6/121.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i6.121

INTRODUCTION

Endoscopic submucosal dissection (ESD) is a useful, minimally invasive procedure that is used in the management of early gastric cancer[1,2]. The insertion route of the endoscope is usually the oral route. We herein report a unique ESD technique using a gastrostoma in a patient with early gastric cancer without an esophagus.

CASE REPORT

A 69-year-old man with middle thoracic esophageal cancer [T4b (trachea) N2 M0 StageⅢC] and 2 gastric cancers (T1aN0M0 StageⅠA, T1bN0M0 StageaⅠA) received chemoradiotherapy and was scheduled to undergo subtotal esophagectomy after gastric ESD. However, left lower esophageal perforation induced by vomiting suddenly occurred, and he urgently underwent esophago-proximal gastrectomy and gastrostomy without reconstruction (Figure 1). The resected specimen showed a complete response to pretreatment of the esophageal cancer and radical resection of one gastric cancer. Radical resection of the other gastric lesion was necessary before reconstruction of the gastric tube. The fistula of gastrostoma was gradually dilated from 6.7 to 9.3 mm using a urethral balloon catheter in order to pass the endoscope (GIF-Q260J; Olympus, Tokyo, Japan) after 4 wk as an outpatient.

At nine months after emergent operation, gastric ESD was performed through only the gastrostoma. ESD was performed with the patient awake. The gastric lesion was located at the middle posterior wall (Figure 2A), so the patient was placed in the supine position. Just after the insertion of the scope into the stomach, Funada-type gastric wall fixation (Create Medic, Tokyo, Japan) was performed at two opposite points (Figure 2B). Marking was performed around the boundary of the lesion using a needle knife. A sufficient amount of glycerol solution was injected into the submucosal layer. After making a small incision at the anal side, we connected the incision from the anal side to the surrounding lesion using an IT Knife2 (Olympus). We felt dissection to be difficult due to the large amount of vessels and fibrosis in the submucosal layer. A hemoclip (Olympus) with thread was attached to the specimen, and the thread was pulled *via* the gastrostoma (Figure 2C). The specimen was able to be removed *en bloc* in seven hours, showing radical resection pathologically (Figure 3). Gastric tube reconstruction through the posterior sternal route was performed at six months after ESD. He has not developed recurrence of esophageal and gastric cancer in the two years since the emergent operation.

DISCUSSION

ESD is a useful, minimally invasive procedure that is used in the management of early gastric cancer[1,2]. ESD is also actively performed for cases of residual gastric cancer, since this disease is generally considered to be difficult to treat effectively. The insertion route of the endoscope is usually the oral route. However, we herein report a unique ESD technique using a gastrostoma in a patient with early residual gastric cancer without an esophagus.

Five cases of gastric ESD performed in combination *via* routes other than the mouth have been reported[3-7] (Table 1). Among them, two reports of animal experiments involved gastric ESD *via* the mouth using a percutaneous endoscopic gastrostomy (PEG) device[6,7]. All five of these reports used a gastrostoma to perform endoscopic mucosal resection or ESD more easily. When reconstruction is performed in cases of esophageal cancer, the stomach is commonly used because it has an abundant blood flow[8]. Our patient scheduled to undergo reconstruction had a stomach without a connection to the mouth. Therefore, ESD had to be performed *via* only the gastrostoma.

As preparation, the fistula of the gastrostoma must be expanded to make it large enough for the endoscope to pass through. We previously reported a gradual tube dilation method before PEG for obstructive esophageal cancer[9]. This is a safe method, because it does not involve sudden expansion. While the method took longer than usual because our subject was an outpatient, we were able to expand to 9.3 mm without complications. The patient's posture during ESD was supine because to ensure the stability of the endoscope. However, the lesion at the posterior wall became invisible when bleeding occurred, and without the traction of gravity, the lesion was very difficult to dissect. We were able to resolve this issue by towing the specimen with a thread clip[10]. Of particular note, the thread attached to the clip was pulled *via* the fistula in our case. Bleeding may be substantial during ESD of a stomach isolated from the esophagus due to poor venous return. We recommend

Table 1 Cases of gastric endoscopic submucosal dissection performed in combination via routes other than the mouth

Ref.	Asano *et al*[3]	Tokumo *et al*[4]	Nishiwaki *et al*[5]	Delius *et al*[6]	Storm *et al*[7]	Sasaki
Year	1993	1997	2005	2008	2016	2018
EMR/ESD	EMR	EMR	ESD	ESD	ESD	ESD
Subject	Human	Human	Human	Pig	Pig	Human
Number	1	10	2	10	3	1
Use of an oral endoscope	Traction	EMR	ESD	ESD	ESD	None
Use of a gastrostoma	EMR	Traction	Auxiliary endoscope	Traction	Traction	ESD and Traction
Diameter of the gastrostoma (mm)	8	2.6	8	2.5	10, 16	9.3
Period from PEG to EMR/ESD	3 wk	Immediate	3 wk	Immediate	Immediate	7 wk[1]
Gastropexy	Used	Used	None	None	None	Used

[1]This period was required to expand the fistula diameter from 6.7 to 9.3 mm. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; PEG: Percutaneous endoscopic gastrostomy.

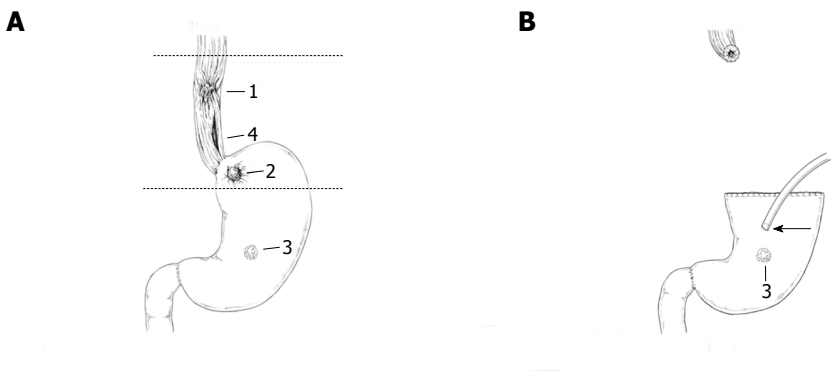

Figure 1 Schematic illustration of esophagectomy. A: This schematic illustration shows the middle thoracic esophageal cancer (1T4b), two gastric cancers (2T1b,3T1a), esophageal perforation (4) and the cutting line of the emergent operation (dotted line); B: After the emergent operation, one gastric cancer (3) remained at the middle posterior wall with the gastrostoma at the anterior wall (arrow).

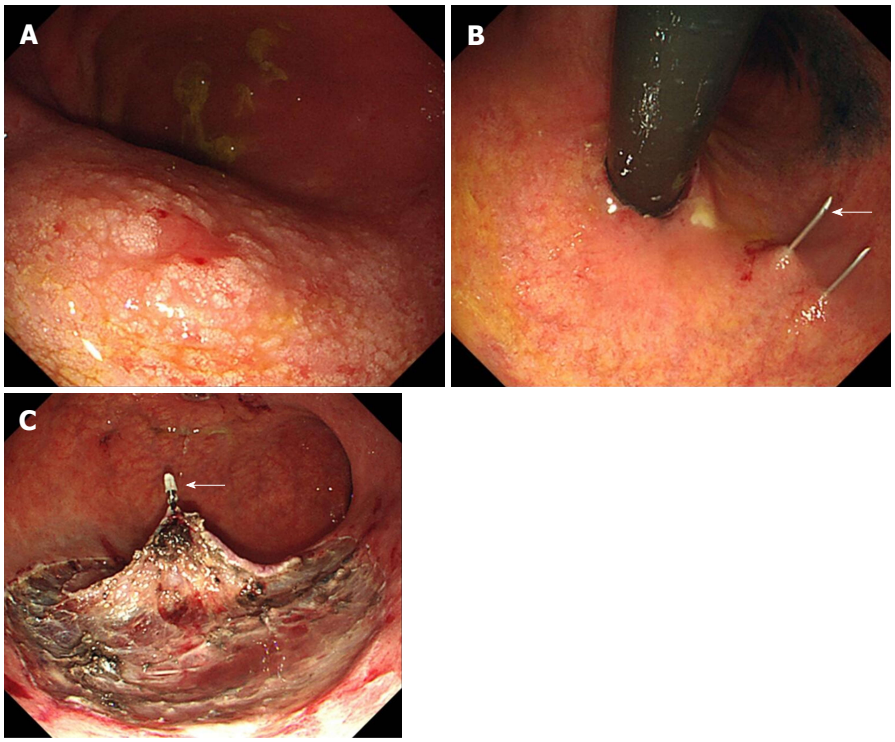

Figure 2 Results of gastric endoscopic submucosal dissection. A: The remnant gastric lesion located at the middle posterior wall showed a mucosal cancer lesion about 10 mm in diameter; B: Just after the insertion of the scope into the stomach, Funada-type gastric wall fixation (arrow) (Create Medic, Tokyo, Japan) was performed at two opposite sites; C: A hemoclip (Olympus, Tokyo, Japan) with thread (arrow) was attached to the specimen, and the thread was pulled *via* the gastrostoma.

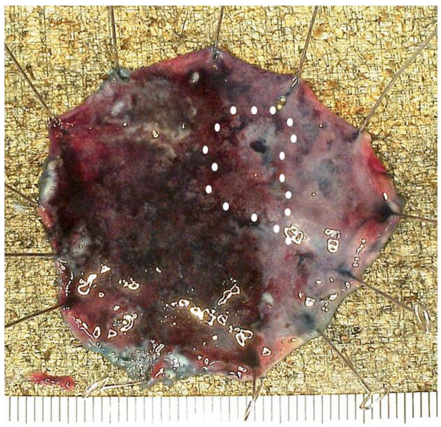

Figure 3 Gross appearance of the resected gastric mucosa is shown. A superficial depressed tumor measuring 14 mm × 10 mm (white dot) was observed macroscopically.

frequent hemostasis to ensure safe ESD. Regarding the gastric wall fixation, if it is necessary to perform ESD without a PEG device, the Funada-type fixation should be performed to ensure safety.

In conclusion, we successfully performed gastric ESD *via* only the fistula of a gastrostoma. To ensure success, the gradual tube dilation of the fistula, traction with a hemoclip and thread through the gastrostoma and frequent hemostasis should be considered.

ARTICLE HIGHLIGHTS

Case characteristics

A 69-year-old man with advanced esophageal cancer and 2 early gastric cancers received chemoradiotherapy and he was scheduled to undergo subtotal esophagectomy after gastric endoscopic submucosal dissection. However, left lower esophageal perforation suddenly occurred, and he urgently underwent esophago-proximal gastrectomy and gastrostomy.

Clinical diagnosis

The patient had one early cancer in the residual stomach without a connection to the esophagus.

Imaging diagnosis

The only *via*ble approach to the residual stomach was the gastrostoma.

Treatment

The fistula of the gastrostoma was gradually dilated to allow the endoscope to pass through. Gastric endoscopic submucosal dissection was performed *via* only the gastrostoma. A hemoclip with thread was attached to the specimen, and the thread was pulled *via* the gastrostoma. The specimen was able to be removed *en bloc*. Gastric tube reconstruction was performed.

Experiences and lessons

We successfully performed gastric endoscopic submucosal dissection through only the fistula of a gastrostoma. To ensure safety and success, the gradual tube dilation of fistula, traction with a hemoclip and thread through the gastrostoma and frequent hemostasis should be considered.

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CASE REPORT

Diagnosis of intraductal papillary mucinous neoplasm using endoscopic ultrasound guided microbiopsies: A case report

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Author contributions: Rift CV performed the microscopic evaluation and NGS-analysis of the tissue, and wrote the manuscript in equal collaboration with Kovacevic B, who also obtained written consent from the patient; Hasselby JP and Toxværd A provided laboratory and facilities as well as assistance in the tissue analysis; Klausen P coordinated and provided the collection of the tissue; Vilmann P performed the EUS and obtained the microbiopsy; Kalaitzakis E, Karstensen JG, Plougmann J and Hansen CP were involved in editing the manuscript.

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Abstract

Pancreatic cysts are increasingly diagnosed due to expanding use of cross-sectional imaging, but current diagnostic modalities have limited diagnostic accuracy. Recently, a novel through-the-needle microbiopsy forceps has become available, offering the possibility of obtaining cyst-wall biopsies. We present a case of 41-year-old male with chronic pancreatitis and a 2-cm pancreatic cyst, initially considered a pseudocyst. Subsequently, endoscopic ultrasou-

nd guided microbiopsies were successfully obtained, which surprisingly revealed an intraductal papillary mucinous neoplasm of mixed subtype with low grade dysplasia. In conclusion, obtaining biopsies from the wall of the pancreatic cystic lesions with this novel instrument is feasible and, as demonstrated in this case, can possibly alter the clinical outcome. Microbiopsies offered enough cellular material, allowing supplemental gene mutation analysis, which combined with other modalities could lead to a more individual approach when treating pancreatic cysts. However, prospective studies are warranted before routine clinical implementation.

Key words: Microbiopsy; Pancreatic cyst; Endoscopic ultrasound-fine needle aspiration; Intraductal papillary mucinous neoplasm; Chronic pancreatitis

Core tip: We present a case of a pancreatic cyst with an initial diagnosis of a pseudocyst altered to an intraductal papillary mucinous neoplasm of mixed type with low grade dysplasia through the use of endoscopic ultrasound guided microbiopsies obtained with a novel through-the-needle microbiopsy forceps, rendering the possibility of microscopic evaluation and genetic analysis of the cyst.

Rift CV, Kovacevic B, Karstensen JG, Plougmann J, Klausen P, Toxværd A, Kalaitzakis E, Hansen CP, Hasselby JP, Vilmann P. Diagnosis of intraductal papillary mucinous neoplasm using endoscopic ultrasound guided microbiopsies: A case report. *World J Gastrointest Endosc* 2018; 10(7): 125-129 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i7/125.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i7.125

INTRODUCTION

Pancreatic cysts are increasingly diagnosed due to expanding use of cross-sectional imaging[1]. Whereas some of the cysts are completely benign, others are considered malignant or pre-malignant [intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasia (MCN)]. Endoscopic ultrasound (EUS) represents a cornerstone in preoperative diagnosis of these cysts, but cannot be used as a stand-alone modality[2]. EUS-guided fine needle aspiration (EUS-FNA) cytology has a relatively high specificity of 90.6%, but low sensitivity (64.8%), which is mainly due to absence of sufficient cellular material in the cyst fluid for a definite diagnosis[3,4]. A novel through-the-needle microbiopsy forceps (Moray™, US Endoscopy, Mentor, United States) has recently become available, offering a possibility of obtaining cyst-wall biopsies[5].

CASE REPORT

A 41-year-old male, with substantial alcohol abuse and chronic pancreatitis, was referred to the gastroenterological department due to long-lasting abdominal pain and a 2 cm cyst located in the body of the pancreas. After an initial EUS and subsequent multi-disciplinary conference, the lesion was classified as a pseudocyst, which was considered asymptomatic due to its small size. Due to persisting symptoms and the fact that the cyst had not decreased in size, another EUS was performed six months later, and the cyst was punctured through the stomach wall with a 19 Gauge needle (ExpectFlex™, Boston Scientific, Marlborough, United States). Subsequently, the Moray™ micro-biopsy forceps was introduced though the needle and two microbiopsies from the cyst wall were obtained (Figure 1). Lastly, the cyst was drained and the fluid was sent for carcinoembryonic antigen (CEA) analysis. The total procedural time was 12 min and no adverse events were observed. Cyst-fluid CEA value was 12 μg/L. The microbiopsies were fixed in formalin and processed for histology and immunohistochemical (IHC) staining for MUC1, MUC2, MUC6, MUC5AC, and CDX2. Surprisingly, the biopsies revealed fragments of mucinous epithelium with goblet cells. The nuclei where found basally oriented with focally distinct nucleoli. No mitoses where present. The epithelial cells where positive for MUC1 and MUC5AC and focally positive for CDX2 and MUC2. The underlying stroma consisted of fibroblasts and collagen tissue without any bleeding. Conclusively, the features seen on the biopsies were consistent with IPMN of mixed type: pancreatobiliary and intestinal subtype. Subsequently, the biopsies were examined by next generation sequencing (NGS) using the Ion AmpliSeq Cancer Hotspot Panel v2 (Life Technologies, Carlsbad, United States). The multigene panel explores selected regions of 50 cancer-associated genes, among others *KRAS, GNAS, CDKN2A* and *SMAD4* genes. We were able to obtain adequate and fine quality DNA for NGS analysis, which was performed with approximately 2 million mapped reads and a uniformity of about 97%. No mutations were found. The patient was planned for follow-up in 6 mo.

DISCUSSION

Obtaining biopsies from the wall of the pancreatic cystic lesions with the use of a through-the-needle microbiopsy forceps seems feasible. The jaws of the forceps with an opening width of 4.3 mm are easily identified on EUS and as such can be guided to obtain biopsies from different areas of interest (Figure 1). Needle-based confocal laser endomicroscopy (nCLE) is a comparative technique, also used in conjunction with a 19G needle. Several studies have shown that the procedure has a high specificity (close to 100%), but the rather low sensitivity of approximately 60% for predefined epithelial structures[6,7]. There are currently no data on the efficacy of nCLE to predict dysplasia. On the other hand, acquirement of tissue samples with the use of the microbiopsy forceps enables further diagnostic possibilities (*e.g.*, immunohistochemistry, next-generation sequencing). Conventional EUS-FNA

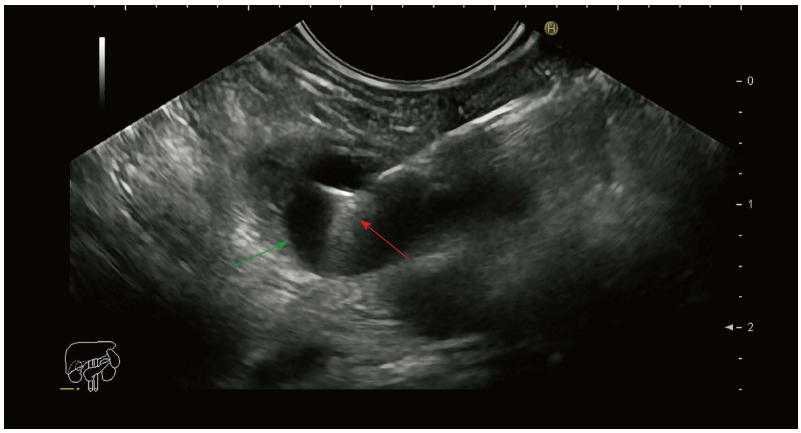

Figure 1 Endoscopic ultrasound image of the pancreatic cyst punctured with a 19 gauge needle with a microbiopsy forceps. Green arrow: Cyst wall; Red arrow: Microbiopsy forceps.

is considered safe with a low associated risk of hemorrhage (0.69%)[8]. Furthermore, most cases of intracystic hemorrhage resolve spontaneously and do not require further management. Microbiopsy forceps procedure appears safe with no adverse events reported, although the use has been limited[9,10]. This novel instrument requires the use of a larger 19G needle, which possibly is associated with a higher risk of adverse events[8]. This should be however seen in the light of an increased diagnostic yield. Obtaining samples from lesions in the head of the pancreas or the uncinate process can be technically challenging with a 19G needle, especially when the forceps is introduced. However, the procedure seems to be associated with rather high technical success rates[9,10].

In this case, the biopsies offered adequate tissue for histology and IHC staining and secured a diagnosis of IPMN with low grade dysplasia. The lesion was presumably of a mixed type: Pancreatobiliary subtype due to positivity in MUC1 and MUC5AC stains and the intestinal subtype due to positivity in CDX2 and MUC2 stains with the presence of goblet cells (Figure 2). When compared to gastric and oncocytic subtypes, pancreatobiliary and intestinal subtypes are associated with progression to high grade dysplasia and invasive carcinoma[11]. Previously, surgical series have shown that the clinical behavior of an invasive carcinoma derived from the pancreatobiliary type IPMN has a significantly poorer prognosis than those associated with the intestinal subtype[12,13]. On the other hand no mutations in genes controlling cell cycle and arrest (*KRAS, CDKN2A*, *SMAD4*, *PIK3CA*) or DNA repair (*TP53*) were found, the presence of which would also have rendered a poorer prognosis[14]. Even though GNAS and concomitant KRAS mutations is considered specific of IPMN, the sensitivity is low[15], as to why a negative result of the NGS analysis does not rule out underlying pathology as seen in this case.

As a new diagnostic tool, the Moray™ microbiopsy forceps offers new diagnostic challenges for both endoscopists and pathologists, one of these being the issue of contamination of the tissue obtained by the microbiopsy forceps during the procedure. As EUS-guided FNA-needle either passes through the duodenum or the stomach, contamination with gastric or duodenal epithelium is possible and commonly seen in cytology specimens. In this case the cyst was punctured through the stomach wall, indicating the presence of goblet cells in the microbiopsy is not due to contamination from the duodenum. The endoscopist should therefore always note the location of the echo-endoscope when puncturing the lesion. Nuclear atypia such as high nuclear to cytoplasmic ratio, irregular nuclear membranes, and prominent nucleoli are also helpful characteristics for the pathologist to distinguish contamination from neoplasia in cytology specimens[16] and is by our experience applicable in the interpretation of microbiopsies.

Although calcification of the pancreas is usually considered to be one of the signs of chronic pancreatitis, it can also be associated with IPMN[17,18]. The exact pathogenic mechanism is unknown, but it is believed that extensive mucus production causes obstructing pancreatitis and formation of calcifications, the presence of which might lead to diagnostic confusion[19]. In the case mentioned above, the microbiopsy forceps has not only contributed to additional diagnostic information, but has also altered the initial diagnosis from a benign pseudocyst to a side branch IPMN with low grade dysplasia, causing a significant change in the treatment. Taken the patient's history, EUS characteristics with no dilated pancreatic duct, and low CEA-concentration in the cyst fluid into account, without the micro-biopsies, no further follow-up would be instigated. After a multidisciplinary conference, the patient was instead referred for a surveillance program. Even though the use of the microbiopsy forceps seems feasible, at present there is only limited clinical experience with this instrument and further studies are warranted in order to determine its diagnostic value in pancreatic cysts.

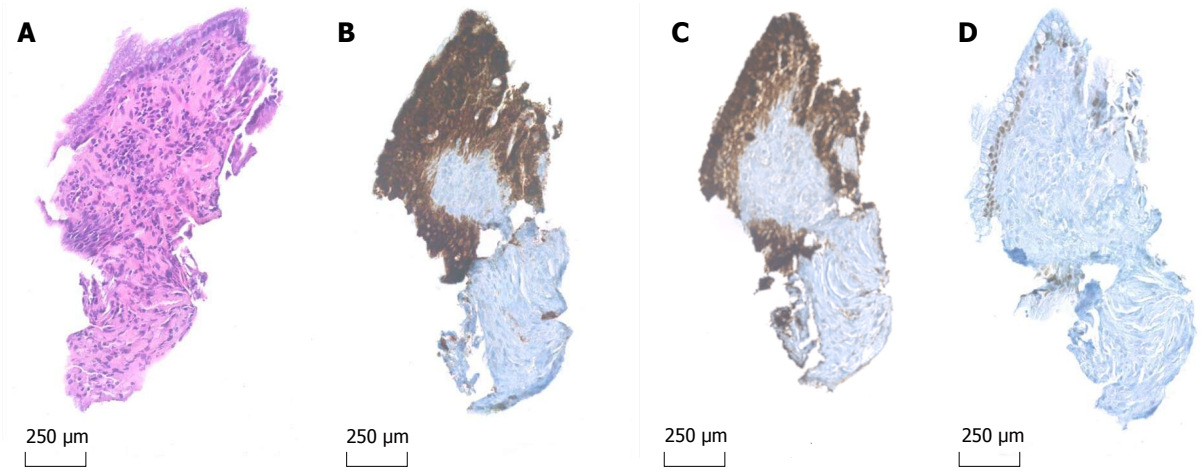

Figure 2 Microbiopsy specimen 20 × original magnification. A: Hematoxylin and eosin stain (A) reveals fragments of mucinous epithelium with goblet cells and basally oriented nuclei; B-D: The epithelial cells are immunohistochemical positive for MUC1 (B), MUC5AC (C) and focal positive for CDX2 (D), indicative of IPMN of mixed type: Pancreatobiliary and intestinal.

ARTICLE HIGHLIGHTS

Case characteristics

A 41-year-old male with chronic pancreatitis and abdominal pain.

Clinical diagnosis

A 2 cm cyst located in the body of the pancreas.

Differential diagnosis

Mucinous cyst.

Laboratory diagnosis

A low level of cyst fluid carcinoembryonic antigen.

Imaging diagnosis

Endoscopic ultrasound suggested a pseudocyst.

Pathological diagnosis

Microbiopsies yielded the diagnosis of an intraductal papillary mucinous neoplasm of mixed type with low grade dysplasia.

Treatment

Clinical follow-up.

Related reports

Pancreatic cysts are increasingly diagnosed due to expanding use of cross-sectional imaging. Endoscopic ultrasound cannot be used as a stand-alone modality.

Term explanation

The wall of a pseudocyst has no epithelial lining, as to why presence of epithelial cells excludes the diagnosis of a pseudocyst.

Experiences and lessons

Obtaining microbiopsies from the wall of a pancreatic cyst and subsequently performing microscopic evaluation as well as NGS-analysis has to our best knowledge not previously been reported. The technique seems feasible and, as demonstrated in this case, can possibly alter the clinical outcome.

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SYSTEMATIC REVIEWS

Comparison between endoscopic sphincterotomy *vs* endoscopic sphincterotomy associated with balloon dilation for removal of bile duct stones: A systematic review and meta-analysis based on randomized controlled trials

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Author contributions: de Clemente Junior CC and Franzini TP contributed equally to the work; de Clemente Junior CC conceptualized and designed the review together with Bernardo WM; de Clemente Junior CC, Luz GO, dos Santos MEL, Marinho FRT, Coronel M and de Moura EGH carried out the analysis; de Clemente Junior CC and Sakai P drafted the initial manuscript; de Moura DTH, Cohen JM contributed to the major review changes and language; all authors reviewed and approved the final manuscript as submitted.

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Abstract

AIM

To compare gallstones removal rate and incidence of bleeding, pancreatitis, use of mechanical lithotripsy, cholangitis and perforation between isolated sphincterotomy *vs* sphincterotomy associated with balloon dilation of papilla in choledocholithiasis through the meta-analysis of randomized clinical trials.

METHODS

We conducted a systematic review according to the PRISMA guidelines. Literature search was restricted to randomized controlled trials (RCTs) on MedLine, Cochrane Library, LILACS, and EMBASE database platforms in July 2017. The manual search included references of retrieved articles. We extracted data focusing on outcomes: The primary endpoint was the stones removal rate; Secondary endpoints were rates of pancreatitis, bleeding, use of mechanical lithotripsy (ML), perforation and cholangitis.

RESULTS

Eleven RCTs with 1824 patients were included. EST was associated with more post-endoscopic retrograde cholangiopancreatography (ERCP) bleeding [FE RD-0.02, CI (-0.03, -0.00), I^2 = 33%, P = 0.05] and more need of mechanical lithotripsy in general [RE RD-0.16, CI (-0.25, -0.06), I^2 = 90%, P = 0.002] and in subgroup analysis of stones greater than 15 mm [RE RD-0.20, CI (-0.38, -0.02), I^2 = 82%, P = 0.003]. Incidence of pancreatitis [FE RD-0.01, CI (-0.03, 0.01), I^2 = 0, P = 0.36], cholangitis [FE RD-0.00, CI (-0.01, 0.01), I^2 =0, P = 0.97] and perforation [FE RD-0.01, CI (-0.01, 0.00), I^2 = 0, P = 0.23] was similar between the groups as well as similar stone removal rates in general [FE RD-0.01, CI (-0.01, 0.04), I^2 = 0, P = 0.23] and pooled analysis of stones greater than 15 mm [FE RD-0.02, CI (-0.02, 0.07), I^2 = 11%, P = 0.31].

CONCLUSION

Through meta-analysis of randomized clinical trials we found that isolated sphincterotomy was associated with more post-ERCP bleeding and more need for mechanical lithotripsy. However, there was no statistical difference in the stone removal rate between isolated sphincterotomy and sphincterotomy associated with balloon dilation in the approach to remove gallstones.

Key words: Sphincterotomy; Papillotomy; Dilation; Cholangiopancreatography; Endoscopic retrograde; Endoscopic retrograde cholangiopancreatography; Cholangiography

Core tip: Our initial motivation was to determine if there is a preferential endoscopic approach in choledocholithiasis, comparing efficacy and safety data between the two most widespread endoscopic methods, which is sphincterotomy with *vs* without large balloon dilation. Through the systematic review, it was possible to perform the meta-analysis of a large sample of patients obtained from properly conducted randomized clinical trials. We found that endoscopic sphincterotomy associated with large balloon dilation was a safer method compared to isolated sphincterotomy, since this last group carried an increased risk of post ERCP bleeding and required more frequent complementation with use of mechanical lithotripsy.

de Clemente Junior CC, Bernardo WM, Franzini TP, Luz GO, dos Santos MEL, Cohen JM, de Moura DTH, Marinho FRT, Coronel M, Sakai P, de Moura EGH. Comparison between endoscopic sphincterotomy *vs* endoscopic sphincterotomy associated with balloon dilation for removal of bile duct stones: A systematic review and meta-analysis based on randomized controlled trials. *World J Gastrointest Endosc* 2018; 10(8): 130-144 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i8/130.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i8.130

INTRODUCTION

Endoscopic sphincterotomy as well as balloon dilation of major papilla are recognized endoscopic treatment approaches to choledocholithiasis. These two techniques, however, are associated with adverse events such as bleeding, perforation and pancreatitis. Additionally, gallstones cannot be removed in approximately 5% to 10% of patients using sphincterotomy or balloon dilation alone[1].

Sphincterotomy presents high resolution rates for most cases, but in complex situations, especially regarding large stones, the resolution can become a challenge[2]. Endoscopic balloon dilation of the duodenal major papilla is part of the available arsenal for choledocholithiasis resolution, but its isolated application was practically abandoned at the present time due to the unsatisfactory results and greater risk of pancreatitis when compared to isolated sphincterotomy, restricting its indication to selected cases with high hemorrhagic risk.

Is there a preferential approach in choledocholithiasis with lower rates of adverse events while maintaining high effectiveness?

To compare stones removal rate and incidence of adverse events such as bleeding, pancreatitis, perforation, cholangitis and use of mechanical lithotripsy between isolated sphincterotomy *vs* sphincterotomy associated with balloon dilation in choledocholithiasis through the meta-analysis of randomized clinical trials.

MATERIALS AND METHODS

This systematic review was conducted according to the PRISMA Statement (Preferred Reporting Items for Systematic reviews and Meta-Analyses)[3].

Inclusion criteria were defined according to the parameters established in PICO Model: (1) Participants (P): Patients with choledocholithiasis, over 18 years old; (2) interventions (I) and comparisons (C): To compare isolated sphincterotomy (ES) *vs* sphincterotomy associated with balloon dilation (ESBD); (3) outcomes (O): Primary-Stones removal rate, Secondary: bleeding, pancreatitis, use of mechanical lithotripsy (ML), cholangitis and perforation; and (4) study design: Randomized clinical trials (RCT). There were no restrictions on language or date of publication.

Information sources
The search was performed in the electronic databases MedLine (*via* PubMed), Cochrane Library, LILACS, EMBASE, the CAPES database (Brazil), and gray/manual literature from included references of retrieved articles.

Search
The keywords used to perform the search were (Cholangiopancreatograph* OR Endoscopic Retrograde OR ERCP OR Cholangiograph*) AND (Sphincterotom* OR papillotom*), without the use of filters.

Selection of studies
The evaluation of eligibility and selection of articles was done independently and standardized by two reviewers based initially on the title and abstract. In doubtful cases the full text was consulted prior to inclusion when it was possible. Disagreements among the reviewers were resolved by consensus or with the assistance of a third author. The present study involves only randomized clinical trials comparing exclusively isolated sphincterotomy (ES) *vs* combined sphincterotomy and balloon dilation of papilla (ESBD).

Data collection process
Data extraction from selected clinical trials was performed independently by the two authors in spreadsheets until consensus was obtained on all data in case of divergence. Only published data were considered.

The variables searched were: stone removal rates, pancreatitis, cholangitis, bleeding, perforation and use of mechanical lithotripsy. The raw numbers were used for analysis.

Statistical analysis
For all outcomes, absolute risk difference was weighted by intention-to-treat analysis (ITT) and the 95%CI and $P < 0.05$ as statistically significant.

Treatment effect and heterogeneity of the studies[4] were analyzed by the method proposed by Higgins *et al*[5], called I^2, with fixed (FE) and random effects (RE), using Review Manager software version 5.3. The difference between the outcomes was calculated by the risk difference (RD), with fixed effect, for the dichotomous variables and as difference of mean for the continuous variables. Sensitivity analysis was used to attempt to identify a study with a higher likelihood of outlier publication when the heterogeneity, calculated using the chi-square test and quantified by the method proposed by Higgins *et al*[5], called I^2, was higher or equal to 50%. If this was not present the random effect was used in the analysis. For the synthesis of results, analytical graphs were generated using funnel plot and forest plot.

RESULTS
Initial search identified 4194 articles. After reviewing the title and abstracts, 4158 were excluded because they were not RCTs. Thirty six articles were fully evaluated, 25 were excluded because they were retrospective, compared to other methods or because they were systematic reviews. At the end 11 RCTs were included. A total of 1824 patients with choledocholithiasis were evaluated, of which 914 were submitted to sphincterotomy plus balloon dilation and 910 underwent isolated sphincterotomy (Figure 1).

Risk of bias
Of the 11 RCTs, none cited blinding, two presented significant differences in population in relation to some variable and one did not present complete data (Table 1).

The studies were classified by methodological quality according to the JADAD Score[6] (Table 2).

The following outcomes were analyzed according to the data presented by each study: stone removal rate, pancreatitis, bleeding, cholangitis, perforation and use of mechanical lithotripsy (Table 3).

Stone removal rate
All included studies[7-17] evaluated stone removal rate. The meta-analysis of the results (n = 1824 patients) demonstrated heterogeneity of I^2 = 54% (Figure 2). Sensitivity analysis was performed with funnel plot, which identified an outlier study (Karsenti)[15] (Figure 3). By removing it from the analysis, heterogeneity has disappeared (I^2 = 0). Considering a total of 1674 patients in this analysis, no statistical difference was observed between the two methods (Figure 4).

Stone removal rate in patients with stones greater than 15 mm
Six studies[9,11,12,14,16,17] presented data relevant to this meta-analysis, totaling a number of 484 patients, being not statistically different between the groups (Figure 5).

Pancreatitis
All included studies[7-17] evaluated the presence of post-procedure pancreatitis as an adverse event totaling 1802 patients, there was no statistical difference between the groups (Figure 6).

Bleeding
All included studies[7-17] evaluated post-procedure bleeding as an adverse event in a total of 1802 patients, there was statistical difference between the groups, being ESBD a protective factor (P = 0.05) (Figure 7).

Cholangitis
All included studies[7-17] evaluated the presence of post-procedure cholangitis as an adverse event in a total of 1802 patients, there was no statistical difference between the groups (Figure 8).

Use of mechanical lithotripsy in general
All included studies[7-17] evaluated the use of mechani-

Table 1 Descriptive table of bias in therapeutic studies

Study	Heo, 2007	Kim TH, 2009	Kim HG, 2009	Hong, 2009	Teoh, 2013	Li, 2013	Qian, 2013	Guo, 2015	Takeshi, 2015	Karsenti, 2017	Chu, 2016
Question	ESBD *vs* ES	ESBD *vs* ES	ESBD *vs* ES	ESBD *vs* ES	ESBD *vs* ES	ESBD *vs* ES	ESBD *vs* ES	ESBD *vs* ES	ESBD *vs* ES	ESBD *vs* ES	ESBD *vs* ES
Randomization	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Allocation	Yes	Do not quote	Do not quote	Do not quote	Yes	Yes	Yes	Do not quote	Do not quote	Yes	Yes
Blindness	No	No	No	No	No	No	No	No	No	No	No
Losses	No	No	No	Do not quote	No	Yes	Yes	No	No	No	Yes
Prognosis	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Statistical difference in the population with the highest rate of periampular diverticulum in the ESBD group	Homogeneous	Age significantly higher in ES population compared with ESBD population	Homogeneous
Outcomes	Extraction rate of stones, bleeding, pancreatitis, perforation, use of ML and cholangitis	Extraction rate of stones, bleeding, pancreatitis, perforation, use of ML	Extraction rate of stones, bleeding, pancreatitis, perforation, use of ML and cholangitis	Extraction rate of stones, bleeding, pancreatitis, perforation and cholangitis	Extraction rate of stones, perforation, use of ML and cholangitis	Extraction rate of stones, perforation, use of ML and cholangitis	Extraction rate of stones, perforation, use of ML, cholangitis. And recurrence of choledocolithiasis	Extraction rate of stones, bleeding, pancreatitis, perforation, use of ML and cholangitis	Extraction rate of stones, bleeding, perforation, use of ML and cholangitis	Extraction rate of stones, bleeding, pancreatitis, perforation	Extraction rate of stones, bleeding, pancreatitis, perforation, use of ML and cholangitis
ITT	Yes	Yes	Yes	Yes	Yes	Modified ITT analysis	Yes	Yes	Yes	Yes	No

ML: Mechanical lithotripsy; ITT: Intention-to-treat analysis.

cal lithotripsy, totaling a number of 1802 patients. Heterogeneity of 90% (Figure 9) was observed, then sensitivity analysis was performed with funnel plot, which did not identify only one outlier study (Figure 10), therefore it was assumed true heterogeneity, and then the random effect was used in the evaluation (Figure 11). There was a statistically significant difference between the groups with ES associated with balloon dilation (ESBD) as a protective factor against need for ML (P = 0.002).

Use of mechanical lithotripsy in patients with stones greater than 15 mm

From available data it was possible to extract and to analyze a subgroup with patients who had stones greater than or equal to 15 mm. Six studies[9,11,12,14,16,17] presented data relevant to this meta-analysis totaling 432 patients. Heterogeneity of 82% (Figure 12) was observed, then sensitivity analysis was performed with funnel plot, which did not identify only one outlier study (Figure 13), therefore it was assumed true heterogeneity, and then the random effect was used in the evaluation (Figure 14). There was a statistically significant difference between the groups with ES associated with balloon dilation (ESBD) as a protective factor against need for ML (P = 0.03).

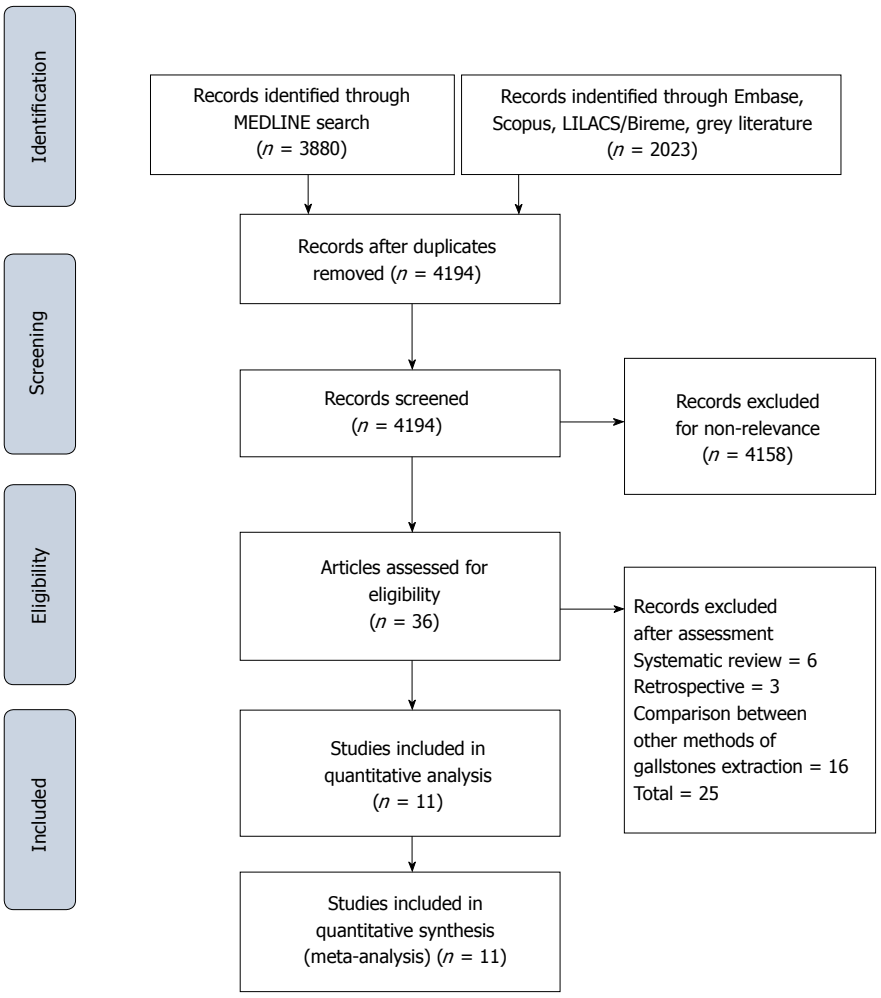

Figure 1 Flow diagram of studies included in the meta-analysis.

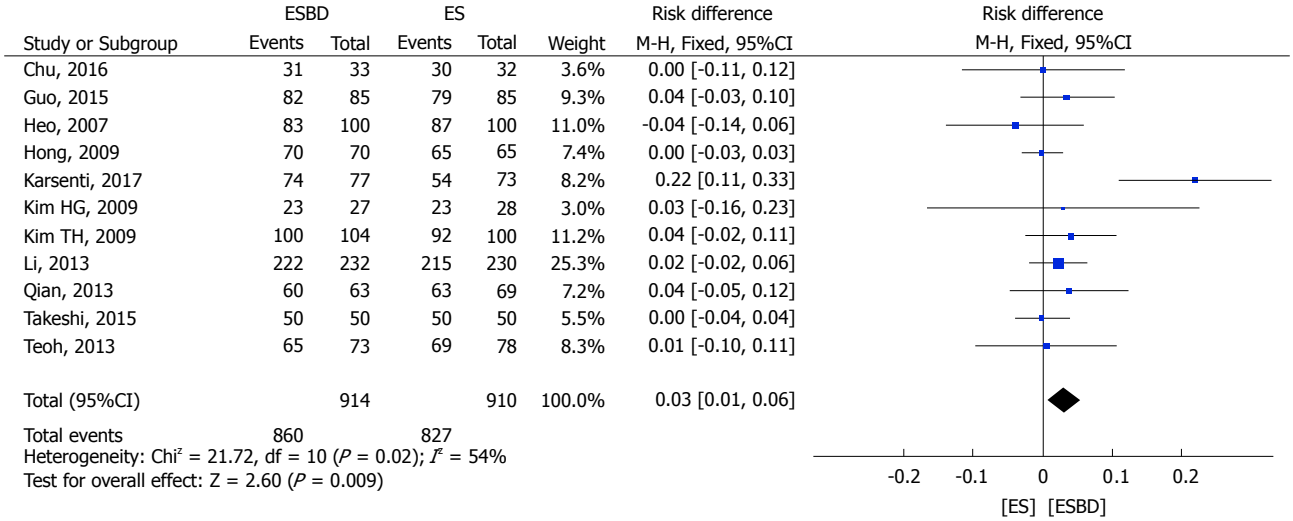

Figure 2 Stone removal rate forest plot enrolling all studies.

Perforation

All included studies[7-17] evaluated the presence of perforation during the procedure as an adverse event in a total number of 1802 patients, there was no statistical

Table 2 JADAD score

	R	aR	B	aB	W	Total
Chu, 2016	1	1	0	0	1	3
Karsenti, 2017	1	1	0	0	1	3
Guo, 2015	1	0	0	0	1	2
Takeshi, 2015	1	-	0	0	1	2
Teoh, 2013	1	1	0	0	1	3
Qian, 2013	1	1	0	0	1	3
Li, 2013	1	1	0	0	1	3
Kim HG, 2009	1	0	0	0	1	2
Kim TH, 2009	1	0	0	0	1	2
Hong, 2009	1	-	0	0	1	2
Heo, 2007	1	1	0	0	1	3

R: Randomization; Ar: appropriate randomization; B: Blinding; aB: Appropriate Blinding; W: Withdrawals.

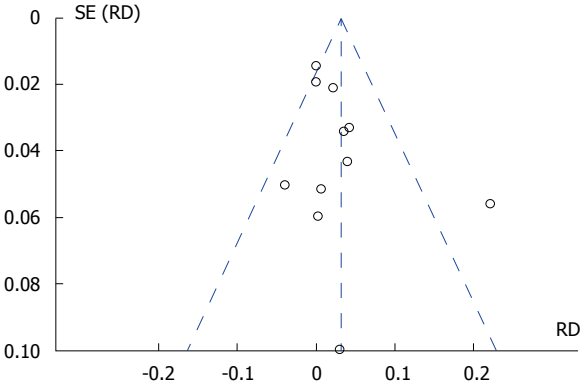

Figure 3 Funnel plot showing one outlier study in the stone removal rate analysis.

difference between the groups (Figure 15).

DISCUSSION

Eleven RCTs with a total of 1824 patients were included in this systematic review and meta-analysis. Regarding efficacy there was no statistical difference in primary outcome stipulated as stone removal rate. The analysis from data of included studies showed statistical difference in safety between the methods since incidence of post-ERCP bleeding was higher in EST group.

Systematic reviews of randomized clinical trials on choledocholithiasis treatment methods in the past compared isolated sphincterotomy *vs* isolated dilation[18-20].

Feng *et al*[18] found a lower mechanical lithotripsy (ML) use and a lower bleeding frequency in isolated dilation group in the general analysis.

Liu *et al*[19], by including non-randomized and randomized studies, found in his meta-analysis that isolated dilation caused more pancreatitis after ERCP and increased need for ML, whereas isolated ES had lower rates of bleeding. Jin *et al*[20] identified lower ML use in the group submitted to isolated dilation both in general and subgroup of gallstones larger than 15 mm analysis.

In recent years it is remarkable in the literature a greater interest in comparing the ESBD *vs* ES methods by randomized clinical trials or by retrospective studies and even by systematic reviews. An important landmark in this sense was reported by Ersoz *et al*[21], who performed the first attempt to combine sphincterotomy and large balloon dilation to extract difficult bile duct stones in order to minimize adverse events rate. This technique successfully removed the stones in 89% of cases with disproportion between gallstones and distal bile duct, in addition to 95% in cases with giant stones, with adverse event rates significantly lower than in previous studies that prioritized one technique over the other without associating them.

Posterior studies have revealed the promising effect of sphincterotomy associated with balloon dilation of papilla in choledocholithiasis[22-26]. Inversely proportional is the number of published articles comparing single dilation to any other method.

Liu *et al*[22] analyzed non-randomized and randomized clinical trials comparing sphincterotomy associated with balloon dilation (ESBD) *vs* isolated sphincterotomy (ES) identifying in a separated analysis into subgroups a lower occurrence of bleeding in the ESBD from RCT analysis (n = 355) and in the non-randomized clinical trials (NRCT) the group of patients retrospectively submitted to ESBD obtained a higher success in the gallstones removal rate, as well as a lower need for ML and a lower rate of adverse events in general. In this same subgroup of NRCTs, patients were sub grouped according to presence of gallstones greater than 15 mm, reaching statistical difference in the lower use of ML when compared to ES group.

A meta-analysis of Yang *et al*[23] demonstrated that the ESBD group had a lower rate of adverse events and a lower use of ML when compared to the ES group, which was more evident in the subgroup with patients with gallstones greater than 15 mm. It is important to note that this review included among the selected papers the clinical trial of Stefanidis that compares ESBD *vs* ES plus ML, not having an ES only arm in this study.

Stefanidis *et al*[24] and Xu *et al*[25] included four randomized clinical trials involving 496 patients. In order to avoid the possible inclusion bias of the aforementioned Stefanidis study, which was also included in his selection and evaluates different methods from the other three RCTs contained in the review, Xu *et al*[25] chose to separate the analysis of this trial, losing in some meta-analysis its 90 patients. By doing so, he obtained statistically significant difference concluding that ESBD reduces the use of ML in patients with stones greater than 15 mm. After an isolated analysis of the study of Stefanidis, Xu concludes that there is statistical difference in the sample obtaining a higher rate of cholangitis in patients who performed ML after ES, still citing as probable causes: trauma to the wall of the bile

Table 3 Frequency of outcomes based on systematic review

	Sphincterotomy	Sphincterotomy associated with balloon dilation	*P*
Stone removal rate	773/837 (92.3%)	786/837 (93.9%)	0.10
Stone removal rate with stones greater than 15 mm	218/240 (90.8%)	228/244 (93.4%)	0.14
Pancreatitis	48/891 (5.3%)	40/911 (4.4%)	0.16
Bleeding	31/891 (3.4%)	18/911 (1.9%)	0.02
Cholangitis	7/891 (0.78%)	7/911 (0.76%)	0.48
Perforation	5/911 (0.54%)	0/891 (0)	0.08
Use of mechanical lithotripsy	262/910 (28.8%)	105/914 (11.5%)	< 0.00001
Use of mechanical lithotripsy with stones greater than 15 mm	115/218 (52.7%)	54/214 (25.2%)	< 0.00001

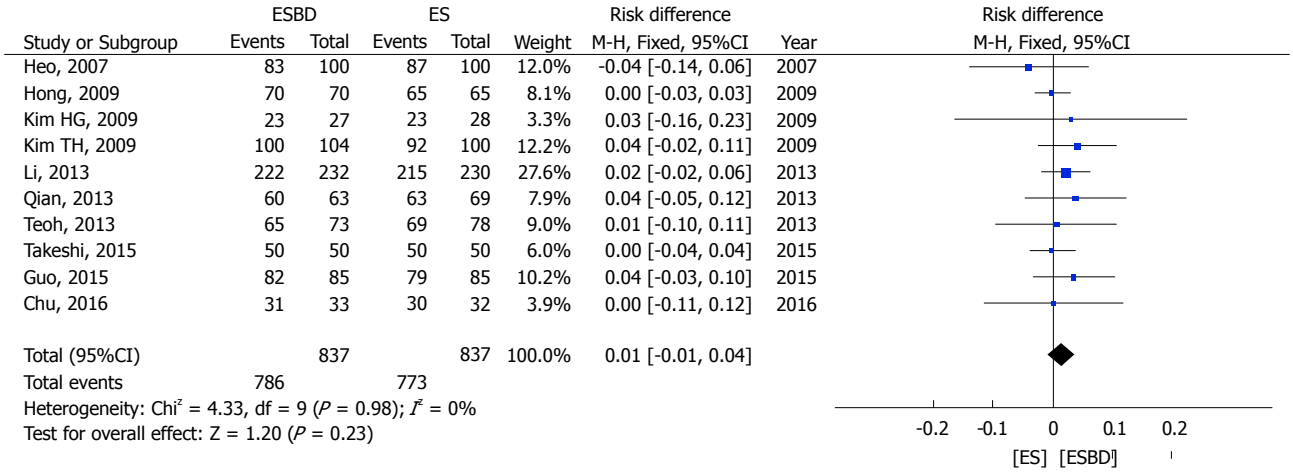

Figure 4 Stone removal rate forest plot after removing the outlier study.

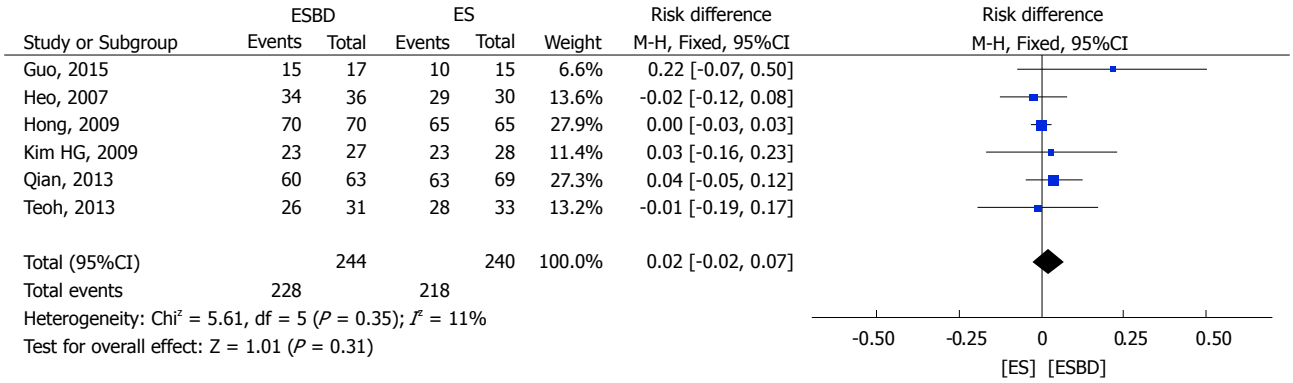

Figure 5 Forest plot of stone removal rate in patients with stones greater than 15 mm.

duct by the lithotripter wire, inadequate sphincterotomy and edema at the site of sphincterotomy.

The last meta-analysis on this topic was made by Park and published in July 2017, this analysis show that ESBD had superior efficacy to endoscopic papillary balloon dilation (EPBD) in terms of stone removal in the first endoscopic session. Mechanical lithotripsy was less frequently required in ESBD than in EPBD. Post-ERCP pancreatitis tended to be less common in ESBD and EST than in EPBD, although the difference was not statistically significant. However, ESBD and EST carried a higher risk of post-ERCP bleeding than did EPBD. The author used indirect analysis to compare the outcomes and identified significant inconsistency between direct and indirect evidence in outcomes such as post-ERCP bleeding and perforation, which was attributed to an extremely low incidence. They selected 25 trials, of which 17 compared EST *vs* balloon dilation (EPBD). Only seven articles with 1253 patients compared EST to ESBD, the two methods that our review compares, since it is not part of the current guidelines the isolated use of balloon dilation, except in selected cases of irreversible coagulopathy. Among the seven selected, Stefanidis's above-mentioned work is present[26].

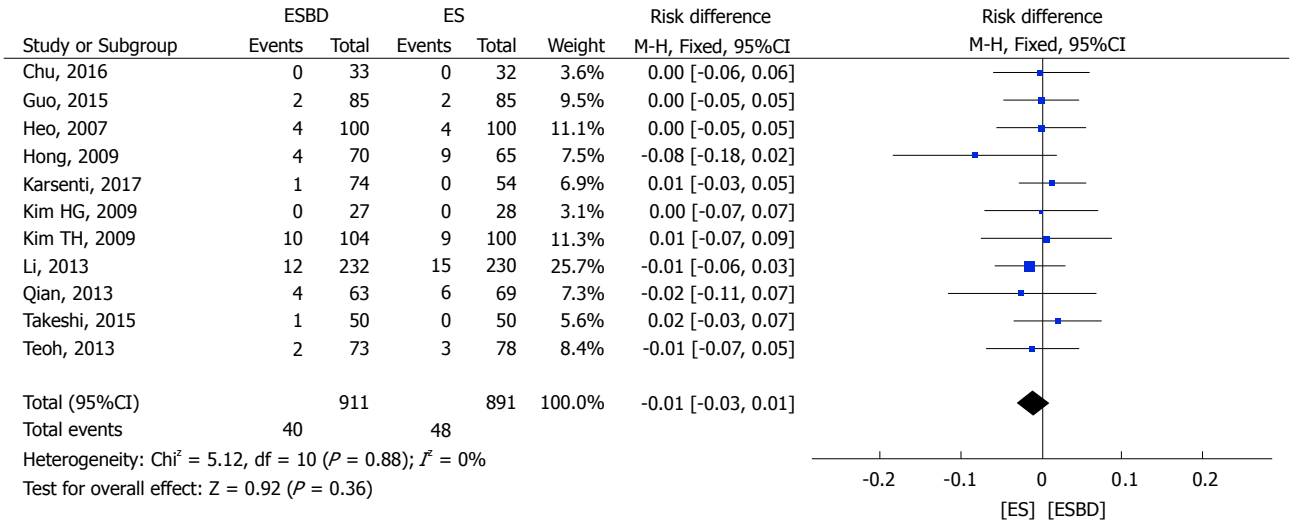

Figure 6 Forest plot of post-endoscopic retrograde cholangiopancreatography pancreatitis rate.

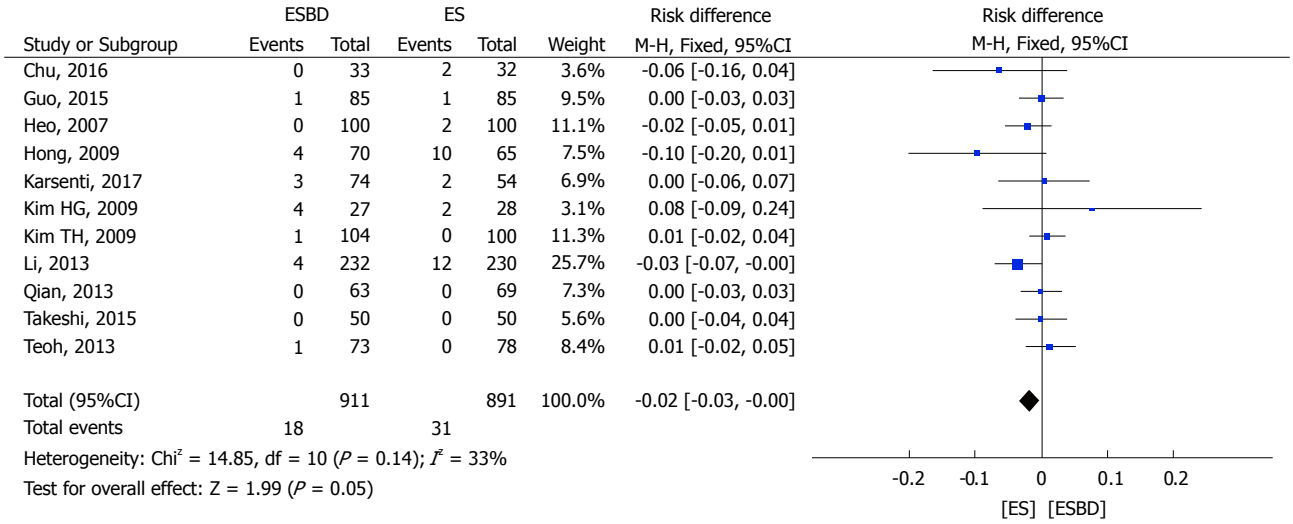

Figure 7 Forest plot of post-procedure bleeding rate (*P* = 0.05).

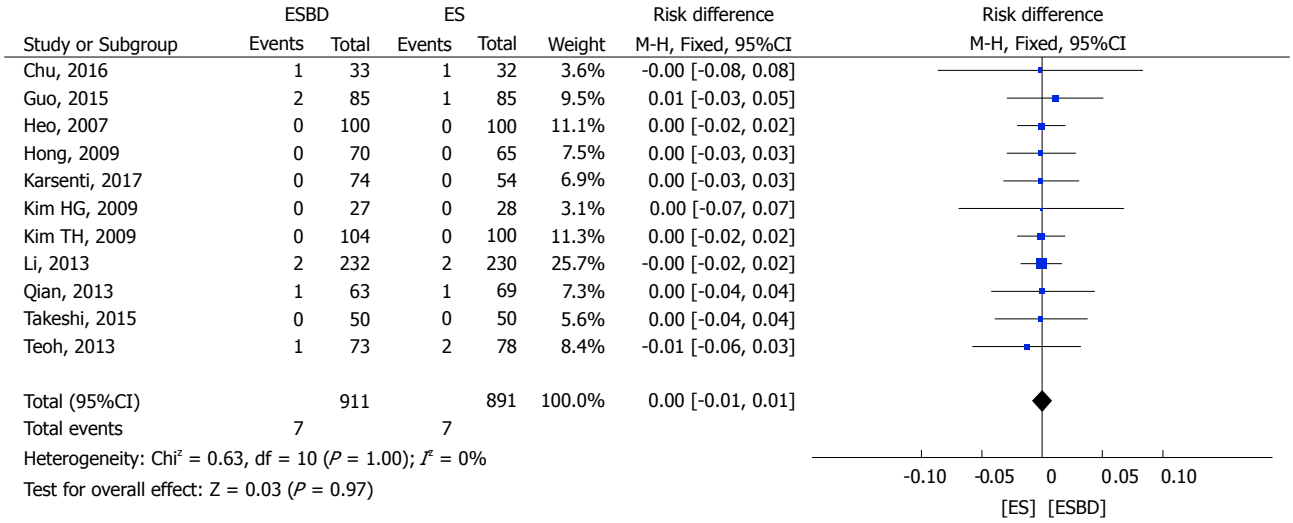

Figure 8 Forest plot of post-procedure cholangitis rate.

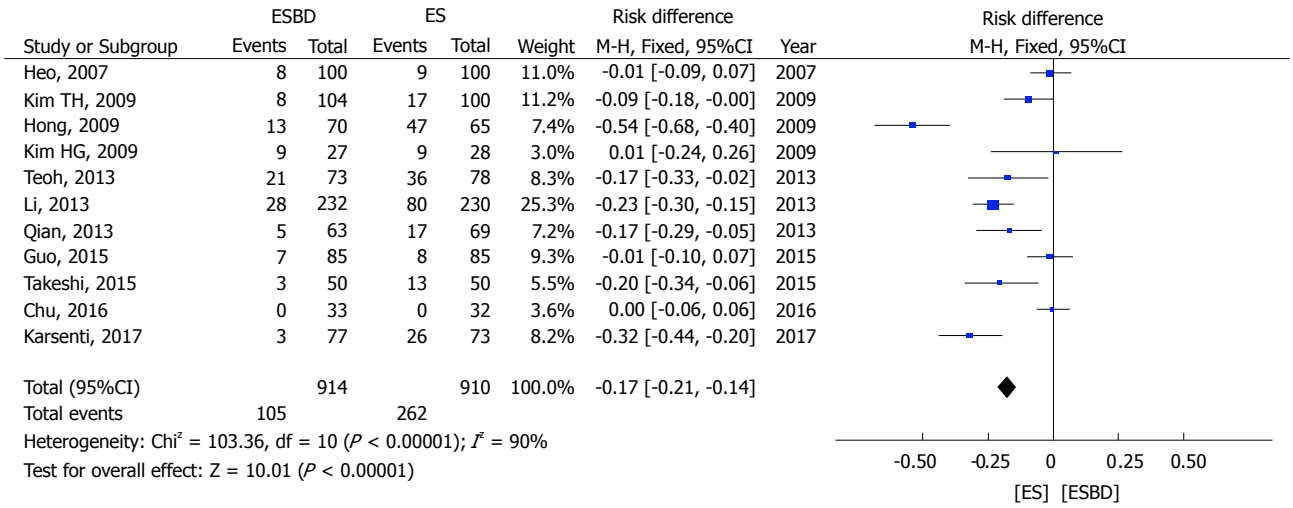

Figure 9 Forest plot with fixed effect comparing the use of mechanical lithotripsy (*P* < 0.00001).

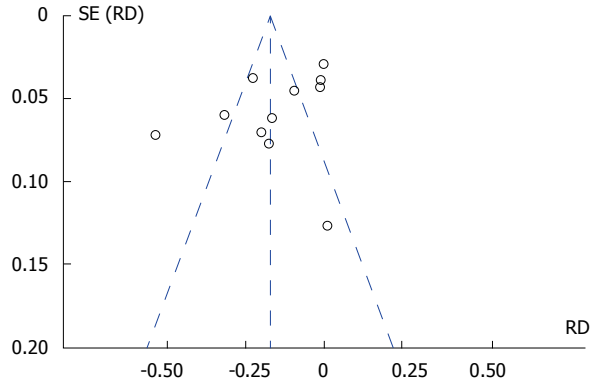

Figure 10 Funnel plot showing true heterogeneity in the use of mechanical lithotripsy general analysis.

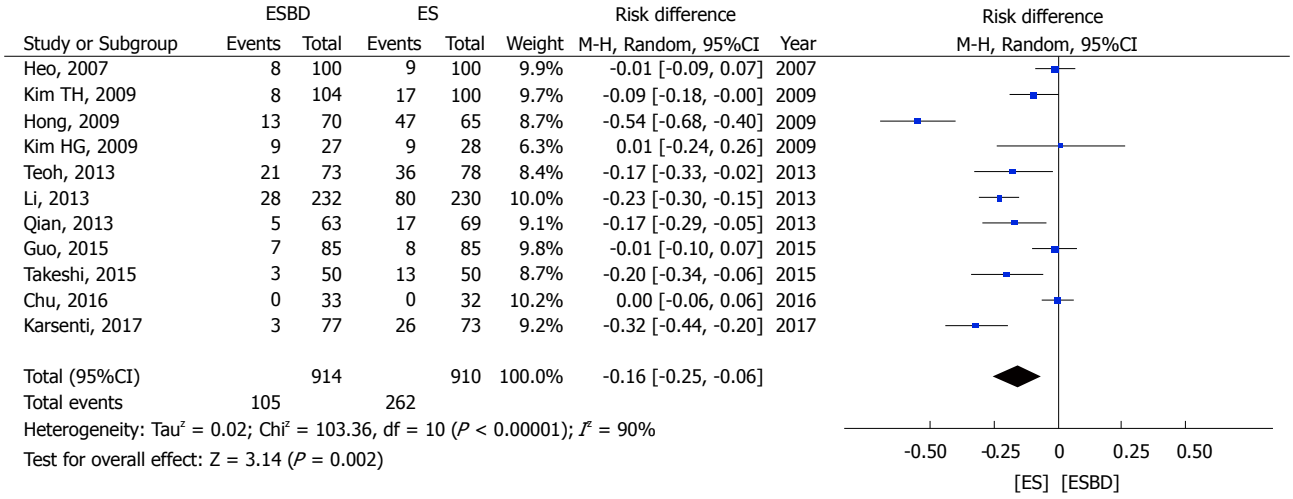

Figure 11 Forest plot with random effect comparing the use of mechanical lithotripsy (*P* < 0.002).

The literature review of the previous meta-analysis shows that authors did follow diverse methodology and were faced with limitations related to the selection of available studies, either by grouping different methods in the same analysis group, or by grouping prospective to retrospective studies or finally reaching a low total number of patients when they tried a more rigorous selection. However, we can identify among the studies, a lower tendency to use ML when balloon dilation is associated to sphincterotomy, especially in large

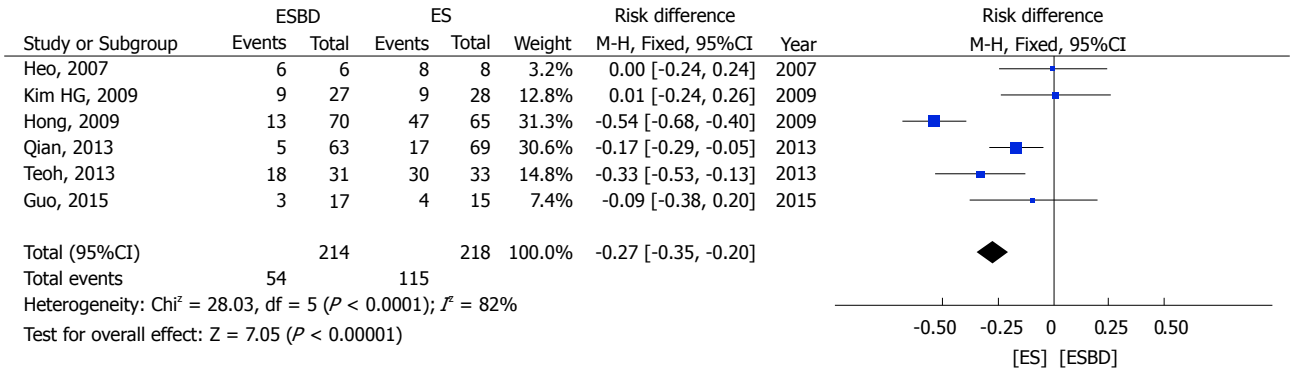

Figure 12 Forest plot with fixed effect comparing the use of mechanical lithotripsy in patients with stones greater than 15 mm (*P* < 0.00001).

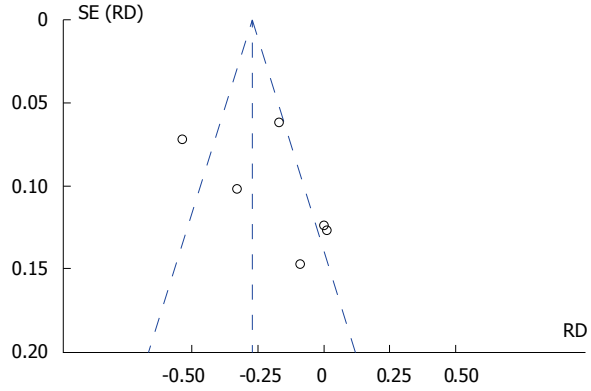

Figure 13 Funnel plot showing true heterogeneity in the use of mechanical lithotripsy in patients with stones greater than 15 mm analysis.

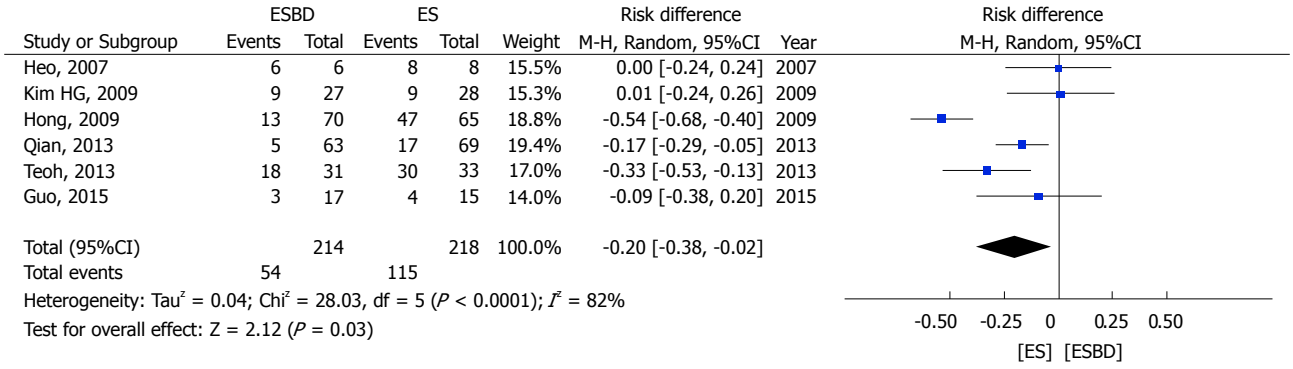

Figure 14 Forest plot with random effect comparing the use of mechanical lithotripsy in patients with stones greater than 15 mm analysis (*P* = 0.03).

gallstones.

This systematic review sought to homogenize the selection of clinical trials to compare the outcomes of the two most commonly used endoscopic methods in the extraction of gallstones from common bile duct, isolated sphincterotomy (ES) and sphincterotomy associated with balloon dilation (ESBD), besides presenting the largest sample involved up to the present moment. The incorporation of recent trials updates the understanding of the choledocholithiasis approach, and the sampling and selection of only randomized clinical trials provide greater magnitude and accuracy.

The selected RCTs applied, in general, similar exclusion criteria among themselves, such as: Active acute pancreatitis; cholangitis; acute cholecystitis; intrahepatic duct stones; pancreatobiliary malignancy; surgical history involving the biliary tree (not including the gall bladder) or gastrointestinal tract, such as the stomach or small bowel (Billroth Ⅱ or Roux-en-Y reconstruction), which can change the papillary location; coagulation disorders; currently taking clopidogrel; pregnancy and inability to give informed consent.

Regarding safety, all selected trials define post-ERCP bleeding according to the Cotton consensus[27] with the exception of not being able to extract this information from the only three selected trials published in abstract

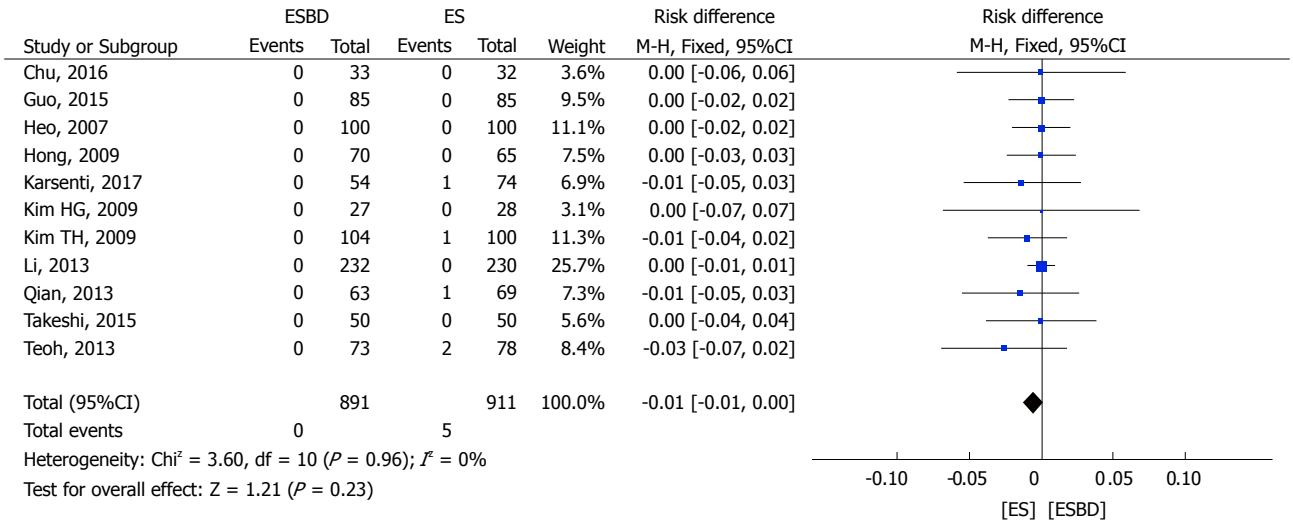

Figure 15 Forest plot comparing perforation rates during the procedure.

format[10,15,16]. Of our eleven selected trials, four tended to have more bleeding in the EST group[8,13,16,17], but only Li *et al*[13] presented statistical difference, its sample was significantly larger than the sample from each of the other trials, hence its presence was decisive for the final result, however, without compromising the analysis of heterogeneity (I^2 = 33%). We obtained that EST group presented more post-ERCP bleeding (3.4% *vs* 1.9%, *P* = 0.02) with a total of 1802 patients included in this analysis. This corroborates with the previous findings in 2013 systematic review done by Liu[22]. It is worth to mention that its result was generated from a separated analysis with only three RCTs selected with a total of 355 patients, of which 155 were extracted from a single clinical trial that addressed only patients with periampullary diverticulum, adding an important selection bias to the analysis[28]. The recently published meta-analysis by Park CH did not observe this difference in bleeding risk between ESBD and EST, but obtained that both ESBD and EST had more bleeding than EPBD[26].

Although there is a precedent in the literature on this finding, care should be taken when checking the presence of bias in the analysis, also identified by Park *et al*[26], regarding the difference in sphincterotomy extension among selected trials, an important isolated variable related to the risk of bleeding, as assessed in a retrospective study done by Park *et al*[29].

All studies included in this review proceeded to the technique of partial sphincterotomy (one-third or half of the conventional length) associated with balloon dilation *vs* total sphincterotomy (performed on the full length of the transverse fold), with the exception of Karsenti´s trial[7], who underwent total sphincterotomy in all patients. This peculiarity did not change the results, since there is no tendency for a greater risk of post-procedure bleeding in any of the groups of his clinical trial. On the other hand, its full length cut approach may have been the main cause of the discrepancy in their results compared to the other trials in primary outcome assessment (stone removal rate), being evident when its inclusion in this analysis increased the heterogeneity of the group from I^2 = 0 to I^2 = 54%, therefore was identified as the only outlier study after sensitivity analysis was performed with funnel plot and withdrawn from that analysis. The author advocates against the use of small sphincterotomy as a cautious attitude against adverse events from results based on previous trials showing safety in total sphincterotomy prior to dilation[17,30], obfuscating the association found in Park SJ[29] retrospective study. Finally, Karsenti *et al*[7] obtained in their trial a clear advantage in the stone removal rate in favor to ESBD group, in addition to a lower need for ML in the same group without difference between techniques in the adverse events rate from a sample of 150 patients.

In our clinical experience at the Hospital das Clínicas of the University of São Paulo Medical School, endoscopists underwent total sphincterotomy prior to dilation in all selected complex cases without presenting rates of adverse events higher than those found in the literature. In our procedures the balloon was kept inflated during three minutes to avoid bleeding and reinflated for the same period if hemorrhage is noted.

Perforation was a rare event, affecting only five of 1802 patients effectively submitted to ERCP, being all from EST group and conducted with conservative non-surgical resolution. This demonstrates how techniques and accessories have evolved bringing greater safety to the procedure.

Regarding efficacy, in the assessment of primary outcome defined as stone removal rate, from available data it was possible to extract and to analyze a subgroup with patients who had stones greater than or equal to 15 mm with the final sum of 484 patients. Despite the tendency in favor to the ESBD group, there

was no statistical difference among the groups. This outcome was expected to be the one that most could have differentiated the methods efficacy about the balloon dilation association in the process, perhaps the subgroup sample was too small to evidence it. So it may be required more large-scale specific RCTs.

However, ML was less needed in ESBD group both in general and in subgroup analysis with stones greater than 15 mm, reinforcing previous data in the literature[7,10,11-13,15,16]. Therefore this association should be part of the approach decision algorithm according to physician's experience with one technique or another, since if he opts less often for dilation he will be more susceptible to the need for ML.

We found that ESBD was a safer method compared to ES since ES group carried a higher risk of post-ERCP bleeding and required more frequent therapeutic complementation with use of mechanical lithotripsy, being exposed to a greater theoretical risk of bile duct injury, in addition to a potential longer procedure cost and time. In terms of efficacy, we obtained statistical similarity between groups, with tendency to superiority in ESBD group.

The review of the literature necessary to perform this work, coupled with the authors' clinical experience in their reference services, has led to the hypothesis that it is safe to perform the total sphincterotomy prior to large balloon dilation. However, in order to add a greater degree of scientific evidence, we suggest a pertinent study design to confirm this hypothesis: A large multicentric randomized clinical trial with standardized techniques and assessments based on up-to-date consensus involving patients with complex gallstones (greater than 15 mm or in number greater than 10 or with size disproportion between stone and distal CBD) comparing partial *vs* total sphincterotomy, both associated with large balloon dilation.

The future research should also consider the latest technologies incorporated into the available tools arsenal for the management of difficult bile duct stones, such as the use of cholangioscopy with target endobiliary therapies without the need for large biliary dilation and sphincterotomies, which can reduce possible adverse events. A recent randomized controlled trial totaling 100 patients comparing cholangioscopy *vs* papillary large balloon dilation for complex biliary stones management performed by Gastrointestinal Endoscopy Unit of the University of São Paulo Medical School concludes that the two techniques presented similar high success rates and low incidence of adverse events. Furthermore, the association of the methods improved biliary clearance, thus they can be complementary to each other[31].

Finally we present the flow chart of current clinical approach in our reference service (Figure 16).

The first limitation of this systematic review appeared in the initial search, because there are insufficient number of specific clinical trials for giant gallstones (≥ 15 mm), and studies with relatively large gallstones are heterogeneous in the sample and subdivided into groups with different cutoff size of the stones (12 mm, 15 mm or 20 mm). Only six studies of the eleven have pooled stones larger than 15 mm.

There was heterogeneity in technical details of procedures between the RCTs, such as different time of balloon insufflation and different length of sphincterotomy, this last seems to be an isolated variable that generates conflict in results interpretation when grouping different techniques in systematic reviews, this way we can infer that it is not only a limitation of the paper, but perhaps a point to be discussed and explored in future trials.

The nature of the intervention did not allow blinding after randomization. There was population heterogeneity between groups after randomization with regard to age in Karsenti trial and on the presence of periampular diverticulum on Guo trial.

We included three trials published in abstract format; we consider that it brings a limitation for the biases analysis, since they could not be fully evaluated in these works, such as adequate randomization or possible losses. In addition, it is important to emphasize the impossibility of accessing in these trials the adverse events definitions adopted (post-ERCP hemorrhage and pancreatitis). It was not possible to extract sphincterotomy technique data (small or total) from only one trial published in abstract format[16].

Regarding the results of these studies, the inclusion of the abstracts was not considered an absolute limitation, since the availability of all required data for the meta-analysis was a pre-requisite for inclusion in our study.

Through meta-analysis of randomized clinical trials we found that there was no statistical difference in the stone removal rate between isolated sphincterotomy and sphincterotomy associated with balloon dilation in the approach to remove gallstones. However, isolated sphincterotomy was associated with more post-ERCP bleeding and more need for mechanical lithotripsy.

ARTICLE HIGHLIGHTS

Research background

Endoscopic retrograde cholangiopancreatography (ERCP) has become one of the most important techniques for the treatment of choledocholithiasis, a pathology with an important prevalence in the population, which incidence increases with age, with an estimated 5% to 10% of patients with cholelithiasis at the time of cholecystectomy even without any predictive factors. The techniques and endoscopic instruments have evolved a lot in the last decades, with a significant improvement in effectiveness and safety, but we still have challenging situations (gallstones larger than 15 mm or in number greater than 10 or when there is a disproportion between stone size and the distal bile duct caliber). In this sense, we should seek solidified data in the available scientific literature to support our most appropriate therapeutic decision.

Research motivation

Endoscopic sphincterotomy as well as balloon dilation of duodenal major papilla are recognized endoscopic treatment approaches to choledocholithiasis.

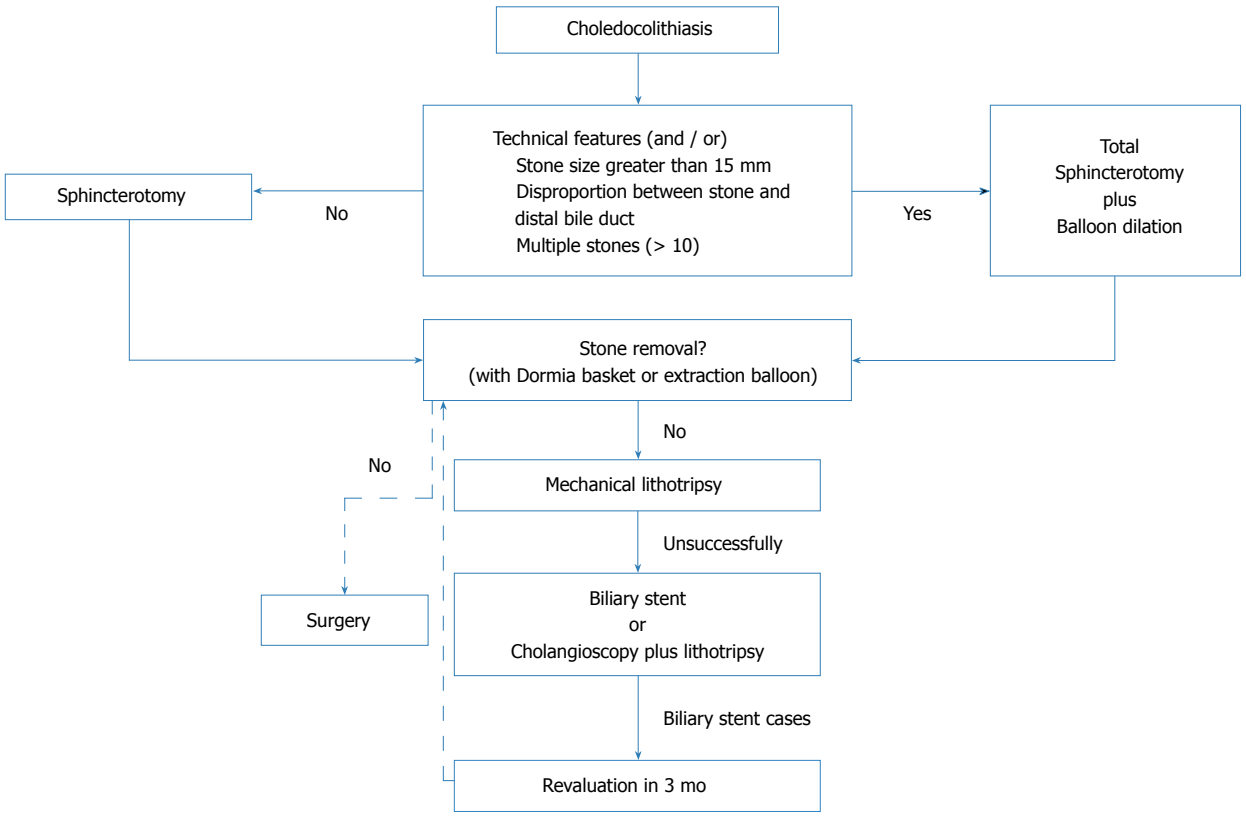

Figure 16 Flow chart of current clinical approach in our reference service.

These two techniques, however, are associated with adverse events such as hemorrhage, perforation and pancreatitis. Additionally, gallstones cannot be removed in approximately 5% to 10% of patients, especially those with difficult duct biliary stones. Our initial motivation was to know if there is a preferential approach in choledocholithiasis with lower rates of adverse events while maintaining high effectiveness. From the literature review about the subject, we realized some characteristics that we interpreted as important limitations in the previous works. Thereafter, this study tried to remove these limitations and to follow a rigorous methodological approach in the selection and analysis of clinical trials in order to enhance the knowledge about safety and efficacy data.

Research objectives

We want to compare efficacy and safety data between the two most widespread endoscopic approach methods in choledocholithiasis: endoscopic sphincterotomy *vs* endoscopic sphincterotomy associated with large balloon dilation. It was possible to obtain in the literature a large sample of patients taken from properly conducted clinical trials. We believe that future systematic reviews on this issue can be based on our selection and analysis methodology and just add new trials which shall be published in order to update and to bring a greater dimension to the theme.

Research methods

This systematic review was conducted according to the PRISMA Statement (Preferred reporting items for systematic reviews and meta-analyses). The search was performed in the electronic databases MedLine (*via* PubMed), Cochrane Library, LILACS, EMBASE, the CAPES database (Brazil), and gray literature. The incorporation of recent trials updates the understanding of the choledocholithiasis approach, and the sampling and selection of only randomized clinical trials provide greater magnitude and accuracy.

Research results

Eleven randomized controlled trials (RCTs) with 1824 patients were included. EST was associated with more post-ERCP bleeding (P = 0.05) and more need for mechanical lithotripsy in general (P = 0.002) and in subgroup analysis of stones greater than 15 mm (P = 0.003). Incidence of pancreatitis, cholangitis and perforation was similar between the groups as well as similar stone removal rates in general and in pooled analysis of stones greater than 15 mm. We obtained the largest sample already described in the literature that directly compares the EST *vs* sphincterotomy associated with balloon dilation (ESBD) methods in choledocholithiasis through data extracted from published randomized clinical trials. We were expecting that the primary outcome defined as stone removal rate have differentiated the methods efficacy about the balloon dilation association at least for the subgroup analysis of patients with stones greater than 15 mm, but, despite the tendency to favors the ESBD group, there was no statistical difference among the groups. Perhaps the subgroup sample (484 patients) was too small to evidence it. So it may be required more large-scale specific RCTs.

Research conclusions

Through the direct meta-analysis of the largest sample ever pulled exclusively from randomized clinical trials addressing choledocholithiasis, we found that isolated sphincterotomy was associated with higher post-ERCP bleeding as well as an increased need for mechanical lithotripsy than when associated with balloon dilation. Regarding efficacy, stone removal rate tended to be better in ESBD than in EST, although the difference was not statistically significant. This study sought to remove the bias from the lack of methodological rigor applied in the selection and analysis of clinical trials identified in the previous reviews, thus obtaining more purified results, even though they are similar. We found that ESBD was a greater safety method compared to isolated sphincterotomy (ES) since ES group carried a higher risk of post-ERCP bleeding and required more frequent therapeutic complementation with use of mechanical lithotripsy, being exposed to a greater theoretical risk of bile duct injury, in addition to a potential longer procedure cost and time. In terms of efficacy, we obtained statistical similarity between groups, with tendency to superiority in stone removal rate for the ESBD group. This study proposes that the complement with balloon dilation after sphincterotomy of the papilla is associated with greater safety in ERCP for choledocholithiasis, since isolated sphincterotomy was associated with more post-ERCP bleeding. Taking into account the fact that mechanical lithotripsy

(ML) was less needed in ESBD group both in general and in subgroup analysis with stones greater than 15 mm, this association should be part of the approach decision algorithm according to physician's experience with one technique or another, since if he opts less often for dilation he will be more susceptible to the need for ML. This systematic review sought to homogenize the selection of randomized clinical trials and to compare the outcomes of the two most commonly used endoscopic methods in the extraction of gallstones from common bile duct: isolated sphincterotomy ES and ESBD, besides presenting the largest sample involved up to the present moment submitted to direct analysis. The incorporation of recent clinical trials updates the understanding of the choledocholithiasis approach, and the sampling and selection of only randomized clinical trials provide greater magnitude and accuracy. All the phenomena found had already occurred separately in previous studies, so, this study corroborates and reinforces with the findings of the literature. To achieve greater impact through direct analysis of the largest sample taken exclusively from the RCT so far, we can confirm some findings from the literature review as a higher risk of bleeding in the EST group compared to ESBD and less need for ML in the ESBD group when performing ERCP for choledocholithiasis resolution.

Research perspectives

The legitimacy of comparing these two methods through meta-analyzes always seems to be influenced by the technical differences applied in each trial, such as the sphincterotomy length, once it shows an evident disturbance in the results of this study. Continuous assessment of efficacy and safety data for difficult cases of choledocholithiasis, focusing on compares the outcomes between partial *vs* total sphincterotomy, both associated to large balloon dilation. A pertinent study design to the theme would be a large multicentric randomized clinical trial with standardized techniques and assessments based on up-to-date consensus involving patients with complex gallstones (greater than 15 mm or in number greater than 10 or with size disproportion between stone and distal CBD) comparing small vs total sphincterotomy, both associated with large balloon dilation.

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REVIEW

Clinical update on the management of pseudopapillary tumor of pancreas

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Abstract

Solid pseudopapillary neoplasm (SPN) is a rare tumor with malignant potential which is generally located in the tail of pancreas. The prevalence of SPN has increased with widespread use of cross sectional imaging. SPN is often misdiagnosed due to nonspecific clinical presentation and accurate diagnosis is essential for optimal management. Endoscopic ultrasound-FNA with immunohistochemistry can help in preoperative diagnosis. Surgery is the treatment of choice and a successful R0 resection is curative. Overall, SPN has a good prognosis. This review article focuses on pathogenesis, diagnosis and management of SPN.

Key words: Pancreatectomy; Pancreatic cysts; Beta-catenin; Endoscopic ultrasound-fine needle aspiration; E-cadherin; Immunohistochemistry

Core tip: Solid pseudopapillary neoplasm (SPN) is a rare pancreatic tumor that predominantly affects young females. SPNs are usually indolent but they do have malignant potential. The pathogenesis of SPN is not entirely clear. Accurate diagnosis is essential in the management of SPN. Endoscopic ultrasound guided fine needle aspiration with immunohistochemistry can help distinguish SPNs from other aggressive pancreatic tumors preoperatively. Surgical resection with clear margins is curative and should be offered whenever feasible. The prognosis of SPN is good even in the presence of metastasis.

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INTRODUCTION

Pancreatic cysts are diagnosed more frequently because of increasing use of computed tomography (CT) and magnetic resonance imaging (MRI). They are found incidentally in more than 2 percent of CT and MRI for unrelated reasons[1,2]. According to World Health Organization (WHO) classification, pancreatic cysts are classified based on histology into serous, mucinous cystic neoplasm, intraductal papillary mucinous neoplasm (IPMN) and solid pseudopapillary neoplasm (SPN)[3]. SPN had various names in the past including Frantz's tumor, solid and papillary tumor, solid-cystic tumor, papillary cystic tumor as well as solid and papillary epithelial neoplasm[4]. SPN accounts for about 3% of resected pancreatic cystic tumors[5]. SPNs are more common in females who are in their second or third decade of life. Less than 10% of SPNs are diagnosed in men. They are commonly found in the tail of pancreas[7,8].

PATHOGENESIS

The cellular origin of SPN is unclear. During normal pancreas development, beta-catenin signaling within the beta-catenin/Wnt pathway is necessary and in the adult organ this pathway is usually downregulated[9]. The majority (85%-90%) of SPN have exon-3 mutations and in 10%-15% mutations are present in other exons[10]. The aberrant protein expression in SPN is strongly correlated with mutations in beta-catenin gene[10]. Mutations in beta-catenin gene exon-3 lead to Wnt signaling activation which plays an important role in the development of SPN[11]. Cell cycle-associated proteins like cyclin D1 and cyclin D3 are overexpressed in SPN because of deregulation of cell cycle[12,13]. The role of genetic aberration of EWS/FLI-1 in SPN was studied. FLI-1 is identified in endothelial and mesodermal tissues[14] and it is the earliest marker of blood vessels during embryogenesis[15]. Although FLI-1 was expressed in SPN, it was not accompanied by CD 34 positivity or EWS/FLI-1 translocation[16]. Hence, the diagnosis of SPN is less likely if EWS/FLI-1 translocation is positive. Chromosome 11 is vulnerable to specific genetic changes as it harbors several genes for proteins (cyclin D1, FLI-1, progesterone receptor and CD56) which are overexpressed in SPN[17]. The low tumor growth rate in SPN is explained by the role of cyclin-dependent kinase inhibitors p^{21} and p^{27} in controlling the activated Wnt/beta-catenin signaling pathway[17]. SPNs are considered hormone sensitive because they express progesterone receptor[18]. P^{21}, P^{27} and cyclin D1 expression is influenced by estradiol and progesterone[19,20]. BCL9 and BCL9L play an important role in enhancing Wnt signaling by increasing beta-catenin transcriptional activity and tumorigenesis[21]. BCL9L is differentially expressed among various pancreatic neoplasms [overexpressed in pancreatic ductal adenocarcinoma (PDAC) but decreased in SPN] but BCL9 did not show any difference[22] (Figure 1).

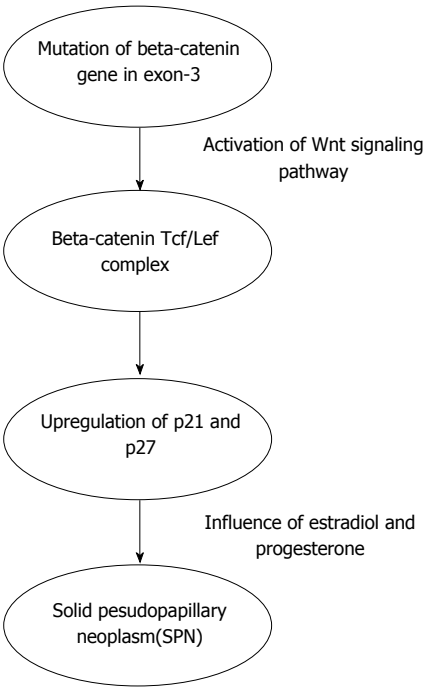

Figure 1 Pathogenesis of solid pseudopapillary neoplasm.

HISTOLOGY AND MORPHOLOGY

Grossly, SPN appear as solid and cystic components with areas of hemorrhage, calcifications, with a rim of fibrous capsule[23]. They are well-demarcated and invasion of adjacent organs like spleen and duodenum is rare[4]. Cut sections of SPN show alternate solid and yellow areas with cystic, necrotic and hemorrhagic zones. The solid portions of the tumor are usually composed of uniform, polygonal epithelioid cells with vascularized stroma which are not cohesive in arrangement[24]. Hyaline globules are periodic acid-shiff (PAS) intracytoplasmic inclusions that are immunoreactive for alpha1. Hyaline globules are classically associated with SPN. However, hyaline globules are positive in about 5% of pancreatic neuroendocrine tumors (PanNETs)[25]. Insidious pattern of invasion, clear cells and nuclear groove can help distinguish SPN from PanNETs[25]. Electron microscopy shows abundant mitochondria in polygonal cells and sparse endoplasmic reticulum. Tumor cells have round to oval nuclei with occasional indentation of eccentrically located nucleolus and peripheral clumping of chromatin[26]. Tumor cells contain membrane covered corpuscles are similar to zymogen granules about 8-1.2 micro meter in diameter[27].

Histological variants of SPN include clear cell, pleomorphic and oncocytic[24]. Clear cell variant contains multiple cytoplasmic vacuoles with solid and diffuse growth pattern. Pleomorphic variant contains polymorphism (variation in nuclear size, shape, hyperchromasia and multinucleate) in more than 20% of total tumor area. Oncocytic variant contains mostly oncocytic cells. Histological features suggestive of aggressive behavior of SPN include extensive necrosis, nuclear atypia, high

mitotic rate and sarcomatoid areas[24]. Angioinvasion, perineural invasion and deep invasion of adjacent surrounding pancreatic parenchyma are considered potentially malignant features[4] (Figures 2 and 3).

Immunohistochemistry

In general, the immunostaining of SPN is positive for beta-catenin (nuclear and cytoplasmic), vimentin, synaptophysin, progesterone receptor (nuclear), CD56, NSE (neuron-specific enolase), CD10, and E-cadherin (loss of membrane and nuclear)[10]. Nuclear betacatenin expression and membranous E-cadherin loss are important immunoprofiles useful in distinguishing SPN from other pancreatic neoplasms[28]. E-cadherin is a transmembrane protein that mediates cell adhesion through interactions with catenins and it is linked to the actin skeleton. The exact mechanism for the loss of E-cadherin expression is not clear. Tang *et al*[29] proposed that loss of E-cadherin is a result of promoter silencing and overexpression of transcription repressors such as Snail. Pseudopapillary pattern of SPN is explained by loss of cell cohesiveness by loss of E-cadherin[30]. Enzyme histochemistry for trypsin, alpha-1 antitrypsin, chymotrypsin, amylase and lipase give inconsistent results and they are not useful in differentiating SPN from other pancreatic neoplasms. CD 10 is usually positive (80%) in the majority of SPN[10]. CD 10 is an endopeptidase which reduces the local concentration of biologic modulators by catabolizing them[31]. It is hypothesized that cell proliferation in SPN is from increased biologic modulators because of decreased CD10 expression[10].

CD 56 and CD10 are also positive in PanNET, acinar cell carcinoma (ACC), renal cell carcinoma (RCC) and malignant melanoma (MM). Progesterone receptor is positive in PanNET, ACC and MM. Synaptophysin is positive in PanNET and ACC. Yang *et al*[32] showed in their systematic study that Ki-67 index $\geqslant$ 4% was significantly associated with decreased recurrence free survival (RFS) and disease specific survival (DSS) in SPN. Ki-67 is a cell-proliferation marker used for evaluation of proliferative activity in tumors. Ki-67 is expressed in all phases of the cell cycle (G1, S, G2 and M)[33]. They concluded that Ki-67 should be routinely included in immunohistochemical staining of SPN.

Kim *et al*[34] identified androgen receptor (AR), lymphoid enhancer-binding factor 1 (LEF-1) and transcription factor for immunoglobulin heavy-chain enhancer 3 (TFE3) as putative diagnostic markers of SPN in addition to beta-catenin. This study showed that the sensitivity and specificity of beta-catenin in SPN were 98.9% and 97% respectively. when beta-catenin, LEF-1 and TFE3 were combined, the sensitivity and specificity of SPN diagnosis increased to 100% and 91%, respectively[34]. They concluded that when these markers are incorporated in to immunohistochemical panel, they can help differentiate SPN from pancreatic adenocarcinoma and neuroendocrine tumor. LEF-1 is a member of the lymphoid enhancer binding factor 1/T-cell factor (LEF1/TCF) complex and it acts as a regulator

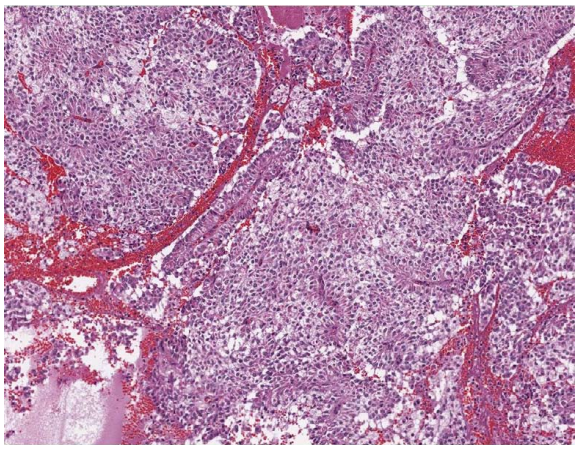

Figure 2 Histological appearance of solid pseudopapillary neoplasm. A hematoxylin and eosin (H and E) stain of a solid pseudopapillary neoplasm demonstrating eosinophilic neoplastic cells with vacuolated cytoplasm and pseudopapillary appearance.

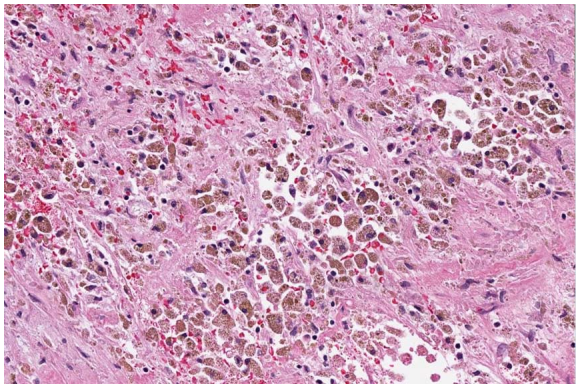

Figure 3 Cytoplasmic and nuclear staining of beta-catenin.

of the Wnt/CTNNB1 signaling pathway. When LEF-1 interacts with CTNNB1, it leads to upregulation of LEF-1 in SPN. CTNNB1 is primarily located in the cytoplasmic plasma cell membrane and it plays a key role in the Wnt signal transduction pathway. Singhi *et al*[35] analyzed the immunohistochemical staining for LEF-1 and CTNNB1 in pancreatic tumors. They concluded that abnormal CTNNB1 accumulation with nuclear LEF-1 expression was found in both SPN and pancreatoblastoma but with diffuse nuclear LEF-1 expression in SPN[35].

TFE3 is a member of the microphthalmia (MiT) family of transcription factors. MiT transcription factors regulate cellular proliferation, survival, motility, metabolism, melanocyte development by binding to target promoters[36]. These are deregulated during oncogenic process. TFE3 is expressed in 74.7% of SPN[34]. Park *et al*[37] showed activation of androgen receptor signaling pathway in SPN and they demonstrated increased AR expression at transcriptional and translational levels. This study confirmed high level of nuclear androgen receptor expression in all SPN (14/14). Kim *et al*[34] showed AR expression in 81.3% of SPN.

SOX-11 is a member of the SOX (SRY-related HMG-box) family of transcription factors. They play an

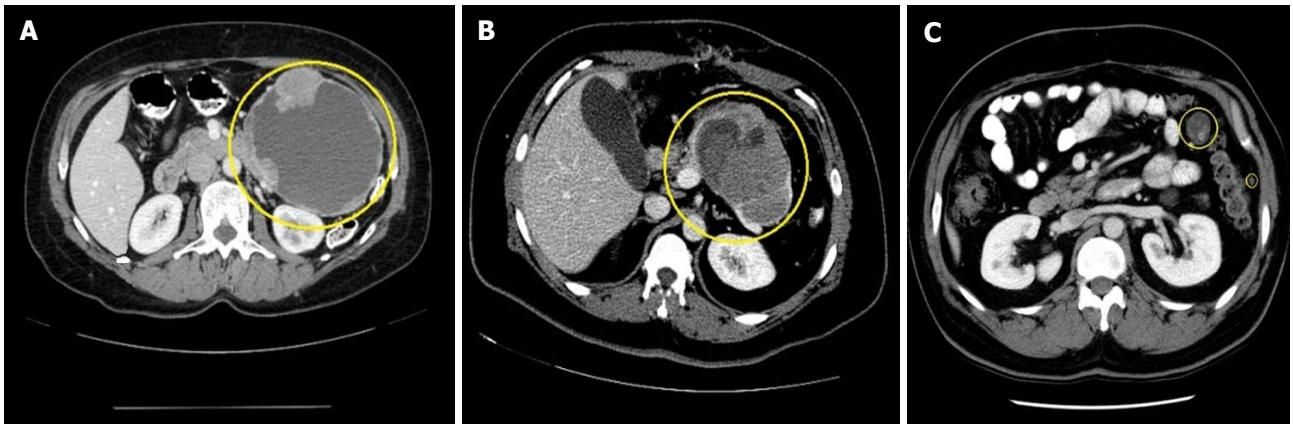

Figure 4 Computed tomography appearances. A: A pancreatic tail solid pseudopapillary neoplasm. Note the characteristic enhancing solid spaces at the periphery of an encapsulated SPN, accompanied by centrally located cystic space; B: Pancreatic tail solid pseudopapillary neoplasm with septation. The cystic component of SPN with degeneration is characterized by a heterogenous hypoattenuation on CT; C: Abdominal metastatic lesions of SPN. SPN: Solid pseudopapillary neoplasm; CT: Computed tomography.

important role in cell differentiation, sex determination, development of the central nervous system, hematopoietic, and other organ systems by regulating lineage and tissue-specific gene expression[38]. SOX proteins have been shown to be key modulators of Wnt/beta-catenin signaling pathway. However, the interaction between SOX-11 and Wnt/beta-catenin signaling is not reported so far. Harrison *et al*[39] showed a sensitivity and specificity of 100% and 84%, respectively in expression of SOX-11 in SPN. They concluded that immunohistochemistry with beta-catenin, SOX-11 and TFE3 should be combined to achieve optimal sensitivity and in diagnosing SPN. Foo *et al*[40] evaluated the nuclear reactivity of SOX-11 in SPN and they showed that the sensitivity and specificity was 100%, respectively in EUS-FNA specimens.

CLINICAL PRESENTATION AND DIAGNOSIS

Symptoms are nonspecific. SPNs can present with palpable abdominal mass, indigestion, abdominal discomfort, epigastric pain, nausea, vomiting, asthenia, itching, weight loss, back pain, early satiety, bloating, jaundice and pancreatitis[23,27,41,42]. SPN outside the pancreas can occur in the retro-peritoneum , liver, stomach, mesentery, duodenum, omentum, ovary or lung[43,44]. The most common manifestation of malignant acting SPN is peripheral parenchymal infiltration[45]. SPN can also be found in regional lymph nodes, portal vein, colon, spleen and blood vessels[24,46,47].

Differential diagnosis of SPN include cystic tumors like cyst adenoma, cystadenocarcinoma, microcystic adenoma, PanNET, lymphangioma, sarcoma, cystic islet cell tumors, acinar cell cystadenocarcinoma, discogenic cysts, pseudocysts and hydatid cysts[48].

Ultrasonographic (US) examination of SPN shows homogeneous, hypoechoic mass with hyperechoic rim and contrast enhanced ultrasound (CEUS) shows hyperenhancement of the rim in the arterial phase[49]. CEUS can identify the cystic areas of the tumor and the peripheral rim of SPN better than US which improves the diagnosis of SPN[49]. Contrast CT and MRI are superior to US in identifying capsule and intramural hemorrhage which are more specific characteristics for diagnosing SPN[50].

CT features of SPN include encapsulated mass with varying solid and cystic components secondary to hemorrhagic degeneration (Figure 4). At the periphery of the mass, calcification and solid areas can be identified[51]. On multiphasic CT scan appear as a solid pancreatic mass with sharp borders[52]. During CT pancreatic phase, there is weak enhancement when compared to the surrounding pancreatic parenchyma and in hepatic venous phase there is gradual increase in enhancement of small SPNs[52]. Typical SPN on CT has surrounding capsule with demarcation between solid and cystic components and hypoattenuation during pancreatic phase[50,51]. Atypical SPNs on CT have no surrounding capsule, solid or cystic component with hyper attenuation during pancreatic phase and dense internal calcification with no defined margin[52]. Park *et al*[53] studied CT imaging features of SPNs in males and females. The results showed that lobulated shape is more common among males and oval shape in females[53].

MRI is considered superior to CT in terms of correlation of clinicopathological and radiological findings of SPN[54]. It has advantage over CT especially when the patient has contrast allergy or renal insufficiency. SPN is identified on MRI as an encapsulated lesion with both solid and cystic component as well as hemorrhage without septation[54]. Yu *et al*[54] proposed three MRI features (Type 1, Type 2 and Type 3) that correlated with clinicopathological features. Type1 image in SPN is completely solid, homogeneously hypointense on T1W1 image and slightly hyperintense when compared to surrounding pancreatic parenchyma on T2W1 image. Type 2 image in SPN has both solid

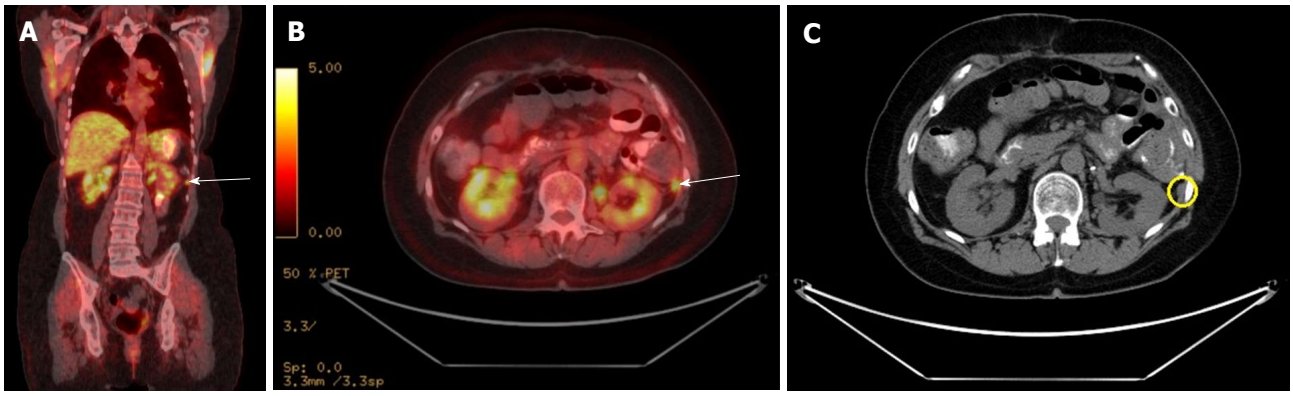

Figure 5 F-18 fluorodeoxy glucose avid solid pseudopapillary neoplasm metastases and metastatic solid pseudopapillary neoplasm to mesentery. A: FDG avid SPN metastases to mesentery; B: FDG avid metastatic SPN to mesentery; C: CT appearance of the FDG avid lesion. SPN: Solid pseudopapillary neoplasm; CT: Computed tomography; FDG: F-18 fluorodeoxy glucose.

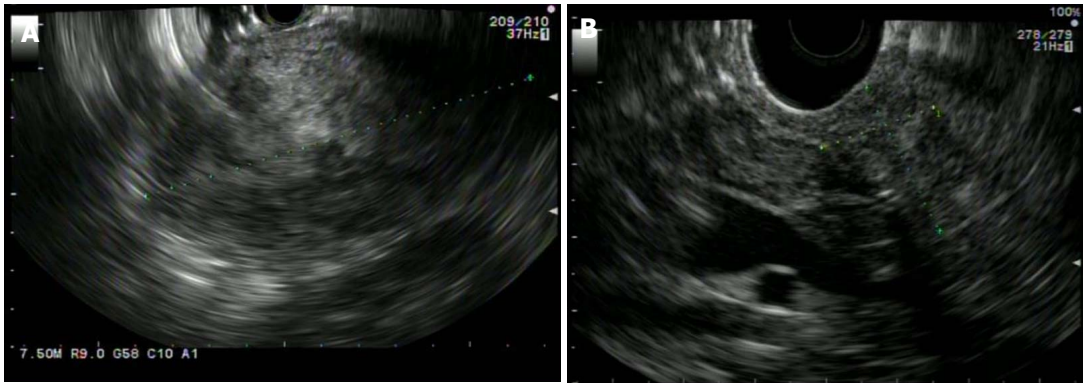

Figure 6 Endoscopic ultrasound appearances. A: SPN adjacent to the gastric wall. SPN demonstrates heterogenous echogenicity on EUS, with hyperechoic foci representing solid areas with surrounding hypoechoic cystic spaces; B: A pancreatic head SPN. EUS: Endoscopic ultrasound; SPN: Solid pseudopapillary neoplasm.

mass and hemorrhage, hypointense with surrounding heterogeneously hyperintense area on T1W1 image and hyperintense areas on T1W1 appear more hyperintense on T2W1 image. Type 3 image in SPN has massive hemorrhage, mainly hyperintense with intermediate and hypointense area on T1W1 image and hyperintense areas on T1W1 appear more hyperintense on T2W1 image.

The F-18 fluorodeoxy glucose (FDG) uptake of SPN on positron emission tomography (PET) is not well studied. Dong *et al*[55] showed that FDG uptake of SPN on PET is related to tumor cellularity, proliferative index or histological malignancy. SPN with a greater proportion of solid component has more FDG uptake than with cystic or hemorrhagic component (Figure 5). Small SPN has more FDG uptake because they have less cystic component. Hence, increased FDG uptake does not necessarily correlate with malignancy. Sato *et al*[56] suggested that high FDG uptake should be appropriately correlated by use of clinical, lab and radiologic findings. Nakamoto *et al*[57] evaluated the usefulness of delayed FDG-PET scanning in distinguishing between benign and malignant pancreatic lesions. False positives were seen in patients with acute pancreatitis and autoimmune pancreatitis, but clinical information helped distinguish benign from malignant. They concluded that delayed FDG-PET scanning at 2 h post injection can help differentiate benign from malignant pancreatic lesions when interpreted carefully[57].

SPN is characterized on EUS as a well circumscribed, hypoechoic, heterogeneous solid mass with cystic, hemorrhagic and calcified components found predominantly on the body and tail of pancreas (Figure 6). EUS-Fine needle aspiration (EUS-FNA) can help in more definitive diagnosis of SPN (Figure 7). It is safe, reliable and can provide cytological specimens preoperatively which can guide targeted surgical approach[58]. Stoita *et al*[58] showed that a preoperative diagnosis of SPN was achieved from EUS-FNA cytology in 83% (5/6, 1/6 had insufficient sample) of cases. Jani *et al*[59] conducted a multicenter study on the role of EUS-FNA in preoperative diagnosis of SPN. Results showed that EUS-FNA had 75% (21/28) accuracy. Two/28 had insufficient EUS-FNA sample or acellular for accurate diagnosis. Five/28 were preoperatively misdiagnosed as panNET because of immunostaining results. This study recommends immunohistochemical staining with vimentin, CD10 and beta-catenin for more definitive diagnosis of SPN. EUS-FNA sample with immunohistochemical staining can differentiate SPN, panNET and acinar cell carcinoma[60].

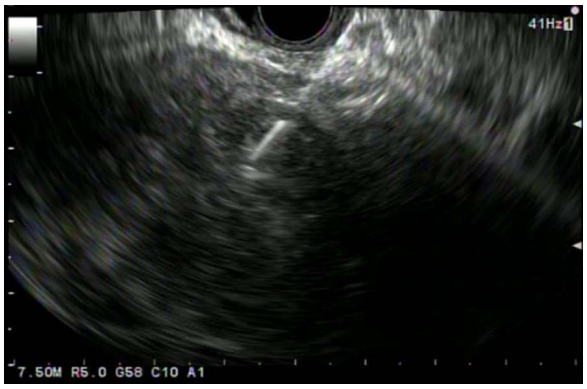

Figure 7 Endoscopic ultrasound guided fine needle aspiration of solid pseudopapillary neoplasm located in body/tail pancreas (Transgastric approach).

SPN is positive for beta-catenin, vimentin, CD10 and CD56. PanNET is positive for chromogranin [50%-70% of PanNET (functioning and non-functioning)] and synaptophysin. Acinar cell carcinoma is positive for trypsin and chymotrypsin.

EUS-Fine needle biopsy (EUS-FNB) has advantage of providing adequate tissue sample for more accurate diagnosis of SPN. Maimone *et al*[61] showed that preoperative diagnosis of SPN was achieved in all 5/5 patients. This study concluded that EUS-FNB with ProCore needle (biopsy needle with side fenestrations 19G or 22G) provides good quality and quantity of sample which can increase the yield of preoperative diagnosis of SPN. EUS-FNA can lead to tumor seeding along the needle tract especially in pancreatic adenocarcinoma[62]. Micames *et al*[63] evaluated the frequency of peritoneal carcinomatosis in non-metastatic pancreatic cancer patients diagnosed with percutaneous FNA *vs* EUS-FNA. EUS-FNA has lower likelihood of tract seeding compared to percutaneous FNA because of the shorter needle tract. They concluded that EUS-FNA should be the preferred method to obtain tissue sample for potentially resectable localized pancreatic cancer[63]. However, no case reports of tumor seeding with EUS-FNA of SPN were published so far.

Hirooka *et al*[64] described a case report of peritoneal dissemination after EUS-FNA of IPMN located in pancreatic body. They concluded that pancreatic lesions located in the body/tail have more risk because of needle passage through lesser sac. Kita *et al*[65] described another case report of needle tract seeding (NTS) in posterior wall of stomach after EUS-FNA of pancreatic cancer located in pancreatic body. They concluded that NTS is rare in pancreatic head lesions as the needle passage is through duodenum and usually they undergo pancreaticoduodenectomy which includes needle tract (duodenal bulb). However, pancreatic lesions located in body/tail have higher risk of NTS as the needle passage is through transgastric (lesser sac) and they usually undergo distal pancreatectomy which doesn't include needle tract (lesser sac)[65]. Hence, there is more risk of peritoneal dissemination or NTS with transgastric than transduodenal approach.

Sakamoto *et al*[66] described a case report of NTS after EUS-FNA of pancreatic adenocarcinoma located in pancreatic tail. Also, application of low suction during EUS-FNA decreases the blood contamination and increases the diagnostic accuracy[67]. The technique involves the stylet where it is slowly withdrawn from the needle and in and out motion is performed with in the target lesion. During needle strokes, if the needle is pulled out too far, and/or because of difficult recognition of the sidehole on EUS images, the tissue collected can exit out of the needle hole and there is potential for NTS. Hence, they concluded that slow-pull technique with side-hole needle should be avoided in cases scheduled for resection of pancreatic body/tail cancer to prevent NTS[66].

MANAGEMENT

Surgical resection is the treatment of choice for SPN and organ preservation is advocated if feasible[68]. Distal pancreatectomy with spleen preservation is recommended for SPN located in corpus and tail of the pancreas[69]. Central pancreatectomy with distal pancreatojejunostomy or pancreaticogastrostomy is preferred for SPN located in the neck of the pancreas[70,71]. However, central pancreatectomy is associated with pancreaticoenteric anastomotic leak because of the oversewn proximal pancreatic remnant and distal pancreaticoenteric anastomosis site yielding two potential sources of pancreatic leakage and hence it should be performed in only experienced centers[72]. Pylorus preserving pancreaticoduodenectomy (PPD) is recommended for SPN located in the head of pancreas to decrease dumping syndrome, diarrhea, delayed gastric emptying and marginal ulceration[73]. Enucleation can be done for small SPN distant from pancreatic duct, but it is associated with high risk of pancreatic fistula[70,74]. Spleen preservation is contraindicated if there is splenomegaly, vascular (splenic artery and vein) and hilar involvement[69]. Incidence of lymph node metastasis is very rare in SPN and hence routine lymphadenectomy is not indicated[75]. Enbloc resection with microscopic clear margins is advocated especially when SPN involves portal vein, superior mesenteric vein/artery, spleen, duodenum and for locally progressed[70,76].

Metastasectomy of the liver is advocated at the time of primary resection or even for the recurrences when feasible[68,70,74]. The role of chemotherapy and radiation in SPN is not clear. Surgical treatment of metastasis in SPN is not standardized but debulking can be performed[77]. Hah *et al*[78] reported an unresectable SPN treated effectively by surgical resection of the primary tumor with preoperative chemotherapy (cisplatinum, ifosfamide, etoposide, and vincristine) followed by intraoperative radiofrequency ablation of metastatic liver lesions. Preoperative chemotherapy with fluorouracil and radiation followed by gemcitabine can be attempted in unresectable SPN to decrease the size

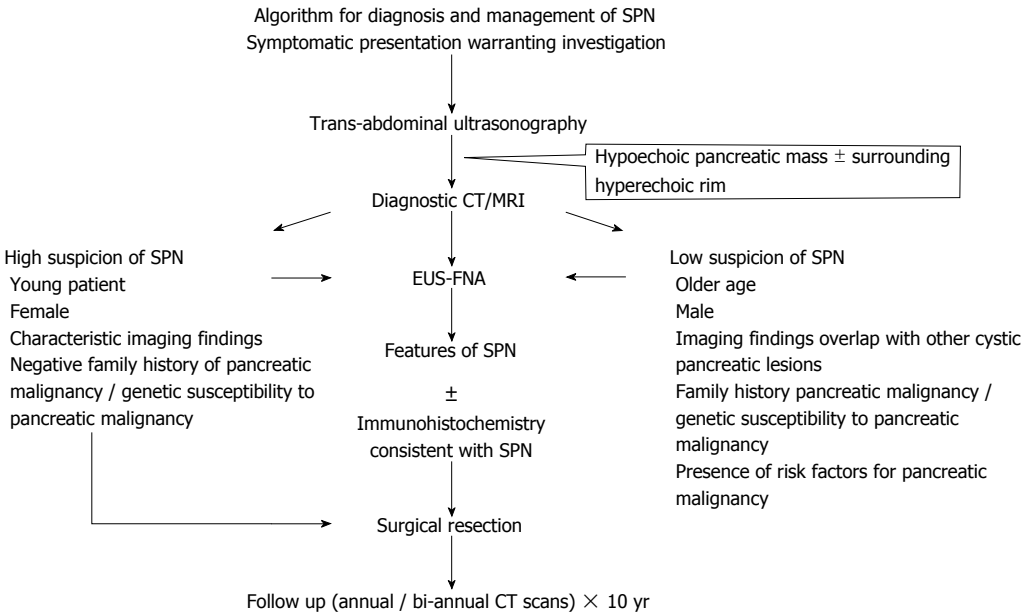

Figure 8 Proposed algorithm for the diagnosis and management of solid pseudopapillary neoplasm.CT: Computed tomography; MIR: Magnetic resonance imaging; SPN: Solid pseudopapillary neoplasm; EUS-FNA: Endoscopic ultrasound-fine needle aspiration.

of the tumor before definitive surgery[79]. Morikawa *et al*[80] reported patient treated with paclitaxel after she had recurrent liver and lymph node metastasis 3 mo after surgery. This patient was previously treated with partial liver resection and chemotherapy with S-1 and gemcitabine. The patient was alive after 20 mo of follow up without disease progression[80]. SPN is considered radiosensitive and radiotherapy can be attempted in tumors considered unresectable[81]. Peritoneal carcinomatosis (PC) can occur with intra operative rupture of SPN. Honore *et al*[82] showed that PC can be successfully treated with complete cytoreductive surgery (CCRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) with irinotecan and oxaliplatin. Extensive liver metastasis from SPN can be treated with trans arterial chemoembolization (TACE). Prasad *et al*[83] showed TACE with gemcitabine and lipoidal followed by gelfoam embolization is effective in treatment of multiple liver metastasis in SPN.

Postoperative complications include wound infection, bleeding, delayed gastric emptying, pseudomembranous colitis, pneumonitis, steatorrhea, pseudocyst, intestinal obstruction, pancreatic fistula, abscess, portal vein thrombosis and recurrence of the tumor[70,71,75,84,85]. Recurrence of SPN is not uncommon after surgery and it is variable. Papavramidis showed that 31/467 (6.6%) had recurrence after 1-10 years of follow up and the most common sites of metastasis were liver and lymph nodes[47]. Tipton *et al*[75] showed 2/14 (14%) had recurrence after a median follow up of 3 mo to 20 years. Machado *et al*[70] showed 2/34 (6%) had recurrence after a mean follow up of 84 mo. Tang *et al*[24] showed that most commonly metastasize to the liver and peritoneum.

Overall 5-year survival for SPN is about 97%, even in the presence of metastasis[24]. Pathological features indicative of aggressive behavior include diffuse growth pattern, high mitotic activity, nuclear atypia, tumor necrosis and component of sarcomatoid carcinoma[24]. There are no specific guidelines for follow up after surgery but SPN with pathologic features indicative of aggressive behavior may require extended period of follow up. Estrella *et al*[86] showed that muscular vessel invasion (tumor cells in the luminal spaces of blood vessels with circumferential smooth muscle layers), tumor (T) stage by European Neuroendocrine tumors society (ENETS) classification, ENETS stage grouping and stage grouping by the American joint committee on cancer (AJCC) were important predictors in disease specific survival of patients with SPN after surgical resection[86]. Recurrence rate was 5/39 (13%) after a median follow up of 76 mo. Ten-year disease specific survival was 96% and metastatic/recurrent disease was significantly associated with large tumor size ($P < 0.001$)[86]. Butte *et al*[7] showed that tumor size at presentation in SPN is associated with malignancy. Kato *et al*[87] showed that tumor doubling time of SPN according to the formula of Schwartz and coworkers is 765 d.

To our knowledge, we came across one review article from our literature search, which summarized the molecular pathogenesis and clinical features of SPN[88]. In our review article, we proposed algorithms for pathogenesis and management in addition to histology and morphology, immunohistochemistry, clinical presentation and diagnosis of SPN using currently available literature. We discussed EUS-FNA and EUS-FNB in preoperative diagnosis of SPN. SOX11, LEF1, TFE3, and AR that can be putative diagnostic markers in SPNs are discussed. Overall, this review article is comprehensive and guides in the management of SPN (Figure 8).

CONCLUSION

Over the last decade, there has been a tremendous increase in the number of SPN cases reported in the literature. A diagnosis of SPN inferred from imaging studies can be adequate to guide surgical resection without preoperative pathological assessment. Nonetheless, EUS-FNA with immunohistochemistry helps in establishing a preoperative diagnosis. A multidisciplinary team approach involving the radiologist, endoscopist, pathologist, oncologist as well as the surgeon improves treatment accuracy and helps in effective management of SPN. Surgical resection should be offered when feasible. Referral to experienced centers for surgery can minimize complications. Future studies should standardize the follow up duration, and the frequency as well as type of diagnostic imaging for surveillance after surgical resection. Overall prognosis of SPN is excellent even in the presence of metastasis.

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REVIEW

Endoscopic diagnosis and treatment of superficial non-ampullary duodenal tumors

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Abstract

The diagnostic and treatment guidelines of superficial non-ampullary duodenal tumors have not been standardized due to their low prevalence. Previous reports suggested that a superficial adenocarcinoma (SAC) should be treated *via* local resection because of its low risk of lymph node metastasis, whereas a high-grade adenoma (HGA) should be resected because of its high risk of progression to adenocarcinoma. Therefore, pretreatment diagnosis of SAC or HGA is important to determine the appropriate treatment strategy. There are certain endoscopic features known to be associated with SAC or HGA, and current practice prioritizes the endoscopic and biopsy diagnosis of these conditions. Surgical treatment of these duodenal lesions is often related to high risk of morbidity, and therefore endoscopic resection has become increasingly common in recent years. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are the commonly performed endoscopic resection methods. EMR is preferred due to its lower risk of adverse events; however, it has a higher risk of recurrence than ESD. Recently, a new and safer endoscopic procedure that reduces adverse events from EMR or ESD has been reported.

Key words: Endoscopic resection; Endoscopic mucosal resection; Superficial non-ampullary duodenal tumor; Endoscopic submucosal dissection; Closure

Core tip: Although superficial non-ampullary duodenal tumors are rare, they can progress to cancer and metastasize, and therefore early diagnosis and treatment of these duodenal tumors is essential. Pretreatment diagnosis for high-grade adenoma or superficial adenocarcinoma helps to determine the appropriate treatment strategy. Endoscopic resection has been adopted as an effective and minimally invasive treatment

for these duodenal lesions; however, even though endoscopic mucosal resection has a lower risk of adverse events, it has a higher risk of recurrence than endoscopic submucosal dissection. Recently, a new and safer endoscopic procedure that reduces adverse events of endoscopic resection has been reported.

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INTRODUCTION

The incidence of duodenal polyps has been reported as 1.0%-4.6% in patients undergoing an upper endoscopy[1-4]. Non-ampullary duodenal cancer is extremely rare, accounting for only 0.5% of all malignancies in the gastrointestinal tract[5]. Superficial non-ampullary duodenal tumors (SNADETs) are defined as lesions that are limited to the mucosa or submucosa, including adenoma and adenocarcinoma. According to a European study, the prevalence of duodenal villous adenoma was 0.1%-0.4% in patients undergoing a diagnostic or screening endoscopy[1,6]. Both duodenal adenomas in familial adenomatous polyposis (FAP) and sporadic non-ampullary adenomas have the potential to progress to carcinomas based on the adenoma-carcinoma sequence theory, similar to colonic adenomas[7-13]. In addition, superficial non-ampullary carcinomas occur *de novo*. Detection and treatment of SNADETs at an early stage is essential for good prognosis because of the poor prognosis of advanced duodenal carcinomas[14,15]. Conventionally, these lesions were removed surgically, but this procedure was associated with a high rate of morbidity and mortality[16-18]. Recently, endoscopic resections (ER) have been conducted for neoplasms in other organs including the esophagus, stomach, and colon, and ER appears to be an ideal treatment alternative to surgical resection for patients with SNADETs. However, ER for SNADETs is related to a high rate of adverse events, including delayed bleeding and perforation[19,20]. Standard diagnosis and treatment have not been established due to the low prevalence of SNADETs; therefore, this study provided the current evidence for diagnosis and treatment of sporadic SNADETs.

RISK FACTORS OF SNADETS

FAP is known to be associated with the incidence of SNADETs[7,21]. Several other factors are believed to be associated with sporadic SNADETs, including smoking, colorectal neoplasm, and *Helicobacter pylori* (*H. pylori*) infection. Smoking was identified as a risk factor for SNADETs or small bowel adenocarcinoma (SBA)[22-24], with reported odds ratios of 2.7-4.6. Colorectal neoplasm was reported as a risk factor of SBA and sporadic duodenal adenoma[22,25-28]; the reported odds ratio for sporadic duodenal carcinoma among patients with a history of colorectal cancer was 3.74. In addition, *H. pylori* infection was identified as a risk factor for SNADETs[22]. A previous study reported that superficial non-ampullary duodenal epithelial carcinoma in patients infected with *H. pylori* was significantly located on the oral side of the major papilla compared to that in patients who were not infected with *H. pylori*[29]. Although gastric cancer and atrophic gastritis mainly result from *H. pylori* infection, the relationship between SNADETs and gastric cancer or atrophic gastritis remains controversial[22,25,29].

CHARACTERISTICS OF SNADETS

SNADETs mainly exist in the descending part of the duodenum[30-32], with 90% of treated SNADETs located from the first to second portion of the duodenum[31-35]. Of note, tumor location is not associated with final histological grade[31].

The gross type of SNADETs were classified according to the Paris endoscopic classification[36]. The gross morphology is based on endoscopic findings and divided into protruded pedunculated (Ⅰp), protruded sessile (Ⅰs), semipedunculated (Ⅰsp), superficial elevated (Ⅱa), or superficial shallow or depressed types (Ⅱc). The elevated type was the most frequent gross type of SNADETs[20,31]. If two or more components were detected, the lesion was diagnosed as a mixed pattern, such as Ⅱa + Ⅱc or Ⅱa + Ⅰs.

PRETREATMENT DIAGNOSES OF SNADETS

Endoscopic diagnoses were made by qualified endoscopists at the time of routine endoscopy, magnifying endoscopy (ME), and chromoendoscopy with indigo carmine (Figure 1). At present, there are no standard criteria for the endoscopic diagnosis of SNADETs and current practice includes obtaining biopsy specimens after endoscopic diagnoses. C4.1 or HGA lesions diagnosed by biopsy were reported to have the potential to progress to malignant lesions[9,10,37], especially for lesions ⩾ 20 mm in size[13,38]. Another study stated that C4.1 tumors diagnosed by biopsy using the Vienna classification with nodular or rough surfaces with a red color were more likely to progress to adenocarcinoma during the follow-up period[13]. Malignant potential is quite different between C3 and C4.1 Vienna classified tumors and between LGA and HGA lesions diagnosed by biopsy. C3 or LGA lesion diagnosed by biopsy showed a low risk of progression to adenocarcinoma[13,39], for which follow-up without ER may be acceptable due to a high risk of adverse events.

The associations between endoscopic diagnoses and final pathological diagnoses of resected specimens

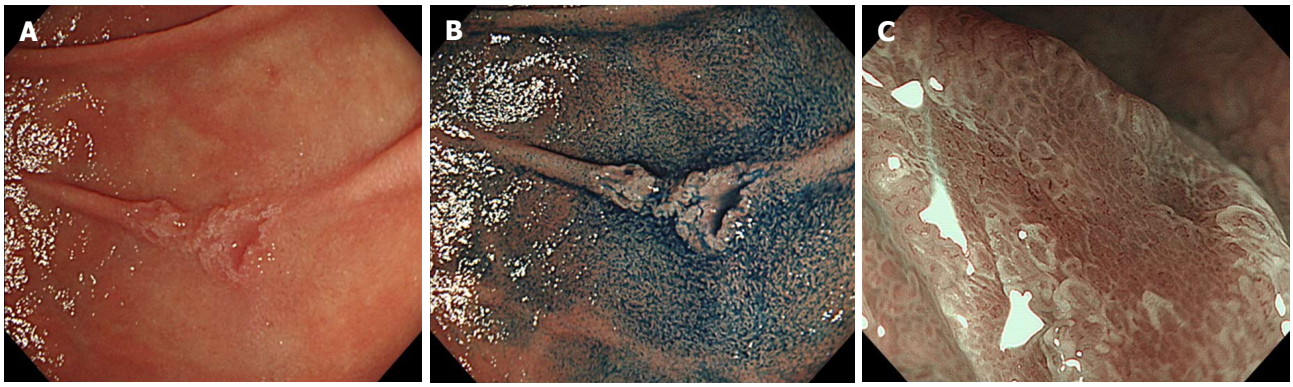

Figure 1 Endoscopic findings of a superficial non-ampullary duodenal tumor. A: A shallow depressed lesion (Ⅱc) is observed in the second portion of the duodenum; B: Chromoendoscopy with indigo carmine; C: Magnifying endoscopy with narrow band imaging.

were reported in duodenal lesions. With regard to lesion size, mean tumor diameter of high-grade adenoma (HGA) lesions or superficial adenocarcinoma (SAC) lesions was significantly larger than that of low-grade adenoma (LGA) lesions[20]. The rate of lesions > 5 mm in diameter in HGA or SAC lesions was significantly higher than that in LGA lesions. Further, all submucosal adenocarcinoma lesions are ⩾ 10 mm in diameter[20]. According to pathological diagnosis based on the Vienna classification, category 4 (C4) tumors had significantly larger diameters than category 3 (C3) tumors[40]. With regard to the color of lesions, a solitary or predominantly red color was significantly more frequent in HGA or SAC lesions than those in LGA lesions[20]. A solely red colored lesion was reported as an indicator of carcinoma[31]. Furthermore, all submucosal cancers were reported to be red[20]. With regard to the macroscopic characteristics of SNADETs, depression and mixed-type morphology are reported to be associated with carcinoma[31,41]. Furthermore, submucosal cancers exhibited 0 - Ⅰ or 0 - Ⅱa + Ⅱc types[20]. The features of these lesions on ME with narrow band imaging (NBI) was also reported, and have been described as consisting of a microsurface pattern and microvascular pattern, which assists endoscopic diagnosis[40,42,43]. In addition, Kikuchi *et al*[44] proposed a diagnostic algorithm using ME with NBI for SNADETs. However, the importance of pretreatment biopsy diagnoses of SNADETs remains controversial. Discordance between pretreatment biopsy diagnoses and final pathological diagnoses was reported in duodenal lesions[13,19,43,45,46], as well as gastric epithelial lesions[47]. Some patients with biopsy diagnoses of HGA before resection were reported to have their diagnoses upgraded from HGA to adenocarcinoma after resection[39]. Pretreatment biopsy diagnoses had greater specificity and similar accuracy, but lower sensitivity compared with pretreatment endoscopic diagnoses[20,31]. Furthermore, Kakushima *et al*[31] reported that pre-treatment diagnoses of carcinomas *via* endoscopy or biopsy were limited to 88% (57/65) of carcinoma lesions. All lesions of carcinomas cannot be diagnosed before treatment, even if biopsy was conducted. Unintended fibrosis may be induced by the biopsy because the duodenal wall is thin, which may make ER more difficult[41,48,49]. Recently, Kakushima *et al*[50] suggested a useful scoring system to determine C3 and C4 lesions. This system was based on lesion diameter, color, macroscopic type, and nodularity that were easily observed *via* endoscopy. A lesion that scored ⩾ 3 points was judged as C4 or higher. The scoring system's diagnostic accuracy rate was 86%, and the scores of C4 or higher lesions were significantly higher than those of C3 lesions ($P < 0.001$). This system helps clinicians decide upon a suitable treatment strategy for SNADETs without biopsy diagnosis.

Some studies categorized SNADETs as LGA, HGA, or SAC based on histological diagnosis[20,39]. On the other hand, the revised Vienna classification was also used as the diagnostic classification for SNADETs in other reports[13,40,42,44]. These two classifications were inconsistent, and there remains difficulty in creating a unified classification.

RISK OF LYMPH NODE METASTASIS AND INDICATIONS FOR ER

Conventionally, surgical removal was conducted for SNADETs; however, high rates of morbidity and mortality were reported. ER was recently recommended as an alternative treatment for SNADETs. Cancer without lymph node metastasis may be indicated for ER. Previous case series have suggested that intramucosal carcinoma has no lymph node metastasis, whereas submucosal carcinoma carries a risk of lymph node metastasis of up to 25%[39,51]. Therefore, indications for ER should be limited to clinically confirmed intramucosal carcinomas, including HGA.

ER FOR SNADETS

ER was applied to SNADETs as an alternative and less invasive treatment to conventional surgical resection. However, ER for SNADETs remains a challenging treatment because it is a technically difficult procedure

with a high adverse events risk. The posterior wall of the duodenum sticks to the retroperitoneum at the superior and lower duodenal angles. It is often difficult to maintain an appropriate visual field during endoscopy while using the endo-knife because the duodenum is located deep within the abdomen and has a narrow and bent lumen. Double-balloon enteroscopy was reported as useful for maneuverability[52]. In addition, achieving mucosal lift *via* local injection is difficult because of numerous folds and Brunner glands. Therefore, although endoscopic muscosal resection (EMR) and endoscopic submucosal dissection (ESD) are mainly performed ER techniques for SNADETs, endoscopic techniques to resect superficial SNADETs have not yet been standardized.

EMR AND SNARE POLYPECTOMY

EMR is a procedure that uses a snare and was the preferred technique used in majority of previous studies. This procedure was developed to resect sessile or flat lesions limited to the superficial layers. EMR was conventionally used not only for en bloc resection, but also for piecemeal resection. A meta-analysis verified the safety and effectiveness of EMR for non-ampullary duodenal polyps, including 90% of adenomas[53]. The mean size of specimens resected *via* EMR was 13-35 mm. The rate of complete ER without remnant part was 93% [95% confidence interval (CI): 89%-97%]; however, the en bloc resection rate was only 45% and the piecemeal resection rate was 55%, with 29% of cases requiring adjuvant argon plasma coagulation after EMR. Furthermore, 10% of cases required multiple procedures to achieve initial complete ER. EMR adverse events included delayed bleeding [5% (95%CI: 2%-7%)] and perforation [1% (95%CI: 1-3%)]. Endoscopic management could be achieved for all intraprocedural perforations, while surgery was required for delayed perforations. The recurrence rate after EMR was 15% over a 6-72 mo follow-up period. The rate of successful endoscopic removal of recurrent lesions was 62% (95%CI: 37%-87%). Surgical intervention was required in only 2.4% (95%CI: 0.6%-4.0%) of cases. There was no procedure-related mortality. Additionally, the safety and usefulness of EMR, as well as the favorable long-term prognosis of this technique, were previously reported[19,33,37,54-57]. However, other reports suggested that lesions > 2 cm in diameter tend to require a piecemeal resection *via* EMR, leading to higher recurrence[33,49,54,58-60]. Increasing tumor circumference in the duodenal lumen was reported as the strongest negative predictor of successful endoscopic treatment including EMR for SNADETs[61].

Recently, underwater EMR (UEMR) was invented as a new technique of EMR. This technique fills the duodenal lumen with physiological saline without a submucosal injection and is based on a similar principle as conventional EMR, which lifts the mucosa and submucosa away from the deeper muscularis propria layer to achieve successful ER. The effectiveness of UEMR for the treatment of small SNADETs within 20 mm was reported[62]. Closure with endoclip was achieved for all lesions due to small mucosal defects after UEMR, and this may have accounted to the lack of any associated adverse events (*i.e.*, delayed perforation and bleeding).

Additionally, cold polypectomy, including cold snare polypectomy (CSP) and cold forceps polypectomy (which were originally used for colorectal neoplasms), was adopted as a method for small SNADETs. One study compared resection width and depth of polyps treated with CSP and HSP, and found that although the resection depth after CSP was more superficial compared to that after HSP, resection depth was adequate following both techniques, and suggested that CSP may have a superior safety profile to HSP for colorectal subcentimeter polyps[63]. In another study, the effectiveness of cold polypectomy in treating both sporadic and multiple SNADETs was reported without adverse events[64].

ENDOSCOPIC SUBMUCOSAL DISSECTION

ESD was invented for en bloc resection of gastrointestinal lesions where it is frequently used for the treatment of gastric, colonic and esophageal lesions, but rarely used for duodenal lesions. This may be partly explained by the fact that ESD requires a high skill level and a qualified operator with thorough knowledge of duodenal anatomy, which is characterized by an abundance of blood vessels in the submucosal layer and a thin muscle layer[65]. However, in qualified hands, ESD has been reported to achieve complete resection (en bloc resection without positive margin) in 80%-100% of SNADETs[34,43,45,49,66,67] (Figure 2). The size of tumors that are treated *via* ESD is larger than that *via* EMR. The rate of en complete resection using ESD is higher than that using EMR, which contributes to accurate histopathological assessment of vertical and horizontal surgical margins, and results in a lower risk of local recurrence[49,58,68-70].

ESD has been reported to be associated with a higher rate of perforation than EMR, even among tumors of the same size[48,68,71,72]. Electrocauterization, which is a major risk factor for delayed perforation after endoscopic treatment, is more frequently required during ESD than during EMR[73]. The rates of intraoperative and delayed perforations were reported as 6.3%-50.0% in ESD cases and 0%-14.3% in EMR cases[34,58,66,67,74-76]. Moreover, emergency surgery has been performed in 3.3%-25.0% of patients who underwent duodenal ESD as a result of uncontrollable intraoperative or delayed perforations[46,49,66,67,77]. Perforations occurred in the anal portion of the ampulla of Vater because exposure of the duodenal wall to pancreatic juice and bile enzymes caused proteolysis or chemical irritation[34]. Therefore, ESD should be performed in clinically appropriate patients with SNADETs in order to avoid such serious adverse events. Moreover, clinicians should take into

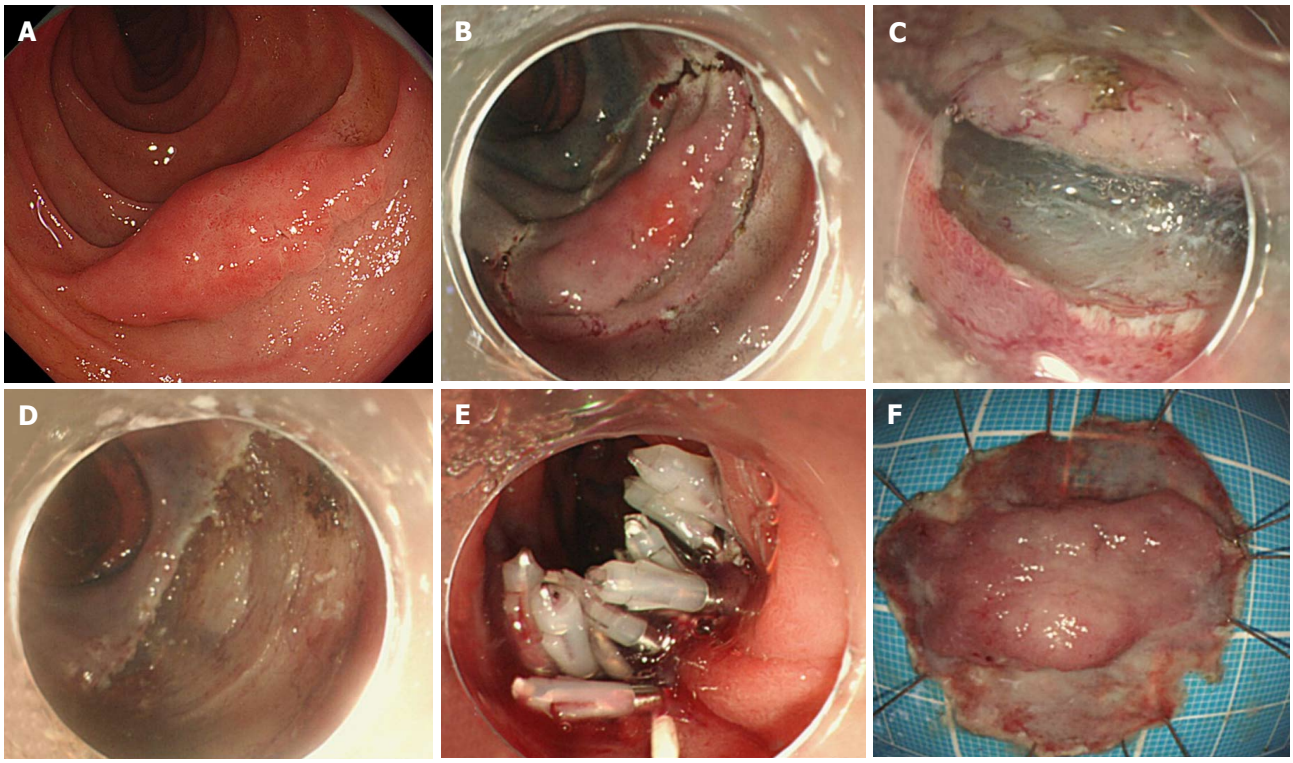

Figure 2 Endoscopic submucosal dissections for a superficial non-ampullary duodenal tumor. A: Protruded sessile type (Ⅰ s) larger ⩾ 20 mm in size; B: Mucosal incision around the lesion; C: Submucosal dissection of the lesion after mucosal incision; D: Mucosal defect after endoscopic submucosal dissection; E: Closure of mucosal defect using multiple endoclips; F: Resected specimen.

account the fact that the length of hospital stay is longer in patients that underwent ESD compared to EMR due to the higher incidence of adverse events in the former[58]. Therefore, lesions that are resectable using EMR should not be resected using ESD. ESD is recommended for lesions > 20 mm or those suggestive of carcinoma, which can likely be resected en bloc. Where duodenal ESD was indicated, cases tended to be performed under general anesthesia, and this was especially true for larger lesions, in order to ensure safety and to facilitate transition to surgery in the case of an adverse event[58,68]. Recently, the pocket-creation method using an ST hood was proposed as a safe and quick alternative for duodenal ESD[78], which facilitates access into the submucosal layer *via* the ST hood. The evidence summarized above demonstrates that ESD is still a challenging procedure due to its high adverse events rate; and therefore, regardless of the procedure used, an appropriate closure technique after ESD is required.

CLOSURE OF THE MUCOSAL DEFECT AFTER ER

Closure of the mucosal defect after ER has been suggested as a countermeasure for duodenal perforation, which may reduce the risk of hazardous adverse events, as well as ESD in the colon[66,79]. Simple prophylactic closure using an endoclip after duodenal ER was reported to reduce the risk of delayed bleeding[80]. However, complete closure could not be achieved with a conventional clip, especially for a large ulcer after ESD, because the size of a conventional clip is too small. Furthermore, the grasp strength of a conventional clip is insufficient to maintain closure. In fact, some clips drop off, resulting in reports of delayed perforation[81]. The combination of endoclip and Endoloop using a double-channel endoscope was reported for closure of large mucosal defects after ER[82-84]. Recently, closure *via* the string clip suturing method was developed, which can be completed with a single-channel endoscope[85]. Furthermore, the over-the-scope clip (OTSC) (Ovesco Endoscopy AG, Tubingen, Germany), polyglycolic acid (PGA) sheets (Neoveil; Gunze Co., Kyoto, Japan) with fibrin glue (Beriplast P Combi-Set; CSL Behring Pharma, Tokyo, Japan), and laparoscopic-endoscopic cooperative surgery (LECS) were recently reported as possible measures of closure for large mucosal defects after duodenal ESD.

OTSC was invented as a device for closure of mucosal defects in acute gastrointestinal perforation and anatomic leaks, in addition to being a hemostatic device for bleeding lesions[86,87], and has been used for closure of gastrointestinal tract defects after ESD in the duodenum. Mori *et al*[88] reported the clinical outcome of prophylactic closure after ESD using OTSC, and found no occurrences of delayed bleeding and delayed perforation. If the mucosal defect after ER is > 20 mm, prophylactic closure with the OTSC is recommended for safe and reliable closure, in spite of its higher medical

costs compared to other available closure devices.

The combination of PGA and fibrin glue has been generally used and proven safe in various surgeries[89-92]. These materials were applied to endoscopic treatment of the esophagus, stomach, and colon[93-95], and were found to reduce the risk of post-ESD bleeding[93]. Similarly, some case reports showed the efficacy of shielding over ulcers after ER in the duodenum[81,96,97]. These materials are naturally absorbable, but remain on the lesion for approximately 1 wk, which is when delayed bleeding and perforation are likely to occur[81]. This procedure may be particularly useful in lesions that are difficult to close endoscopically or through surgery because of their anatomical location.

LECS was developed as a treatment procedure for gastrointestinal tumors[98]. This procedure is also applied to duodenal tumors to reduce the risk of adverse events. SNADETs are mainly treated with laparoscopic reinforcement after ESD, which is called duodenal LECS (D-LECS)[99]. In this procedure, the mucosal defect is closed appropriately and tightly after laparoscopic suturing of the duodenal wall from the serosal side. No severe postoperative adverse events were reported. Laparoscopic surgery can also assist the ESD procedure by repositioning the duodenum. Furthermore, if perforation occurred during the ESD procedure, the perforation can be closed endoscopically and laparoscopically, which is easier than endoscopy alone. D-LECS was completed in a closed manner with no risk of tumor dissemination. However, ESD and LECS are most expensive than EMR, and LECS is not covered by the national insurance system. Although ESD and LECS may be more cost-effective in the long-term because of their associated low recurrence rates, we have to take into consideration the high cost of ESD and LECS.

CONCLUSION

Although SNADETs are rare, they have a potential of progression to cancer or further metastasis. Therefore, the development of diagnosis and treatment procedures at an early stage is important. However, these developments may have occurred slower than those in other gastrointestinal organs and are not yet standardized. Hence, developing unified criteria and algorithms for diagnosis and treatment of SNADETs is an important clinical priority.

EMR may be the current first-line treatment for SNADETs to prevent malignant progression. For smaller lesions, UEMR or cold polypectomy may be safer. Although ESD has a higher risk of adverse events, a higher en bloc resection rate can be achieved, which is suitable for larger lesions or lesions that are highly suspicious of carcinoma. Closure techniques and the shielding method for mucosal defect after ESD were reported as useful methods for preventing ESD adverse events. These new methods may overcome adverse events in ESD.

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MINIREVIEWS

Endoscopic therapy for Barrett's esophagus and early esophageal cancer: Where do we go from here?

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Abstract

Since Barrett's esophagus is a precancerous condition, efforts have been made for its eradication by various ablative techniques. Initially, laser ablation was attempted in non-dysplastic Barrett's esophagus and subsequently, endoscopic ablation using photodynamic therapy was used in Barrett's patients with high-grade dysplasia who were poor surgical candidates. Since then, various ablative therapies have been developed with radiofrequency ablation having the best quality of evidence. Resection of dysplastic areas only without complete removal of entire Barrett's segment is associated with high risk of developing metachronous neoplasia. Hence, the current standard of management for Barrett's esophagus includes endoscopic mucosal resection of visible abnormalities followed by ablation to eradicate remaining Barrett's epithelium. Although endoscopic therapy cannot address regional lymph node metastases, such nodal involvement is present in only 1% to 2% of patients with intramucosal adenocarcinoma in Barrett esophagus and therefore is useful in intramucosal cancers. Post ablation surveillance is recommended as recurrence of intestinal metaplasia and dysplasia have been reported. This review includes a discussion of the technique, efficacy and complication rate of currently available ablation techniques such as radiofrequency ablation, cryotherapy, argon plasma coagulation and photodynamic therapy as well as endoscopic mucosal resection. A brief discussion of the emerging technique, endoscopic submucosal dissection is also included.

Key words: Endoscopic mucosal resection; Barrett's esophagus; Dysplasia; Adenocarcinoma; Endoscopic therapy; Radiofrequency ablation

Core tip: Endoscopic treatment has become the standard

of care for Barrett's esophagus with dysplasia and/or early adenocarcinoma. The treatment primarily consists of resection of any visible lesions by either endoscopic mucosal resection or rarely, endoscopic submucosal dissection followed by ablation of metaplastic epithelium by one of the many available techniques (radiofrequency ablation being the most commonly used). While periodic surveillance is still required after complete eradication of intestinal metaplasia, these treatment modalities have proven to decrease the incidence of esophageal adenocarcinoma, improve the quality of life and are cost effective.

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INTRODUCTION

Barrett's esophagus (BE), defined as an extension of salmon colored mucosa into the esophagus for a distance ⩾ 1 cm above the gastroesophageal junction with biopsies confirming intestinal metaplasia (IM)[1], increases the risk of progression to esophageal adenocarcinoma (EAC). In non-dysplastic BE (NDBE), the risk of development of EAC is 0.3% annually[2] which increases to 0.5% in BE with low grade dysplasia (LGD)[3] and 7% with high grade dysplasia (HGD)[4]. While BE with HGD or intramucosal cancer (IMC) were traditionally treated by esophagectomy, the pendulum has swung from surgical to endoscopic management over the last 2 decades owing to the lower morbidity, lower cost and similar long term survival rates with endoscopic treatment compared to esophagectomy[5-9].

Endoscopic resection of visible lesions if any, followed by ablation of the rest of the BE epithelium is the current standard of care for management of BE with confirmed dysplasia and IMC[1,10,11]. Since there is a small risk of recurrence (7.1% per patient year for IM, 1.3% for LGD and 0.8% for HGD/EAC)[12], periodic surveillance is recommended after complete eradication of BE. Amongst the ablation modalities, photodynamic therapy (PDT) was one of the first techniques used for ablation and over time, various other techniques like argon plasma coagulation (APC), cryotherapy and radiofrequency ablation (RFA) have been developed with RFA being the most widely used modality currently. (Table 1)The underlying principle behind the ablation therapies is that under conditions of maximal acid suppression, injury to BE mucosa leads to regeneration of normal squamous mucosa.

The focus of this review is to examine the evidence for efficacy of various ablation modalities and the resection techniques used for eradication of BE such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD).

Literature search was conducted by an experienced librarian using Ovid Medline and PubMed from 1990 to present using the search terms "Barrett's", "esophageal adenocarcinoma", "endoscopic treatment", "ablation", "radiofrequency ablation", "cryotherapy", argon plasma coagulation", "photodynamic therapy", "multipolar electrocoagulation", "endoscopic mucosal resection", "endoscopic submucosal dissection". Only articles in English language were reviewed.

RADIOFREQUENCY ABLATION

RFA is currently the most widely used technique to treat BE with dysplasia due to its ability to deliver uniform ablation to a consistent depth of the esophageal wall.

Technique

RFA causes tissue necrosis by using direct contact current to generate thermal injury. Circumferential BE longer than 3 cm is ablated by circumferential technique and non-circumferential segments or segments < 3 cm are ablated by focal technique[13]. Currently available catheters for RFA are Barrx 360 Express catheter for circumferential ablation and Barrx 90, Barrx 90 Ultra, Barrx 60 or through-the-scope (TTS) for focal ablation.

Circumferential ablation

Barrx 360 Express catheter consists of a 4 cm long bipolar electrode situated at the end of 85 cm shaft. After washing the esophagus with water or N-acetylcysteine, a guidewire is passed through the biopsy channel and the endoscope is removed. The catheter is then passed over the guidewire. The catheter, which has external markings is placed 1 cm above the proximal extent of BE under endoscopic visualization. When the pedal is pressed, the balloon inflates and self-adjusts depending on the esophageal diameter and radiofrequency energy is delivered resulting in circumferential ablation. The catheter is then advanced distally and ablation performed in a sequential manner. After the ablation is completed, the coagulum is scrapped off using a cap attached to the tip of the endoscope and the steps are repeated. Endoscopy is repeated in 8-12 wk to ablate any residual areas (with circumferential or focal method depending on residual segment).

Focal ablation

Depending on the surface area that needs to be ablated, focal catheters are selected; for example, Barrx 60 ablates 150 mm^2, Barrx 90 ablates 260 mm^2 and 90 ultra ablates 520 mm^2. The catheter is externally attached to the tip of the endoscope in the 12 O' clock position and advanced to the target area. After the tip of the endoscope is deflected to get the catheter in contact with the mucosa, radiofrequency energy is applied twice. After scraping the coagulum off, the procedure is repeated. TTS catheter can be passed through the

Table 1 Comparing the efficacy and complication rate of various endoscopic techniques

Technique	Efficacy	Complication rate
Radiofrequency ablation	CE-D: 92%-98%[15,16]	Strictures: 5%-6%[26]
	CE-IM: 88%-91%[15,16]	Chest pain: 3.8% Bleeding: 1%
Cryotherapy	CE-D: 95%[30,33] CE-IM: 88%[30,33]	Strictures: 3%-13%[33,34] Bleeding: 2%
Argon plasma coagulation	CE-IM: 58%-78%[38,40]	Stricture: 4%[40,47]
		Bleeding: 4% Perforation: 2%
Photodynamic therapy	CE-D: 80%[50,51]	Photosensitivity: 69%[57]
	CE-IM: 43%-53%[50,51]	Stricture: 36%[58]

CE-D: Complete eradication of dysplasia; CE-IM: Complete eradication of intestinal metaplasia.

biopsy channel of the scope.

Efficacy

In a landmark study conducted by Shaheen *et al*[14], 127 patients were randomized to RFA (42 each with HGD and LGD) or sham procedure (21 with HGD and 22 with LGD). The primary outcomes measured were complete eradication of dysplasia (CE-D) and eradication of intestinal metaplasia (CE-IM). After 12 mo, among patients with LGD, CE-D was seen in 90.5% patients with RFA compared to 22.7% in the sham group ($P < 0.001$). Similarly, CE-D was noted in 81% patients with HGD after RFA compared to 19% in control group ($P < 0.001$). CE-IM was seen in 77.4% in the RFA group compared to 2.3% in sham group ($P < 0.001$). Progression of dysplasia was seen more frequently in the control group (16.3% *vs* 3.6%, $P = 0.03$). During follow up of this cohort reported separately, patients in the sham group who had persistence of IM were allowed to cross over to the RFA group. After 3 years, CE-D and CE- IM was noted in 98% and 91% patients respectively[15].

To assess the utility of ablation in patients with LGD, Phoa *et al*[16] performed a randomized clinical trial comparing RFA to endoscopic surveillance in BE with LGD patients and looked at the primary outcome of progression to HGD or EAC over a follow up period of 3 years. One hundred and forty patients were randomized in a 1:1 ratio to receive RFA or endoscopic surveillance (at 6 mo, 12 mo and then annually after randomization). In the ablation group, patients were less likely to progress to HGD/EAC compared to surveillance group (1.5% *vs* 26.5% respectively, $P < 0.001$) or to EAC (1.5% *vs* 8.8% respectively, $P = 0.03$). CE-D and CE-IM was noted in 92.6% and 88.2% patients respectively. Of these patients, CE-D and CE-IM was maintained in 98.4% and 90% of patients respectively over the follow up period. Similar results supporting the use of RFA to treat LGD have been reported by Small *et al*[17] and by Qumseya *et al*[18] in a recent meta-analysis.

Recurrence

Recurrence of IM or dysplasia can occur after CE-IM. Hence, ongoing surveillance is mandatory. In the United States RFA registry, recurrence of BE has been noted in 20% patients over a follow up of 2.4 years and dysplasia was reported among 14% of those who had BE recurrence[19]. Recurrence was higher with older age, longer length of BE segment and in non-Caucasians.

In a recent meta-analysis of patients who achieved CE-IM after RFA, IM recurrence rate was 5.8 per100 patient years. The majority of recurrences were amenable to repeat endoscopic eradication therapy (EET)[20]. Neither BE nor dysplasia recurs at a constant rate. Of 119 patients in the AIM Dysplasia trial, IM recurrence rate was 10.8 per 100 person-years and dysplasia recurrence rate was 5.2 per 100 person-years[21]. There was a greater probability of recurrence in the first year following CEIM than in the following 4 years combined.

Cost-effectiveness

Among patients with HGD, RFA is more cost effective compared to surveillance followed by esophagectomy when EAC is detected[22] or proceeding straight to esophagectomy[23]. In LGD patients, RFA might be cost effective but it comes at a cost of $40915 per prevented event of progression[24]. After RFA, patients have reported significant improvement in quality of life, less stress about esophageal cancer or esophagectomy[25].

Complications

RFA is a safe procedure due to the limited depth of ablation. The most common complication after RFA is stricture formation which occurs in 5%-6% patients[26]. The other complications include post-procedure chest pain (3.8%), bleeding (1%) and perforation (0.6%).

CRYOTHERAPY

Cryotherapy involves the principle of rapid freezing and slow thawing of the tissue in multiple cycles leading to immediate cellular injury. Delayed effects include loss of microcirculation leading to anoxia and stimulation of cytotoxic T cells[27]. The cryogens which have been utilized in BE ablation are liquid Nitrogen (TrueFreeze Cryospray, CSA Medical, Lexington, Massachussets), Nitrous oxide (Coldplay CryoBalloon Focal Ablation System, C2 Therapeutics, Redwood City, California) and liquid carbon dioxide (Polar wand, GI Supply, Camp Hill, Pa). The Polar Wand system production ceased in March 2016 and will not discussed further in this review.

CRYOSPRAY WITH LIQUID NITROGEN

Technique

Liquid nitrogen is delivered through Cryospray catheter

that is passed through the biopsy channel of the endoscope. The liquid nitrogen rapidly expands into gas and freezes tissues to -196 degree Celsius. A decompression tube passed along the endoscope allows for venting during the session. The noncontact delivery allows ablation of uneven surfaces such as nodules, masses and plaques. The site is frozen for 20 s each for a total of 2 cycles, allowing for cooling for at least 45 s between the cycles.

Efficacy

Johnston *et al*[28] first reported the use of cryotherapy to treat BE in 11 patients with dysplasia degree varying from NDBE to HGD of which 9 patients completed the treatment. Out of these 9 patients, 7 (78%) had CE-IM. In 98 patients with BE and HGD (14 had previously undergone other ablation treatments), after a follow up of 10.5 mo, remission of HGD was seen in 97%, CE-D was seen in 87% and 57% had CE-IM (only 60 patients had completed all cryotherapy treatments at the time of reporting of results)[29]. The eradication response appears to be durable for up to 5 years. Over a follow up period of 5 years in 40 patients with HGD or EAC, complete remission of HGD, CE-D and CE-IM was seen in 93%, 88% and 75% of patients respectively[30]. Incidence of recurrent HGD/EAC was 1.4% per person years. Compared to RFA, patients undergoing cryotherapy are less likely to have CE-IM but efficacy of both techniques to eradicate dysplasia is similar[31]. Cryotherapy can also be used in BE refractory to RFA. In a recently published meta-analysis comprising 148 BE patients treated with cryotherapy for persistent dysplasia or IM after RFA, CE-D was 76.0% and CE-IM was 45.9%[32].

CRYOBALLOON FOCAL ABLATION SYSTEM

Technique

The balloon catheter is passed through the working channel of therapeutic endoscope and attached to a handle that contains cartridge with liquid nitrous oxide. On pressing the trigger, the balloon is inflated and the cryogen is delivered to the ablation site for 10 s cooling the tissue to -85 degree C.

Efficacy

In 41 patients with LGD (n = 13), HGD (n = 23) or IMC (n = 5), 1-year CE-D and CE-IM rates were 95% and 88%, respectively. CE-D rate was significantly lower (67%) in those with ultra-long BE compared with those with < 8 cm (100%, P = 0.02)[33].

Complications of Cryotherapy

Minor adverse events reported with Cryospray include chest pain, esophagitis, sore throat, lip ulcer, esophageal ulcers, and dysphagia[34]. Strictures have been reported in 3% to 13% of treated patients. With cryoballoon, 9.7% patients developed strictures and 2% had minor bleeding[33].

ARGON PLASMA COAGULATION

Technique

In APC, ionized argon gas is used to ablate BE. After placing a grounding pad on the patient, the machine containing the argon gas and coagulator is turned on and ablation is performed using an APC probe set to a flow rate of 1.6 liter/minute and power setting of 40-90 W. A recent advance is hybrid APC where a submucosal cushion is created before performing APC.

Efficacy

In 1998, Van Laethem *et al*[35] described their experience with use of APC. They included 31 patients with BE (26 had NDBE and 5 had LGD). After a mean of 2.4 treatments, 19/31 patients had CE-IM. On one year follow up, 9/31 patients had no histological evidence of recurrence of BE. Among the 9 patients with BE treated by Grade *et al*[36], endoscopically, squamous re-epithelialization was seen in all 9 patients but histologically, 2 of these patients had evidence of IM. Similar results were also reported by Byrne *et al*[37] in Europe. A randomized controlled trial comparing APC to periodic surveillance in 40 patients with NDBE or BE with LGD[38] reported CE-IM in 58% with APC compared to 15% in surveillance group; (P < 0.001). Use of APC for treatment of BE with HGD was reported by Attwood *et al*[39] in 2003 in 29 patients. These patients were followed up for a mean of 37 mo. HGD was successfully treated in 25 patients and 22 of these patients had CE-IM. Of the other 3 patients, HGD resolved after multiple treatments and in 1 patient, LGD persisted. A multicenter study by Manner *et al*[40] on 60 patients with NDBE reported CE-IM in 77% with APC. Recurrence rate of 18% was reported in 3 year follow up[41]. The majority of data published on APC has been on NDBE and the utility of treating BE in the absence of dysplasia and exposing patients to side effects has been repeatedly questioned[42-44] and thus this strategy fell out of favor.

Recently, use of APC following submucosal injection (Hybrid APC) to treat residual BE after endoscopic resection of early EAC was described by Manner *et al*[45] in a series of 60 patients. CE-IM was observed in 78% patients. Injection of normal saline in the submucosa limited the depth of thermal ablation and resulted in stricture formation in only 1 patient.

Compared to RFA which requires around 30 procedures to effectively treat the lesions, the learning curve of APC is shorter.

Complications

Self-limiting odynophagia or dysphagia is commonly reported after APC[46]. In their multi-center study, Manner *et al*[40] reported bleeding in 3.9%, stenosis in

3.9% and perforation in 2% of the patients.

PHOTODYNAMIC THERAPY

Technique

PDT relies on the principle that once a photosensitizer is administered and activated by light, superoxide and hydroxyl free radicals are formed that cause apoptosis of the cells. The metaplastic and neoplastic cells[47] have more affinity for photosensitizer leading to preferential damage of the BE epithelium with preservation of normal squamous mucosa. In the United States, an intravenously administered photosensitizer, porfimer sodium (Photofrin, Wyeth-Ayerst Lederle Parenterals, Carolina, PR) and in Europe, an orally administered agent 5-aminolevulinic acid (Levulan, DUSA Pharmaceuticals, Wilmington) or intravenously administered m-tetrahydroxyphenyl chlorin (Foscan, Biolitech, Pharma Ltd, Dublin, Ireland) are used. Porfimer sodium is administered at a dose of 2 mg/kg intravenously. Approximately 48 h later, upper endoscopy is performed and red light is transmitted either by optical fiber or balloon diffusing fibers that are passed through the endoscope. Porfimer sodium is activated by red light (wavelength of 630 nm) at energy of 130-200 J/cm. Endoscopy may be repeated 2-3 d later to assess the mucosal damage and re-treat if needed.

Efficacy

After the successful use of PDT in 2 patients with early EAC was described by Overholt *et al*[48] in 1993, its use in 4 patients with BE and LGD and 1 patient with BE and HGD was reported by Laukka *et al*[49] in 1995. In a large series of 100 patients (14 with LGD, 73 with HGD and 13 with EAC) treated with PDT[50], CE-IM and CE-D was observed in 43 and 79 patients respectively. In a multicenter randomized trial of 208 patients with BE and HGD with follow up of 24 mo, 52% patients in the PDT group had CE-IM compared to 7% in the omeprazole only group ($P < 0.001$). Thirteen percent of patients in PDT group developed EAC during follow up compared to 28% in omeprazole group ($P = 0.006$). Five year follow up data[51] reported that probability of maintaining complete remission was higher in the PDT group compared to omeprazole only group (48% *vs* 4%, $P < 0.0001$) and progression to cancer continued to remain low in the PDT group (15%) when compared to omeprazole group (29%) ($P = 0.027$). In a Markov Monte Carlo Model, Hur *et al*[52] proved that PDT was more effective than just periodic surveillance of HGD and esophagectomy with an incremental cost effective ratio of $12400/quality adjusted life year (QALY) and $3,300/QALY compared to surveillance and esophagectomy respectively. Similar results were also reported later by Shaheen *et al*[53].

The length of BE segment predicts the likelihood of complete ablation of BE with PDT[54]. Patients with BE $\geqslant$ 3 cm are less likely to have CE-IM compared to those with BE < 3 cm. After eradication, smoking, older age and presence of residual non dysplastic BE are associated with higher likelihood of recurrence[55].

Complications

Photosensitivity is the commonest side effect being reported in up to 69% patients after PDT treatment using porfimer sodium[56] because of absorption of porfimer sodium by the skin from the systemic circulation which is then activated by light. The reaction is mild in majority of the cases and occurs in sun-exposed areas. After PDT, patients are advised to apply sunscreen, fully cover the exposed body parts when going in sunlight for 4-6 wk. Esophageal stricture is another side effect occurring in around 36% patients[56]. The other side effects include vomiting, dyspepsia and chest pain. Treatment with 5-aminolevulinic acid is associated with lower incidence of photosensitivity reactions and stricture formation[57] but it is not commonly used in the United States.

ENDOSCOPIC RESECTION TECHNIQUES

In patients who have nodular BE with dysplasia/EAC limited to the mucosa or visible lesions with HGD/EAC, resection of the lesions is done by EMR followed by ablation of the rest of the Barrett's mucosa by RFA because there can be 30% risk of metachronous lesions in the rest of the mucosa. Endoscopic resection is largely limited to cancers confined to the mucosa because of extremely low risk of lymph node metastasis in these lesions.

ENDOSCOPIC MUCOSAL RESECTION

EMR is performed either by Lift-suck-cut technique or by Ligate and cut technique. The ligate and cut technique is the more commonly used due to shorter procedure time and less cost while having a similar side effect profile[58].

Ligate and cut technique

Once the lesion is identified, the margins of the lesions are marked using APC. A modified variceal band ligator is then mounted on the endoscope with the handle attached to the proximal end of the working channel. The rubber cap that is attached to the tip of the endoscope has 6 bands and is connected to the handle by a tripwire. After the scope is introduced into the esophagus, the lesion is sucked into the cap and a rubber band is released using the handle after which the lesion is resected using a snare.

Lift-suck-cut technique

After a clear EMR cap is fitted on the tip of the endoscope, the endoscope is advanced to the lesion and the submucosa is lifted by injection of normal saline.

The snare is then passed and positioned in the groove on the distal end of the cap. After a pseudopolyp is created by suctioning the lesion into the cap, the snare is positioned across the base and cautery is applied to resect the lesion.

Efficacy

Ell *et al*[59] were among the first to describe the use of EMR to treat EAC/HGD in a series of 64 patients (61 with EAC and 3 with HGD). The patients were divided into low and high risk groups based on tumor size, macroscopic appearance of lesion, grade on histology, evidence of submucosal invasion. In the low risk group, 34/35 patients showed complete remission at 12 mo follow up. During that follow up period, 6 patients had developed recurrence (4 had local recurrence and 2 had metachronous lesions) that was treated endoscopically. Of note, these patients had EMR of the lesions only without any treatment of the surrounding BE.

To resect the visible lesions by EMR and then to treat the rest of the Barrett's segment to prevent metachronous cancer, Buttar *et al*[60] described the technique of combining EMR with PDT in a series of 17 patients in 2001. PDT was done 4 wk after EMR. Sixteen out of 17 patients remained in remission after a median follow up period of 13 mo and BE was successfully eradicated in 53% patients. In an effort to completely eradicate the lesions and surrounding BE, the concept of using endoscopic resection of entire BE segment over multiple sessions to remove all metaplastic tissue called as stepwise radical endoscopic resection (SRER) has evolved. Various studies reported excellent outcomes with CE-IM rates varying from 86% to 96%[61-63].

Once the use of RFA to treat dysplastic BE started becoming more popular, Gondrie *et al*[64] reported good efficacy with combined use of EMR and RFA in a small series of 12 patients. A multi-center randomized trial compared EMR followed by RFA to EMR for eradication of the entire BE segment[65]. Twenty two patients were randomized to the focal EMR plus RFA and 25 patients to SRER groups respectively. With SRER, complete remission of neoplasia was achieved in 100% of patients and CE-IM in 92% patients. In focal EMR+ RFA group, complete remission of neoplasia as well as CE-IM was achieved in 96% patients. A lower complication rate was noted with focal EMR+RFA technique making this technique the preferred one for treating BE with visible lesions. The United States multicenter consortium reported follow up results of 592 patients (71% had HGD or EAC and 55% had undergone EMR). After 24 mo, CE-IM was seen in 56% patients[66] and recurrence of neoplasia was only seen in 1 patient. In a series of 1000 patients treated by EMR for EAC and different ablative techniques for the rest of BE, Pech *et al*[67] reported that complete remission was initially achieved in 96.3% patients. While 14.5% patients had recurrence, it was endoscopically treated in 115/140 patients resulting in long-term complete remission rates of 93.8%. In 2016, Baret *et al*[68] did report successful outcomes with EMR followed by RFA in a single session in patients with short segment BE but again, this method is not widely practiced yet.

While the use of EMR to treat EAC confined to the mucosa has been extensively studied as described above, its utility in treating EAC confined to submucosa has also been studied. In 2008, Manner *et al*[69] described their experience about 21 well differentiated EAC patients who had submucosal invasion confined to upper 1/3rd of submucosa without any lymph/vessel invasion. One of these patients had surgery before EMR and one died before completion of EMR. Of the remaining 19 patients, after a mean of 2.8 sessions of EMR, complete remission after EMR was achieved in 18 patients. Over a 5 year follow up period, recurrent neoplasia was seen in 3 patients and metachronous neoplasia in 2 patients. These lesions were successfully treated by EMR (4 patients) and APC (1 patient).

Complications

Tomizawa *et al*[70] reported on the safety outcomes of 684 patients who underwent EMR for BE (majority of whom had HGD/EAC). Bleeding and strictures were reported in 1.2% and 1% patients respectively. With stepwise radical EMR, the incidence of stricture formation was much higher varying between 27%and 37%[61,71] depending on the size of lesion. Perforation has been reported to occur infrequently varying from 0.2% to 1.3%[72].

ENDOSCOPIC SUBMUCOSAL DISSECTION

ESD is a technique originally developed in Japan for removal of early gastric neoplasms and subsequently extended to resection of early neoplastic lesions in other parts of gastrointestinal system. It is generally difficult to resect lesions greater than 2 cm en-bloc using EMR technique. The advantage of ESD over EMR is the ability to resect lesions *en bloc* irrespective of size. ESD can be considered in cases wherein the lesion is larger than 15 mm, when there is poor lifting, or with endoscopic features imply possible submucosal invasion[73].

Technique

Circumferential coagulation markers are placed around the lesion. Solution is then injected into the submucosal space to lift the lesion. Using an electrosurgical knife, a circumferential incision is made around the lesion after which the submucosa is carefully dissected and the lesion is removed en-bloc.

Efficacy

The use of ESD for visible lesions combined with RFA for the rest of the BE segment was described by Neuhaus *et al*[74] in 2012 on 30 patients (EAC in 24 and HGD in 6). ESD was successful in removing the lesions in

29 patients. Of the 28 patients that were followed up, remission from neoplasia was seen and in 1 patient who had residual cancer, EMR was successful in removing the cancer. 15 patients had complete remission of intestinal metaplasia by ESD alone. Of the other 13, 10 had RFA done of which 8 had complete remission of metaplasia. In a recently published meta-analysis of ESD in early BE neoplasia , complete and curative resection rates were 74.5% and 64.9% respectively[75]. Incidence of recurrence after curative resection was 0.17% at a mean follow-up 22.9 mo.

Because ESD is time consuming, requires more training and expertise, along with higher complication rates and since good outcomes have also been achieved with EMR, the utility of ESD in small lesions has been questioned. Terheggen *et al*[76] randomized 40 patients with BE HGD and IMC to EMR or ESD. Disease free margins were achieved more frequently with ESD compared to EMR (10 of 17 *vs* 2 of 17; $P = 0.01$). However, there was no difference in complete remission from neoplasia at 3 mo (ESD 15 of 16 *vs* EMR 16 of 17; $P = 1.0$). During a mean follow-up period of 23 mo, recurrence of cancer was observed in 1 case in the ESD group. The study concluded that though there are theoretical advantages to ESD, it has little clinical relevance as additional treatment is performed for residual BE after EMR.

ESD has a much steeper learning curve compared to EMR.

Complications

In a meta-analysis, the pooled estimates for perforation and bleeding were 1.5% (95%CI: 0.4%-3.0%) and 1.7% (95%CI: 0.6%-3.4%), respectively. Esophageal stricture rate was 11.6% (95%CI: 0.9%-29.6%)[75]

WHERE DO WE GO FROM HERE?

Endoscopic eradication therapy has proven to be a highly effective and durable technique for the management of BE associated neoplasia with minimal morbidity. It is the standard of care in management of BE with HGD, confirmed and persistent LGD and IMC and can be considered in selected cases of submucosal cancer. In spite of high eradication rates, three concerns remain: resistance, progression and recurrence. Patients with persistent metaplasia or dysplasia after three sessions of ablation are considered to be resistant and can contribute up to 21% of patients presenting for EET[77]. In these patients esophageal acid exposure needs to be assessed and adequate control can be achieved by increasing acid suppressive regimen or fundoplication. Alternative eradication methods such as cryotherapy[32] or EMR can be tried. Secondly progression to worse grade of dysplasia occurs in 1.7%-3.6% of patients during EET[14,18]. Endoscopists need to be vigilant of this fact and counsel the patients accordingly. Recurrence of IM or dysplasia after CE - IM occurs at an annual rate of 4.8% and 2% respectively[20]. Hence, ongoing surveillance is strongly recommended in post ablation period.

The European society of gastrointestinal endoscopy recommends that BE expert centers should meet the following criteria: annual case load of $\geqslant$ 10 new patients undergoing endoscopic treatment for HGD or early carcinoma per BE expert endoscopist; endoscopic and histological care provided by endoscopists and pathologists who have followed additional training; at least 30 supervised endoscopic resection and 30 endoscopic ablation procedures to acquire competence in technical skills, management pathways, and complications[78].

Finally, one of the main areas of future research is identifying BE patients who are at high risk for progression and therefore may benefit from prophylactic EET. Accurate risk stratification models including clinical and endoscopic features and biomarkers need to be developed to identify these patients.

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MINIREVIEWS

Proposed approach to the challenging management of progressive gastroesophageal reflux disease

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Abstract

The progression of gastroesophageal reflux disease (GERD) in patients who are taking proton pump inhibitors (PPIs) has been reported by several investigators, leading to concerns that PPI therapy does not address all aspects of the disease. Patients who are at risk of progression need to be identified early in the course of their disease in order to receive preventive treatment. A review of the literature on GERD progression to Barrett's esophagus and the associated physiological and pathological changes was performed and risk factors for progression were identified. In addition, a potential approach to the prevention of progression is discussed. Current evidence shows that GERD can progress; however, patients at risk of progression may not be identified early enough for it to be prevented. Biopsies of the squamocolumnar junction that show microscopic intestinalization of metaplastic cardiac mucosa in endoscopically normal patients are predictive of future visible Barrett's esophagus, and an indicator of GERD progression. Such changes can be identified only through biopsy, which is not currently recommended for endoscopically normal patients. GERD treatment should aim to prevent progression. We propose that endoscopically normal patients who partially respond or do not respond to PPI therapy undergo routine biopsies at the squamocolumnar junction to identify histological changes that may predict future progression. This will allow earlier intervention, aimed at

preventing Barrett's esophagus.

Key words: Barrett's esophagus; Gastroesophageal reflux disease; Endoscopy; Progression; Treatment

Core tip: A review of the literature on gastroesophageal reflux disease (GERD) progression and the associated physiological and pathological changes was performed. Current evidence shows that GERD can progress; however, patients at risk of progression may not be identified early enough for it to be prevented. We propose that endoscopically normal patients who partially respond or do not respond to PPI therapy undergo routine biopsies at the squamocolumnar junction to identify histological changes that may predict future progression. This will allow earlier intervention, aimed at preventing Barrett's esophagus.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) has been defined as a condition that develops when the reflux of stomach contents into the esophagus causes troublesome symptoms such as heartburn and/or regurgitation[1]. This primarily symptomatic definition is not a precise guide to the objective presence of disease. There is not always a clear correlation between reflux symptoms and objective evidence of the disease such as esophagitis or increased esophageal acid exposure on 24-h pH monitoring. Patients may have typical reflux symptoms in the absence of endoscopic esophagitis [referred to as non-erosive reflux disease (NERD)][1], or endoscopic esophagitis in the absence of typical reflux symptoms[2,3]. In both situations, a 24-h esophageal pH monitoring study is required to confirm the presence of the disease.

In practice, it is common for primary care physicians to initiate treatment with a trial of proton pump inhibitors (PPIs) in patients with symptoms of GERD. If symptoms are relieved, the diagnosis of GERD is confirmed. However, studies have shown that the PPI trial has a limited ability to identify GERD, particularly if the patient presents with atypical symptoms[4,5]. In the absence of a complete response to PPI treatment, the PPI dose is usually doubled[6]. If this does not lead to symptom resolution, a 24-h pH study, with or without impedance, should be performed in the absence of PPI treatment to determine whether or not the patient has GERD. Further increase in PPI dose or prescription of an alternative PPI is recommended in the event of a positive GERD diagnosis following pH monitoring[6]. This approach to the diagnosis and treatment of GERD has popularized the notion that patients whose symptoms persist under PPI therapy have not received a sufficiently high dose. The possibility of progression of GERD under PPI therapy is not commonly considered by physicians. Despite this, progression of GERD under therapy has been demonstrated by several clinical investigators[7-10], and has raised concern that PPI treatment may not address all aspects of the disease. The pathology of early disease is not fully understood because endoscopy is indicated only when PPI treatment is ineffective, and biopsy is not recommended in patients who appear endoscopically normal[6,11]. This may prevent early identification of endoscopic risk factors for visible Barrett's esophagus (BE), the pre-malignant lesion of esophageal adenocarcinoma[12]. Furthermore, the structure and functional status of the lower esophageal sphincter (LES) in patients who have an incomplete response to PPI therapy is rarely evaluated, despite its important role in the disease[7].

GERD PROGRESSION

Two scenarios have been proposed regarding the natural history of GERD. The first is that GERD can be categorized as either NERD or erosive reflux disease (ERD), and that patients remain in their diagnosed category[13,14]. The second is that GERD is a spectrum disorder, with NERD at one end of the spectrum, and BE and esophageal adenocarcinoma at the other, with the possibility of disease progression over time[9,15]. Current evidence appears to support the hypothesis that GERD is progressive, with several studies showing progression in cohorts of patients with different initial disease categorizations[8,10,15,16].

One of the largest studies of GERD progression (the ProGERD study) involved 2721 patients from Germany, Switzerland, and Austria[8]. Patients were categorized endoscopically as having NERD or ERD, and those with ERD were further categorized based on Los Angeles (LA) classification grades (A-D) at baseline; patients with evidence of BE were excluded from the analysis of progression. Patients underwent an initial endoscopy followed by 4-8 wk of esomeprazole therapy. Maintenance therapy was then provided by each patient's primary care physician; patients were followed for 5 year during which they underwent repeat endoscopies. Progression to BE (confirmed by endoscopy and biopsy) was observed in 5.9% of patients with NERD, 12.1% of patients with mild-to-moderate ERD (LA grade A/B) and 19.7% of patients with severe ERD (LA grade C/D). Overall, 10% of patients had progressed to BE by the end of the 5-year follow-up period, clearly demonstrating disease progression in a proportion of patients receiving PPI therapy. This study also established that although the treatment of GERD with PPIs can improve symptoms and heal erosive esophagitis, it does not appear to prevent progression to BE.

Pace *et al*[15] reported data from a study of 33 patients

with NERD who were referred to a gastrointestinal clinic in Milan, Italy and followed for 10 year. Patients were endoscopically normal but had an abnormal 24-h esophageal pH at baseline (acid exposure > 5%). Within 5 year of a GERD diagnosis, 17 of the 18 patients (94.4%) who underwent endoscopy had esophagitis. All of the patients were taking PPIs, either at the recommended dose (11/18) or at half the recommended dose (7/18). When active therapy was discontinued during follow-up, symptoms of GERD returned in 96.6% of available patients [median follow-up time 10 year (range 7-14 year)]. This study demonstrated that NERD is a chronic disease that can progress in severity over time in patients taking PPIs, and therefore requires protracted medical therapy. It further demonstrated that the absence of endoscopic esophagitis at presentation is not a positive prognostic factor.

GERD progression in patients undergoing PPI therapy has been shown to be related to a defective LES. In a study of 40 Swedish patients with GERD (confirmed by increased esophageal acid exposure on 24-h pH monitoring) who were treated with PPIs and followed up for 21 year, progression to BE occurred in 45% of patients (18/40)[7]. Manometric evaluation of the LES was performed at the beginning of the study and at the end of the follow-up period. Progression was associated with a significant reduction in mean intra-abdominal LES length on manometry (P = 0.01) and significantly greater esophageal acid exposure on pH monitoring (P = 0.004) than was observed in patients who did not experience disease progression. Furthermore, a trend towards increased use of PPIs and an increase in the number of patients who developed erosive esophagitis was observed over the 21-year period. These results implied that patients with a long duration of GERD were at risk of progression despite PPI treatment and that this was likely to be due to deterioration of the LES during the course of therapy. This study was the first to introduce this concept, which has since led to the prospective examination of LES function prior to PPI therapy in patients with GERD.

The concept that PPI efficacy decreases with increased damage to the LES, and with increased compromise in esophageal body function, has been corroborated in a prospective study of patients with GERD[17]. In this study, a defective LES was defined as LES pressure of less than 8 mmHg and/or abdominal length of less than 1.2 cm. If more than 20% of peristaltic contractions were ineffective, the esophageal body was regarded as being compromised. PPI failure, shown by the recurrence of symptoms or esophagitis, was reported in 7.7% of patients (2/26) with a normal LES and normal esophageal body, 38.1% of patients (24/63) with a defective LES and normal esophageal body, and 79.5% of patients (31/39) with a defective LES and a compromised esophageal body. These results strongly indicated that PPI therapy is less effective in patients with a defective LES than in those with a normal LES, and that a compromised esophageal body contributes further to PPI inefficacy.

In an effort to further understand the mechanical factors implicated in GERD progression, Lord *et al*[18] investigated the effects of distorted hiatal anatomy, the manometric condition of the LES, and esophageal exposure to acid and bile, on GERD severity. The study population comprised 39 patients with NERD, 42 patients with mild ERD (esophagitis that was healed with PPI therapy), 35 patients with severe ERD (esophagitis that persisted despite PPI therapy), and 44 patients with BE. All patients were taking PPIs prior to subsequent surgical treatment. Patients with severe ERD or BE had a significantly higher prevalence of distorted hiatal anatomy, a defective LES, and esophageal acid exposure. Esophageal bile exposure was significantly higher in patients with BE than those with NERD, mild ERD or severe ERD. The significant anatomical and physiological differences between patients with mild ERD and those with severe ERD are indicative of differences in the mechanical properties of the antireflux barrier. Variability in PPI dose is therefore not the only contributing factor to GERD severity, and treatment with PPIs is unlikely to prevent progression in patients with advanced abnormalities in hiatal anatomy and LES function; major antireflux surgery is usually required in such patients. Where PPIs are ineffective, early intervention with an LES augmentation procedure may prevent progression to severe ERD, and obviate the requirement for major antireflux surgery.

The most important information gained from the aforementioned studies is that treatment with PPIs does not prevent progression to BE in a proportion of patients, and that damage to the LES is significantly more prevalent in these patients compared with those whose disease does not progress. These findings encourage the identification of individuals at risk of GERD progression through manometric evaluation of LES function and 24-h esophageal pH monitoring. These patients may be candidates for a surgical procedure to improve LES function that may, consequently, improve PPI efficacy[18].

MEDICAL TOOLS FOR THE EVALUATION OF GERD PROGRESSION

Upper endoscopy is recommended in patients with atypical symptoms who do not respond to PPI therapy[6]. Narrow band imaging (NBI), which enhances the contrast between the esophageal mucosa and the gastric mucosa, has improved visualization of the morphology of the squamo-columnar junction (SCJ) (Figure 1) and been demonstrated to improve the endoscopic diagnosis of GERD. In a study of 107 patients with NERD (n = 36), ERD (n = 41) or no disease (n = 30), which compared conventional endoscopy with NBI, micro-erosions, increased vascularity, and pit patterns at the SCJ were clearly visible using NBI, but were not visible using conventional endoscopy[19]. Furthermore, NBI proved useful in distinguishing patients with NERD from healthy individuals. NBI is not expected to replace conventional endoscopy in the diagnosis of GERD; however, it can be

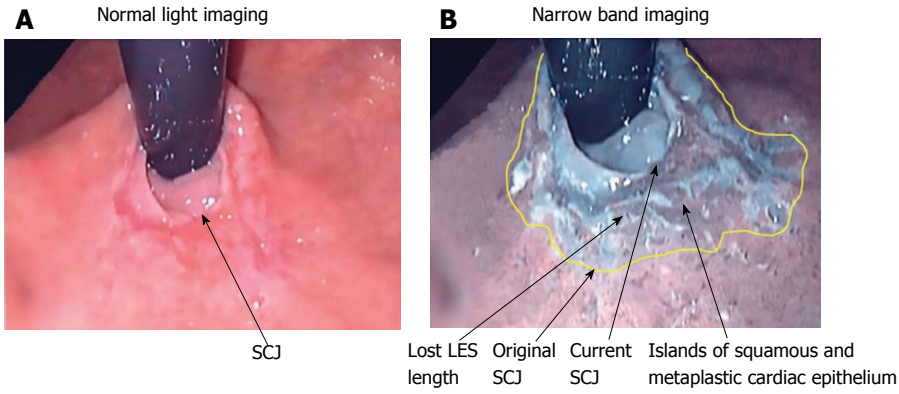

Figure 1 Retroflex endoscopic view of the squamocolumnar junction in advanced gastroesophageal reflux disease. A: Normal white light image displays a slightly irregular SCJ with normal squamous epithelium extending up the esophagus; B: Narrow band image shows multiple islands of squamous epithelium below the SCJ, surrounded by newly formed metaplastic cardiac epithelium. The splayed out original SCJ (indicated by the yellow line), and damaged portion of the LES between the original SCJ and the current SCJ, take on the appearance of stomach. Loss of esophageal muscle due to inflammation results in a reduction in the abdominal length of the LES and loss of the LES barrier function. Images used with permission from Dr. Peters, Case Western University, Cleveland, OH, United States. GERD: Gastroesophageal reflux disease; LES: Lower esophageal sphincter; SCJ: Squamocolumnar junction.

useful for differentiating patients with NERD from patients with ERD, and for grading patients with ERD, and can therefore help to identify patients with severe disease who may be at risk of progression.

Ambulatory reflux monitoring can confirm the presence of GERD in patients with normal endoscopy and atypical symptoms[20,21]. The primary outcome of a 24-h pH monitoring study is the acid exposure time. Wireless pH monitoring allows the extension of the study time beyond 24 h, which has been demonstrated to increase the diagnostic yield[22]; however, wireless monitoring is expensive and therefore not widely available[21]. An alternative is pH-impedance monitoring, which is considered the gold standard[21]. This method detects all reflux (liquid, gas or mixed) regardless of acidity, and defines the direction of flow. A recent study investigated the potential of pH-impedance monitoring to predict symptomatic outcome over a 5-year period in 94 patients with GERD who were not taking PPIs. The investigators reported that phenotyping of GERD according to the strength of evidence of reflux from pH-impedance testing efficiently stratified symptomatic outcome, and could be useful in planning disease management[23]. In a study of GERD progression, patients with progressive disease had significantly increased esophageal acid exposure than those whose disease did not progress[7]. pH-impedance monitoring may therefore be useful in the identification of patients who may be at risk of progression.

Conventional water-perfused manometry and, more recently, high resolution manometry (HRM) are used to evaluate LES and esophageal body function in patients with GERD. The technical advantages of HRM include its high density of recording sites, advanced solid-state sensor technology, and sophisticated plotting algorithms, as well as its superior speed and ease of performance compared with conventional manometry[21,24]. However, a recent study comparing conventional manometry with HRM in the assessment of the LES in 55 patients with foregut symptoms, reported no difference between the two techniques in their measurement of resting LES pressure[24]. Furthermore, LES overall and abdominal length were consistently overestimated by HRM compared with conventional manometry. Consequently, HRM could limit the detection of LES abnormalities, leading to difficulties in the identification of LES abnormalities as a cause for PPI inefficacy.

PATHOLOGY OF GERD PROGRESSION

The identification of factors associated with progression to BE and the need for surgical intervention, are key to managing those patients whose disease is progressive. This requires an understanding of the pathophysiology and pathology of GERD. Physiological and pathological studies have introduced the concept that GERD begins at the SCJ. In the absence of squamous epithelial injury, the SCJ and the gastroesophageal junction are concordant[11,25]. As squamous epithelial injury occurs, metaplastic cardiac epithelium forms and the SCJ separates from the gastroesophageal junction and moves upwards into the esophagus. This process causes damage to the LES, resulting in greater esophageal exposure to acid and bile.

A normal LES occupies the entire abdominal esophagus and a small portion of the thoracic esophagus, and is lined with squamous epithelium. Gastric distension or postprandial non-pressurized gastric dilation causes transient effacement of the distal LES into the stomach (Figure 2)[25]. Effacement results in the uptake of the distal portion of the LES by the expanding fundus of the distended stomach. This results in loss of abdominal LES length and exposure of the squamous epithelium to acidic gastric juice in the acid pocket[26]. The subsequent inflammatory injury to the unprotected squamous epithelium results in metaplasia of the squamous epithelium to cardiac epithelium (Figure 1)[25,27]. Indeed,

Table 1 Hallmarks of gastroesophageal reflux disease in patients with and without cardiac mucosa on biopsies of the gastroesophageal junction

	Findings on multiple biopsies of the GEJ		
	No cardiac epithelium (n = 88)	Cardiac epithelium (n = 246)	P
% time pH < 4	1.1 ± 4.6	6.0 ± 7.4	< 0.01
% hiatal hernia	25	55.1	< 0.01
LES pressure (mmHg)	13.2 ± 12.8	8.0 ± 8.0	< 0.01
LES abdominal length (mm)	1.6 ± 1.1	1.0 ± 1.2	< 0.01
LES overall length (mm)	3.0 ± 1.2	2.2 ± 1.6	< 0.01
% defective LES	27.2	62.3	< 0.01
% esophagitis	11.2	33.2	< 0.01

Values are medians ± interquartile range unless otherwise stated. Data are from Oberg *et al*[27]. GEJ: Gastroesophageal junction; LES: Lower esophageal sphincter.

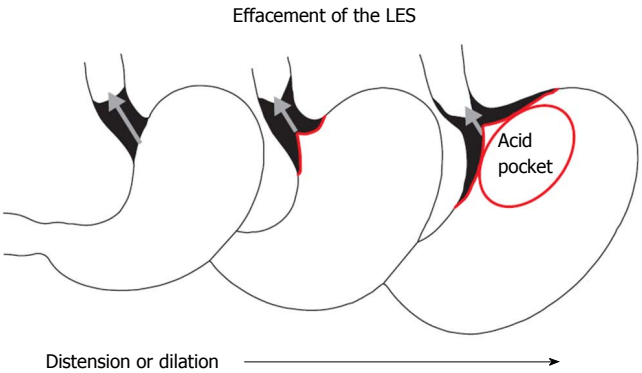

Figure 2 Effacement of the lower esophageal sphincter as a result of gastric distension or dilation. Exposure of the squamous mucosa covering the effaced portion of the LES to gastric juice results in inflammation, the formation of metaplastic cardiac mucosa, and progressive loss of LES length. The red line represents the squamous epithelial covering of the effaced portion of the LES (in black) as it is taken up by the expanding gastric fundus. LES: Lower esophageal sphincter.

biopsies of the SCJ from 714 symptomatic patients with GERD who were endoscopically normal showed that in an acidic environment, the acid-damaged squamous epithelium heals by forming cardiac epithelium[11]. In an additional study of 334 patients with GERD symptoms and no visible evidence of BE, biopsies of the SCJ showed cardiac epithelium in 246 patients (73.7%)[27]. When present, cardiac epithelium was significantly associated with increased esophageal acid exposure, a structurally defective LES, and erosive esophagitis (Table 1). Strikingly, inflammation in the form of carditis was present in 237/246 patients (96%) and was associated with a significantly shorter LES, significantly lower LES pressure, and a significantly higher prevalence of a structurally defective LES than no carditis (Table 2)[27]. Individuals who had both carditis and esophagitis had a significantly greater prevalence of a structurally defective LES and greater esophageal acid exposure than individuals with carditis alone (Table 3)[27].

The presence of metaplastic cardiac mucosa at the SCJ results in the formation of a squamo-oxyntic gap between the oxyntic gastric mucosa in the proximal stomach and the remaining squamous esophageal mucosa within the LES (Figure 3)[28]. The length of the squamo-oxyntic gap has been shown to be directly proportional to the prevalence of intestinal metaplasia (IM) of the cardiac epithelium (*i.e.*, the formation of goblet cells). In a study of 1655 patients with GERD, IM was observed in: 24.3% of patients with a gap shorter than 1 cm; 83.5% of patients with a gap of 1-5 cm; and 100% of those with a gap longer than 5 cm[28]. The authors proposed that the length of the squamo-oxyntic gap could be used as a cellular criterion to diagnose GERD. Furthermore, the length of the gap provides an accurate assessment of GERD severity, and IM of the cardiac epithelium within the gap is the most accurate indicator of disease progression and the risk of esophageal adenocarcinoma.

These findings strongly support the concept that GERD starts at the SCJ with acid-induced cardiac metaplasia of the injured and inflamed effaced squamous epithelium of the most distal portion of the LES. This process can result in LES damage. These initial changes are subtle and microscopic, and a patient with early GERD is likely to appear endoscopically normal. A manometric assessment of the LES, measurement of esophageal acid exposure, and biopsies at and below the SCJ are therefore required for these changes to be identified.

IDENTIFICATION OF PATIENTS RISK OF PROGRESSION TO BARRETT'S ESOPHAGUS

In the ProGERD study, 171 patients who were endo-

Table 2 Hallmarks of gastroesophageal reflux disease in patients with and without carditis on biopsies of the gastroesophageal junction

	Findings on multiple biopsies of the GEJ		
	No carditis (n = 9)	Carditis (n = 237)	P
% time pH < 4	3.1 ± 4.5	6.1 ± 7.2	0.14
LES pressure (mmHg)	10.6 ± 12.4	7.8 ± 8.2	0.03
LES abdominal length (mm)	1.4 ± 0.4	1.0 ± 1.2	0
LES overall length (mm)	3.3 ± 0.7	2.2 ± 1.6	0.02
% defective LES	11.1	63.7	< 0.01

Values are medians ± interquartile range unless otherwise stated. Data are from Oberg *et al*[27]. GEJ: Gastroesophageal junction; LES: Lower esophageal sphincter.

Table 3 Hallmarks of gastroesophageal reflux disease in patients with carditis in the presence or absence of erosive esophagitis

	Carditis		
	No erosive esophagitis (n = 155)	Erosive esophagitis (n = 82)	P
% time pH < 4	4.1 ± 6.5	9.2 ± 7.0	< 0.01
% hiatal hernia	44.2	78.0	< 0.01
LES pressure (mmHg)	10.0 ± 8.8	5.6 ± 5.0	< 0.01
LES abdominal length (mm)	1.0 ± 1.2	0.6 ± 0.8	< 0.01
LES overall length (mm)	2.4 ± 1.4	2.1 ± 1.6	< 0.06
% defective LES	54.2	81.7	< 0.01
% intestinal metaplasia	8.3	19.5	0.02

Values are medians ± interquartile range unless otherwise stated. Data are from Oberg *et al*[27]. LES: Lower esophageal sphincter.

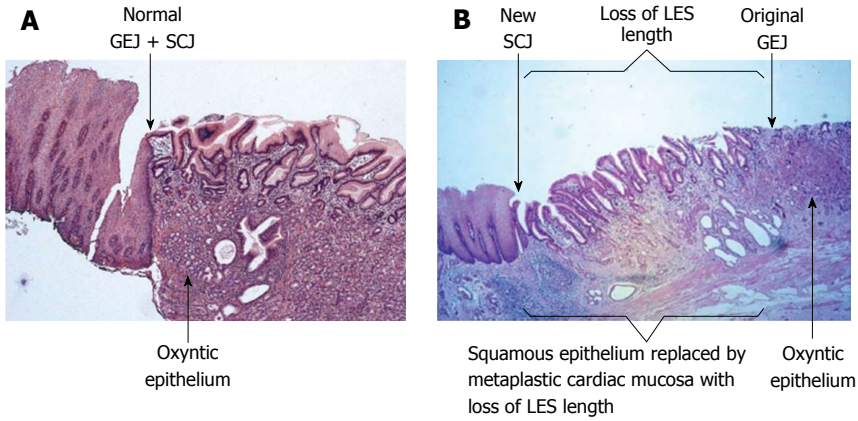

Figure 3 The histology of the squamo-oxyntic gap. A: The normal junction of the esophagus and stomach is the abutment of the proximal limit of the gastric oxyntic epithelium and the distal limit of the squamous epithelium; B: Squamo-oxyntic gap: Squamous epithelium is replaced by metaplastic cardiac mucosa resulting in loss of LES length, as shown by manometry. Images provided by Dr. Parakrama Chandrasoma. GEJ: Gastroesophageal junction; GERD: Gastroesophageal reflux disease; LES: Lower esophageal sphincter; SCJ: Squamocolumnar junction.

scopically normal had microscopic IM on biopsy of the SCJ before any therapy[29]. After the 4-8-wk PPI treatment phase of the study, 128 of these patients had a follow-up endoscopy and biopsy of the SCJ; all had persistent microscopic IM. With continued PPI therapy, and endoscopy and biopsy at 2 and 5 year of follow-up, endoscopically visible BE was seen in 25.8% (33/128) of patients[29]. The implication of this finding is that a biopsy showing microscopic IM at the SCJ in a patient who is endoscopically normal indicates a high risk of progression to visible BE, a precursor to esophageal cancer.

An additional population-based study in Sweden assessed the risk of esophageal cancer in 796492 adults taking maintenance PPIs for different indications in 2005-2012. Of 201744 individuals taking PPIs for GERD, 316 developed esophageal cancer. The reported standardized incidence ratio (SIR) of esophageal cancer in patients with GERD who were taking PPIs was 6.87 (95%CI: 6.13-7.67). Furthermore, the SIRs of esophageal cancer were also increased among individuals without GERD, who used PPIs for indications not associated with any increased risk of esophageal cancer (*e.g.*, individuals taking PPIs due to maintenance treatment with non-steroidal anti-inflammatory drugs and aspirin). The authors concluded that the long-term use of PPIs is associated with increased risk of esophageal

cancer in the absence of other risk factors[30].

Of concern is that the American College of Gastroenterology guidelines for the diagnosis and management of GERD recommend endoscopic examination only for patients who have an incomplete response to PPI treatment, and recommend routine biopsy only for those with visible evidence of a columnar-lined esophagus of more than 1 cm in length[6]. The histological and pathological features of early disease have therefore not been investigated. Contrary to these guidelines, we propose that patients who are undergoing endoscopy to investigate an incomplete response to PPI therapy, and who have no visible evidence of a columnar-lined esophagus, undergo a routine biopsy of the SCJ. We hypothesize that in a significant minority of such patients, biopsies of the SCJ will reveal the presence of microscopic IM. Based on the findings of the ProGERD study, these patients are at risk of progression to visible BE and are candidates for early preventive treatment[29]. Our hypothesis will need to be tested in the clinical setting to determine whether potentially progressive disease can be identified through routine biopsy of the SCJ in this subgroup of patients, and whether progression can be prevented through earlier intervention. In addition, the number of biopsies required, the cost-effectiveness, and the associated risk of bleeding[31] must be considered before acceptance of this proposed approach in clinical practice.

PREVENTION OF PROGRESSION

Acid suppression therapy is notably effective in patients who have a normal LES but less so in those who have a structurally defective LES[17]. Permanent structural alterations to the LES resulting from repeated effacement and chronic inflammation are difficult to correct without surgical intervention. The likelihood of symptom control and prevention of disease progression in patients with persistent symptoms on PPI therapy is greater if surgical correction of a compromised LES is carried out earlier rather than later. Nissen fundoplication has been demonstrated to prevent BE if performed before it develops, and if the fundoplication remains competent[32,33]. A study of 15 patients with microscopic IM at the SCJ in the absence of endoscopically visible BE showed complete regression of microscopic IM in 73.7% of patients (11/15) following early fundoplication[34]. In a separate control group of 45 patients with endoscopically visible BE, only 4.4% of individuals (2/45) showed regression of BE following fundoplication[34]. Despite the ability of the fundoplication procedure to induce significant regression of microscopic IM and prevent development of visible BE, the associated complications (including, dysphagia, bloating, and the inability to burp or vomit[35]) have discouraged the early use of this approach to prevent progressive disease.

Over the past decade, minimally invasive outpatient LES augmentation procedures have been developed[36-39]. Examples include the implantation of a collar of magnetic beads around the inferior border of the LES to prevent its effacement into the stomach[38]; the delivery of radiofrequency to the LES to reduce LES compliance[36]; neuromodulation of the LES through electrical stimulation to increase LES resting pressure[37]; and incisionless partial fundoplication performed using a flexible endoscope introduced to the stomach *via* the mouth[39]. Clinical studies have demonstrated the efficacy of LES augmentation in eliminating reflux symptoms and healing esophagitis in patients with GERD who have an incomplete response to PPI therapy[36,37,39,40]. These procedures avoid the complications associated with Nissen fundoplication, are reversible if required, and may therefore be appropriate for early surgical intervention with the goal of preventing disease progression. The effectiveness of these procedures to induce regression of microscopic IM at the SCJ and prevent progression to endoscopically visible BE and subsequent adenocarcinoma should be investigated in future clinical studies.

A proposed treatment algorithm that features early use of LES augmentation procedures to prevent GERD progression is shown in Figure 4. The algorithm emphasizes the use of endoscopy, manometry, and esophageal pH monitoring to assess patients with an incomplete response to PPI therapy. Following endoscopy, individuals are stratified into four groups: (1) patients with visible BE; (2) those with persistent esophagitis; (3) those who are endoscopically normal but have microscopic IM of the SCJ (identified by biopsy); and (4) patients who are endoscopically normal but have metaplastic cardiac mucosa with a squamo-oxyntic mucosal gap (identified by biopsy of the SCJ). LES augmentation is recommended for patients in groups (2) and (3) following a manometric evaluation of LES function. LES augmentation for patients in group (4) is only recommended if manometric evaluation reveals a permanently damaged LES. Nissen fundoplication should be considered for patients with extensive damage to the LES after a thorough discussion of the associated complications.

CONCLUSION

It is important that patients with GERD who are at risk of progression are identified early in the course of their disease in order to prevent the development of BE or other complications. This requires the early use of endoscopy, manometry and esophageal pH monitoring in those with an incomplete response to PPI therapy. In contrast to current management guidelines, we propose routine biopsy of the SCJ in such patients if their esophageal endoscopic evaluation is normal. If microscopic IM is identified, an LES augmentation procedure should be considered with the aim of preventing disease progression to endoscopically visible BE. This proposed approach must first be tested in the clinical research setting to confirm that the encouraging results obtained with the Nissen fundoplication procedure can be reproduced with an LES augmentation procedure.

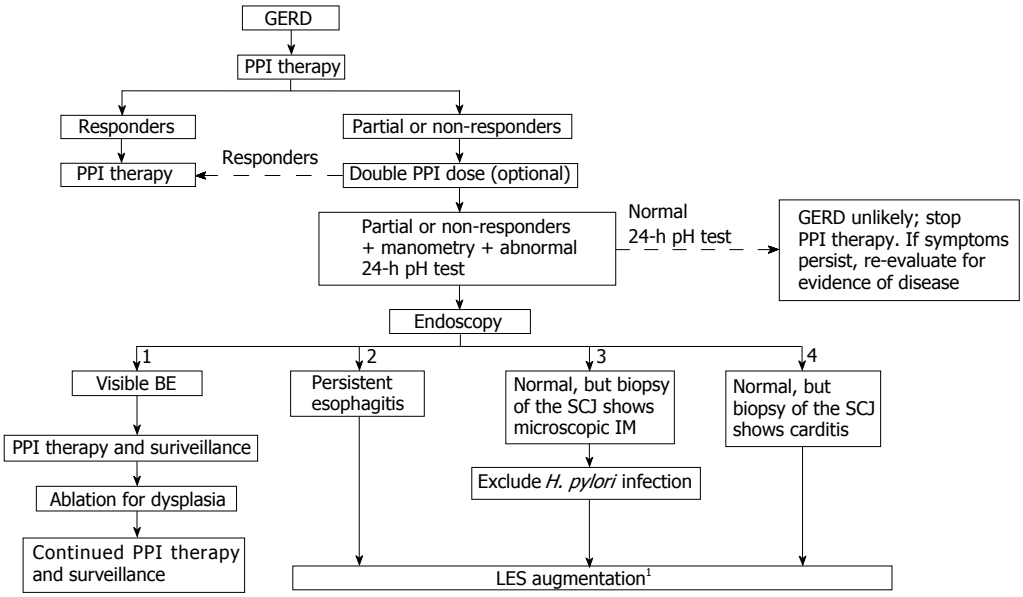

Figure 4 Proposed algorithm for the treatment of patients with progressive gastroesophageal reflux disease. Patients who do not respond to PPI therapy and who have an abnormal 24-h esophageal pH should undergo endoscopy. Patients can be stratified into four groups following endoscopy: (1) patients with visible BE; (2) patients with persistent esophagitis; (3) patients with a normal endoscopy who have microscopic IM of the SCJ; and (4) patients with a normal endoscopy who have carditis at the SCJ. Patients in groups (2), (3) and (4) should undergo manometric assessment of LES function; those with a defective LES may be candidates for LES augmentation. [1]If more than 2 permanently defective LES components consider Nissen fundoplication. BE: Barrett's esophagus; GERD: Gastroesophageal reflux disease; LES: Lower esophageal sphincter; IM: Intestinal metaplasia; PPI: Proton pump inhibitor; SCJ: Squamocolumnar junction.

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MINIREVIEWS

Capsule endoscopy: Current status and role in Crohn's disease

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Abstract

Capsule endoscopy (CE) has proved to be an important non-invasive tool for diagnosis and monitoring Crohn's disease patients. It has the advantage of excellent visualization of digestive tract mucosa, a good tolerability and safety in well-selected patients. The risk of retention can be diminished by good selection of patients using imaging techniques and by the use of patency capsule. The aim of a capsule examination is not only an early diagnosis but also a very good stratification of prognosis, thus directing the treatment strategy for either a step up or top-down approach and also permitting the optimization of the treatment depending on the findings. When symptoms and biomarkers point to a change in the disease's activity we can either adjust the treatment directly as recommended in CALM study or choose in selected patients to visualize the digestive mucosa through a CE and take a decision afterwards. The appearance of the new capsule from Medtronic-the Pillcam Crohn's might be an important step forward in diagnosis, evaluating disease extent, the severity of the disease, prognosis, management in a treat to target approach, with treatment modifications according to the data from CE examination. Serial examinations in the same patient can be compared and a more objective evaluation of the lesions modification from one exam to another can be performed. We present the latest developments and current status and evidence that in selected patients capsule can be a tool in a treat to target approach.

Key words: Capsule endoscopy; Crohn's disease; Treat to target; Optimise; Colon capsule

Core tip: The target in inflammatory bowel disease has changed during the last years from controlling symptoms to achieving mucosal healing as the final goal

of treatment. C-reactive protein and fecal calprotectin have proved their efficacy in monitoring and guiding the treatment in Crohn's disease as shown by the pivotal CALM study. More and more evidence tends to support a role of iterative capsule endoscopy (CE) examinations. Evidence is based on small bowel and pillcam colon 2 capsule examinations. The appearance of the new capsule from Medtronic-Pillcam Crohn's might be an important step forward in diagnosis, evaluating disease extent, the severity of the disease, prognosis, management in a treat to target approach, with treatment modifications according to the data from CE examination.

Goran L, Negreanu AM, Stemate A, Negreanu L. Capsule endoscopy: Current status and role in Crohn's disease. *World J Gastrointest Endosc* 2018; 10(9): 184-192 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i9/184.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i9.184

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disease affecting the entire gastrointestinal tract but most frequently involving the small bowel (SB)[1]. According to different studies, 70%-90% of CD patients have SB involvement[2,3], and 30% of them have exclusive SB disease[4]. SB disease, particularly jejunal disease, is considered to be a risk factor for strictures and is associated with a larger number of surgical procedures[5]; thus, evaluation of the small bowel becomes of great interest in the diagnosis and management of CD patients. In the past, assessing the small bowel was limited due to an inability to visualize the mucosa through conventional methods. As new techniques emerged, the introduction of capsule endoscopy (CE) in 2000[6] offered us the possibility of evaluating the small bowel.

CE is indicated in CD for diagnosis in patients with suspected disease, evaluation of mucosal healing and disease activity in established CD, confirmation of recurrence after surgery, evaluation of patients with overt or obscure gastrointestinal bleeding and evaluation of celiac disease patients with inexplicable symptoms regardless of treatment[7].

CE imaging interpretation

When describing the images obtained by CE, findings suggestive of CD are erythema, mucosal edema, ulcerations or ulcers, strictures, fistulas and mucosal fissures[8]. The reason why all clinical, biochemical and endoscopic findings must be put together when establishing a diagnosis is that CE findings are nonspecific, and up to 15% of normal individuals may have minor mucosal breaks[9]. Another argument is that mucosal erosions are not pathognomonic for CD, being present in two thirds of patients with nonsteroidal anti-inflammatory (NSAID)-induced enteropathy[10]. Although sometimes it is difficult to differentiate CD from NSAID lesions only using CE findings, concentric diaphragmatic strictures are considered characteristic for mucosal injury after NSAID use[11]. Other differential diagnoses based of CE mucosal findings are intestinal tuberculosis, ischemia, tumors, lymphoma, Behcet's disease or radiation enteritis[9].

Scoring systems in CE

A limitation of CE is the lack of definitive diagnostic criteria for CD. Two scoring systems are currently used when assessing CE findings, the Lewis Score (LS) and more recently the Capsule Endoscopy Crohn's Disease Activity Index (CECDAI). The LS is an incorporated software algorithm that separates the small bowel into three parts and assigns points to different CD characteristic findings (strictures, ulcers, fistulas) in each of the segments. It takes into consideration the severity and the reproducibility of each lesion found[12]. The most affected part of the small bowel with its accumulated number of points represents the final score. A score < 135 is clinically insignificant or normal; a score between 135 and 790 corresponds to mild inflammation and a score > 790 points to moderate-to-severe inflammation.

He *et al*[13] studied the relationship between LS, clinical activity indices, level of C-reactive protein (CRP) and small bowel transit time (SBTT) in 150 pediatric and adult CD patients. For pediatric patients they used the abbreviated Pediatric Crohn's Disease Activity Index (aPCDAI), while for adult patients, the Harvey-Bradshaw Index (HBI) was used. A strong correlation between the clinical activity indices and CRP was found in all patients, while the correlation between the CRP and the LS was moderate. The correlation between the LS and clinical activity indices was moderate in pediatric patients but weak in adult patients. The LS in pediatric patients was reduced after treatment, but in adult patients there was no difference that was statistically significant[13]. Similar results were obtained by Yang *et al*[14] on 58 patients with established or suspected CD[14]. It seems that the LS correlates better than the CECDAI score with fecal calprotectin levels, mainly when the level is less than 100 μg/g[15].

The CECDAI splits the small bowel into proximal and distal segments and evaluates the inflammation, presence of strictures and extent of disease in each segment. A segmental score is calculated by multiplying the inflammation with the extent of the disease and then adding the presence of strictures if they exist. The final score is obtained by adding the two results[16]. The CECDAI score was validated in patients with small bowel CD showing a good correlation between endoscopists from different centers[17]. The correlation between the two scoring systems is very strong, but no significant correlation with CRP and HBI was obtained.

CE INDICATIONS IN CD

CE in suspected CD

The diagnosis of CD is based on clinical symptoms, endoscopic and radiologic findings and it is confirmed

by histology results. The range of symptoms and laboratory findings that can support the diagnosis in a patient with suspected CD is wide, and it includes chronic diarrhea, abdominal pain, anemia, changes in CRP, erythrocyte sedimentation rate (ESR), elevated fecal calprotectin level, hypoalbuminemia and extraintestinal manifestations[17]. Further, the next step is a total ileocolonoscopy, with biopsies and radiologic exams if needed. Classical radiology has a very limited place in diagnosis; computed tomography enterography (CTE) or magnetic resonance enterography (MRE) are the preferred imaging modalities.

Approximately 27% of CD patients have disease limited to the ileum; thus, a normal ileocolonoscopy does not exclude a CD diagnosis[18]. On the other hand, there are cases when the ileum cannot be visualized properly, or the ileocolonoscopy and the radiologic investigations are inconclusive. For these situations, a CE is indicated in establishing a diagnosis rather than a double-balloon endoscopy (DBE), which is more invasive[7].

Since there is no gold standard for the diagnosis of CD, the studies made until now evaluate the diagnostic yield and not the diagnostic accuracy of CE. Based on these studies, there was an obviously superior diagnostic yield with small bowel CE compared with SB radiography, ileocolonoscopy, CTE, but not MRE[19]. In a South Korean study, the diagnostic yield of CE in the suspected CD group was 59.7%, and the therapeutic management was changed in 70.2% of these patients[20]. Jensen *et al*[21] found similar sensibility and specificity for CE and MRE in CD patients.

CE *vs* other investigations: When compared to other means of investigating CD patients, CE has proved its efficiency. In a recent meta-analysis made by Choi *et al*[22], in patients with suspected CD, CE had a superior diagnostic yield compared to small bowel follow-through and enteroclysis (EC) and is comparable to CTE and MRE. In patients with established CD, the diagnostic yield of CE compared to EC was greater, and CE identified significantly more lesions in the terminal ileum compared with ileoscopy[22].

In another meta-analysis, for suspected CD cases, CE was superior to SBR, CTE and ileocolonoscopy, and in established CD cases, CE also proved superiority over CTE, PE and SBR. There were similar results between CE and MRE[19]. Other studies evaluated the diagnostic yield of CE compared with other forms of investigation. Albert *et al*[23] compared CE with MRE and fluoroscopic enteroclysis in a prospective study of 52 suspected or established CD patients. CE detected small bowel lesions in 93% of patients, whereas MRI was effective in 78% of patients and fluoroscopy in 33% of cases. They concluded that CE and MRI are complementary in the diagnosis of CD; CE identified small bowel lesions that MRI might fail to spot, but MRI was able to detect extraluminal complications and transmural inflammation[23]. Similar results were also obtained in the pediatric population, with CE and MRI having comparable specificity and sensibility[24]. In patients with small bowel disease, CE had a lower diagnostic yield (57.6%) than that of single-balloon enteroscopy (SBE) (69.7%)[25].

CE in unclassified IBD: Nearly 15% of patients with colonic inflammatory disease have unclassified/undetermined colitis at the time of diagnosis[26], with 30% of them being reclassified as CD later on during the course of disease[27]. In a study of 120 patients with UC and unclassified inflammatory bowel disease (IBD), 15.8% had capsule endoscopic findings characteristic of CD. Almost all of these patients had a small-bowel follow-through (SBFT) before CE, and in only one of them were CD findings described[28]. In the pediatric population, a study conducted with 28 patients revealed that 4 out of 5 patients with UC were reclassified as CD after CE examination. At the same time, the patients with CD had more extensive bowel disease at CE, and the majority had newly diagnosed jejunal disease[29]. Nevertheless, although CE is useful in establishing a diagnosis in patients with IBDU, a negative examination does not exclude a further CD diagnosis[30].

CE in established CD

During the last decade, the treatment dogma in IBD has changed from having clinical control of the symptoms to reversing inflammation and obtaining mucosal healing, thus limiting progression and bowel damage[31]. The definition of mucosal healing includes the absence of visible endoscopic inflammation that is associated with fewer complications on long-term evolution, and the gold-standard evaluation method is ileocolonoscopy[32]. A CE diagnostic yield of 85.7% was found in patients with established disease, and findings may lead to management changes in 64% of patients[33].

Deep remission is now the endpoint in IBD patient treatment, and it is defined by clinical, biochemical and endoscopic remission. Mucosal healing in the small bowel was achieved in only 15.4% of patients in clinical remission in a study made by Kopylov *et al*[34]. They also proved that CRP and fecal calprotectin have a poor correlation with active SB inflammation[35]; therefore, the evaluation of mucosal healing might be a new indication for CE.

Hall *et al*[36] evaluated 43 symptomatic CD patients by clinical active disease indices, looking at CRP, fecal calprotectin and CECDAI score at the beginning of treatment and again after 52 wk. The study showed that biochemical response was correlated with endoscopic remission in 42% of patients[36]. In another study, it was confirmed that mucosal healing does not correlate with clinical remission[37].

In the Canadian Capsule Endoscopy Guidelines, CE is indicated in CD patients with clinical symptoms and signs which are not explained by an ileocolonoscopy or other imaging modalities[7] and for possible lesions that are inaccessible with conventional investigations[38]. In a retrospective study of small bowel CE made by

Dussault *et al*[39] on CD patients for unexplained anemia, inconsistency between symptoms and ileocolonoscopy aspect, a full evaluation of disease extent and assessment of mucosal healing showed that 38 out of 71 patients had suffered a change in their management due to a severe lesion found on CE[39]; similar results were shown by Kim *et al*[20].

Another study showed similar results, with 62% of patients having their treatment changed and 40% of patients initiating a new treatment, with Budesonide being the most frequent treatment introduced in their therapy[40]. Regarding the pediatric IBD patients, abnormal CE findings in 86% of patients led to treatment step-up in 75% of them, with the important decision to add an anti-TNF agent in the majority of cases. Evaluation after one year showed significant improvement in clinical and biological status. In the same study, the CE findings excluded IBD in 94% of patients in the suspected CD group[41]. Based on these studies, a change in therapeutic management in established CD patients can be correctly made based on CE findings. Another indication for CE in the case of an established diagnosis is for patients with suspected CD recurrence after surgery[7]. Postsurgical recurrence of CD has a high rate[42] after one year of ileocolonic resection, and frequently the recurrence is proximal to the surgical anastomosis, with the recommendation that an ileocolonoscopy be performed within 6 mo to one year after surgery[43]. The endoscopic recurrence precedes the apparition of clinical symptoms, and a severe endoscopic aspect offers a poor prognosis[44]. CE can play a role in identifying patients with recurrences after surgery, being a non-invasive method and likely offering us a better visualization of the neoterminal ileum. Bourreille *et al*[45] evaluated 31 CD patients by CE and ileocolonoscopy within 6 mo after surgery, and recurrence was defined by a Rutgeerts score $\geqslant$ 1[44]. In 68% of patients who had suffered recurrence, the sensitivity of CE in detecting the lesions of the neoterminal ileum was lower than that of ileocolonoscopy. On the other hand, more than two-thirds of patients had lesions outside the reach of ileocolonoscopy[45]. Moreover, another study found different conclusions - that CE is more effective than ileocolonoscopy in detecting recurrences - after CE identified 68% of patients with disease relapses compared to 25% identified by ileocolonoscopy[46]. Postsurgical anatomy may play a role in the inability of the colonoscope to reach the neoterminal ileum.

In other words, current evidence supports CE as a reasonable choice for evaluating a patient after surgery when ileocolonoscopy is contraindicated or the neoterminal ileum cannot be intubated or when the patients refuses an endoscopic evaluation[47].

CE IN COLON EVALUATION

Colonic capsule has been designed and mostly used for colorectal cancer screening, reaching a sensitivity of 88% in detecting polyps compared to standard colonoscopy[48]. Most of the data that we have now about CE in CD are gained using the small bowel capsule endoscopy (SBCE), but the Pillcam Colon 2 has proved useful in the evaluation of the entire gastrointestinal mucosa, showing great accuracy in detecting mucosal changes. When comparing the Pillcam Colon 2 with ileocolonoscopy, MRE, and small intestine contrast sonography, the colon capsule endoscopy (CCE) had better results for small bowel lesions than the other techniques in detecting colonic inflammation, with sensitivity, specificity, and positive and negative predictive values that were 89% and 100%, 100% and 91% in a study with a pediatric population[49]. The CE also showed better tolerability than ileocolonoscopy.

D'Haens *et al*[50] used the second-generation Pillcam Colon Capsule Endoscope (PCCE-2) in order to assess its safety and feasibility compared to colonoscopy in 40 patients with active colonic CD. The results showed that the colon capsule findings underestimated severity, the total ulcerated area and disease activity score, with a rate of missing ulcers of 14%. PCCE-2 had an ulcer recognition sensitivity of 86%, but a specificity of only 40%[50]. Overall, the colon capsule was safe to use and well tolerated and no adverse event was reported. In a small study from our team that included 6 patients with suspected or established CD who refused colonoscopy or had incomplete examinations, the colonic capsule was safe to use and played an important role in patient's therapeutic management[51].

PILLCAM CROHN'S® CAPSULE

The use by many clinicians of the Pillcam Colon 2 as a tool for an endoscopy of the entire digestive tract in CD lead to the appearance of the new capsule from Medtronic - Pillcam Crohn's®. This might be an important step forward in the diagnosis and evaluation of disease extent, severity, prognosis, and management in a treat-to-target approach, with treatment modifications based on data from CE examinations since it is specially designed to detect CD lesions.

Pillcam Crohn's is similar to PillCam C2 and allows complete examination of the gastrointestinal tract. It comes with the new IBD-dedicated software (Rapid 9), in which the small bowel is divided into three segments, and the colon is divided into two parts (right and left). Two new descriptors are introduced: The most severe lesion (MSL) and the most common lesion (MCL) and the extent of involvement in the specific segment are analyzed; these are also shown visually in a GI tract map which allows fast comparison with previous examinations. The LS for the small bowel is still available for use.

With this software, serial examinations in the same patient can be compared, and a more objective evaluation of the lesion modification from one exam to another can be performed. Leighton *et al*[52] compared the diagnostic yield of the new capsule with ileocolonoscopy, showing at least as good as, if not even better than ileocolonoscopy results, with a diagnostic yield of 83% compared with 70% for ileocolonoscopy.

In Italy, 18 patients with suspected or known CD were assessed by CE with the new Crohn's PillCam capsule[53]. In the suspected CD group, approximately one-half of patients had major inflammatory lesions, most of them being in the third tertile. In 75% of these patients, the diagnosis was confirmed. In the established CD group, 90% of patients had important lesions in the terminal and neoterminal ileum. No adverse events were reported.

Another study made in Israel included 49 patients who were examined by the new capsule in order to assess the system's capacity to visualize and examine the small bowel and the colon[54]. From 71% of patients who had established CD, 31% of them had proximal inflammatory lesions. All recordings were of good quality, and no retention of the capsule was reported.

Studies with Crohn's capsule are ongoing in the pediatric population, based on encouraging results in 48 children with CD who underwent pan-enteric capsule endoscopy (PCE) with Pillcam Colon 2. In this study, treatment was adapted according to the PCE findings, and the results were compared afterward[55]. At week 52, 28 patients who had mucosal healing at the PCE evaluation had fewer disease relapses, reduced hospitalization rates and decreased treatment escalation. The diagnostic yield of PCE in this study was 54% compared to 37% of MRE. Regarding costs, Saunders *et al*[56] found that using VCE compared to other investigations would notably reduce costs and, at the same time, improve quality of life for CD patients, especially in those after surgical intervention or with considerable symptoms.

CE IN A "TREAT-TO-TARGET" CONCEPT

The target in IBD has changed during the last years from controlling symptoms to achieving mucosal healing as the final goal of treatment. The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative group published a guideline to define the targets in IBD patient treatment[57]. In CD, the endpoints are composite according to this guide. Clinical remission, endoscopic remission, resolution of inflammation signs on cross-sectional imaging and decline of CRP and calprotectin, which is with histological remission as the final goal are the targets to be pursued. Patients that reach the targets are less likely to suffer surgeries, hospitalizations and their quality of life is better. The biomarkers CRP and fecal calprotectin have proved their efficacy in monitoring and guiding the treatment in CD, as shown by the pivotal CALM study[58]. In this study, optimizing biologic therapy based only on clinical symptoms resulted in worse outcomes than when combining biomarkers with symptoms in a proactive monitoring setting since there is a discordance between symptoms and mucosal healing.

In the study of Lazarev *et al*[5], with 2015 patients analyzed, 14% had proximal involvement, and notably, jejunal involvement was associated with patterns of stenosis, which predict more hospitalizations and further surgery. Due to these CE findings, the author proposed revising the Montreal Classification, as jejunal involvement should be considered a separate phenotype due to the prognostic implications of this location[5]. Lesions with proximal location at CE examination have a poor prognostic value, similar to the ileal location that most frequently develops a stenotic pattern. Maybe these patients may need to be treated earlier and more aggressively with a more rapid step up or in a top-down approach based on capsule findings to prevent the ulterior complications.

A prospective study from Israel in 89 patients who underwent biomarker evaluation, MRE exams, patency capsule tests and then VCE every 6 mo concluded that CE predicts short-term and long-term disease relapses compared to calprotectin, which is a good predictor of exacerbation in the short term[59]. The authors also suggest that an worst-segment LS under 350 might be the target with clinical impact for mucosal healing. Similarly, after surgery where the majority of patients will relapse, CE could identify the lesions earlier since it is more accepted than colonoscopy and treatment would be initiated promptly.

CONTRAINDICATIONS AND RISKS

When we talk about risks in performing a CE examination, the biggest concern is capsule retention, which is defined as the failure to excrete the capsule in 2 wk or more, which prompts the need of medical, endoscopic or surgical intervention[60]. Thereby, patients with known stenotic disease or with a history of bowel obstruction have an increased risk of capsule retention. In patients with suspected obstruction, imaging investigations should be done before CE, but they do not completely exclude capsule retention totally[61]. Usually, patients with capsule retention are asymptomatic[62], but they may experience symptoms of a complete bowel obstruction. Depending of the nature of the stricture, the patient may excrete the capsule after corticosteroid treatment if the stricture is an inflammatory one or with endoscopic or surgical intervention.

The risk of capsule retention varies according to different studies and ranges from 1.4%[20] to 2.6%[63] in patients with suspected disease and up to 13% in patients already diagnosed[64]. In patients with suspected CD, the risk of capsule retention is similar to that of other indications, being higher in patients with established CD. Capsule retention in patients with diagnosed strictures reaches 21%[65].

To avoid capsule retention, the patency capsule was developed, which is identical in shape and dimensions to the renal capsule. The advantage of the patency capsule is that its components enable it to dissolve after ingestion, and the barium it contains helps us to identify its location through radiologic exams. If not excreted, it can be localized by radiography or computed tomography[66]. Currently a second generation patency capsule is used-the Agile® capsule, which with two timer plugs, one at each end, dissolves faster (30 h compared to 80 h)[67].

Patients with suspected strictures who have a

successful passage of the patency capsule also should have a high chance of a successful passage of the CEE. However, cases of patency capsule retention requiring surgery and also few cases of capsule impaction after successful patency examination were reported[67].

Some clinicians see capsule retention as a good indicator of lesions, allowing a change in management of the patient-device assisted endoscopy with capsule removal and dilation, surgery, modification of treatment. The Canadian guideline and the European Society of Gastrointestinal Endoscopy (ESGE) Technical Review regarding small bowel CE recommend that, in case of suspected strictures or symptoms of obstruction, imaging exams should be performed on the first intention, and if there is a high risk of retention, a patency capsule should be administered before CE[7,68]. The ESGE Technical Review recommends observation in cases of asymptomatic capsule retention and treatment with steroids if indicated[68]. When capsule retrieval is indicated, device-assisted enteroscopy is the recommended method[68].

CONCLUSION

CE has proved to be an important noninvasive tool for the diagnosis and monitoring of CD patients. It has the advantage of excellent visualization of digestive tract mucosa, a good tolerability and safety in well-selected patients. The risk of retention can be diminished with careful selection of patients using imaging techniques and by the use of a patency capsule.

The aim of a capsule examination is not only to produce an early diagnosis but also to provide a very good stratification of prognosis, thus directing the treatment strategy for either a step-up or top-down approach and permitting the optimization of the treatment, depending on the findings. In patients with a high suspicion of CD, since the negative predictive value of CE examination is more than 96%, perhaps in the future, the pan-enteric CE could be used as a screening tool even before ileocolonoscopy. In established CD, it is very important to assess the extent and the severity of the disease dynamically in order to make the best decision about the treatment and its optimization. For the best assessment of the bowel damage, both mucosal and extramucosal, an ideal approach will include both CE and MRE. A similar approach can be used when monitoring patients with suspected post-surgery CD recurrence, where acceptance of capsule examination is higher. Based on CE findings, treatment can be optimized in order to avoid recurrence and a new surgical intervention.

When symptoms and biomarkers point to a change in the disease's activity, we can either adjust the treatment directly, as recommended in CALM study, or choose to visualize the digestive mucosa in selected patients through a CE and make a decision afterward. We believe that increasing evidence tends to support a role of iterative CE examinations in treat to target approach, the only issues being related to costs and potential impaction risks, which are not negligible. The new Crohn's Capsule is promising, and perhaps we are not that far away from using such capsule technologies for drug delivery and tissue sampling in CD patients[69].

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ORIGINAL ARTICLE

Case Control Study

Anesthetic management and associated complications of peroral endoscopic myotomy: A case series

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Abstract

AIM

To investigate the anesthetic management of peroral endoscopic myotomy (POEM) and its associated complications.

METHODS

This study was a single-center, retrospective, observational study comprising a case series of all patients who underwent POEM in our hospital from April 2015 to November 2016. We collected data regarding patient characteristics, anesthetic methods, surgical factors, and complications using an electronic chart.

RESULTS

There were 86 patients who underwent POEM in our hospital during the study period. Preoperatively, patients were maintained on a low residue diet for 48 h prior to the procedure. They were fasted of solids for 24 h before surgery. There was one case of aspiration (1.2%). During POEM, patients were positioned supine with the upper abdomen covered by a clear drape so

that pneumoperitoneum could be timeously identified. In three cases, the peak airway pressure exceeded 35 cmH_2O during volume controlled ventilation with tidal volumes of 6-8 mL/kg and subsequent impairment of ventilation. These cases had been diagnosed with spastic esophageal disorders (SEDs) and the length of the muscular incision on the esophageal side was longer than normal.

CONCLUSION

In the anesthetic management of POEM, it is important to prevent aspiration during induction of anesthesia and to identify and treat complications associated with CO_2 insufflation.

Key words: Peroral endoscopic myotomy; Anesthetic management; Ventilatory impairment

Core tip: In the anesthetic management of peroral endoscopic myotomy (POEM), it is important to identify and treat complications associated with CO_2 insufflation. In this retrospective case series, we experienced three cases of ventilatory complications caused by CO_2 insufflation. These cases had been diagnosed with spastic esophageal disorders and the length of the muscular incision on the esophageal side was longer than usual. In particular, pneumoperitoneum needs to be carefully assessed for during the procedure, especially when a longer muscular incision is necessary. Significantly, this is the first case series report of ventilatory impairment occurring as an anesthetic complication of POEM using CO_2 insufflation.

Nishihara Y, Yoshida T, Ooi M, Obata N, Izuta S, Mizobuchi S. Anesthetic management and associated complications of peroral endoscopic myotomy: A case series. *World J Gastrointest Endosc* 2018; 10(9): 193-199 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i9/193.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i9.193

INTRODUCTION

Until recently, treatment options for esophageal achalasia have comprised pharmacological therapy, endoscopic pneumatic balloon dilation and surgical intervention such as Heller's myotomy[1,2]. Peroral endoscopic myotomy (POEM) is a novel procedure that has become established as the best treatment option for esophageal achalasia, as POEM is safer and less invasive than other surgery, and is expected to offer long-lasting symptom control[3-6]. While POEM is performed under general anesthesia, few reports exist about its anesthetic management, particularly regarding anesthetic complications. We describe here the anesthetic management and associated complications in 86 patients who underwent POEM for esophageal achalasia at our institution.

MATERIALS AND METHODS

This study was a single-center, retrospective, observational study comprising a case series of all patients who underwent POEM in our hospital from April 2015 to November 2016. Kobe University Hospital institutional Review Board approved this observational study. The institutional Review Board of Kobe University Hospital Number of assessment report: 1587. Written informed consent has been obtained from the patients.

Statistical analysis

We collected data regarding patient characteristics, anesthetic methods, surgical factors, and complications using an electronic chart. The patient characteristics include age, sex, body mass index, preoperative symptoms, previous intervention, diagnosis and preoperative Eckardt score. The anesthetic methods include type and dose of anesthetic agents during anesthesia. The surgical factors include duration of anesthesia, duration of surgery, length of muscular incision, perioperative adverse events, hospital stay and Eckardt score 2 mo later. The results are shown as the median (25%-75%, interquartile range) and number (%). Differences in the Eckardt score before and after POEM were compared with the Mann-Whitney *U* test. We used SPSS 20.0 software to perform statistical analysis. A P value < 0.05 was defined as being statistically significant.

RESULTS

Patient characteristics

There were 86 patients who underwent POEM in our hospital during the period April 2015 to November 2016. Table 1 summarizes the patient characteristics. The median age was 51 years, and 35 of the patients were male (41%). The median BMI was 20.6 kg/cm^2. Regarding pathology, esophageal achalasia was the cause in 80 cases (93.0%), jackhammer esophagus in five (5.8%) and diffuse esophageal spasm in one (1.2%).

Preoperative management and induction of anesthesia

Table 2 summarizes key anesthetic and surgical factors. In the first two cases, esophagoscopy was performed under sedation before induction of anesthesia to ensure complete evacuation of esophageal contents. However, because Friedrich *et al*[7] reported that esophagoscopy under sedation elevated the risk of aspiration, we did not evacuate esophageal contents *via* esophagoscopy before induction in any of the following cases. Instead, a low residue diet was maintained for 48 h prior to the procedure. Patients were fasted of solids for 24 h and then of clear liquids for 2 h before the procedure. Patients were placed in the semi-Fowler's position prior

Table 1 Patient characteristics

Characteristics	Values
Age median (range); yr	51 (42-66)
Sex male (%)	35 (41)
BMI median (range); kg/cm^2	20.6 (18.6-22.8)
Preoperative symptoms; *n* (%)	
Weight loss	44 (51)
Chest pain	51 (59)
Dysphagia	84 (98)
Regurgitation	78 (91)
Previous interventions; *n* (%) (overlapping)	
None	44 (51)
Pharmacological therapy	21 (24)
Endoscopic pneumatic balloon dilation	20 (23)
Surgical myotomy	4 (5)
Diagnosis; *n* (%)	
Esophageal achalasia	80 (93)
Jackhammer esophagus	5 (6)
Diffuse esophageal spasm	1 (1)
Preoperative Eckardt score median (range); point	6 (4-7)

Table 2 Anesthetic and surgical factors

Parameters	Values
Cricoid pressure; *n* (%)	26 (46)
Maintenance with inhalational agents; *n* (%)	78 (91)
Duration of anesthesia mean ± SD; min	117 ± 31
Duration of surgery mean ± SD; min	83 ± 31
Length of muscular incision	
Esophageal side average ± SD; cm	10.4 ± 3.9
Gastric side average ± SD; cm	2.7 ± 0.7
Total average ± SD; cm	13.1 ± 3.9
Perioperative adverse events; *n* (%)	
Aspiration	1 (1)
Subcutaneous emphysema	21 (24)
$EtCO_2$ > 50 mmHg during procedure	34 (40)
Upper abdominal needle decompression required	12 (14)
Airway pressure > 35 cmH_2O during operation	3 (3)
Mucosal injury not requiring invasive treatment	9 (10)
Mediastinitis with antibiotic therapy	1 (1)
Hospital stay mean ± SD; d	5.45 ± 2.18
Eckhart score 2 mo later; median (range); point	0 (0–1)

to induction of anesthesia and rapid sequence induction (RSI) was performed in all cases. We left the decision to use cricoid pressure up to the attending anesthesiologist; this was performed in 36 cases (42%). Anesthesia was induced with propofol (1.0-3.0 mg/kg), rocuronium (0.6-1.2 mg/kg), and either continuous intravenous infusion of remifentanil at 0.2-0.4 μg/kg/min or intravenous administration of remifentanil 50-100 μg.

There was one case of aspiration (1.16%) during induction of anesthesia, a female patient in her twenties. Because preoperative esophagoscopy revealed a moderate amount of residue in the esophagus, we had evacuated the esophageal contents with esophagoscopy two days before the procedure and maintained the patient on a low residue diet for 48 h prior to POEM, fasted of solids and liquids as previously described. Esophageal manometry revealed elevation of both integrated relaxation pressure (57 mmHg; normal < 15 mmHg) and lower esophageal sphincter pressure during expiration (52 mmHg; normal 10-35 mmHg). After administration of remifentanil 100 μg, propofol 3.0 mg/kg, and rocuronium 1.2 mg/kg, we recognized reflux of liquid contents before laryngoscopy. This was immediately suctioned, followed by intubation. We then suctioned aspirated vomitus through the endotracheal tube as soon as possible *via* bronchoscopy. Aspirated contents were found to be liquid, without solid particles. As the patient's respiratory status did not worsen, surgery went ahead as scheduled, and POEM performed in its entirety. After surgery, the patient was extubated in the operating room after full emergence from anesthesia and was returned to the ward after recovery. The postoperative course was uneventful and there were no respiratory complications such as pneumonia.

Intraoperative events

Intraoperative monitoring included routine use of noninvasive blood pressure, electrocardiography, pulse oximetry, capnography (End tidal CO_2: $EtCO_2$), urinary catheterization and eardrum temperature monitoring. Anesthesia was maintained with sevoflurane (1.0%–1.5%), desflurane (3.0%–5.0%), or propofol (target controlled infusion of 2.5–3.5 μg/mL) with a mixture of 40% oxygen in air. Inhalational maintenance (sevoflurane or desflurane) was chosen in 78 cases (91%).

We left decisions regarding ventilation up to the attending anesthesiologist. During POEM, patients were positioned supine with the upper abdomen covered by a clear drape so that pneumoperitoneum could be identified immediately. In 21 cases (24.4%) subcutaneous emphysema was noted. In 34 cases (39.5%) $EtCO_2$ exceeded 50 mmHg. Among these, needle decompression of the upper abdomen was necessary in twelve cases (14.0%). In three cases, the peak airway pressure exceeded 35 cmH_2O under 6-8 mL/kg volume controlled ventilation. Of these three cases, two were diagnoses of jackhammer esophagus and the other a case of diffuse esophageal spasm.

Table 3 shows the characteristic of these three cases. In all three cases, the $EtCO_2$ had increased to more than 60 mmHg, peak airway pressure exceeded 35 cmH_2O, and SpO_2 decreased between 60 to 90 min after surgery commenced. Following needle decompression of the upper abdomen, the $EtCO_2$ and the peak airway pressure decreased immediately and ventilatory parameters improved in two cases. In the other case, the $EtCO_2$ remained abnormally high (177 mmHg) and it was necessary to stop surgery for about over 1 h because needle decompression did not result in immediate improvement. The $EtCO_2$ and peak airway pressure decreased gradually after interruption of CO_2 insufflation. Then, ventilatory parameters improved, surgery restarted and POEM proceeded uneventfully. After full emergence from anesthesia, the patient was extubated in the operating room and transferred to

Table 3 Characteristics of three cases

Characteristics	Case 1	Case 2	Case 3
Age; yr	74	61	73
Sex	Female	Male	Female
BMI; kg/cm^2	25.9	23.4	21.5
Preoperative symptoms			
Weight loss	Yes	None	None
Chest pain	Yes	None	Yes
Dysphagia	Yes	Yes	Yes
Regurgitation	Yes	Yes	Yes
Previous intervention	Pharmacological therapy	None	None
Lower esophageal sphincter pressure; mmHg	31	64	51
Diagnosis	Diffuse esophageal spasm	Jackhammer esophagus	Jackhammer esophagus
Duration of anesthesia; minutes	163	141	229
Maintenance of anesthesia	inhalation	inhalation	inhalation
Length of muscular incision			
Esophageal side; cm	18	15	19
Gastric side; cm	3	3	4
Maximum $EtCO_2$; mmHg	67	63	177
Maximum peak airway pressure under 6-8 mL/kg volume controlled ventilation; mmHg	37	40	46

BMI: Body mass index.

Table 4 Review of anesthetic management of peroral endoscopic myotomy in the existing literature

Author	*n*	Preparation for POEM	Aspiration at induction	CO_2-related complications
Löser *et al*[9]	173	Liquid diet 2 to 5 d prior to POEM Nil per os overnight (for at least eight hours) Esophagoscopy was performed one day before POEM	None	Subcutaneous emphysema in 49 cases Pneumothorax in 1 case
Jayan *et al*[10]	21	Low residue diet 48 h before POEM Fasted from 20:00 on day before POEM	None	Subcutaneous emphysema in 5 cases
Goudra *et al*[11]	24	Fasting times for both solids and liquids were variable	1	No comment
Yang *et al*[12]	52	Clear liquid diet for 48 h before POEM Nil per os after midnight on day of POEM	None	Peak airway pressure > 35 cmH2O in 5 cases
Tanaka[13]	28	Nil per os for 24 h before POEM Esophagoscopy was performed before induction of anesthesia	None	Subcutaneous emphysema in 1 case

POEM: Peroral endoscopic myotomy.

the intensive care unit. The patient was discharged on postoperative day 9. Okada *et al*[8] described this case previously in detail.

Other complications and postoperative course

Other complications included esophageal mucosal injury in nine cases (10.5%), all of which were treated by endoscopic clipping of the mucosa. There was one case of postoperative mediastinitis that required six weeks of antibiotic therapy. There were no cases of postoperative pneumonia. The number of days from surgery to discharge was an average of 5.45 ± 2.18 in-hospital days. The median preoperative and two-month postoperative Eckardt scores were 6 (4-7) and 0 (0-1), respectively. The median Eckardt score was accepted as indicating significant improvement of symptoms (P < 0.001).

DISCUSSION

In this retrospective case series, we experienced one case of aspiration which occurred at induction of anesthesia, and three cases of ventilatory complications caused by CO_2 insufflation. Significantly, this is the first case series report of ventilatory impairment occurring as an anesthetic complication of POEM using CO_2 insufflation.

Until now, there have been five reports of the anesthetic management of POEM[9-13]. These are summarized in Table 4. All reports concluded that prevention of aspiration during induction of anesthesia and awareness of CO_2-related complications, such as mediastinal emphysema, were very important factors to consider. One case of aspiration (0.3%) occurred during induction of anesthesia in the 298 patients described in the five reports. In that particular case, rapid induction was chosen as the induction method and the authors concluded that rapid sequence induction was safer for patients with esophageal achalasia[11]. Tanaka *et al*[13] used esophagoscopy to evacuate esophageal contents prior to induction of anesthesia in all cases. On the other hand, Yang *et al*[12] suggested that it was possible

to perform induction safely by maintaining patients on a clear liquid diet for 48 h prior to the procedure, instead of endoscopic evacuation of esophageal contents immediately before the procedure.

In the first two cases of our series, we evacuated esophageal contents *via* esophagoscopy under sedation prior to the procedure, according to the recommendation of Tanaka *et al*[13]. However, Friedrich *et al*[7] examined 15690 endoscopies under sedation and revealed a 0.1% incidence of respiratory infection following endoscopy. We felt the risk of esophagoscopy under sedation outweighed the benefits in patients who already had a high risk of aspiration, such as those with esophageal achalasia. As such, from the third case onwards we did not perform esophagoscopy before the procedure, and instead maintained patients on a low residue diet for 48 h preoperatively, fasting them of solids and liquids as previously described. RSI was chosen in all cases for induction of anesthesia. Despite these measures, we experienced one instance of aspiration during induction. In this case, preoperative esophagoscopy showed a moderate amount of residue in the esophagus, while esophageal manometry revealed elevated lower esophageal sphincter pressure during expiration (52 mmHg). It is generally known that anesthetic agents decrease lower esophageal sphincter pressure[14,15]. Upper esophageal sphincter pressure is similarly decreased by these agents[14,15]. However, these reports relate to a case without esophageal pathology, and the effects of anesthetic agents on esophageal sphincter pressure in achalasia patients are not yet known.

Given that esophageal achalasia is characterized by incomplete relaxation of the lower esophageal sphincter, we speculated that the aspiration occurred because only the upper esophageal sphincter pressure decreased upon administration of anesthetic agent, there was a moderate amount of esophageal content, and the lower esophageal sphincter pressure was high. Following this case, we decided to insert a gastric tube awake in all cases thought to be at high risk of aspiration, in order to evacuate secretions and reduce esophageal pressure prior to induction of anesthesia. These included cases with obvious residue during preoperative esophagoscopy, elevated lower esophageal sphincter pressure and severe esophageal dilatation.

It is known that complications associated with CO_2 insufflation, such as subcutaneous emphysema, mediastinal emphysema and pneumoperitoneum are common during POEM, because of the need to secure an operative field[16,17]. As such, it is important to keep the upper abdomen exposed to identify pneumoperitoneum timeously. If pneumoperitoneum occurs, it should be treated with rapid needle decompression of the upper abdomen. However, some reports have concluded that while subcutaneous emphysema, mediastinal emphysema and pneumoperitoneum were common during POEM, these did not cause serious complications and no special intervention was required[18, 19]. In the previous five reports[9-13], $EtCO_2$ increased during POEM, but no case of ventilatory impairment occurred. Our report is the first one describing ventilatory impairment during POEM. The target diseases of the three cases concerned were jackhammer esophagus and diffuse esophageal spasm. These diseases are classified as Spastic Esophageal Disorders (SEDs). Because POEM allows for a longer length of muscular incision on the esophageal side, POEM is more useful than laparoscopic Heller operation for SEDs, and may become first-line treatment for SEDs in the future[20]. In our 86 patients, the average length of the lateral esophageal muscle layer incision was 10.4 ± 3.9 cm. The incision length in the three cases with ventilatory impairment were 18 cm, 19 cm and 15 cm on the esophageal side, considerably longer than average. In these three cases, we thought that the longer incision length led to massive leakage of CO_2 into the mediastinum.

In SEDs, abnormal peristalsis of the esophageal body occurs frequently, worsening the operative field for incision on the esophageal side. Therefore, CO_2 insufflation during POEM for SEDs tends to increase for securing the operative field; as such, CO_2-related complications may occur more frequently. In our hospital, when $EtCO_2$ exceeds 50 mmHg, we check for the presence of subcutaneous emphysema and pneumoperitoneum by palpation and visual inspection. Should pneumoperitoneum be present, this is treated by placement of a needle to upper abdomen. Surgeons are also notified if $EtCO_2$ increases significantly and are asked minimize CO_2 insufflation as much as possible. Should reducing CO_2 insufflation be difficult to secure an operative field, we consider administration of scopolamine to inhibit esophageal peristalsis. However, as Tanaka *et al*[13] has pointed out, this carries a risk of tachycardia.

There are several limitations to this study. Firstly, this was a single-center retrospective observational study, and thus the incidence of complications associated with anesthetic management of POEM is uncertain. Secondly, this was a small, single-center study with and weak generalizability. Thus, our findings should be validated in other sites. Finally, there were no specific criteria for needle placement in the upper abdomen to decrease $EtCO_2$. Thus, mild pneumoperitoneum might have been overlooked and would have affected the results. In this regard, a future prospective study should be conducted with an established protocol for upper abdominal needle decompression.

In conclusion, prevention of aspiration during induction and prompt recognition and treatment of CO_2-related complications are important factors in the anesthetic management of POEM. The risk of peak airway pressure elevation and ventilatory impairment caused by CO_2 insufflation is higher in cases which require a longer than normal muscular incision on the esophageal aspect. Given the risk of pneumoperitoneum, this should be checked for during

the procedure and treated by immediate needle decompression of the upper abdomen.

ARTICLE HIGHLIGHTS

Research background

Peroral endoscopic myotomy (POEM) is a novel procedure that has become established as the best treatment option for esophageal achalasia, as POEM is safer and less invasive than other surgery, and is expected to offer long-lasting symptom control. While POEM is performed under general anesthesia, few reports exist about its anesthetic management, particularly regarding anesthetic complications.

Research motivation

Fatal anesthetic complications sometimes occurred during POEM, but few reports exist about them. Hence, we describe here the anesthetic management and associated complications in 86 patients who underwent POEM for esophageal achalasia at our institution.

Research objectives

We describe here the anesthetic management and associated complications in 86 patients who underwent POEM for esophageal achalasia at our institution.

Research methods

This study was a single-center, retrospective, observational study comprising a case series of all patients who underwent POEM in our hospital from April 2015 to November 2016. We collected data regarding patient characteristics, anesthetic methods, surgical factors, and complications using an electronic chart.

Research results

There were 86 patients who underwent POEM in our hospital during the study period. There was one case of aspiration (1.2%). In three cases, the peak airway pressure exceeded 35 cmH2O during volume controlled ventilation with tidal volumes of 6-8 mL/kg and subsequent impairment of ventilation. These cases had been diagnosed with spastic esophageal disorders (SEDs) and the length of the muscular incision on the esophageal side was longer than normal.

Research conclusions

Our report is the first one describing ventilatory impairment during POEM. In the anesthetic management of POEM, it is important to identify and treat complications associated with CO2 insufflation. In particular, pneumoperitoneum needs to be carefully assessed for during the procedure, especially when a longer muscular incision on the esophageal side is necessary.

Research perspectives

Because POEM allows for a longer length of muscular incision on the esophageal side, POEM is more useful than laparoscopic Heller operation for SEDs, and may become first-line treatment for SEDs in the future. We speculated that the longer incision length led to massive leakage of CO2 into the mediastinum. In this regard, a future prospective study should be conducted about complications associated with CO2 insufflation in POEM for SEDs.

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ORIGINAL ARTICLE

Retrospective Study

Frequency of hospital readmission and care fragmentation in gastroparesis: A nationwide analysis

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Abstract

AIM

To evaluate rates and predictors of hospital readmission and care fragmentation in patients hospitalized with gastroparesis.

METHODS

We identified all adult hospitalizations with a primary diagnosis of gastroparesis in the 2010-2014 National Readmissions Database, which captures statewide readmissions. We excluded patients who died during the hospitalization, and calculated 30 and 90-d unplanned readmission and care fragmentation rates. Readmission to a non-index hospital (*i.e.*, different from the hospital of the index admission) was considered as care fragmentation. A multivariate Cox regression model was used to analyze predictors of 30-d readmissions. Logistic regression was used to determine hospital and patient factors independently associated with 30-d care fragmentation. Patients readmitted within 30 d were followed for 60 d post discharge from the first readmission. Mortality during the first readmission,

hospitalization cost, length of stay, and rates of 60-d readmission were compared between those with and without care fragmentation.

RESULTS

There were 30064 admissions with a primary diagnosis of gastroparesis. The rates of 30 and 90-d readmissions were 26.8% and 45.6%, respectively. Younger age, male patient, diabetes, parenteral nutrition, ⩾ 4 Elixhauser comorbidities, longer hospital stay (> 5 d), large and metropolitan hospital, and Medicaid insurance were associated with increased hazards of 30-d readmissions. Gastric surgery, routine discharge and private insurance were associated with lower 30-d readmissions. The rates of 30 and 90-d care fragmentation were 28.1% and 33.8%, respectively. Younger age, longer hospital stay (> 5 d), self-pay or Medicaid insurance were associated with increased risk of 30-d care fragmentation. Diabetes, enteral tube placement, parenteral nutrition, large metropolitan hospital, and routine discharge were associated with decreased risk of 30-d fragmentation. Patients who were readmitted to a non-index hospital had longer length of stay (6.5 *vs* 5.8 d, $P = 0.03$), and higher mean hospitalization cost ($15645 *vs* $12311, $P < 0.0001$), compared to those readmitted to the index hospital. There were no differences in mortality (1.0% *vs* 1.3%, $P = 0.84$), and 60-d readmission rate (55.3% *vs* 54.6%, $P = 0.99$) between the two groups.

CONCLUSION

Several factors are associated with the high 30-d readmission and care fragmentation in gastroparesis. Knowledge of these predictors can play a role in implementing effective preventive interventions to high-risk patients.

Key words: Gastroparesis; Hospital readmission; Care fragmentation

Core tip: Gastroparesis is associated with high 30-d readmission, and 1 in 4 readmissions occur at a hospital different from the index hospitalization. Measuring same-hospital readmission rates without accounting for non-index hospitalization underestimates readmission rates by 20%. Several factors are associated with 30-d readmission and care fragmentation, and can play a role in implementing effective preventive interventions to high-risk patients. Care fragmentation is associated with increased cost of readmissions and longer hospital stays. Optimizing post discharge care coordination and data sharing between hospitals could decrease care fragmentation and cost of care.

Qayed E, Muftah M. Frequency of hospital readmission and care fragmentation in gastroparesis: A nationwide analysis. *World J Gastrointest Endosc* 2018; 10(9): 200-209 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i9/200.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i9.200

INTRODUCTION

Gastroparesis is a chronic illness that leads to upper gastrointestinal symptoms of nausea, vomiting, early satiety, and abdominal pain. In the United States, epidemiologic data estimates the incidence of gastroparesis at 2.4 per 100000 person-years and the prevalence at 9.6 per 100000 person-years[1]. Hospital admissions related to gastroparesis have increased over the past two decades. In one study of the nationwide inpatient sample database, annual hospital admissions for gastroparesis increased from 3978 in 1997 to 16460 in 2013[2]. The same study found an increase in hospital charges for gastroparesis admissions from $13350 to $34585 over the same period. Gastroparesis has become of increasing relevance due to its association with poorer quality of life, significant psychological distress, anxiety and depression[3-6].

Given the increasing burden of gastroparesis on patients' quality of life and on healthcare costs, it is important to identify factors related to hospital readmissions. Knowledge of these predictors can play a role in implementing preventive interventions in high-risk patients. However, few studies addressed this topic. Uppalapati *et al*[7] found that poor glycemic control, infection, and non-adherence with medical therapy correlated with increased hospital admission rates in gastroparesis. Bielefeldt *et al*[8] found that more than half of emergency department visits for gastroparesis resulted in admission. Age, cardiovascular, renal, and infectious comorbidities were found to correlate with higher admission rates[8]. None of these studies estimated the readmission rates and risk factors for readmission in gastroparesis.

Due to the chronicity of symptoms of gastroparesis, post discharge care coordination could play an important role in preventing hospital readmission. One negative consequence of lack of care coordination is care fragmentation. This occurs when the patient is discharged from one hospital (index hospital) and is readmitted to a different (non-index) hospital. Studies of care fragmentation in various medical and surgical conditions show that this phenomenon is common and correlates with increased adverse outcomes, hospitalization, and healthcare costs[9-13]. In addition, readmissions to different hospitals leads to underestimation of readmission if the first hospital conducts a readmission analysis that is limited to its institutional database[13].

Given the increasing number of hospitalizations and rising healthcare costs in gastroparesis, we performed this analysis using a nationwide database to study several aspects of hospitalization in gastroparesis. First, we evaluate the rates and predictors of hospital readmission in gastroparesis. Second, we assess the

Table 1 Elixhauser comorbidity variables

Comorbidity variables
Paralysis
Other neurological disorders
Chronic pulmonary disease
Diabetes without chronic complications
Diabetes with chronic complications
Hypothyroidism
Renal failure
Liver disease
Chronic peptic ulcer disease
Human Immunodeficiency Virus or Acquired Immunodeficiency Syndrome
Lymphoma
Metastatic cancer
Solid tumor without metastasis
Rheumatoid arthritis/collagen vascular diseases
Coagulation deficiency
Obesity
Weight loss
Fluid and electrolyte disorders
Blood loss anemia
Deficiency anemias
Alcohol abuse
Drug abuse
Psychosis
Depression
Congestive heart failure
Valvular disease
Pulmonary circulation disorder
Peripheral vascular disorder
Hypertension

frequency and predictors of care fragmentation using statewide data, and its effect on underestimation of hospital readmission. Lastly, we evaluate the effect of care fragmentation on several outcomes including in-hospital mortality, length of stay, costs, and 60-d readmissions.

MATERIALS AND METHODS

We used the National readmission database (NRD) from 2010 to 2014 as the study data source. The NRD is developed by the Agency for Healthcare Research and Quality (AHRQ) as part of the Healthcare Cost and Utilization Project (HCUP). It is a database of all-payer hospitalizations drawn from a sample of 22 state inpatient databases, and accounts for 49.3% of all hospitalizations in the United States[14]. Each hospitalization contains several patient and hospital related variables. The database and description of data elements are publicly available through the HCUP website[15]. Using special patient linkage numbers, the NRD allows tracking of patients who are admitted to any hospital within a state, but not across state lines. The database cannot follow patients across different calendar years, and therefore each year of the database is analyzed separately. The Institutional Review Board determined that the study was exempt from review because the database does not contain protected health information and it cannot be linked to any specific subject.

Study population

We used the International Classification of Diseases, Ninth Revision; Clinical Modification (ICD-9-CM) to identify all adult (age $\geqslant$ 18 years) hospitalizations with the primary discharge diagnosis of gastroparesis (code 536.3). For the purpose of 30-d readmissions, we excluded patients who were discharged in the month of December of each year, in order to have a full 30-d post discharge follow up period to capture readmissions. For the purpose of 90-d readmissions analysis, we excluded records of patients discharged in the month of October, November, and December. We also excluded records of those who died during admission, and records that represent same-day stay pairs of records (patient discharged and readmitted the same day). To avoid duplication, we excluded records that fit the criteria for an index admission, but were also identified as re-admissions within 30 d of a previous index admission. We included these records in the readmission analysis. We used predefined tracking variables included in the NRD to identify all-cause unplanned readmissions within a 30 and 90-d period post discharge. As per the recommendations of the Center for Medicare and Medicaid Services, we excluded planned (elective) readmissions[16].

Demographic and hospital variables

Patient socio-demographic variables included age, sex, and median household income for patient's ZIP Code. Other variables included primary payer information, length of stay, and discharge disposition. Hospital-related variables included hospital control/ownership status, bed size, and metropolitan status. To control for the risk of readmission, we used the Elixhauser readmission index, which is a validated comorbidity measure derived from 29 comorbidity variables (Table 1). Hospital charges were converted to costs using charge-to-cost ratios provided by the HCUP. We used the consumer price index to inflate costs to 2017 dollars as outlined by the United States Bureau of Labor Statistics[17]. Procedures were identified using ICD-9-CM for procedure codes in any of the procedure fields of the admission record as follows: Gastrostomy 43.11-43.19; jejunostomy 46.32, 46.39; pyloroplasty 44.21, 44.22; pyloromyotomy 43.3; partial gastrectomy 43.5-43.8; total gastrectomy 43.9; parenteral nutrition 99.15.

Outcomes

We measured the rates of all-cause 30 and 90-d readmissions and care fragmentation. Index-hospital readmissions were identified as readmissions in which the same hospital identification (ID) code is identified on both the initial hospitalization and the readmission record. Non-index readmissions were identified as readmissions in which a different hospital ID is identified on the readmission record. According to this readmission status, patients were classified into one of three groups:

(1) patients with only an index hospital readmission within the 30 or 90-d post discharge period; (2) patients with both index and non-index readmission(s) during follow up; and (3) patients with only a non-index readmission. Patients who were transferred from a non-index hospital to an index hospital were considered as if they were admitted to an index-hospital. This was done because the NRD combines hospital transfers into one discharge record. Care fragmentation was calculated by dividing the number of patients who had any non-index hospitalization (groups 2 and 3) by the total number of readmissions. To calculate the underestimation of hospital readmissions if only index hospital readmissions were used, we divided the number of patients with only a non-index readmission by the total number of readmissions.

Statistical analysis

Categorical variables were described as number (percentage); while continuous variables were reported as as mean (standard deviation). Baseline characteristics of patients who did and did not experience a readmission were compared using the chi-square test for categorical variables and the *t* test for continuous variables. Multivariable Cox proportional hazards regression was used to analyze predictors of 30-d readmissions. Multivariable logistic regression was used to analyze predictors of 30-d care fragmentation. Covariates with $P < 0.2$ on univariate analysis were entered into the model and retained if the P is < 0.05. Results of multivariable analysis were expressed using adjusted hazard ratio (aHR) or adjusted odds ratio (aOR) and 95%CI. We used Cox proportional hazards regression to evaluate the relationship between non-index readmission (care fragmentation) and readmission length of stay. Patients with a hospital stay > 30 d were censored at 30 d. We used a multivariable linear regression model to evaluate the relationship between non-index readmission and total costs of hospital stay during the first readmission. Logistic regression was used to evaluate the effect of care fragmentation on in-hospital mortality during the first readmission. A 2-tailed P of 0.05 was used as the threshold for statistical significance.

RESULTS

Readmissions

During the study period, there were 30064 total admissions for gastroparesis that fit the inclusion criteria (Figure 1). The mean age was 49.6 years (SD = 17), and 74.2% were females. Of these, 8057 (26.8%) had at least one readmission within 30-d. Table 2 shows the characteristics of patients, stratified by readmission status. Patients who experienced a 30-d readmission were more likely to be younger, male, had longer index hospitalization (> 5 d), Medicare and Medicaid insurance, Diabetes, and $\geqslant$ 4 Elixhauser comorbidities. Figure 2 shows independent predictors of 30-d readmission. Younger age, male patient, diabetes, parenteral nutrition, $\geqslant$ 4 Elixhauser comorbidities, longer hospital stay (> 5 d), large and metropolitan hospital, and Medicaid insurance were associated with increased hazards of 30-d readmissions. Gastric surgery, routine discharge and private insurance were associated with lower 30-d readmissions.

Care fragmentation and underestimation of readmission

The rate of 30 and 90-d care fragmentation is shown in Figure 3 and Table 3. Of all 30-d readmissions, 28.1% of patients were readmitted to a non-index hospital, while 22% of patients were readmitted exclusively to a non-index hospital (which represents underestimation of readmission). Corresponding numbers for 90-d period are 33.8% and 19.5%, respectively.

Figure 4 shows independent predictors of care fragmentation during the first 30-d readmission. Younger age, longer hospital stay (> 5 d), self-pay or Medicaid insurance were associated with increased risk of 30-d care fragmentation. Diabetes, enteral tube placement, parenteral nutrition, large metropolitan hospital, and routine discharge were associated with lower odds of readmission to a non-index hospital during the first 30-d readmission.

Outcomes of patients with and without care fragmentation during the first 30-d readmission are shown in Table 4. Patients readmitted to a non-index hospital had a longer mean hospital stay (6.5 *vs* 5.8 d, $P = 0.03$), and higher mean hospitalization costs ($15645 *vs* $12311, $P < 0.0001$) compared to those who were readmitted to the same index hospital. There were no differences in mortality (1.3% *vs* 1.0%, $P = 0.84$), or subsequent 60-d readmission rate (55.3% *vs* 54.6%, $P = 0.99$) between the two groups.

DISCUSSION

Patients with gastroparesis develop chronic symptoms of nausea, vomiting, abdominal pain, and weight loss. Refractory and severe symptoms can lead to recurrent hospitalizations. In this study, we found that the readmission rate for gastroparesis is substantial (26.8% at 30 d and 45.6% at 90 d), and that several clinical, demographic and hospital factors are associated with readmission in gastroparesis. Patients with multiple comorbidities and long initial hospitalization have a higher risk of readmission. Longer length of stay was found to be independently associated with increased risk of 30-d readmission. This could be reflective of the severity of gastroparesis symptoms independent of comorbidities, which were controlled for in the model. Younger patients (age 18-44) had a higher risk of readmission compared to older ones. A prospective observational study of 262 gastroparesis patients treated at 7 tertiary referral centers reported that patients older than 50 years were more likely to have

Table 2 Patient and hospital characteristics of admissions for the primary diagnosis of gastroparesis (*n* = 30064), stratified by readmission status, National Readmission Database, 2010-2014

Patient characteristics	30-d readmission		
	No *n* (%) 22007 (73.2%)	Yes *n* (%) 8057 (26.8%)	*P*
Age, mean (SD), yr	50.1 (17.2)	48 (16.3)	< 0.0001
Age category, *n* (%)			< 0.0001
18-44 yr	8766 (39.8)	3658 (45.4)	
> 45 yr	13241 (60.2)	4399 (54.6)	
Sex, *n* (%)			0.1590
Male	5625 (25.6)	2124 (26.4)	
Female	16382 (74.4)	5933 (73.6)	
Length of stay in days, mean (SD)	4.8 (5.2)	5.6 (6.0)	< 0.0001
Length of stay > 5 d	5843 (26.6)	2734 (33.9)	< 0.0001
Diabetes	4610 (20.9)	1998 (24.8)	< 0.0001
Diabetic ketoacidosis	161 (0.7)	73 (0.9)	0.1270
Enteral feeding tube placement	704 (3.2)	293 (3.6)	0.0605
Jejunostomy	445 (2.0)	168 (2.1)	
Gastrostomy	185 (0.8)	84 (1.0)	
Both jejunostomy and gastrostomy	74 (0.3)	41 (0.5)	
Gastric surgery	495 (2.2)	97 (1.2)	< 0.0001
Partial gastrectomy	231 (1.0)	54 (0.7)	
Pyloroplasty	223 (1.0)	32 (0.4)	
Other (total gastrectomy, pyloromyotomy)	41 (0.2)	11 (0.1)	
Total parenteral nutrition	753 (3.4)	380 (4.7)	< 0.0001
Number of Elixhauser comorbidities			< 0.0001
< 4	14302 (65.0)	4562 (56.6)	
⩾ 4	7705 (35.0)	3495 (43.4)	
Elixhauser readmission index mean (SD)	17.6 (13.7)	21.3 (14.6)	< 0.0001
Total cost for index admission mean/median (IQR)	$10502/$7573 ($4880-$11858)	$13126/$7760 ($4810-$13750)	< 0.0001
Primary payer, *n* (%)[1]			< 0.0001
Medicare	8855 (40.3)	3335 (41.5)	
Medicaid	3770 (17.2)	1811 (22.5)	
Private	7039 (32.1)	2108 (26.2)	
Self-pay, no charge, other	2285 (10.4)	787 (0.8)	
Income quartiles *n* (%)[2]			0.1100
1st quartile	6968 (32.2)	2636 (33.3)	
2nd quartile	5668 (26.2)	2023 (25.5)	
3rd quartile	5029 (23.2)	1882 (23.7)	
4th quartile	3970 (18.3)	1386 (7.5)	
Discharge disposition, *n* (%)[3]			< 0.0001
Discharged home (routine discharge)	18041 (82.0)	6217 (77.2)	
Transfer: Short-term hospital	113 (0.5)	45 (0.6)	
Transfer: Other type of facility	1184 (5.4)	393 (4.9)	
Home health care	2236 (10.2)	1186 (14.7)	
Against medical advice	431 (2.0)	216 (2.7)	
Hospital characteristics			
Hospital control, *n* (%)			0.0460
Government nonfederal	3014 (13.7)	1070 (13.3)	
Private (not-for-profit)	14523 (66.0)	5247 (65.1)	
Private investor owned	4470 (20.3)	1740 (21.6)	
Bed size, *n* (%)			0.0070
Small	2115 (9.6)	692 (8.6)	
Medium	5577 (25.3)	1993 (24.7)	
Large	14315 (65.0)	5372 (66.7)	
Teaching status, *n* (%)			< 0.0001
Metropolitan non-teaching	9204 (41.8)	3379 (41.9)	
Metropolitan teaching	10975 (49.9)	4161 (51.6)	
Non-metropolitan	1828 (8.3)	517 (6.4)	

[1]There were 74 records with missing values for payer type; [2]Income quartiles are based on median household income by patient ZIP code. There were 502 records with missing values for income quartiles; [3]There were 2 missing values for discharge destination.

Table 3 Summary of 30 and 90-d readmissions, underestimation of readmissions, and fragmentation of care in patients hospitalized with gastroparesis, National Readmission Database, 2010-2014

Time	% Readmission (No/total No)	% Underestimation of readmission (No/total No)	% Fragmentation of care (No/total No.)
30-d	26.8% (8057/30064)	22% (1769/8057)	28.1%(2260/ 8057)
90-d	45.6% (11987/26284)	19.5%(2334/11987)	33.8%(4049/11987)

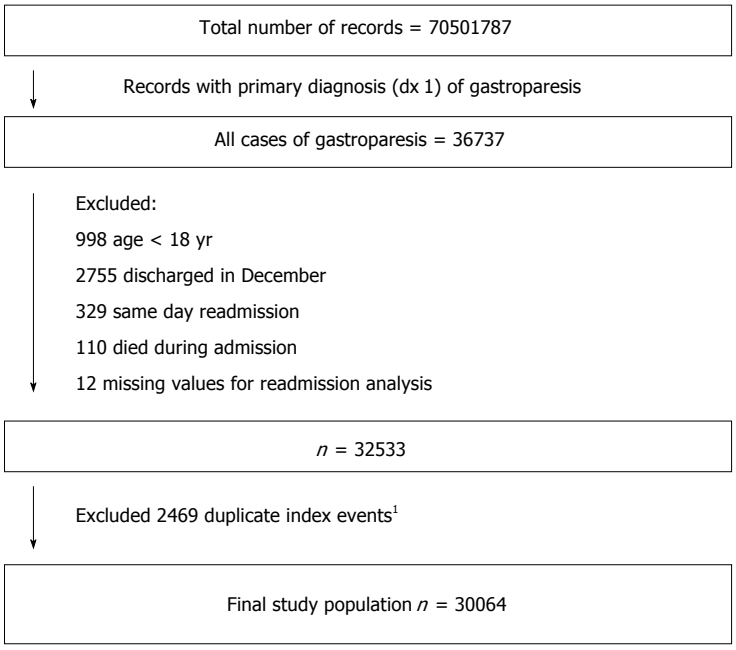

Figure 1 Data selection for Gastroparesis admissions. [1]Duplicate index events are records that fit the criteria for index gastroparesis admission, but were also identified as readmissions within 30 d of a previous index gastroparesis admission. These records were not analyzed as a separate index admission, but were included in the readmission analysis.

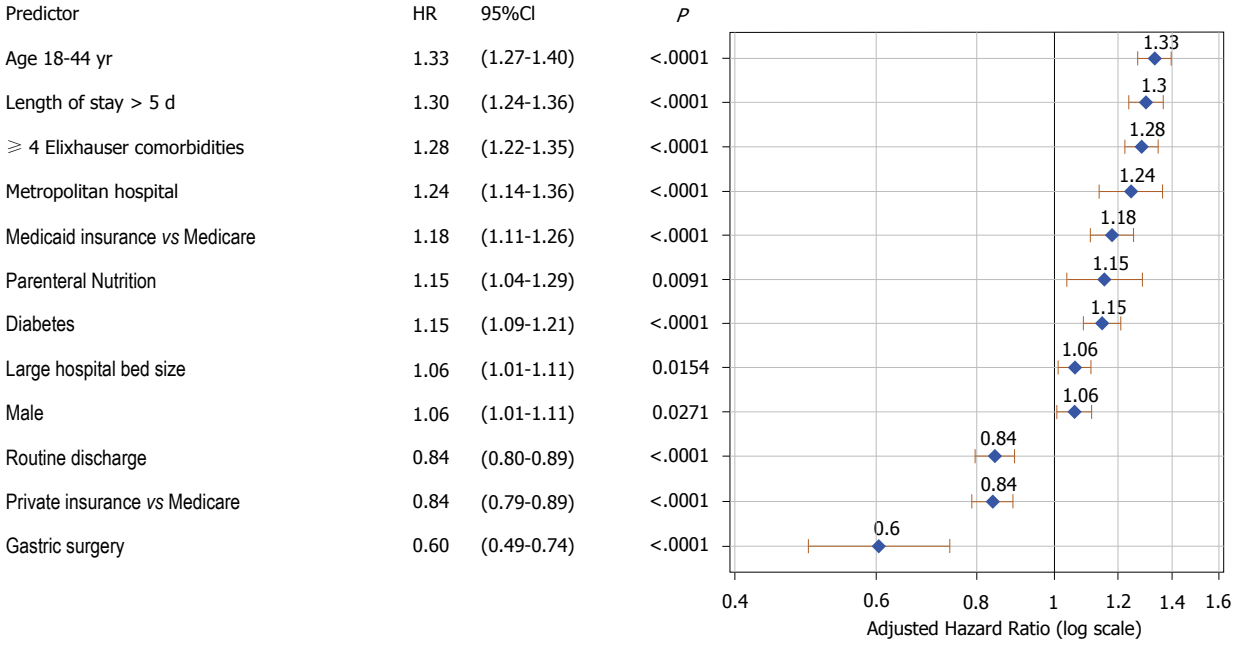

Figure 2 Multivariable proportional hazard analysis of predictors of 30-d readmission in Patients hospitalized with gastroparesis, National Readmission Database, 2010-2014.

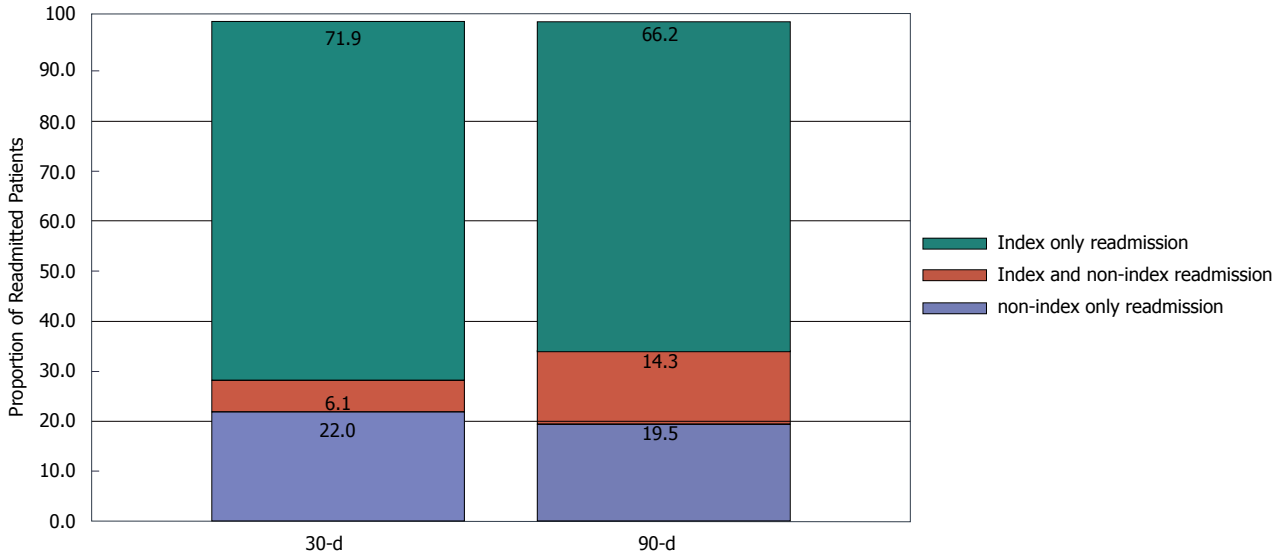

Figure 3 Proportion of 30 and 90-d readmissions to index and non-index hospitals. Blue represents non-index only readmissions, which is also the percent underestimation of care if only institutional databases are used. Blue and red represent fragmentation of care.

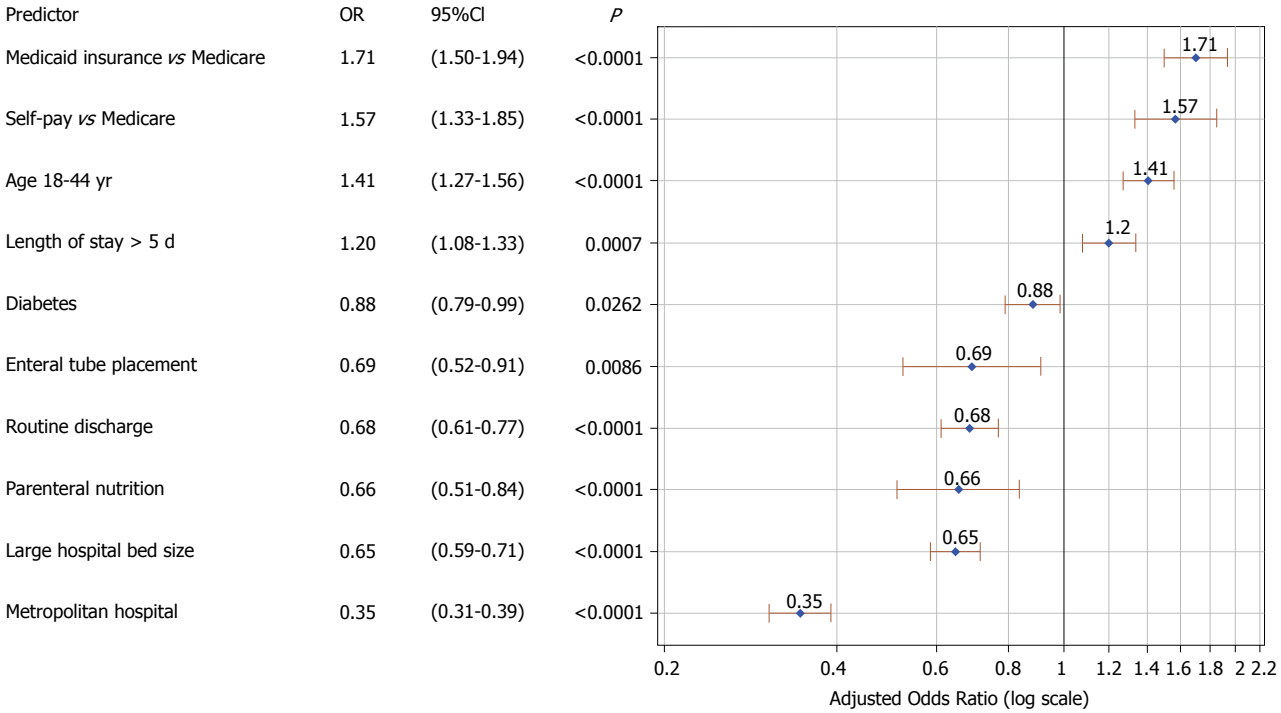

Figure 4 Multivariable logistic regression analysis of predictors of 30-d readmission to non-index hospital (care fragmentation) in patients hospitalized with gastroparesis, National Readmission Database, 2010-2014.

symptom improvement compared to younger patients (OR: 3.35, 94%CI: 1.62-6.91, P = 0.001)[18]. It is unclear why younger patients tend to do worse than older ones, but it could be related to better adaptation and tolerance of older patients to their medical illness[18]. Diabetes was associated with increased risk of readmissions, which could be related to complications of diabetes and not necessarily to the severity of gastroparesis. The aforementioned study did not find a difference in symptoms improvement between diabetic and idiopathic gastroparesis[18]. Medicaid insurance was associated with increased risk of readmissions compared to Medicare, while private insurance was associated with lower risk. No previous study examined the relationship of insurance status with gastroparesis readmissions. A report published by the AHRQ analyzed trends of hospital readmission for all illnesses by insurance type, and found that Medicare was associated with the highest risk, followed by Medicaid, self-pay/uninsured, and private insurance[19]. One possible explanation is that Medicare patients are older and have more comorbidities than patients with other types

Table 4 Association of admission to a non-index hospital during the first readmission (care fragmentation) with in-hospital costs, length of stay, mortality, and 60-d readmission

	30-d first readmission			
	Readmission to index hospital	Readmission to non-index hospital	Comparison	*P*
Total cost for first readmission, mean/median (IQR)	$12311/$7508 ($4659-$13204)	$15645/$8598 ($5281-$15472)	Difference in cost: 3803$ (2777-4829)[1]	< 0.0001
Length of stay in days, mean (SD)	5.8 (6.5)	6.5 (8.2)	Adjusted HR (95%CI): 1.07 (1.01-1.13)[2]	0.03
In-hospital Mortality	1.30%	1.00%	Adjusted OR (95%CI): 0.95 (0.57-1.57)[3]	0.84
60-d readmission	54.60%	55.30%	Adjusted HR (95%CI): 0.99 (0.94-1.06)[4]	0.99

[1]Results from multivariable linear regression including age, sex, and Elixhauser mortality score; [2]Results from multivariable proportional hazards model including age, sex, Elixhauser readmission index. The risk predicted in the length of stay analysis is for later discharge from the hospital, HR > 1 indicates increased risk of later discharge; [3]Results from multivariable logistic regression model including age, sex, Elixhauser mortality score; [4]Results from multivariable proportional hazards model including age, sex, Elixhauser readmission index, and discharge disposition. HR: Hazard ratio; CI: Confidence interval; OR: Odds ratio.

of insurance. In our study, we controlled for age and other variables, and found that Medicaid was associated with higher readmission. This could be partly related to the several social and economic challenges facing this patient population, which precludes adequate outpatient follow-up and compliance with treatment[20]. Large, metropolitan hospitals were associated with increased readmission risk. A small percentage of patients in our study underwent gastric surgery during their admission for gastroparesis (2%), and this was associated with lower 30-d readmissions. This is consistent with few previous studies in which pyloroplasty and partial gastrectomy resulted in symptom improvement in selected patients with gastroparesis[21,22]. We did not find a benefit of gastrostomy or jejunostomy tube placement on readmission rates for gastroparesis. There are limited data on the benefit of gastric and enteral tubes in gastroparesis. A systematic review of 5 small studies evaluating gastrostomy (n = 26) and jejunostomy (n = 32) found that these treatments decrease symptoms of nausea and vomiting, although jejunostomy was associated with significant complications[23]. Parenteral nutrition is used in patients with refractory symptoms, malnutrition, and inability to tolerate enteral feeding. Despite its nutritional benefits, we found that parenteral nutrition was associated with increased hospital readmission. This could be related to the increased risk of infectious and metabolic complications. These patients require close monitoring and care to prevent complications and readmissions.

We found that 28%-34% of readmissions occur at a different (non-index) hospital. This suggests that examining readmission rates using institutional databases is insufficient, and leads to underestimation of readmissions by 22%. When gauging the efficacy of therapeutic interventions (such as drug therapy, Botulinum toxin injection, transpyloric stent, gastric peroral endomyotomy), both index and non-index hospital readmissions should be measured. This is particularly important in single-arm, retrospective evaluations in which it is not possible to conduct a thorough patient follow-up. Measuring non-index readmissions can be done by linking hospital or insurance databases, or conducting regular telephone interviews. We identified several predictors of 30-d care fragmentation in gastroparesis. Self-pay/uninsured patients and Medicaid beneficiaries had higher likelihood of care fragmentation. Large, metropolitan hospitals were associated with decreased care fragmentation. As such, it appears that despite a higher risk of readmission in large metropolitan hospitals, patients are more likely to return to these facilities compared to smaller, non-metropolitan hospitals.

We found that care fragmentation in gastroparesis leads to higher readmission length of stay and overall costs (Table 4). This could be related to inefficient and redundant workup, such as radiologic and endoscopic procedures. In the ambulatory setting, one study found that patients with fragmented care received twice as many radiologic and diagnostic tests compared to patients with least fragmented care[24]. Currently, there is national emphasis on inter-operability of electronic health record (EHR) systems. Medicare and Medicaid EHR programs created incentives for healthcare systems to utilize EHRs that are capable of providing patients copies of their medical records, and of exchanging information between different EHR systems regardless of the vendor[25]. Once these EHRs are in place, it is possible that the availability of medical records to all providers across hospitals could partially mitigate the higher costs of fragmented care. We did not find a difference in mortality and in 60-d readmission rate following the first readmission between patients who were readmitted to an index and non-index hospital. This suggests that addressing care fragmentation in gastroparesis could reduce healthcare costs but does not change the natural history or morbidity of the disease. Other studies conducted on patients with heart failure and other critical illnesses found higher mortality in patients admitted to a non-index hospital[12,26,27].

Our study has several strengths. It is the largest study to estimate the rate of hospital readmissions in patients admitted with gastroparesis, and the only one to study care fragmentation in this disease. We

used statewide data to track discharges within states across different hospitals, and then calculate the rate of underestimation of care if only institutional databases are used. In addition, this is the only study that evaluates the predictors of readmission and care fragmentation in a large nationally representative sample.

There are several limitations to this analysis. The NRD, similar to most other hospital administrative databases, does not contain important clinical parameters such as medications, laboratory values, and imaging studies. Therefore, we cannot categorize the severity and etiology of gastroparesis using this database, nor analyze clinical predictors of outcomes in gastroparesis. We tried to adjust for predictors of care fragmentation; however, other factors play a role in non-index hospitalizations. These include patients' preference, place of residence and proximity to the index hospital. These should be taken into account in planning post discharge follow-up.

In conclusion, patients with gastroparesis are prone to frequent hospital admissions. Our study highlights the high readmission and care fragmentation rates in gastroparesis, and identifies several predictors of these outcomes. Post discharge care coordination that focuses on high-risk patients could reduce hospital readmission and fragmentation of care, leading to improved quality of life and lower overall costs of care.

ARTICLE HIGHLIGHTS

Research background

Gastroparesis is a chronic disorder that can lead to debilitating symptoms resulting in recurrent hospitalizations. These hospital admissions can be costly, especially if the patient is admitted repeatedly to different hospitals. Hospital readmissions can be underestimated if non-index readmissions (*i.e.*, readmissions to a different hospital) are not captured during follow up.

Research motivation

Knowledge of the predictors of hospital readmissions can help design interventions that focus on high risk factors. Estimating the rate of care fragmentation provides further insight into the burden of gastroparesis on patients and the healthcare system. It also highlights the need to refine the methods to calculate hospital readmission.

Research motivation

The study aims to evaluate the rate of hospital readmissions in gastroparesis, and to estimate the proportion of readmissions to index and non-index hospitals (care fragmentation). We also sought to study factors related to readmission and care fragmentation, and their effect on future outcomes such as length of stay, costs, mortality, and readmissions.

Research methods

We used the national readmission database to identify all adult admissions with primary diagnosis of gastroparesis. We calculated the rate of 30 and 90-d statewide hospital readmissions and care fragmentation. We analyzed factors related to hospital readmission and care fragmentation using multivariable models.

Research results

We found a high rate of hospital readmission in gastroparesis (26.8% at 30 d and 45.6% at 90 d). Around one fourth of readmissions occur at a different hospital, and 20% occur exclusively at a different hospital. This means that 20% of all 30-d readmissions will not get captured if local hospital databases are used to track patients. Readmission to a different hospital within 30-d was associated with higher hospitalization costs and length of stay. We identified several sociodemographic and clinical factors that are associated with hospital readmission and care fragmentation. Gastric surgery is associated with decreased risk of readmission, while enteral tube insertions (gastrostomy or jejunostomy) did not affect readmissions.

Research conclusions

This is the first population based study to highlight the high rate of hospital readmission and care fragmentation in gastroparesis. It is also the first to report several sociodemographic and clinical factors related to these outcomes, which can be used to identify high-risk patients.

Research perspectives

In addition to reducing hospital readmissions, hospitals should also attempt to decrease care fragmentation because it is associated with increased costs of care. Hospital readmissions are a major cause of morbidity in gastroparesis. Trials involving different interventions for gastroparesis should also evaluate the effect of these interventions on reducing hospital readmissions.

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ORIGINAL ARTICLE

Randomized Controlled Trial

Randomised controlled trial comparing modified Sano's and narrow band imaging international colorectal endoscopic classifications for colorectal lesions

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Author contributions: Zorrón Cheng Tao Pu L organized and analysed the raw soft copy data, created tables and figures and drafted the final version of the manuscript; Cheong KL, Koay DSC and Yeap SP collected the raw hard copy data, and provided interim analysis and drafts; Ovenden A contributed with the conversion of data from hard copy to soft copy and with the logistics for data collection and storage; Raju M assisted with editing and proofreading of the final manuscript; Ruszkiewicz A contributed with specialized Pathology input from the design to the final manuscript; Chiu PW, Lau JY and Singh R designed and coordinated the study. Singh R performed all colonoscopies in this study; All authors reviewed and approved the final manuscript.

Institutional review board statement: This study was approved by the Australian Human Research Ethics Committee (TQEH/LMH/MH).

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Abstract

AIM

To assess the utility of modified Sano's (MS) *vs* the

narrow band imaging international colorectal endoscopic (NICE) classification in differentiating colorectal polyps.

METHODS

Patients undergoing colonoscopy between 2013 and 2015 were enrolled in this trial. Based on the MS or the NICE classifications, patients were randomised for real-time endoscopic diagnosis. This was followed by biopsies, endoscopic or surgical resection. The endoscopic diagnosis was then compared to the final (blinded) histopathology. The primary endpoint was the sensitivity (Sn), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) of differentiating neoplastic and non-neoplastic polyps (MS Ⅱ/Ⅱo / Ⅲa / Ⅲb *vs* I or NICE 1 *vs* 2/3). The secondary endpoints were "endoscopic resectability" (MS Ⅱ/Ⅱo/Ⅲa *vs* Ⅰ/Ⅲb or NICE 2 *vs* 1/3), NPV for diminutive distal adenomas and prediction of post-polypectomy surveillance intervals.

RESULTS

A total of 348 patients were evaluated. The Sn, Sp, PPV and NPV in differentiating neoplastic polyps from non-neoplastic polyps were, 98.9%, 85.7%, 98.2% and 90.9% for MS; and 99.1%, 57.7%, 95.4% and 88.2% for NICE, respectively. The area under the receiver operating characteristic curve (AUC) for MS was 0.92 (95%CI: 0.86-0.98); and AUC for NICE was 0.78 (95%CI: 0.69, 0.88). The Sn, Sp, PPV and NPV in predicting "endoscopic resectability" were 98.9%, 86.1%, 97.8% and 92.5% for MS; and 98.6%, 66.7%, 94.7% and 88.9% for NICE, respectively. The AUC for MS was 0.92 (95%CI: 0.87-0.98); and the AUC for NICE was 0.83 (95%CI: 0.75-0.90). The AUC values were statistically different for both comparisons (P = 0.0165 and P = 0.0420, respectively). The accuracy for diagnosis of sessile serrated adenoma/polyp (SSA/P) with high confidence utilizing MS classification was 93.2%. The differentiation of SSA/P from other lesions achieved Sp, Sn, PPV and NPV of 87.2%, 91.5%, 89.6% and 98.6%, respectively. The NPV for predicting adenomas in diminutive rectosigmoid polyps (n = 150) was 96.6% and 95% with MS and NICE respectively. The calculated accuracy of post-polypectomy surveillance for MS group was 98.2% (167 out of 170) and for NICE group was 92.1% (139 out of 151).

CONCLUSION

The MS classification outperformed the NICE classification in differentiating neoplastic polyps and predicting endoscopic resectability. Both classifications met ASGE PIVI thresholds.

Key words: Colorectal polyps; Colorectal adenomas; Colorectal neoplasm; Colorectal lesions; Randomised controlled trial; Colonoscopy; Magnifying colonoscopy; Endoscopic imaging

Core tip: Endoscopic differentiation of colorectal polyps can be daunting. Especially with serrated lesions. The Modified Sano's (MS) classification, the first classification that included sessile serrated adenoma/polyps was developed in 2013. In this randomised controlled trial we compare the accuracies of the well-established narrow band imaging international colorectal endoscopic classification and the MS classification. Although both classifications have met the ASGE PIVI statement thresholds for predicting histology in diminutive rectosigmoid polyps and post-polypectomy surveillance, MS was statistically more accurate.

Zorrón Cheng Tao Pu L, Cheong KL, Koay DSC, Yeap SP, Ovenden A, Raju M, Ruszkiewicz A, Chiu PW, Lau JY, Singh R. Randomised controlled trial comparing modified Sano's and narrow band imaging international colorectal endoscopic classifications for colorectal lesions. *World J Gastrointest Endosc* 2018; 10(9): 210-218 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i9/210.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i9.210

INTRODUCTION

The majority of colorectal polyps are small and benign[1]. Current practice mandates biopsies or removal and pathological interpretation to confirm the diagnosis. With technological advancement in the endoscopy imaging field, the adoption of strategies such as "diagnose, resect and discard" for proximal polyps and "do not resect" for rectosigmoid hyperplastic polyps (HPs) has become possible[2,3]. Apart from being cost-effective and perhaps time-efficient, these strategies could potentially reduce the risks of complications associated with polypectomy[4]. For larger lesions, advanced imaging modalities may have a role especially if required to differentiate early cancers confined to the intramucosal layer or infiltrating more than 1000 μm into the submucosa[5-8]. *In vivo* prediction of colorectal lesions is hence of utmost importance.

Numerous technologies including iScan, flexible spectral imaging colour enhancement (FICE) and narrow band imaging (NBI) have been available to assist in interrogating the surface pattern and microvascular architecture of colorectal polyps. A systematic review comparing standard white light endoscopy, chromoendoscopy and NBI with or without magnification concluded that magnified chromoendoscopy and NBI were the two most accurate modalities in predicting polyp histology[9]. Several studies have demonstrated that NBI is equivalent to chromoendoscopy in distinguishing neoplastic and non-neoplastic colonic polyps. A recent meta-analysis involving 28 studies reported high accuracy with NBI in diagnosing colorectal polyps based on an area under the hierarchical summary receiver-operating characteristic (HSROC) curve of 0.92[10]. Additionally, when high confidence predictions are made, the sensitivity (Sn) and negative predictive value (NPV) exceeded 90%. Sessile serrated adenoma/polyp (SSA/P) was not considered

Table 1 Narrow band imaging international colorectal endoscopic classification of colorectal polyps was based on 3 features including colour, vessel, architecture and surface pattern

	NICE Ⅰ	NICE Ⅱ	NICE Ⅲ
Colour	Same or lighter than background	Browner than background	Dark brown relative to background +/- patchy whiter areas
Vessels	None or isolated lacy vessels	Brown vessels surrounding white structures	Disrupted or missing vessels
Surface pattern	Dark or white spots of uniform size, or homogeneous absence of pattern	Oval, tubular or branched white structure surrounded by brown vessels	Amorphous or absent surface pattern
Likely pathology	Hyperplastic	Adenoma	Deep submucosal invasive cancer

NICE: Narrow band imaging international colorectal endoscopic.

separately in these studies[10-13].

Differentiation of polyps can also be made using NBI with magnified endoscopy (NBI-ME) utilizing various classifications including the Sano's classification, modified Sano's (MS) classification, NBI international colorectal endoscopic (NICE), Hiroshima, Showa, Workgroup serrAted Polyps and Polyposis (WASP), JNET and Jikei classifications and 1 published classification for FICE with magnified endoscopy (FICE-ME)[5,11,14-17]. Many of these classifications have been validated in various studies. There are however no comparative data to date on the diagnostic accuracy of these different classifications. Recently the new WASP classification has emerged which included the differentiation of SSA/Ps from HP, but with inconsistent results[18]. The Sano's classification was modified to include a classification for SSA/P in 2013[19]. As the original Sano's classification was solely based on capillary pattern, the surface pattern was incorporated in the MS classification, in order to improve its diagnostic capability. The MS classification is defined in accordance with the colour, capillary network surrounding the pit pattern and surface pattern evaluated under magnification. By contrast, the NICE classification of colorectal polyps is based on 3 features including colour, vessel architecture and surface pattern evaluated not necessarily under magnification (Figure 1 and Table 1, respectively). Both the NICE and MS have been found to be independently valid tools for predicting polyp histology according to the American Society for Gastrointestinal Endoscopy (ASGE) Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) statement[5,6,19,20].

The ASGE's PIVI statement[20] regarding colonic polyps has advised thresholds for endoscopic imaging, namely: (1) an endoscopic technology (when used with high confidence) should provide > 90% agreement in determining post-polypectomy surveillance intervals; and (2) the technology (when used with high confidence) should provide > 90% NPV for adenomatous histology for rectosigmoid polyps.

This was introduced to further guide endoscopists using new technologies into achieving measurable outcomes and aiding the incorporation of novel technologies into clinical practice.

There are no randomised trials comparing MS and NICE classifications. The aim of this study is to compare the accuracy of NBI with dual focus (DF) magnification in differentiating colorectal polyps using the NICE and the MS classifications. The NPV for neoplastic prediction (cancer, adenomas and SSA/Ps) within diminutive rectosigmoid polyps and the post-polypectomy surveillance intervals for each classification (based on the ASGE PIVI statement thresholds) was also evaluated.

MATERIALS AND METHODS

Study design

This study was approved by the Australian Human Research Ethics Committee (TQEH/LMH/MH) and is registered on clinicaltrials.gov (No. NCT02963207). Written informed consent was obtained from each patient prior to colonoscopy. Data were collected at the site of investigation by a research nurse and analysed by a study statistician. Only the endoscopist knew which arm of the trial the patient was on during the endoscopic diagnosis of the lesion. Neither the patient nor the pathologist was aware of the classification used on the lesion.

Randomisation

A concealed container containing 2 cards which randomised the participants to either MS or NICE classifications arm was used. Each week, a research nurse randomly selected a card from the concealed container. This generated allocation was then conveyed to the endoscopist.

Study population

All patients undergoing colonoscopy for any indication at the Lyell McEwin Hospital endoscopy unit were evaluated for eligibility by the researchers. Patients were recruited from June 2013 onwards. Inclusion criteria were age of 18 years or older with endoscopic findings of colonic polyps (of any size). Key exclusion criteria included known history of inflammatory bowel disease, familial polyposis syndrome, coagulopathy, thrombocytopenia, incomplete procedure due to poor bowel preparation or acute angles, current pregnancy and no polyps detected during the procedure.

All colonoscopies were performed by a senior endoscopist with a high level of expertise using the 190 series with DF capability (Exera Ⅲ NBI system; Olympus Co. Ltd, Japan). This processor allows the NBI image to be enhanced by 150%. The DF function enables

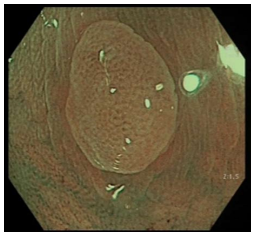
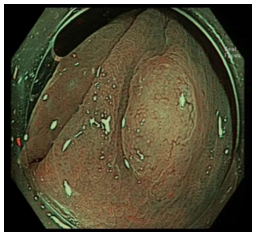
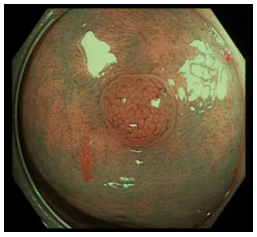
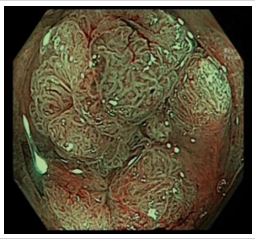
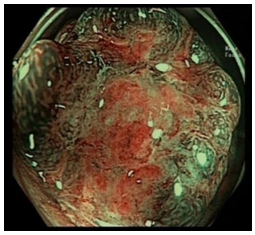
MS classification (predicted histology)	Description	Example
Category Ⅰ (HP)	Pale colour ± round pits with central brown star-like dots or bland appearance ± minute capillaries that may meander across polyp	
Category Ⅱo (SSA/P)	Pale or light dark colour ± open pits ± 3 out of 5: cloud-like surface, inconspicuous margins, mucous cap, irregular shape and varicose microvascular vessels[1]	
Category Ⅱ (tubular adenoma with low grade dysplasia)	Light dark or dark colour ± white linear or oval pits ± linear or oval regular capillary network surrounding pits	
Category Ⅲa (high grade dysplasia/ villous or tubulovillous adenoma/superficial cancer)	Light dark or dark colour ± white villous/cerebriform pits ± tortuous/branched mildly regular capillary network surrounding pits[2]	
Category Ⅲb (invasive cancer)	Dark surroundings with pale central area ± loss of pits and vascular pattern	

Figure 1 Modified Sano's classification is defined as below. [1]If no open pits and 2 serrated features = classified as low confidence for SSA/P; if 1 serrated feature = low confidence for HP; if no features = high confidence for HP. [2]Can have slight loss of pit pattern and vascularity when leaning towards superficial cancer.MS: Modified Sano's; HP: hyperplastic polyp; SSA/P: Sessile serrated adenoma/polyp.

magnification of up to 70×. Both are push button techniques and image enhancement with magnification occurs within 1-2 s.

Endoscopic imaging and classification of polyps

The patients whom had colonic polyps had their polyps assessed in real-time with NBI-DF. DF was used in both groups to standardize the evaluation. The endoscopist studied the lesion carefully at least for one minute. The size of the polyp was estimated by the endoscopist based on the size of the cap (outer diameter of 15 mm) and/or size of the snare/forceps. The polyp was initially examined in white light, then NBI, followed by magnification. Image acquisition was further enhanced with a distal cap attachment to the scope (short transparent cap from Olympus® - D-201, approximately 4 mm from distal end). Efforts were made to obtain a crisp clear still image with water pump and simeticone when needed (no dyes used). Histology in real-time of individual polyps was then predicted using either the NICE or the MS classification, with a confidence level (low/high).

The endoscopist scored each polyp found and the final endoscopic diagnosis was recorded by the research nurse who was present in the endoscopy suite. A clinical judgement was deemed as high in confidence when the endoscopist found a polyp with clear features of one subtype, as described in the classifications shown in Figure 1 and Table 1. If there was any uncertainty or doubt, the prediction was recorded as low confidence.

Table 2 Demographics of study participants

Classification	Modified Sano's	NICE	*P* value
age (mean ± SD)	62.18 ± 14.06	64.41 ± 11.36	NS
M:F (% male)	191:118 (62%)	178:76 (70%)	NS
Indication *n* (%)			
Screening	156 (50)	115 (45)	NS
Surveillance	86 (28)	88 (35)	
Symptoms	63 (20)	49 (19)	
Others	4 (1)	2 (1)	
Total	309	254	

NICE: Narrow band imaging international colorectal endoscopic; NS: Non-significant.

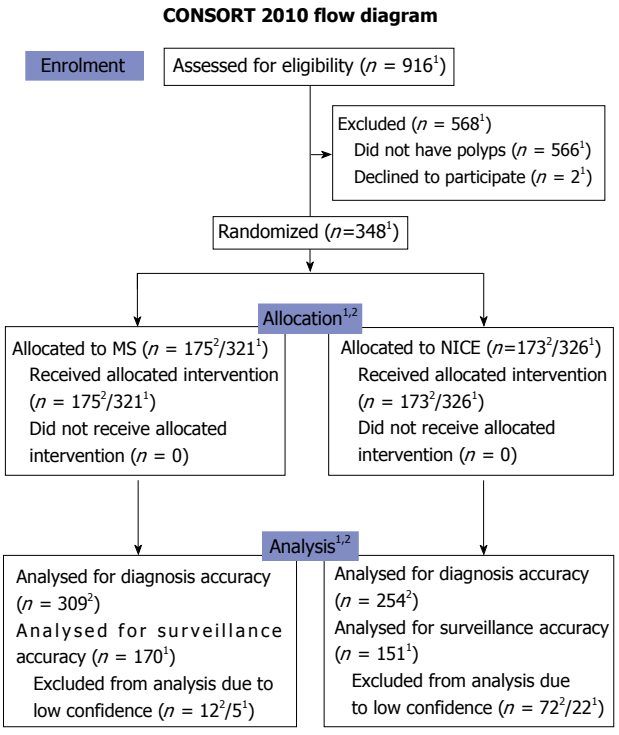


Figure 2 CONSORT 2010 flow diagram. [1]Patients; [2]Polyps. MS: Modified Sano's; NICE: Narrow band imaging international colorectal endoscopic; SSA/P: Sessile serrated adenoma/polyp.

All polyps were photographed and stored for future reference. No video recording was done. This was followed by biopsies and surgical resection in cases of predicted invasive cancer, or endoscopic resection to the remaining lesions. The histopathology was evaluated initially by a non-gastrointestinal (non-GI) specialist pathologist due to personnel limitations. However, if the diagnosis was uncertain the slides were forwarded to a specialist GI pathologist. The pathologists were blinded to the classification used and the prediction of the polyp by the endoscopist. The endoscopy diagnosies was then compared to the final histopathological diagnosis.

Study endpoints

The primary endpoint of the study was to prospectively evaluate the Sn, specificity (Sp), positive predictive value (PPV) and NPV of neoplastic (cancer, adenoma or SSA/P) *vs* non-neoplastic (HP, inflammatory) polyps based on either classification (MS Ⅱ, Ⅱo, Ⅲa and Ⅲb *vs* MS Ⅰ or NICE 2, 3 *vs* NICE 1).

In addition, we assessed the concept of "suitability of endoscopic resection" of these polyps (MS Ⅱ, Ⅱo, Ⅲa *vs* MS Ⅰ, Ⅲb or NICE 2 *vs* NICE 1, 3) and the diagnostic accuracy of SSA/Ps by the MS classification. To assess the ability of the NICE and MS classifications to match the PIVI-1 thresholds, high confidence NBI predictions of polyp histology were given an endoscopy-based surveillance interval. This was then compared with the recommended interval based on histologic assessment. For this calculation, polyps histologically classified as SSA/Ps but classified as NICE 1 or MS Ⅰ were excluded. This was thought to mitigate bias as NICE has no separate SSA/P classification. As for the PIVI-2 thresholds, we calculated the negative predictive value (NPV) of high confidence NBI predictions for adenomatous histology of diminutive polyps using histology as a reference.

Statistical analysis

The sample size was calculated based on number of polyps. The primary aim was to test the performance of NBI diagnosis for polyp differentiation. Thus, it was estimated that a total sample size of 560 polyps would be required to have an 80% power with an alpha error of 0.05 to appreciate an increment of 7% in the prediction of histology with the MS classification.

Statistical analysis was performed by using statistical software, Stata 13.0 (StatCorp, TX, United States). Continuous variables are reported as either a mean ± SD or median and range. Means were reported unless the data were nonparametric. The Student's *t* test was used to analyse continuous variables, and a Pearson χ^2 analysis was used for categorical variables. Statistical significance was set at a 2-sided *P* value of 0.05 or less. The analysis applied to the classifications was in regards to the polyps, while the analysis for post-polypectomy surveillance was based on patients.

RESULTS

A total of 348 patients were included from June 2013 until June 2015 (Figure 2). The trial was terminated as we have reached the stipulated sample size. Both groups had similar demographics (Table 2). The total number of polyps predicted with high confidence in the MS classification was 309 out of 321 (96.3%). This was significantly higher in proportion as compared to that in the NICE arm (254 out of 326 polyps or 78% - as shown in Table 3). Characteristics of the polyps were not significantly different between both arms except for the mean size of polyps which was larger for the NICE arm (Table 3).

Primary endpoint

The Sn, Sp, PPV and NPV in differentiating neoplastic from non-neoplastic polyps were 98.9%, 85.7%, 98.2%

Table 3 Characteristics of colon polyps

Classification	Modified Sano's	NICE	*P* value
Confidence level *n* (%)			
High	309 (96.3)	254 (78)	<0.0001
Low	12 (3.7)	72 (22)	
Total	321	326	
Distribution based on size			
⩽ 5 mm	151	127	NS
6-9 mm	63	42	
⩾ 10 mm	95	85	
Size (mean ± SD, mm)	10.17 ± 11.30	14.48 ± 19.47	0.0036
Polyp distribution *n* (%)			
Right colon	95 (31)	101 (40)	NS
Transverse colon	60 (19)	52 (20)	
Descending colon	34 (11)	27 (11)	
Rectosigmoid colon	120 (39)	74 (29)	
Total	309	254	
Paris *n* (%)			
1p	28 (9)	18 (7)	NS
1s	190 (61)	156 (61)	
2a	81 (26)	71 (28)	
2b	4 (1)	1 (1)	
2c	5 (2)	6 (2)	
3	1 (1)	2 (1)	
Others	12	15	
Total	309	254	

NICE: Narrow band imaging international colorectal endoscopic; NS: Non-significant.

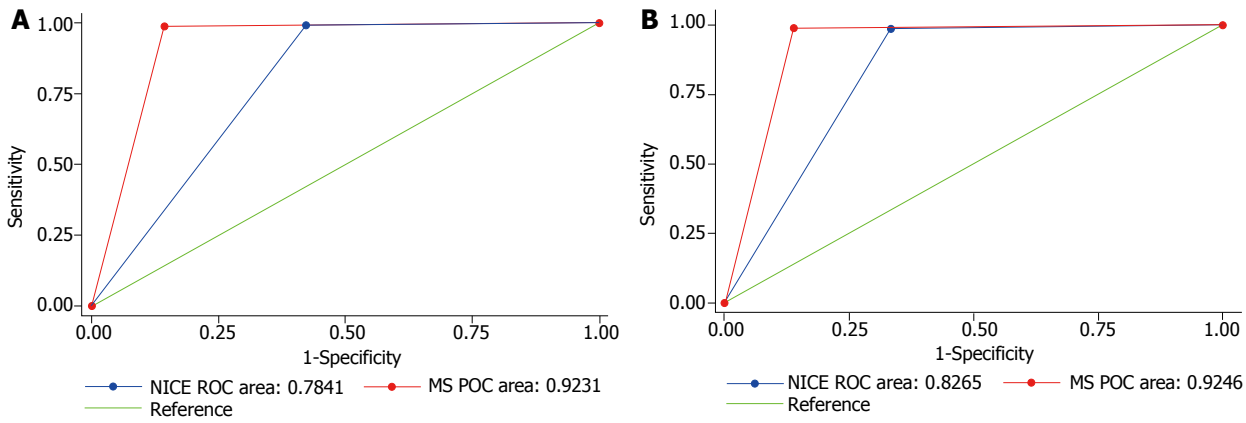


Figure 3 Receiver operating characteristic curves of modified Sano's and narrow band imaging international colorectal endoscopic classification. A: For neoplastic differentiation; B: For endoscopic resectability. MS: Modified Sano's; NICE: Narrow band imaging international colorectal endoscopic; SSA/P: Sessile serrated adenoma/polyp.

and 90.9% for MS and 99.1%, 57.7%, 95.4% and 88.2% for NICE respectively. The MS arm had an area under the receiver operating characteristic curve (AUC) of 0.92 (95%CI: 0.86-0.98), whilst NICE had an AUC of 0.78 (95%CI: 0.69-0.88). There was a statistically significant difference between the MS and NICE's AUC values (P = 0.0165) (Figure 3A).

Secondary endpoints

The Sn, Sp, PPV and NPV in predicting 'endoscopic resectability' were 98.9%, 86.1%, 97.8% and 92.5% for MS and 98.6%, 66.7%, 94.7% and 88.9% for NICE respectively. The MS group had an AUC of 0.92 (95%CI: 0.87-0.98), whereas NICE had an AUC of 0.83 (95%CI: 0.75, 0.90). There was also a statistically significant difference between the AUC values (P = 0.0420) (Figure 3B).

The accuracy for diagnosis of SSA/P with high confidence using Ⅱo on MS classification was 93.2%, and differentiation of SSA/P from other lesions achieved 87.2% of Sp, 91.5% of Sn, 89.6% of PPV and 98.6% of NPV (Table 4).

Classification of polyps according to size is shown in Table 3. Of the high confidence polyps in the MS arm, 150 (48.5%) were diminutive (5 mm or less), 60 (19.5%) were small (6-9 mm) and 99 (32%) were large (⩾ 10 mm). In the NICE arm, there were 254 polyps detected with high confidence which included 127 (50%) diminutive, 42 (16.5%) small and 85 (33.5%) large polyps.

The NPV for diminutive rectosigmoid polyps were 96.6% and 95% in MS and NICE arms respectively. The

Table 4 Accuracy of modified sano's Ⅱo class for sessile serrated adenoma/polyp

	SSA/P	Other histology
MS Ⅱo	43 (13)	5 (1.54)
Other MS classification	4 (1.23)[1]	273 (84)

[1]SSA/P histology was correlated with either Ⅰ or Ⅱo on MS. SSA/P: Sessile serrated adenoma/polyp; MS: Modified Sano's.

Table 5 Results of *in vivo* prediction for post-polypectomy surveillance interval

	Modified Sano's	NICE
Total patients	175	173
Accurate	167	139
Overcalled[1]	2	8
Undercalled[2]	1	4
Excluded	5	22

[1]Surveillance colonoscopy interval prediction with classification was premature compared to the determined by final histology; [2]Surveillance colonoscopy interval prediction with classification was delayed compared to the determined by final histology. NICE: Narrow band imaging international colorectal endoscopic.

calculated accuracy of post-polypectomy surveillance for MS group was 98.2% (167 out of 170) and for NICE group was 92.1% (139 out of 151).

In the MS arm, there were 20 out 309 (6.4%) high confidence polyps' inaccuracies. Misdiagnoses which were made were as follows: MS Ⅰ (3 SSA's and 1 normal mucosa), MS Ⅱ (3 normal mucosa, 1 inflammatory polyp, 1 traditional serrated adenoma, 4 tubular adenoma with high grade dysplasia, 1 tubulovillous adenoma with low grade dysplasia and 1 villous adenoma with high grade dysplasia), MS Ⅱo (2 tubular adenoma with low grade dysplasia and 1 HP) and MS Ⅲa (1 tubular adenoma with low grade dysplasia and 1 villous adenoma with invasive carcinoma).

In the NICE arm, there were 18 out of 254 (7.1%) inaccuracies in high confidence polyps - NICE Ⅰ (1 normal mucosa, 2 tubular adenomas with low grade dysplasia), NICE Ⅱ (5 normal mucosa, 5 HPs, 1 inflammatory polyp, 1 focal colitis cystica profunda, 1 cancer) and NICE Ⅲ (1 tubulovillous adenoma with high grade dysplasia).

These resulted in 10 overcalled and 5 undercalled cases on the *in vivo* prediction for post-polypectomy surveillance interval (Table 5).

DISCUSSION

NBI is one of the most easily available and commonly used image-enhanced endoscopic modality. There are many NBI classifications for colorectal lesions, but only two thus far have included SSA/P separately (WASP and MS). The WASP classification was derived from NICE aiming to differentiate HP from SSA/P[18]. The classification does not address the differentiation of adenoma and invasive cancer. A simple, comprehensive and reliable classification is pivotal in clinical practice.

Hewett *et al*[4] has initially shown NICE subtypes 1 and 2 using non-magnified NBI. The accuracy, Sn and NPV for small colorectal polyps were 89%, 98% and 95%, respectively. The study did not include SSA/Ps. In this study, the MS classification has been proven to be more effective in differentiating neoplastic colorectal polyps (*i.e.*, cancer or adenoma or SSA/P) from non-neoplastic polyps (*i.e.*, inflammatory or HP) when compared to the NICE classification. This is probably attributed to the former's design which has a sub-division for SSA/Ps. This subdivision may have given the MS classification an upper-hand over the NICE classification as some of the HP misdiagnosed by the NICE were in fact SSA/Ps.

In this study, both NBI classifications were able to meet the PIVI benchmarks as the post-polypectomy surveillance prediction accuracy and NPV for diminutive rectosigmoid polyps exceeded 90% in the two study arms. These findings are compatible with the results of the previous meta-analysis of 20 studies on NBI with and without magnification. The pooled NPV found was 91% for adenomatous histology[21].

SSA/Ps have been recognized as precancerous lesions and they account for up to one third of all sporadic colorectal cancers[22]. They may have been misdiagnosed due to the challenges both endoscopists and pathologists faced in distinguishing them from HPs for the past years.

Several investigators sought to discriminate SSA/Ps from HPs *via* NBI (without magnification) based on several specific endoscopic features with varying results[23-26]. A recently published prospective study by Yamashina *et al*[27] reported very high sensitivity (98%) but only modest Sp 59.5% for diagnostic criteria of SSA/Ps through identification of "expanded crypt openings" and "thick branched vessels" on magnified NBI. The WASP classification was not used for comparison in this study as it was only recently published and not available when our study began[18]. Similarly, although the JNET is currently being considered a gold standard in regard to polyp classification (excluding SSA/Ps), this had not been published by the time the study started.

The clinical use of real-time histology is already used in standard practice to evaluate "suitability for resection". This means that if a lesion is endoscopically considered to be an invasive cancer or if it is predicted to be benign (*e.g.,* distal diminutive HPs), endoscopic resection will not be attempted. Moreover, further benefits of endoscopic diagnosis may add to this "suitability for resection". Two cost-analysis studies have proven the "diagnose, resect and discard" technique is cost-effective for diminutive polyps[28,29]. There are nevertheless several issues for consideration. For this technique to be adopted globally there should be a standard NBI classification that is easy for inexperienced endoscopists to learn and apply. There is potential risk for litigation if the endoscopists' histology prediction is inaccurate and with a possibility of patients developing advanced pathology during the inter-surveillance period. In addition, the risk of bleeding

and perforation associated with polypectomy may be increased if the endoscopist 'overcalled' any lesion. The MS classification could step in to allow these techniques with the more accurate up-to-date endoscopic diagnosis classification.

This study has limitations. All procedures were performed by a single expert. This may not be generalizable. Although other studies within our centre have validated the usefulness of the MS classification compared to NICE and JNET[30], studies utilizing the MS classification must be performed in other endoscopy centres by experts and non-experts to evaluate its reproducibility. The group randomization process used (per week instead of per patient) was not conventional and could have contributed to uneven distribution among both arms. However, this was not translated in demographic differences (Table 2). The reason for doing so was to mitigate possible confusion on which classification should be used for each patient and in order to allow a consistent mental focus on one classification at a time.

In conclusion, this study demonstrated that the MS classification was superior in differentiating non-neoplastic from neoplastic polyps and more accurately guided the endoscopic resection when compared to the NICE classification. MS is also accurate for predicting SSA/P histology, a subtype neglected by NICE. Nevertheless, both classifications met PIVI thresholds in managing diminutive polyps and determining post-polypectomy surveillance period.

ARTICLE HIGHLIGHTS

Research background

Prediction of polyp histology may prevent unnecessary polypectomies and reduce cost.

Research motivation

The endoscopic differentiation of benign and malignant polyps is sometimes difficult, especially when looking into serrated lesions. Very few endoscopic classifications include the differentiation of sessile serrated lesions [*e.g.,* modified Sano's (MS)]. These have not being widely used partially due to lack of reliable comparison with the currently used classifications [*e.g.,* narrow band imaging international colorectal endoscopic (NICE)]. The comparison of established classifications with a classification including serrated polyps' differentiation in a randomised trial could help to support the use of the newer and more comprehensive classifications.

Research objectives

The main objective of this randomised controlled trial is to compare the established adenoma *vs* non-adenoma NICE classification and the newer neoplastic *vs* non-neoplastic MS classification.

Research methods

This was a single centre randomised controlled trial (pathologist blinded) comparing the NICE classification with the MS classification for the endoscopic prediction of histology of colorectal lesions during colonoscopy.

Research results

MS classification had significantly higher proportion of high confidence diagnoses compared to NICE. Overall, the MS area under the receiver operating characteristic curve (AUC) was 0.92 and NICE AUC was 0.78 (P = 0.0165). For predicting "endoscopic resectability", MS AUC was also 0.92 and NICE AUC was 0.83 (P = 0.0420). The accuracy for diagnosis of SSA/P by MS classification was 93.2%. The NPV for diminutive rectosigmoid polyps were 96.6% and 95% in MS and NICE arms respectively. The calculated accuracy of post-polypectomy surveillance was 98.2% for MS and 92.1% for NICE. Utilizing MS, 6.4% of high confidence polyps were misdiagnosed. Utilizing NICE, 7.1% were misdiagnosed.

Research conclusions

The MS classification has shown to be accurate in diagnosing colorectal lesions including sessile serrated adenoma/polyp. Both classifications surpassed the ASGE PIVI thresholds. MS classification may currently be the most accurate and comprehensive endoscopic classification for differentiation of colorectal polyps.

Research perspectives

The use of classifications that incorporate the differentiation of serrated polyps such as the MS classification may be necessary. These should become the standard for adequate characterization of colorectal lesions. Nonetheless validation in different centres is required.

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CASE REPORT

Successful stent-in-stent dilatation of the common bile duct through a duodenal prosthesis, a novel technique for malignant obstruction: A case report and review of literature

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Abstract

For patients suffering from both biliary and duodenal obstruction, endoscopic retrograde cholangiopancreatography (ERCP) with stent placement is the treatment of choice. ERCP through an already existing duodenal prosthesis is an uncommon procedure and furthermore no studies have reported installing a covered metal stent onto an already existing bare metal stent in the common bile duct (CBD). We describe a rare case of a stent-in-stent dilatation of the CBD through an already existing self-expanding metal stent in the second part of duodenum for the patient presenting with jaundice in setting of biliary and duodenal obstruction from pancreatic adenocarcinoma. The biliary obstruction was relieved with a decrease in bilirubin levels post-stenting.

Key words: Bare metal stent; Endoscopic retrograde cholangiopancreatography; Common bile duct; Self-expanding metal stent; Jaundice; Biliary obstruction; Gastric outlet obstruction

Core tip: Patients with gastric outlet obstruction

from duodenal, ampullary or pancreatic malignancy frequently develop biliary obstruction. These patients usually undergo prophylactic biliary stent placement as the likelihood of developing biliary stricture or obstruction is very high. Here, we present a case of a patient who already had a duodenal and biliary stent which required placement of a covered metal stent into the existing common bile duct prosthesis to relieve his biliary obstructive symptoms.

Virk GS, Parsa NA, Tejada J, Mansoor MS, Hida S. Successful stent-in-stent dilatation of the common bile duct through a duodenal prosthesis, a novel technique for malignant obstruction: A case report and review of literature. *World J Gastrointest Endosc* 2018; 10(9): 219-224 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i9/219.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i9.219

INTRODUCTION

Malignant gastric outlet obstructions (GOOs) often present with associated malignant biliary stenosis either on initial presentation or later in the clinical course[1]. Most patients get biliary stenting before having duodenal stents placed as it is difficult to access the papilla through the self-expanding metal stents (SEMS) in the duodenum[2-4] even though recent studies have shown that biliary stenting is feasible with high success rate through the duodenal stent[3,5]. We describe even a rarer case in which the patient already had a bare metal stent (BMS) in the common bile duct (CBD) and SEMS in the duodenum who needed further biliary stenting.

CASE REPORT

A 78-year-old man presented with complaints of abdominal pain, nausea and emesis. CT imaging showed findings consistent with GOO. A year prior in July 2016 he had presented to our facility with obstructive jaundice secondary to a pancreatic head mass (3 mm × 2 mm) with sonographic evidence suggesting both superior mesenteric artery and portal vein invasion. He underwent endoscopic retrograde cholangiopancreatography (ERCP) and successful dilatation of the CBD with the placement of a 10 mm × 6 cm BMS approximately 5 cm into the CBD (Figure 1). Biopsy of the mass confirmed adenocarcinoma.

During hospitalization in October 2017, esophagogastroduodenoscopy (EGD) showed retained fluid in the gastric body. There was a malignant appearing, intrinsic moderate stenosis in the second part of the duodenum suggesting type II GOO. The biopsy showed active duodenitis with gastric metaplasia and inflammatory exudates consistent with an ulcer. This area was traversed and stented with a 22 mm × 12 cm WallFlex stent using fluoroscopic guidance (Figure 2). Three days later the patient underwent repeat EGD for acute, new onset jaundice and failure to respond to medical treatment. Endoscopic evaluation showed a patent WallFlex SEMS without any migration. Endoscopic retrograde cholangiopancreatography (ERCP) with fluoroscopy was simultaneously performed and confirmed the previously placed duodenal and biliary stents. The scope was passed through the duodenal stent with precision fluoroscopic guidance and the bile duct containing the previously placed CBD stent (10 mm × 6 cm BMS) was deeply cannulated with the short-nosed traction auto-tome and guidewire. Contrast was injected and ductal flow of contrast was adequate. Contrast extended to the main bile duct; however, the lower third of the main bile duct, the middle third of the main bile duct and CBD was completely obstructed by what appeared to be a mass with tumor ingrowth (the same mass that had eroded and obstructed the duodenum previously). A 0.035-inch × 260 cm straight guidewire (Hydra Jag wire) was passed into the biliary tree. Dilatation of the duodenal stent side was accomplished with a Hurricane 10 mm × 4 cm balloon dilator and was successful. One 10 mm × 4 cm covered metal stent (CMS) was placed 3 cm into the previous 10 mm × 6 cm BMS within the CBD. Bile and clear fluid flowed through the stent and the stent was in proper position (Figure 3). The patient's total bilirubin dropped from 5.7 to 3.5 the next day. Four days later, his total bilirubin was 1.5, his acute symptoms had resolved and he was discharged from the hospital.

Relevant patient information: BMI 26.6, non-smoker. History: Coronary heart disease and percutaneous coronary intervention, cerebrovascular accident, atrial fibrillation, pulmonary embolism, nonresectable pancreatic adenocarcinoma, hypothyroidism, depression and hypertension.

DISCUSSION

We have seen that patients who have GOO from duodenal, ampullary or pancreatic malignancy frequently develop biliary obstruction which may require either surgical or endoscopic intervention[1]. Usually we can divide patients into any one of the following three categories depending on the chronological order of the obstruction, *i.e.*, biliary obstruction before the duodenal obstruction, concurrent biliary and duodenal obstruction or biliary obstruction after duodenal obstruction. In most cases duodenal obstruction happens later during the disease course[4,6,7]. Further classification can be done based on anatomic location of the duodenal obstruction in relation to the papilla. GOO type Ⅰ has duodenal obstruction before the papilla, type Ⅱ involves the papilla and type Ⅲ is post papilla. GOO-Ⅱ is the most difficult to manage via endoscopic stenting whereas GOO-Ⅲ is the easiest to manage[4,6,7].

Before the advancement of endoscopic intervention, biliary bypass surgery was the treatment of choice[8]. With recent advancements in the endoscopic field (such as placement of biliary and duodenal SEMS), safer and

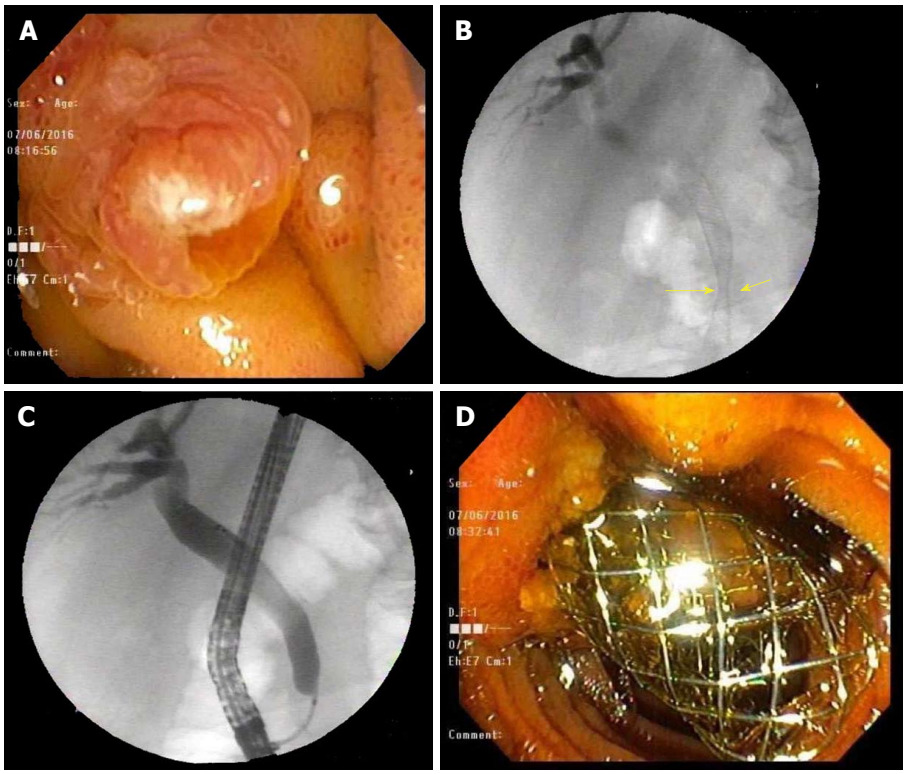

Figure 1 Initial endoscopic retrograde cholangiopancreatography findings. A: Area of the papilla visualized in the 2nd part of the duodenum; B: CBD malignant stricture visualized in the distal CBD with aid of fluoroscopy during ERCP; C: Cannulating the CBD; D: BMS interested into the CBD visualized protruding from the papilla in the 2nd portion of the duodenum. CBD: Common bile duct; ERCP: Endoscopic retrograde cholangiopancreatography; BMS: Bare metal stent.

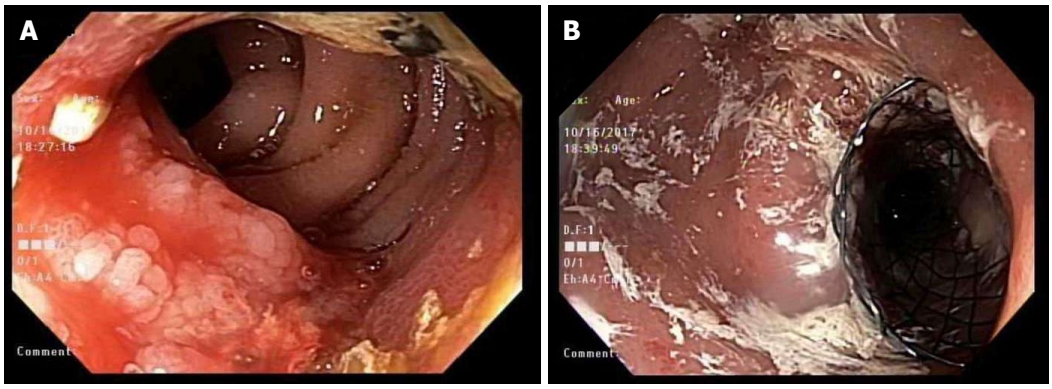

Figure 2 Esophagogastroduodenoscopy findings 15 mo after initial endoscopic retrograde cholangiopancreatography. A: Duodenal mass visualized encroaching in the lumen of 2nd portion of duodenum; B: SEMS placed over the area of the encroaching mass in the 2nd portion of the duodenum. SEMS: Self expanding metal stent.

more cost-effective ways have emerged to help improve the quality of life of patients who are otherwise not surgical candidates[9].

Typically, patients who present with malignant GOO typically undergo prophylactic biliary stent placement as the likelihood of developing biliary stricture or obstruction is very high; moreover, data in the past has shown that an estimated 60% of patients receiving duodenal stents also end up with biliary stents[2]. For patients who do not undergo biliary stenting (usually placed during the placement of an enteral stent), the gastroenterologist will have to uniquely perform the ERCP through an already existing duodenal stent. Our patient case fell under an even rarer clinical scenario in which not only did the patient have a duodenal stent, but he also had CBD prosthesis. To our knowledge this is the first case of true stent-in-stent placement of a BMS into the CBD through an already existing duodenal and CBD stent.

Studies in the past have explored risk factors and success rates of ERCP biliary metallic stenting in patients with an already existing SEMS due to duodenal obstruction. A study done by Yao *et al*[10] showed that for malignant duodenal stricture with SEMS, ERCP with biliary metallic stenting was safe and effective. The study showed that 60 mm duodenal

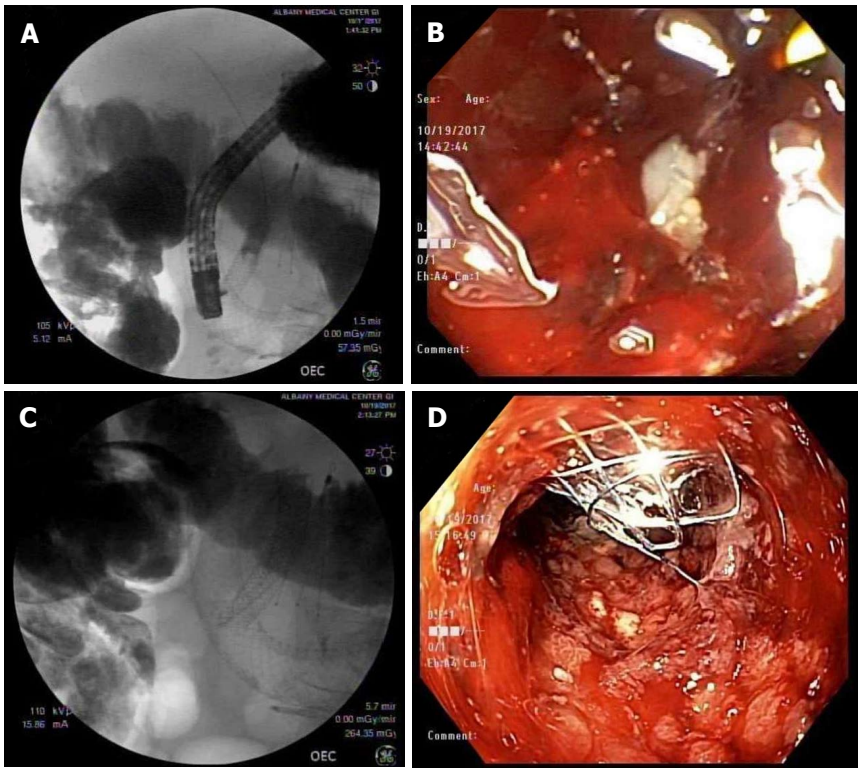

Figure 3 Endoscopic retrograde cholangiopancreatography to place a subsequent 2nd common bile duct stent through an existent duodenal stent. A: CBD BMS and duodenal prosthesis (SEMS) visualized on the 2nd ERCP before inserting the CMS into the CDB; B: Endoscopic visualization of the papilla site filled with debris and tumor invasion; C: CMS deployed on the existing BMS in the CBD through the SEMS in the duodenum; D: Endoscopic visualization of the CBD stent protruding through the papilla in the 2nd portion of duodenum after the completion of the 2nd ERCP. CBD: Common bile duct; BMS: Bare metal stent; SEMS: Self expanding metal stent; CMS: Covered metal stent; ERCP: Endoscopic retrograde cholangiopancreatography.

stent had ERCP success rate of 88% as compared to longer 80-90 mm stents that had a success rate of 18.2%. Furthermore, type 1 (GOO above the ampulla) and 2 (GOO at the level of ampulla) GOO with stricture length greater than 3.5 cm had lower ERCP success rates than strictures with a length less than 3.5 cm. GOO type 3 (GOO distal to the ampulla) had 100% ERCP success rate. To summarize, a stricture length of > 3.5 cm and duodenal stent length of 80-90 mm were independent risk factors for the failure of ERCP in patients with prior SEMS in the duodenum[10].

A study done by Hamada *et al*[11] evaluated time to recurrent biliary obstruction (TBRO) in patients who underwent endoscopic biliary drainage combined with a duodenal stent. The median TBRO was 450 d but no information about subsequent intervention was mentioned[11]. Another study done by Moon *et al*[5] on 8 patients with duodenal and biliary obstruction showed that biliary stenting following a duodenal SEMS is highly successful and feasible but no data was mentioned for patients having persistent biliary obstruction after the abovementioned procedure.

Another way to relieve CBD obstruction is endoscopic ultrasound-guided biliary drainage (EUS-BD). This is a relatively new technique in which a fistula is made between the biliary duct and intestine[12]. This method has been shown to be equivalent to percutaneous biliary drainage (PTBD) and is used as a salvage procedure after ERCP has failed and can be utilized in patients with or without duodenal stenosis[13,14]. A study done by Dhir *et al*[14] in patients that failed one or more ERCP attempts revealed that the short-term outcome of EUS-BD were comparable to that of ERCP. Similarly, another study done by Moon *et al* showed that EUS-BD is a therapeutic option when ERCP approach through the lumen of the duodenal SEMS fails. EUS-BD could be performed through the duodenum or through an existing mesh of a duodenal stent[3].

The treatment of initial malignant biliary stenosis resulting in GOO- Ⅱ that is alleviated with a duodenal SEMS is the most common scenario of biliary and duodenal obstruction intervention. It is easier to stent the duodenal obstruction after stenting the biliary obstruction but not vice versa[7]; however, Moon *et al*[3,5] have shown great success in biliary stenting through duodenal stents. In our case, even though the patient had an existent biliary stent, accessing the CBD was difficult due to tumor invasion and bloody debris (Figure 3B). There was zero visualization of the papilla making fluoroscopy the only way to visualize and cannulate the CBD as compared to the naïve papilla (Figure 1A) that is seen during the initial CBD stent placement.

There have been previous studies showing plastic biliary stents that were combined with biliary and

duodenal metal stenting[15,16], but to our knowledge, the above studies did not include patients with duodenal SEMS and CBD BMS who required further biliary stenting. Additionally, there are no published guidelines to follow in these scenarios. Our patient had an existing duodenal prosthesis along with a CBD BMS and was still experiencing biliary obstructive symptoms. The placement of the duodenal stent did not affect the patency of the existing CBD BMS. Considering ERCP as the first line therapy, we deployed a CMS on top of the BMS. This technique worked for our patient as a successful palliative and quality of life measure and was without any complications. By the time of hospital discharge, he had clinically improved and his total bilirubin continued to normalize.

While recently published literature has addressed initial stent placed into the CBD through a duodenal prosthesis for biliary obstruction, this is the first known case of inserting a second stent into the previous CBD stent through the duodenal prosthesis. In the future, endoscopists can consider this technique to stent an already existing CBD stent for alleviating malignant biliary obstruction in patients who are otherwise not candidates for surgical intervention. Researchers and clinicians should continue to investigate this modality and future utilization will allow us to identify any new findings or complications associated with this unique technique.

ARTICLE HIGHLIGHTS

Case characteristics

The patient with a bare metal stent (BMS) in the common bile duct (CBD) and self-expanding metal stent (SEMS) in the duodenum presented with worsening jaundice symptoms.

Clinical diagnosis

On esophagogastroduodenoscopy (EGD) patient was found to have gastric outlet obstruction (GOO) type II and worsening jaundice due mass obstructing the CBD.

Differential diagnosis

Pancreatic, duodenal or ampullary mass.

Laboratory diagnosis

Main laboratory testing for a biliary and duodenal obstructing mass would be a tissue biopsy obtained via endoscopic guided technique.

Imaging diagnosis

CT scan of the abdomen was used initially to find GOO followed by esophagogastroduodenoscopy (EGD).

Pathological diagnosis

Adenocarcinoma of the pancreas was found on biopsy.

Treatment

Covered metal stent (CMS) was placed into the previous BMS within the CBD through the already existing duodenal SEMS with relief of jaundice symptoms.

Related reports

To our knowledge other case reports don't have concomitant BMS in the CBD and SEMS in the duodenum while getting CMS in the CBD stent.

Experiences and lessons

Even though accessing the papilla through an already existing duodenal SEMS and CBD BMS may be difficult, endoscopists can try cannulating the CBD to relieve patient's obstructive biliary symptoms, and if need deploy another stent.

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REVIEW

Introduction of endoscopic submucosal dissection in the West

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Abstract

Endoscopic submucosal dissection (ESD) is well established in Asia as a modality for selected advanced lesions of both the upper and lower gastrointestinal tract, but ESD has not attained the same niche in the West due to a variety of reasons. These include competition from traditional surgery, minimally invasive surgery and endoscopic mucosal resection. Other obstacles to ESD introduction in the West include time commitment for learning and doing procedures, a steep learning curve, special equipment, lack of mentors, cost issues, interdisciplinary conflicts, concern regarding complications and lack of support from institutions and interfacing departments. There are intrinsic differences in pathology prevalence (*e.g.*, early gastric cancer) between the two regions that are less conducive for ESD implementation in the West. We will elaborate on these issues and suggest measures as well as a protocol to overcome these obstacles and hopefully allow introduction of ESD as a tenable option for appropriate patients.

Key words: Endoscopic submucosal dissection; Gastric cancer; Barrett's esophagus; Endoscopy training; Colon cancer; Rectal cancer

Core tip: Endoscopic submucosal dissection (ESD) is a well-accepted and widely employed modality in Asia for resection of advanced mucosa-derived lesions of the gastrointestinal tract including early cancer However ESD is not widely utilized in the West for a variety of reasons including lack of mentors, steep learning curve, cost issues and concern for complications. The authors describe these obstacles to the implementation of ESD in the West and measures to overcome them and begin an ESD program. We give a Western perspective on the current status of ESD for lesions of the esophagus, stomach and colorectum.

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INTRODUCTION

Endoscopic submucosal dissection (ESD) has enabled resection of larger and more histologically advanced epithelial - based lesions including early cancer of the upper and lower gastrointestinal tract as well as a broad array of submucosal lesions, that previously had necessitated surgical removal. ESD allows *en-bloc* resection with precise pathological staging and potential cure. It was invented in Japan where now it is well-established and subsequently permeated into the other East Asian areas[1]. ESD has been slow to be adopted in the West, and its penetration in the United States is especially poor. This disparity regarding ESD availability and implementation respectively in the East and West has had extensive examination with perspective from both areas[2,3]. However, ESD may have finally arrived in the West as it is now critically reviewed in mainstay American gastroenterology journals[4,5].

ESD is a minimally invasive endoscopic/surgical procedure technique for curative resection of advanced lesions including early gastrointestinal (GI) cancer. If curative, it can obviate surgery (laparoscopic or open) that otherwise would be needed for resection. This essence of the value of ESD is less obvious when comparisons are made to endoscopic mucosal resection (EMR) rather than to surgery. The value of ESD is more enhanced when early GI cancer is readily identified at endoscopy. This is arguably done better in the East (especially Japan) where the endoscopist is more apt to spend more time examining the entire gastric mucosal surface, employ magnification, chromoendoscopy and light filtering technique such as NBI and generally better appreciate the appearance of early GI cancer. The accepted classification systems for early GI cancer emanate predominantly from the East. There are mass screening programs for gastric cancer in Japan (not in the West) with both the endoscopist and pathologist vigilant for early gastric cancer (EGC).

The European Society of Gastrointestinal Endoscopy (ESGE) consensus guidelines on the role of ESD in the resection of more common mucosal - derived lesions of the GI tract reflect a relatively limited niche[6]. This panel concluded that most rectal and colonic superficial lesions can be effectively removed with traditional snare polypectomy and/or EMR. ESD is considered for colorectal lesions with a significant suspicion of limited submucosal invasion based on an irregular (non-granular) surface or depressed morphology that are not amenable to snare removal. EMR is the preferred approach for removal for Barrett's lesions with curative intent in that ESD has not been demonstrated to be superior. ESD, however, may be considered for Barrett's lesions larger than 15 mm, poorly lifting lesions and lesions with a concern for submucosal invasion. The panel did recommend ESD to achieve endoscopic *en-bloc* resection of superficial esophageal squamous cell cancers with the exclusion of those with obvious submucosal invasion. EMR may be considered for SCC's < 10 mm. ESD, though, was acknowledged as the first option to provide complete resection and accurate pathological staging. Also, ESD was recommended as the treatment of choice for most gastric superficial lesions. EMR may be an acceptable option for lesions < 10-15 mm and low probability of advanced pathology (Paris 0-ⅡA)[6]. Thus ESD is the accepted standard for EGC if tumor size < 2 cm, intramucosal, intestinal gastric cancer histology and no ulceration.

BARRETT'S ESOPHAGUS AND CANCER

The 2015 ESGE guidelines favor EMR over ESD for Barrett's esophagus and early cancer except for larger and more advanced lesions[6]. The two modalities were comparable in terms of recurrence and complication rate with ESD more time consuming[7] (Table 1). In a small randomized controlled trial (20 subjects each group) comparing ESD to EMR for Barrett's high-grade dysplasia or early cancer (< 3 cm), the two groups were comparable again in terms of remission, occurrence and need for surgery[8]. Complete resection was five times more likely in the ESD group, though the two severe adverse events was seen in the ESD group as well. Their compilation of ESD data reflects success with *en-bloc* resection though some series had significant complication rates (Table 2). Some ESD groups had no strictures but others had a stricture rate up to 50%[9-11]! More recent comparative studies and commentary reinforced the feasibility and safety of ESD in the West for BE and EAC with better R0 resection rates than EMR and the de facto choice for larger (> 3 cm), nodular, scarred and ulcerated lesions[12-14].

The Western centers foray into ESD for early esophageal cancer reflects mixed results and a fairly steep learning curve. A multicenter ESD study with resection of HGD or EAC had a R0 resection, curative and stricture rate of 76%, 70% and 15%[12]. Our center's resection experience with resection of cancer (EAC and SCC) and HGD yielded an *en-bloc*, R0, curative and stricture rate of 98%, 83%, 74% and 10% respectively (Figure 1). There was a significant decrease in procedure time with experience[15].

ESD in the esophagogastric junction is technically difficult and should be restricted only to higher volume specialized centers. Barrett's is less frequent in Japan where is more overall ESD expertise and this may hinder ESD in its comparison with EMR for BE resection results.

ESD

Early gastric cancer

Five pioneering Western ESD centers detailed their results for resection of gastric cancer[16-20] (Table 3). *En-*

Table 1 Endoscopic mucosal resection *vs* endoscopic submucosal dissection for early Barrett's and esophagogastric junction neoplasia

Outcome	ESD-6 Asian studies No. of studies	*n* (%)	EMR-10 Western studies No. of studies	*n* (%)	Odds ratio (95%CI)	*P*-value
Recurrence rate	6	1/333 (0.3)	5	10/380 (2.6)	8.55 (0.91, 80.0)	0.06
Perforation	6	5/335 (1.5)	9	8/686 (1.2)	1.07 (0.20, 5.62)	0.94
Delayed bleeding	6	7/335 (2.1)	9	8/686 (1.2)	0.46 (0.12, 1.75)	0.26
Stricture	5	7/207 (3.4)	7	3/456 (0.7)	0.21 (0.03, 1.41)	0.11
Method	No. of studies		Pooled procedure time (95%CI)			
EMR	2		36.7 (34.5, 38.9)			
ESD	5		83.3 (57.4, 109.2)			

Modified from Komeda *et al*[7]. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

Table 2 Endoscopic submucosal dissection for Barrett's high-grade intraepithelial neoplasia and early adenocarcinoma

Reference	Chevaux *et al*[9]	Kagemento *et al*[10]	Höbel *et al*[11]	Tergheggen *et al*[8]
Subjects	75	19	22	17
Study design	Retrospective	Retrospective	Retrospective	Prospective
Rates of resection				
En-bloc	90%	100%	96%	100%
R0 resection rate	64%	85%	82%	59%
Curative rate	64%	65%	77%	93%
Adverse events				
Bleeding	3%	4%	9%	0%
Perforation	4%	0%	5%	12%
Stricture	60%	15%	14%	0%

Modified from Terheggen *et al*[7].

Table 3 Endoscopic submucosal dissection for early gastric cancer in the West

Reference	*N*	Follow-up (yr)	Mortality (%)	*En-bloc* resection (%)	Curative resection (%)	Surgery (%)	Recurrence (%)
Cardoso *et al*[16]	15	1	0	80	74	8	8
Catalano *et al*[17]	12	2.5	0	92	92	8	8
Probst *et al*[18]	91	2.3	0	87	72	12	5.6
Schumacher *et al*[19]	28	2	3.4	90	64	7	11
Pimental-Nunes *et al*[20]	136	2.2	0	94	82	7	7

Modified from Oyama *et al*[2].

bloc resection was obtained in over 80% of subjects with 64%-92% achieving cure. However, there was a 10%-20% complication rate with no mortality in 4/5 series and 3% mortality in one series.

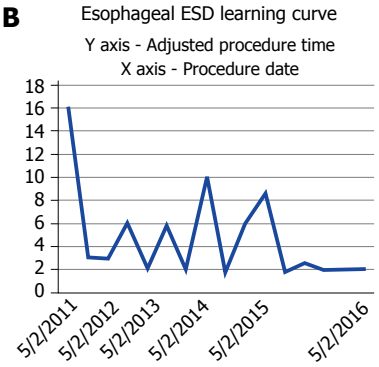
The Japanese suggested expanded criteria for ESD in EGC to include larger lesions (> 3 cm), ulcerated lesions of smaller size (< 3 cm), superficial submucosal lesions < 500 micrometers and possibly diffuse histology EGC if < 20 mm and consistent with absolute criteria above[21] (Table 4). Long-term outcomes of patients with expanded criteria including larger lesions (> 3 cm), ulcerated lesions of smaller size (< 3 cm) have excellent reported results in a Japanese multi-center prospective study[22]. However, enthusiasm in the West for ESD in EGC was tempered by a study demonstrating increased tendency for lymph node metastases in EGC for non-Asian subjects matched to Asian subjects with similar histopathological findings[23]. A German study of EGC subjects having surgery demonstrated a lymph node metastases rate of 21%/16%/40% respectively, for $sm_1/sm_2/sm_3$ tumor extension[24]. Thus, there is debate among European medical societies about extrapolation of the Japanese expanded criteria to European subjects.

A more recent European study validated the success of ESD in EGC even with expanded criteria subjects as well showing improved technical performance with greater speed and better clinical results[25] (Table 5). However, the racial/regional differences issue in EGC still somewhat lingers in that complete resection rates were less than most Asian studies and there was a 1% mortality compared to a negligible rate in Asia. There was a non-statistical superiority of survival of subjects with guideline entry criteria compared to those with expanded criteria but this appeared at 7 years with a 13.2% mortality with guideline criteria and 18.4% with expanded criteria (Figure 2).

A

ESD characteristics *n* = 41	
En-bloc resection, *n* (%)	40 (97.5)
Procedure time (min), median (range)	92 (10-291)
Lesion size (cm), mean diameter (range)	1.9 (0.5-3.9)
Total AEs *n* (%)	8 (20%)
Early AEs (within 24 h)	
Self-limited bleeding (no endoscopy)	1 patient
Prophylactic stent at time of ESD	1 patient
Transient self-limited pain and fever	1 patient
Glue to cover deep mp defect	1 patient
Late AEs (beyond the first 24 h)	
Strictures [all successfully dilated over a median of 3 sessions (1-4)]	4 patients
Histopathology *n* = 41	
RO resection, *n* (%)	7 (17)
at lateral margin	4 (57.1)
at deep margin	1 (14.2)
at both margins	2 (28.5)
Depth of invasion of carcinomas	34 cancers
Adenocarcinoma	
Pt1a	17 (63%)
Pt1b	9 (33%)
pT2 (R0 including superficial muscularis)	1 (4%)
Squamous cell carcinoma	
Pt1a	5 (71%)
Pt1b	2 (29%)

B



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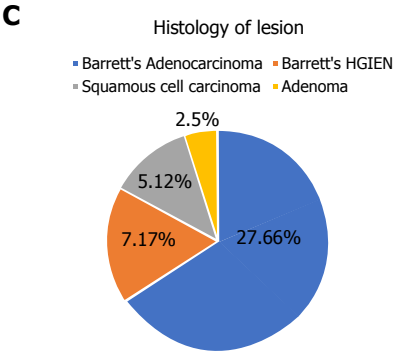

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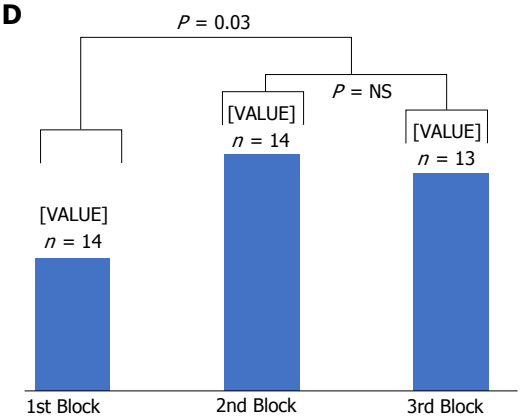

Figure 1 NYU Winthrop esophageal endoscopic submucosal dissection experience. A: ESD characteristics and histopathology; B: Histology of lesions; C: Learning effect on procedure time; D: Learning effect on R0 resection rate. AEs: Adverse events; ESD: Endoscopic submucosal dissection.

Colorectal ESD

The predominance of colon polyps and cancer relative to early gastric cancer in the West would theoretically allow Western physicians to garner needed ESD experience, but unfortunately, Western societal guidelines and thought leaders are not encouraging in this regard. As mentioned, the 2015 ESGE guidelines relegates ESD for colorectal lesions that are larger, likely more invasive or clearly not amenable to EMR[6]. In the United States, Dr. Ginsburg stated: "ESD over EMR for the vast majority of colorectal neoplasms (*i.e.*, adenomas) cannot be reconciled with the increased risk and procedure duration"[26]. Dr Rex stated: "Colorectal ESD, and *en-bloc* resection in general, are powerful concepts that currently come with a high price tag for most American colonoscopists. However, we acknowledge that as with many evolving technologies, deciding whether to learn colorectal ESD is "gray" not "black and white"[27]. Rex's group calculated the NNT for ESD to obviate surgery is 7 which was characterized as "a lot of work" but arguably individual patients may disagree! Moreover, this calculation may be flawed in that they only consider lesions with superficial SM invasion. However, there are two other scenarios where ESD can spare patients from colectomy: Aborted EMR due to fibrosis/non-lifting/difficulty in snare positioning-approximately 5% in Moss[28]) and intractable recurrences after EMR (approximately 2%) Including these scenarios, the NNT may be as low as approximately 5! A cogent argument favoring ESD over EMR is the high relative *en-bloc* resection and potential curative rates. A recent meta-analysis comparing the two modalities favored ESD with pooled odds ratio (OR) for *en-bloc* resection, cure and recurrence respectively of 6.8, 4.3 and 0.08

Table 4 Endoscopic submucosal dissection for early gastric cancer

Histology	Depth					
	Mucosal cancer				Submucosal cancer	
	No ulceration		Ulcerated		SM1	SM2
	⩽ 20	> 20	⩽ 30	> 30	⩽ 30	Any size
Intestinal	1	3	3	4	3	4
Diffuse	2	4	4	4	4	4

[1]Guideline criteria for ESD; [2]Consider surgery; [3]Expanded criteria for ESD; [4]Surgery (gastrectomy + lymph node dissection). ESD: Endoscopic submucosal dissection.

Table 5 Major Western endoscopic submucosal dissection series for early gastric cancer *n* (%)

	Guideline criteria	Expanded criteria	Out of indication	*P*-value
179 subjects	53 subjects	87 subjects	30 subjects	
Post ESD endoscopic follow-up	53/53 (100)	84/87 (97)	27/39 (69)	< 0.001
Follow-up median (mo)	51	56	36	NS
Curative resection	47/53 (89)	65/87 (75)	0	0.07
Local recurrence	0	4/84 (5)	3/27 (11)	0.06
Post ESD surgery	0	3/87 (3)	12/39 (31)	< 0.001
Metastases	0	1/84 (1)	3/27 (11)	0.005
Gastric cancer mortality	0	0	3 (8)	0.004
All-cause mortality	7 (13)	16 (18)	11 (28)	0.19

One hundred and seventy-nine ESD procedures for EGC over 12 years-about 15/year (modest compared to Asian centers). This Western center's learning curve: 1st block of ESD's (1-96) compared to 2nd block (97-191). R0 resection increased from 60% (57/96) to 93% (88/95) ($P < 0.001$). Median procedure time decreased from 148 to 110 min ($P < 0.001$). Modified from Probst *et al*[25]. ESD: Endoscopic submucosal dissection; NS: Not significant; EGC: Early gastric cancer.

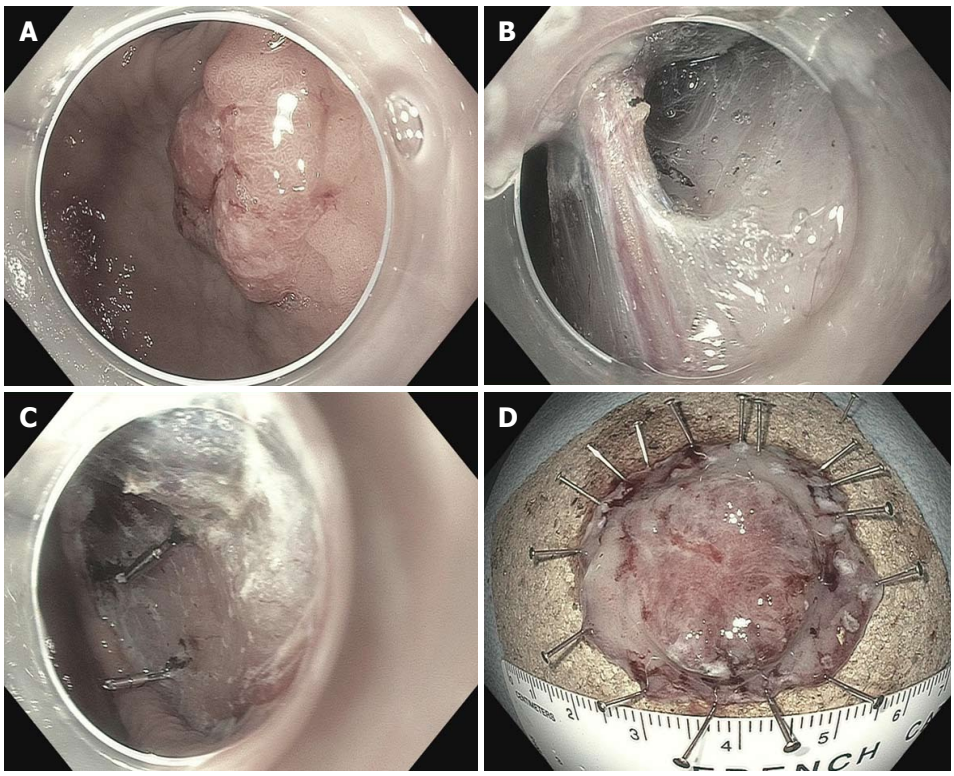

Figure 2 Endoscopic submucosal dissection of early gastric cancer (NYU-Winthrop).

respectively[29]. "Enhanced" EMR with cold snare and water immersion minimally lessened this relative disparity with the cold snare group showing 18% recurrence at 5 mo for lesion > 2 cm[30] and the water immersion group had a 10% recurrence rate for these lesions at 6 mo[31].

Cost analysis comparisons of colon EMR *vs* ESD would favor the former in the short run because of

Table 6 Cost analysis-endoscopic submucosal dissection vs endoscopic mucosal resection for colorectal lesions

ESD *vs* Wide-field EMR for large sessile and lateral spreading lesions > 2 cm: Cost analysis
Selective ESD prevented 19 additional surgeries per 1000 cases at slightly lower cost compared with WF-EMR
U-ESD could prevent an additional 13 surgeries per 1000 cases compared with S-ESD but at substantially increased cost of > 21000 dollars (Australian) per surgery avoided
Expanded ESD criteria (Japanese Gastrointestinal Endoscopy Society) adding mainly granular lesions > 4 cm added little additional benefit
Authors stated U-ESD is "unjustified" given WF-EMR effectiveness for benign lesions of LR-SMIC
Subgroup analysis of only rectal lesions concluded WF-EMR including trans-anal resection was as effective as S-ESD and still less costly
Because of the higher prevalence of SMIC in the rectum, the incremental cost per surgery avoided by U-ESD decreased to $87066 and dropped to $32132 among non-granular rectal lesions. U-ESD became the least costly and most effective strategy among higher risk non-granular Paris 0-is rectal lateral spreading lesions
Study design: Selective ESD strategy was employed for lesions suspicious for SMIC-all others had WF-EMR. Pathology after ESD revealing high - risk SMIC necessitated surgery. LR-SMIC on pathology at the ESD were considered cured

After Behin. *Gut* 2017. U-ESD: Universal ESD; ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; LR-SMIC: Low prevalence of low risk submucosal invasive cancer; WF-EMR: Wide field endoscopic mucosal resection; S-ESD: Selective endoscopic submucosal dissection; SMIC: submucosal invasive cancer.

longer procedure time and associated anesthesia as well as need for more expensive equipment with ESD, but ESD is more cost-effective in the long term because of its significantly better curative resection rate with less incumbent need for subsequent surveillance colonoscopy[32]. Another group compared various strategies for sessile lesions and lateral spreading colorectal lesions > 2 cm including wide field EMR (WF-EMR), selective ESD (S-ESD) and universal ESD[33] (Table 6). Selective ESD was performed when there was concern for submucosal invasion including lesions that were non-lifting, Paris 2C in appearance or with Kudo V pit pattern. S-ESD was preferred for all but rectal lesions. However, the study design favored EMR by including 18% rectal lesions, and in earlier work by the same group, there was 16% recurrence after EMR at 4 mo with an additional 4% new recurrences in those patients at 16 mo for a total of 20% cumulative recurrence by 16 mo[28]. For ESD, recurrence rate in a meta-analysis of 104 colorectal ESD studies[34]: 1% at 19 mo and 0.04% if R0 resection! In another meta-analysis[35] comparing colon EMR *vs* ESD, recurrence was 0.9% for ESD.

Starting an ESD program

The Western ESD pioneers will likely have their R_0 resection rates and significant complications closely scrutinized by their gastroenterology colleagues, surgeons, tumor boards and administration (Table 7). Cost-effectiveness will be an ongoing debate at most institutions but, if curative resection and significant AE rate are satisfactory, one can effectively advocate for ESD by emphasizing the benefits of having an ESD program (Table 8). Enhanced EMR methods such as circumferential mucosal incision (CMI) or circumferential submucosal incision (CSI) followed by snare removal have not shown R_0 or curative resection rates comparable to traditional ESD but can help build ESD skills[36,37]. The performance of ESD is often a multi-hour endeavor and anesthesia, nursing and ancillary personnel should be aware of their roles. Ergonomic consideration should be given to both the operator and the patient-two deaths in a European study may have related to thrombosis[6,38,39]. In addition, both the patient and pathology should be appropriately triaged (Table 7). Appropriate medical or other discipline clearance should be obtained beforehand. Endoscopic and pathologic data should be evaluated with caution. Concordance of biopsy and resected specimen pathologic diagnosis of gastric polyps > 5 mm is only 55%-77%[40,41]. Concordance of biopsy and resected specimen pathologic diagnosis of colon polyps in one study was only 60%[42].

There are progressive phases or stages typically necessary for development of ESD skills. Initially, one acquires basic knowledge *via* texts, reviews and courses. Lesions should be properly assessed including use of enhanced imaging. Knowledge of electrosurgical generators and their appropriate settings for the various ESD stages as well as familiarity with the common electrosurgical knives. Overall, one should develop an understanding of ESD techniques, indications, limitations, risks and expected outcomes. Subsequently, training can be obtained in *ex vivo* animal models including pig esophagus/stomach and bovine rectum. Expenses may be possibly defrayed by industry support in anticipation of equipment necessary for an ESD program. Before embarking on ESD cases in humans, one should observe live ESD cases by experts; probably a minimum of 20 cases. Trainees can likely assist in ESD cases by their mentor experts. A trip to Japan with concentrated exposure and ideally hands-on experience can also be useful[43]. These experts may also travel to regional meetings. Experts may also view a video of your technique with suggestions[44]. The 2010 ESGE White Paper suggested performance of 30 ESDs reaching speed of 30 min/5 cm lesion in live animals as well as management of simulated complications such as bleeding and perforation prior to clinical ESD[45,46].

Once the operator begins to perform clinical ESD, there must be a sufficient volume of cases to maintain and improve techniques. This would be a minimum of two cases per month but preferably at least a case weekly[2,47]. In the "step-up" approach of transitioning from clinical training to competence, one would do

Table 7 Caveats for the endoscopic submucosal dissection pioneer

Start clinical ESD only after extensive pre-clinical training
Start with easier lesions
Avoid "unprincipled ESD"
Record and monitor closely outcomes and complications- consider registry and videos
Be familiar with techniques for endoscopic management of complications
The main complications (perforation and bleeding) can almost always be managed (or even prevented in the case of bleeding) by skillful application of clips and coagulation
Experience with endoscopic clip placement and coagulation grasper application is essential (experience with endoscopic suturing is highly desirable)
Avoid mistakes in selecting and scheduling cases-many referral reports lack detailed information on morphology, size, location, prior manipulation
Morphology (*e.g.*, Paris classification) may suggest a more advanced lesions that was appreciated on the index endoscopy and biopsy that may require expedited scheduling
Index biopsies may be misleading (obtained from the periphery rather than depressed areas of 2c or 1s lesions missing a carcinoma)
Biopsies yielding only dysplasia may result in a publicly delayed resection of cancer
Concordance of biopsy results and ultimate post-resection pathology is fair at best
EDUCATE your referring physicians-AVOID inappropriate India ink tattooing and "partial snare resections"/hot forceps/jumbo forceps for "diagnosis or "attempted" hasty resections (tackling lesions where probability of complete EMR is low)
Lack of experience in delineating early GI cancer main lead to excessive sampling biopsies
DISCOURAGE APC to" vaporize "grossly" evident residual tumor or aggressive/many biopsies of delicate flat lesions (SSA's)
ENCOURAGE: (1) detailed descriptions: size, morphology; (2) lots of pictures; (3) giving print out with color pictures to the patient and d) having referring physicians transit "money" shots of lesion to you
Put post - resection specimens on corkboard and educate pathologist about specifics of resection
Pathologists should properly orient specimens with ⩽ 2 mm slices
Pathology report should comment on adequacy of resection including deep and lateral margins with measurement of submucosal invasion with micrometer measurements as well as the differentiation (G1-G3)
Optimally there should be desmin staining of the muscularis mucosa noting the pattern of SM invasion, *e.g.*, budding
Comment should be made regarding lymphovascular invasion with elastin Van Gieson stain to delineate venules and the D2 – 40 immunostain for lymphatics (important)
Multidisciplinary input and communication including nursing, technicians, anesthesiologists, surgeons and oncologists
The patient should be evaluated as dictated by medical history by internists, cardiology and pulmonary medicine with particular attention to anticoagulants and antiplatelet drugs
Ergonomic considerations are given to both ESD operator and patient

ESD: Endoscopic submucosal dissection; GI: Gastrointestinal.

Table 8 Benefits of institution endoscopic submucosal dissection program

Potential benefit in avoiding surgery/organ resection
"Downstream revenue "from increased services and subsequent referral to surgery/oncology of patients (possibly up to 20% of ESD's performed)
Enhancement of overall institutional prestige
ESD is a necessity for any institution purporting to be a tertiary referral center for luminal GI tract
Enhanced recruitment of trainees and faculty after establishment of ESD program

ESD: Endoscopic submucosal dissection; GI: Gastrointestinal.

20-30 supervised cases-optimally in the antrum or rectum where management of complications is easiest with a subsequent 20-30 cases in more challenging areas with the goal of achieving > 80% *en-bloc* resection and < 10% complications in 20 consecutive cases[45]. The next phase is the transition from competence to proficiency-usually > 80 cases. This is mostly a result of self- training to attain proficiency with an *en-bloc* resection rate ⩾ 90% and dissection speed ⩾ 9 cm^2/h. "Master classes" and/or additional observation of live cases by experts may help at this stage (refine skills and acquire more advanced tips and tricks). The next and last phase is mastery after hundreds of cases with a curative rate > 80% and teaching of other physicians. The difficulty of ESD varies by location with the proximal stomach, colon flexures and ileocecal valve/appendiceal areas and ESD in the small intestine including the duodenum reserved for true experts (Figures 3 and 4).

CHALLENEGES FOR WESTERN ESD OPERATOR

The Western ESD operator is at a distinct disadvantage compared to his Asian counterpart with the latter having widespread acceptance, existent infrastructure, choices of mentors and ample pathology. In the West, the relative paucity of early gastric cancer cases relative to colon and esophageal pathology is a particular challenge. As mentioned, the Western endoscopist may be less attuned to the appearance of EGC. There are about eight times more cases of gastric cancer in Japan than in the United States[48]. SEER database analysis over a recent decade in the United States noted 43769 cases of gastric adenocarcinoma of which

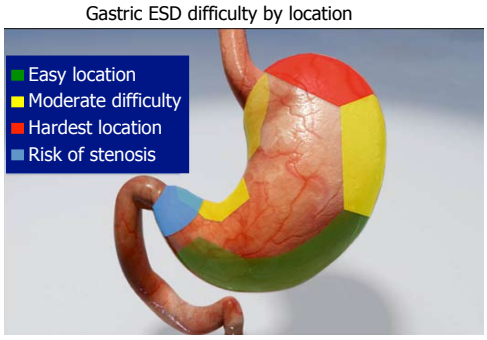

Figure 3 Gastric endoscopic submucosal dissection difficulty by location. ESD: Endoscopic submucosal dissection.

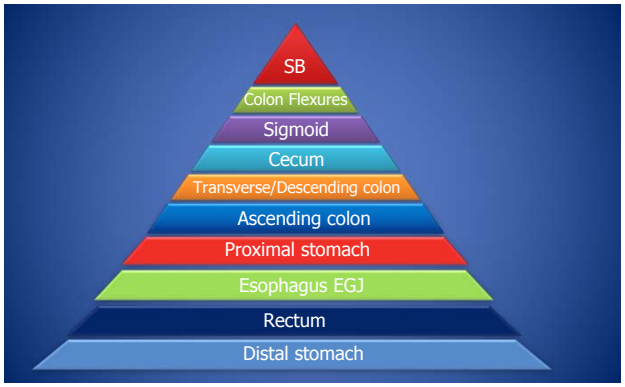

Figure 4 Relative endoscopic submucosal dissection difficulty by location. ESD: Endoscopic submucosal dissection; EGJ: Esophagogastric junction.

1826 were EGC-only 203 cases yearly[49]! Absence of suitable lesions was the main perceived obstacle to ESD implementation in the West as per a survey of 40 ESD trainees at a conference[50]. There are different approaches in the West to this obstacle of too few EGC cases. The "step-up" approach for "untutored learning" in the West recommends starting with UGI lesions where ESD is easier and most beneficial (resecting early cancers). But this approach is problematic for several reasons. UGI lesions are rare (unlike colon lesions) and would make it difficult to achieve the 2 lesions/mo requirement. An R1/Rx resection (a common error during ESD learning) is much more detrimental in the UGI tract than in the colon; especially if high risk colon lesions are avoided during learning. For UGI lesions (often carcinomas) patient would be subjected to highly morbid surgery (esophagectomy/gastrectomy) whereas for colon adenomas/HGIEN careful follow-up/ further endoscopic treatment is sufficient for most R1 resections[51].

Another approach to the relative paucity of early gastric cancer in the West for the ESD operator is to have a prevalence based or ad hoc strategy[51]. Berr described this relatively untutored ad hoc strategy where 80% of his first 50 cases were in the colorectum, and he clearly documented improved rates of *en-blo* and R_0 resection as well as a lower perforation rate and increased speed of dissection with increasing experience[51]. A South Korean study of colorectal ESD without prior gastric ESD experience noted the same positive trends as the Berr group with more cases and the performance > 100 ESDs, rectal ESD and lack of submucosal fibrosis were independent predictors of success[52]. Competence was defined as 80% *en-bloc* resection rate and statistically significant decrease in operative time[53]. An Italian endoscopist with prior EMR experience did not transition to colon ESD until ESD competence was demonstrated in the rectum[54]. All lesions were > 2 cm, and again increased *en-bloc* resection rates were noted with increased experience as well as decreased operative time, but defined competence was noted after only five cases in the rectum but required 20 cases in the colon[54].

NYU Winthrop ESD experience

The NYU Winthrop ESD experience was also untutored with gradual progression of skills (Figure 5). There was progression from ESD to natural orifice translumi-nal endoscopic surgery (NOTES) including POEM, submucosal tunnel endoscopic resection (STER) and endoscopic full-thickness resection (EFTR)[55]. The initial four year experience reflected the learning curve with 53% and 75% *en-bloc* resection rates respectively for early mucosal neoplasms and submucosal tumors[56] (Table 9). We studied the relative utility of various electrosurgical devices during this period[57]. We have performed over 500 ESD's with progressively faster dissection rate and presently an *en-bloc* resection > 90% (Figure 6). We have resected early mucosal neoplasms and submucosal lesions from the esophagus, stomach, duodenum and colorectum as well as ileocecal valve polyps that extended into the ileum[55,56].

ESD complications

The significant adverse events of hemorrhage and perforation are more common in ESD then with EMR, and a major concern for the fledgling ESD operator, though, as mentioned, the complication rate diminishes usually with experience and likely is better managed by the more seasoned operator[46,50]. The ESD resection bed should be copiously irrigated to assess for vessels that may cause subsequent post - resection bleeding. The main complications (perforation and bleeding) can almost always be managed (or even prevented in the case of bleeding) by skillful application of clips and coagulation Experience with endoscopic clip placement and coagulation grasper application is essential (experience with endoscopic suturing is highly desirable) (Table 7). There is controversy as to the necessity of closing the ESD post-resection defect. Proponents of closure cite less delayed bleeding and perforation as well as earlier discharge with associated decreased cost, but the data is limited to date[58]. Opponents argue that closure may complicate subsequent surveillance or further resection at the ESD site by creating artificial

Table 9 Western Center initial endoscopic submucosal dissection series *n* (%)

EMNS		SETs	
Total Lesions	38 (43)	Total lesions	51 (57)
Size, mean millimeters (range)	26 (5-90)	Size, mean millimeters (range)	18 (8-55)
Complete *en-bloc* resection (R0 deep + lateral margins)	20 (53)	Complete *en-bloc* resection (completeness assessed endoscopically)	38 (75)
		Complete 2-piece resection	5 (10)
		incomplete resection	8 (15)
Histologic diagnosis		Histologic diagnosis	
T1 carcinomas/adenomas with HGD	16 (42)	GIST	12 (23)
Adenomas w/o HGD	10 (26)	Pancreatic rests	11 (21)
No residual adenoma granulation tissue	11 (29)	Lipomas	8 (16)
Unclassified	1 (3)	Carcinoids	6 (12)
		Granular cell tumors	3 (6)
		Leiomyomas	8 (16)
		Other	3 (6)

SETs: Subepithelial tumors; EMNS: Early mucosal neoplasm; GIST: Gastrointestinal stromal tumors; HGD: High grade dysplasia.

Figure 5 Chronology of endoscopic submucosal dissection development in a Western Center. ESD: Endoscopic submucosal dissection; STER: submucosal tunnel endoscopic resection; EFTR: endoscopic full-thickness resection.

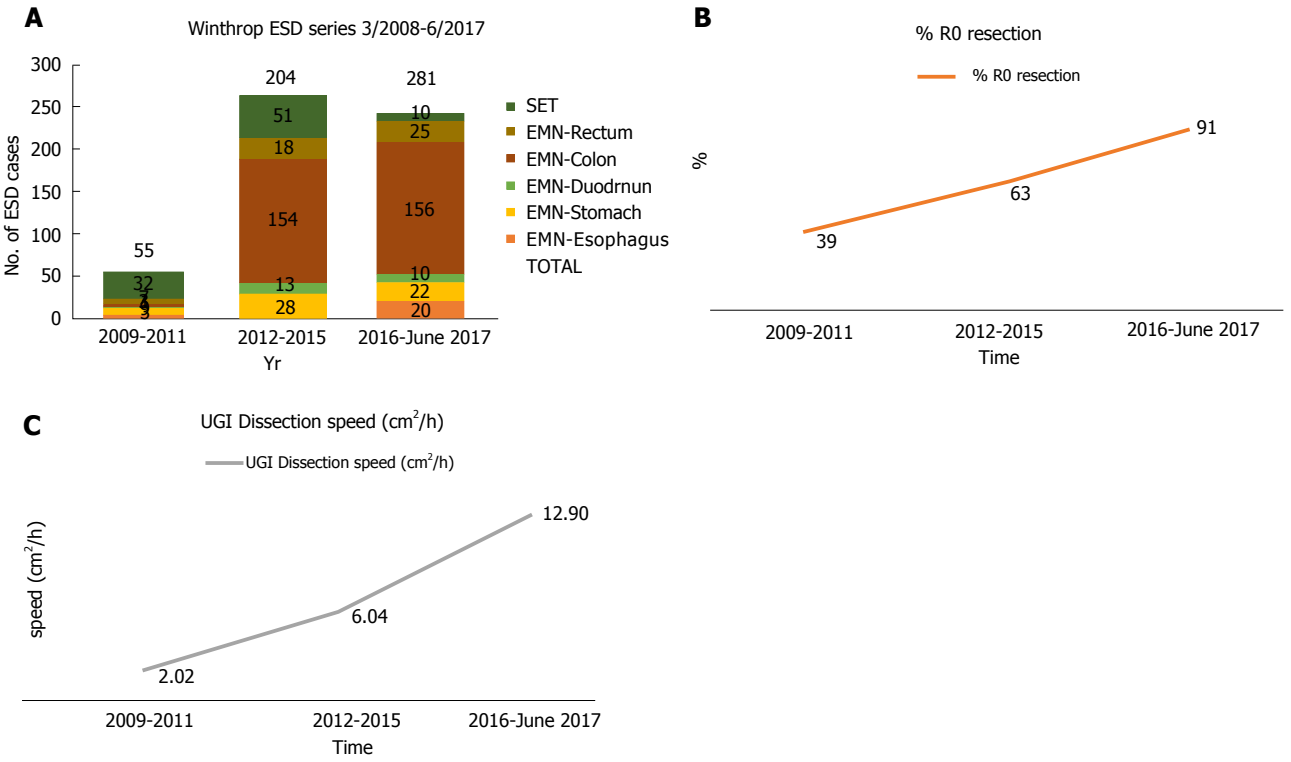

Figure 6 NYU-Winthrop endoscopic submucosal dissection experiences. A: ESD pathology; B: ESD R0 rates; C: UGI ESD dissection speed. ESD: Endoscopic submucosal dissection.

nodules or other "lesions" and/or burying residual neoplastic tissue and questionable cost-effectiveness[59]. Use of an omental patch may help in perforation closure either with clips or endoscopic sutures. Berr noted the relatively low rate of colonic ESD complications in early operators reported in the Japanese literature (< 12.5%) may not extrapolate to the Western experience[51]. The Japanese trainees were tutored by experts and reportedly completed less than half of their initial procedures. A more "real-life" elaboration of the

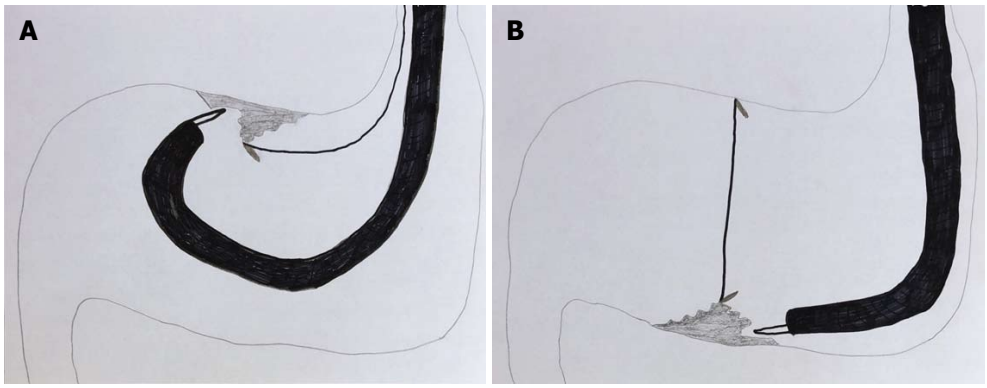

Figure 7 Traction in endoscopic submucosal dissection. A: Traction *via* clip on string; B: Traction *via* pulley effect with two clips.

initial ESD French experience noted 11% and 18% hemorrhage and perforation rate respectively with *en-bloc* and R_0 resection rates of 77%/73% respectively[60]. Berr[51] had suggestions for the "colon heavy-untutored/prevalence based" ESD learners based on his retrospective video analysis of his own work including avoiding: (1) wide SM injection around the lesion (which forces a "perpendicular" instead of "tangential approach"); (2) injection deep to muscle layer (lack of submucosal fluid cushion); (3) disruption of vessels leading to hematoma and loss of transparency of submucosa; (4) dissection without direct vision of the tip of the knife; (5) contact coagulation of small vessel directly on colonic proper muscle layer; and (6) mucosal incision using knife in "pullback fashion" across a haustral fold[51].

Another peril of over-extrapolating ESD results from Japan to the West concerns pathology. One should be cautious concerning extended Japanese indications for gastric ESD (particularly SM1 invasion) (Table 4). The local pathologist may not be as accurate and experienced as expert Japanese pathologists (all SM1 invasion is not created equal (extensive *vs* focal, tumor budding, *etc*.) As reviewed, some surgical studies purport to show that early gastric cancer in the West may behave more aggressively[23,24]. One must discuss risk of metastatic cancer (even after "curative ESD") and metachronous cancers and need for surveillance as even intramucosal carcinoma has a low but not negligible rate of metastasis (*e.g*., 1%-2% for Barrett's intramucosal carcinoma or HGD[61]). The recurrence rate of T1b carcinoma in the rectum (4.2%-4.5%) is higher than in the colon (1.5%-1.9%)[4-6]. Follow-up colonoscopy as well as periodic CEA, abdominal ultrasonography, and thoracic and abdominal CT should be performed. However, no clear consensus was reached regarding the particular method and time of surveillance[62]. Metachronous lesions occur in 10%-30% in early 3-5 years follow-up post gastric, esophageal, colon resection[4,5]. Endoscopic surveillance is important.

Rectal ESD

Rectal ESD merits specific mention as it is in fierce competition with burgeoning techniques of trans-anal surgery including trans-anal endoscopic microsurgery (TEMS), trans-anal minimally invasive surgery (TAMIS) and a host of other platforms. Surgeons have the apparent advantage of better and innovative equipment including robotic devices as surgical resection *via* endoscopy is a natural extension for this discipline. A provocative meta-analysis compared ESD and TEM for rectal lesions demonstrated a relative procedure time, *en-bloc* resection rates, R_0 resection rates, recurrence rates for ESD/TEM of 96/67 min, 88%/99%, 75%/88%, 2.6%/5.2% respectively[63]. The overall complication and emergency surgery rates were about the same (8%, 1.5%). The ESD group had a perforation/hemorrhage rate of 3.7%3.5%, but the surgery group had the more troubling and durable complications of suture leak and fistula (3.2%/0.5%). The surgery group had the distinct advantage in terms of less needed abdominal surgery for oncologic indications or recurrence (8.4% *vs* 2.9%). However, closer scrutiny determines that the ESD group had much more advanced pathology with almost 90% of pathology showing cancer *vs* 10% in the TEM group. Thus, rectal ESD is currently holding its own against these innovative surgical procedures.

Traction

The ESD operator should be aware of gravity during the performance of the section in terms of endogenous fluid and expected blood with consideration of patient repositioning. A practical way to facilitate resection is to employ traction (Figure 7). Traction is the equivalent of a second operator and examples in ESD ranges from simply having a forceps or snare outside the scope channel to setups employing endo-clips, endo-loops, suture thread or floss to create spring or pulley effect. More sophisticated methods employ a second scope, percutaneous access or magnets[64]. Traction may improve performance; especially in trainees and those with modest experience[65].

ESD technology

As mentioned, acquiring skills in ESD is a gateway to innovative resection methods such as STER and EFTR.

Technological innovations are inevitable with many past and future innovations coming from the West. Some of these innovations will make it easier for physicians with a background in EMR to begin ESD, while others will allow experienced ESD operators to perform more challenging cases and to do so more quickly. The already crowded arena of electrosurgical devices and injection solutions will expand. Novel scissors-type knives were invented to facilitate ESD and increase trainee completion rates[66,67]. There is an array of devices being developed as adjuncts to ESD performance. This includes platform devices to allow a variety of instruments to be used synergistically similar to the operating room setup[68]. Balloon devices can allow stabilization of the colonoscope during ESD, and this includes the traditional double balloon endoscope and the DiLumen device (expressively developed for ESD)[69]. Thullim laser is an alternative to the electrosurgical knives powered by monopolar electrosurgical units[70].

CONCLUSION

ESD originated in Japan and is a well-accepted modality in Asia for larger and advanced epithelial-derived neoplasms of the upper and lower gastrointestinal tract. In the West, there is evident interest in ESD as demonstrated by the content of the main gastroenterology and endoscopy journals and national meetings of the related societies. However, ESD has clearly not become part of mainstream endoscopy practice. This is due to multiple factors including the relatively steep learning curve, relative lack of resources for learning ESD including few potential mentors, cost issues, longer procedural time and concern for complications. In addition, societal thought leaders have generally not supported ESD development. Despite this, the consensus (even in the West) is that ESD is the premier modality for resection of EGC and squamous cell esophageal cancer with the exception of small non-advanced lesions. ESD has a more modest niche for Barrett's lesions compared to EMR and surgery though this is still debated. A prime obstacle to ESD implementation in the West is the relative lack of early gastric cancer compared to Asia. The irony is that there is ample colorectal pathology in the West amenable to ESD, but this colon ESD implementation is discouraged by the thought leaders; perhaps because of the relative success of wide-field EMR and the usual relative indolent nature of colon adenoma recurrence. Nonetheless, ESD has clear advantages in the colon and elsewhere in terms of superior *en-bloc* and curative resection rates with associated low recurrence rates. Some ESD "pioneers" have essentially self-tutored themselves in ESD with the more prevalent colorectal lesions. Those embarking on an ESD program should do appropriate preparatory work and avail themselves of international mentors and animal labs before doing clinical work as their resection results and complications will be closely scrutinized. They should also be conservative initially with their choice of potential lesions-especially in the stomach- as there may be biological differences in EGC between the West and the East. We feel that it is inevitable that ESD will eventually be ingrained in mainstream endoscopy practice in the West. This will occur as a result of burgeoning ESD data from the West supporting its validity and utility in this population as well as more potential ESD tutors and perhaps formal society-sanctioned traineeships. The growing demand for basic and adjunctive ESD equipment will spur new devices likely largely derived from the West.

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REVIEW

Artificial intelligence in gastrointestinal endoscopy: The future is almost here

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Abstract

Artificial intelligence (AI) enables machines to provide unparalleled value in a myriad of industries and applications. In recent years, researchers have harnessed artificial intelligence to analyze large-volume, unstructured medical data and perform clinical tasks, such as the identification of diabetic retinopathy or the diagnosis of cutaneous malignancies. Applications of artificial intelligence techniques, specifically machine learning and more recently deep learning, are beginning to emerge in gastrointestinal endoscopy. The most promising of these efforts have been in computer-aided detection and computer-aided diagnosis of colorectal polyps, with recent systems demonstrating high sensitivity and accuracy even when compared to expert human endoscopists. AI has also been utilized to identify gastrointestinal bleeding, to detect areas of inflammation, and even to diagnose certain gastrointestinal infections. Future work in the field should concentrate on creating seamless integration of AI systems with current endoscopy platforms and electronic medical records, developing training modules to teach clinicians how to use AI tools, and determining the best means for regulation and approval of new AI technology.

Key words: Artificial intelligence; Machine learning; Gastrointestinal endoscopy; Computer-assisted decision making; Computer-aided detection; Colonic polyps; Colonoscopy; Computer-aided diagnosis; Colorectal adenocarcinoma

Core tip: Artificial intelligence (AI) appears poised to transform several industries, including clinical medicine. Recent advances in AI technology, namely the improvement in computational power and advent of deep learning, will lead to the near-term availability of clinically relevant applications in gastrointestinal endoscopy, such as real-time, high-accuracy colon polyp detection and classification and fast, automatic processing of wireless capsule endoscopy images. Applications of AI toward gastrointestinal endoscopy will likely exponentially rise in the coming years, and attention should be paid toward regulation, approval, and effective implementation of this powerful technology.

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INTRODUCTION

Artificial intelligence (AI) has transformed information technology by unlocking large-scale, data-driven solutions to what once were time intensive problems. Over the past few decades, researchers have successfully demonstrated how AI can improve our ability to perform medical tasks, ranging from the identification of diabetic retinopathy to the diagnosis of cutaneous malignancies[1,2]. As the medical community's understanding and acceptance of AI grows, so too does our imagination of the many ways in which it can improve patient care, expedite clinical processes, and relieve the burden of medical professionals.

Gastroenterology is a field that requires physicians to perform a myriad of clinical skills, ranging from dexterous manipulation and navigation of endoscopic devices and visual identification and classification of disease to data-driven clinical decision-making. In recent years, AI tools have been designed to help physicians in performing these tasks. Research groups have shown how deep learning can assist with a variety of skills from colonic polyp detection to analysis of wireless capsule endoscopy (WCE) images[3,4]. As the number of applications of AI in gastroenterology expands, it is important to understand the extent of our success and the hurdles that lie ahead. In this review, we aim to (1) provide a brief overview of artificial intelligence technology; (2) describe the ways in which AI has been applied to gastroenterology thus far; (3) discuss what value AI offers to this field; and finally (4) comment on future directions of this technology.

ARTIFICIAL INTELLIGENCE TECHNOLOGY

Artificial intelligence is machine intelligence that mimics human cognitive function[5]. Research in AI began in the 1950s with the earliest applications being in board games, logical reasoning, and simple algebra. Interest in the field grew over the next few decades due to the exponential increase in computational power and data volume.

Machine learning is an artificial intelligence technique in which computers use data to improve their performance in a task without explicit instruction[6]. Examples of machine learning include an application that learns to identify and discard spam emails or a thermostat that learns household temperature preferences over time. Machine learning is often classified into two categories - supervised and unsupervised learning. In supervised learning, a machine is trained with data that contain pairs of inputs and outputs[7]. The machine learns a function to map the inputs to outputs, which can then be applied toward new examples. Linear and logistic regression, which are often employed in clinical research, are examples of supervised machine learning because they produce a regression function that correlates inputs to outputs based on observed data. In unsupervised learning, machines are given data inputs that are not explicitly paired to labels or outputs[7]. The machine is tasked with finding its own structure and patterns from the set of objects. An example of unsupervised learning is clustering, in which a system creates clusters of similar data points from a large data set.

Feature learning refers to a set of techniques within machine learning that asks machines to automatically identify features within raw data as opposed to the features being explicitly labeled[8]. This technique enables machines to learn features and infer functions between inputs and outputs without being provided the features in advance. A subset of feature learning is deep learning, which harnesses neural networks modeled after the biological nervous system of animals. Deep learning is especially valuable in clinical medicine because medical data often consist of unstructured text, images, and videos that are not easily processed into explicit features.

Machine learning, and more specifically deep learning, has been widely applied in tasks such as gaming, weather, security, and media. Recent notable examples include AlphaGo beating the world's premier Go player, facial recognition within iPhone images, and automatic text generation[9-11].

Deep learning has also shown significant promise in performing clinical tasks. Researchers from Stanford trained a deep convolutional neural network (CNN) on 129450 skin lesion images consisting of 2032 different diseases, and showed that the network performed on par against 21 board-certified dermatologists in distinguishing keratinocyte carcinomas from benign seborrheic keratosis and malignant melanomas from

benign nevi[2]. Other research groups have applied machine learning to identify diabetic retinopathy from fundus photographs, classify proliferative breast lesions as benign or malignant, and predict clinical orders[12-14].

APPLICATIONS OF AI IN GASTROENTEROLOGY

Automatic colonic polyp detection

Automatic colon polyp detection has been one of the primary areas of interest for applications of artificial intelligence in gastrointestinal endoscopy. Generally speaking, automatic polyp detection constructs are designed to alert the endoscopist to the presence of a polyp on the screen through either a digital visual marker or sound.

Numerous studies have demonstrated that endoscopists with higher adenoma detection rates during screening colonoscopy more effectively protect their patients from subsequent risk of colonic cancer[15,16]. Corley *et al*[15], for example, in their evaluation of 314872 colonoscopies performed by 136 gastroenterologists showed that every 1.0% increase in adenoma detection rate was associated with a 3.0% decrease in the risk of cancer (hazard ratio, 0.97; 95%CI: 0.96 to 0.98). However, adenoma miss rates during screening colonoscopy remain relatively high, and have been estimated to be anywhere from 6%-27%[17]. Reasons for missing polyps are myriad, and can include inadequate mucosal inspection (for instance behind folds in the right colon), lack of recognition of subtle mucosal findings representing flat polyps, and variable prep quality. Importantly, there is evidence that some missed polyps are actually present on the visual field, but are not recognized by the endoscopist[18-20].

In the past two decades, several computer-aided detection (CADe) techniques have been proposed to assist endoscopists in the detection of polyps that would otherwise have been missed[21-24]. The ideal automatic polyp detection tool must have (1) high sensitivity for detection of polyps; (2) decreased rate of false positives; and (3) low latency so that polyps can be tracked and identified in near-real time. This last objective has eluded researchers up until recently as automatic polyp detection during live or recorded video can be affected by camera motion, strong light reflections, lack of focus of the traditionally used wide-angle lens, variation in polyp size, location and morphology, and the presence of vascular patterns, bubbles, fecal material and other distractors that may serve as false positives[25].

CADe in optical colonoscopy was first utilized and validated using still images obtained from endoscopic videos. Most of the modalities described below all utilize some combination of the following techniques: pre-processing of an image or series of images in order to discard noise, a feature extraction tool that identifies and extracts a feature or mix of features within the image (*e.g.*, texture, shape or color), and a machine-learning or deep learning classification that uses these features to identify polyps[25].

A number of methods for CADe were proposed in the 1990s. Early attempts included the use of region-growing methods - a pixel-based image segmentation approach - for the extraction of large intestinal lumen contours and for the detection of lower gastrointestinal tract pathology[21-23]. By the end of the 1990s, research efforts mostly combined texture, color, or mixed analysis methods with intelligent pattern classification to aid in the detection of lesions in static endoscopic images[23]. These efforts included work targeting both microscopic features and macroscopic characteristics of lesions within the colon in order to predict the likelihood of neoplastic and pre-neoplastic lesions[26,27]. The concurrent development of neural networks helped push the field forward. Early grey-level texture analysis of endoscopic images included utilization of texture spectrum[24], co-occurrence matrices[28,29], Local Binary Pattern (LBP)[30], and wavelet-domain co-occurrence matrix features[31]. Using this last approach, Karkanis *et al*[31] developed one of the earliest examples of polyp detection software. Known as CoLD (Colorectal Lesions Detector), the software utilized second-order statistical features, calculated on the wavelet transformation of each image to discriminate amongst regions of normal or abnormal tissue. An artificial neural network performed the classification of these features, obtained from still images alone, and the work achieved a detection accuracy of more than 95%[32,33].

Other groups developed methods that utilized color features. Tjoa and Krishnan[34] combined texture spectrum and color histogram features to broadly analyze colon status as "normal" or "abnormal". In 2003, Karkanis *et al*[35] used a color feature extraction scheme built on wavelet decomposition (Color Wavelet Covariance or CWC) to develop a computer-aided detection method with a higher sensitivity than previous methods that were built on grey-level features or color-texture inputs. The CWC method demonstrated a 90% sensitivity and 97% specificity for polyp detection when utilized on high-resolution endoscopy video-frames[35]. In 2015, Zheng *et al*[36] created an intelligent clinical decision support tool that utilized a Bayesian fusion scheme combining color, texture and luminal contour information for the detection of bleeding lesions and luminal irregularities in endoscopic images. In 2006, Iakovidis *et al*[23] developed a pattern recognition framework that accepted standard low-resolution video input and achieved a detection accuracy of greater than 94.5%.

These early works were based on the analysis of static endoscopic images and video frames. Subsequent work focused on translating polyp detection methods to real-time video analysis. In 2016, Tajbakhsh *et al*[37] developed a CADe system that used a hybrid context-shape approach, whereby context information was used to remove non-polypoid structures from analysis

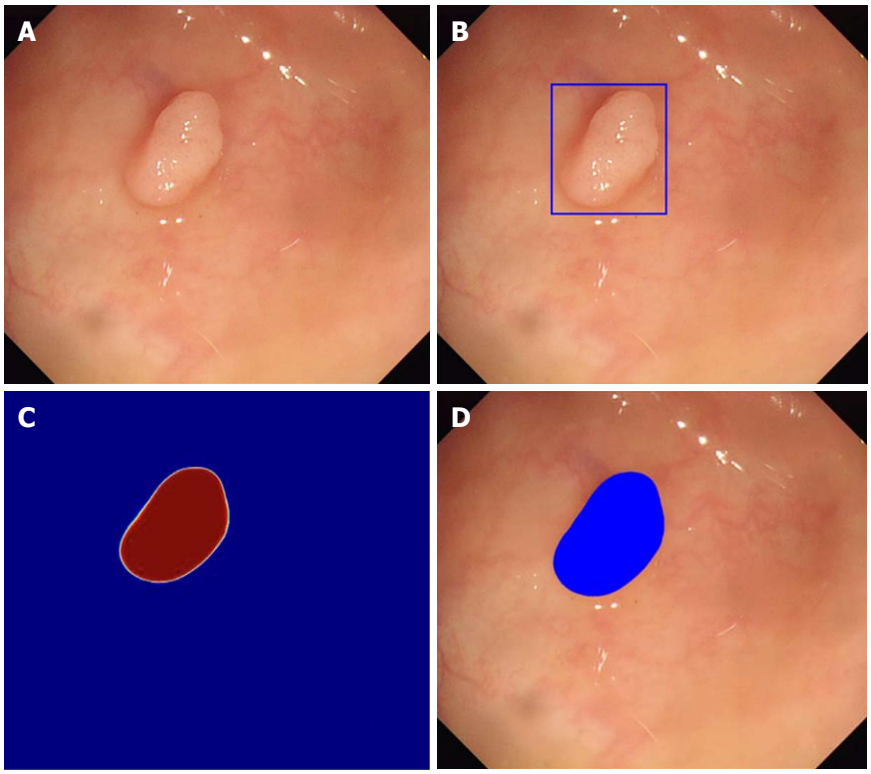

Figure 1 Automatic polyp detection by Wang *et al*[40]. A: Original image obtained during colonoscopy; B: Automatic detection by box method; C: Probability map whereby red indicates high probability of polyp and blue indicates low probability of polyp; D: Automatic detection by paint method whereby blue coloring indicates location of polyp.

and shape information was used to localize polyps. Using this system, Tajbakhsh *et al*[37] reported an 88% sensitivity for real-time polyp detection. Perhaps more importantly, this group showed a latency, defined as the time from the first appearance of a polyp in the video to the time of its first detection by the software system, of only 0.3 s. The limitation to this study was its retrospective nature and limited clinical generalizability, as the system was tested on only twenty-five unique polyps[37].

Subsequent work in optical colonoscopy focused on validating real-time polyp detection modalities on larger colonoscopy image databases. Fernández-Esparrach *et al*[38] developed a method for utilizing energy maps based on localization of polyps and their boundaries - a so-called Window Median Depth of Valleys Accumulation (WM-DOVA) energy map method. Using this method on 24 videos containing 31 different polyps, this group demonstrated a sensitivity of 70.4% and a specificity of 72.4% for detection of polyps[38]. Wang *et al*[25] developed a method that utilized edge-cross section visual features and a rule-based classification to detect "polyp edges". This Polyp-Alert software was trained on 8 full colonoscopy videos and subsequently tested on 53 randomly selected full videos. The system correctly detected 42 of 43 (97.7%) polyps on the screen and did so with very little latency. However, the software had an average of 36 false-positives per colonoscopy video analyzed[25]. False positives commonly resulted from protruding folds, the appendiceal orifice and ileocecal valve, and areas of the colon with residual fluid[25].

Both of these approaches were based on traditional machine learning methods with explicit feature specification. More recently, several groups have begun to incorporate deep learning methods into CAD systems. At Digestive Disease Week 2016, Li *et al*[39] presented perhaps the first example of a deep learning system for polyp detection. This group trained a convolutional neural network on 32305 colonoscopy images, and achieved an accuracy of 86% and sensitivity of 73% for polyp detection[39]. This study was instrumental in showing that a deep learning based computer vision program could accurately identify the presence of colorectal adenomas from colonoscopic images. Wang *et al*[40] recently presented their deep learning polyp detection software at the 2017 meeting of the World College of Gastroenterology. This system, built on a SegNet Architecture system was developed using a retrospective set of 5545 endoscopist-annotated images from colonoscopies performed in China and subsequently validated prospectively using 27461 colonoscopy images from 1235 patients (Figure 1)[40]. It is currently being testing in a single-center prospective feasibility study[40]. More recently, Misawa *et al*[41] developed a deep learning based AI system, which was trained on 105 polyp-positive and 306 polyp-negative videos. The system was tested on a separate data set, and was able to detect 94% of polyps with a false positive detection rate of 60%[41].

Deep learning methods hold the promise of increasing

diagnostic accuracy and processing large amounts of data quickly. Future work must continue to develop methods that balance a high sensitivity with low latency and improved false positive rates.

Optical biopsy

Once a lesion has been detected, computational analysis may help predict polyp histology without the need for tissue biopsy, a subfield sometimes referred to as computer-aided diagnosis (CADx). The field of optical biopsy is several decades old, but the addition of deep learning and the increasing complexity of computational analytic methods have led to recent developments in this field. The ability to diagnose small polyps such as diminutive adenomas in-situ *via* optical diagnosis may allow for adenomas to be resected and discarded rather than sent for sometimes unnecessary histopathologic examination[42]. This "resect and discard" strategy has been estimated to promise upwards of $33 million dollars in savings per year in the United States alone[43]. A similar "diagnose and disregard" strategy has been suggested for diminutive polyps such as hyperplastic polyps in the rectosigmoid colon, where non-neoplastic polyps are identified *via* optical biopsy and left in place.

Historically, advanced imaging modalities have been the main areas of investigation for optical biopsy. These include chromoendoscopy, narrow spectra technologies (Narrow Band Imaging, i-Scan, and Fujinon intelligent color enhancement), endocytoscopy, and laser-induced fluorescence spectroscopy. In Japan, chromoendoscopy, defined as the topical application of stains or pigments to improve tissue localization during endoscopy, is widely used to further characterize small polyps during standard screening and surveillance colonoscopy[44]. The Kudo pit-pattern is one of the most widely known classification systems used to classify and predict the histopathology of a given lesion[27]. Takayama *et al*[45] found that chromoendoscopy combined with magnifying endoscopy (in this case an endoscope that magnified images by a factor of 40) achieved a sensitivity for the diagnosis of dysplastic crypt foci of 100%.

Narrow band imaging (NBI) is another endoscopic optical modality where blue and green light is used to enhance the mucosal detail of a polyp in order to better characterize vessel size and pattern[46]. The NBI International Colorectal Endoscopic (NICE) classification uses color, vessels and surface pattern to differentiate between hyperplastic and adenomatous histology[47]. However, NBI, like chromoendoscopy, has been shown to have significant interobserver and intraobserver variability[48,49]. Interobserver variance generally stems from differences in expertise, while intraobserver variance is affected by experience, personal well-being, levels of distraction, and stress[50].

The existence of inter- and intraobserver variance and steep learning curves have likely contributed to the slow pace of adoption of these techniques beyond specialized medical centers. The use of CADx modalities may allow for decreased variance amongst providers, increased standardization, and, perhaps most importantly, more widespread adoption by non-experts in the field[51]. Following a similar developmental trajectory as the field of automatic polyp detection (CADe), the first CADx systems were developed using static colonoscopic images and image series. In 2010, Tischendorf *et al*[50] developed a computer-based analysis algorithm for colorectal polyps using magnifying NBI, with a subsequent automatic classification scheme using machine learning. This system achieved a sensitivity of 90% compared to a human sensitivity of 93.8% when using the same database of 209 polyp images (with corresponding biopsy)[50]. In a follow up study on smaller polyps in 2011, Gross *et al*[52] reported a 95% sensitivity in the computer based-algorithm group compared to a 93.4% sensitivity in a human expert group and 86.0% sensitivity in a human non-expert group. Both of these studies were limited, however, in that they involved off-site computer analysis of static images.

Subsequent work by Takemura *et al*[53] and Kominami *et al*[54] translated machine learning methods to real-time clinical use. Takemura *et al*[53] developed a custom software (HuPAS version 3.1, Hiroshima University, Hiroshima, Japan) that utilized a "bag-of-features" representation of NBI images and hierarchical k-means clustering of local features. In an initial study using static images, this group showed a sensitivity of 97.8%, specificity of 97.9%, and accuracy of 97.8% for diagnosis of neoplastic lesions. Diagnostic concordance between the computer-aided classification system and the two experienced endoscopists was 98.7%[53]. In a follow up study, this same group developed a real-time software to automatically recognize polyps, and then analyze and classify them as neoplastic or non-neoplastic[54]. This approach yielded a sensitivity 93.0%, a specificity of 93.3%, accuracy of 93.2%, and concordance between the image recognition software and human endoscopic diagnosis of 97.5%[54]. Though this was a study on just 41 patients with 118 colorectal lesions, it was the first of its kind to demonstrate that CADx in real-time is feasible and comparable to human diagnostics using magnified NBI.

Several other advanced endoscopy imaging modalities have similarly benefited from advances in CAD. Endocytoscopy (EC) is an ultra-high magnification technique that provides images of surface epithelial structures at cellular resolution[55]. In 2015, Mori *et al*[56] developed the EC-CAD system, a machine-learning CAD system that uses nuclear segmentation and feature extraction to predict pathologic classification (*i.e.*, non-neoplastic, adenoma and cancer, unable to diagnose). In a pilot study consisting of images from 176 polyps and 152 patients, the system showed a sensitivity of 92.0% and specificity of 79.5% compared to a sensitivity of 92.7% and specificity of 91% by expert endoscopists[56]. Misawa *et al*[57] then developed an EC system that utilized NBI rather than dye staining, and developed

Table 1 Summary of clinical studies involving computer-aided detection and computer-aided diagnosis in real time (during live colonoscopy or video recording)

Reference	Year	Type of CAD	Endoscopic Modality/ Input	Processing Modality	Study Design	Sensitivity	Specificity	Accuracy	Latency	Notes
Wang *et al*[25]	2015	CADe	White-Light Endoscopy	Polyp-Edge Detection Algorithm and Shot Extraction	Retrospective	-	-	97.7%[1]	0.02 s	36 false-positives per video
Fernández-Esparrach *et al*[38]	2016	CADe	White-Light Endoscopy	WM-DOVA	Retrospective	70.4%[2]	72.4%[2]	-	-	Accuracy and latency reported for this study
Tajbakhsh *et al*[37]	2016	CADe	White-Light Endoscopy	Hybrid Context-Shape Extractor, Edge Mapping	Retrospective	88.0%[2] for CVC-ColonDB 48.0% for ASU-Mayo	-	-	0.3 s	0.1 False positives per frame
Wang *et al*[40]	2017	CADe	White-Light Endoscopy	Deep learning, built on SegNet Architecture	Retrospective	91.6%[2]	96.3%[2]	100.0%[1]	0.04 s	
Misawa *et al*[41]	2018	CADe	White-Light Endoscopy	Deep learning, built on a DCNN	Retrospective	90.0%[2]	63.3%[2]	76.5%[1]	-	
Kominami *et al*[54]	2016	CADx	Magnifying NBI	Bag of features representation, SVM output	Prospective	93.0%[3]	93.3%[3]	93.2%[4]	-	97.5% concordance between automatic diagnosis and endoscopic diagnosis
Komeda *et al*[75]	2017	CADx	A mix of White-Light Endoscopy, NBI and Chromoendoscopy	Deep learning, built on a CNN	Retrospective	-	-	75.1%[5]		
Byrne *et al*[59]	2017	CADx	White-Light Endoscopy and NBI	Deep learning, built on a DCNN	Retrospective	98.0%[3,6]	83.0% [3,6]	94.0%[4]	0.05 s	For 19 polyps the system was unable to reach a credibility score threshold of ⩾ 50%
Mori *et al*[58]	2017	CADx	Endocytoscopy and NBI	Texture analysis, automatic vessel extraction, SVM output	Prospective	97.0%[3]	67.0%[3]	83.0%[4]		

[1]Tracking accuracy or detection rate, defined as number of polyps detected by software/total number of polyps present in videos; [2]Sensitivity and specificity for the detection of polyps; [3]Sensitivity and specificity for the diagnosis of neoplastic versus non-neoplastic lesions; [4]Accuracy defined as differentiation of adenomas from non-neoplastic lesions; [5]Accuracy of a 10-hold cross-validation is 0.751, where the accuracy is the ratio of the number of correct answers over the number of all the answers produced by the CNN; [6]Sensitivity and specificity in this case are calculated based on histology of 106/125 polyps in the video test set. For the remaining 19 polyps the system was unable to reach a credibility score threshold of ⩾ 50%; CADx: Computer-aided diagnosis; CADe: Computer-aided detection; SVM: Support vector machine; WM-DOVA: Window median depth of valleys accumulation; NBI: Narrow band imaging; CNN: Convolution neural network; DCNN: Deep convolution neural network.

a machine learning CAD system referred to as AI-assisted endocytoscopy to analyze EC-NBI images produced by this instrument. This system uses texture analysis and automatic vessel extraction, which is analyzed by a support vector machine and outputs a 2-class diagnosis (non-neoplastic or neoplastic) in real time with a 0.3 second latency[57]. In a recent validation study using 100 randomly selected images of colorectal lesions, the AI-assisted endocytoscopy achieved a sensitivity of 85% for the diagnosis of adenomatous polyps, a specificity of 98%, and an accuracy of 90% (Figure 2)[57]. Mori *et al*[58] recently reported on the results of a prospective study further studying the AI-assisted endocytoscopy system. This single-center study in Yokohama, Japan involved 88 men and women with 126 polyps. The system demonstrated a sensitivity of 97%, specificity of 67%, accuracy of 83%, and positive and negative predictive values of 78% and 95% with extremely low latency.

With the advent of deep learning, real-time optical analysis of polyps may be possible using white-light alone, without the aid of advanced, endoscopic imaging modalities such as chromoendoscopy, NBI, endocytoscopy or laser-induced autofluorescence spectroscopy (Table 1). In 2017, Byrne *et al*[59] developed and trained an AI deep convolution neural network (DCNN) on both unaltered white-light and NBI colonoscopy video recordings (Figure 3). The network was tested on 125 videos of consecutively encountered diminutive polyps, and achieved a 94% accuracy of classification for 106 of the 125 videos (for 19 polyps the system was unable to reach a credibility score threshold of ⩾ 50%). For these 106 polyp videos, the system was able to detect adenomas with a sensitivity of 98% and a specificity of 83%[59]. Furthermore, the model worked in quasi

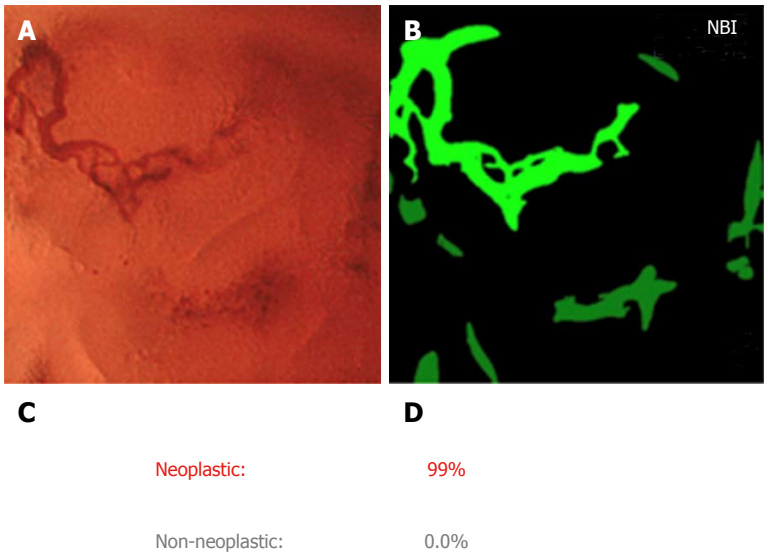

Figure 2 Output from artifical intelligence-assisted endocytoscopy system by Misawa *et al*[57]. A: Input from endocytoscopy with narrow band imaging; B: Extracted vessel image whereby green light represents extracted vessel image; C: System outputs diagnosis of neoplastic or non-neoplastic; D: Probability of diagnosis calculated by support vector machine classifier. NBI: narrow band imaging.

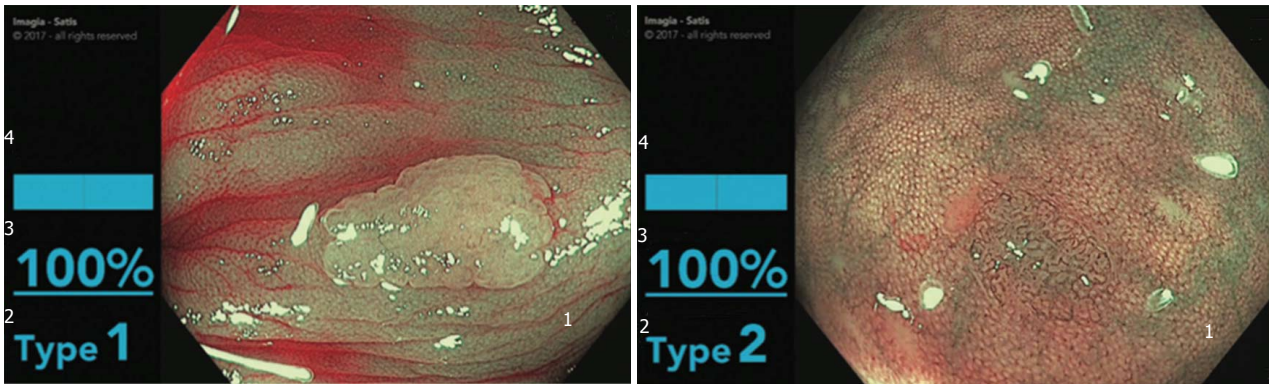

Figure 3 Automatic polyp classification system. 1: Input from narrow band imaging; 2: Computer diagnosis of NICE type 1 (hyperplastic) *vs* NICE type 2 (adenomatous); 3: Probability of diagnosis; 4: Computer determined confidence in diagnosis probability. Obtained with permission from Dr. Michael Byrne (Division of Gastroenterology at Vancouver General Hospital and UBC).

real-time with a delay of just 50ms per frame[59]. This work is also significant in that it achieved the diagnostic thresholds set forth by the Preservation and Incorporation of Valuable Endoscopic Innovations initiative set forth by the American Society for Gastrointestinal Endoscopy. This initiative states that in order for optical biopsy to reach an acceptable threshold to support the "resect and discard" or "diagnose and leave strategies", there must be ⩾ 90 % agreement for post-polypectomy surveillance intervals for the "resect and discard" strategy, and ⩾ 90% negative predictive value (NPV) for adenomatous histology for the "diagnose and leave" strategy[60].

Future work in this field must by necessity continue to refine sensitivity, specificity, accuracy, PPV and NPV of real-time optical classification methods while working to combine CADe and CADx modalities.

EGD and capsule endoscopy

Compared to applications in colonic polyp detection and classification, there have been fewer applications of deep learning in other areas of gastroenterology. However, the existing applications deserve recognition for their novelty and promise. One notable application is the use of CNN to diagnose *Helicobacter pylori* (*H. pylori*) infection by analysis of gastrointestinal endoscopy images[61]. *H. pylori* is strongly linked to gastritis, gastroduodenal ulcers, and gastric cancer, so prompt and effective diagnosis and eradication of this infection is important[62]. Existing diagnostic methods for *H. pylori* infection including urea breath test and stool antibody testing are highly sensitive and specific, but can be logistically difficult to schedule and process. In this study by Itoh *et al*[61], researchers developed a CNN trained on 149 gastrointestinal endoscopy images and tested on 30 images. The resulting sensitivity and specificity of the CNN for detection of *H. pylori* infection was 86.7% and 86.7% with an AUC of 0.956, which is significantly better than the performance of human

endoscopists[61,63].

Deep learning with convolutional neural networks has also been applied toward endoscopic detection of gastric cancer. In 2018, Hirasawa *et al*[64] constructed a CNN-based diagnostic system which was trained on more than 13000 endoscopic images of gastric cancer. The system was then tested on 2296 images and in just 47 s, correctly diagnosed 71 of 79 gastric cancer lesions for a sensitivity of 92.2%. However, the positive predictive value was only 30.6% as a result of several false positives. This study highlights the potential of deep learning systems to accurately and quickly detect cancer. One can expect that with more training data and improved computational hardware, both the accuracy and analysis speed will only improve.

Several studies have demonstrated applications of deep learning in wireless capsule endoscopy (WCE). A major challenge of WCE for busy clinicians is the time-intensive nature of reviewing the images. However, deep learning offers a solution to both problems - it provides quick analysis of large-volume data and uses representation learning to extract its own features from unstructured images. Capsule endoscopy can be used to identify mucosal changes characteristic of celiac disease, but visual diagnosis has low sensitivity[65]. Zhou *et al*[66] trained a CNN using capsule endoscopy clips from patients with and without celiac disease, and reported a sensitivity and specificity of 100% for distinguishing celiac disease patients from controls in a testing set of ten patients. Further, the study found that the evaluation confidence of the system was correlated to the severity of the small bowel mucosal lesions.

Deep learning in WCE has also been shown to be effective in detection of small bowel bleeding. The first several studies to demonstrate computer-aided diagnosis of bleeding from WCE images used RGB and color texture feature extraction to help distinguish areas of bleeding from non-bleeding[67-69]. More recent studies, including by Xiao *et al*[70] and Hassan *et al*[71], used deep learning and feature learning to achieve sensitivities and specificities as high as 99% for detection of gastrointestinal (GI) bleeding. Further research and validation of these models may allow for a fast and highly effective means of detecting GI bleeding, with less work for the interpreting physician.

Similar image processing methods have even been applied to infectious disease detection in WCE. He *et al*[72] developed a CNN to detect hookworms, a cause of chronic infection affecting an estimated 740 million people in areas of poverty[72,73]. Hookworm infections cause chronic intestinal blood loss resulting in iron-deficiency anemia and hypoalbuminemia, and are especially dangerous in children and women of reproductive age due to its adverse effects in pregnancy[73]. In this study, He *et al*[72] tested a CNN on 440000 WCE images, and developed a system with high sensitivity and accuracy for hookworm detection. Applications of deep learning to hookworm detection and diagnosis of other infectious disease in the gastrointestinal tract may provide significant clinical value worldwide, especially in low-resource settings, if the cost of capsule endoscopy can be substantially lowered.

VALUE OF AI IN GASTROENTEROLOGY

As seen from the examples of CAD in gastroenterology described above, there are numerous potential benefits to the development and integration of CADx and CADe systems in everyday practice. In general, using artificial intelligence as an adjunct to standard practices within GI has the potential to improve the speed and accuracy of diagnostic testing while aiming to offload human providers from time-intensive tasks. In addition, CAD systems are not subject to some of the pitfalls of human-based diagnosis such as inter- and intraobserver variance and fatigue.

We are entering an age where CAD tools, applied in academic research settings, can at least match, and sometimes exceed human performance for the detection or diagnosis of endoscopic findings in a variety of modalities within gastroenterology[74]. Current prospective studies generally utilize CADe and CADx as a "second reader", where information derived from CAD systems serve to support the endoscopist's diagnosis. When used in this fashion, CAD modalities can assist human providers with time-intensive, data-rich tasks. Several studies have shown that human observation of standard colonoscopy video by either nurses or trainees may increase an individual provider's polyp and adenoma detection rates[18-20]. The CADe systems described above, when integrated into daily practice, may offer a reliable, and ever-vigilant "second observer," which could provide particular value for junior gastroenterologists or endoscopists with low adenoma detection rates[38].

FUTURE DIRECTIONS

As applications of artificial intelligence in gastroenterology continue to increase, there are several areas of interest that we believe will hold significant value in the future. First, the technical integration of artificial intelligence systems with existing electronic medical records (EMR) and endoscopy platforms will be important to optimize clinical workflow. New AI applications must be able to easily "read in" data from a video input or EMR, allowing the systems to use the data for training and real time decision support. A seamless integration in the endoscopy suite will be crucially important in encouraging clinician adoption.

Second, AI systems must continue to expand their library of clinical applications. As discussed in this review, there are several promising studies that demonstrate how AI can improve our performance on clinical tasks such as polyp identification, detection of small bowel bleeding, and even endoscopic recognition of *H. pylori* and hookworm infection. Future research should continue to identify new clinical tasks that are well-suited to machine learning tools. For example, analysis

of WCE for diagnosis of celiac disease suggests that similar methodologies may be effective in diagnosing inflammatory bowel disease or providing more objective scoring of mucosal IBD activity during treatment. From a performance perspective, AI systems in clinical endoscopy will need to eliminate latency in detection to facilitate the real-world applicability of these technologies.

Third, further research is needed to understand the ethical and pragmatic considerations involved in the integration of artificial intelligence tools in gastroenterology practice. To begin, what is the general physician sentiment toward artificial intelligence? Is AI considered a threat or a tool by the gastroenterology community? A deeper understanding of the end-user is crucial to dictating how these tools should be designed and deployed. If AI tools are accepted by physicians, how will we train individuals to use these technologies effectively? Will the learning curve for using these systems be prohibitive? If so, further research is needed to describe the most effective training methods for physician practices beginning to adopt AI technology. In today's technology-driven environment, it is clear that data security is of utmost importance, especially when dealing with protected health information. As the number of AI tools increases, so too should our efforts toward designing security systems and encryption methods to safeguard clinical data. Finally, the clinical community needs to decide on standards for approval and regulation of new AI technologies, including potential implications for legal matters including medical malpractice.

CONCLUSION

Artificial intelligence is an exciting new frontier for clinical gastroenterology. Artificial intelligence techniques like deep learning allow for expedited processing of large-volume unstructured data, and in doing so enable machines to assist clinicians in important tasks, such as polyp detection and classification. Several research groups have shown how artificial intelligence techniques can provide significant clinical value in gastroenterology, and the number of applications will likely continue to expand as computational power and algorithms improve. As the field evolves, a watchful eye is needed to ensure that security, regulation, and ethical standards are upheld.

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MINIREVIEWS

Screening and surveillance methods for dysplasia in inflammatory bowel disease patients: Where do we stand?

Michail Galanopoulos, Emmanouela Tsoukali, Filippos Gkeros, Marina Vraka, Georgios Karampekos, Gerassimos J Matzaris

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Abstract

Patients with long-standing ulcerative colitis (UC) and extensive Crohn's colitis (CC) are at increased risk for dysplasia and colorectal cancer (CRC). Several studies have shown that UC extending proximal to the rectum, CC involving at least 1/3 of the colon, co-existence of primary sclerosing cholangitis, undetermined or unclassified colitis, family history of CRC and young age at diagnosis appear to be independent risk factors for inflammatory bowel disease (IBD) - related CRC. Therefore, screening and surveillance for CRC in IBD patients is highly recommended by international and national guidelines, whilst colonoscopy remains the unequivocal tool in order to detect potentially resectable dysplastic lesions or CRC at an early stage. Although the importance of screening and surveillance is widely proven, there is a controversy regarding the time of the first colonoscopy and the criteria of who should undergo surveillance. In addition, there are different recommendations among scientific societies concerning which endoscopic method is more efficient to detect dysplasia early, as well as the terminology for reporting visible lesions and the management of those lesions. This article concisely presents the main endoscopic methods and techniques performed for detecting dysplasia and CRC surveillance in patients with IBD focusing on their evidence-based accuracy and efficiency, as well as their cost-effectiveness. Finally, newer methods are mentioned, highlighting their applicability in daily endoscopic practice.

Key words: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Dysplasia; Colorectal cancer;

Endoscopy; Chromoendoscopy; Surveillance

Core tip: There is an established association between inflammatory bowel disease (IBD) and colorectal cancer (CRC). Therefore, surveillance of these patients for CRC is crucial and recommended by international guidelines. In this review we present the main endoscopic methods and techniques performed for detecting dysplasia and CRC surveillance in patients with IBD, highlighting chromoendoscopy with targeted biopsies as the gold standard method. Finally, newer methods are mentioned, examining their applicability in daily endoscopic practice.

Galanopoulos M, Tsoukali E, Gkeros F, Vraka M, Karampekos G, Matzaris GJ. Screening and surveillance methods for dysplasia in inflammatory bowel disease patients: Where do we stand? *World J Gastrointest Endosc* 2018; 10(10): 250-258 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i10/250.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i10.250

INTRODUCTION

Patients with inflammatory bowel disease (IBD) have a higher incidence of colorectal cancer (CRC) compared to the general population, even though only 1% of all CRC cases are attributed to IBD[1]. The incidence rates reported by Eaden *et al*[2,3], as well as the St. Mark's group in the United Kingdom, showed comparable cumulative probabilities of CRC and dysplasia, approximately 8% and 18% by 20 and 30 years of ongoing disease, respectively. According to Bernstein *et al*[4], both Crohn's disease (CD) and ulcerative colitis (UC) patients face an increased risk for colon cancer [relative risk (RR) 2.64 and 2.75, respectively]. Factors linked to an increased incidence of CRC include: prolonged duration of colitis, extensive colonic involvement, presence of primary sclerosing cholangitis (PSC), positive family history for CRC and, according to some studies, earlier onset and severity of inflammation[1,5-9] (Table 1). Oncogenesis in IBD has been well described as a result of chronic inflammation, leading *via* low- and high-grade dysplasia, finally, to CRC[1,10-24] (Figure 1). Dysplasia is divided into two categories: (1) Endoscopically visible dysplastic lesion, *e.g*., polyps, which are detected by targeted biopsies or resection of endoluminal masses; and (2) Endoscopically invisible dysplasia which is detected by blinded random biopsies on endoscopically normal lumen and is characterized as the most dependable marker for increased CRC risk in IBD patients[1,25,26]. The resection of visible dysplasia, in combination with a rigorous follow-up program has been shown to be a safe alternative to colectomy for select patients[27,28]. On the other hand, a study by Picco *et al*[29] showed that the detection rate for dysplasia with the use of white light endoscopy (WLE) was 9.3%, compared to 21.3% when using both WLE and dye-spray chromoendoscopy (DCE). This demonstrates the need for the implementation of a surveillance strategy in IBD patients based on better techniques and technologies, aiming at reducing the prevalence of metachronous lesions during follow-up. However, uncertainties exist regarding the soundness of this approach on preventing CRC. In a recent systematic review, people undergoing periodic surveillance for CRC were not found to have lower mortality when compared to those under no surveillance (RR 0.81, 95%CI: 0.17 to 3.83)[30,31].

Nevertheless, the current recommendations favor DCE with targeted biopsies of any identified lesions[1,26,32,33] (Figure 2). Whenever DCE is not available, WLE with random, four quadrant biopsies every 10 cm should be performed with additional targeted biopsies from visible lesions. Other endoscopic modalities, like narrow band imaging (NBI), i-SCAN and autofluorescence imaging, did not achieve superior dysplasia detection rates when compared to standard (SD)- or high-definition (HD) WLE in randomized controlled trials[34-39].

Taking all these into consideration, the aim of our review is the brief and up-to-date description of the basic screening endoscopic modalities, as well as their efficacy and accuracy for CRC surveillance in IBD patients.

STANDARD-DEFINITION AND HIGH-DEFINITION WHITE LIGHT ENDOSCOPY

The standard method in CRC surveillance has until recently been SD colonoscopy, with the use of targeted as well as random quadrant biopsies every 10 cm, which amounts to at least 33 biopsies to achieve 90% confidence of detecting dysplasia. However, this technique ultimately inspects less than 1% of the mucosal surface of the colon[40]. According to a Dutch study examining long-standing UC, the overall rate of dysplasia detection with SD colonoscopy was 0.19[36]. With the advent of HD endoscopes and monitors, the endoscopist is able to better identify dysplastic lesions. A study by Subramanian *et al*[41] comparing SD to HD colonoscopy for dysplasia screening in UC, reported a three-fold increase in the yield of the HD endoscope combined with targeted, as well as random biopsies, especially in the right colon. Based on the aforementioned study, the SCENIC consensus statement by American Society for Gastrointestinal Endoscopy (ASGE) favors HD- over SD-WLE when implementing a surveillance program, even though the HD cost remains a limitation[33]. This improvement in detection of dysplastic lesions by HD-WLE and targeted-biopsy sampling changed the therapeutic considerations regarding colectomy, favoring more conservative approaches[41]. Furthermore, it was pointed out that the increased turnout with HD colonoscopy is probably a true reflection of the increased yield of this technique[41]. Nevertheless, based on the same study, neither

Table 1 Colorectal cancer risk factors and surveillance

High risk factors
Annual surveillance
Extensive colonic involvement (pancolitis, CD with > 50% colonic involvement)
Moderate-severe endoscopic or histological active inflammation sustained over time
PSC
Disease commencing at age < 15 yr
Family history of sporadic CRC in a first-degree relative < 50 yr
Presence of a stricture or dysplasia detected during the previous 5 yr
High risk factors in case of pouch existence
Dysplasia
Previous CRC
Type C mucosa
Intermediate risk
Every three years surveillance
Mild or moderate endoscopic/histological inflammation sustained over time
Family history of sporadic CRC in a first-degree relative older than 50 yr
Presence of inflammatory polyps
Low risk factors
Every five years surveillance
Pancolitis without inflammation
Left-sided UC or CD with < 50% colonic involvement

CRC: Colorectal cancer; CD: Crohn's disease; PSC: Primary sclerosing cholangitis; UC: Ulcerative colitis.

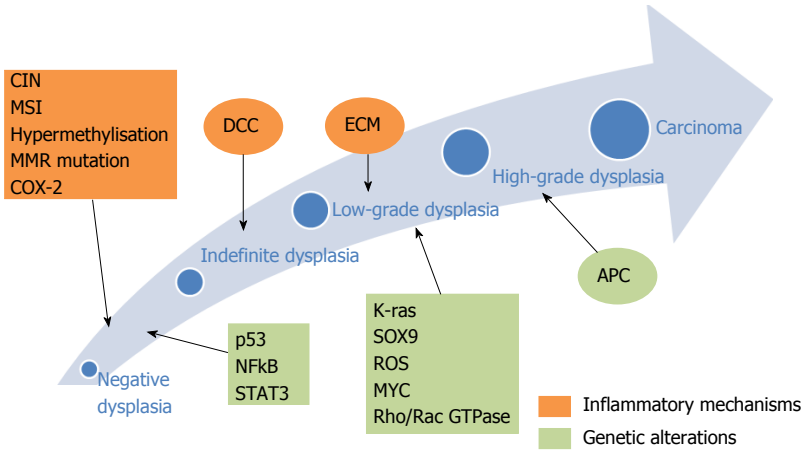

Figure 1 Colitis-associated colon cancer sequelae. COX-2: Cyclooxygenase-2; ECM: Extra-cellular matrix; MMR: Mismatch repair mutation; DCC: Deleted in colorectal carcinoma; APC: Adenomatous polyposis coli; MSI: Microsatellite instability; CIN: Chromosomal instability; ROS: Reactive oxygen species; K-ras: Kirsten rat sarcoma 2 viral oncogene homolog; p53: Tumor protein p53; NF-kB: Nuclear factor kappa-light-chain-enhancer of activated B cells; STAT3: Signal transducer and activator of transcription 3; *SOX9*: SRY-box 9 gene.

significant change in the detection of lesions with high grade dysplasia nor early carcinoma or flat lesions were observed.

On the contrary, the study by van den Broek *et al*[36] showed no substantial difference in clinical outcomes for patients, in whom low grade dysplasia was revealed using random biopsies, thus advocating the use of improved visualization through advanced techniques[36,41].

Concluding, even though the most widespread technique for dysplasia surveillance in IBD until recently has been the WLE with random biopsies, it is arduous and protracted[40]. Furthermore, the diagnostic reliability of WLE is challenged in a recent review, which found a sensitivity of 76%[42]. Therefore, this method's practicability has been clearly questioned and the research for the development of diagnostic modalities is supported[43].

RANDOM BIOPSIES

Four quadrant biopsies every 10 cm throughout the colon has been the gold standard of IBD surveillance for more than 30 years. This approach originates from the theory of "flat dysplasia", which suggests that dysplasia is difficult to visualize in colitis-affected mucosa[40,44]. Random biopsy only samples less than 1% of the luminal mucosa; has a subpar detection rate (< 2 per 1000 biopsies taken) and when used in conjunction with advanced endoscopic techniques, it does not affect clinical decisions[44]. A large retrospective analysis by van den Broek *et al*[36] reviewing 1010 colonoscopies during 10 years of surveillance stated that the result of random biopsy surveillance was poor, and neoplasia was detected only in four patients with random biopsies.

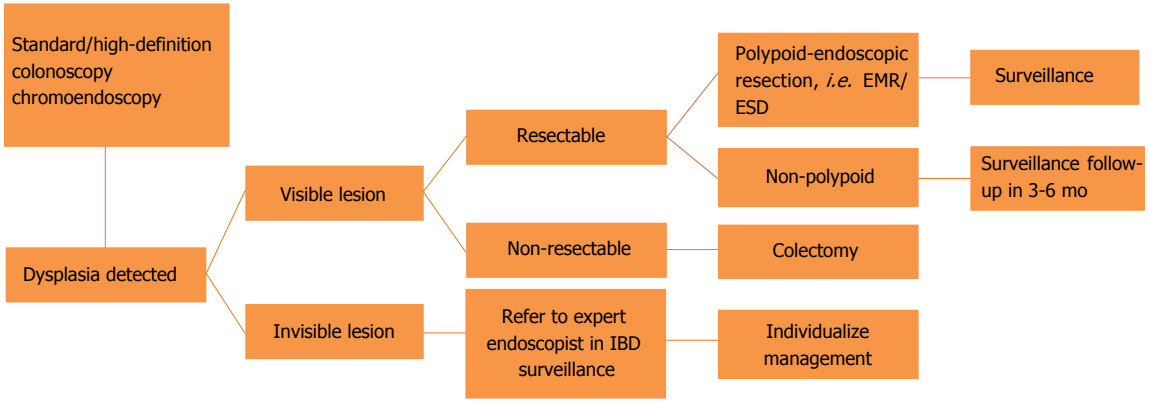

Figure 2 Algorithm for colorectal cancer surveillance in inflammatory bowel disease patients. IBD: Inflammatory bowel disease; EMR:

Additionally, neoplasia was macroscopically visible in 94% of colonoscopies[43,44]. Current guidelines by British Society of Gastroenterology (BSG) and ASGE advocate the use of DCE without the need for random biopsies; however, it is suggested that random biopsies be acquired during HD colonoscopy, if DCE is not available or technically feasible[26]. Random biopsies remain a reasonable alternative if there are conditions that lower the diagnostic yield, such as inflammation, pseudo-polyposis, poor preparation or a poorly visualised mucosa[26,45].

DYE-SPRAY CHROMOENDOSCOPY

Several studies have proven the efficacy of DCE in the detection of dysplasia in patients with IBD. DCE may reduce the need for random biopsies and may allow prolonged surveillance-interval, leading to cost reduction, as well as an increase the detection sensitivity of dysplastic lesions per examination[46].

This technique helps to augment dysplasia detection by topical application of dye on the colonic mucosa during colonoscopy. Areas that are macroscopically elevated or depressed, friable, obscure in vasculature, and with a villous or nodular pattern, can be detected more easily and biopsies can be taken. The most common dyes that in use are methylene blue and indigo carmine[47]. Dye solution can be sprayed by catheter, or flushing pumps, or administered as controlled release tablets, taken with bowel preparation[48]. When performing DCE, it is important to avoid active disease and to have adequate bowel preparation. Paris classification seems to be the standard method to describe any visible lesion, and targeted biopsies should be taken from any suspected area. If the lesion is well-defined, *en-bloc* endoscopic resection should be performed and biopsies should be taken from the adjacent mucosa. In case the lesion is unresectable, the endoscopist should take biopsies and tattoo the area.

Kiesslich *et al*[49] were the pioneers conducting a large randomized study with 263 individuals with long-standing UC. In the DCE-group, there was a statistically important correlation between the endoscopic estimation of the level and extent of inflammation of the colon ($P = 0.0002$) and the histology report, when compared to WLE ($P = 0.0002$) (89% *vs* 52% $P < 0.0001$). Additionally, more targeted biopsies were possible and these biopsies detected significantly more intraepithelial neoplasia (INs) when performing DCE (32 *vs* 10 $P = 0.003$). In a well-designed prospective study, Hurlstone *et al*[50] examined 350 patients with long-standing UC undergoing colonoscopy surveillance with high-magnification chromoscopic colonoscopy (HMCC) comparing the data with matched controls who had undergone WLE. The HMCC-group found significantly more intraepithelial neoplasias compared to controls (69 *vs* 24 $P < 0.0001$), and only 0.16% of the random biopsies have shown INs *vs* 8% from the targeted biopsies. Furthermore, Marion *et al*[51] studied 102 patients with IBD who underwent in a single examination, initially a WLE with random biopsies, then a targeted biopsy protocol and finally, DCE with targeted biopsies. They reported that biopsies obtained by the latter method detected significantly more dysplastic lesions than random biopsies with WLE ($P = 0.001$), as well as more than WLE with targeted biopsies ($P = 0.057$).

According to Subramanian *et al*[52] meta-analysis study including a large number of patients, the overall difference between the DCE and WLE in the detection of dysplasia was approximately 7% (95%CI: 3.2-11.3), with the former showing a better rate of dysplastic lesions detected by targeted biopsies, as well as a higher rate of detection for flat lesions at 27% (95%CI: 11.2-41.9). On the other hand, the omission of random biopsies during chromoendoscopy will result in missing endoscopically invisible dysplasia. According to another meta-analysis, Wu *et al*[47] reported that DCE offers median to good sensitivity and a very good accuracy for revealing lesions with dysplasia in UC after analyzing six randomized controlled trials with 1.528 patients. The pooled sensitivity and specificity for DCE with targeted biopsies were 83.3% (95%CI: 35.9%-99.6%) and 91.3% (95%CI: 43.8%-100%) respectively, with conventional colonoscopy demonstrating lower rates. Soetikno *et al*[53] in a well-designed meta-analysis with 665 patients with IBD, demonstrated that the pooled positive percentage of DCE over WLE for the

discernment of dysplasia of any grade per patient was 7% (95%CI: 3.3%-10.3%), as well as the possibility to miss dysplasia was 93% lower by performing chromoendoscopy with targeted biopsies (the pooled OR was 0.07; 95%CI: 0.03-0.21). Interestingly, according to a prospective study, Marion *et al*[54] showed that apart from the superiority of DCE when compared to WLE, a DCE examination without any findings was considered as the most probable indicator for a patient without any level of dysplasia, whereas an exam with any sort of findings was positively correlated with earlier referral for colectomy(hazard ratio, 12.1; 95%CI: 3.2-46.2).

Nevertheless, lately, the advantages of DCE over WLE have come into question, as well as the practicability of applying DCE in a real world setting of hectic endoscopy units. Trying to highlight this problem, a large retrospective non-randomized trial with different types of endoscopes used over time showed that the performance of DCE for IBD surveillance did not increase detection of dysplasia compared with WLE with targeted and random biopsies (11% *vs* 10%, P = 0.80)[55]. The number of lesions with neoplasia was also comparable between the DCE and WLE groups (P = 0.30).

As a final point, an interesting cohort analysis regarding cost-effectiveness was conducted by Konijeti *et al*[56], that compared DCE with targeted biopsies to WLE with random biopsies at various surveillance intervals and no surveillance at all. Chromoendoscopy was more efficient in the detection of dysplasia and cost more effective when compared with WLE. DCE exhibited cost-effectiveness relative to patients not undergoing any surveillance when performed at intervals bigger than 7 years.

VIRTUAL CHROMOENDOSCOPY SYSTEMS

Technological progression has enabled newer modalities based on older technologies for mucosal assessment. Given the success rate of chromoendoscopy in assessing colonic mucosa, the newest endoscopic devices have filters and algorithms that enable the mimicry of chromoendoscopy by filtering some light wavelengths to better underline abnormal tissues, while foregoing the limitating factors of chromoendoscopy. Dye-less or virtual chromoendoscopy has been developed by three major manufacturers for their respective endoscopic platforms. NBI filters out red and green light bands while contributing more to blue light bands at the 415 nm wavelength. This modality allows for visualization of the vasculature of the upper mucosa and different patterns correlating to different degrees of mucosal inflammation and predicts disease relapse. In the same vein, the i-Scan system provides detailed analysis, which is based on principles similar to NBI, with parameters allowing the processing of light through specific algorithms. This process provides detailed analysis based on vessel, mucosal pattern or surface architecture (i-Scan v, i-Scan p and i-Scan SE, respectively), with each analysis being readily available during endoscopy[57].

It has been reported that the yield of surveillance can be improved by the use of autofluorescence with NBI[36]. According to a study by Dekker *et al*[34], 52 suspicious lesions were detected in 17 patients using NBI, in comparison to 28 lesions in 13 patients detected with WLE. The pathology of the targeted biopsies revealed neoplasia in 11 patients; neoplasia was detected in 4 patients with both those modalities, in another 4 neoplasia was detected only by use of NBI, and in 3 patients neoplasia was discovered only by WLE, demonstrating non-statistical significance (P = 0.705) for those three modalities. In addition to targeted biopsies, 1522 random biopsies were taken in the context of surveillance. The pathology of these biopsies added only 1 patient with dysplasia that remained undetected by both NBI and WLE[34]. A prospective multicenter study by Leifeld *et al*[35] concluded that the two techniques did not differ in the statistical probability of lesion detection, but NBI required less withdrawal time (23 min *vs* 13 min, respectively P < 0.001) and biopsy samples (11.9 *vs* 38.6 biopsy specimens, respectively P < 0.001), when compared to WLE. These results are backed by a randomized study by Ignjatovic *et al*[38], which revealed no difference between the two modalities, regarding the detection of dysplasia. Overall, NBI does not seem to achieve a significantly higher probability of dysplasia detection, compared to conventional HD colonoscopy.

In the same vein Pellisé *et al*[58] conducted a prospective, randomized, controlled trial comparing NBI to DCE in 60 patients with long-standing inactive colonic IBD. The authors reported that NBI was less time-consuming (P < 0.01), equally effective in detecting dysplastic lesions and had a lower rate of false-positive biopsies (P = 0.001). However, NBI missed suspicious lesions with a non-significant miss rate difference of 30.7% (95%CI: -64.2% to 2.8%). As a result, the study surmised that NBI should not be standard modality for surveillance.

In general, NBI did not substantially differ from DCE, a claim that needs to be verified by more robust data pooling. A possible explanation is that NBI can more readily identify non-neoplastic inflammatory lesions than WLE, which were not pooled in the meta-analysis comparing those techniques[37]. Furthermore, the iterations of NBI are different in those studies, with older generation systems producing suboptimal, darker images[37,42]. Based on the current level of evidence, DCE remains the standard technique for the surveillance in IBD patients.

A large randomized prospective study comparing HD-iScan and HD-WLE to standard DCE did not prove inferiority for those two techniques, with the question of whether i-Scan and HD-WLE will benefit an expert endoscopist remaining unanswered[39]. The authors conclude that they need more multiple-operator studies

to assess the helpful potential of these new techniques.

CONFOCAL LASER ENDOMICROSCOPY

One of the newest tools in the arsenal of mucosal assessment for dysplasia is the confocal laser endomicroscopy (CLE) that allows *in vivo* microscopic inspection and evaluations of a targeted lesion in the gastrointestinal tract. This new and evolving method is used in conjunction with HD-WLE and DCE to further define suspicious lesions and assess their histology, by performing real time analysis of the cellular and subcellular characteristics at high resolution. The technique is based on fluorescence, which requires the addition of fluorescein intravenously or topically, but results in high quality images, comparable to traditional histology.

Kiesslich *et al*[59] first used the endoscope-based integrated system in 2007 to demonstrate that neoplastic changes in patients with UC can be identified with very good accuracy (94.7% sensitivity, 98.3% specificity, 97.8% accuracy), compared with standard surveillance endoscopy. Overall, 4.75-fold more neoplastic areas could be identified than with a WLE (P = 0.005), while requiring only half the number of biopsy samples (median 21.2 in the CLE group *vs* 42.2 undergoing surveillance endoscopy), despite the fact that CLE prolonged colonoscopy by an additional 10 min on average (P > 0.05). A recent study by Wanders *et al*[60], on the application of integrated CLE for surveillance in CD, which was terminated early due to critical equipment failure at 4 of the 5 participating centers, came up with a much lower diagnostic yield, with sensitivity of 42.9%, specificity of 92.4% and accuracy of 86.7%. The authors concluded that the technique probably will not be used in the daily practice of screening for CRC in patients with colitis.

A recent study of the probe-based CLE (pCLE) comes from Sweden where it was used for the surveillance of dysplasia in patients with PSC-IBD, a population with 6-fold increase in the incidence of CRC compared with the average risk for CRC population[61]. The study showed good diagnostic accuracy, with the estimated accuracy at 96%, sensitivity at 89% and specificity at 96%, with a low PPV at 41%, but with a very high NPV at 99% for the pCLE. The authors noted that the yield for accuracy fell when assessing areas with mucosal inflammation being misinterpreted as dysplasia. This study challenges the earliest attempts at pCLE systems for CRC surveillance in IBD patients by van den Broek *et al*[62], where the authors reported much lower diagnostic yield.

CONCLUSION

Despite the fact that DCE with targeted biopsies is the gold standard technique for IBD surveillance, it has some limitations. The need for adequate bowel preparation, the long procedure time, and its operator dependence are some of them. Moreover, the presence of active mucosal inflammation or post-inflammatory polyps may affect the images of chromoendoscopy and, in these cases random biopsies are still justified. There are no sufficient data about the effectiveness of the different dyes in detecting dysplasia and there are some concerns about methylene blue inducing DNA damage but have not yet been validated. Two recent editorials have questioned the SCENIC consensus, because chromoendoscopy and targeted biopsies have not been shown to improve CRC mortality[63,64]. Even when accounting for those limitations, chromoendoscopy remains a validated technique that becomes more and more recommended for CRC surveillance in IBD patients, whilst white light endoscopy with random biopsies should only be performed when the skill or the equipment for chromoendoscopy is unavailable.

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MINIREVIEWS

Endoscopic retrograde cholangiopancreatography-induced and non-endoscopic retrograde cholangiopancreatography-induced acute pancreatitis: Two distinct clinical and immunological entities?

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Abstract

Acute pancreatitis (AP) is common gastrointestinal disease of varied aetiology. The most common cause of AP is gallstones, followed by alcohol abuse as an independent risk factor. With the increased need for invasive techniques to treat pancreatic and bile duct pathologies such as endoscopic retrograde cholangiopancreatography (ERCP), AP has emerged as the most frequent complication. While severe AP following ERCP is rare (0.5%), if it does develop it has a greater severity index compared to non-ERCP AP. Development of a mild form of AP after ERCP is not considered a clinically relevant condition. Differences in the clinical presentation and prognosis of the mild and severe forms have been found between non-ERCP AP and post-endoscopic pancreatitis (PEP). It has been proposed

that AP and PEP may also have different immunological responses to the initial injury. In this review, we summarise the literature on clinical and inflammatory processes in PEP *vs* non-ERCP AP.

Key words: Acute pancreatitis; Endoscopic retrograde cholangiopancreatography; Post endoscopic retrograde cholangiopancreatography pancreatitis

Core tip: Acute pancreatitis (AP) is the most frequent complication after endoscopic retrograde cholangiopancreatography (ERCP) and although low prevalence is found, if it develops it has greater severity index compared to non-ERCP AP. The differences in factors influencing appearance, clinical presentation and prognosis of ERCP induced and non ERCP induced AP were found, lead to opinion that mechanism by which they induce inflammation, may also be different. It would be of great importance to find immunological components that can distinguish patients with tendency to develop severe AP from patients with mild form, especially in ERCP induced AP where organ failure occurs half time earlier.

Plavsic I, Žitinić I, Mikolasevic I, Poropat G, Hauser G. Endoscopic retrograde cholangiopancreatography-induced and non-endoscopic retrograde cholangiopancreatography-induced acute pancreatitis: Two distinct clinical and immunological entities? *World J Gastrointest Endosc* 2018; 10(10): 259-266 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i10/259.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i10.259

INTRODUCTION

Acute pancreatitis (AP) is a common gastrointestinal disease with a reported incidence of 13-45 cases per 100000 persons annually[1]. According to the revised Atlanta classification, diagnosis of AP requires two of three following features: upper abdominal pain of acute onset, often radiating through to the back; serum amylase or lipase activity greater than three-times the normal level; and findings on cross-sectional abdominal imaging consistent with AP[2]. The severity of AP can be divided into mild, moderately severe or severe forms based on the presence or absence of persistent organ failure and local and systemic complications (Table 1). The mild form of AP is characterised by inflammation and the synthesis of proinflammatory cytokines in the affected area. The moderate and severe forms are characterised by the release of proinflammatory molecules into the circulation, causing systemic inflammatory response syndrome (SIRS)[3].

Gallstones are most common cause of AP, followed by alcohol abuse as an independent risk factor[2].

Invasive techniques used for the treatment of pancreatic and bile duct pathologies, such as endoscopic retrograde cholangiopancreatography (ERCP), carry a certain risk of complications. The most frequent of these is AP. Large variations in the reported incidence and severity of post-endoscopic pancreatitis (PEP) has led to unobjective risk evaluation, mostly consisting of retrospective studies. Kochar *et al*[4] reported an overall PEP incidence of 9.7%, while in high-risk patients the incidence was 14.7%. It is important to record why ERCP is performed, whether for therapeutic or diagnostic reasons, as patients may have an underlying condition that may affect the incidence of complications[5]. Most records report increased PEP after therapeutic ERCP[6].

AP is a disease of varied aetiology. Each produces a similar disease pattern, indicating that they all converge at a common point to initiate a cascade of events resulting in AP[7,8]. Messmann *et al*[5] found that people with AP are usually admitted to hospital several hours or even days after the initiation of symptoms. Therefore, it is impossible to determine the exact time of injury and initiation of the inflammatory phase. Instead, studies use PEP as a human model to examine the initial cytokine and acute-phase response in the first hours after initiation. It has been reported that PEP can serve as an ideal model for investigating the initial inflammatory phase in non-ERCP-induced AP.

An alternate opinion is that AP and PEP may actually be different disorders. This assumption is based on the differences in clinical presentation and prognosis of the mild and severe forms[9,10]. The triggers for the two disorders differ, and consequently, the mechanism by which they induce inflammation may also differ[11].

CLINICAL PRESENTATION

Different clinical outcomes of non-ERCP-induced AP and PEP have been found in several studies[9,10,12] (Table 2). Patients that developed post-ERCP pancreatitis initially had a higher APACHE Ⅱ score (key prognostic factor in predicting mortality) compared to AP of other aetiologies[10]. The APACHE Ⅱ score takes approximately 48 h to achieve a good predictive index. Therefore, whether this score represents a good method to differentiate initial disease severity prognosis (within 24 h), and if it can be reliably used to compare non-ERCP AP and PEP, remain questionable[9].

As mentioned earlier, severe AP following ERCP is rare (0.5%), but if it does develop, it does so with a greater severity index when compared to non-ERCP AP. Fung *et al*[10] reported that the extent of parenchymal necrosis is greater in PEP patients. There was also a higher rate of infected necrosis in the PEP group in their study. In PEP, the infection occurs earlier than in acute non-ERCP-induced pancreatitis. Due to small number of patients with ERCP induced acute necrotising pancreatitis (ANP) and low statistical power of their study, results should be interpreted with caution. All the same, these results should be taken into consideration, since the presence of infection and its extent is more important

Table 1 Severity of acute pancreatitis

Mild	Absence of both (peri) pancreatic necrosis and organ failure
Moderate	Presence of sterile (peri) pancreatic necrosis and transient organ failure
Severe	Infected (peri) pancreatic necrosis or persistent organ failure

for disease prognosis than pancreatic necrosis[10]. Organ failure develops early in the severe form of AP, either present at admission or 24 h later. In PEP, organ failure occurs twice as fast as in non-ERCP AP[3].

The mild form of ERCP-induced pancreatitis has a shorter and milder disease course with only a temporary increase in the level of enzymes in the blood (up to 48 h), suggesting a non-specific pancreatic reaction to injury, not necessary inflammation. Patients with mild post-ERCP pancreatitis have been reported to have a significantly shorter duration of pain and need for analgesia and parenteral hydration. All patients involved in this study, indicated for ERCP, were studied after they had been discharged from hospital because the acute condition can influence the intensity of inflammation[9]. Studies on drug effectiveness on the prevention of post-ERCP AP use the reduction in total post-ERCP AP incidence as the final measurement. So far, results have shown a reduction in the mild form but not the severe form. The primary goal should be a reduced incidence of severe PEP, as the mild form is not a clinically relevant condition[13-16].

MECHANISM OF INJURY

Non-ERCP pancreatitis

As previously mentioned, the most common causes of non-ERCP AP are gallstones and alcohol abuse[2]. The primary location of injury for both causes are acinar cells[17]. Gallstones lead to duct obstruction and blocking of acinar exocytosis, leading to the colocalization of zymogen and lysosomal granules and early activation of pancreatic enzymes. Alcohol leads to oxidative and non-oxidative damage. The non-oxidative pathway involves increased levels fatty acid ethyl ester, whereas the oxidative pathway is characterised by the accumulation of acetaldehyde, acetate and NADH. Alcohol also modifies the intracellular redox state by diminishing the NAD/NADH ratio and increasing the lactate/pyruvate ratio, ultimately leading to metabolic alterations and acinar cell injury[18].

Post-endoscopic pancreatitis

The factors influencing PEP incidence are multifactorial. These include patient-related factors, operator-related factors and method-related factors. Patient-related factors involve age, sex, pre-existing pancreatitis, prior history of post-ERCP pancreatitis, sphincter of Oddi dysfunction, and small bile duct and pancreatic divisum. Operator-related factors are associated with the experience of the endoscopist. The method-related factors are the most important because in them lies the greatest possibility for controlled intervention. Method-related factors cause mechanical injury a number of different ways. Combined operator and method- related factor as repeated and difficult papilla cannulation can lead to oedema and obstruction of free juice flow and sphincter of Oddi spasm. This mechanism may resemble the damage caused by gallstone obstruction. Furthermore, osmolarity and the ionic nature of the contrast media can cause chemical injury. Injecting contrast media are responsible for hydrostatic injury, which is one of the main causes of pancreatitis after ERCP[19]. Another factor is increased duct pressure, which can cause early activation of pancreatic enzymes[20]. However, microbiological factors related to contaminated endoscope and translocation from the intestines is not considered to play a major role.

INFLAMMATORY PROCESS

General

It is considered that the first pancreatic event, in any of these circumstances, occurs at the level of acinar cells[21]. Intrapancreatic trypsinogen activation and NFκB activation represent the two main initial triggers for AP[8,22]. Sah *et al*[22] reviewed studies that used animal models to show that NFκB activates and induces inflammation without the need for trypsinogen activation. Therefore, these two events represent two independent cellular events.

The early events in AP include inhibition of zymogen secretion, altered intracellular Ca^{2+} homeostasis that modifies pH values (Figure 1), intrapancreatic activation of trypsinogen and other zymogens and activation of cell death pathways (NFκB)[8,18].

The initial injury of the acinar cells caused by zymogens is sterile[23] (Figure 2).

Sterile inflammation requires two distinct signals through the activation of pattern recognition receptors (PRRs) (Figure 3). PRRs, like Toll like receptor (TLR) and NOD like receptor (NLR), are part of the innate immune response[23].

Randomised controlled trials have been used to study the use of allopurinol in the prevention of post-ERCP AP. Allopurinol reduces the production of uric acid. Uric acid uses DAMPs (NLR receptors) to trigger an inflammatory response. These studies found that allopurinol decreases the incidence of post-ERCP AP[24,25], indicating that the innate immune cells play a role in AP after ERCP[21]. Shamoon *et al*[26] in their study, emphasise the importance of innate immune cells and derived inflammatory mediators as therapeutic targets in AP in early phase of the disease (24-48 h).

The balance between pro- and anti-inflammatory immune response determines the prognosis in AP. A fall in the co-expression of HLA-DR on $CD14^+$ monocytes is considered a standard laboratory indicator of compensatory anti-inflammatory immune response syndrome (CARS)[27]. The severe form of AP is frequently associated with immune suppression, which increases the risk

Table 2 Differences in post-endoscopic pancreatitis *vs* non- endoscopic retrograde cholangiopancreatography induced acute pancreatitis clinical presentation

	PEP	non-ERCP-induced AP	Conclusion
Fung *et al*[10] ERCP-induced acute necrotising pancreatitis *vs* ANP induced by other causes	Higher APACHE Ⅱ scores on admission More extensive pancreatic necrosis Higher rate of infected necrosis	Lower APACHE Ⅱ scores on admission Less extensive pancreatic necrosis Lower rate of infected necrosis	ANP is more severe when ERCP-induced
Testoni *et al*[12] ERCP induced AP *vs* non ERCP induced AP		No statistical difference: severity of the pancreatitis mortality rate (double in severe PEP) hospitalisation	
	In mild form serum amylase fell 50% in 38.9 h. Peak serum amylase halved within 48 h in 92%	In mild form serum amylase fell 50% in 46, 4 h. Peak serum amylase halved within 48 h in 73.6%	Statistical difference ($P < 0.001$) Mild form of PEP a sort of pancreatic reaction, instead of true episode of acute pancreatitis
Abid *et al*[9] Mild form: ERCP induced AP *vs* non ERCP induced AP	Shorter duration of pain; Shorter time of intravenous hydration; Shorter time to resumption of oral diet; Shorter hospital stay ($P < 0.001$)		ERCP-induced AP mild attacks run a significantly shorter and milder course than non-ERCP related mild attacks

PEP: Post-endoscopic pancreatitis; ERCP: Endoscopic retrograde cholangiopancreatography; AP: Acute pancreatitis.

Figure 1 Altered Ca^{2+} homeostasis- change from physiologic intracellular transient Ca^{2+} spikes to pathologically sustained global Ca^{2+} rise, can lead to significantly lower pH values and cause early enzyme activation.

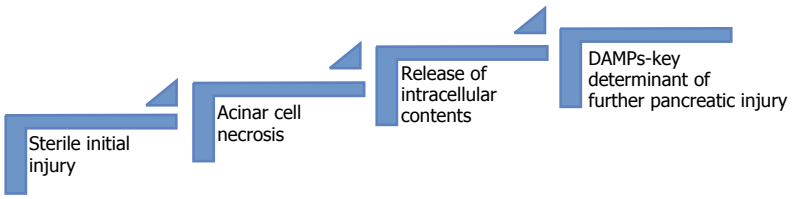

Figure 2 Sterile injury causes acinar cell necrosis, the release of intracellular contents, and activation of damage-associated molecular patterns that further determine pancreatic injury.

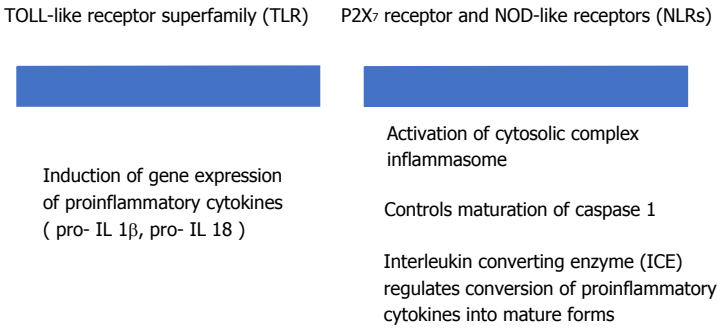

Figure 3 Activation of pattern recognition receptors.

of infection, organ failure and death[28]. Kylanpaa *et al*[3] reported that impaired cellular immunity causes complications related to infection in AP at a later stage of the disease. Furthermore, Testoni *et al*[12] reported that infection in PEP occurs during or immediately after the procedure. For this reason, infection in non-ERCP AP is considered a secondary event, while in PEP it is considered the primary event.

IMMUNE COMPONENTS

While the role of different cytokines in AP has been

extensively studied, the role of cellular immunity is poorly evaluated[28]. Innate immune cells are the major leukocyte population in the inflamed pancreas[29].

Monocytes and macrophages

Monocytes and macrophages are the main inflammatory cell populations in AP, and both play active roles in AP progression. The production of proinflammatory factors like tumour necrosis factor (TNF)-α in pancreatic cell stimulates the activation of macrophages in distal organs including the peritoneum, spleen, liver and lungs. Monocyte chemoattractant protein (MCP)-1 and macrophage migration inhibitory factor (MIF) play important roles in AP. Bhatia *et al*[30] reported that blocking MCP-1 synthesis reduces the severity of AP. Furthermore, antibodies against MIF improve survival in rats with AP[31]. The expression of HLA-DR on monocytes gives a good indication of monocyte function. In cases of immunosuppression, decreased monocyte HLA-DR expression predicts the development of organ failure[32].

Neutrophils

Neutrophils play a central role in the development of local and systemic complications, therefore, researchers have investigated the depletion of neutrophils as a therapeutic option for AP. Anti-neutrophil serum (ANS) exhibited a marked attenuation in intrapancreatic trypsin activation, ameliorated choline-deficient ethionine supplemented (CDE) diet-induced pancreatitis and completely prevented lung injury[33,34]. The depletion of neutrophils associated with ANS did not influence macrophage infiltration, but it did decrease the number of lymphocytes in the pancreas[29].

T cells

Progression of AP is accompanied by a change in the number and ratio of $CD4^+$ and $CD8^+$ lymphocytes[35]. $CD4^+$ lymphocytes are especially important as they act as co-stimulators of macrophage activation via antigen presentation and the release of proinflammatory cytokines. They have been reported to have a direct cytotoxic effect on acinar cells through Fas ligand expression[36]. Depletion of $CD4^+$ lymphocytes reduces the severity of AP[21]; however, $CD4^+$ lymphocytes are a heterogeneous population and some release IL-22, which has an anti-inflammatory effect[37].

Natural killer cells

Natural killer (NK) cells are predominantly studied in response to infection and immunosurveillance against tumours. They are part of the innate immune system, giving them the ability to respond without prior sensitisation. They also carry certain abilities of adaptive immunity, as they are primed during development, their receptors can exhibit antigen specificity, they undergo clonal expansion during infection and generate long-lived memory cells[38]. Natural killer cells can undergo clonal-like expansion through specific and non-specific immune responses. While the specific response occurs *via* interaction of their activating receptors with viral antigens, the non-specific response is driven by the production of cytokines and proliferation following exposure to proinflammatory cytokines in the absence of TCR signals and co-stimulation[39,40]. Natural killer cells have immunological memory, which enables them to react faster and more aggressively in familiar surroundings. The most important cytokines produced by NK cells after activation are TNF-α and IFN-γ[41]. It is thought that NK cells that produce proinflammatory cytokines can contribute to dysregulation of the immune response as seen in sepsis[42]. The cytokine IL-15 pays a role in the maintenance of NK cells. The half-life of mature NK cells is about 1 wk, but in the absence of IL-15 they disappear in 48 h. These cells can also serve as an immunotherapeutic target.

Dabrowski *et al*[28] reported significant depletion of the NK cell population on the first day of severe AP, while there was no significant change in NK cell number in mild AP. These findings are consistent with the idea that severe forms of AP are related to immune suppression. Profound inhibition of innate cell immunity can be explained by the migration of NK cells and natural killer T (NKT) cells to the site of inflammation.

Natural killer T cells

Natural killer T cells are generally autoreactive and can recognise both exogenous and endogenous ligands. There are two types of NKT cells, type Ⅰ and type Ⅱ. Type Ⅰ is more prevalent in mice and can be either pathogenic or protective, although they have a greater propensity to be pathogenic. Type Ⅱ is prevalent in humans, and predominantly protect against inflammation and autoimmune disease. Different self-antigens can stimulate type Ⅰ NKT cells, and some of these antigens are present at elevated levels during inflammation[43].

In patients with severe AP there is a reduction in the number of peripheral lymphocytes, especially monocytes and cytotoxic T lymphocytes[28,44].

Cytokines

The most important anti-inflammatory cytokine is interleukin (IL)-10. It down-regulates the production of proinflammatory cytokines and the expression of HLA-DR on monocytes. If the compensatory anti-inflammatory response is too intense, however, it may lead to immunosuppression and complications including infection. The concentration of IL-10 is highest in the early phase of severe AP. As infection is considered to be one of the prognostic factors related to disease severity, IL-10 may be a promising predictive marker of organ failure[45]. There are conflicting reports for the use of IL-10 in the prevention of post-ERCP AP. In a randomised double-blind study, Deviere *et al*[46] showed a reduced incidence of post-ERCP AP after IL-10 usage, although this was not supported by a study by Dumot *et al*[47].

As a key proinflammatory mediator, IL-6 regulates

the synthesis of acute-phase proteins in the liver as well as macrophage-conditioned tissue damage[48]. It reaches its peak value 24-48 h after clinical expression. In necrotising pancreatitis, the peak levels of IL-6 occur after 24 h[5]. Minkov *et al*[48] concluded that IL-6 represents an independent factor for predicting severity in acute non-ERCP pancreatitis.

The highest values of C-reactive protein (CRP) are recorded after 48–72 h, which is later than that of IL-6[5]. Although CRP has been identified as a late marker in laboratory monitoring[49], Messman *et al*[5] found that both IL-6 and CRP peak earlier in patients with ANP.

IL-1β-mediated signalling is required for full pancreatic and distal organ injury and inflammation[50], and is the pivotal inflammatory mediator in cell death associated with sterile inflammation[51]. Serum levels of IL-1β do not correlate with AP severity in humans, although it has been found that the values peak after 24 h and are greater in patients with severe AP compared to mild AP[52]. In animal models, peak serum IL-1β precede peak serum IL-6 values[50,53]. It is possible that IL-1β is required for the induction of IL-6 production, which is strongly correlated with disease severity in humans[54]. IL-1β and TNF-α are considered the primary cytokines that initiate and propagate most of the consequences of the SIRS in AP[55,56]. IL-6 prevents the synthesis of IL-1β and TNF-α[57].

Kilciner *et al*[49] compared early changes (within 24 h) in the serum levels of IL-2, IL-4, TNF-α and IL-6 in the development of post-ERCP pancreatitis. They used patients who underwent ERCP as well as a control group consisting of patients with non-ERCP AP caused by gallstones, drugs or alcohol. They found that IL-4, an anti-inflammatory cytokine, was significantly lower in post-ERCP and non-ERCP AP patients compared to patients who did not develop pancreatitis. The TNF-α level was not significantly different after 24 h in patients who developed PEP compared to those who did not develop pancreatitis after ERCP. After 24 h, the IL-6 levels did not differ from the control group, but they were significantly higher compared to patients who did not go on to develop pancreatitis after ERCP.

The role of IL-18 may depend on the presence of other cytokines. It plays an important role in the local immune response to pancreatic injury[23], and can also be found in serum. It has been described to prime NK cells, and NK cells that were unable to receive IL-18 signals were found to have defective cytotoxicity and cytokine secretion after stimulation[38].

AP is the most frequent complication after the ERCP procedure. Although the incidence of AP after ERCP is low, it is reported to occur in 0.5% of patients, PEP has a greater severity index compared to non-ERCP AP[10]. As the mild form of PEP is not a clinically relevant condition, it would be useful to identify early markers to predict whether a patient will develop the severe form of PEP.

The serial changes in amylase and lipase levels in patients without PEP suggest the existence of subclinical pancreatic damage. Messmann found that amylase and lipase levels increased equally among all patients after ERCP[5]. Amylase and lipase are released into the systemic circulation due to disturbed transport and increased ductal permeability; however, they are not thought to be responsible for inducing further inflammation. Based to these findings, we conclude that serum amylase values can't serve as an adequate future therapeutic goal.

The role of cytokines, especially IL-10, IL-6 and TNF-α, have been extensively studied for the prediction of disease severity[45,48,55,56]. These cytokines can be used to predict the severity of PEP after 12-24 h; however, measurements taken 4 h after the procedure showed no significant difference between patients who developed PEP and those who did not develop PEP[51,58].

Further research on the initial inflammatory response is necessary, particularly as organ failure has been reported to occur earlier in severe forms of AP, either at admission or 14 h later. Furthermore, in PEP, organ failure occurs twice as fast than in non-ERCP AP[44]. Direct comparison of the initial inflammatory response between PEP and non-ERCP AP would be of significant importance to clarify these statements. Found difference in clinical response to initial injury might be explained by different initial immune response[59].

Infection is considered to be the most important prognostic factor for disease severity. Similarities between cytokines and inflammatory mediators in sepsis and AP are often compared. Kjaergaard *et al*[60] reported that the expression of NKG2D receptors on NK cells and CD14 on monocytes can be valuable prognostic markers of an unbalanced immune response, and may predict a worse outcome for critically ill patients. Also, Guo *et al*[61] presented natural killer cells as critical to eliminate pathogens during the early phase of sepsis and prevent patients from developing secondary infection. We suggest that similar components should be used in PEP and non ERCP AP.

In addition to searching for adequate biomarkers to assess disease severity, it is our opinion that novel therapeutic strategies for both of these conditions lie in uncovering the immune pathways.

CONCLUSION

The most frequent complication after ERCP is AP. In most cases, it is not a clinically relevant condition, but in 0.5% of patients it has a greater severity index compared to non-ERCP AP. In severe PEP, infection occurs earlier than in acute non-ERCP-induced pancreatitis, and organ failure occurs twice as fast. Treatment of AP, regardless of the cause, is primarily supportive and implies a certain economic burden in the healthcare system worldwide. More thorough clarification of disease pathogenesis is needed, in order to find adequate immune target to predict and consequently prevent severe form of the disease.

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MINIREVIEWS

Concise review on the comparative efficacy of endoscopic ultrasound-guided fine-needle aspiration *vs* core biopsy in pancreatic masses, upper and lower gastrointestinal submucosal tumors

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Abstract

Endoscopic ultrasound (EUS)-guided fine needle aspiration with or without biopsy (FNA/FNB) are the primary diagnostic tools for gastrointestinal submucosal tumors. EUS-guided fine needle aspiration (EUS-FNA) is considered a first line diagnostic method for the characterization of pancreatic and upper gastrointestinal lesions, since it allows for the direct visualization of the collection of specimens for cytopathologic analysis. EUS-FNA is most effective and accurate when immediate cytologic assessment is permitted by the presence of a cytopathologist on site. Unfortunately, the accuracy and thus the diagnostic yield of collected specimens suffer without this immediate analysis. Recently, a EUS-FNB needle capable of obtaining core samples (fine needle biopsy, FNB) has been developed and has shown promising results. This new tool adds a new dimension to the diagnostic and therapeutic utility of this technique. The aim of the present review is to compare the efficacy of EUS-FNA to that afforded by EUS-FNB in the characterization of pancreatic masses and of upper and lower gastrointestinal submucosal tumors.

Key words: Efficacy; Safety; Gastrointestinal masses;

Fine needle aspiration and biopsy

Core tip: Endoscopic ultrasound (EUS)-guided sampling is the first diagnostic option for gastrointestinal submucosal and pancreatic lesions. In the past, fine needle aspiration (FNA) was the main method to obtain tissue for histological examination, however, it was associated with limited diagnostic accuracy. In the last decade, fine needle biopsy (FNB) needle was introduced into clinical practice, which allows for more tissue acquisition and improvement in diagnostic yield. In this updated minireview, we provide an overview on the role of EUS-FNA and FNB in certain gastrointestinal lesions. In addition, we provide a summary on the efficacy and safety profile of each procedure with reporting the recent guidelines recommendation.

Khoury T, Sbeit W, Ludvik N, Nadella D, Wiles A, Marshall C, Kumar M, Shapira G, Schumann A, Mizrahi M. Concise review on the comparative efficacy of endoscopic ultrasound-guided fine-needle aspiration *vs* core biopsy in pancreatic masses, upper and lower gastrointestinal submucosal tumors. *World J Gastrointest Endosc* 2018; 10(10): 267-273 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i10/267.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i10.267

INTRODUCTION

Endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) is considered the initial diagnostic tool for the assessment of gastrointestinal lesions including pancreatic, submucosal, and lymphatic lesions[1]. Despite the extensive utilization of this technique, it possesses several key limitations. Among these limitations is the wide variability in the diagnostic yield of collected specimens, as well as the loss of histological architecture in the obtained specimens.

The variability of yield is currently mitigated by performing cytopathologic examination on site immediately after the collection of the specimen. Furthermore, onsite cytopathologic evaluation not only increases diagnostic yield, but does so more efficiently, permitting fewer needle passes and, presumably, decreasing the risk of complications[2,3]. Unfortunately, onsite cytopathologic evaluation is not widely available. Therefore, the ability to offer quality EUS-FNA is geographically restricted to those centers with cytopathology.

In addition, FNA is unable to adequately preserve tissue architecture for histopathologic analysis. This is particularly important in the evaluation of gastrointestinal stromal tumors and lymphomas[4,5]. Furthermore, FNA is unable to provide adequate tissue for further analysis with immunohistochemistry, phenotyping, or genetic analysis so as to allow for personalized treatment.

Fortunately, a novel EUS-fine needle biopsy (FNB) has been developed, permitting the collection of core biopsies *via* an endoscopic approach. This technique has been examined in several studies and has been found to enable the acquisition of large amounts of tissue with conserved architecture sufficient for histologic analysis[6,7]. In recent years, several studies reported the diagnostic yield of EUS-FNA and EUS core needle biopsy for various gastrointestinal lesions. Thus, the aim of the present minireview is to compare the efficacy of EUS-FNA *vs* EUS-FNB of various gastrointestinal lesions.

EUS-GUIDED FNA AND FNB

Currently, two subsets of needles are available for tissue acquisition (FNA and FNB). In the beginning, only FNA needles were available and the size of the needle was either 19 or ranged from 22 to 25-gauge. Once FNB needles were developed, they initially utilized the Trucut biopsy needle (QuickCore® needle; Cook Medical Inc., Winston-Salem, NC, United States), but its production was stopped later due to its overloaded firing mechanism and adverse events. Since then, three different FNB needles have been produced, which are easier to use than FNA needles. Examples include the Procore® needle, which is characterized by a cutting bevel (reverse for 19, 22 and 25-gauge and 20-gauge antegrade beveled side slot) at the needle tip (Cook Medical Inc.), the Acquire™ end-cutting needle, which is characterized by a three-point needle tip (22 and 25-gauge; Boston Scientific Corp., Marlborough, MA, United States), and the SharkCore™ needle, which is characterized by six distal cutting edges at the needle tip (19, 22 and 25-gauge; Medtronic, Minneapolis, MN, United States)[8]. Regarding needle sizes, several studies have examined the impact of needle sizes on diagnostic accuracy and yield. Generally, a larger needle size (19 gauge) will obtain more tissue for histological assessment than the smaller 22 and 25-gauge needles. However, the limiting factor in usage of 19-gauge needles is its higher rate of complication and technical failure. On the other hand, the smaller needle sizes (22 and 25-gauge) are more technically feasible[8]. Moreover, when cytology is supposed to be enough for making a diagnosis, such as the case in pancreatic lesions, previous meta-analysis demonstrated similar diagnostic yield of 22 and 25-gauge needles and non-superiority of the larger 19-gauge needle in diagnostic yield[9]. On the other hand, when tissue histology and architecture are needed for better assessment, such as in the case of gastrointestinal stromal tumors (GIST), lymphoma and autoimmune pancreatitis, a larger 19-gauge needle is preferred. A retrospective study reported the diagnostic yield of the SharkCore™ needles with EUS-FNA needles of solid upper gastrointestinal masses. More histological specimens were obtained with the SharkCore™ needles compared to EUS-FNA needles (59% *vs* 5%, $P < 0.001$)[10]. Furthermore, a recent study compared the SharkCore™ biopsy needle with

a standard EUS-FNA needle in cases of suspected gastrointestinal stromal tumors. Tissue adequacy was obtained in 100% in EUS-FNB as compared to 65% in the EUS-FNA groups (P = 0.006). A diagnosis was reached by immunohistochemical staining in 52.7% of cases compared to 87% in the EUS-FNA group (P = 0.01)[11].

SAFETY PROFILE

EUS-FNA has been associated with a high safety profile with minor intra- and post-procedural adverse events[12]. Moreover, the ASGE standards of practice committee has reported EUS-FNA to be a procedure with a high safety profile[13]. A recent systemic review article of 51 studies with 10941 patients overall reported EUS-FNA-related morbidity and mortality of 0.98% and 0.02%, respectively, with an acute pancreatitis rate of 0.44% and post-procedure pain occurring in 0.34% of patients[14]. Another systemic review that focused on EUS-FNA of pancreatic cystic lesions (40 studies, 5124 patients) reported overall morbidity of 2.66% and mortality of 0.19%[15].

EUS-guided core biopsy using the 19-gauge Trucut needle [notably, Trucut Biopsy needle (EUS guided) is no longer being used, as the company stopped making this needle] has also been reported to be safe, with an adverse events rate reaching up to 2%[16]. This is reflected throughout the literature by an accumulation of evidence on the safety of these procedures, indicating a relatively similar complication rate between them of 1%-2%[17]. Moreover, another study has reported minor conservatively treated complications of low-grade fever and asymptomatic pneumoperitoneum in the immediate post-procedural time, with none of the patients experiencing major or life-threatening complications[18]. The newer above-mentioned FNB needles were shown to have a high safety profile without increased risk or procedure-related complications. Finally, several studies demonstrated that there was no difference in morbidity and mortality between EUS-FNA and FNB procedures[11,19,20].

EUS-FNA *VS* FNB IN PANCREATIC MASSES

Rapid and accurate diagnosis of pancreatic masses is very important given the poor prognosis associated with pancreatic cancer. EUS-FNA is the main initial diagnostic modality for tissue acquisition of pancreatic lesions[21,22]. Recently, the European society of gastrointestinal endoscopy (ESGE) released recommendation for the diagnosis of pancreatic lesions. ESGE recommends EUS-guided sampling for pathological diagnosis as a first diagnostic test (Strong recommendation, moderate quality evidence). In the case of the presence of suspected pancreatic malignancy with negative or indeterminate diagnosis, ESGE recommends either performing revision on the initial pathology specimens obtained or to repeat EUS-guided tissue acquisition or surgery (Weak recommendation, low quality evidence). For pancreatic cystic lesions, ESGE recommends EUS-guided tissue acquisition for biochemical and cytological evaluation, except for radiologically appearing benign cysts less than 1 cm in diameter (Strong recommendation, low quality evidence)[23].

The reported diagnostic accuracy of EUS-FNA for pancreatic mass lesions is variable and ranges from 78% to 95%[24], the sensitivity and specificity were reported to be 64% to 95% and 75% to 100%, respectively[24,25]. This value is declining for EUS-FNA in other organs such as mediastinal masses and gastrointestinal stromal tumors[26,27].

The diagnostic yield of EUS-FNA might be adversely affected in the absence of onsite cytopathologic assessment[28,29]. Furthermore, in the setting of chronic pancreatitis, the accuracy is declining[30]. A previous study by Gleeson *et al*[31] reported a 5%-7% false positive rate when obtaining tissue for cytological examination by EUS-FNA. To overcome this disadvantage, a new fine needle biopsy was used in pancreatic lesions, and subsequently there was an increased trend for the application of an FNB device designed to have a reverse bevel at the tip to obtain a core sample. It contains the characteristics of both FNA and a core biopsy needle[32]. This needle features greater flexibility for improved core tissue collection. In comparing the efficacy between FNA and FNB, a previous study demonstrated similarity in the diagnostic yields of EUS-FNB and EUS-FNA[33]. In these studies, both needles were similar in diagnostic accuracy for malignant lesions, however the number of needle passes to obtain adequate tissue was significantly lower in the FNB group. Another study by Atalawi *et al*[34] demonstrated that the sensitivity for pancreatic cancer diagnosis was 98%, while the specificity reached 100%. Moreover, another study showed that FNB was associated with significantly higher diagnostic yield compared to FNA (93.8% *vs* 28.1%, $P < 0.01$)[35]. Several other studies have shown superiority of EUS-FNB over the FNA method in obtaining adequate histopathological samples and higher diagnostic yields[32,32-38]. Additionally, Aadam *et al*[36] reported a significant rescue effect of FNA crossover to FNB. A recently released ESGE guideline recommended the use of 25 or 22-gauge needles for sampling pancreatic solid masses with no difference between FNA of FNB needles[39]. However, in the case of requirement for complete tissue architecture, such as lymphoma and GIST, the ESGE guideline recommends the use of a large bore FNB needle (19 or 22-gauge)[39].

EUS-FNA *VS* FNB FOR UPPER GASTROINTESTINAL SUBMUCOSAL TUMORS

Submucosal tumors of the gastrointestinal system are most frequently located in the stomach and the

proximal small intestine[40]. Nevertheless, they may present in any part of the gastrointestinal tract. The most common subepithelial tumors are GISTs[41-44]. In the past, the most widely accepted approach was surgical extraction of these gastrointestinal masses. However, there is increasing evidence supporting the need for precise histological diagnosis that could alter the patient's management and prevent unnecessary surgeries for asymptomatic and benign lesions[45-49]. The use of cytological examination has been questioned by several previous reports. For example, FNA of gastrointestinal submucosal tumors was associated with only 61% diagnostic accuracy[50]. Wittmann *et al*[51] reported no difference between FNA and the Procore needle. Bang *et al*[52] found a similar diagnostic accuracy and number of needle passes needed for pathological diagnosis by using 22-gauge FNA and FNB techniques. However, this study was limited by a very small number of participants. During the last several years, different needles were implemented into clinical practice to improve the diagnostic yield of gastrointestinal submucosal lesions. A previous study reported the pooled analysis of EUS-FNB for malignancy. The diagnostic accuracy, sensitivity, specificity, positive predictive value and negative predictive value reached 85.96%, 90.2%, 99%, 100% and 78.9%, respectively[53]. Another study showed that FNB was superior in extra-intestinal lesions[54].

Jeong *et al*[45] reported that the use of Trucut biopsy of submucosal tumors changed patient management in 30% of cases. Moreover, there is growing evidence supporting the use of EUS-FNB over FNA techniques[55] given its higher diagnostic yield. A recent randomized multicenter clinical trial using EUS-FNB showed feasible histopathological diagnosis of intestinal lesions with diagnostic accuracy of approximately 93% compared to EUS-FNA[53]. Another randomized controlled study reported a statistically significant better diagnostic yield of EUS-FNB compared to EUS-FNA in various gastrointestinal lesions[36] and, very recently, the use of FNB compared to FNA in gastric sub-epithelial tumors was associated with statistically significant higher diagnostic yield, higher proportion of adequate cellularity and reduced number of needle passes[56].

Although the literature is still lacking and only a few studies have been conducted, the present evidence might be sufficient to favor the use of FNB needles in gastrointestinal submucosal lesions until the establishment of guideline consensus in the field.

EUS-FNA *VS* FNB FOR RECTAL AND PERI-RECTAL TUMORS

Although EUS-guided procedures have been most studied for pancreatic and upper gastrointestinal lesions, they have also been used in the lower gastrointestinal tract. In this context, they are primarily useful for evaluation of rectal or perirectal lesions because of the difficult scope access beyond the rectum. Throughout the literature, there are only a few reports on FNA/FNB guided biopsy for lesions of the lower digestive tract[57-59]. Previous studies have reported equal efficacy of FNA and FNB and similar diagnostic accuracy in 10 of 11 patients[59]. Similarly, the diagnostic yield of EUS-FNA in rectal and sigmoid lesions (cancer and GIST) reached 90% in ten patients[57]. This diagnostic yield of EUS-FNA was consistent among other studies. Sasaki *et al*[58] reported a EUS-FNA diagnostic yield of 95.5% (21 of 22) in colorectal submucosal and extrinsic lesions. Prior studies have reported approximately 80%-90% diagnostic accuracy of EUS-FNA in diagnosing sub-epithelial tumors of the gastrointestinal tract[60,61]. On the other hand, a recent study has reported a decreased diagnostic accuracy of FNA/FNB in lower gastrointestinal lesions of approximately 50%[18]. Notably, this low accuracy was associated with small lesions less than 20 mm in size, suggesting that EUS-FNA/FNB may require further improvement for optimal diagnostic utility in the detection of smaller lesions. Furthermore, in this study, the use of FNB was effective as it was sufficient for tissue acquisition to make a diagnosis of recurrent lymphoma after failure of EUS-FNA to obtain sufficient material for histopathological examination. In seven patients, the specimen obtained by EUS-FNB led to changes in the presumptive diagnosis - two of them were later diagnosed with malignancy *via* FNB after having received a diagnosis of benign mass by FNA, while the remaining five patients were diagnosed as having malignancy according to FNA that later were ruled out *via* FNB[18]. Thus, EUS-FNB can be considered a complementary procedure to overcome the limitations of EUS-FNA to enhance histopathological diagnoses. Notably, some exaggerated interventions for benign lesions can be obviated given the higher diagnostic yield of EUS-FNB. Thus, although the reported literature is insufficient, there may be an argument for considering EUS-FNB as an initial diagnostic *vs* using it concurrently with FNA. Further studies are needed to establish the clinical applications and diagnostic accuracy of EUS-FNB needles in lower gastrointestinal tumors.

CONCLUSION

FNA and FNB are both accepted as safe procedures with a low complication rate of approximately 1%-2%. At present, FNA is best performed with immediate onsite cytopathologic review, which is not broadly available. FNB is not limited in this regard, and it further provides information on a tissue's architecture and provides a greater sample yield allowing for further analyses, such as genetic sequencing and phenotyping to be performed, thereby allowing for provision of a more personalized treatment plan. Recently, several guidelines have been published. Ang *et al*[8] addressed the enhanced diagnostic importance in tissue acquisition and improved diagnostic accuracy when using FNB needles. Moreover, recent ESGE released guidelines recommended the use of either FNA or FNB needles (22 or 25-gauge) for routine

Table 1 Summary of efficacy and safety of endoscopic ultrasound-guided fine needle aspiration with or without biopsy procedures

Procedure	Diagnostic accuracy	Safety (complications)	Mortality
Pancreatic, upper and lower GIST: Gastrointestinal stromal tumors; Submucosal tumors[1]			
EUS-FNA	Variable	Low	None
ROS available	High		
ROS unavailable	Low-moderate		
EUS-FNB	High	Low	
Other gastrointestinal lesions (lymphoma, GIST and chronic pancreatitis)			
EUS-FNA	Low	Low	None
EUS-FNB	High	Low	

[1]Excluding lymphoma, GIST and chronic pancreatitis. ROSE: Rapid on-site evaluation; GIST: Gastrointestinal stromal tumors; EUS: Endoscopic ultrasound; FNA: Fine needle aspiration; FNB: Fine needle biopsy.

EUS-guided sampling of solid masses and lymph nodes. However, when the aim of the sampling is to obtain core tissue with more preserved architecture, the ESGE recommended the use of smaller 19 or 22-gauge FNB needles (low quality evidence, weak recommendation)[39]. Thus, in light of current evidence, we recommend considering application of those recommendations, as it appears that a strong argument can be made for FNB given that it provides a greater amount of information with fewer needle passes and fewer resources without appreciably increasing the risk of complication to the patient (Table 1). Finally, the decision of the type and needle size should be individualized according to the suspected lesion to be sampled.

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MINIREVIEWS

Role of endoscopy in caustic injury of the esophagus

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Abstract

Caustic injury of the esophagus is a problematic condition challenging endoscopists worldwide. Although the caustic agents and motives are different among countries and age groups, endoscopy still plays an invaluable role in diagnosis and treatment. Endoscopy can determine the severity of caustic ingestion which is of great importance in choosing appropriate treatment. However, some aspects of endoscopy in diagnosis of caustic injury remain controversial. Whether or not all patients need endoscopy, when to perform endoscopy and how to assess the severity are just some examples of these controversies. Due to lack of randomized controlled trials, many findings and suggestions are inconclusive. Computerized tomography scan of the chest and abdomen gains popularity in assessing the severity of caustic injury and avoiding unnecessary surgery. If esophageal stricture eventually develops, endoscopic dilatation is a mainstay. Maneuvers such as steroid injection and esophageal stent may be used in a refractory stricture. Nevertheless, some patients have to undergo surgery in spite of vigorous attempts with esophageal dilatation. To date, caustic injury remains a difficult situation. This article reviews all aspects of caustic injury of the esophagus focusing on endoscopic role. Pre-endoscopic management, endoscopy and its technique in acute and late phase of caustic injury including the endoscopic management of refractory stricture, and the treatment outcomes following each endoscopic intervention are thoroughly discussed. Finally, the role of endoscopy in the long term follow-up of patients with esophageal caustic injury is addressed.

Key words: Endoscopy; Diagnosis; Corrosive ingestion; Caustic injury; Esophagus; Stricture

Core tip: This mini-review comprehensively covered evidence-based endoscopy for caustic injury of the esophagus including pre-endoscopic management, endoscopic role in the acute and late phase of caustic injury, endoscopic management of refractory stricture and its outcomes. Tips and tricks to perform diagnostic and therapeutic endoscopy in these patients are also

discussed.

Methasate A, Lohsiriwat V. Role of endoscopy in caustic injury of the esophagus. *World J Gastrointest Endosc* 2018; 10(10): 274-282 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i10/274.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i10.274

INTRODUCTION

Caustic injury of the upper gastrointestinal tract remains one of the most challenging conditions presented to both gastroenterologists and surgical endoscopists. Endoscopy plays a major role in diagnosing and assessing the severity of caustic injury as well as guiding an appropriate treatment. Recently, computerized tomography (CT) scan of the chest and abdomen is increasingly used as complementary tool in the evaluation of caustic injury. Despite of advances in emerging technologies and treatments, severe morbidities and even death following the ingestion of caustic agents are evident in clinical practices thus suggesting the complexity of this condition.

Esophageal necrosis with subsequent perforation requiring emergency surgery may develop in the acute phase of caustic injury. Meanwhile, esophageal stricture (often being a complex stricture) is a late sequela of caustic injury which can be difficult to treat. Understanding fundamental knowledge of this condition will ensure the endoscopist to pursue the best course for the patient.

Although optimal management in the caustic injury of the esophagus remains rather inconclusive due to the lack of large epidemiologic studies and randomized clinical trials in the field, this narrative review summarizes current evidence on the role of endoscopy in the diagnosis and treatment of caustic injury of the esophagus. For the literature review, we used standard search strategies involving two online databases (PubMed and Scopus) using key words of caustic injury, corrosive ingestion, esophagus, endoscopy, diagnosis, treatment, dilatation, and surgery.

IMPACT OF CAUSTIC INJURY ON THE ESOPHAGUS

Caustic injury of the esophagus is a world-wide phenomenon. It was reported that in 2016 there were 176828 cases of caustic injury in the Unites States-accounting for 9.28% of all poisoning cases. The majority occurred in children with accidental ingestion[1]. Alkali ingestion is often seen in western countries, while acid ingestion is more common in Asian countries[2]. In Thailand, caustic ingestion involved 19.5% of poisoning cases and its incidence has been increasing[3]. Morbidity following caustic ingestion was high with a mortality rate of 8%. About one-third of patients with caustic ingestion eventually required surgery[4].

PATHOPHYSIOLOGY

Caustic injury occurs when substance with pH < 2 or pH > 12 is ingested. Due to the "liquefactive necrosis" of alkali substance, caustic injury from alkali can cause more damage to gastrointestinal tract than the "coagulative necrosis" of acid ingestion. Earlier report suggested that alkali usually destroyed the esophagus and acid mainly damaged the stomach[5]. However, later endoscopic study contradicted this notion by showing that among acid ingestion patients, esophageal injury was seen in 87.8% and gastric injury in 85.4% of the patients[6]. Recent evidence indicated that acid ingestion caused more injury to the stomach (31% *vs* 13%) while the incidence of esophageal injury was similar between acid and alkali ingestion[7]. Gastroesophageal reflux from impaired lower esophageal sphincter function[8] and loss of esophageal motility[9] are also results of a caustic damage to the esophagus. Meanwhile, caustic injury to the duodenum appeared to be infrequent and less severe owing to pyloric spasm.

Since a caustic injury to the esophagus usually starts within a few minutes after ingestion, any attempt to lavage or induce vomiting will cause the agent to reflux into the esophagus thus resulting in a further damage. A caustic injury to the esophagus can be divided into in 3 phases as following[10]: (1) Phase of acute necrosis and thrombosis occurs in 1-4 d after caustic ingestion; (2) phase of ulceration and granulation occurs in 3-12 d after caustic ingestion. During this period, mucosal sloughing, bacterial invasion and granulation formation are evident. The esophagus is in the most friable phase. Any manipulation such as endoscopic examination or dilatation should be done with great care; and (3) healing phase begins from 3 wk after injury. It usually takes 1-6 mo to complete wound healing. Attempt to perform surgery for stricture cases unamenable to dilatation should wait beyond this period.

PRE-ENDOSCOPIC TREATMENT

Stabilization of the patient is an ultimate goal during acute injury. Signs for airway injury *e.g.,* hoarseness, stridor and poor ventilation are diligently sought for and immediately treated (if any). An evaluation for laryngeal edema should be pursued by direct laryngoscopy. A careful history taking includes the substance ingested, the amount and time of ingestion, pre-hospital treatment and the cause of ingestion. In addition to airway management, other pre-endoscopic management includes volume resuscitation, nil per os (NPO), avoidance of emetics and neutralizing agents, no insertion of nasogastric tube, and administration of broad-spectrum intravenous antibiotics[11]. Chest and abdominal X-ray is often an initial investigation for evaluating an extension of injury. Psychiatry consultation should be done in case of suicidal attempt.

Table 1 Assessment of severity: endoscopic score and computerized tomography score

Grade	Endoscopic score[16]	score[21]
Ⅰ	Edema and hyperemia of the mucosa	No definite swelling of esophagus wall (< 3 mm, within normal limit)
Ⅱ	Ⅱa: Friability, hemorrhages, erosion, blisters, whitish membranes, exudates and superficial ulcerations Ⅱb: IIa with deep or circumferential ulceration	Edematous wall thickening (> 3 mm) without periesophageal soft tissue infiltration
Ⅲ	Ⅲa: Small scattered areas of necrosis Ⅲb: Extensive necrosis	Edematous wall thickening with periesophageal soft tissue infiltration plus well-demarcated tissue interface
Ⅳ	Perforation	Edematous wall thickening with periesophageal soft tissue infiltration plus blurring of tissue interface or localized fluid collection around the esophagus or the descending aorta

ENDOSCOPY IN THE ACUTE PHASE OF CAUSTIC INJURY

Since clinical signs such as drooling and oral burn are not accurate predictors for caustic injury to the esophagus[12,13], endoscopy is therefore considered as the most important investigation to diagnose of this injury. Early endoscopy is recommended because about 30% of patients with caustic ingestion will have no injury to the esophagus and can be discharged promptly. Endoscopy is usually done within 24-48 h after ingestion. However, many experts have recommended endoscopy as soon as possible[14,15] because delayed endoscopy was associated with prolonged hospital stay and increased hospital expense[16]. Although some reports confirm the safety of endoscopy performed up to 96 h after ingestion[17], initial endoscopy after 48 h of ingestion is not advised because the injured esophagus may enter the phase of ulceration and granulation - in which the esophagus becomes fragile and easily perforated[18]. Nevertheless, as long as the principles of gentle handling of the endoscopy are maintained, endoscopy after 48 h in selected cases might be possible.

In the past, endoscopists were not encouraged to pass the scope beyond circumferential burn due to the fear of esophageal perforation[19]. However, with advances in endoscopic examination and more skills in endoscopy, complete endoscopic evaluation beyond this point is possible with no complication[20]. Endoscopy is beneficial to confirm the followings: existence of injury, degree of injury, and area of injury - which could guide a treatment and predict a prognosis.

All adult patients (in which suicide attempt was the most common cause) should undergo endoscopy, but there is controversy regarding endoscopy in children (in which accidental ingestion was the most common cause)[21]. Most authors agreed that endoscopy should be done in children with signs of drooling, dysphagia, oral lesions, respiratory distress and intentional ingestion[22,23]. Beyond these scenarios, clinical observation may be appropriate.

Endoscopy is contraindicated in patients with a suspicion of gastrointestinal perforation, necrosis of oral cavity and compromised airway. Gentle handling and avoidance of air over-insufflation is always recommended. The comparison of modified endoscopic findings classified by Zargar *et al*[17] (Figure 1) and CT grading by Ryu *et al*[24] are shown in Table 1.

HOW DOES THE ENDOSCOPIC FINDINGS RELATE TO PROGNOSIS?

Classification and severity of caustic injury help predicting outcomes. Intentional ingestion, acid ingestion and high volume of ingestion were associated with a high grade of mucosal injury[4]. The patients with grade Ⅲb had longer hospital stay and higher rates of complication compared than those with grade Ⅲa[21]. However, a great variety of incidences in the degree of injury has been evident[4,7,11,12,18,21,25-28](Table 2). Discrepancy between inter-observers might reflect the difficulty to interpret the endoscopic findings especially when there was time lapsed before endoscopy. Treatment could be different according to the grading of severity as followings[11].

Grade Ⅰ (edema and erythema) or grade IIa (erosions and ulcers)

Since esophageal stricture will not occur in mild degree of injury, oral feeding can be resumed immediately and the patient can be discharged.

Grade Ⅱb (circumferential ulceration)

Oral feeding can start once the patient can swallow saliva - often after 24-48 h after ingestion. Stricture will ensue in 30%-70% of these patients[29]. Therefore, barium swallowing is recommended at 3 wk after ingestion to detect the stricture and early dilatation will be performed accordingly.

Grade Ⅲa (scattered areas of necrosis)

Risk of perforation cannot be neglected in these patients and esophageal stricture may occur more than 90%.

Grade Ⅲb (extensive necrosis)

Emergency surgery is recommended. However, some physicians might use CT scan to confirm true necrosis of the esophagus because endoscopists may be unable to distinguish between superficial necrosis and transmural necrosis.

Table 2 Variations in the degree of injury according to Zargar's classification from articles published after year 2000 in adult patients

Author	Year	Patients	Grade Ⅰ	Grade Ⅱ	Grade Ⅲ
Alipour Faz *et al*[4]	2017	313	42.5%	16.9%	20.1%
Ducoudray *et al*[7]	2016	n/a	n/a	n/a	39.7%
Cabral *et al*[11]	2012	315	12.7%	22.9%	29.2%
Chang *et al*[25]	2011	389	14.7%	39.3%	42.4%
Cheng *et al*[21]	2008	273	n/a	n/a	30%
Tohda *et al*[26]	2008	95	49.4%	26.3%	13.7%
Havanond *et al*[12]	2007	148	17%	41%	1%
Satar *et al*[27]	2004	37	67.5%	n/a	0%
Poley *et al*[18]	2004	179	40%	30%	30%
Rigo *et al*[28]	2002	210	32%	13%	6%

n/a: Not available.

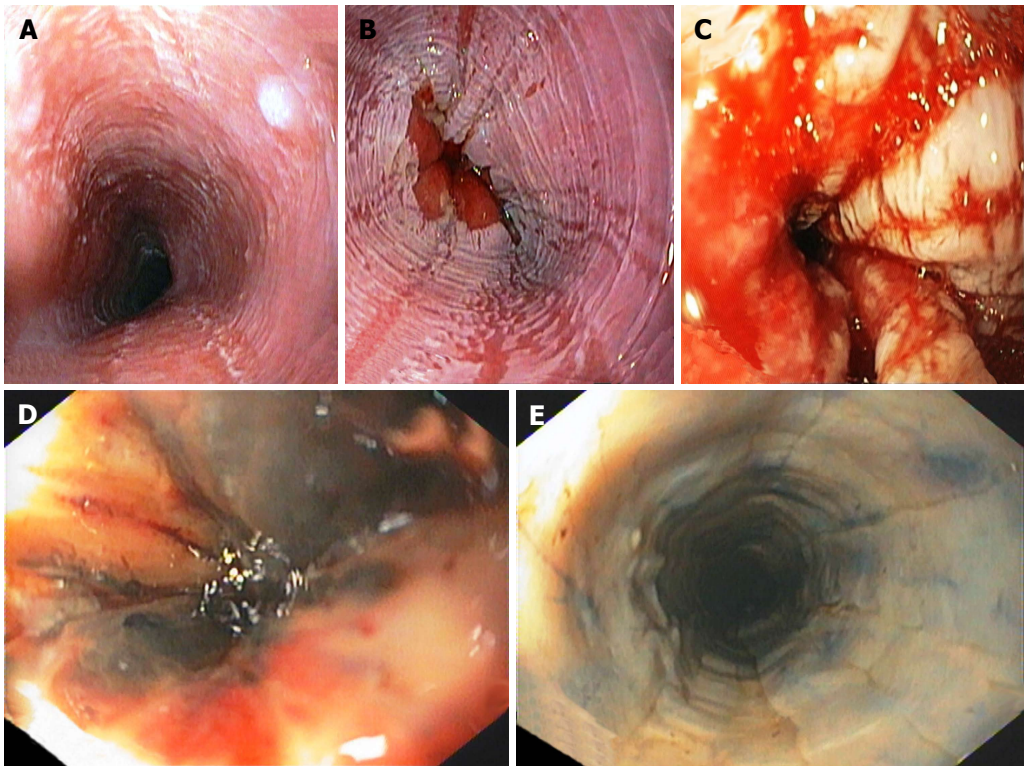

Figure 1 Modified Zargar's endoscopic classification of mucosal injury caused by ingestion of caustic substances. A: Edema and erythema; B: Erosions and ulcers; C: Circumferential ulceration; D: Scattered areas of esophageal necrosis; E: Extensive esophageal necrosis.

CT SCAN AND EUS IN THE EVALUATION OF CAUSTIC INJURY

It is evident that endoscopy is not always accurate in determining the extent of caustic injury (Figure 2). Depending on the endoscopic findings alone, grade Ⅲ injury would be over-estimated and unnecessary surgery was done in 15% of these patients[30]. Some authors showed that the accuracy in the diagnosis of grade Ⅱ and Ⅲ injury was 48% and 87%, respectively[31]. Recently, CT grading scores was developed in 2010 (Table 1) and shown to have a higher sensitivity and specificity than endoscopic score[24]. CT findings of transmural necrosis include esophageal wall blurring, peri-esophageal fat stranding and no enhancement of esophageal wall after intravenous contrast administrated. Recent studies showed that CT could prevent unnecessary esophagectomy in some patients with grade Ⅲb endoscopic score[32]. Although CT scan might underestimate the severity of caustic injury compared to endoscopy, it could provide further information about the involvement of adjacent organs *e.g.*, lung and pleural cavity[33]. Nevertheless, CT scan cannot replace endoscopy in the evaluation of caustic injury especial in those with mucosal damage[34]. The combination of endoscopy and CT scan has been utilized in clinical setting - in which surgery could only be performed in case with grade Ⅲb endoscopy and CT score[35].

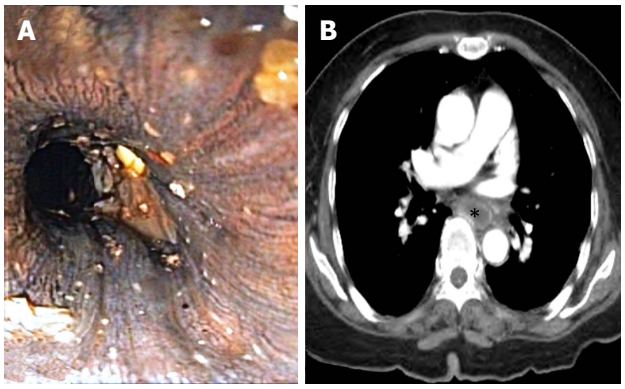

Figure 2 Endoscopic view suggested extensive mucosal necrosis of the esophagus -Grade Ⅲb modified Zargar's endoscopic classification, but CT scan revealed mucosal enhancement of the esophagus indicating tissue viability. A: Endoscopic view; B: Computerized tomography scan. Notably, esophageal lumen is marked with asterisk.

At present, combined use of endoscopy and CT scan, especially in case with grade Ⅲb endoscopic score, should help in the decision whether or not to operate.

Endoscopic ultrasonography (EUS) has some advantages over endoscopy and CT scan because it can delineate the layers of esophageal wall. If caustic injury is confined to submucosa in the EUS, the injured esophagus required a fewer sessions of esophageal dilatation than those with muscularis propria involvement[36]. Miniprobe EUS has been shown to predict stricture formation following caustic injury by visualizing the structure of esophageal wall[37]. However, the routine of EUS in clinical practice needs to be determined.

ENDOSCOPY IN THE LATE PHASE OF CAUSTIC INJURY

Endoscopy plays an important role in the treatment of caustic-related esophageal stricture. Caustic stricture is often complex and difficult to dilate[38]. Patients at risks for stricture were those with high endoscopic grade, ingestion of strong acid or alkali, leukocytosis and low thrombin ratio[39]. As acute inflammatory response to caustic agents lasts about 2 wk, early esophageal dilatation is usually done at 3 wk after caustic ingestion. After 8 wk, scar tissue is completely formed and the result of endoscopic dilatation is poor. Since good nutritional status is strongly related to a successful dilatation of esophageal stricture[40], early feeding *via* jejunostomy should start as soon as patients are clinically stable - especially in those with a significant damage in the esophagus and the stomach.

Practically, barium swallowing is done at 2-3 wk after caustic ingestion. Barium swallowing will provide crucial and relevant information on the stricture - which could determine the safety and success of endoscopic dilatation. This information includes:

(1) location and length of the stricture; (2) morphology of the stricture: tortuosity, angulation; (3) nature of the stricture: simple or complex; (4) complications of the stricture: concealed perforation, diverticulum; and (5) configuration of the stomach: any accompanying gastric stricture.

Esophageal dilatation can be done using various types of dilators. It can be performed under the combination endoscopy and fluoroscopy or endoscopy alone[41]. Commonly used esophageal dilatators are followings(Figure 3).

Bougie dilator (Maloney-Hurst dilator)

This dilator is easy to use but has no channel to insert guide-wire. It is suitable for short and straight stricture.

Wire-guided Polyvinyl dilator (Savary-Gilliard dilator)

This dilator passes through the stricture *via* guide-wire under fluoroscopy. It is appropriate for tortuous, angulated and long stricture. Sensation of resistance during dilatation can be noted on this dilator thus resulting in protecting against over-dilatation.

Through-the-scope balloon dilator (CRE balloon dilator)

This instrument can be used through-the-scope. It can reach area where Savary dilator cannot access. However, there is no sensation of resistance if over-dilatation occurs.

CRE balloon dilators achieve its dilatation effect by radial force while Savary and Maloney dilators exert its action *via* both radial and longitudinal forces. Although the mechanisms are different, all dilators seem to have comparable success rate and rate of perforation of 0.1%-0.4%[42]. Concerning the safety of an instrument, balloon dilator is preferred over Bougie dilator in children[43]. Techniques of esophageal dilatation are noted in Table 3.

In order to prevent the over-dilatation of esophageal stricture, the rule of 3 is recommended as "never dilate more than 3 dilators of progressively increasing diameter after considerable resistance is encountered"[44]. Although some retrospective study showed that non-adherence to this rule did not increase the risk of esophageal perforation[45], we believe that the rule remains useful as a landmark during dilatation and a preventive measure of over-dilatation. Success rate of esophageal dilatation varied from 25% to 95% depending on the severity of caustic stricture[46-48].

ENDOSCOPY IN REFRACTORY CAUSTIC STRICTURE OF THE ESOPHAGUS

Caustic stricture that could not be dilated to 14 mm over 5 sessions done with bi-week interval is defined as refractory stricture[49]. For refractory stricture, various modalities are advocated including electrocision, intralesional steroid injection, mitomycin-C injection, and esophageal stent.

Electrocision

Electrocautery could be applied to caustic stricture as

Table 3 Techniques of esophageal dilatation

Early dilate (usually starting from 3 wk after caustic ingestion)
Use appropriate type and size of dilator
Maintain a dilator in lumen of the esophagus while dilating
Concern the rule of 3: Never dilate more than 3 dilators of progressively increasing diameter after considerable resistance is encountered
Weekly or bi-weekly dilate to obtain luminal competency at 40 Fr
Dilate per scheduled, not on demand
If chest pain occurs after dilatation, esophageal perforation must be rule out using contrast esophagography

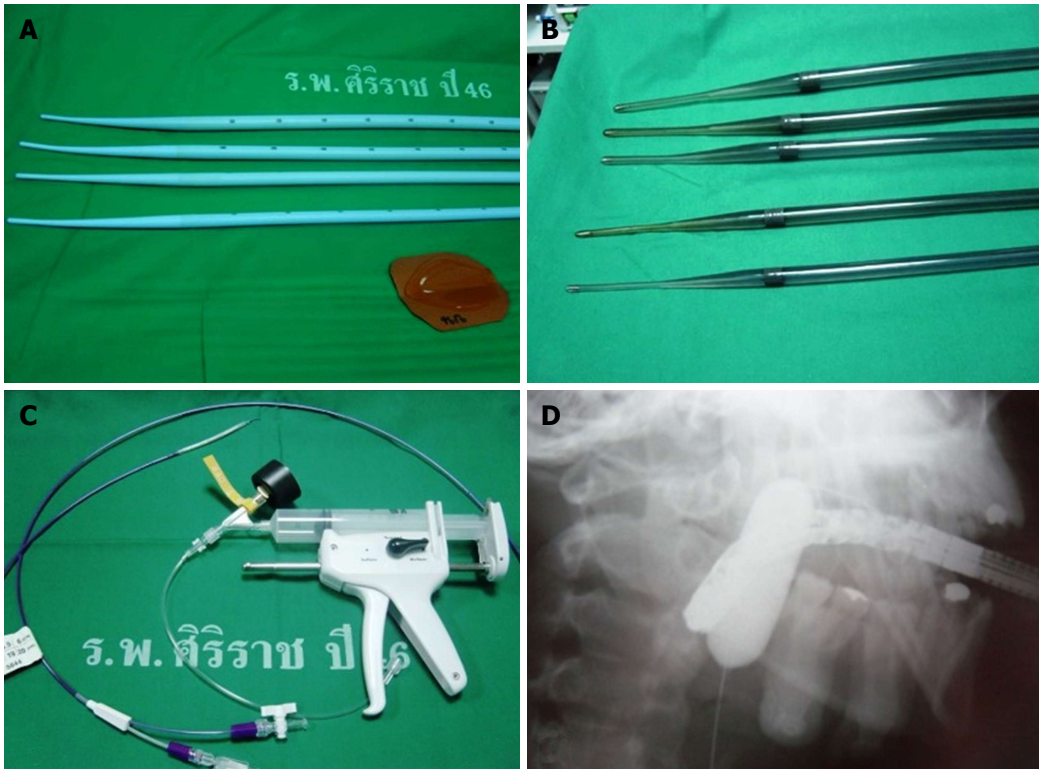

Figure 3 Various types of dilator. A: Maloney-Hurst dilator; B: Savary-Gilliard dilator; C: Balloon dilator; D: Balloon dilator during dilatation seen with fluoroscopy.

it has been used in the treatment of Schatzki's ring and anastomotic stricture with good results[50]. Multiple longitudinal incisions are made with needle knife through working channel of the endoscopy until the rim of the stenosis disappears. This maneuver proves to be a useful adjunct in esophageal dilatation.

Intralesional steroid injection

In this method, prior to bougie dilatation, triamcinolone acetonide (40 mg/mL) 1 mL is diluted to 2 mL and injected at the stricture site in 4 quadrants. Combination of steroid injection and bougie dilatation could achieve more dilatation, improve dysphagia and reduce dilatation sessions[51].

Mitomycin-C injection

Injection of mitomycin-C into the stricture site was shown to improve dysphagia score and easy passage of dilators[52-54] because mitomycin-C inhibited fibroblast proliferation and scar formation without interfering wound healing[55]. A randomized controlled trial showed a reduction in dilatation sessions if applying mitomycin-C during dilatation[56]. Mitomycin-C is beneficial in difficult or complex caustic stricture and can be combined with other modalities such as electrocision and esophageal stent[57].

Esophageal stent

Caustic stricture resistant to dilatation can be treated with esophageal stent insertion. Self-expandable plastic stent (SEPS) or fully-covered self-expandable metallic stent (FCSEMS) and recently, biodegradable stent are available. Practically, SEPS and FCSEMS are kept in place for 6 wk and should be removed before 12 wk. All types of esophageal stent have comparable efficacy but biodegradable stent has an advantage in non-requirement of stent removal. The clinical success of stent application in caustic stricture (*i.e.*, free of dysphagia) was 33% with a migration rate of 40%[58,59]. Since its clinical success is about one-third and not last-longing, esophageal stent is considered as a last resource in the treatment of caustic injury.

INDICATIONS FOR SURGERY IN CAUSTIC-INDUCED ESOPHAGEAL STRICUTRE

Esophageal dilatation for caustic-induced stricture injury has lower success rate than esophageal stricture related to other etiologies[60]. Esophageal replacement is considered in patients who fail endoscopic therapy. Up to 50%-70% of patients with caustic stricture required surgery[46,61]. Stomach is used as a conduit if possible because it has less morbidity and mortality than colonic interposition[62]. If colonic interposition is required, transverso-splenic to ileocolic segment with blood supply *via* left colic artery provided excellent function in 75% of the patients[63]. In general, surgery should wait 6 mo after caustic ingestion for stabilizing patient, improving nutritional status, and allowing enough time to full attempt of endoscopic therapy.

THE ROLE OF ENDOSCOPY IN THE LONG TERM FOLLOW-UP OF ESOPHAGEAL CAUSTIC INJURY

Since caustic injury of the esophagus has been associated with 1000-fold increased risk of esophageal carcinoma[61], patients with high-graded caustic injury (especially that with esophageal stricture) should undergo endoscopic surveillance. The incidence of caustic-associated esophageal cancer ranges from 0%-30% and bypass surgery seems to have no influence on cancer development[64]. The time interval between caustic injury and malignant transformation of the esophagus was reported to be several decades[65]. As a result, endoscopic surveillance of the injured esophagus should start at about 15-20 years after an injury and it should be done every 2 or 3 years[66].

CONCLUSION

Endoscopy plays a crucial role in the diagnosis, assessment of severity, treatment and surveillance in patients with caustic injury of the esophagus. Meanwhile, CT scan of chest and abdomen has been increasingly used to improve accuracy in the diagnosis and severity assessment in difficult cases of esophageal caustic injury. Choice of endoscopic management and surveillance are considered mainly based on the grading of mucosal severity. Patients with high-graded mucosal injury are associated with increased risk of caustic-induced esophageal stricture which could be difficult to dilate due to its complex anatomy and extensive fibrosis. Better techniques or instruments for endoscopic dilation need to be developed to overcome this problem. Since caustic injury significantly increased risk of esophageal carcinoma, scheduled endoscopic surveillance every 2 or 3 years should perform at 15-20 years after an injury-especially in individuals with high-graded mucosal injury or those with esophageal stricture. Due to the complex nature of disease, caustic injury of the esophagus remains one of the most challenging clinical conditions presented to endoscopists.

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MINIREVIEWS

Linear endoscopic ultrasound evaluation of hepatic veins

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Abstract

Liver resection surgery can be associated with significant perioperative mortality and morbidity. Extensive knowledge of the vascular anatomy is essential for successful, uncomplicated liver surgeries. Various imaging techniques like multidetector computed tomographic and magnetic resonance angiography are used to provide information about hepatic vasculature. Linear endoscopic ultrasound (EUS) can offer a detailed evaluation of hepatic veins, help in assessment of liver segments and can offer a possible route for EUS guided vascular endotherapy involving hepatic veins. A standard technique for visualization of hepatic veins by linear EUS has not been described. This review paper describes the normal EUS anatomy of hepatic veins and a standard technique for visualization of hepatic veins from four stations. With practice an imaging of all the hepatic veins is possible from four stations. The imaging from fundus of stomach is the easiest and most convenient method of imaging of hepatic veins. EUS of hepatic vein and the tributaries is an operator dependent technique and in expert hands may give a mapping comparable to computed tomographic and magnetic resonance imaging. EUS of hepatic veins can help in identification of individual sectors and segments of liver. EUS guided interventions involving hepatic veins may require approach from different stations.

Key words: Endoscopic ultrasound; Hepatic vein; Portal vein; Liver segments; Caudate lobe; Inferior vena cava; Liver; Cantlie line; Falciform ligament; Gall bladder

Core tip: A standard technique for hepatic veins imaging by linear endoscopic ultrasound (EUS) has not been described. EUS of hepatic veins can help in identification of individual sectors and segments of liver. This review paper describes the normal EUS anatomy of hepatic veins and a standard technique for visualization of hepatic veins from four stations.

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INTRODUCTION

Liver resection surgery is associated with significant perioperative mortality and morbidity[1]. Despite refinements in hepatic surgical techniques, vascular complications still occur. A detailed knowledge of the vascular anatomy and pre-surgical planning of vascular anastomosis on a vessel-to-vessel basis is essential for successful, uncomplicated liver surgeries[2-5]. A wide variety of imaging strategies are used to provide comprehensive preprocedural information about hepatic angioarchitecture[6]. Currently multidetector computed tomographic (CT) and magnetic resonance angiography are complementary modalities of hepatic angioarchitecture evaluation[7]. Ultrasound offers the advantage of Doppler assessment[8,9]. Despite comprehensive evaluation many smaller vessels may not be picked up, however from a surgical point of view these smaller vessels are insignificant and are tied up during surgery. The identification of these smaller vessels and specifically accessory veins of liver is sometimes important as they may drain a complete segment of liver. Separate segmental venous anastomosis is required for such cases to maintain sufficient hepatic venous drainage and to prevent postoperative complications resulting from the venous obstruction. An adequate maintenance of segmental hepatic venous drainage is also important as there is no adequate venovenous shunt between hepatic venous systems[10,11]. Linear endoscopic ultrasound (EUS) can offer a detailed evaluation of hepatic veins, help in assessment of liver segments and can offer a possible route for EUS guided vascular endotherapy involving hepatic veins. A standard technique for visualization of hepatic veins by linear EUS has not been described. This article describes the normal EUS anatomy of hepatic veins.

APPLIED ANATOMY: LIVER LOBES, SECTORS AND HEPATIC VEINS

The anatomical classification of the liver, which divides the right and left lobe by the attachment of the falciform ligament is no longer accepted in routine terminology. The true physiological classification divides right and left hemi-liver by an imaginary line of Cantlie. Typically, the Cantlie's line is 1 cm to the right of the middle hepatic vein (MHV), and corresponds to an important surgical plane in the sagittal axis that extends craniocaudally from the medial aspect of the gallbladder fossa to the left margin of inferior vena cava (IVC) (Figure 1A). Posteroinferiorly this line passes from gallbladder fossa to the main bifurcation of hepatic pedicle (portal triad) and then to retrohepatic IVC.

The hepatic veins are thin-walled anechoic vessels which do not have any valves, originate from the core (central) vein of the liver lobule and drain blood toward the IVC. The hepatic veins can be segregated into three major veins (right, middle and left) and many accessory veins or short hepatic veins. The three major hepatic veins are 6 to 15 mm in diameter, have no course outside liver and open directly into the supra hepatic part of IVC in the bare area of the liver (Figure 1B). The major veins are intersegmental in their course and divide the liver into four sectors; right anterior, right posterior, left medial and left lateral. The divisions separating the sectors are called portal fissures, which do not correspond to any superficially visible clefts but within each of which runs a hepatic vein. The right hepatic vein lies in the right portal fissure and separates the right hemi liver into anterior and posterior sectors. The right hepatic vein is the longest vein, passes through the segment I and lies parallel to the gallbladder fossa. The left hepatic vein (LHV) lies in the left portal fissure which is very close to the course of ligamentum venosum and separates the left hemi liver into medial and lateral sectors. The MHV lies in the middle portal fissure and separates the anterior division of right liver from medial division of left liver (Figure 1A). The accessory veins join the retro or intrahepatic part of IVC and are usually smaller in diameter (Figure 1B). The basic organisation of the segments and sectors of liver in relationship with hepatic vein tributaries is shown in Figure 2.

TECHNIQUES OF EVALUATION

The images given in this pictorial essay are taken by Pentax UTK 3870 UT from cases undergoing EUS examination. The imaging of hepatic veins is usually aided by proper identification of the IVC and the gallbladder both of which are discussed as important home bases for imaging of hepatic veins.

Imaging of IVC

IVC can be visualized from different positions during EUS. The appearance of IVC may vary from rounded to an elongated axis depending on the axis of imaging and the angulation of the probe in these positions (Figures 3-7). It is usually possible to image the entire length (approximately 6 to 8 cm) of intrahepatic/retrohepatic part of IVC in a single frame at 1 to 3 cm distance from the probe in an axis parallel to the probe near the esophagogastric junction. In this position the surface closer to the probe corresponds to the posterior surface of IVC and the surface away from the probe corresponds to the anterior surface of IVC (Figure 8). The position and course of each of the hepatic vein is usually best assessed from the abdominal part of esophagus. Slight clockwise or anticlockwise rotation can trace the lateral surfaces

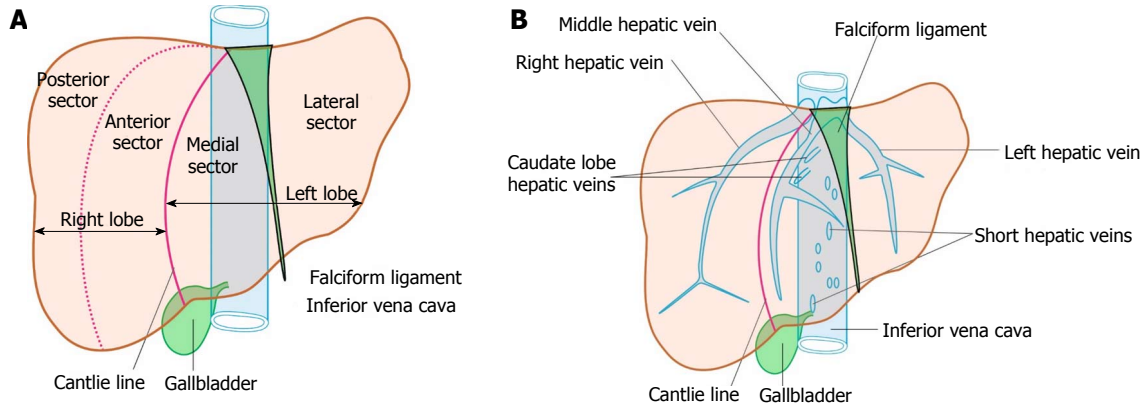

Figure 1 Anatomy of liver. A: The four sectors of liver, *i.e.*, right anterior, right posterior, left medial and left lateral; B: The three major veins, emerge from the posterior surface of the liver and open immediately into the supra hepatic part of inferior vena cava (IVC) just before it pierces the diaphragm. Short hepatic/accessory veins drain into lower part of IVC. The accessory veins and the caudate lobe veins join the anterior and lateral aspect of IVC.

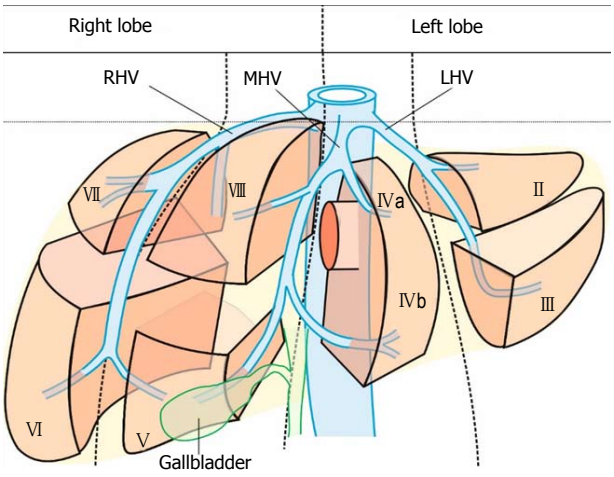

Figure 2 The segments and sectors of liver and their relationship with hepatic vein tributaries. MHV: Middle hepatic vein; RHV: Right hepatic vein; LHV: Left hepatic vein.

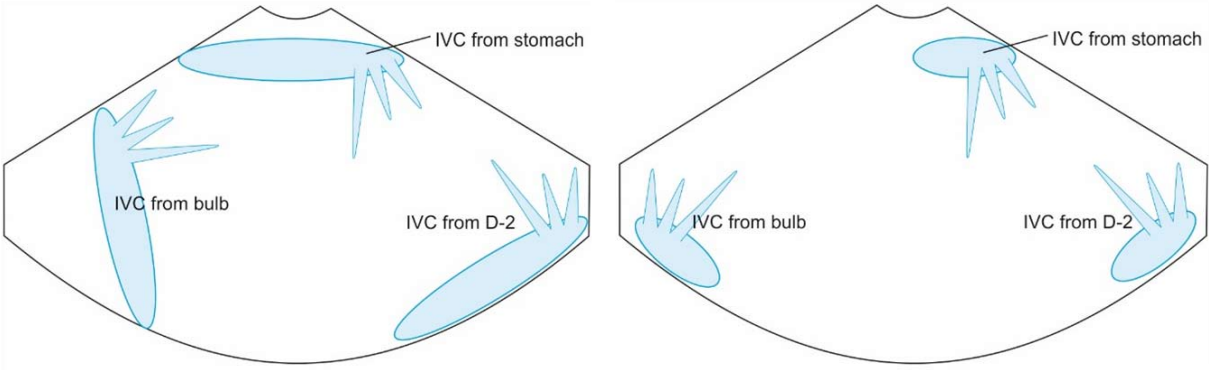

Figure 3 The appearance of inferior vena cava from three stations in a rounded or elongated axis.

of the IVC. The supra hepatic, or retro hepatic course of IVC can be followed for assessment of hepatic veins which join the anterior or lateral surface of IVC. No vein joins the posterior surface of IVC. During imaging from abdominal part of esophagus and stomach the spiral course of IVC in the liver is easily traced from above downwards from an anteriorly placed position of the IVC near the right atrium to a posteriorly placed position of the IVC in abdomen (Figures 4, 5, 8 and 9). The imaging of IVC and the hepatic veins is also possible from duodenal bulb and descending duodenum but the longer distance of hepatic veins and IVC from the bulb

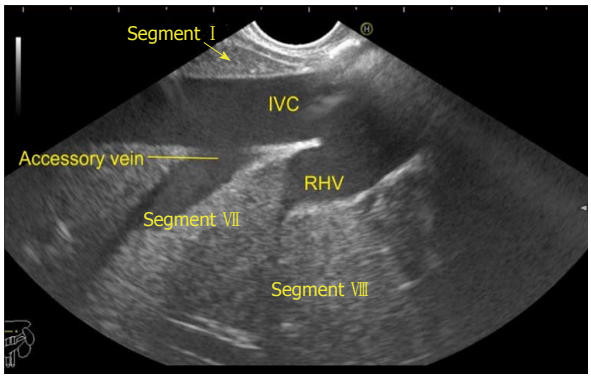

Figure 4 Inferior vena cava running parallel to the probe in a long axis from abdominal part of esophagus. RHV: Right hepatic vein; IVC: Inferior vena cava.

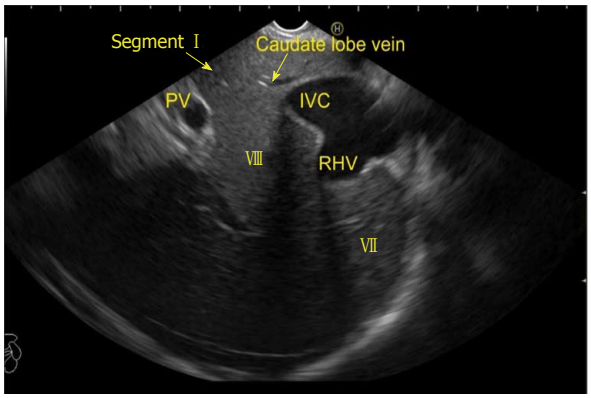

Figure 5 This figure shows inferior vena cava running parallel to the probe in a long axis. In this image slight up angulation of the probe shows inferior vena cava in a more oval axis. PV: Portal vein; RHV: Right hepatic vein; IVC: Inferior vena cava.

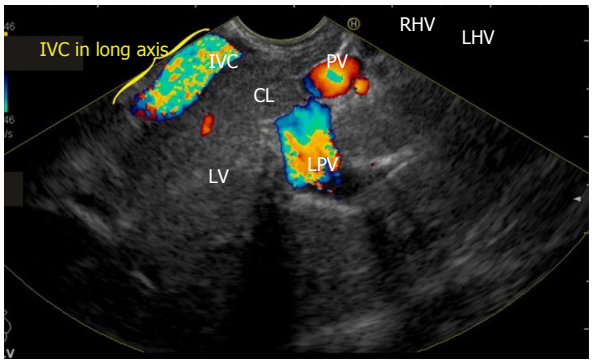

Figure 6 This figure shows inferior vena cava running from 7 o'clock position to 11 o'clock position on the far side of the screen in a long axis from the duodenal bulb. PV: Portal vein; RHV: Right hepatic vein; LHV: Left hepatic vein; IVC: Inferior vena cava; CL: Caudate lobe; LPV: Left portal vein.

and descending duodenum may make it technically difficult to acquire similar amount of information (Figures 6 and 7).

Imaging of gallbladder

The gallbladder lies in a shallow fossa on the down sloping visceral surface of liver and can be visualized from

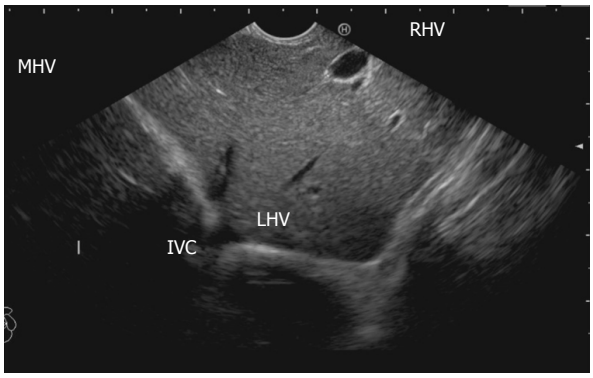

Figure 7 This figure shows inferior vena cava in a rounded axis from duodenal bulb. MHV: Middle hepatic vein; RHV: Right hepatic vein; LHV: Left hepatic vein; IVC: Inferior vena cava.

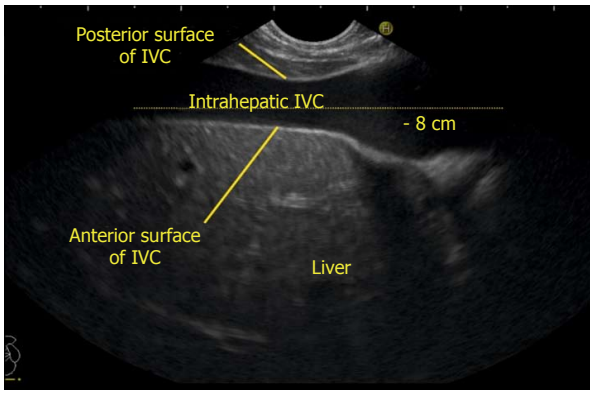

Figure 8 During imaging from the abdominal part of esophagus, the anterior surface of inferior vena cava is always found in close contact with the liver parenchyma whereas the posterior or lateral surface of the inferior vena cava is variably covered. IVC: Inferior vena cava.

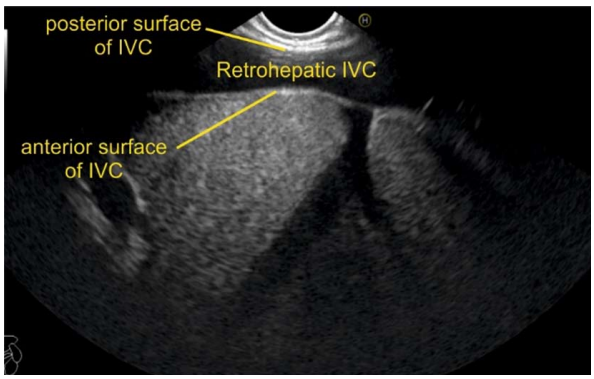

Figure 9 If the inferior vena cava is surrounded on all sides by liver parenchyma it is called as intrahepatic, if it is surrounded only anteriorly or anterolaterally it is called as retrohepatic. In this case, right hepatic vein is seen joining the retrohepatic part of inferior vena cava. IVC: Inferior vena cava.

the stomach, the duodenal bulb and from the descending part of duodenum. It is located near the right end of porta hepatis, its neck is highest, its fundus lowest. The location of gallbladder helps in following the course of hepatic vein; the right hepatic vein runs parallel to the upper surface of gallbladder (Figure 10), the MHV runs towards the neck of gallbladder (Figure 10) and the LHV

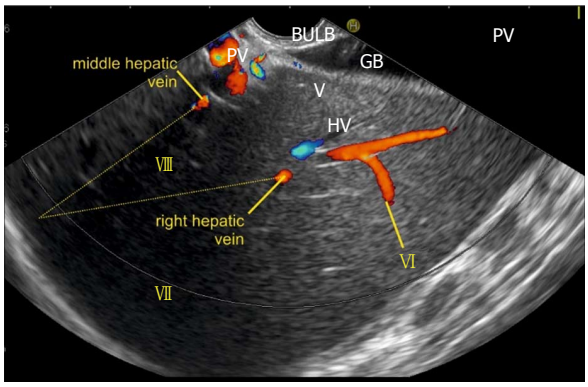

Figure 10 This image from duodenal bulb shows the right and middle hepatic vein. The right hepatic vein goes parallel to the surface of gallbladder and the middle hepatic vein goes towards the neck of gallbladder. GB: Gall bladder.

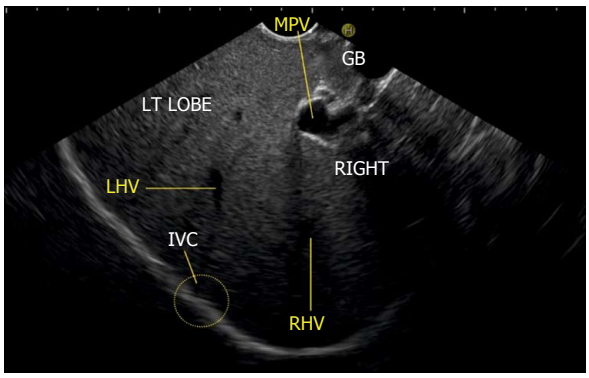

Figure 11 The inferior vena cava is not seen in this image but rotation of the scope shows the approximate area of inferior vena cava (yellow circle) where the left and right hepatic veins merge into inferior vena cava. MHV: Middle hepatic vein; RHV: Right hepatic vein; LHV: Left hepatic vein; IVC: Inferior vena cava.

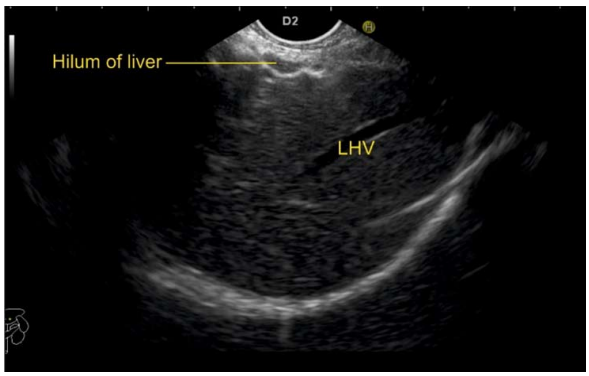

Figure 12 While imaging through the left lobe, the left hepatic vein is seen as a long vascular channel coursing towards the right side of the image into inferior vena cava which is usually seen in a rounded shape in a transverse axis. LHV: Left hepatic vein.

runs away from the neck of the gallbladder (Figures 11 and 12).

EVALUATION OF HEPATIC VEINS

The course of hepatic veins and the hepatic vein branches is described from four stations: the abdominal part of esophagus, the fundus of stomach, the duodenal bulb and the descending duodenum (Figure 13). The imaging from each station may be done in following steps: (1) Demarcation of right and left lobe is done by following the course of MHV. The course of left and right hepatic vein helps in identification of the four sectors (Figure 14); (2) Further subdivision of the sectors into independent liver segments is possible by following the tributary free part of each hepatic vein and tracing the direction and path of travel of the tributaries (Figure 15); and (3) The location and side of appearance of 1st major tributary of each hepatic vein is helpful for segmental identification (Figures 15-18).

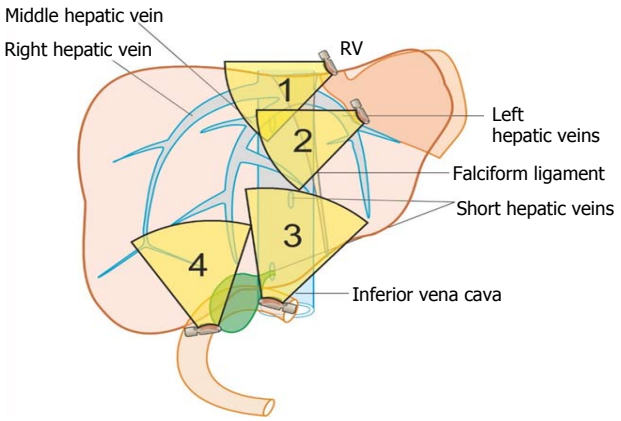

Figure 13 The imaging of hepatic veins can be done from four stations: the abdominal part of esophagus, the stomach, the duodenal bulb and the 2nd part of duodenum.

Evaluation from abdominal part of esophagus

The abdominal part of esophagus lies very close to the entry point of left and MHV into the suprahepatic part of IVC. Initially the LHV is identified in an open position to the left (Figures 12 and 14A). The course of LHV divides the left lateral and left medial sector (Figure 14A). Slight clockwise rotation traces the joining of MHV at an angle of about 60° with the IVC (Figures 14B and 16). The presence of MHV divides the left medial (IVa) from right anterior sector (Figures 14B and 16). On further rotation, the right hepatic vein is seen, which divides the right anterior from right posterior sector (Figures 14C and 17). Usually in this position the merger of right hepatic vein is seen when the IVC is seen in an axis parallel to the probe (Figure 17). With a single movement of clockwise rotation from abdominal part of esophagus, the three hepatic veins can be identified within the portal fissures and the four sectors can be separated according to the order of appearance of hepatic veins (Figure 13).

Evaluation from the stomach

A EUS examination of most of the liver lobe, sectors and hepatic veins is possible from the visceral surface of liver which is in contact with stomach and forms the gastric impression on the under surface of liver (Figure

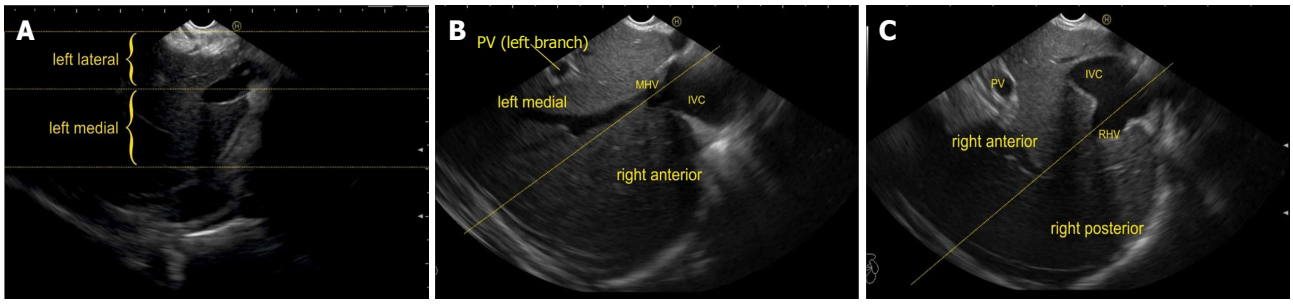

Figure 14 The images from abdominal part of esophagus shows presence of left (A), middle (B), and right hepatic vein (C) dividing the liver into four sectors. MHV: Middle hepatic vein; RHV: Right hepatic vein; LHV: Left hepatic vein; IVC: Inferior vena cava; PV: Portal vein.

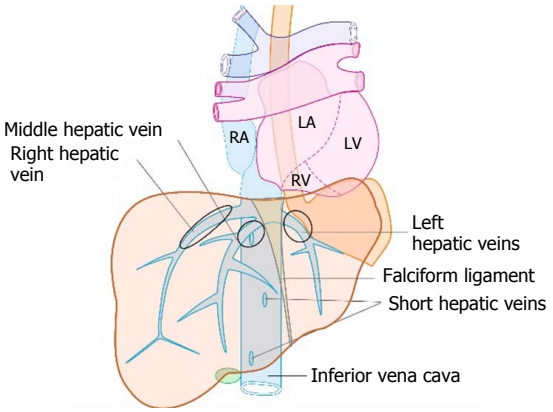

Figure 15 The tributary free part of each hepatic vein is shown.

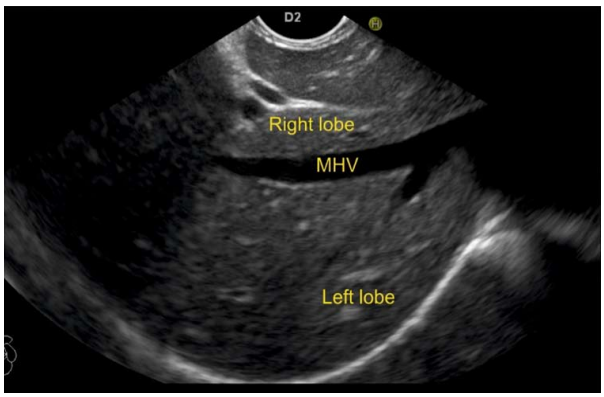

Figure 16 The middle hepatic vein has got tributaries on the right and the left side. The right side tributaries drain segment Ⅷ and segment Ⅴ. The left side tributaries drain segment Ⅳ. MHV: Middle hepatic vein.

19A and B). An open position to left places the tip of the transducer close to left lateral sector of liver in stomach. A clockwise rotation from an open position to the left brings into view the umbilical part of left branch of portal vein within the umbilical fissure which lies close to left edge of transverse fissure. Further clockwise rotation traces the transverse fissure from the left edge of the fissure to the right edge and moves the beam of probe from the left lateral sector to left medial sector (Figure 20). On continued rotation the beam moves towards the right anterior sector where the gallbladder

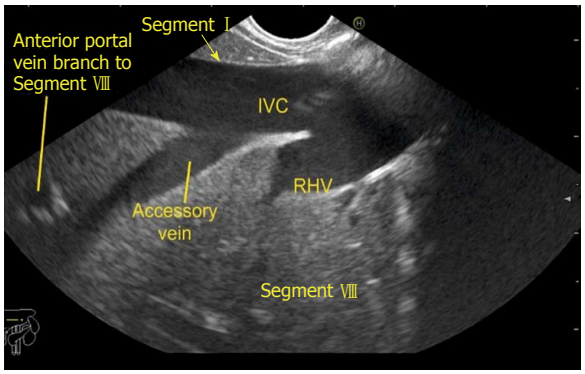

Figure 17 The right hepatic vein is seen joining at an angle of around 60°. The segment Ⅷ is seen between hepatic vein and IVC. RHV: Right hepatic vein; IVC: Inferior vena cava.

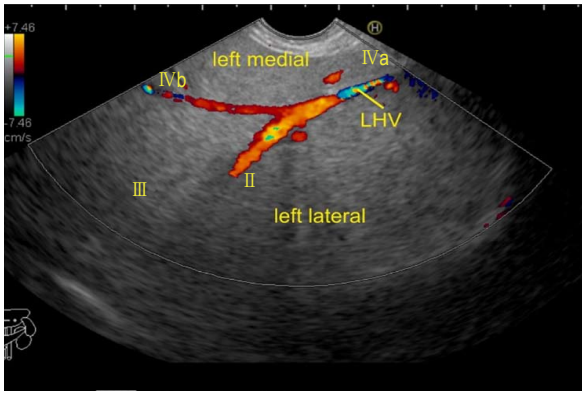

Figure 18 The left hepatic vein is seen running parallel to the probe. The segment Ⅱ, Ⅲ, Ⅳa and Ⅳb veins are seen. In this case the imaging is done from the visceral surface of the liver and from an area close to the antrum and body. Hence, the segment Ⅳb appears closer than segment Ⅲ. LHV: Left hepatic vein.

is seen (Figure 21).

Evaluation from the duodenal bulb

Imaging from duodenal bulb requires positioning of the scope in the duodenal bulb where clockwise and anticlockwise rotation results in appearance of left and right lobe (Figure 22). The presence of MHV is seen moving towards the neck of gall bladder and this divides the liver into right and left lobe (Figure 23).

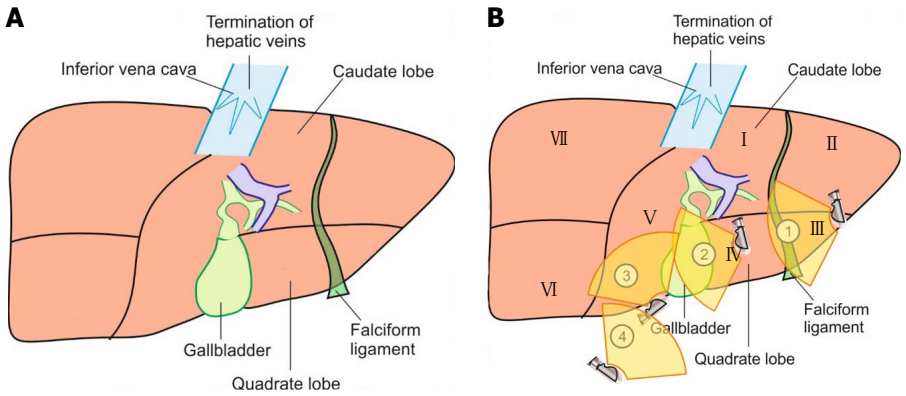

Figure 19 Visceral surface of liver. A: The visceral surface of the liver is shown. All the segments of liver except segment VIII are related to the visceral surface of the liver; B: The imaging from visceral surface of liver can be done from four positions.

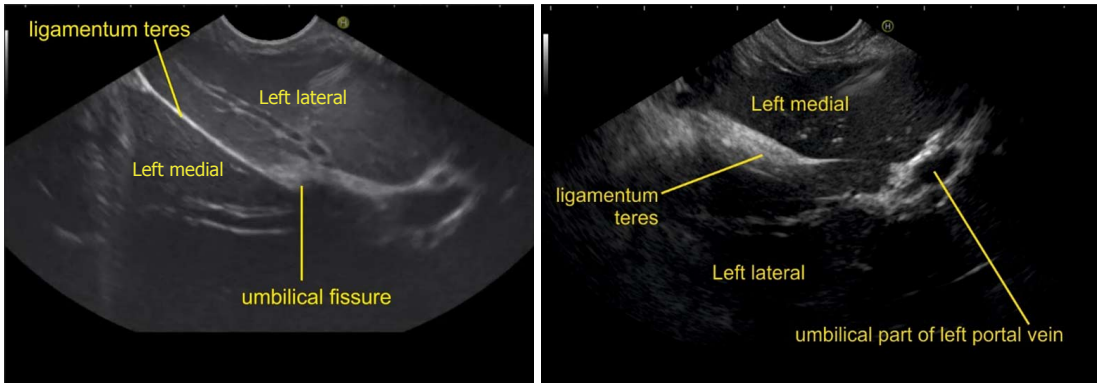

Figure 20 Imaging from visceral surface of liver shows the left lateral and left medial segment below the level of umbilical fissure separated by ligamentum teres.

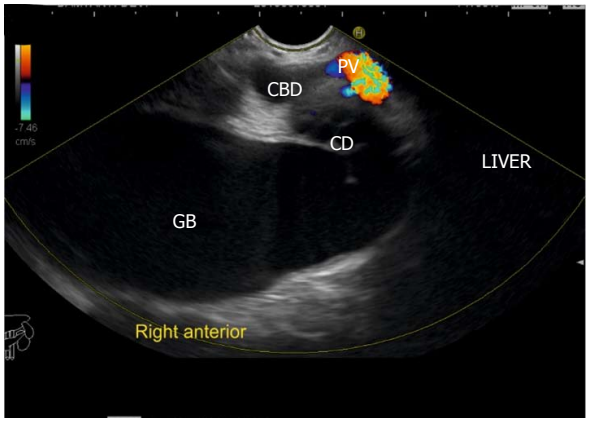

Figure 21 This image shows right anterior sector from stomach. CBD: Common bile duct; CD: Cystic duct; GB: Gallbladder.

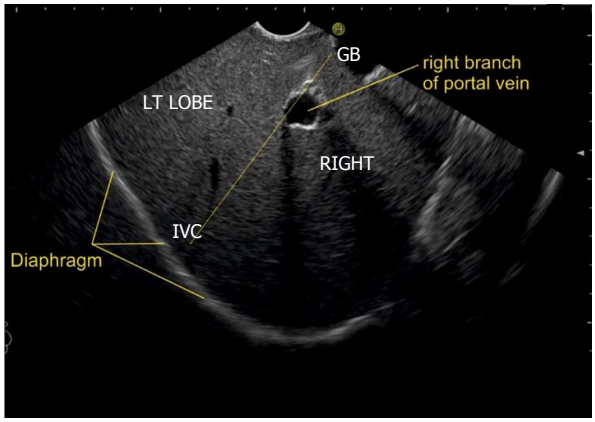

Figure 22 This image from duodenal bulb shows an imaginary line (dotted yellow line) going from inferior vena cava towards the gallbladder. This line divides the right and left lobe of liver. The right branch of portal vein is seen as a rounded structure within the liver parenchyma in the path of this line. GB: Gallbladder; IVC: Inferior vena cava.

Further division into sectors is possible by clockwise rotation to visualize the left lobe (Figure 24) and anticlockwise rotation to visualize the right lobe (Figure 25). Imaging from the duodenal bulb usually visualizes the gallbladder neck near the liver hilum at 12 o'clock position, fundus at 3 o'clock position (Figures 23 and 25) and in this position the IVC is seen moving from 6 to 9 o'clock positions (Figure 24). A clockwise rotation moves the beam towards the duodenum and towards the retrorenal part of IVC whereas as an anticlockwise rotation traces the IVC towards the right lobe of liver.

Evaluation from the descending duodenum

The evaluation of the hepatic veins from descending duodenum is possible by extreme anti-clockwise rotation

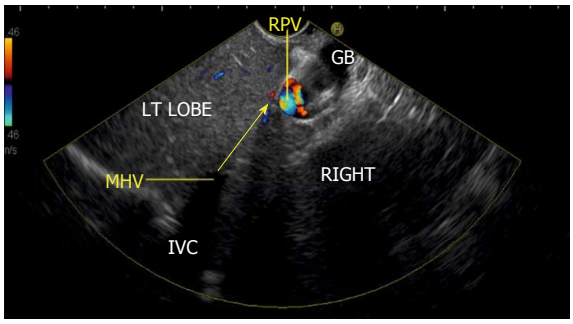

Figure 23 This image shows that the middle hepatic vein going towards the neck of gallbladder (yellow arrow). MHV: Middle hepatic vein; GB: Gallbladder; IVC: Inferior vena cava; RPV: Right portal vein.

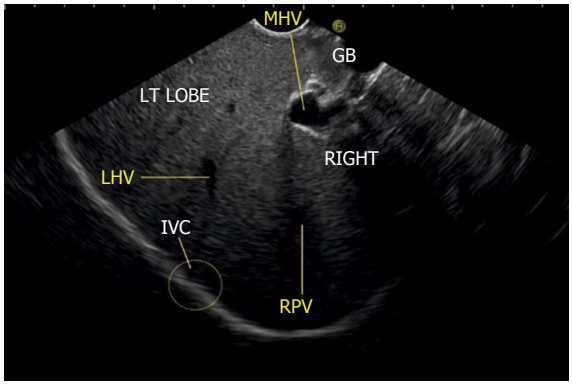

Figure 24 This image shows the course of left hepatic vein on clockwise rotation in duodenal bulb. MHV: Middle hepatic vein; GB: Gallbladder; RHV: Right hepatic vein; LHV: Left hepatic vein; IVC: Inferior vena cava.

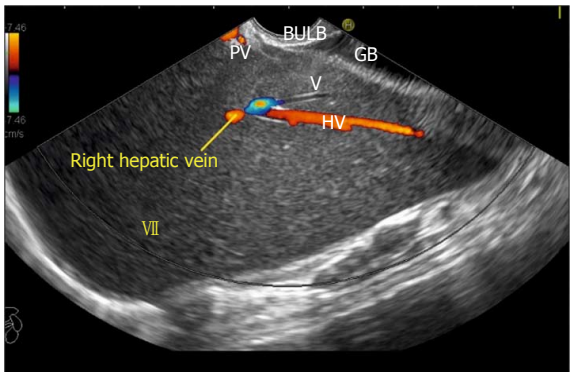

Figure 25 Imaging from duodenal bulb with anticlockwise rotation to visualize the right lobe. The middle hepatic vein is seen coursing from the neck of the gallbladder and the right hepatic vein is seen coursing parallel to the upper surface of gallbladder. An imaginary line can be drawn back to the approximate position of merger into inferior vena cava which is not seen in this frame.

coupled with upwards angulation to prevent the slipping of the scope back into the stomach. During this rotation, the beam moves traces the IVC from behind the kidney towards the heart and sequentially rotates towards the axis of imaging across the right lobe of the liver, the gallbladder fossa and the left lobe of liver. In this position the IVC gradually moves from 9 o'clock position towards 4 o'clock position (Figure 26). During this rotation, the MHV (Figure 27), the RHV (Figure 28) and the LHV (Figure 29) appear one by one and help in identification of all the sectors of liver.

Evaluation of short hepatic/accessory veins

The accessory veins have significant variations in their number and size and the size may be larger, smaller or of the same size as the main hepatic veins. Larger size accessory veins usually provide independent and complete drainage of blood from a complete liver segment[11]. A universal classification of accessory veins is not given in literature and a simple description of accessory veins may mention all veins joining the IVC caudal to the main veins as right, middle or left inferior hepatic veins. Sometimes the accessory veins are classified into two groups according to the side that enter into IVC. The left side veins are called caudal hepatic veins, while the right sided veins are referred to as inferior right hepatic veins. On EUS the evaluation of the anterior and lateral wall of IVC below the joining of main hepatic vein is done in a craniocaudal axis (no vein joins the posterior aspect of IVC) for assessment of accessory veins (Figures 30-32). The number and diameter of hepatic veins joining IVC can be counted. The caudate lobe venous drainage is independent and occurs directly by two small fairly constant veins that enter the left side of IVC (Figure 5). In cases of liver donor, the caudate lobe usually remains in the donor because it directly drains into the IVC. The vena caval openings are considered as large openings with the diameter of 1.5-2 cm and medium when the diameter is 0.5-1.0 cm[11,12]. The distance of accessory vein from the main hepatic vein is important as it may be difficult to apply a single clamp if distance between accessory vein and the confluence of the hepatic vein 5 cm in the coronal plane.

DISCUSSION

EUS of hepatic vein and the tributaries is an operator dependent technique and in expert hands may give a mapping comparable to CT and magnetic resonance imaging. EUS of hepatic veins can help in identification of individual sectors and segments of liver. EUS offers additional superiority in assessing the flow dynamics of individual hepatic veins and can provide an opportunity for assessment of the anatomical features of hepatic vein length, diameter, pattern of joining, and evaluation of segmental venous drainage. Knowledge of the presence of supernumerary right hepatic veins or an inferior hepatic vein may facilitate extrahepatic or intrahepatic venous ligation during resection of the right hemi liver[13-16]. Studies done in animal models have shown a possible route for EUS guided intrahepatic portosystemic shunt from IVC and hepatic vein to portal vein[17]. The EUS anatomy of portal venous system has been well defined[18-20]. The assessment of hepatic veins can be also

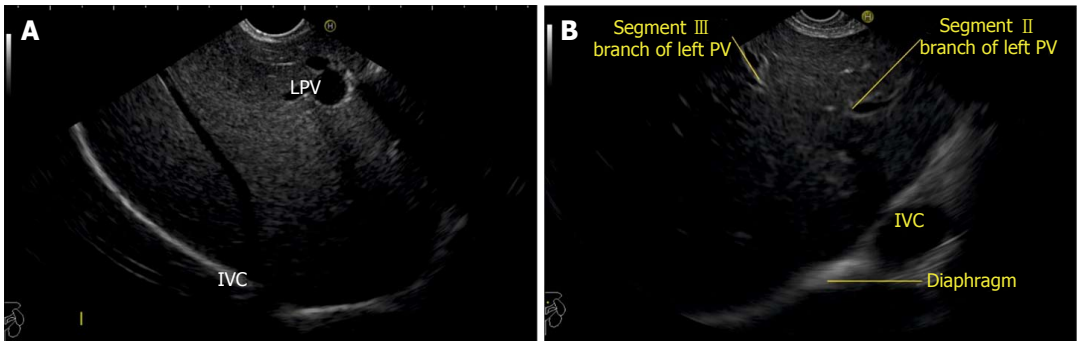

Figure 26 Endoscopic ultrasound from descending duodenum. A: Figure showing right hepatic vein; B: On anticlockwise rotation from 2nd part of duodenum, the inferior vena cava gradually moves from 9 o'clock position towards 4 o'clock position. LPV: Left portal vein; PV: Portal vein; IVC: Inferior vena cava.

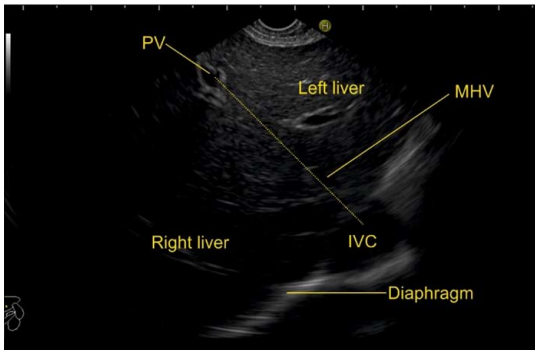

Figure 27 This figure shows the course of middle hepatic vein proceeding towards the portal vein by the dotted line and dividing the right anterior sector from the left medial sector. MHV: Middle hepatic vein; PV: Portal vein; IVC: Inferior vena cava.

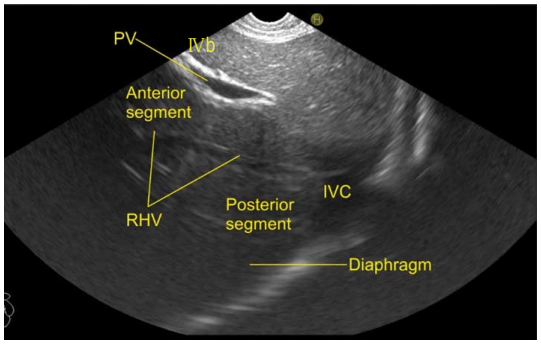

Figure 28 This figure shows the course of right hepatic vein dividing the anterior and posterior sector of right lobe of liver. PV: Portal vein; RHV: Right hepatic vein; IVC: Inferior vena cava.

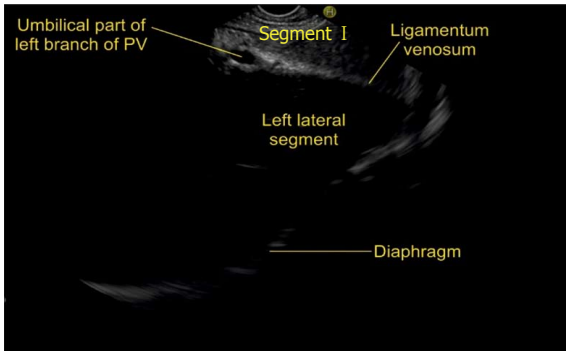

Figure 29 This figure shows the course of ligamentum venosum proceeding towards the umbilical part of portal vein and dividing the left lateral segment from the caudate lobe. The separation of left lateral and left medial segment is done by the course of left hepatic vein but more posteriorly near the liver hilum the ligamentum venosum separates left lateral segment from the caudate lobe. PV: Portal vein.

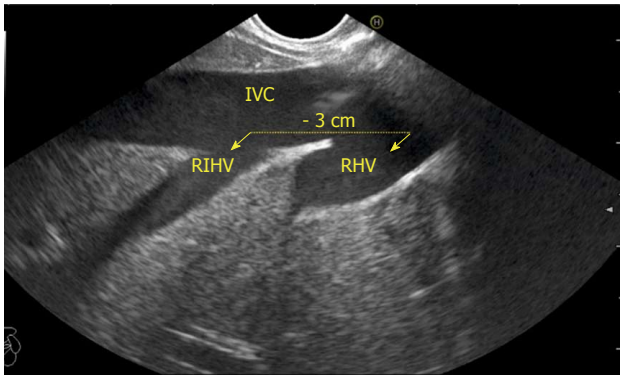

Figure 30 This image shows the presence of prominent right inferior hepatic vein below the right main hepatic vein. This vein has a size almost similar to main right hepatic vein and provides segmental drainage of a complete segment. The distance between right hepatic vein from the right inferior hepatic vein in this image is 3 cm. IVC: Inferior vena cava; RHV: Right hepatic vein; RIHV: Right inferior hepatic vein.

useful for assessing the path and possible techniques of specific hepatic vein puncture in planning a EUS guided procedures involving hepatic veins and portal vein (Figure 33).

CONCLUSION

This article describes a standard technique for visualization of hepatic veins. With practice an imaging of all the hepatic veins is possible from four stations. The imaging from fundus of stomach is the easiest and most convenient method of imaging of hepatic veins. EUS guided interventions may require approach from different stations. Knowledge of the hepatic venous territories and "venous drainage map" may provide

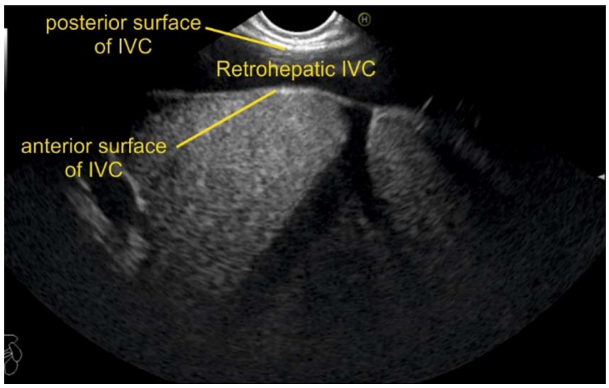

Figure 31 This image shows the right inferior accessory hepatic vein draining the right posterior sector. The presence of liver parenchyma above the joining of the vein points to retro rather than suprahepatic course of the vein. In this case the main right hepatic vein was absent and all the venous drainage was provided by the accessory vein. IVC: Inferior vena cava.

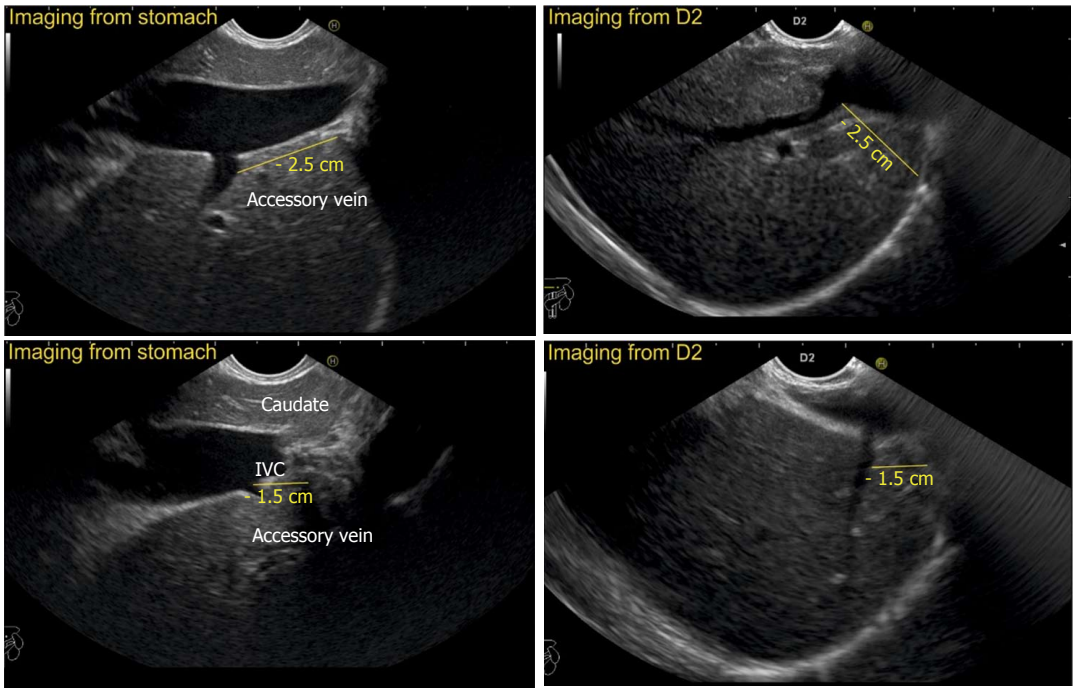

Figure 32 In this case, two accessory veins are seen about 1.5 cm and 2.5 cm below the diaphragm. A comparative imaging of the same accessory vein is shown from stomach and second part of duodenum.

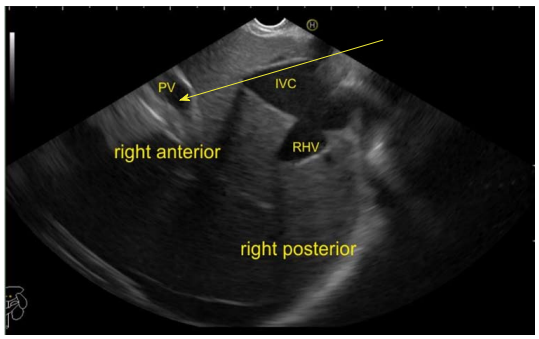

Figure 33 The imaging is done from abdominal part of esophagus and the main portal vein is seen on the far side of the screen. A possible communication is shown between the inferior vena cava and the main portal vein by the arrow. PV: Portal vein; RHV: Right hepatic vein; IVC: Inferior vena cava.

useful information for complex liver surgeries and therapeutic procedure involving hepatic veins.

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ORIGINAL ARTICLE

Case Control Study

Economical effect of lumen apposing metal stents for treating benign foregut strictures

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Abstract

AIM

To evaluate the clinical and economical efficacy of lumen apposing metal stent (LAMS) in the treatment of benign foregut strictures.

METHODS

A single center retrospective database of patients who underwent endoscopic treatment of benign foregut strictures between January 2014 and May 2017 was analyzed. A control group of non-stented patients who underwent three endoscopic dilations was compared to patients who underwent LAMS placement. Statistical tests performed included independent *t*-tests and five-parameter regression analysis

RESULTS

Nine hundred and ninety-eight foregut endoscopic dilations were performed between January 2014 and May 2017. 15 patients underwent endoscopic LAMS placement for treatment of benign foregut stricture. Thirty-six patients with recurrent benign foregut strictures underwent three or more endoscopic dilations without stent placement. The cost ratio of endoscopic dilation to LAMS (stent, placement and retrieval) is 5.77. Cost effective analysis demonstrated LAMS to be economical after three endoscopic dilation overall.

LAMS was cost effective after two dilations in the Post-surgical stricture subgroup.

CONCLUSION

Endoscopists should consider LAMS for the treatment of benign foregut strictures if symptoms persist past three endoscopic dilations. Post-surgical strictures may benefit from LAMS if symptoms persist after two dilations in a post-surgical. Early intervention with LAMS appears to be a clinically and economically viable option for durable symptomatic relief in patients with these strictures.

Key words: Benign esophageal stricture; Endoscopy economics; Stent economics; Self expandable metallic stents; Esophageal diseases

Core tip: The findings of our study will be helpful with clinical decision making when treating benign strictures of the esophagus and foregut. The main finding of our study is that lumen apposing metal stents have the potential to have an economical advantage over repeated dilations in the treatment of recurrent benign foregut strictures. Reports of placing lumen apposing stents as an alternative to serial endoscopic dilation have been reported, however no economic analysis has been published.

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INTRODUCTION

Pathological or therapeutic disruption of the foregut tissue is common, yet diverse in both its etiology and severity. Surgical anastomosis, peptic injury, radiation, caustic ingestion, eosinophilic esophagitis, Schatzki rings and esophageal webs all disrupt the innate tissue and predispose to luminal stricture formation[1,2]. The mechanism by which esophageal strictures develop is hypothesized to be the result of fibrous tissue production and collagen deposition stimulated by deep ulceration or chronic inflammation[3,4]. The principle symptoms of foregut stricture disease include, dysphagia, early satiety, epigastric pain, heart burn, nausea and vomiting. The current gold standard treatment of foregut strictures is endoscopic dilation. It is not uncommon for patients to undergo multiple dilations to achieve remission, while some have persistent disease forcing clinicians to face challenging management decisions. Currently, there are no established reliable predictors to identify which strictures will respond optimally to dilation. Additionally, there is no expert consensus regarding the frequency of dilations necessary to define a refractory structure[5].

An evolving, but "off label" treatment for benign foregut strictures is placing stents for sustained esophageal patency. The use of self-expandable metal stents (SEMS) has the benefit of providing an ongoing radial force to suppress the stricture and maintain luminal patency. The SEMS design has been innovated upon, ultimately resulting in the creation of the lumen apposing metal stent (LAMS). LAMS are short, self-expanding, fully covered, metal stents with large flanges that anchor the stent at both ends.

Clinical guidelines, supported by large studies and systemic reviews have validated the use of stents as an acceptable salvage therapy in the treatment of refractory benign and malignant strictures; however, these studies did not include LAMS[5-10].

The objective of this study is to examine the use of LAMS in the treatment of benign foregut strictures. Case series and case reports have documented the use of LAMS in benign strictures of various etiology at different locations in the foregut[11-17]. We aim to illustrate the clinical effectiveness and economics of LAMS.

MATERIALS AND METHODS

Institutional review board approval was obtained for the development of a retrospective database to evaluate the efficacy of LAMS in the treatment of benign foregut strictures. The database used for this study included all patients who underwent endoscopic dilation or LAMS placement for treatment of benign foregut strictures at a single non-university tertiary care center. The database was constructed by manual review of the electronic health record (EHR) system of a large regional health system. This retrospective case-control study was reported in accordance with the STROBE statement[18].

Current procedural terminology (CPT) codes were used to identify the most recent 1000 controlled radial balloon dilation (CRE) and Savary-Gilliard dilations of the foregut. All endoscopic procedures performed between January 2014 and May 2017 was reviewed, 998 procedures were identified. These procedures were reviewed to isolate all patients who underwent three or more CRE or Savary-Gilliard dilations during the 40-mo period, and 36 patients fit these criteria. Three or more dilations were selected as our inclusion criteria for recurrent strictures based on the fact that LAMS placement required a minimum of two endoscopies and LAMS placement is rarely first line therapy at our institution. The 36 patients' medical records were interrogated to establish a control group for the comparison of LAMS versus serial endoscopic dilation.

Fifteen patients underwent endoscopic LAMS placement for treatment of benign foregut stricture disease. The LAMS were placed without electrocautery or sutures with the intention of maintaining luminal patency for 90 d or until surgical revision. The LAMS utilized were 10 mm in length, fully covered, with bilateral 21 mm or 24

Table 1 The mean time between dilations for all patients in the recurrent dilation group

	n	Mean time between dilations (d)	SD	*t*	*P*
Male	20	146.8	169.7	-0.01	0.9
Female	16	147.5	141.1		
Non-Surgical	31	137.6	159.9	-1.1	0.3
Surgical	5	205.7	121.4		

mm flanges. When deployed the stent self-expanded to a luminal diameter of 10 mm or 15 mm (Axios™ Stent, Boston Scientific©, Marlborough, MA, United States). The patients who underwent LAMS placement consented to undergoing treatment with a medical device in an "off label" non-United States Federal Drug Enforcement Agency (FDA) approved indication.

Clinical end points were the number of symptom free days and the number of days between endoscopic dilations. The number of symptom free days and days between each endoscopic procedure was determined by documentation in the EHR and reported as mean time between dilations (MTBD) and mean symptom free days (MSFD). The review of EHR documentations was performed by a physician who is not a gastroenterologist to prevent potential bias. Complications were defined as removal of the stent prior to the intended 90-d duration of placement or hospital admission for gastrointestinal symptoms. Endoscopies performed prior to this study's 2014 start date were reviewed when available.

Statistical analysis

All statistical analysis was performed by a biostastician using IBM SPSS Statistics for Windows, Version 24 (IBM Corp., Armonk, NY, United States). Statistical tests performed included independent *t*-tests and five-parameter regression analysis with the independent variable being endoscopic dilations as pair indices and the dependent variable being time. All patients that lacked sufficient follow up to accurately characterize their post stent clinical course were included in the descriptive statistical analysis and excluded from the case control analysis. Statistical significance was determined using a threshold of $P = 0.05$.

Economic analysis

The economic analysis was designed utilizing the recommendations of the International Association of Health Technology Agencies to increase generalizability to clinical gastroenterologists[19]. The 2016 Medicare National Average Payment fee schedule that was issued by Center for Medicare and Medicaid Services in January of 2016 was used to determine the cost of endoscopic interventions. A 2% reduction was calculated on all costs to reflect the sequestrations placed by the United States government on all Medicare rates. The cost we associated with each endoscopic dilation is the mean cost of a CRE and Savary-Gilliard dilations. The cost of the LAMS was the specific per unit cost at our institution. The breakeven number for using a stent is calculated by dividing the delta between the MSFD and MTBD by the coefficient of the regression.

RESULTS

Recurrent dilation group

Strictures of non-anastomotic origin accounted for 86.1% ($n = 31$). Five post-surgical strictures located at anastomotic sites accounted for 13.9% of the recurrent dilation group (Table 1). Patients' ages ranged from 26 to 90 years with a median of 66 years of age. The majority of patients were men (55.6%, $n = 20$). The MTBD was 147 ± 156 d.

The regression results demonstrate that after the initial endoscopic dilation, patients with recurrent benign esophageal strictures will have a decreased time between subsequent dilations that averages 28 d. The reduction of time between subsequent dilations was 20 d in non-surgical strictures and 64 d in postoperative strictures.

LAMS group

The LAMS group consisted of 15 patients who underwent endoscopic LAMS placement as an adjunctive treatment for various benign strictures of the foregut (Table 2). Strictures occurred post surgically at locations including: Gastrojejunal anastomosis (GJ), Roux-en-Y gastric bypass (RYGB), vertical band gastroplasty (VBG), esophagogastric anastomosis (EG). The majority of the LAMS group were post-surgical strictures, of which 27% ($n = 4$) resulted from weight loss surgeries. Thirteen percent ($n = 2$) of patients had post procedural dysphagia and abdominal pain leading to elective premature LAMS removal (Table 2). Patient eight obtained partial relief of dysphagia on the initial LAMS which recurred promptly after LAMS removal prompting insertion of a second LAMS 21 d later intended to provide symptomatic relief prior to surgical intervention. Patient 14 underwent LAMS placement for a persistent peptic stricture of the duodenal bulb which initially relieved some symptoms, however; symptoms recurred and the LAMS was removed and replaced 74 d later for worsening symptoms.

The median length of follow up was 299 d (range, 7-628). The median duration of the endoscopic LAMS placement was 14.7 min (range, 3.3-68.3), LAMS removal had a median endoscopy duration of 14.7 min (range, 1.7-28.2).

Sixty percent ($n = 8$) of the LAMS group had sufficient follow up for inclusion in a multivariate regression

Table 2 Pre and post lumen apposing metal stent details for the all patients who underwent endoscopic treatment during a 40-mo period at a non-university tertiary care center

Patient	Age (yr)	Gender	Anastomotic Stricture (Yes/No)	Stricture location	Prior foregut surgery	EGD dilations prior to stenting	Duration of stent insertion (d)	Stent migration (Yes/No)	Adverse Events	Symptomatic relief	Post stent Interventions
1	59	M	Yes	GJ	RYGB	2	168	No	No	Yes	No
2	46	F	Yes	GJ	RYGB	3	91	No	No	Yes	No
3[1]	62	F	Yes	GJ	Distal gastrectomy	3	90	No	No	Yes	Surgical Revision
4[1]	86	M	No	Pyloric channel	Subtotal gastrectomy	3	138	No	No	Yes	No
5[1]	90	M	No	Distal esophagus	Nissen fundoplication	3	91	No	No	Yes	No
6	78	F	No	Distal esophagus	Nissen fundoplication	4	31	No	No	Yes	No
7	65	F	No	Pyloric channel	No	2	< 159	Yes	No	Yes	No
8[1]	65	F	No	Mid Gastric Body	VBG	1	Stent 1: 184, Stent 2: 162	No	No	Yes	Surgical VBG removal
9	73	F	No	Pyloric channel	No	2	98	No	No	Yes	No
10	78	F	No	Mid Gastric Body	VBG	3	-	-	No	Yes	-
11	72	M	Yes	EG	ILE	0	50	No	No	Yes	No
12[1]	56	M	Yes	EG	ILE	4	15	No	Yes-Chest pain	No	Yes-EGD dilation
13[1]	73	F	Yes	EG	Total gastrectomy	3	7	No	Yes-Abdominal Pain	No	Yes-EGD dilation
14	69	M	No	First duodenal segment	No	1	Stent 1: 116 Stent 2: 265	No	No	No	-
15	78	M	No	Duodenal bulb	No	3	20	No	Yes- Obstructive jaundice from stent pressure	No	-

[1]Indicates patients included in the multivariate regression analysis. M: Male; F: Female; GJ: Gastro-jejunal anastomosis; RYGB: Roux-en-Y gastric bypass; VBG: Vertical band gastroplasty; EG: Esophago-gastric anastomosis; D1: Duodenal segment 1; D2: Duodenal segment 2.

analysis (Table 3). Of the eight patients in the LAMS group included in the multivariate analysis, 63% (n = 5) had benign esophageal strictures, and 25% (n = 2) had pyloric stenosis. No difference was seen when performing an independent t test comparing patient gender and MSFD (t = - 0.014, P = 0.95) in patients treated with LAMS. Similarly, surgical versus non-surgical stricture etiology did not demonstrate a difference in MSFD (t = 0.72, P = 0.511).

Clinical comparison

Comparing the MTBD of the 36 patients in the dilation group with that of the LAMS group showed a higher number of symptom free days in each analyzed subcategory (Table 4). Significant differences in the MTBD are demonstrated when comparing all patients in the LAMS group versus their recurrent dilation counterpart (P = 0.011). Sub-analysis dividing the patients by gender and surgical setting (if the stricture was post-surgical) showed that males who underwent LAMS placement reported significantly more symptom free days than their recurrent dilation group counterpart (P = 0.013) (Table 4).

Table 3 Regression analysis of the time between dilation (d) for patients who underwent lumen apposing metal stent placement

	R^2	Intercept	Coefficient	*F*	*P*
Mean overall	68.3%	220.3	-27.8	8.6	0.04
Mean female	16.9%	192	-17.4	0.8	0.41
Mean male	96.1%	250	-39.3	99.3	0.001
Mean surgical	62.2%	96.2	-63.3	6.5	0.06
Mean nonsurgical	62.8%	188.3	-19.4	6.7	0.06

Table 4 The comparison of clinical outcomes in the lumen apposing metal stent and recurrent dilation groups

	Group	*n*	Mean symptom free days	SD	*t*	*P* (two tail)
Overall	Dilation	36	153	153.7	2.9	0.01
	LAMS	8	327	156.9		
Male	Dilation	20	147	169.04	3.5	0.01
	LAMS	3	347	73.7		
Female	Dilation	16	160	137.2	2.1	0.09
	LAMS	5	353	190.9		
Nonsurgical	Dilation	31	144	158.7	1.5	0.26
	LAMS	3	298	165.6		
Surgical	Dilation	5	209	114.08	2.06	0.07
	LAMS	5	382	148.8		

LAMS: Lumen apposing metal stent.

Table 5 The economic analysis for lumen apposing metal stent utilization

	MSFD	MSFD/Cost Ratio	MTBD	Coefficient from Regression	Breakeven *n*
Overall	327	56.7	153	27.8	3.4
Male	347	60.1	147	39.3	2.2
Surgical	382	66.2	209	63.3	2.2

MSFD: Mean symptom free days; MTBD: Mean time between dilations (d).

Economic analysis results

The average cost of an endoscopic dilation is $1282, whereas the cost of a LAMS is $4060, endoscopic insertion and endoscopic removal cost $2399 and $937 respectively. The total cost for the LAMS and endoscopic insertion and removal is $7396; thus, a cost ratio is 5.7. Dividing the overall MSFD for the LAMS group and the recurrent dilation group by the cost ratio demonstrates that LAMS placement only became economical when the time between dilation is less than or equal to 57 d (Table 5). The overall MTBD for the recurrent dilation and LAMS group is 152 d. The overall breakeven number for using LAMS is 3.5 dilations, thus endoscopic LAMS placement is economical after the three dilations.

DISCUSSION

The use of esophageal prosthesis began over a century ago and progressed into commercially available applications in the 1970s. The current generation of SEMS were initially used in the biliary tree before being developed into esophageal specific applications in the 1990's[20]. The recommended use of SEMS is most clearly defined in the malignant stricture population; however, ambiguity exists in the use of SEMS in benign strictures of the gastrointestinal tract. Complications of stent migration and variability in efficacy of SEMS have limited their use in benign strictures.

The FDA approved the first LAMS in 2012 for the endoscopic treatment of pancreatic pseudocysts[21]. There is a paucity of published experience using LAMS in the treatment of benign foregut strictures, with only three studies, including ours, containing 15 or more patients[11,12]. The limited number of studies utilizing LAMS in benign stricture disease is primarily due to the low use of "off label" non-FDA approved devices. As such, we believe our results along with Irani *et al*[12] and Yang *et al*[11]'s showcase the utility of LAMS in the treatment of benign foregut strictures.

Clinical outcomes

Our results are most similar to the prospective multicenter trial performed by Yang *et al*[11]. Yang *et al*[11]'s cohort included 23 patients who underwent an average of 3.7 endoscopic dilations prior to LAMS placement. As such, this demonstrated the generalizability of our control group, which included individuals who underwent three or more endoscopic dilations. In addition to the 23 foregut LAMS placements, Yang *et al*[11]'s cohort included four colonic stricture stent placements with 60 d (IQR, 40-90 d) median duration of LAMS placement compared to our median of 96 d (IQR, 41-161 d). Both our cohort

and Yang *et al*[11]'s did not experience any tissue overgrowth or technical difficulties with LAMS removal; yet, these issues were encountered in Irani *et al*[12]'s series. The adverse events related to LAMS extraction could be more prevalent in Irani *et al*[12]'s series due to their 300 d median follow up time post LAMS insertion, which is slightly larger than both Yang *et al*[11]'s and our own cohort, which had median follow up times of 100 and 299 d respectively. Yang *et al*[11], Irani *et al*[12] and our own cohort all reported encountering patients with pain following LAMS insertion that was severe enough to prompt premature LAMS removal, the mean incidence of premature LAMS removal due to pain was 6% (range, 4.3%-7%). Our study included a unique adverse event after LAMS was placed across a duodenal bulb stricture (Table 2, Patient 15), in which the distal flange of the stent created backpressure on the intraduodenal segment of the common bile duct leading to abdominal pain and obstructive jaundice resulting in stent removal 20 d after placement.

Stent migration

In 2015, Fuccio *et al*[9] performed a meta-analysis of SEMS use in refractory benign esophageal stricture. Fuccio *et al*[9]'s meta-analysis reported a stent migration rate of 36% in fully covered self-expanding metal stents (FCSEMS)[9]. Twenty-two percent of the patients in Fuccio *et al*[9]'s analysis who underwent FCSEMS placement met the Kochman *et al*[22]'s criteria for refractory benign esophageal stricture meaning they underwent at least five dilation sessions and/or cycles with dilation to at least 14 mm.

LAMS migration was confirmed in one of 15 patients in this study although a second stent migration could have occurred in the single patient lost to follow up (Table 2, Patient 11). Our reported LAMS migration rate of 6.7%-13.3% of patients is consistent with the two largest studies of LAMS that collectively had a migration rate of 7.5% in their 58 cases[12,13].

Clinical success

Eighty-one percent of patients in our study had symptomatic relief. Repeat endoscopic procedures after LAMS placement was limited to stent exchanges in two patients and a non-therapeutic endoscopy in one patient. LAMS successfully controlled symptoms in two patients prior to undergoing revision gastric surgery. Approximately 83% of patients were symptom free at 100 d after LAMS removal in Yang *et al*[11]'s study, and the clinical success rate at 6 mo follow up was 61% in Irani *et al*[12]'s study.

Economic analysis

The cost breakeven point of the overall group is 3.5 and 2.2 dilations in the post-surgical group, which shows that stent placement may have an economical advantage over recurrent dilation after the third dilation. The male subgroup demonstrated a cost breakeven point after the second dilation; however, this finding is limited by a lack of sufficient number of subjects to provide a female subgroup analysis. Although our study did not utilize Kochman *et al*[22]'s criteria for refractory benign esophageal strictures as an inclusion requirement, applying our breakeven point for LAMS placement would demonstrate LAMS to be cost effective in all benign recurrent esophageal strictures as defined by Kochman *et al*[22].

Endoscopists should welcome LAMS as a second line therapy for benign foregut strictures, as it has shown to be a clinically and economically effective treatment modality for managing the devastating symptoms of benign foregut strictures.

An interesting secondary finding from the analysis of the control group was the time between dilations was decreasing by 28 d between each dilation. This surprising finding should be expanded on in further studies that aim to elucidate the pathogenesis of benign foregut stricture formation.

The most significant limitation of our study beyond those inherent to retrospective analysis is the low sample size; however, this is to be expected in the study of a non-FDA approved use of a medical device. The absence of a formal symptom scoring system at post procedure clinic visits and the inability to follow all subjects long term makes our data mildly vulnerable to subject reporting and selection bias. More prospective trials are needed to develop a professional consensus on the role of LAMS in the treatment of benign foregut strictures.

ARTICLE HIGHLIGHTS

Research background

The use of lumen apposing metal stents (LAMS) began in 2012 as a treatment modality for pancreatic pseudocysts. Currently, LAMS are being used in various endoscopic procedures such as pancreatic pseudocyst drainage.

Research motivation

The key question of our study is How effective and economical is the use of LAMS in the treatment of benign foregut strictures.

Research objectives

The main objective of this study was to determine how to appropriately utilize LAMS in the treatment of benign foregut strictures. Benign foregut strictures frequently recur therefore this study will contribute to the literature used to determine treatment strategies for these difficult recurrent strictures.

Research methods

The research methods that were adopted to realize our objective was a single center retrospective case-control study. The case-control study was complemented by a cost effectiveness analysis.

Research results

The cost breakeven point of using a LAMS compared to repeat endoscopic dilation was 3.5 and 2.2 dilations in patients with benign foregut strictures and post-surgical strictures, respectively. Our results demonstrate that stent placement may have an economical advantage over recurrent dilation once a patient has undergone three endoscopic dilations. The optimal duration of stent placement to provide maximum efficacy and minimum adverse events remains unknown, further prospective multicenter studies are needed.

Research conclusions

This study presents the novel finding that inserting a LAMS instead of serial

dilations can be a cost-effective treatment. We believe our results demonstrate that recurrent endoscopic dilation of benign foregut strictures can be optimally treated by LAMS in well selected patients. In summary, this study demonstrates that the interval between endoscopic dilations decreases overtime after each subsequent dilation. The use of LAMS for benign foregut strictures has been reported however we utilized an economic analysis to prove our hypothesis that there is a potential cost savings.

Research perspectives

This study has important clinical implications particularly in the United States where the placement of a LAMS for any reason other than evacuating a pancreatic pseudocyst is not Federal Drug Enforcement Agency approved. Endoscopists can incorporate the findings of this study into their clinical practice when treating patients whose benign foregut strictures continue to require endoscopic dilations.

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ORIGINAL ARTICLE

Retrospective Study

Yield of capsule endoscopy in obscure gastrointestinal bleeding: A comparative study between premenopausal and menopausal women

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Abstract

AIM

To evaluate differences in capsule endoscopy (CE) performed in the setting of obscure gastrointestinal bleeding (OGIB) among premenopausal women (PMW) and menopausal women (MW).

METHODS

Retrospective, single-center study, including female patients submitted to CE in the setting of OGIB between May 2011 and December 2016. Patients were divided into 2 groups according to age, considering fertile age as $\leqslant$ 55 years and postmenopausal age as > 55 years. The diagnostic yield (DY), the rebleeding rate and the time to rebleed were evaluated and compared between groups. Rebleeding was defined as a drop of Hb > 2 g/dL or need for transfusional support or presence of melena/hematochezia.

RESULTS

A hundred and eighty three female patients underwent CE for OGIB, of whom 30.6% (n = 56) were PMW and 69.4% (n = 127) were MW. The DY was 30.4% in PMW and 63.8% in MW. The most common findings were angiodysplasias in both groups (PMW: 21.4%, MW: 44.9%) (P = 0.003). In PMW, only 1.8% required therapeutic endoscopy. In 17.3% of MW, CE findings

led to additional endoscopic treatment. Rebleeding at 1, 3 and 5 years in PMW was 3.6%, 10.2%, 10.2% and 22.0%, 32.3% and 34.2% in MW. Postmenopausal status was significantly associated with higher DY (P < 0.001), TY (P = 0.003), rebleeding (P = 0.031) and lower time to rebleed (P = 0.001).

CONCLUSION

PMW with suspected OGIB are less likely to have significant findings in CE. In MW DY, need for endoscopic treatment and rebleeding were significantly higher while time to rebleed was lower.

Key words: Diagnostic yield; Obscure gastrointestinal bleeding; Premenopausal women; Menopausal women; Capsule endoscopy

Core tip: Patients with negative findings in oesophagogastroduodenoscopy and colonoscopy with suspected obscure gastrointestinal-bleeding benefit from further capsule endoscopy (CE) study. Premenopausal women are frequently referred for CE. However in this subset of patients the pretest probability of positive findings is thought to be low. This paper compared the diagnostic yield (DY) as well as therapeutic yield (TY), rebleeding, hospitalization and mortality between premenopausal and menopausal women. We found that menopause status was significantly associated with positive findings, DY, TY, rebleeding and lower time to rebleed. This may lead to consider the exclusion of other comorbid pathologies in fertile age women before CE.

Silva JC, Pinho R, Rodrigues A, Ponte A, Rodrigues JP, Sousa M, Gomes C, Carvalho J. Yield of capsule endoscopy in obscure gastrointestinal bleeding: A comparative study between premenopausal and menopausal women. *World J Gastrointest Endosc* 2018; 10(10): 301-307 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i10/301.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i10.301

INTRODUCTION

Obscure gastrointestinal bleeding (OGIB) accounts for approximately 5% of all cases of gastrointestinal (GI) bleeding and is usually due to a lesion in the small bowel[1]. OGIB can be classified as overt or occult[2]. In patients who have documented overt GI bleeding (excluding hematemesis) and negative findings on high-quality oesophagogastroduodenoscopy (OGD) and colonoscopy, capsule endoscopy (CE) is recommended as the next diagnostic step[3]. Patients with occult GI blood loss and negative findings in OGD and colonoscopy need comprehensive evaluation, including CE to identify an intestinal bleeding lesion[4]. In premenopausal women (PMW) gynecologic etiologies are the most frequent cause of anemia, although GI bleeding is reported as a cause of anemia in 12%-30%[5,6]. Re-bleeding after negative CE study in PMW is often due to menstrual blood loss[7-9]. Taking this in consideration it is necessary to clarify the differences in DY, TY and rebleeding in OGIB between PMW and MW. In PMW with suspected OGIB CE study may not be the first choice, considering the possibility of gynecologic blood loss and the lower rates of small bowel lesions[10].

Diagnostic yield (DY) of CE has already been evaluated, particularly in OGIB[11-13]. Age is an important factor, and more frequently older patients are referred for OGIB investigation through CE. In this group of patients DY is higher[14].

Few trials have compared CE findings in OGIB according to the menopausal status and some reported a lower DY in CE performed in PMW[10,15].

The present study aimed to evaluate and compare the DY of CE between PMW and menopausal women (MW). Secondary outcomes included a comparison of therapeutic yield (TY), rebleeding, hospitalization and mortality for OGIB between PMW and MW who underwent CE.

MATERIALS AND METHODS

Patient and data collection

A cohort of female patients with OGIB who underwent CE after bidirectional endoscopy at Centro Hospital Vila Nova de Gaia from May 2011 to December 2016 was evaluated. Patients were followed-up until April 2018. Patients were then divided into 2 groups according to age, considering fertile age as ⩽ 55 years and postmenopausal age as > 55 years.

Patient clinical information was retrospectively collected from electronic medical records, and included demographic characteristics (gender, age); comorbidities (cardiovascular, renal, hepatic disease); medical therapy [anticoagulants, antiplatelet and nonsteroidal anti-inflammatory drugs (NSAIDs)]; hemoglobin (Hg) at admission and number of units of packed red blood cells (RBC) transfused prior to CE.

CE

Written informed consent was obtained from all patients. In this study the Mirocam® Video Capsule system was used and the examinations were carried out according to our unit protocol. Patients underwent a clear liquid diet the day before and a fasting period of 12 h before the exam. Oral iron supplements were suspended at least 8 d before the procedure.

After CE ingestion, patients were evaluated 1-2 h after, through realtime visualization and a prokinetic agent was administered if the CE was retained in the stomach. Oral light diet was initiated 4 h after CE ingestion. The recorder was removed 12 h after CE ingestion. Earlier removal of the recorder demanded realtime visualization, confirming a colonic location of

Table 1 Patient characteristics *n* (%)

No. of patients (*n* = 183)	All	PMW (30.6%, *n* = 56)	MW (69.4%, *n* = 127)	*P* value[1]
Age (mean ± SD, yr)	64.3 ± 15.8	43.7 ± 8.0	74.3 ± 7.9	< 0.001
Comorbidities				
Chronic kidney disease	24 (13.1)	0 (0)	24 (18.9)	< 0.001
Coronary artery disease	20 (10.9)	3 (5.4)	17 (13.4)	0.11
Heart failure	47 (25.7)	0 (0)	47 (37.0)	< 0.001
Hepatic disease	7 (3.8)	1 (1.8)	6 (4.7)	0.34
Atrial fibrillation	33 (18.0)	2 (3.6)	31 (34.4)	0.001
Drugs				
Anticoagulation	35 (19.1)	2 (3.6)	33 (26.0)	< 0.001
Anti-platelet drugs	57 (31.1)	6 (10.7)	51 (40.2)	< 0.001
NSAIDs	61 (33.3)	8 (14.3)	53 (41.7)	< 0.001

[1]*t* -test: χ^2 test, as appropriate; *P* value of 0.05 indicating statistical significance; PMW: Premenopausal women; MW: Menopausal women; NSAIDs: Nonsteroidal anti-inflammatory drug.

CE.

CE cleansing was evaluated according to the qualitative scale developed by Brotz *et al*[16], and appropriate cleansing was assumed when graduated as excellent, good or fair.

CE findings were classified as positive and negative findings. Positive findings included bleeding without visible lesions, angiodysplasia, varices, hemangioma, ulcer, erosion, eroded polyps, diverticulum with bleeding stigmata or small-bowel tumor.

The DY was defined as the proportion of CE with positive findings compared to the total number of female patients included in the study. The TY was defined as the proportion of patients performing endoscopic treatment compared to the total number of female patients included in the study. Rebleeding, time to rebleed, hospitalization and mortality were also evaluated. Rebleeding episodes were defined as evidence of melena or hematochezia, a drop in Hg ⩾ 2 g/dL from baseline, and/or the need for transfusion[17-19].

Statistical analysis

Data were analyzed using SPSS version 23.0. Descriptive statistics were used to describe the patient's demographic features, clinical characteristics and type of endoscopic findings. Categorical variables were presented as percentages and numeric variables as means. Results are expressed as percentages or mean ± SD for continuous variables.

The χ^2 test was used to compare non-continuous variables. The *t*-test was used to compare continuous variables. The Kaplan-Meier test was used to calculate the time to rebleed. The Log-Rank test was used to compare the time to rebleed between groups. A $P < 0.05$ was considered to be statistically significant.

RESULTS

Sample analysis

In our study, 183 female patients underwent CE for OGIB, of whom 30.6% were PMW (*n* = 56) and 69.4% were MW (*n* = 127). Patient characteristics are shown in Table 1. The mean age was 64.3 years (SD 15.8). Most patients were referred for occult OGIB (82.5%, *n* = 151), while 17.5% (*n* = 32) had overt OGIB. Iron deficiency anemia (IDA) was the most common indication (81.4%, *n* = 149) followed by melena (9.8%, *n* = 18), hematochezia (7.7%, *n* = 14) and positive fecal occult blood test (1.1%, *n* = 2). Mean Hg value before CE was 9.7 g/dL (SD 2.0). OGIB needing transfusional support was identified in 34.4% (*n* = 63). Indication for CE, mean Hg value and need of transfusional support are shown in Table 2.

Concerning comorbidities, 25.7% had heart failure (*n* = 47), 18% had atrial fibrillation (*n* = 33), 13.1% had chronic kidney disease (*n* = 24) and 3.8% had liver disease (*n* = 7). Drugs increasing bleeding risk were also evaluated: 19.1% took vitamin K antagonists or direct oral anticoagulants, 31.2% were medicated with aspirin or thienopyridines and 33.3% took NSAIDs.

CE findings are presented in Table 3. Small bowel cleansing was considered appropriate in 77.6% (*n* = 142) CE studies. Most patients had positive findings (66.7%, *n* = 122). Angiodysplasias were the most frequent finding (37.7%, *n* = 69) followed by ulcers/erosions (9.8%, *n* = 18) (Figure 1) and mass lesions (8.7%), namely tumors 7.1% [gastrointestinal stromal tumor (GIST) and subepitelial lesions] and polyps 1.6%. Blood in the GI tract was observed in 12.6% CE (*n* = 23), of which in 60.9% no lesions were identified. Angiodysplasias were classified according to the Saurin *et al*[7] classification system as P1 (66.7%, *n* = 46) and P2 (33.3%, *n* = 23). Considering the timing of CE most patients were studied > 14 d (88.0%, *n* = 161) while a minority underwent CE within the first 14 d (48 h-14 d in 8.2%, *n* = 15 and < 48 h in 3.8%, *n* = 7).

The outcomes of CE are shown in Table 4. The DY was 53.6% (*n* = 98), TY 12.6% (*n* = 23). The rebleeding rate was 16.4%, at 1 year, 25.8%, at 3 years and 27.2% at 5 years (Figure 2). The hospitalization rate was 7.1% (*n* = 13) and the global mortality 1.0% (*n* = 2) (Table 4).

Table 2 Indication, mean hemoglobin value and need of transfusional support in all patients, and between premenopausal and menopausal groups *n* (%)

No. of patients (*n* = 183)	All	PMW (30.6%, *n* = 56)	MW (69.4%, *n* = 127)	*P* value[1]
Indication for CE				0.11
Occult OGIB	151 (82.5)	50 (89.3)	101 (79.5)	
Overt OGIB	32 (17.5)	6 (10.7)	26 (20.5)	
IDA	149 (81.4)	50 (89.3)	99 (78.0)	
Positive fecal occult blood test	2 (1.1)	0 (0)	2 (1.6)	
Hematochezia	14 (7.7)	2 (3.6)	12 (9.4)	
Melena	18 (9.8)	4 (7.1)	14 (11.0)	
Hb prior to CE, g/dL	9.7 (± 2.0)	10.4 (± 1.7)	9.3 (± 2.1)	0.001
Need of transfusional support prior to CE	63 (34.4)	7 (12.5)	56 (44.1)	< 0.001

[1]*t*-test: χ^2 test, as appropriate; *P* value of 0.05 indicating statistical significance. CE: Capsule endoscopy; PMW: Premenopausal women; MW: Menopausal women; OGIB: Obscure gastrointestinal bleeding; IDA: Iron deficiency anemia; Hb: Hemoglobin.

Table 3 Capsule Endoscopy findings in all patients, and between premenopausal and menopausal groups *n* (%)

No. of patients (*n* = 183)	All	PMW (30.6%, *n* = 56)	MW (69.4%, *n* = 127)	*P* value[1]
Positive Findings	122 (66.7)	31 (55.4)	91 (71.7)	0.031
CE Findings				
Angiodysplasias	69 (37.7)	12 (21.4)	57 (44.9)	
Ulcers/erosions	18 (9.8)	11 (19.6)	7 (5.5)	
Mass lesions	16 (8.7)	5 (8.9)	11 (8.7)	
Meckel's diverticulum	3 (1.6)	0 (0)	3 (2.4)	
Other	2 (1.0)	2 (3.6)	0 (0)	
Saurin's Classification				0.043
P1	46 (66.7)	11 (91.7)	35 (61.4)	
P2	23 (33.3)	1 (8.3)	22 (38.6)	
Blood in GI tract	23 (12.6)	3 (5.4)	20 (15.7)	0.051
Blood with no lesions	14 (7.7)	1 (1.8)	13 (10.2)	
Adequate small bowel cleansing	142 (77.6)	44 (78.6)	56 (44.1)	0.83

[1]*t*-test: χ^2 test, as appropriate; *P* value of 0.05 indicating statistical significance. CE: Capsule endoscopy; PMW: Premenopausal women; MW: Menopausal women; Saurin *et al*[7] Classification: Positive-P2 (high potential for bleeding) and negative-P1 (uncertain hemorrhagic potential).

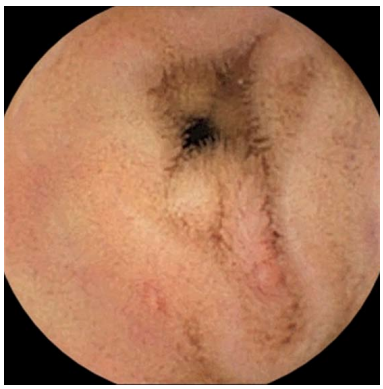

Figure 1 Capsule endoscopy of menopausal women with milimetric erosions in the jejunum.

Per group analysis

The mean age of MW was 73.4 ± 7.9 years and for PMW 43.7 ± 8.0 years. Post-menopausal age was associated with significantly higher comorbidities, namely heart failure (*P* < 0.001), chronic kidney disease (*P* < 0.001) and atrial fibrillation (*P* = 0.001). In this group use of anticoagulants, anti-aggregants and NSAIDs was significantly higher (*P* < 0.001). Mean Hg level at CE study was lower in MW (9.3 ± 2.1 g/dL) compared to PMW (10.4 ± 1.7 g/dL). The need of blood transfusion before CE was significantly higher in MW (44.1% *vs* 12.5%) (*P* < 0.001). IDA was the most common indication in both groups (MW 78.0%; PMW 89.3%).

MW had more frequently positive findings in CE study (71.1% *vs* 55.4%) (*P* = 0.031). Angiodysplasias were the most frequent finding in both groups, diagnosed in 44.9% of MW (*n* = 57) and in 21.4% of PMW (*n* = 12) (*P* = 0.003). MW had more frequently lesions with a high bleeding potential, classified as P2 lesions (38.6% *vs* 8.3%) (*P* = 0.043). Blood in the GI tract was identified more frequently in MW (15.7%, *n* = 20) than PMW (5.4%, *n* = 3) (*P* = 0.051). Cleansing adequacy was not significantly different between groups (*P* = 0.83). Timing to CE was not significantly different between groups (*P* = 0.31). However in MW timing of CE was associated with higher DY (*P* = 0.002) and TY (0.024). In PMW there timing to CE was not associated with higher DY (*P* = 0.23) nor TY (*P* = 0.96).

DY was higher in MW (63.8%, *n* = 81) than PMW (30.4%, *n* = 17), and post-menopausal status was significantly associated with higher DY (*P* < 0.001).

Table 4 Capsule endoscopy outcomes in all patients, and between premenopausal and menopausal groups *n* (%)

No. of patients (*n* = 183)	All	PMW (30.6%, *n* = 56)	MW (69.4%, *n* = 127)	*P* value[1]
Diagnostic yield	98 (53.6)	17 (30.4)	81 (63.8)	< 0.001
Therapeutic yield	23 (12.6)	1 (1.8)	22 (17.3)	0.003
Rebleeding rate	46 (25.1)	5 (8.9)	41 (32.3)	0.031
Time to rebleed, yr				0.001
	1 yr, 16.4	1 yr, 3.6	1 yr, 22.0	
	3 yr, 25.8	3 yr, 10.2	3 yr, 32.3	
	5 yr, 27.2	5 yr, 10.2	5 yr, 34.2	
Hospitalization rate	13 (7.1)	1 (1.8)	12 (9.4)	0.063
Mortality rate	2 (1.0)	0 (0)	2 (1.6)	0.345

[1]*t*-test: χ^2 test, as appropriate; *P* value of 0.05 indicating statistical significance.

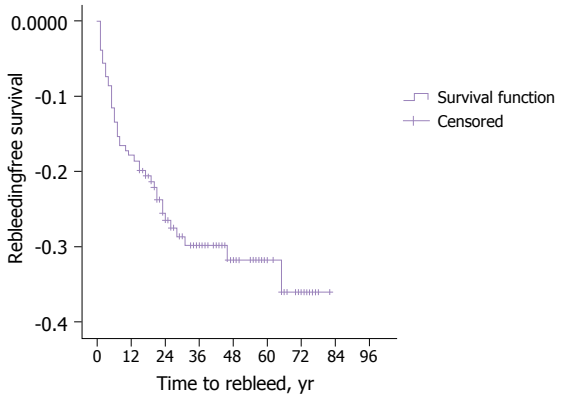

Figure 2 Kaplan-Meier curves according to the time to rebleed.

TY was significantly higher in MW (17.3%, *n* = 22) compared to PMW (1.8%, *n* = 1) (*P* = 0.003).

The rebleeding rate was significantly higher in MW (*P* = 0,031). Considering a follow-up period of 1, 3 and 5 years, MW had a significantly higher rebleeding rate (MW 22.0%; 32.3%; 34.2% *vs* PMW 3.6%; 10.2%; 10.2%) (*P* = 0.001) (Table 4 and Figure 3).

In the MW group hospitalization due to OGIB was higher (MW-9.4%, PMW-1.8%). Mortality due to OGIB in MW was 1.6%, and there was no death in PMW. There was no significant differences between groups concerning hospitalization (*P* = 0.063) and mortality (*P* = 0.345).

DISCUSSION

OGIB, particularly IDA is the most frequent indication (66%) for CE study[20]. Several studies on the DY of CE in IDA were performed. A systematic review from Koulaouzidis *et al*[21] showed a pooled CE DY for detection of small bowel findings of 46%. The literature on CE findings and DY in MW and PMW is sparse and in fact evidence from CE DY in OGIB is heterogeneous and lies in two types of study designs: those specifically designed to evaluate the role of CE in patients with IDA and those that investigated patients with a wider range of indications including overt GI bleeding.

In our study, the DY of CE in MW was significantly higher compared to PMW. TY and the rebleeding rate were also higher while time to rebleed was lower in female patients with post-menopausal status. A retrospective study of Garrido-Durán *et al*[15] documented a DY of CE of 55.0% and 13.7% in MW and PMW respectively. More recently a multicentric retrospective study from Perrod *et al*[10] obtained similar results, with 34.0% for MW and 15.0% for PMW. These results do not substantially differ from our data, regarding DY of CE in OGIB. Nor Garrido-Duran's nor Perrod's studies evaluated TY, rebleeding, time to rebleed, hospitalization nor mortality. In our study MW had more frequently small bowel lesions eligible for endoscopic treatment. There is quite sparse literature in the TY of CE, the rebleeding rate and time to rebleed due OGIB in females comparing pre and post menopause periods. Nevertheless those variable were extensively studied in patients submitted to CE[13,18,19,22,23]. The fact that MW had a higher rate of comorbidities and consumption of anticoagulants, antiplatelet and NSAIDs may partially explain the higher DY, TY and rebleeding rate.

Angiodysplasias were the main findings in CE studies of both groups. Previously published papers comparing PMW and MW had the same outcomes[10,15].

The main achievement of the present study is to bring to evidence the poor results of OGIB investigation through CE in PMW, making clear the need of exclusion of gynecological pathology in this subset of patients[24]. In this population, IDA is often related to gynecological symptoms and gastrointestinal lesions are diagnosed in less than 20% after endoscopic explorations[25].

The present study has some limitations. It has a retrospective design with a small number of patients, therefore a prospective assessment of CE DY in females before and after menopause is warranted. The patients enrolled in the present study were not assessed in a Gynecology appointment in order to confirm menopause diagnosis.

In conclusion PMW with suspected OGIB are less likely to have significant findings in CE. The lower rates of positive findings may be related to gynecological comorbidities, which must be previously excluded. In this group the DY, TY and rebleeding were significantly lower while time to rebleed was higher.

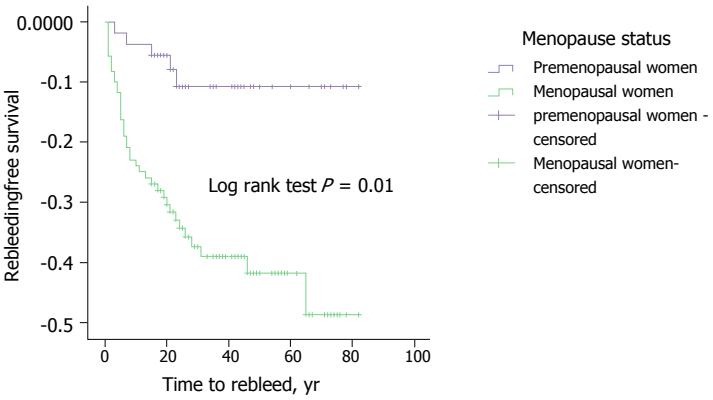

Figure 3 Kaplan-Meier curves according to the time to rebleed between premenopausal and menopausal women.

ARTICLE HIGHLIGHTS

Research background

Findings of capsule endoscopy (CE) for obscure gastrointestinal bleeding (OGIB) investigation performed in females may vary substantially according to menopause status. In this paper we estimated and compared diagnostic yield (DY) of CE as well as its therapeutic yield (TY) and clinical outcomes in premenopausal women (PMW) and menopausal women (MW).

Research motivation

Negative CE may lead to increased health costs and delayed diagnosis when performed in patients who were not fully investigated, as OGIB is an exclusion diagnosis.

Research objectives

To compare the DY of CE for OGIB study and correlated this outcome with menopause presence.

Research methods

The DY, TY, rebleeding rate, hospitalization and mortality were calculated and compared according to menopausal status.

Research results

Postmenopausal age was associated with higher DY, need for endoscopic treatment, rebleeding, and hospitalization.

Research conclusions

PMW with suspected OGIB is less likely to have significant findings in CE. This suggests that fertile age women should be carefully studied, preferably by a multidisciplinary approach, before CE.

Research perspectives

Our study has a retrospective design with a small number of patients, so a prospective comparative assessment of CE findings between PMW and MW with a larger population is warranted. In addition routine evaluation by a Gynecologist may reduce the negative CE burden.

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SYSTEMATIC REVIEW

Systematic review of safety and efficacy of therapeutic endoscopic-retrograde-cholangiopancreatography during pregnancy including studies of radiation-free therapeutic endoscopic-retrograde-cholangiopancreatography

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Abstract

AIM

To systematically review safety/efficacy of therapeutic endoscopic-retrograde-cholangiopancreatography (ERCP) performed during pregnancy, considering fetal viability, fetal teratogenicity, premature delivery, and future postpartum development of the infant.

METHODS

Systematic computerized literature search performed using PubMed with the key words "ERCP" and "pregnancy". Two clinicians independently reviewed the literature, and decided on which articles to incorporate in this review based on consensus and preassigned priorities. Large clinical trials, meta-analyses, systematic reviews, and controlled trials were assigned higher priority than review articles or small clinical series, and individual case reports were assigned lowest priority. Dr. Cappell has formal training and considerable experience in conducting systematic reviews, with 4 published systematic reviews in peer-reviewed journals indexed in PubMed during the last 2 years, and with a PhD in neurophysiology that involved 5 years of training and research in biomedical statistics.

RESULTS

Advances in imaging modalities, including abdominal ultrasound, MRCP, and endoscopic ultrasound, have generally obviated the need for diagnostic ERCP in non-pregnant and pregnant patients. Clinical experience with performing ERCP during pregnancy is burgeoning, with > 500 cases of therapeutic ERCP reported in the literature, aside from a national registry study of 58 patients. These studies show that therapeutic ERCP has a very high rate of technical success in clearing the bile duct of gallstones, and has a relatively low and acceptable rate of maternal and fetal complications. The great majority of births after therapeutic ERCP are full-term, have normal birth weights, and are healthy. A recent trend is performing ERCP without radiation to eliminate radiation teratogenicity. Systematic literature review reveals 147 cases of ERCP without fluoroscopy in 8 clinical series. These studies demonstrate extremely high technical success in endoscopically removing choledocholithiasis, favorable maternal outcomes with rare maternal ERCP complications, and excellent fetal outcomes. ERCP without fluoroscopy generally confirms proper biliary cannulation by aspiration of yellow bile per sphincterotome or leakage of yellow bile around an inserted guide-wire.

CONCLUSION

This systematic literature review reveals ERCP is relatively safe and efficacious during pregnancy, with relatively favorable maternal and fetal outcomes after ERCP. Recommendations are provided about ERCP indications, special ERCP techniques during pregnancy, and prospects for future research.

Key words: Minimally invasive therapy; Endoscopy; Ascending cholangitis; Therapeutic endoscopic-retrograde-cholangiopancreatography; Pregnancy; Radiation teratogenicity

Core tip: This work systematically reviews safety/efficacy of therapeutic endoscopic-retrograde-cholangiopancreatography (ERCP) performed during pregnancy, considering fetal viability, fetal teratogenicity, premature delivery, and future development of the infant after parturition. Systematic computerized literature search was performed using PubMed with key words "ERCP" and "pregnancy". Two clinicians independently reviewed the literature, and decided on which articles to incorporate in this review based on pre-arranged prioritization and consensus. Clinical experience with performing ERCP during pregnancy is burgeoning, with > 500 cases of therapeutic ERCP reported in the literature, plus a national registry study of 58 patients.

Cappell MS, Stavropoulos SN, Friedel D. Systematic review of safety and efficacy of therapeutic endoscopic-retrograde-cholangiopancreatography during pregnancy including studies of radiation-free therapeutic endoscopic-retrograde-cholangiopancreatography. *World J Gastrointest Endosc* 2018; 10(10): 308-321 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i10/308.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i10.308

INTRODUCTION

Endoscopic-retrograde-cholangiopancreatography (ERCP) is currently the standard technique for treating choledocholithiasis and associated complications, such as cholangitis and biliary stricture, in the non-pregnant population. The approach to pregnant women with suspected choledocholithiasis, however, differs somewhat from that for non-pregnant patients because of concerns about the pregnant mother and the fetus, including procedure time, teratogenicity of intra-procedural medications, and fetal radiation exposure. This work systematically reviews ERCP during pregnancy, with a particular focus on differences between the pregnant *vs* non-pregnant patient in patient indications, patient preparation, procedural medications, complications, reducing fetal radiation exposure, and maternal and fetal outcomes.

MATERIALS AND METHODS

Systematic computerized literature search was performed using PubMed with the key words "ERCP" and "pregnancy". Two clinicians independently reviewed the literature, and decided on which articles to incorporate in this review based on consensus. Large clinical trials, meta-analyses, systematic reviews, and controlled trials were assigned higher priority than review articles or small clinical series, and individual case reports were assigned the lowest priority. Data were extracted independently by 2 authors to prevent errors in data extraction. Dr. Cappell has formal training and considerable experience in conducting in conducting systematic reviews, with 4 published systematic reviews in peer-reviewed journals indexed in PubMed during the last 2 years, and with a Ph.D. in neurophysiology that involved 5 years of training and research in biomedical statistics.

RESULTS

Pathophysiology of cholelithiasis and choledocholithiasis

Up to 20% of American adults have cholelithiasis, of whom about 20% develop symptoms or complications during their life-time[1,2]. About 750000 cholecystectomies are performed annually in America. Risk factors for cholelithiasis include advanced age, female gender, obesity, hyperlipidemia, pregnancy, and physical inactivity[2]. Symptoms and complications increase in frequency when gallstones are present > 5 years, and when they are > 10 mm in diameter[3]. The pathophysiology of pregnancy-related lithogenicity includes bile super-

saturated with cholesterol, increased gallbladder volume, diminished gallbladder motility, and changes in the bile salt pool[4-7]. These gestational changes are largely mediated by increased levels of the gestational hormones of estrogen and progesterone[4].

Epidemiology

The prevalence of cholelithiasis during pregnancy varies with the study population. A study performed in India noted only a 1% prevalence[8], whereas a study performed in a Californian Hispanic cohort reported a 5% prevalence[9]. Both cohorts were asymptomatic at study initiation. A prospective study of abdominal ultrasound among > 3000 pregnant subjects without cholelithiasis detected at baseline showed 5% developed cholelithiasis by the second trimester, and 10% developed cholelithiasis by six weeks postpartum[10]. About 1% of this cohort developed symptoms from cholelithiasis. A Mexican study noted that symptomatic gallstone disease during pregnancy usually manifests as acute cholecystitis, even though 19% had choledocholithiasis[11]. Cholelithiasis and hypertriglyceridemia are the primary etiologies of pancreatitis during pregnancy[12,13], whereas alcohol-induced pancreatitis is unusual during pregnancy because expectant mothers generally abstain from alcohol due to its fetal toxicity[14]. Cholelithiasis and choledocholithiasis are sometimes encountered during pregnancy because female gender, concurrent pregnancy, and prior pregnancy are risk factors for cholelithiasis. Fortunately, the endoscopist is infrequently required to perform ERCP, with its attendant risks during pregnancy, because ERCPs can often be delayed to postpartum because patients have minimal clinical findings or can directly undergo cholecystectomy without antecedent ERCP for acute cholecystitis.

Special concerns and modifications of ERCP during pregnancy

The unique maternal and fetal physiologic requirements during pregnancy affect the usual practice of ERCP. The unique maternal and fetal physiologic requirements during pregnancy affect the usual practice of ERCP. ERCP in non-pregnant patients is usually performed with the patient in the prone position to aid in selective bile cannulation and to provide better fluoroscopic imaging compared to other positions. However, this position is not recommended during advanced pregnancy for the following reasons: to avoid patient discomfort from the enlarged, gravid uterus pressing against the hard X-ray platform, to avoid decreased systemic and uterine perfusion from the enlarged gravid uterus compressing the aorta, and to avoid decreased venous return from the enlarged gravid uterus compressing the inferior vena cava[15]. Patients may also require supporting cushions during advanced pregnancy to minimize patient discomfort. Rapid intra-procedural infusion of Ⅳ fluids is generally recommended to promote pancreatic perfusion and decrease the incidence and severity of post-ERCP pancreatitis, but may be inadvisable during pregnancy because of the already expanded extravascular space and salt retention during pregnancy[16]. However, the fetus poorly tolerates maternal systemic hypotension because blood flow is shunted away from the uterus during maternal hypotension[17], and maternal hypotension should, therefore, be aggressively treated, if feasible, before performing ERCP. As for all patients undergoing ERCP, the pregnant patient should have her vital signs stabilized, electrolyte disorders corrected, and major disorders such as sepsis, hypovolemia, and hypoxemia addressed before undergoing ERCP. As in the general population all pregnant patients undergoing anticipated therapeutic ERCP should have a complete hemogram and prothrombin/international normal ratio determination. It is important to test for pregnancy with a beta-HCG determination in women who are undergoing ERCP, are of childbearing age, and have a recent pregnancy history that is uncertain or suggestive of early pregnancy to avoid inadvertent fetal radiation exposure[18].

The mother should be maintained nil per os (NPO) for at least 6 h before ERCP to reduce risks of aspiration of gastric contents. Elective endotracheal intubation should be strongly considered before ERCP, especially during advanced pregnancy, because the gravid uterus, impinges upon the stomach and increases the risk of aspiration of gastric contents[19]. It may, moreover, be necessary to perform ERCP in the supine position, especially during advanced pregnancy, which can further increase aspiration risks[20]. The mother can typically be extubated soon after ERCP in the absence of chronic pulmonary disease.

The American Society for Gastrointestinal Endoscopy promulgated guidelines for endoscopy during pregnancy, including ERCP, which incorporate safety data for commonly used endoscopic medications during pregnancy[21,22], as classified by the United States Food and Drug Administration (FDA) from A (most safe) to D (least safe), with a special category of X, for drugs contraindicated during pregnancy. The general principle is to avoid FDA category X and restrict FDA category D drugs, and substitute FDA category B or C drugs for category D drugs, if feasible, during pregnancy. Indomethacin suppositories are recommended for ERCP in patients at risk for pancreatitis, but indomethacin is an FDA category C drug, with concern about premature closure of a patent ductus arteriosus (PDA) in late pregnancy[22]. Propofol is considered safe (FDA category B), even though it crosses the placenta and causes transient fetal sedation. Meperidine is considered safer (FDA category B) than either fentanyl or morphine (both FDA category C). Moreover, meperidine causes minimal spasm of the sphincter of Oddi, whereas other narcotics may cause problematic spasm of this sphincter during ERCP. Midazolam is considered safer than diazepam, even though both are category D drugs because diazepam has been occasionally associated with cleft palate[23].

Table 1 General principles of endoscopic retrograde cholangiopancreatography during pregnancy

1. Counsel patient, husband, and family on risks vs benefits of ERCP for mother as well as fetus
2. Obtain written informed consent from pregnant patient (not the father)
3. Endoscopist should assess whether his/her experience and skill is adequate for dealing with anticipated biliary pathology in a pregnant patient with this medical history
4. Position patient on left side or supine, if possible, especially during advanced pregnancy
5. Preferentially perform ERCP during second trimester, if possible
6. During late third trimester, delay elective ERCP to after delivery
7. Use safety guidelines (see Table 2) to minimize fetal radiation exposure and risks
8. Consider performing EUS prior to ERCP to assess CBD diameter as well as number, size, and shape of gallstones
9. Multidisciplinary input involving a perinatologist, high-risk obstetrician, obstetric anesthesiologist, radiation safety officer, and surgeon prior to ERCP
10. Administer parenteral fluids consistent with clinical status and pregnancy requirements
11. Reverse metabolic derangements and appropriately intervene to correct abnormalities in vital signs before scheduling ERCP
12. Administer antibiotics and other drugs during ERCP that are considered relatively safe during pregnancy
13. Endoscopist should be familiar with and prepared to use full armamentarium of endoscopic techniques including needle-knife sphincterotomy, transeptal sphincterotomy, choledochoscopy, and IDUS
14. Counsel patients regarding requirements for follow-up visits, especially with stent placement
15. Avoid pancreatic endotherapy during ERCP because this entails a higher risk than biliary endotherapy

ERCP: Endoscopic retrograde cholangiopancreatography; EUS: Endoscopic ultrasound; CBD: Common bile duct; IDUS: Intraductal ultrasound.

Glucagon is used to reduce intestinal spasm and is believed to be generally safe during pregnancy (FDA category B)[24]. Glucagon administration may be justifiable during ERCP if needed to cannulate the choledochus during therapeutic ERCP to prevent maternal cholangitis from choledocholithiasis, but glucagon administration can usually be obviated by prompt choledochal cannulation by an expert endoscopist. Simethicone is used to eliminate troublesome intraluminal bubbles and is believed to be relatively safe during pregnancy (FDA category C)[25]. It should, however, be used only if necessary during ERCP. Informed patient consent for ERCP should include a discussion regarding fetal safety during pregnancy, including fetal toxicity from radiation exposure. In terms of antibiotics, penicillins/cepholosporins/macrolides are generally safe, provided no hypersensitivity occurs, but quinolones/tetracyclines/sulfonamides/Flagyl are not safe[25].

The management of pregnant women with pancreaticobiliary disease requires a multidisciplinary approach, with a clinical team including a gastroenterologist, obstetrician/perinatologist, radiation safety officer, and anesthesiologist, who preferably specializes in obstetric anesthesiology. The requisite experience and expertise is typically found in a tertiary, academic medical center. The gastroenterologist should have significant expertise and experience in ERCP to be best equipped to deal with the challenges and risks of ERCP during pregnancy. The qualifications of an experienced advanced therapeutic endoscopist have not been standardized, but may include both a > 90% bile duct cannulation rate[26], and an adequate annual volume of therapeutic ERCPs (> 40 sphincterotomies per year)[27]. One study demonstrated that low volume ERCP-endoscopists exposed their patients to significantly more radiation during ERCP than high volume ERCP-endoscopists[28]. An experienced endoscopist is more likely to minimize procedural time, anesthesia dosages, and radiation time. An inexperienced gastroenterology fellow should play a limited role in this situation. The anesthesiologist should be in attendance during the entire ERCP, and not rely on a nurse anesthetist for administering sedation. The surgeon plays a critical role in the timing of cholecystectomy, and in providing backup for emergency CBD exploration or for complications after ERCP[29].

Electrocautery is a concern during pregnancy. Amniotic fluid readily conducts electricity which can reach the fetus[21,30]. Biliary sphincterotomy should use only bipolar current to decrease scatter of electricity. Biliary sphincterotomy, if necessary during ERCP, should use minimal cautery with the grounding pad placed on the right side, such as the right arm or right posterior thorax, to minimize electrical conduction to the fetus[22,31]. Strategies to avoid electrocautery include inserting a biliary stent without cautery, but this can be problematic unless delivery is imminent because of a long-term potential for stent clogging. Balloon sphincteroplasty is an alternative to sphincterotomy, but this maneuver can induce pancreatitis[32]. General principles of ERCP during pregnancy are summarized in Table 1.

Fetal radiation exposure is a significant concern because of its potential teratogenic effects and subsequent carcinogenetic effects. Fetal radiation exposure and toxicity depends upon multiple factors, including maternal size, maternal distribution of fat, volume of amniotic fluid, fetal gestational age, and radiation delivery method. The most important factors determining fetal exposure are total radiation time and dosage, both of which should be minimized. Draping the lower abdomen and pelvis of patients with lead shields helps minimize uterine exposure[21]. Lead shielding is best placed below the patient because radiation typically emanates from below[21]. However, radiation scatter within the mother is likely the main source of fetal radiation exposure[33]. Static (spot) films are recommended instead of continuous fluoroscopy to decrease radiation exposure[34]. Also recommended are a modern radiation source, a well collimated unit, and avoidance of "hard-copy" images

Table 2 Maximizing radiation safety of endoscopic retrograde cholangiopancreatography during pregnancy

1. Highly qualified and experienced ERCP endoscopist
2. Limited (solely observational) role of inexperienced gastroenterology fellow during ERCP
3. Informed consent to include discussion of radiation teratogenicity
4. Consult perinatologist
5. Consult radiation safety officer and medical physicist, if available, to minimize fetal radiation exposure
6. Endoscopist performing ERCP should become familiar with fluoroscopy equipment, especially with options to minimize radiation exposure
7. Formal consultation of anesthesiologist before ERCP
8. Anesthesiologist to attend during entire ERCP, even if nurse-anesthetist is present
9. Consider using an obstetric anesthesiologist rather than a general anesthesiologist for ERCP
10. Avoid ERCP for weak indications
11. Avoid solely diagnostic ERCP
12. Strongly consider MRCP as an alternative for diagnostic ERCP in low yield indications
13. Obtain informed, written consent that includes discussion of risks of fetal radiation
14. Perform ERCP at a hospital endoscopy unit rather than an ambulatory center in order to better manage procedural complications
15. Perform ERCP at a tertiary hospital rather than a community hospital where highly specialized consultants are likely to be present
16. Perform ERCP as expeditiously as possible to minimize radiation exposure and anesthesia medications
17. Employ modern and highly collimated radiation unit with the smallest possible field
18. Position patient as far as possible from radiation source consistent with reasonable images
19. If possible, employ "low-dose" radiation protocol in terms of kvp, field size, and frame rate
20. Place lead shield underneath patient between likely fetal area and radiation tube
21. Place dosimeters on patient above expected uterine location and record fluoroscopy time and total radiation dosage
22. Minimize procedure time, procure all anticipated endoscopy equipment within endoscopy room before beginning the procedure
23. Employ static images as opposed to continuous fluoroscopy to reduce radiation exposure
24. Use digital image acquisition technology if possible, instead of film-screen radiography
25. Position patient to permit anterior-posterior beam projection
26. Avoid image magnification
27. Employ last image-hold or fluoroscopy loop recording feature when possible rather than additional fluoroscopy
28. Consider radiation-free ERCP in conjunction with other techniques such as temporary stenting and, if needed, needle-knife and transpapillary sphincterotomy
29. Document ductal clearance without radiation using IDUS or choledochoscopy
30. X-ray image receptor should be placed as close as possible to the patient
31. Adjust patient position between choices of supine, prone, or lateral to minimize fetal radiation exposure

ERCP: Endoscopic retrograde cholangiopancreatography; kVp: Peak kilovoltage; IDUS: Intraductal ultrasound.

that require higher radiation dosage[21]. A radiation safety officer can provide valuable input. Dosimetry monitors can be placed externally on top of the uterus to monitor fetal radiation exposure. In one case, this device demonstrated low radiation exposure to the fetus, and higher radiation exposure to the maternal placenta and spleen[35]. Radiation exposure often exceeds 10 millisievert (mSv) during prolonged ERCP[33]. With recommended precautions, fetal radiation exposure during ERCP should be uniformly < 50-100 mSv, which is considered the radiation threshold for teratogenesis[21,36]. Techniques to reduce radiation exposure are summarized in Table 2.

Fetal radiation exposure is particularly concerning during early pregnancy. Radiation exposure to > 200 mGy could result in growth restriction and congenital anomalies, especially of the eyes, skeleton, and genitalia[31]. Thus, semi-elective ERCP should be deferred to the second trimester when feasible. Untoward outcomes of ERCP–related radiation exposure is not well studied, and they may conceivably manifest only later in childhood. Regardless, radiation exposure should be well documented, if feasible, for retrospective analysis[37]. One study suggested this documentation was unnecessary because of low teratogenicity risk, but this study used limited fluoroscopy time[38].

Outcomes and complications of therapeutic ERCP during pregnancy

Outcome analysis regarding ERCP during pregnancy should consider technical procedural success, fetal outcomes, neonatal health, and birth weight. In a relatively large, retrospective, study of 68 ERCPs during 65 pregnancies, technical success was uniformly achieved[39]. Although 11 patients (16%) developed pancreatitis after ERCP, no other major complications occurred, including maternal hemorrhage, gastrointestinal perforation, or ascending cholangitis; maternal or fetal deaths; and fetal malformations. ERCPs performed during the first trimester had relatively worse fetal outcomes. Fifty-three patients (90%) had a full–term pregnancy after ERCP, but mothers undergoing ERCP during the first trimester had only 73% of deliveries at term, a higher risk of preterm delivery (20%), and higher risk of low-birth-weight infants (21%). In a series of 20 patients undergoing therapeutic ERCPs during pregnancy, there was one neonatal death 26 h after delivery that occurred in a patient who had undergone three therapeutic ERCPs during pregnancy with pancreatic duct stenting at each session for pancreatic duct stenosis after surgical sphincteroplasty[15]. This patient had developed acute pancreatitis after each of her 3 ERCPs. Another mother suffered spontaneous abortion 3 wk

after ERCP. There were no other significant maternal or fetal complications.

A national cohort study of 58 pregnant women undergoing ERCP *vs* a three-fold larger control population of non-pregnant women demonstrated that the major ERCP complications of gastrointestinal perforation, hemorrhage, or infection were not more common during pregnancy, but post-ERCP pancreatitis was significantly increased during pregnancy at 12% *vs* 5% (adjusted odds ratio: 2.8, 95%CI: 2.1-3.8). This increased rate is attributed to avoiding fluoroscopy to verify wire and catheter position and to time pressure to expeditiously perform ERCP during pregnancy[40-42]. This work is important in that it represents the largest study heretofore on ERCP during pregnancy, but is subject to limitations including lack of data on patient comorbidities, maternal alcohol or illicit drug use, endoscopic complications, type of ERCP (diagnostic *vs* therapeutic), ERCP indications, and use or lack of monitored anesthesia care[43]. Also, as aforementioned, usual measures to minimize pancreatitis after ERCP, such as high volume IV fluid infusion, indomethacin suppositories, and pancreatic stents are infrequently used during pregnancy. A recent large, multicenter, study demonstrated that endoscopy during pregnancy is associated with an increased risk of preterm birth or small size for gestational age, but no increased risk of stillbirths or congenital malformations[40-42].

In a series of 18 women undergoing ERCP with biliary sphincterotomy for choledocholithiasis, one patient had a postsphincterotomy bleed and one patient had mild pancreatitis after ERCP and had preterm labor, but fetal outcomes were all favorable[44]. Scant data exist on long term postpartum follow-up after intrapartum ERCP, but this study of 18 women reported normal child development at 6 years[44]. Generally, therapeutic ERCP is believed to be relatively safe and effective during pregnancy, though safety concerns are increased during the first trimester, and there appears to be an increased risk of maternal pancreatitis after ERCP during pregnancy.

Two relatively large systematic reviews, one published in full[45], and the other published as an abstract[46], show that ERCP during pregnancy is relatively safe. In a systematic literature review performed by Cappell in 2011[45], 296 pregnant patients underwent therapeutic ERCP. Fetal outcomes as reported in 254 cases (86%) included: healthy infants at birth in 237, prematurely born infants with low birth weight in 11, late spontaneous abortions in 3, infant death soon after birth in 2, and voluntary abortion in 1. Perinatal mortality was only about 1% despite pregnant mothers undergoing therapeutic ERCP mostly for major gallstone complications, such as obstructive jaundice, ascending cholangitis, or gallstone pancreatitis. Moreover, no congenital anomalies were reported in the infants. However, these very favorable outcomes must be interpreted cautiously because most of the reviewed studies reported outcome only at parturition without subsequent follow-up, and fetal outcome data was absent in 15% of the pooled study patients.

A systematic literature review of 214 ERCP's during pregnancy, published only as an abstract, reported a 5% pancreatitis rate, a 5% preterm birth rate, and about a 1% rate of spontaneous abortions[46]. Technical success of ERCP was high, even though >10% had to undergo stent placement and/or multiple ERCPs. These data on the largest individual studies and prior systematic reviews are summarized in Table 3.

DISCUSSION

Recommendations

In the general population solely diagnostic ERCP is not recommended anymore, and has been replaced by less invasive tests such as endoscopic ultrasound (EUS); and magnetic resonance cholangiopancreatography (MRCP)[47]. ERCP is not recommended unless it is most likely to be therapeutic. The same principle applies during pregnancy: solely diagnostic ERCP is not recommended during pregnancy.

During the past 30 years, therapeutic ERCP during pregnancy has evolved from a novelty described in case reports to accepted practice with refinement of endoscopic techniques paralleling greater clinical experience, better technology, and greater technical expertise[21,31,48-51]. Progress in ERCP has been paralleled by advances in laparoscopic cholecystectomy. The first ERCP during pregnancy was a report in 1990 of five successful cases of biliary sphincterotomy and gallstone extraction for choledocholithiasis or cholangitis[48]. An estimated 500 or more women have been reported undergoing ERCP during pregnancy, aside from a national registry study of 58 patients[42]. Considerations in performing ERCP during pregnancy include clinical indication, maternal clinical status, laboratory results, ancillary radiologic studies, fetal age, endoscopist expertise, and hospital support. Risks *vs* benefits should be assessed for every high risk endoscopic procedure during pregnancy, especially ERCP[45]. Patients with documented choledocholithiasis associated with gallstone pancreatitis, cholangitis, jaundice, significant abdominal pain, pyrexia, leukocytosis, common bile duct dilatation on imaging studies, or grossly abnormal liver function tests need urgent ERCP, just like non-pregnant patients[52]. Patients with significantly elevated liver enzymes and/or a dilated CBD are more likely to harbor choledocholithiasis than patients without these features[53]. Preoperative ERCP is preferred over the alternative of direct cholecystectomy for these indications to avoid the increased morbidity and mortality from complex biliary surgery during cholecystectomy[54]. However, the indication for ERCP is more ambiguous in minimally symptomatic or asymptomatic patients with choledocholithiasis. Evaluation and therapy for uncomplicated cholelithiasis discovered during pregnancy is generally deferred until postpartum. Most patients with acute cholecystitis during pregnancy undergo cholecystectomy without preoperative ERCP[55]. Indeed. cholecystectomy for acute cholecystitis is the third most

Table 3 Literature review of relatively large clinical studies on safety of endoscopic retrograde cholangiopancreatography during pregnancy

First author, yr, reference	Study characteristics	Findings
Tang SJ, 2009[39]	Large retrospective study of 68 ERCPs performed during 65 pregnancies.	Pancreatitis occurred in 11 pregnant patients (16%) after ERCP. No other major maternal complications occurred during pregnancy. No fetal deaths and no fetal malformations occurred. After ERCP 53 patients had deliveries at term (90% rate for known delivery outcomes). However, ERCP performed during first trimester had less favorable outcomes: preterm delivery = 20%, and low-birth-weight infants = 21%
Ludvigsson JF, 2017[42]	National cohort study in Sweden of 58 pregnant patients undergoing ERCP included in a much larger study of 3052 patients undergoing any gastrointestinal endoscopy during pregnancy.	Of 58 pregnant patients undergoing ERCP unfavorable fetal outcomes included: 3 (5.2%) preterm births, 0 (0%) stillbirths, 0 (0%) neonatal deaths, 12 (20.7%) Cesarean sections, 1 (1.7%) Apgar score < 7 at 5 min, 1 (1.7%) small for gestational age, and 3 (5.2%) with any major congenital malformation. All these pregnancy outcomes were similar to that of pregnancy outcomes for mothers not undergoing endoscopy during pregnancy
Jamidar PA, 1995[15]	Retrospective study of therapeutic ERCPs performed during 20 pregnancies.	Two significant complications: one spontaneous abortion 3 wk after ERCP, and 1 neonatal death 26 h. post-partum that occurred after the expectant mother underwent 3 therapeutic ERCPs during pregnancy with pancreatic stenting at each session complicated by post-ERCP pancreatitis. No other significant maternal or fetal complications
Gupta R, 2005[44]	Retrospective study of therapeutic ERCPs performed during 18 pregnancies for choledocholithiasis.	Complications: 1 mild postsphincterotomy bleed; and 1 mild pancreatitis and preterm labor after ERCP. All fetal outcomes were favorable. This study had long-term follow-up after intra-partum ERCP: all 18 infants had normal child development at 6 yr
Cappell MS, 2011[45]	Systematic literature review of 296 pregnant patients undergoing therapeutic ERCP including 254 (86%) in which fetal outcome was reported.	Fetal outcomes as reported in 254 cases included: healthy infants at birth in 237, prematurely born infants with low-birth-weight in 11, late spontaneous abortions in 3, infant death soon after birth in 2, and voluntary abortion in 1. Perinatal mortality was only about 1% despite pregnant mothers undergoing therapeutic ERCP mostly for major gallstone complications, such as obstructive jaundice, ascending cholangitis, or gallstone pancreatitis. No congenital anomalies were reported in the infants. These favorable data must be interpreted cautiously: in this literature review, fetal outcome data were missing in 42 (15%) of reported mothers undergoing ERCP during pregnancy

ERCP: Endoscopic retrograde cholangiopancreatography.

common non-obstetric operation performed during pregnancy[56].

The diagnostic armamentarium for suspected choledocholithiasis in pregnancy differs from the general approach in non-pregnant patients in that radiation-based imaging, such as abdominal CT, is not employed. Transabdominal ultrasound is relatively inexpensive and safe during pregnancy and is typically the initial imaging test. MRCP is especially useful during pregnancy, but raises a concern about a negative exam in the face of disparate clinical and laboratory findings[57]. In one small series, MRCP obviated the need for ERCP in pregnant women with pancreatobiliary abnormalities[58]. EUS is safe in pregnancy and highly accurate, but commits the patient to an endoscopy during pregnancy with its inherent procedural and sedation risks. However, a negative EUS examination can obviate ERCP with its greater attendant risks[59]. EUS also provides data on number, size, location, and morphology of choledocholithiasis for patients requiring ERCP.

Pregnancy stage and fetal development are paramount considerations in the timing of ERCP. ERCPs and cholecystectomies are generally best performed during the second trimester, after organogenesis during the first trimester and before the third trimester with its increased risk of premature delivery[45,60]. Postpartum ERCP is the best option if delay is feasible.

The prospect of ERCP often promotes anxiety in both the mother and endoscopist. Recent studies still show some risks of ERCP during pregnancy[48,61]. The large series by Tang *et al*[39] reported that ERCP can be safely performed throughout pregnancy, but may somewhat impact fetal health when performed during early gestation. An early multicenter series, including 15 first trimester ERCPs (FTE), demonstrated technical success, but had complications of one spontaneous abortion and one neonatal death[15]. Another series with dedicated obstetric input and lead shielding demonstrated good technical success and good fetal outcome, though only one FTE was performed[62]. An Indian series had 4 FTE's, trivial fluoroscopy time, and a six year child follow-up[46]. The two series by Smith *et al*[38] and Kahaleh *et al*[63] were notable for limited fluoroscopy time, technical success, and good fetal outcomes, though two women developed eclampsia during the third trimester after undergoing ERCP. These series noted a slightly higher rate of post-ERCP pancreatitis than in the general population, in accord with cumulative data[40,41].

Most studies of ERCP during pregnancy are limited by relatively small study size, absence of controls,

Table 4 Literature review of case series of radiation-free endoscopic retrograde cholangiopancreatography during pregnancy

First author, yr, reference	Number reported	Indications	Technique of radiation-free ERCP	Outcomes
Shah 2016[75]	Non-radiation ERCP attempted-31 non-pregnant subjects. 26 successfully underwent ERCP without fluoroscopy. 5 required fluoroscopy during ERCP	Adult patients with suspected biliary stones based on abnormal serum liver tests, abdominal imaging, and/or abdominal pain. Underwent EUS per protocol. Patients with suspected large stone burden, complicated stone disease, or difficult anatomy were excluded	Antecedent EUS used as a guide before ERCP. Selective cannulation confirmed by aspirating visible bile in 26 patients. 5 patients required radiation for double wire or precut papillotomy. All patients had EUS. 4 others had ERCP obviated by EUS	No adverse events among patients who underwent bile cannulation, sphincterotomy, and stone removal without fluoroscopy. One patient undergoing ERCP with fluoroscopy had moderated post-ERCP pancreatitis
Ersoz 2016[74]	22 patients: first trimester-2, second trimester-3, third trimester-17	Abdominal ultrasound demonstrates stone/sludge in gallbladder-22 (100%), choledocholithiasis-12, mean total bilirubin = 5.49 ± 1.66 mg/dL, acute cholangitis-2, acute cholecystitis-2	Selective biliary cannulation attempted with sphincterotome and confirmed by bile aspiration. Biliary sphincterotomy and balloon dilation-18/22 had visible gallstones, 3 required transpancreatic papillary septotomy	5 complications after ERCP: epigastric pain without elevated lipase elevation-2, mild pancreatitis treated conservatively-2, minor post-sphincterotomy bleeding successfully treated with epinephrine injection without blood transfusions. All delivered healthy infants at term
Sethi S, 2015[73]	3 patients: 14, 7, or 28 wk pregnant	1 and 2-Dilated CBD and total bilirubin > 5.0 mg/dL after laparoscopic cholecystectomy, 3-Dilated CBD, multiple gallstones and increased total bilirubin level	All cases: EUS-guided ERCP with selective biliary cannulation confirmed by bile aspiration. Biliary sphincterotomy and stone extraction(s) using balloon sweeps or Spyglass technology	Uncomplicated. All mothers did well-rapidly discharged from hospital. Fetal outcomes not reported
Agcaoglu O, 2013[72]	5 patients: mean gestational age = 20 wk, range 12-32 wk	Gallstone pancreatitis and obstructive jaundice-3, cholangitis and obstructive jaundice-2	Selective cannulation confirmed by aspiration or direct visualization of bile. After CBD cannulated guide-wire passed, sphincterotomy completed, and stones extracted by basket or balloon sweep	No maternal or fetal adverse events or short term complications. No long-term follow-up available
Yang J, 2013[71]	24 patients: first or second trimester-9, third trimester-15	All patients had severe biliary pancreatitis. Leukocyte count 15000-29000 × 10^6/L, serum amylase: 500-2000 units/L, increased bilirubin in 20	All patients underwent emergency ERCP without fluoroscopy and endoscopic biliary drainage. 15 patients in third trimester had pregnancy terminated: induced delivery-7, cesarean section-6, full-term normal delivery-2. Then underwent second ERCP with fluoroscopy to remove gallstones. 9 patients in early pregnancy underwent endoscopic retrograde biliary drainage in second ERCP without fluoroscopy. Had biliary stent for average of 3.8 mo	100% technical success rate: CBD stones removed in all 24 patients. Only 2 maternal complications: mild hemorrhage during second ERCP. All infants born healthy. At term births-20, premature births-4 with cesarean section (for severe intrauterine distress)
Huang P, 2017[70]	86 patients (largest series): no fluoroscopy-81 ultra-short duration of fluoroscopy-5. Mean gestational age = 22.5 wk, Range: 15-35 wk	Acute biliary pancreatitis-32, acute cholangitis-23, dilated CBD-20, severe nonbiliary acute pancreatitis-11	Underwent antecedent abdominal ultrasound or MRCP. CBD cannulated using a guide-wire and then catheter over guide-wire. CBD cannulation confirmed by aspiration or oozing of bile. Then endoscopic biliary sphincterotomy and endoscopic nasobiliary drainage or retrograde biliary drainage. 51 had biliary stents	Technical success: 81 without fluoroscopy. Complications in 8.1%:Biliary bleeding-2, acute cholecystitis-1, post-ERCP pancreatitis-2. All babies were healthy at up to 12 mo. follow-up. All babies had normal birth weights (> 3 kg). Mean Apgar score at 5 min = 9
Akcakaya A, 2009[69]	6 patients: mean gestational age = 23 wk, range: 14-34 wk	Choledocholithiasis-4, Cholangitis-1, Persistent biliary fistula after hydatid disease surgery-1 (undergoing 2 ERCPs)	All patients had biliary sphincterotomy and balloon sweeps. Precut sphincterotomy performed with needle-knife for 1 patient with impacted stone	Complete stone extraction confirmed by abdominal ultrasound. No post-ERCP complications, premature birth, abortion or intrauterine growth retardation were observed

Shelton J, 2008[68]	21 patients: first trimester-7, second trimester-9, third trimester-5	Jaundice and biliary colic-11, biliary pancreatitis-8, cholecystitis-1, abnormal intraoperative cholangiogram-1	Guide-wire inserted into CBD followed by sphincterotome over guide-wire. CBD cannulation then confirmed by suction of yellow bile *via* catheter in first 10 cases. In next 11 cases CBD cannulation confirmed by leakage of yellow bile around guide-wire. Then wire-guided biliary sphincterotomy performed followed by balloon sweeps to extract stones. Choledochoscopy used for bile duct clearance in 5 last cases	100% technical success without fluoroscopy. One case of moderate pancreatitis. All then became asymptomatic. Follow-up of 18 pregnancies: Uneventful delivery of healthy babies-17, premature delivery at 35 wk with low birth weight-1
Sharma SS, 2008[64]	11 patients: first trimester-2, second trimester-6, third trimester-3	Abdominal pain and jaundice-11, cholangitis-2, dilated CBD-11, gallstones-8	All had 2-stage procedures. First stage during pregnancy: biliary sphincterotomy and stenting without radiation, bile aspirated to confirm biliary cannulation. Second stage ERCP postpartum: Stents removed, cholangiogram performed. Stones removed by Dormia basket-8, mechanical lithotripsy-1, or open surgery-1, no residual stones-1	Marked symptomatic improvement after first stage of therapy. All had normal, full-term delivery. "Good" maternal and fetal outcomes

ERCP: Endoscopic retrograde cholangiopancreatography; EUS: Endoscopic ultrasound; CBD: Common bile duct; MRCP: Magnetic resonance cholangiopancreatography.

retrospective design, and lack of comparative statistics[45]. Some studies focus on the technical success of the ERCP, without reporting fetal outcome altogether[64,65].

A recent trend is performing radiation-free ERCP (RFE) during pregnancy[34]. Transabdominal ultrasound has guided subsequent RFE, but this technique is cumbersome. In RFE a two-stage procedure may be performed, where the initial ERCP during pregnancy is temporizing, uses minimal or no fluoroscopy, and typically incorporates biliary sphincterotomy and stent placement; the subsequent postpartum ERCP is definitive[64,65]. In a patient presenting in late pregnancy, it is reasonable to perform a moderate sphincterotomy and insert a biliary stent to defer more definitive therapy to postpartum[64]. Performance of ERCP in the first trimester may involve risks of termination of pregnancy, especially if the ERCP is prolonged and entails considerable radiation exposure. Visualization of bile drainage after wire insertion or bile aspiration after catheter cannulation is currently usually used to confirm successful selective biliary cannulation. Shortcomings of this method include wires or catheters can inadvertently enter the cystic duct, chronically obstructed biliary systems may yield "white bile", and curled wires may cause bile duct injury that renders stent insertion difficult.

The initial case of RFE was inadvertent use of a needle-knife for an impacted common bile duct stone[66]. The first clinical series of RFE after ultrasound consisted of 6 pregnant women with acute pancreatitis or cholangitis[67]. The 6 patients underwent selective bile duct cannulation, biliary sphincterotomy, and successful gallstone removal, but two infants were born prematurely, including one with significant complications. Altogether 147 ERCP's have been performed during pregnancy without fluoroscopy in 8 clinical series, reflecting endoscopist ingenuity and technological progress (Table 4)[64,68-75]. These clinical data are extremely promising, with a very high rate of technical success (clearing of CBD stones), low rate of maternal complications, delivery of predominantly healthy babies, mostly normal birth weights, and typical delivery at term (Table 4)[64,68-75]. However, case series from tertiary academic centers may not be extrapolated to community hospitals. Radiation–free ERCP is ideal, but should not be pursued if this unduly prolongs the ERCP and increases the risks of complications, especially pancreatitis. Moreover, brief fluoroscopy with "ultra-short" (< 60 s) radiation exposure may produce as favorable fetal results as radiation-free ERCP.

EUS is now readily available and should be considered prior to RFE. EUS is especially useful to gauge CBD diameter; number, size, and morphology of gallstones; and may occasionally obviate the need for ERCP. Intraductal stone clearance can be demonstrated by a balloon pull-through. Intraductal ultrasound (IDUS) (Figure 1) is an underutilized modality to assess ductal clearance. Particularly expert endoscopists can perform trans-septal sphincterotomy; especially after inserting a low-profile stent into the presumptive pancreatic duct.

Choledochoscopy (cholangioscopy) is very useful to disrupt choledocholithiasis *via* laser therapy or lithotripsy and confirm ductal clearance[68,73,75]. It is less useful and potentially dangerous for selective duct cannulation because the 10 French insertion catheter is somewhat stiff and may not smoothly negotiate an angulated pancreatic duct. The procedure is selected according to the clinical scenario and physician expertise (Figure 2). ERCP is particularly challenging and potentially involves some risk during the first trimester.

Decisions regarding cholecystectomy in pregnant women with biliary disease is entwined with ERCP concerns. As aforementioned, the second trimester is usually the most favorable time for both ERCP and cholecystectomy. Cholecystectomy timing is determined by the patient's clinical course, with or without ERCP. Patients with

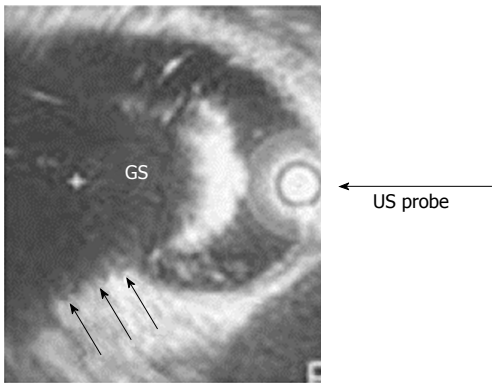

Figure 1 Intraductal ultrasound: Showing a gallstone in the common bile duct.

concomitant cholecystitis should undergo surgery as soon as feasible. A series of seven pregnant patients had good maternal and fetal outcomes after undergoing ERCP with biliary sphincterotomy, and stone extraction, followed by immediate cholecystectomy for biliary pancreatitis[76]. Delaying cholecystectomy may result in biliary complications later during pregnancy or postpartum[77,78].

A first trimester pregnant woman underwent concurrent laparoscopic cholecystectomy and ERCP *via* a rendezvous technique wherein a wire was inserted by the surgeon *via* the cystic duct, through the CBD, and into the small intestine; the endoscopist accessed this wire for cannulation at ERCP[79]. This combined procedure resulted in technical success and favorable fetal outcome. This combined method should minimize risks of pancreatitis, but requires prolonged operative time and extra anesthesia medications for the twin procedures. One endoscopist performed his own rendezvous technique *via* EUS after failed biliary cannulation during standard ERCP, with good results for the mother and the fetus[80].

Future prospects

Pancreatic ERCP during pregnancy may be reported in the future[81]. Magnetic technology currently applied to detect endoscope position during endoscopy (especially colonoscopy) may conceivably be applied to wires and catheters during ERCP[82]. A meta-analysis would be clinically beneficial; it would likely demonstrate comparable maternal and fetal outcomes with minimal radiation *vs* radiation-free ERCP. Clinical studies on efficacy of fetal heart rate monitoring during ERCP would be helpful. Data are sparse for ERCP during the first trimester. Long term follow-up data would be helpful on outcomes of children who received ERCP radiation in utero. Future technological improvements in ERCP may prove beneficial to the pregnant population.

A limitation of this review is that some of the data are from case reports which may be anecdotal and may be subject to reporting bias in that ERCP endoscopists may be more likely to report successful cases of ERCP during pregnancy. However, biases were minimized by systematically reviewing the literature. Errors in abstracting data from the literature were eliminated by two investigators independently reviewing all the analyzed publications. In conclusion, performance of ERCP during pregnancy is a substantial undertaking requiring endoscopist forethought, with potential use of multiple modalities including EUS. ERCP is generally safe during pregnancy. It should generally be avoided during the first trimester, and performed in the first trimester only for urgent and strong indications such as gallstone pancreatitis with documented choledocholithiasis, cholangitis, symptomatic choledocholithiasis, or jaundice. The endoscopist should frankly discuss procedural risks *vs* benefits with the patient. Radiation safety measures are paramount, as is the endoscopist's experience and technical skills. Various strategies and technologies may enhance biliary cannulation and ductal clearance during ERCP. Radiation–free ERCP is ideal, but should not unduly increase procedural time and risk of complications, especially pancreatitis.

ARTICLE HIGHLIGHTS

Research background

Endoscopic retrograde cholangiopancreatography (ERCP) is currently the standard technique for treating choledocholithiasis and associated complications, such as cholangitis, biliary pancreatitis, and biliary stricture, in the non-pregnant population. The approach in pregnant women with suspected choledocholithiasis, however, differs somewhat from that for non-pregnant patients because of concerns about the pregnant mother and the fetus, including procedure time, teratogenicity of intraprocedural medications, and fetal radiation exposure.

Research motivation

This work systematically collates the clinical data from the clinical studies, including the numerous small clinical series, to render these data accessible to clinicians. This work provides a systematic review of the rapidly evolving literature in this clinically booming field to provide highly important and clinically relevant updates on ERCP safety, efficacy, and recent technical improvements in pregnant patients.

Research objectives

This work reports numerous techniques to reduce radiation exposure and other safety precautions to decrease fetal risk from ERCP during pregnancy. Indeed, this work discusses in detail radiation free ERCP during pregnancy to completely eliminate teratogenic risks of radiation.

Research methods

This review encompassed more than 500 cases published in small clinical series and scattered reports, in addition to 58 cases recently reported in a retrospective Swedish registry study.

Research results

This work focuses on techniques to improve ERCP safety during pregnancy, including analysis of the relatively recently introduced radiation-free ERCP to completely eliminate the potential for radiation teratogenicity. Radiation-free ERCP is shown to be a relatively safe, and efficacious technique. However, more clinical data are required on this promising technique.

Research conclusions

This work shows that therapeutic ERCP is a reasonably safe therapy for the mother and the fetus during pregnancy, and it should be performed when indicated for symptomatic choledocholithiasis and its associated complications (including ascending cholangitis, gallstone pancreatitis, and biliary stricture)

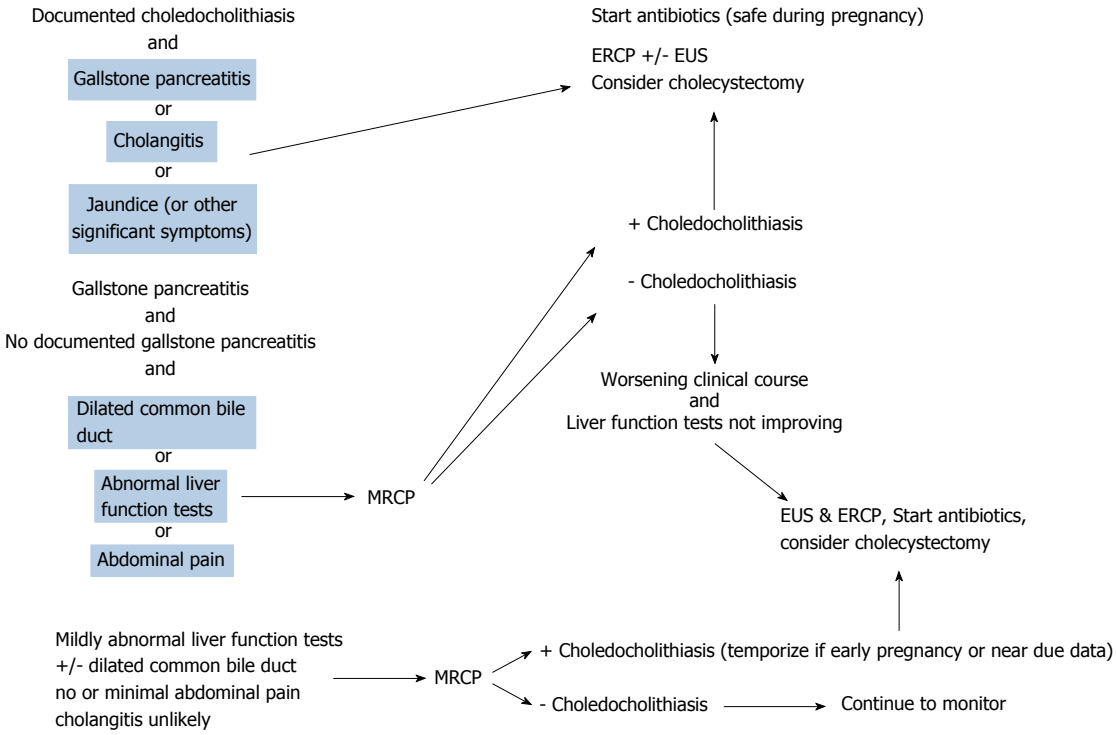

Figure 2 Approach to biliary disease during pregnancy. Patient diagnostic and treatment algorithm depending upon three different clinical presentations. ERCP: Endoscopic retrograde cholangiopancreatography; EUS: Endoscopic ultrasound; MRCP: Magnetic resonance cholangiopancreatography.

during pregnancy. This work confirms that solely diagnostic ERCP should generally not be performed during pregnancy due to the risks of fetal radiation teratogenesis and induction of early labor, and should be replaced by diagnostic MRCP or endoscopic ultrasound. ERCP should not be performed during pregnancy for asymptomatic stones because of potential fetal risks; ERCPs can often be delayed to postpartum because patients have minimal clinical findings, or patients can directly undergo cholecystectomy during pregnancy without antecedent ERCP for acute cholecystitis.

Research perspectives

More data are needed on radiation-free ERCPs. This work describes technique modifications for therapeutic ERCP during pregnancy to improve procedural safety. It is hoped that clinicians adapt these technique modifications during ERCP to further improve ERCP safety and efficacy during pregnancy.

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EDITORIAL

Screening for colorectal cancer in patients with inflammatory bowel disease. Should we already perform chromoendoscopy in all our patients?

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Abstract

Patients with inflammatory bowel disease (commonly known as IBD) have a greater risk of colorectal cancer than the general population. Therefore, they are included in special programs for screening and follow-up. Chromoendoscopy, which has a high diagnostic yield in the detection of neoplasia, is generally the recommended endoscopy technique. However, this procedure does have some disadvantages (long examination time, need for optimal bowel preparation, specialist training), which increase its cost. How then can we overcome these barriers? First, it is necessary to educate hospital managers and directors of the advantages of chromoendoscopy in patients with IBD. Second, at least one endoscopist per center should be a specialist in the technique. Third, we should train nursing staff in the preparation of the dye. Finally, each examination should be given the time it needs. Even though clinical practice guidelines do not yet recommend the use of virtual imaging techniques such as narrow band imaging, a recent study reported no differences between the two approaches for the detection of tumors. Therefore, we believe that all patients should undergo chromoendoscopy. In the future, centers without access to dyes or where other barriers exist should at least perform narrow band imaging.

Key words: Colorectal Cancer; Inflammatory bowel disease; Chromoendoscopy; Surveillance; Narrow band imaging

Core tip: Patients with inflammatory bowel disease are included in special programs for screening and follow-up of colorectal cancer. It is generally recommended that endoscopy be performed using chromoendoscopy, which has a high diagnostic yield for detection of the disease. However, chromoendoscopy does have a series of disadvantages. While some clinical practice guidelines do not yet recommend the use of virtual imaging techniques such as narrow band imaging, a recent study reported that there were no differences between the two approaches for detection of neoplastic lesions. Therefore, we recommend that all inflammatory bowel disease patients undergo chromoendoscopy.

Huguet JM, Suárez P, Ferrer-Barceló L, Iranzo I, Sempere J. Screening for colorectal cancer in patients with inflammatory bowel disease. Should we already perform chromoendoscopy in all our patients? *World J Gastrointest Endosc* 2018; 10(11): 322-325 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i11/322.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i11.322

INTRODUCTION

Patients with inflammatory bowel disease (IBD) have a greater risk of colorectal cancer (CRC) than the general population[1]. Therefore, it is clear that these patients should be included in special programs for screening and follow-up, as attested to in the recommendations of scientific societies and a recent review by Huguet *et al*[2-4]. The general recommendation for endoscopy is that the procedure used should be chromoendoscopy[3-6].

Chromoendoscopy is an imaging technique that uses contrast agents to identify abnormalities in the colonic mucosa. Dysplastic lesions are better highlighted by the addition of topical dyes. Chromoendoscopy has the advantage of detecting an early lesion other than dysplasia associated lesion or mass[7]. Chromoendoscopy is usually performed with methylene blue 0.1% or indigo carmine 0.03% to 0.5%.

Cecal intubation should be performed using a white-light endoscope. The colonic mucosa should then be stained by spray aspirating the excess fluids, carefully evaluating the mucosa, and examining each segment before applying dye in the next one[2].

CHROMOENDOSCOPY *VS* WHITE LIGHT ENDOSCOPY *VS* NARROW BAND IMAGING

Several studies have evaluated the superiority of chromoendoscopy with respect to white light endoscopy[8]. A recent review compared the diagnostic yield of high-definition white light endoscopy, chromoendoscopy, and narrow band imaging (NBI) for detection of cancer in patients with IBD by means of a meta-analysis of the existing literature[9]. The authors found that chromoendoscopy was superior to white light endoscopy for detection of dysplasia in IBD. No differences in diagnostic yield were demonstrated for NBI in comparison with other modalities[9]. Therefore, we have sufficient evidence to recommend implementation of this technique in digestive endoscopy units, as recently shown by Shukla *et al*[10].

Table 1 Disadvantages of chromoendoscopy (Adapted from Marion J and Sands B[17])

Operator barriers:
Training of fellows, gastroenterologists, nurses, and staff
Unknown learning curve
Identifying clinically relevant lesions
Operational barriers:
Availability of dye, equipment
Billing and reimbursement
Time requirement
Prep quality
Confounding of findings by inflammation
Knowledge barriers:
Uncertain natural history of dysplasia detected by CE
Uncertain implications of prior surveillance findings for management

The cost of chromoendoscopy is increased by its disadvantages. It is time-consuming, requires optimal bowel preparation, and is subject to adverse effects caused by application of dye to the intestinal mucosa. In addition, the endoscopist must be specially trained (Table 1). How then can we overcome these barriers? First, it is necessary to educate hospital managers and directors of the advantages of chromoendoscopy in patients with IBD. Second, at least one endoscopist per center should be a specialist in the technique. Third, we should train nursing staff in the preparation of the dye. Finally, each examination should be given the time it needs.

These are some of the reasons why chromoendoscopy is not universally used for CRC screening in patients with IBD. A Japanese study found that only half of those surveyed used the technique[11]. The recommended alternative to chromoendoscopy is high-definition video-colonoscopy and serial colon biopsy (4 every 10 cm)[5], which is also time-consuming if the biopsy specimens are taken as appropriate every 10 cm. In addition, potentially malignant lesions observed during the procedure must be biopsied. Preparation must also be optimal to ensure high-quality imaging. However, the technique is not subject to the possible adverse effects of dyes and does not require special training.

Moussata *et al*[12] recently reported that in selected patients, chromoendoscopy should be accompanied by conventional biopsy. The authors conclude that despite their low yield, random biopsies should be performed in association with chromoendoscopy in patients with IBD and a personal history of cancer, concomitant primary sclerosing cholangitis, or a tubular colon during

colonoscopy[12].

A study carried out in Spanish units with a special interest in chromoendoscopy evaluated the real-world effectiveness of the technique. The rate of non-detection of dysplasia with white light endoscopy was 40/94 (incremental yield of 57.4% for chromoendoscopy). The rate of detection of dysplasia was similar for both experts and nonexperts (18.5% *vs* 13.1%, $P = 0.20$). The authors conclude that chromoendoscopy has a high diagnostic yield for the detection of neoplasia, irrespective of the technology used and the experience available at a specific center. Furthermore, optical diagnosis of chromoendoscopy is very accurate for ruling out dysplasia especially when the technique is performed by an expert[13].

Clinical practice guidelines do not yet recommend NBI-type virtual imaging techniques for endoscopy in CRC screening[3]. Similarly, the SCENIC Consensus Statement does not recommend their use, and in Statement 6, the recommendation is that when performing surveillance with image-enhanced high-definition colonoscopy, NBI is not suggested in place of chromoendoscopy[5]. A Spanish study published in 2011 compared NBI with chromoendoscopy for the detection of colitis-associated intraepithelial neoplasia. The study was prospective, randomized, and crossover in design, and patients underwent both chromoendoscopy and NBI in a random order. The authors concluded that NBI is a useful technique for the detection of dysplasia in patients with long-standing IBD and offers several advantages, namely, efficiency, ease of use, and speed. However, in NBI a relatively high number of cases of intraepithelial neoplasia may go undetected with the result that many patients could go undiagnosed. Therefore, the authors consider that chromoendoscopy should still be considered the technique of choice for detecting dysplasia in patients with long-standing IBD[14].

Nevertheless, recent evidence suggests that NBI-type techniques could be as effective as chromoendoscopy for the detection of dysplasia and CRC. Thus, a recent clinical trial compared the yield of chromoendoscopy with that of virtual chromoendoscopy using NBI in patients with a long history of ulcerative colitis and found no differences between the two techniques for detection of tumors. The authors concluded that given the longer extraction time of chromoendoscopy and easier applicability of NBI, the latter could replace classic chromoendoscopy[15]. Autofluorescence imaging, on the other hand, has not shown any advantages over chromoendoscopy[16].

CONCLUSION

We concur with Shukla *et al*[10] on the need for more studies, particularly longitudinal studies to clarify the role of chromoendoscopy in achieving the objective of reducing morbidity and mortality among patients with colitis-associated CRC, while reducing the number of unnecessary colectomies in patients with clinically insignificant lesions. Similarly, we should stress the need for studies comparing chromoendoscopy and NBI. If both techniques are similarly effective for the detection of neoplasia, the previously mentioned advantages of NBI could lead it to replace chromoendoscopy.

Therefore, we believe that the answer to the question we ask in the title of this editorial 'Should all patients still undergo chromoendoscopy?' is yes. We should perform chromoendoscopy in all patients with IBD who are to be screened and followed up for CRC. In the future, centers without access to dyes or where other barriers exist should at least perform NBI on this patient population.

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REVIEW

Stepwise evaluation of liver sectors and liver segments by endoscopic ultrasound

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Abstract

The liver has eight segments, which are referred to by numbers or by names. The numbering of the segments is done in a counterclockwise manner with the liver being viewed from the inferior surface, starting from Segment I (the caudate lobe). Standard anatomical description of the liver segments is available by computed tomographic scan and ultrasonography. Endoscopic ultrasound (EUS) has been used for a detailed imaging of many intra-abdominal organs and for the assessment of intra-abdominal vasculature. A stepwise evaluation of the liver segments by EUS has not been described. In this article, we have described a stepwise evaluation of the liver segments by EUS. This information can be useful for planning successful radical surgeries, preparing for biopsy, portal vein embolization, transjugular intrahepatic portosystemic shunt, tumour resection or partial hepatectomy, and for planning EUS guided diagnostic and therapeutic procedures.

Key words: Endoscopic ultrasound; Hepatic vein; Liver sectors; Portal vein; Liver segments; Caudate lobe; Cantlie's line; Falciform ligament; Gallbladder

Core tip: Standard anatomical description of the liver segments is available by computed tomographic scan and ultrasonography. A stepwise evaluation of the liver segments by endoscopic ultrasound (EUS) has not been described. In this article, we have described a stepwise evaluation of the liver segments by EUS. This information can be useful for planning successful radical surgeries, preparing for biopsy, portal vein embolization, transjugular intrahepatic portosystemic shunt, tumour resection or partial hepatectomy, and for planning EUS guided diagnostic and therapeutic procedures.

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INTRODUCTION

The French surgeon and anatomist Claude Couinaud described "two lobes" (right and left), "two hemilivers" (right and left), "four sectors," and "eight segments" of the liver. The two lobes are separated by the falciform ligament, the two hemilivers are separated by the Cantlie's line, the four sectors are separated by the planes of three hepatic veins (portal fissures or scissurae), and the eight segments are separated by an imaginary transverse plane passing by the portal vein bifurcation (Figure 1 and Table 1)[1]. Each of the segments is an independent segment and has its own vascular inflow, outflow, and biliary drainage. The segments are referred to by number or by names[2,3]. The numbering of the segments is done in a counter-clockwise manner starting from Segment Ⅰ (the caudate lobe). The segments Ⅱ to Ⅳ belong to the left and segments Ⅴ to Ⅷ belong to the right hemiliver (Table 1)[2-4]. Standard anatomical description of the liver segments is available by computed tomographic (CT) scan[5]. A stepwise evaluation of the liver segments is also described by ultrasonography[6,7]. Endoscopic ultrasound (EUS) has been used for detailed imaging of many intra-abdominal organs and for the assessment of intra-abdominal vasculature[8-11]. A stepwise evaluation of the liver segments by EUS has not been described. In this article, we describe a stepwise evaluation of the liver segments by EUS.

APPLIED ANATOMY AND THE HOME BASES FOR IMAGING

The home bases of liver imaging are given in the figure and the table (Figure 2A and Table 2). The main key of the imaging is following the hepatic vein tributaries and the portal vein branches. The three hepatic veins divide the liver into four vertical sectors: right anterior, right posterior, left medial and left lateral (Figure 1). The plane of portal vein bifurcation creates a transverse plane that crosses the vertical planes and divides the four sectors into eight segments (Figures 1 and 2A, and Table 1). The right hepatic vein lies in the right portal fissure and separates the right hemiliver into anterior and posterior sectors. The left hepatic vein lies in the left portal fissure and separates the left hemiliver into medial and lateral sectors. The middle hepatic vein lies in the main portal fissure and separates the anterior division of right liver from the medial division of the left liver. The main portal vein bifurcates into the right and the left branches, which travel in an imaginary transverse plane of the transverse fissure. The extrahepatic part of the left branch of the portal vein is known as the

Table 1 The sectors and the segments of liver

Four hepatic sectors	Eight hepatic segments
Left lateral sector	Segment Ⅰ - the caudate lobe Segment Ⅱ - posterosuperior Segment Ⅲ - anteroinferior
Left medial sector	Ⅳa - superior segment Ⅳb - inferior segment
Right anterior sector	Segment Ⅴ - inferior segment Segment Ⅷ - superior segment
Right posterior sector	Segment Ⅵ - inferior segment Segment Ⅶ - superior segment

This table shows the relationship of hepatic sectors and hepatic segments. The four segments of left liver are: Ⅰ (caudate); Ⅱ (left lateral superior); Ⅲ (left lateral inferior); and Ⅳ (left medial) [subdivided into superior (Ⅳa) and inferior parts (Ⅳb) by Bismuth]. The four segments of right liver are: Ⅴ (right anteroinferior); Ⅵ (right posteroinferior); Ⅶ (right posterosuperior) and Ⅷ (right anterosuperior). The caudate lobe is often called an independent segment.

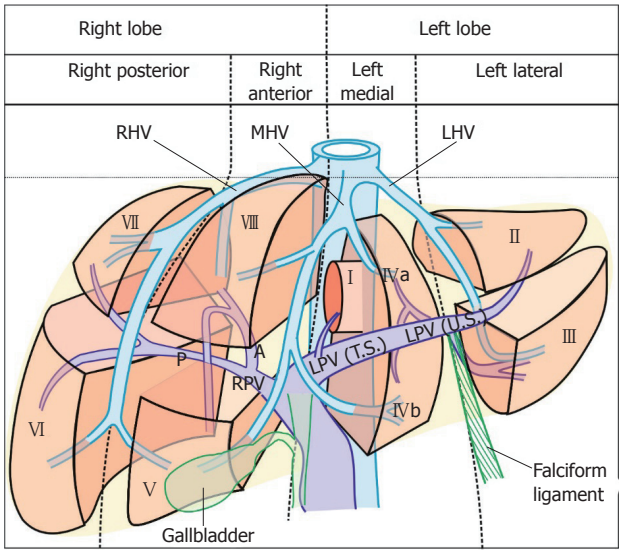

Figure 1 Three vertical planes and a transverse plane divide the liver into four sectors and eight segments. The vertical planes divide the liver into four sectors. The transverse plane divides the liver into superior and inferior segments. LHV: Left hepatic vein; MHV: Middle hepatic vein; RHV: Right hepatic vein; LPV: Left branch of the portal vein; RPV: Right branch of the portal vein.

Table 2 The home bases of imaging for liver segments

Home bases	Defining of segments
Hepatic veins	LHV separates Ⅱ and Ⅲ from Ⅳ (a and b)
	MHV separates Ⅳa from Ⅷ and Ⅳb from Ⅴ
	RHV separates Ⅴ from Ⅵ and Ⅷ from Ⅶ
Portal vein and its branches	Superior segments lie above and inferior segments lie below the transverse fissure
	The LPV supplies segments Ⅱ to Ⅳ
	The RPV supplies segments Ⅴ to Ⅷ
IVC	IVC passes through the bare area of the liver and is related to superior segments in the upper part, segment Ⅰ for most of its course, and with segment Ⅵ close to the lower most part above the right kidney
IVC suprahepatic part	A transverse plane defines the upper limit of superior segments (Ⅱ, Ⅳ, Ⅷ, and Ⅶ)
Ligamentum teres	Separates segment Ⅲ from Ⅳb
Ligamentum venosum	Separates Ⅰ from Ⅳa and Ⅱ
Gallbladder	Neck lies close to segment Ⅴ and fundus close to segment Ⅵ, from stomach Ⅳb comes between the gallbladder and probe

IVC: Inferior vena cava; LHV: Left hepatic vein; MHV: Middle hepatic vein; RHV: Right hepatic vein; LPV: Left branch of the portal vein; RPV: Right branch of the portal vein.

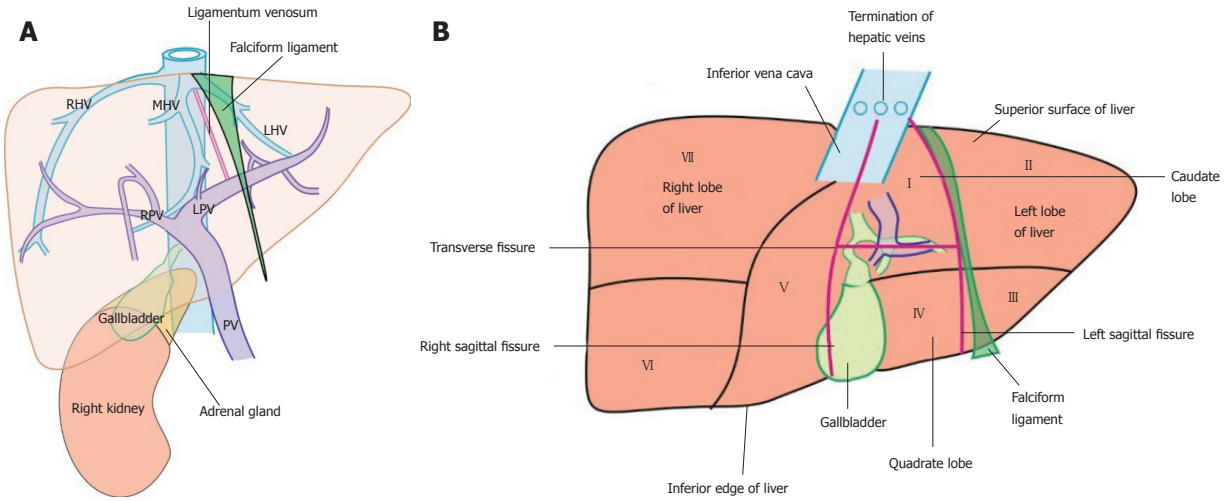

Figure 2 The home bases of imaging and visceral surface of liver. A: The endoscopic ultrasonography home bases of imaging for liver segments include the inferior vena cava (IVC) during its course behind the liver up to the right atrium, three hepatic veins in portal fissures and their joining point into the IVC, the portal vein and its branches in transverse fissure, the right kidney, the ligamentum teres, the ligamentum venosum, and the gallbladder; B: The caudate lobe lies between the stomach and IVC. The hepatic veins join the IVC. The ligamentum venosum and ligamentum teres are attached to the upper and lower border of the left branch of the portal at the angulation between the transverse and umbilical part. The visceral surface of the liver comes in contact with all segments except segment Ⅷ. PV: Portal vein; LHV: Left hepatic vein; MHV: Middle hepatic vein; RHV: Right hepatic vein; LPV: Left branch of the portal vein; RPV: Right branch of the portal vein.

transverse part and the intrahepatic part of left branch of the portal vein is known as the umbilical part. The extrahepatic part of left branch of portal vein lies in the gastrohepatic ligament on its inferior surface. The umbilical part of portal vein is surrounded on all sides by the liver (Figure 1). The right portal vein divides into two branches after entering the liver. The anterior branch supplies the anterior sector of the right lobe, and the posterior branch supplies the posterior sector of the right lobe (Figures 1 and 2A, and Table 2). The gallbladder, the right kidney, the fissures on the under surface of liver, and the ligaments of liver are acting as additional home bases of imaging for liver segments.

The inferior surface of the liver has an H-shaped fissure where the right and left limbs of the H are made by the right and left sagittal fissures, and the transverse limb is formed by the porta hepatis. The left sagittal fissure has upper and lower limbs, which are formed by the fissure for the ligamentum venosum and the fissure for the ligamentum teres. The upper part of the ligamentum venosum is attached to the inferior vena cava (IVC). The lower part of the ligamentum teres extends to the inferior surface of liver (Figure 2B and Table 2). The relationship of the caudate lobe is crucial in understanding the segments of liver. When seen from the stomach the caudate lobe lies between the stomach and the IVC. The hepatic veins join the IVC (Figure 2B).

POSITION OF THE PATIENT AND THE POSITIONS OF OPERATOR

EUS can be done with the patient in a prone, left lateral, or supine position, and the descriptions in this article have been done with the patient in a prone position. The position of the operator can change with the movement of the body (or hand), which transfers the

Table 3 A difference in the segments of imaging from the three positions

Station	Comment	Segments visualized
Abdominal part of the esophagus and stomach	Probe in the esophagus lies close to the left lobe of the liver and in the stomach close to the visceral surface of the liver	Superior segments and caudate lobe are in direct contact with the lower end of esophagus All segments except segment Ⅷ on the visceral surface of liver are in contact with the stomach
Duodenal bulb	Probe lies close to the hilum of the liver	Direct contact with segment Ⅰ and right lobe liver segments Left side segments are seen through caudate lobe, caudate process, and IVC
Second part of duodenum.	Probe lies close to the hilum of the liver	Direct contact with segment Ⅰ and right lobe liver segments Left side segments are seen through caudate lobe, caudate process, and IVC

IVC: Inferior vena cava.

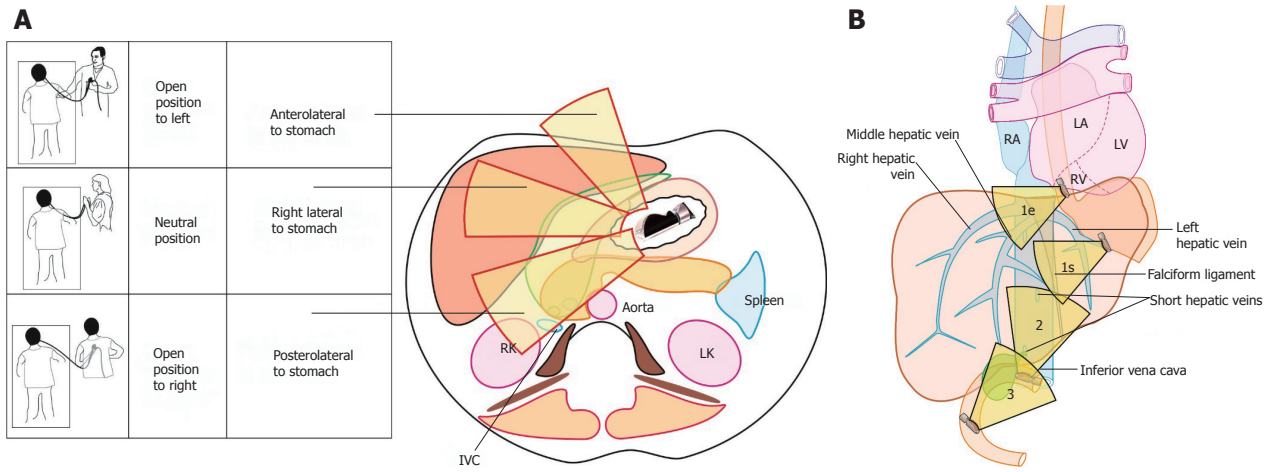

Figure 3 Different operator positions during imaging and three stations of imaging. A: Rotation is the key movement and should be done in a straight position to transfer the effect of rotation to the tip of the ultrasonic transducer. During imaging from the stomach, the open position to left starts imaging structures placed dorsal to the probe in the esophagus and stomach and primarily screens the left lobe of the liver. The neutral position screens the structures near the liver hilum and the open position to right screens the right lobe of liver; B: The three stations of imaging for liver segments: (1) abdominal part of esophagus (1e) and stomach (1s); (2) duodenal bulb; and (3) second part of the duodenum. IVC: Inferior vena cava; RK: Right kidney; LK: Left kidney; RA: Right atrium; LA: Left atrium; RV: Right ventricle; LV: Left ventricle.

effect of rotation towards the tip of the scope when the scope is maintained in a straight position. The three positions are open position to left, neutral position, and an open position to right. In an open position to left, the operator faces the patient's feet. In a neutral position, the operator faces the body of the patient. In an open position to right, the operator faces the head of the patient. A clockwise rotation from an open position to left in the stomach moves the imaging axis of the probe from a dorsal to a lateral and subsequently to a ventral position (Figure 3A). A reverse of this happens when the scope is rotated counterclockwise after seeing the right kidney.

THREE STATIONS OF IMAGING

The imaging is possible from three stations. Station 1: abdominal part of esophagus and stomach; station 2: duodenal bulb; and station 3: 2nd part of duodenum (Figure 3B and Table 3). Each station shows the segments in different anatomical relationships, and the differences in the segmental assessment of imaging are described in the table.

Station 1: Imaging from the lower end of the esophagus and stomach

This station of imaging is the most convenient method of imaging and is discussed in detail. Generally, it requires a rotation of the scope in three positions (Figure 3A) and a shift of the scope in and out to the four different levels (Figure 4A). During this rotation the sectors come close to the probe in the following order left lateral, left medial, right anterior, and right posterior (Table 4).

Imaging from open position to left: From the open position to left, the portal vein branches going to segment Ⅱ and Ⅲ are identified (Figure 5A). Imaging of the intrahepatic part of the left branch of the portal vein (umbilical part) within the umbilical fissure gives a fisheye appearance as it is completely surrounded on all sides by the liver parenchymal tissue (Figure 5B). The fisheye appearance indicates the left edge of the H of the transverse fissure from where the upper and lower limbs of the left sagittal fissure can be followed by slight in and out movement to trace the ligamentum venosum and ligamentum teres (Figures 5B and 5C). Further

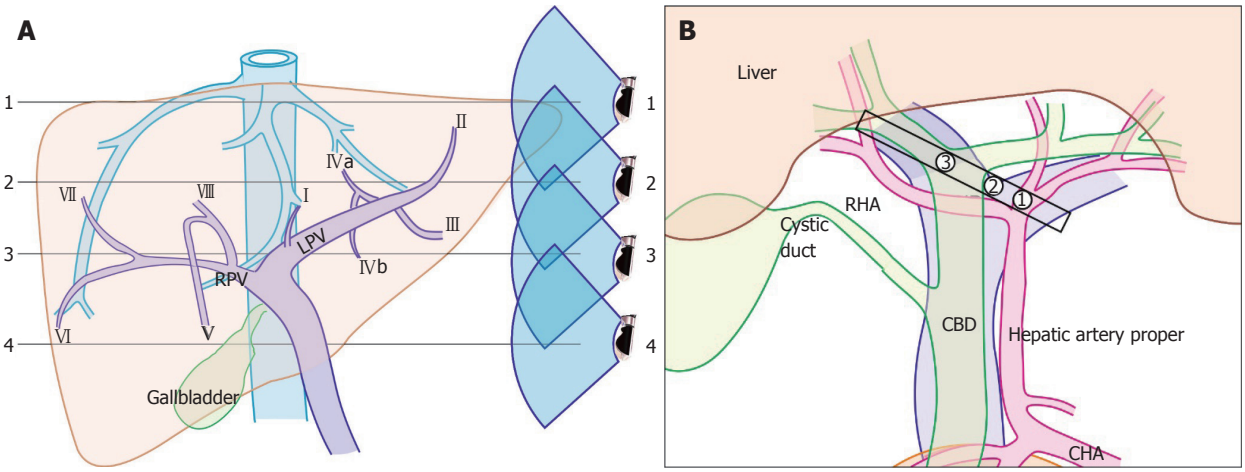

Figure 4 Hepatic vein tributaries with portal vein branches and hilar structures during rotation from left to right edge of transverse fissure. A: The imaging of hepatic vein tributaries and portal vein branches as the home bases during imaging from the abdominal part of the esophagus and stomach; B: The hilar structures with the divisions during a rotation from the left edge of the transverse fissure to the right edge. (1) hepatic artery into two branches; (2) the union of the right and left branch of the portal vein; (3) the division of the common hepatic duct into right and left branches. LPV: Left branch of the portal vein; RPV: Right branch of the portal vein; CHA: Common hepatic artery; RHA: Right hepatic artery; CBD: Common bile duct.

rotation traces the transverse fissure from the left edge of the H towards the right edge of the H and follows the umbilical part of the left branch of the portal vein towards the transverse part of the left branch. During this rotation from the left edge to the right edge, the appearance of the hepatic artery into two branches, the union of right and left branch of the portal vein and the division of the common hepatic duct into right and left branches appear one by one in the transverse fissure (Figures 4B and 5D).

Imaging from the neutral position: Further rotation traces the course of the extrahepatic part of the left branch of the portal vein (transverse part) within the transverse fissure (Figure 6A). At this point the union of right and left branches of the portal vein is seen (Figure 6B). Near the union point the extrahepatic part of the right branch of the portal vein can be seen to join the transverse part of the portal vein from a direction coming from 6 o'clock within the transverse fissure. The right branch of the portal vein is often seen traveling close to the neck of gallbladder. Near the right edge of the transverse fissure, the union of right and left ducts is seen in front of the right branch of the portal vein (Figure 6C). The imaging of the right branch of the portal vein is easy through the caudate process of the liver in the area above the transverse fissure and below the IVC (Figure 6D).

Imaging from an open position to right: Further rotation with slight upward angulation traces the extrahepatic part of the right branch of the portal vein towards the intrahepatic part. Imaging of the intrahepatic part of the right branch of the portal vein usually requires a decrease in frequency to increase penetration depth and an increase in the depth of the imaging to include the entire right lobe of the liver along with the hyperechoic diaphragm, which is seen beyond the convex upper surface of the liver (Figure 7A). Imaging of the right part of liver is easy due to the window made by the IVC and the caudate process (Figure 7B). The right branch of the portal vein can be followed to the division into an anterior and a posterior branch. Usually, with a linear scope the vision of the anterior branch is best seen when the middle hepatic vein is seen on the far side of the screen (Figure 7C). A relatively more posterior view of the course of posterior division of the right portal vein branches is possible through the caudate process between the porta hepatis and the IVC. It is usually possible to see the segmental branches to segment Ⅵ and Ⅶ (Figure 7D).

Station 2: Imaging from duodenal bulb

Neutral position: Imaging from duodenal bulb shows a view of the liver hilum (transverse fissure) where the portal vein is easily identified, with right and left angulation, up and down movements, and in and out adjustments.

Open position to left: The portal vein bifurcation defines the line between superior and inferior segments. A counterclockwise rotation traces the transverse fissure towards the gallbladder and the right edge of the transverse fissure where the right lobe segments are seen.

Open position to right: A clockwise rotation after tracing the portal vein bifurcation traces the transverse fissure towards the left edge of the transverse fissure where the left lobe segments are seen. The lower border of the caudate lobe lies above the bifurcation and above the transverse part of the left branch of the

Table 4 The structures from three positions from station 1

Clockwise rotation from an open position to left	Part of portal vein	Part of hepatic vein	Other home base structures	Main sector of liver visualized	Main segments of liver visualized	Figure number for segment
Open position to left	PⅡ and PⅢ	LHV	Diaphragm and heart	Left medial closer to left lateral[1]	Ⅱ, Ⅲ, and Ⅳ	2A, 2B, 3A, 5A
Neutral position after approximately 60° to 75° clockwise rotation	Fisheye appearance of LPV	MHV	Left edge of transverse fissure attached to ligamentum venosum and ligamentum teres	Left medial closer to probe than right anterior	Ⅰ and Ⅳ	3A, 5B
Open position to right after further approximately 60° to 75° clockwise rotation	RPV dividing into anterior and posterior branches	RHV	Right edge of transverse fissure, IVC, gallbladder, and caudate process	Right anterior closer to probe than right posterior	Ⅴ, Ⅵ, Ⅶ, and Ⅷ	3A, 7A 7C, 7D

[1]When the scope is in maximum open position only the left lateral segment is seen. IVC: Inferior vena cava; LHV: Left hepatic vein; MHV: Middle hepatic vein; RHV: Right hepatic vein; LPV: Left branch of the portal vein; RPV: Right branch of the portal vein.

portal vein.

Station 3: Imaging from descending duodenum

An open position to right places the scope in a parallel axis with the superior mesenteric vein from the descending duodenum. From this position a counterclockwise rotation traces the course of the IVC from a 10 o'clock position to a 4 o'clock position and sequentially brings the hilum of the right kidney, the right lobe of liver, the hilum of the liver and gallbladder, and lastly the left lobe of the liver into view (Figure 8). In this process the segments belonging to the posterior surface and bare area of the liver are easily followed close to the IVC. The first segment close to the lower most part of the IVC just above the adrenal gland and right kidney belongs to segment Ⅵ (Figure 8A). Once the gallbladder is seen segment Ⅴ lies close to the upper surface of the gallbladder. Near the hilum of the liver segment Ⅰ is identified between the portal vein and the IVC. On maximum counterclockwise rotation the probe lies close to the upper most part of the IVC near the joining of the hepatic veins where the superior segments (Ⅶ, Ⅷ, Ⅳa, and Ⅱ) are visualized.

SYSTEMATIC APPROACH TO IDENTIFY LIVER SEGMENTS

The imaging of segments is done in eight steps: (1) identify lobes; (2) identify sectors (right and left portal fissures); (3) identify the plane of superior and inferior segments (transverse fissure/liver hilum); (4) identify left sagittal fissure and the liver ligaments; (5) identify caudate lobe (posterior to transverse fissure); (6) identify left lobe segments; (7) identify quadrate lobe (anterior to transverse fissure); and (8) identify right lobe segments.

Identify lobes (Cantlie's line)

Applied anatomy: The Cantlie's line passes through the middle hepatic vein (main portal fissure) superiorly. It also corresponds to a vertical plane passing diagonally from the middle of the gallbladder fossa anteriorly and inferiorly to the left side of the IVC posteriorly (Figure 2B).

Technique of examination: Identify the IVC. The middle hepatic vein is identified merging into IVC (Figures 9A and 9B).

Identify sectors

Applied anatomy: Each right and left hemiliver is subdivided by the left and right hepatic veins lying in the left and right portal fissures. The course of the left hepatic vein divides the left lobe into the medial and lateral sectors. The course of the right hepatic vein divides the right lobe into the anterior and posterior sectors.

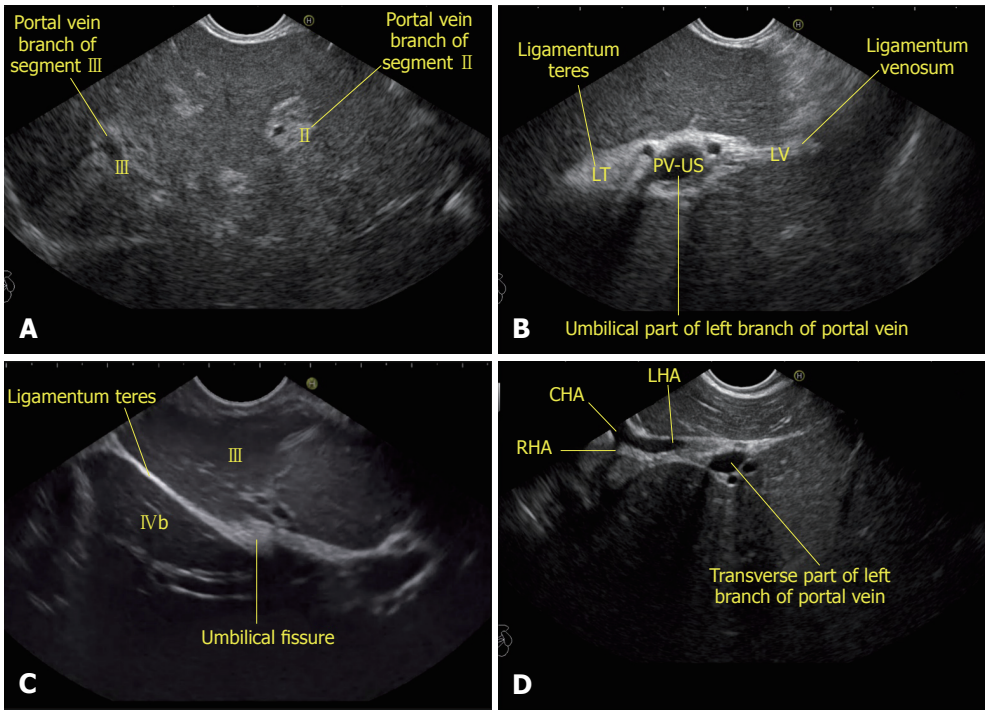

Figure 5 Imaging of liver segments from station 1. A: Imaging from the abdominal part of esophagus showing segments Ⅱ and Ⅲ portal vein branches; B: The fisheye appearance of the umbilical part of the left branch of the portal vein as seen from the abdominal part of esophagus; C: Imaging from the visceral surface of the liver showing that the ligamentum teres is attached to the lower part of the umbilical vein; D: On clockwise rotation near the left edge of the porta hepatis, the umbilical part enters the transverse fissure. At this point the bifurcation of the common hepatic artery can be seen towards the left edge of the transverse fissure. This image shows the entry of the left branch of the common hepatic artery into the transverse fissure. CHA: Common hepatic artery; RHA: Right hepatic artery; LHA: Left hepatic artery.

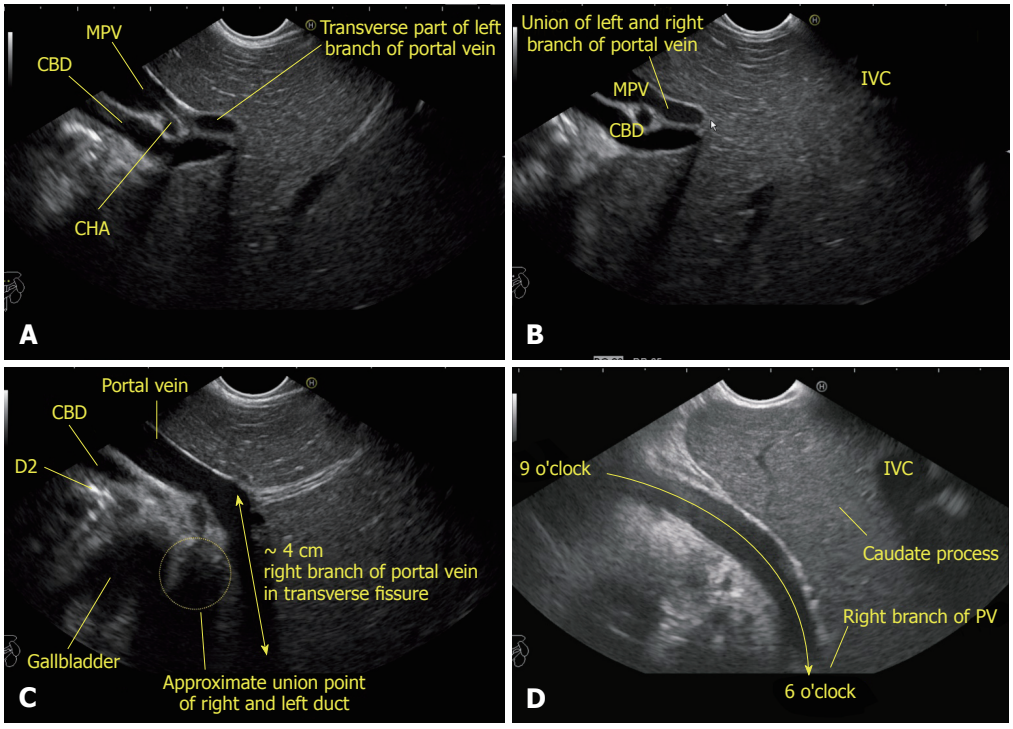

Figure 6 Imaging from neutral position from station 1 showing the tracing of the portal vein and its branches during clockwise rotation from the left to right edge of the transverse fissure. A: Further clockwise rotation traces the course of the left branch of the portal vein (PV) in the transverse fissure; B: Further rotation shows the union of the right and left branch of the PV; C: The approximate 4 cm breadth of the transverse fissure within which the right branch of the PV joins the left branch; D: The imaging of the right branch of the PV is easy through the caudate process of the liver. With slight up angulation, the right branch of the PV is seen in the transverse fissure going from a 6 o'clock to a 9 o'clock position. CHA: Common hepatic artery; IVC: Inferior vena cava; PV: Portal vein; CBD: Common bile duct; MPV: Main portal vein.

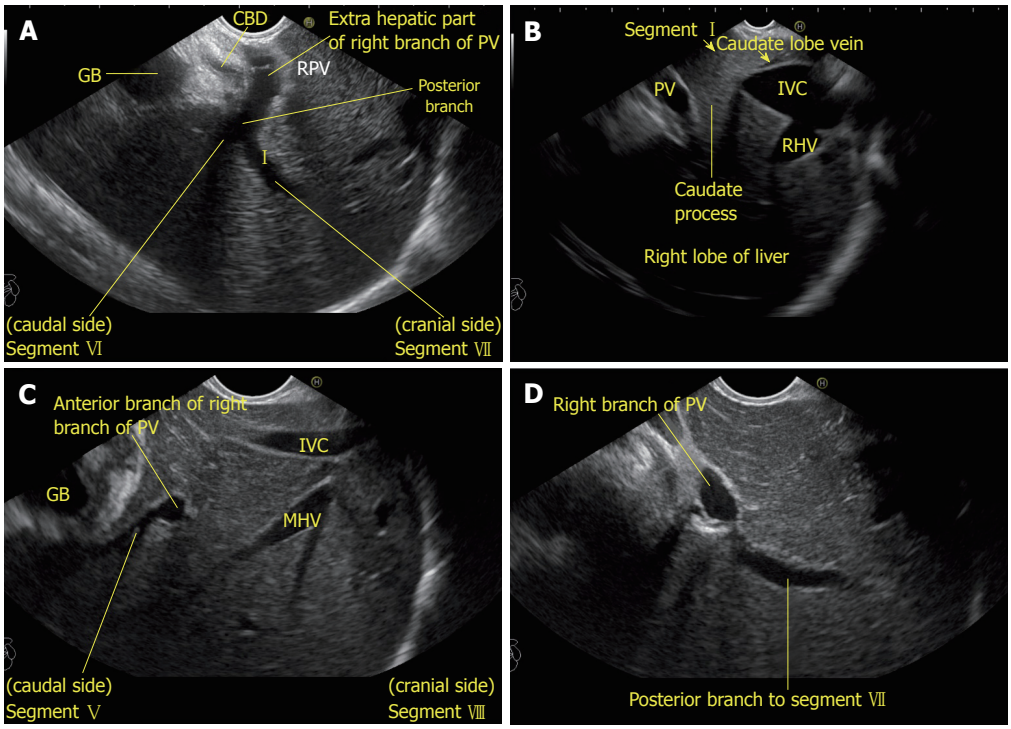

Figure 7 Imaging from station 1 showing the right portal vein and its branches in relation to liver segments. A: Imaging of the intrahepatic/extrahepatic part of the right branch of the portal vein is seen along with the right lobe of the liver and the hyperechoic diaphragm; B: The inferior vena cava and caudate process provide a good window of imaging for the right lobe of the liver (The caudate lobe is connected with the right lobe of liver through the caudate process). In this location, presence of the inferior vena cava may also provide a satisfactory window of imaging; C: A view of the divisions of the right branch of the portal vein is possible through the caudate process. In this case, the anterior branch is supplying segments Ⅴ and Ⅷ of the liver; D: The division of segment Ⅵ and Ⅶ branches is visualized. The upper part of the posterior branch goes towards segment Ⅶ. CBD: Common bile duct; GB: Gallbladder; PV: Portal vein; RHV: Right hepatic vein; MHV: Middle hepatic vein; IVC: Inferior vena cava.

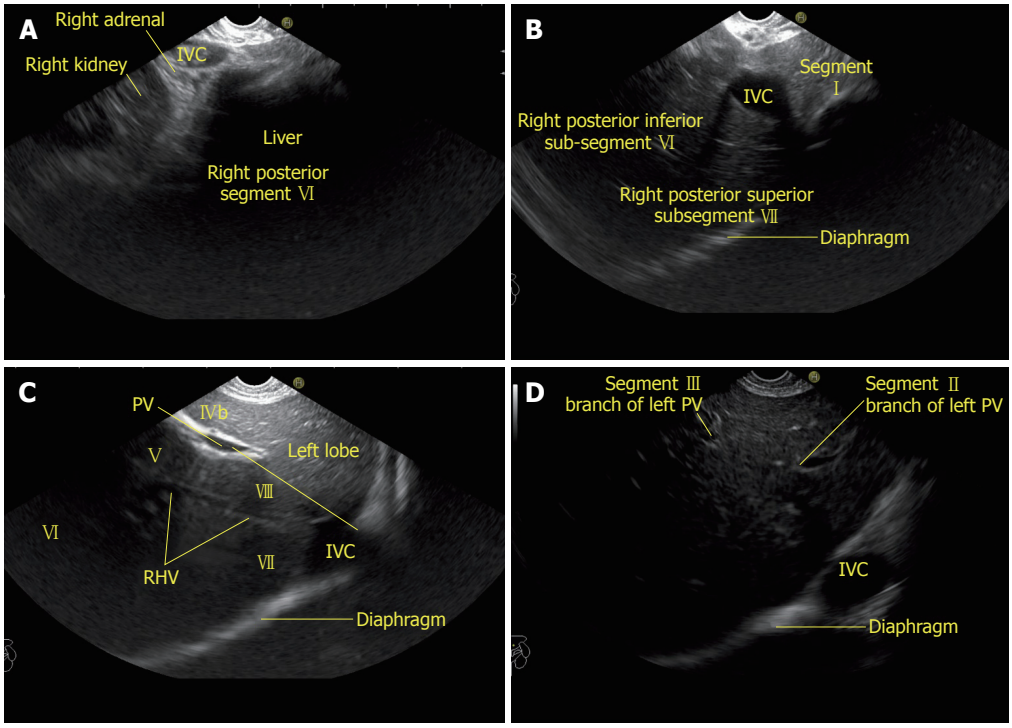

Figure 8 Imaging from the descending duodenum showing the structures visualized during counterclockwise rotation from open position to right. A: Imaging from the descending duodenum showing the right kidney and inferior vena cava (IVC). The right adrenal gland is seen behind the IVC; B: Imaging from the descending duodenum showing the IVC moving towards the diaphragm. The caudate lobe is seen between the probe and the IVC. The caudate lobe indicates the approximate place of the transverse part of the left branch of the portal vein (PV); C: Imaging from the descending duodenum showing the right hepatic vein. It divides the segments of the right lobe. A line between the cranial end of the IVC and the PV gives approximate locations of the right and left half of the liver; D: The segmental branches (Ⅱ and Ⅲ) of the umbilical part of the PV are seen with the IVC at a 4 o'clock position. RHV: Right hepatic vein; IVC: Inferior vena cava; PV: Portal vein.

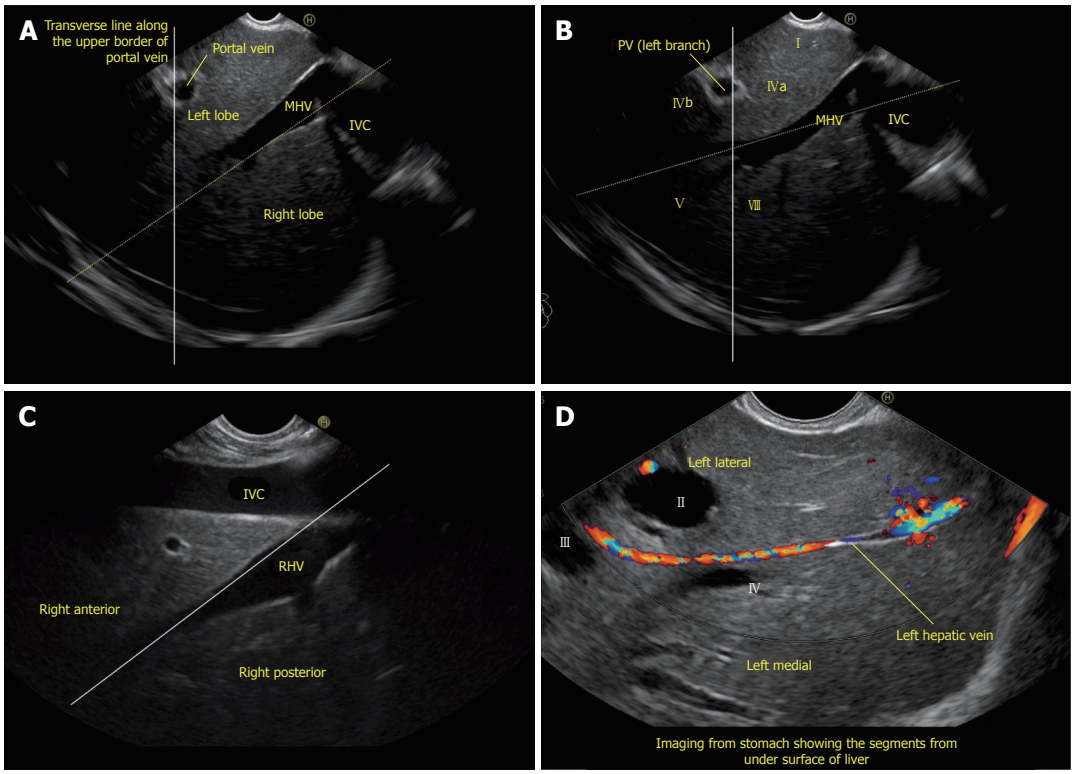

Figure 9 Imaging from station 1 showing hepatic vein branches and their relationship to liver segments. A: The middle hepatic vein lies in the course of the Cantlie's line and separates the left and right lobe of the liver; B: The segmental division is shown for segment Ⅰ, Ⅳa, Ⅳb, Ⅴ, and Ⅷ; C: The right hepatic vein separates the right anterior and right posterior sectors; D: The left hepatic vein separates the left medial and left lateral sectors. MHV: Middle hepatic vein; RHV: Right hepatic vein; IVC: Inferior vena cava; PV: Portal vein.

Technique of examination: Identify the merger of the left and right hepatic veins into the IVC (Figures 9C and 9D).

Identify the plane of superior and inferior segments

Applied anatomy: The portal vein and its branches in the transverse fissure acts as a guide to divide the liver into superior (Ⅶ, Ⅷ, Ⅳa and Ⅱ) and inferior segments (Ⅲ, Ⅳb Ⅴ and Ⅵ). The applied anatomy of fissures and ligaments was already discussed in the home bases section. The joining of the three hepatic veins into the supra hepatic part of the IVC determines the uppermost margin of superior segments related to the IVC.

Technique of examination: The umbilical fissure is identified within the left lobe of the liver. Clockwise rotation along the umbilical fissure traces the transverse plane of the transverse fissure within which the left and right branches of the portal vein are seen (Figures 6C, 6D, and 10).

Identify the left sagittal fissure and the liver ligaments

Applied anatomy: The applied anatomy of fissures and ligaments was already discussed in the home bases section.

Technique of examination: The umbilical fissure is identified within the left lobe of the liver. The ligaments are attached to the upper and lower part of the umbilical fissure (Figure 5C).

Identify the caudate lobe

Applied anatomy: Anatomy texts describe the caudate lobe as a midline, vertically oriented hepatic lobe seen on the posterior aspect of the liver separating a portion of the right and left hepatic lobes in an H configuration. The horizontal bar of the H configuration represents the transverse fissure of the porta hepatis, which includes the horizontal portion of both portal veins. Above the bar is the caudate lobe of the liver and below the bar is the medial segment, or quadrate lobe, of the left lobe of the liver[12].

Technique of examination: The caudate lobe may be imagined as a midline wedge in a sagittal plane with its tip extending cephalad up to the insertion of the left and middle hepatic veins into the IVC and its base or posterior border facing the IVC (Figures 11A and 11B). The right (or medial border) of the pyramid is continuous with the parenchyma of the right lobe of the liver *via* the caudate process (Figure 11C). The anterior border of the caudate lobe is separated from the medial segment of the left lobe of the liver superiorly by the fissure for the ligamentum venosum and inferiorly by the left portal triad and portal bifurcation (Figure 11D). A clockwise rotation after identification of the left lobe of the liver from an open position to left will help in identification of the ligamentum venosum (Figure 11D).

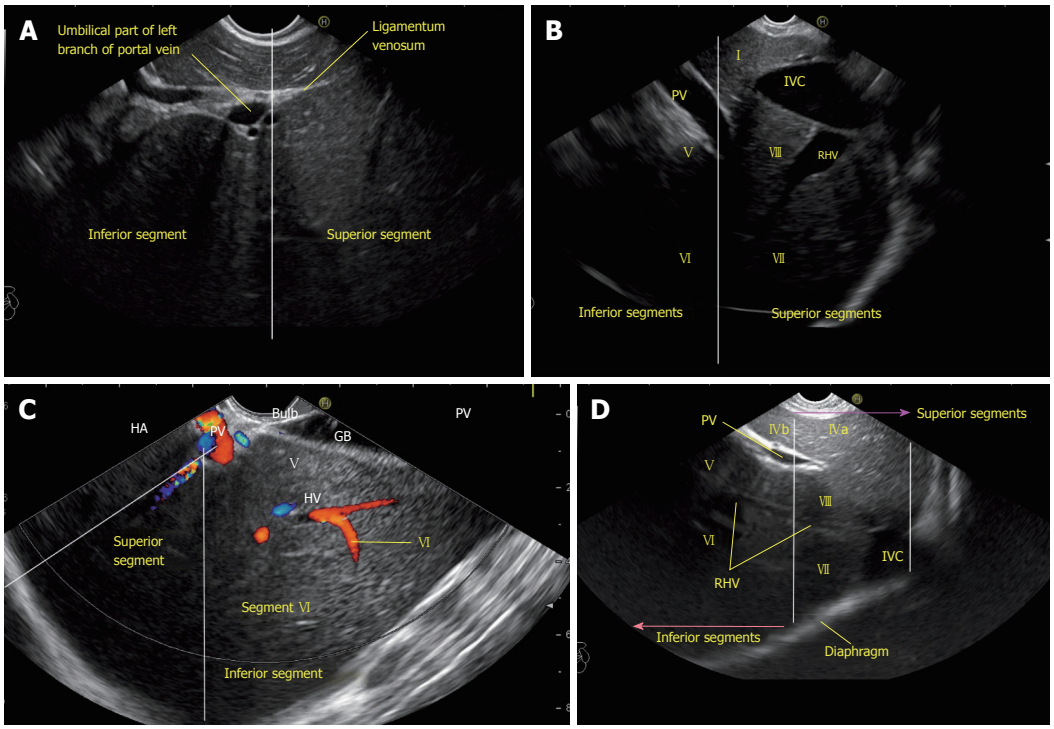

Figure 10 The division of superior and inferior liver segments by the portal vein and its branches. A: Line at the level of the upper border of the umbilical segment of the portal vein dividing the superior and inferior segments; B: The white line divides the superior and inferior segments. This diagram from the esophagus shows the right side of the liver through the caudate lobe of the liver and the inferior vena cava. The presence of hepatoduodenal ligament around the portal vein may not allow a similar quality of visualization of the inferior segments (Ⅴ and Ⅵ); C: This image from station 2 (duodenum bulb) shows the right and middle hepatic veins. The right hepatic vein is parallel to the surface of the gallbladder, and the middle hepatic vein is towards the neck of the gallbladder. Only the right lobe is seen through the gallbladder; D: The right hepatic vein drains segments Ⅵ and Ⅶ and a variable portion of segments Ⅴ and Ⅷ. Segment Ⅰ has direct drainage into the intrahepatic/retrohepatic part of the inferior vena cava. RHV: Right hepatic vein; IVC: Inferior vena cava; PV: Portal vein.

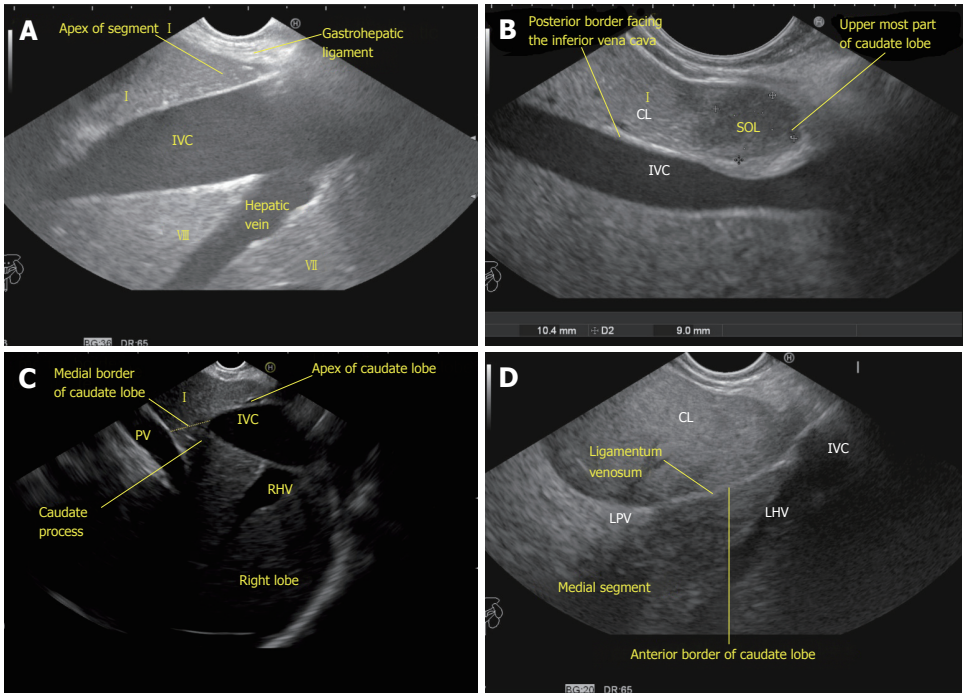

Figure 11 The caudate lobe, its boundaries, and its relationships. A: The apex of the caudate lobe lies like a wedge near the joining of the hepatic veins. The base faces the inferior vena cava; B: A small metastatic space-occupying lesion is seen near the tip of the caudate lobe of the liver near the diaphragm between the probe and the inferior vena cava. Anterior margin of lesion is limited by the fissure for the ligamentum venosum; C: The continuity of the caudate lobe into the right lobe of the liver *via* the caudate process; D: The ligamentum venosum proceeds towards the umbilical part of the portal vein and divides the left medial segment from the caudate lobe. The ligamentum venosum is the anterior border of a pyramidal shaped caudate lobe. The attachment of the ligamentum venosum demarcates the lowest limit of the anterior border. SOL: Space-occupying lesion; LHV: Left hepatic vein; LPV: Left branch of the portal vein; RHV: Right hepatic vein; IVC: Inferior vena cava; PV: Portal vein.

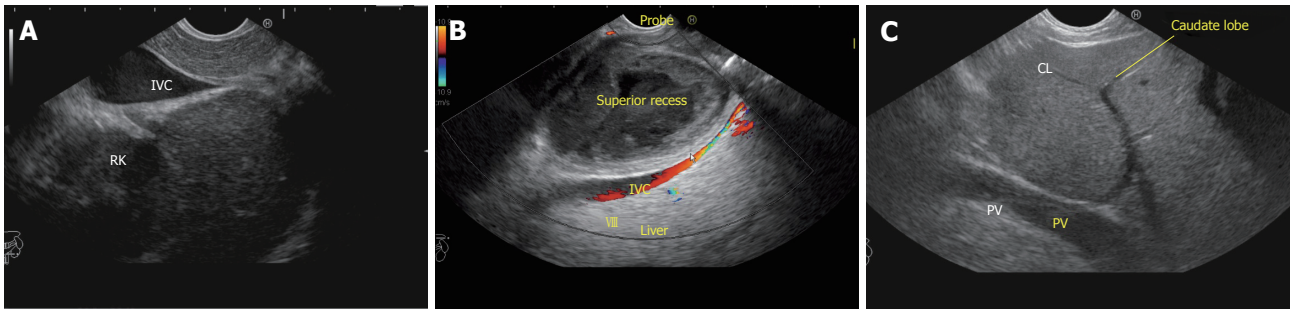

Figure 12 The caudate lobe, its boundaries, and its relationships. A: The exit of the inferior vena cava from the liver demarcates the lowest limit of the posterior border. The right kidney is seen through the inferior vena cava. Segment Ⅵ lies above the right kidney; B: The left border of the caudate lobe lies close to superior recess of the lesser sac, which is filled with fluid in this case; C: The vascular supply of the caudate lobe from the right branch of the portal vein. The right and left lobes of the liver lie on either side of the right and left sagittal fissures, and the caudate and quadrate lobes lie posterior and anterior to the transverse fissure. RK: Right kidney; IVC: Inferior vena cava; PV: Portal vein.

The upper border of the umbilical part of the left branch of the portal vein is attached to ligamentum venosum and serves as an accurate anatomic boundary of the lowermost limit and anterior margin of the caudate lobe (Figure 11D).

The caudal margin of the caudate lobe form the cephalad margin, or lintel, of the foramen of Winslow and projects into the lesser sac where it is related to the right crus of the diaphragm and inferior phrenic artery. The left (or lateral border) of the caudate lobe projects into the superior recess of the lesser peritoneal sac and is covered anteriorly by the gastrohepatic ligament (lesser omentum), which separates it from segments Ⅱ and Ⅲ anteriorly and segment Ⅷ in the right lateral wall (Figure 12B). The vascular inflow and biliary drainage to the caudate lobe comes from both the right and left pedicles. The right side of the caudate, the caudate process, largely derives its portal venous supply from the right portal vein or the bifurcation of the main portal vein (Figure 12C). The left portion of the caudate derives its portal venous inflow from the left portal vein.

Caudate process a two-way window for imaging of the right and left lobe of the liver in EUS: The caudate lobe, caudate process, and the IVC act as a window of imaging from the left side to the right side of the liver and vice versa. While imaging from the abdominal part of the esophagus and stomach the window allows left to right visualization. While imaging from the duodenal bulb and the second part of the duodenum the window allows right to left visualization (Figures 11C, 11D, 12A, 12C, and 13).

Identify the left lobe

Applied anatomy: The left lobe lies anterior to the esophagogastric junction and the fundus of stomach.

Technique of examination: The segments of the left lobe are best visualized with slight up tilting of the scope from the fundus of stomach. In this position, the left part of the heart is visualized through the diaphragm and the left hepatic vein is easily identified as the border between the left medial and two left lateral segments (segment Ⅲ anterior-inferior and segment Ⅱ posterior-superior). Further demarcation of segment Ⅱ as the upper segment and segment Ⅲ as the lower segment is possible by the plane passing by the portal vein bifurcation (Figures 14A and 14B). This plane is not usually visualized during imaging of the left lateral segments (Ⅱ and Ⅲ) in an open position to left where the fisheye appearance of the umbilical part is not visualized. A line can be extrapolated from the upper border of the fisheye appearance of the left branch of the portal vein for proper demarcation (Figure 14B). The visualization of the left medial segment is seen between the probe and the middle hepatic vein (Figure 14C). The presence of the middle hepatic vein and of the upper border of the left branch of the portal vein indicates the area where segment Ⅰ communicates with segment Ⅳ (Figure 14D).

Identify segment Ⅳa and Ⅳb (quadrate lobe)

Applied anatomy: Segment Ⅳ is located between the plane passing by the middle hepatic vein on the right and the axis of the umbilical scissura on the left. This segment can be divided into an upper (Ⅳa) and a lower (Ⅳb) segment by a horizontal line passing through the umbilical portion of the left branch of the portal vein. The Ⅳb segment (quadrate lobe) is demarcated on the visceral surface anteriorly by the inferior edge of the liver, on the right side by the gallbladder fossa, posteriorly by the porta hepatis, and on the medial side by the fissure for the ligamentum teres (Figures 14B and 14D).

Technique of examination: Segment Ⅳ is easily identified near the middle hepatic vein. The identification of the gallbladder, ligamentum teres, and umbilical fissure also helps in identification of the liver segments (Figure 14D).

Identify right lobe segments

Applied anatomy: The right liver consists of anterior and posterior segments, divided by the presence of

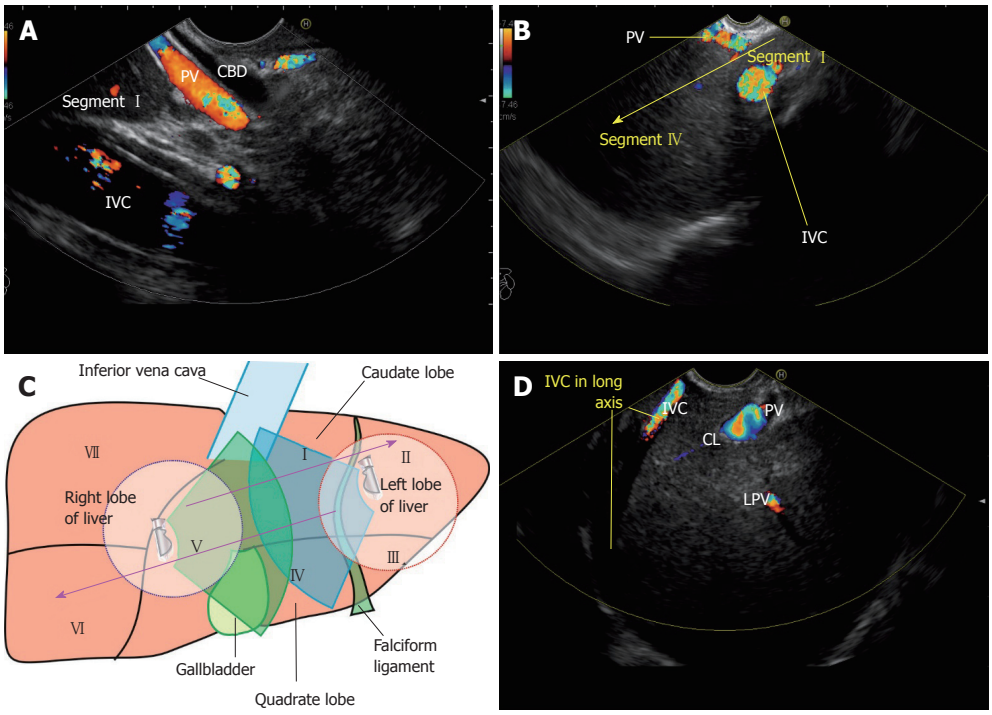

Figure 13 The caudate lobe from different stations of imaging. A: An image of the caudate lobe through the portal vein in front of the inferior vena cava from the duodenal bulb; B: An image of the caudate lobe between the portal vein and the inferior vena cava from the descending duodenum; C: The caudate process acts as a two-way window for imaging of the right and left lobes of the liver in endoscopic ultrasonography. The red circle shows the approximate area of gastric impression on the visceral surface of the left lobe of the liver and shows that the imaging of the right lobe is possible through the caudate lobe and caudate process. The blue circle shows the approximate area of duodenal impression on the visceral surface of the right lobe of the liver and that the imaging of the left lobe is possible through the caudate lobe and caudate process; D: An image of the left lobe of the liver through the caudate lobe from the duodenal bulb. IVC: Inferior vena cava; PV: Portal vein; CBD: Common bile duct; CL: Caudate lobe; LPV: Left branch of the portal vein.

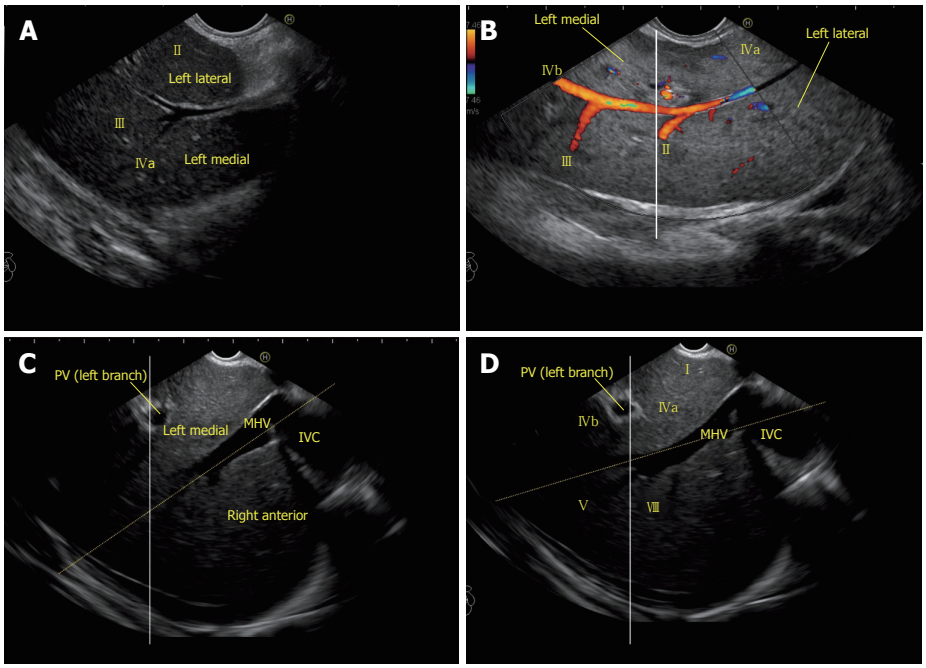

Figure 14 Hepatic veins dividing liver segments. A: Image showing left lobe segments; B: The upper and lower tributaries of the hepatic vein indicate the upper and lower segments of the left lateral and left medial sectors. Segments Ⅱ, Ⅲ, Ⅳa, and Ⅳb veins are seen. In this case, the imaging is done from the visceral surface of the liver and from an area close to the antrum and body. Hence, segment Ⅳ appears closer to the probe than segment Ⅲ. It must be clear that while imaging from the lower end of the esophagus that the left lateral segment is closer while during imaging from the visceral surface of the liver that the orientation of a segment may vary depending on the location of probe (for example, near the antrum segment Ⅳ is closer than segment Ⅲ, and near the fundus and proximal body segment Ⅲ is closer than segment Ⅳ). The white line is an extrapolated line that has been drawn in an approximate axis from the upper part of the umbilical part of the left branch of the portal vein; C: A line going through the middle hepatic vein separates the left medial and right anterior sectors; D: A line along the upper part of the transverse fissure (along the upper edge of the portal vein) subdivides the upper and lower segments of the left medial (segments Ⅳa and Ⅳb) and right anterior (segments Ⅷ and Ⅴ) segments. MHV: Middle hepatic vein; IVC: Inferior vena cava; PV: Portal vein.

Table 5 The representation of liver segments

Home base structure	Comment	Figure No.
Hepatic veins	The main left hepatic vein drains the two lateral segments of the left lobe (segments Ⅱ and Ⅲ)	9D
	The middle vein drains segment IV and the anterior sector of the right lobe (segments Ⅴ and Ⅷ)	9B
	The right vein drains the remainder of the right lobe (segments Ⅵ and Ⅶ) and a variable portion of segments Ⅴ and Ⅷ	9C
Hepatic vein tributaries	The higher tributary of LHV going towards the diaphragmatic and costal surface belongs to segment Ⅱ	9D
	The higher tributary of MHV going towards the diaphragmatic and costal surface belongs to segment Ⅷ	9B, 14C, 14D
	The higher tributary of RHV going towards the diaphragmatic and costal surface belongs to segment Ⅶ	15A, 15C
	The tributary of LHV going towards the liver hilum drains segment Ⅳa	14B
	The tributary of MHV going towards the liver hilum drains segment Ⅳb	14D
	The tributaries of RHV going towards the liver hilum drains segments Ⅴ and Ⅷ	9C
Right and left branches of the portal vein	The right branch of the portal vein supplies the right liver (segments Ⅴ to Ⅷ)	7A, 7B, 7C, 7D
	The left branch of the portal vein supplies the left liver (segments Ⅱ to Ⅳ)	5A, 5B, 5C, 5D, 6A, 6B
	The caudate lobe receives direct branches from both the right and left branches	12C
Segmental branches of the portal vein	The extrahepatic part supplies segment Ⅰ	11D
	The anterior branch of the RPV supplies segments Ⅴ and Ⅷ	7C
	The posterior branch of the RPV supplies segments Ⅵ and Ⅶ	7D
Right kidney	Lies lateral to the infrahepatic part of the IVC	8A
Caudate lobe	Forms an important anatomical landmark	10A, 10B, 10D, 11A, 11B, 11C

IVC: Inferior vena cava; LHV: Left hepatic vein; MHV: Middle hepatic vein; RHV: Right hepatic vein; LPV: Left branch of the portal vein; RPV: Right branch of the portal vein.

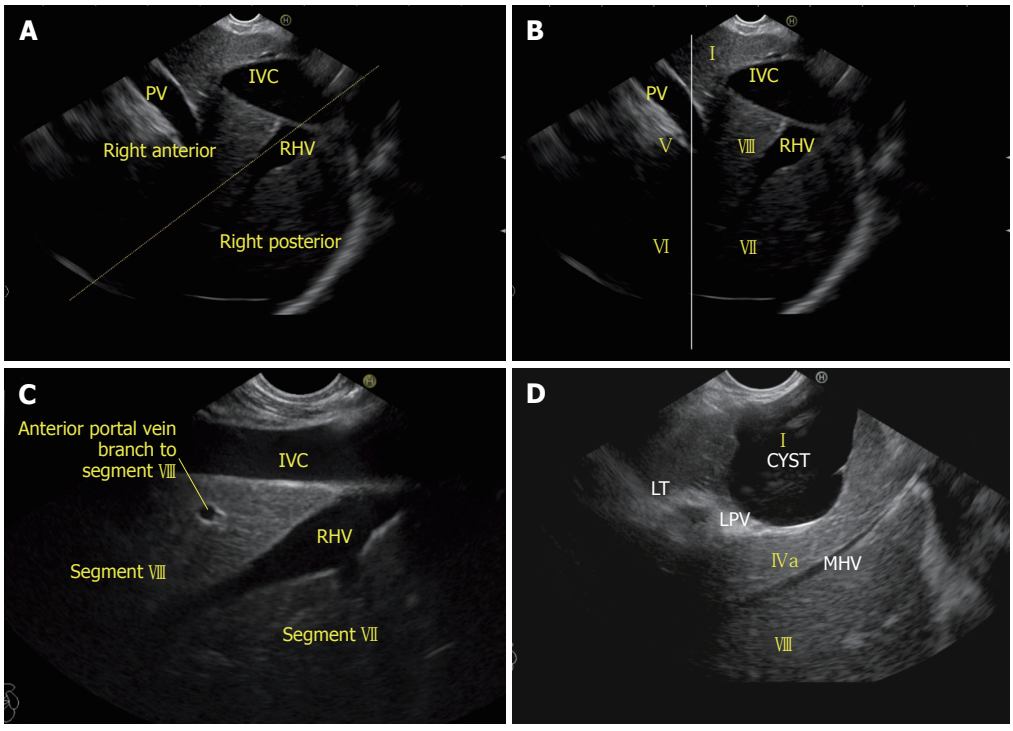

Figure 15 Liver sectors and liver segments are visualized. A: The inferior vena cava (IVC) runs parallel to the probe in a long axis. A line along the right hepatic vein divides the liver into anterior and posterior sectors; B: The right lobe of the liver contains segments Ⅴ to Ⅷ. The segments are seen through the caudate process. The white line is drawn along the upper border of the curving part of the portal vein; C: The right hepatic vein is seen joining the IVC at an angle of around 60°. Segment Ⅶ is seen above the hepatic vein and segment Ⅷ is seen between the hepatic vein and the IVC; D: The middle hepatic vein drains segment Ⅳ, segment Ⅴ, and segment Ⅷ. RHV: Right hepatic vein; LPV: Left branch of the portal vein; IVC: Inferior vena cava; PV: Portal vein.

the right hepatic vein in the right portal fissure (Figure 15A).

Technique of examination: A simple crossover of lines passing through the upper border of the left branch of the portal vein and along the axis of the right hepatic vein will divide the right hemiliver into four segments (Figure 15).

CONCLUSION

Table 5 summarizes the evaluation of different liver

segments from different positions by EUS. Routine use of Couinaud's liver segmentation may be important in planning successful radical surgery. This description will allow better preparation for biopsy, portal vein embolization, transjugular intrahepatic portosystemic shunt, tumour resection, or partial hepatectomy for transplantation. Such advance planning will reduce intra- and post-operative difficulties and complications. In this article, we have given a detailed description of EUS anatomy of the liver and liver segmentation. This information may be useful in planning EUS guided diagnostic and therapeutic procedures involving liver pathologies[13,14].

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ORIGINAL ARTICLE

Observational Study

Polysomnographic assessment of respiratory disturbance during deep propofol sedation for endoscopic submucosal dissection of gastric tumors

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Abstract

AIM

To investigate that polysomnographic monitoring can accurately evaluate respiratory disturbance incidence during sedation for gastrointestinal endoscopy compare to pulse oximetry alone.

METHODS

This prospective observational study included 10 elderly patients with early gastric cancer undergoing endoscopic submucosal dissection (ESD) under propofol sedation. Apart from routine cardiorespiratory monitoring, polysomnography measurements were acquired. The primary hypothesis was tested by comparing the apnea hypopnea index (AHI), defined as the number of apnea and hypopnea instances per hour during sedation, with and without hypoxemia; hypoxemia was defined as the reduction in oxygen saturation by $\geqslant$ 3% from baseline.

RESULTS

Polysomnography (PSG) detected 207 respiratory disturbances in the 10 patients. PSG yielded a significantly greater AHI (10.44 ± 5.68/h) compared with pulse oximetry (1.54 ± 1.81/h, $P < 0.001$), thus supporting our hypothesis. Obstructive AHI (9.26 ± 5.44/h) was significantly greater than central AHI (1.19 ± 0.90/h, $P < 0.001$). Compared with pulse oximetry, PSG detected the 25 instances of respiratory disturbances with hypoxemia 107.4 s earlier on average.

CONCLUSION

Compared with pulse oximetry, PSG can better detect respiratory irregularities and thus provide superior AHI values, leading to avoidance of fatal respiratory complications during ESD under propofol-induced sedation.

Key words: Polysomnography; Hypoxemia; Propofol; Endoscopic submucosal dissection; Pulse oximetry; Sedation

Core tip: Our aim was to demonstrate respiratory disturbances using polysomnography (PSG) during propofol sedation for gastric endoscopic submucosal dissection. Among the ten patients, 207 respiratory disturbances were identified by PSG. Apnea hypopnea index (AHI), defined as the number of apnea and hypopnea per hour, detected by PSG was significantly greater than that detected by pulse oximeter. Obstructive AHI was significantly greater than central AHI. The 25 instances of respiratory disturbances with hypoxemia were detected on an average of 107.4 s before they were detected by pulse oximetry. PSG would be useful for monitoring respiratory conditions with better detectability of AHI.

Urahama R, Uesato M, Aikawa M, Yamaguchi Y, Hayano K, Matsumura T, Arai M, Kunii R, Isono S, Matsubara H. Polysomnographic assessment of respiratory disturbance during deep propofol sedation for endoscopic submucosal dissection of gastric tumors. *World J Gastrointest Endosc* 2018; 10(11): 340-347 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i11/340.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i11.340

INTRODUCTION

Sedation is widely used to acquire a stable surgical field, better endoscopic images, and to reduce patient discomfort during gastrointestinal (GI) endoscopy[1-3]. Contrary to light conscious sedation usually used in short diagnostic GI endoscopy, deep sedation is required to minimize patient movement during extended and painful endoscopic procedures, such as endoscopic submucosal dissection (ESD) or endoscopic retrograde cholangiopancreatography. Propofol sedation has been reported to improve outcomes after ESD surgery and shorten procedure time[4]. However, propofol has dose-dependent respiratory depressant effects[5]; therefore, the incidence of fatal respiratory complications associated with deep sedation is of significant concern when ensuring the safety of the GI endoscopic procedures[6].

Recent guidelines on GI endoscopy strongly recommend pulse oximetry and careful monitoring of breathing during sedation[7,8]. Unlike the low incidence of hypoxemia (0.13%–0.46%) during conscious sedation for short GI endoscopy procedures[9,10], a relatively large prospective study including 799 patients undergoing propofol sedation for advanced GI endoscopic procedures reported that hypoxemia (arterial oxygen saturation, SaO_2 < 90%), detected by pulse oximeter, occurred in 12.8% of the participants and that respiratory disturbances detected by a capnometer and requiring airway maneuvers, such as chin lift, occurred in 14.4% patients, even when under supervision by an anesthesiologist[11]. Because these studies only assessed the incidence of critical hypoxemia in the study population, it is unclear as to how many non-critical respiratory disturbances occurred in addition to these critical events. Thus, we hypothesized that pulse oximetry alone may underestimate the incidence of adverse respiratory episodes during propofol sedation, particularly in patients who receive supplemental oxygen. Furthermore, propofol can depress both inspiratory pump muscles and upper airway dilating muscles, thereby leading to either central or obstructive disordered breathing[12].

Although strategies for preventing respiratory disturbances significantly depend on the type of breathing abnormality encountered (central or obstructive), to the best of our knowledge, no previous study has systematically characterized breathing patterns and

disturbances under sedation during GI endoscopy. Therefore, primarily, we tested the hypothesis that pulse oximetry underestimates respiratory disturbances during propofol sedation in patients undergoing ESD surgery; we also aimed to characterize breathing patterns under sedation. We employed polysomnography to assess state of consciousness, nature of breathing abnormalities, and oxygenation during sedation for GI endoscopy.

MATERIALS AND METHODS

Subjects

This prospective, observational study was approved by the institutional Ethics Committee (#1902-2014, Graduate School of Medicine, Chiba University, Chiba, Japan), and written informed consent was obtained from each patient after the aim and potential risks of the study were completely explained to each patient. Inclusion criteria were adult patients undergoing ESD surgery for early gastric cancer under propofol sedation with expected procedure duration of < 2 h. Exclusion criteria were patients with severe comorbidities, including presence of high risk of aspiration and allergies to propofol and pentazocine. Totally, 10 elderly patients (6 males and 4 females; mean age 71.4 years,) were enrolled between 2014 and 2015.

Preparation of subjects

Prior to propofol sedation, electrodes for standard polysomnography (PSG) were attached to all patients (PSG-1100, Nihon Kohden, Tokyo, Japan), in addition to routine patient monitors for GI endoscopy (pulse oximetry, electrocardiogram, and intermittent blood pressure measurements). Bilateral central and occipital electroencephalograms, bilateral electrooculograms, submental electromyogram, airflow measurement with a nasal pressure prong and an oro-nasal thermistor, thoraco-abdominal wall motions with piezo-respiratory effort sensors, SaO_2, and snoring over a microphone were recorded and relevant data were stored in a computer for further analyses. The patients, lying on their left side, received 2 L/min of oxygen through a nasal prong. Following a slow intravenous injection of propofol (1-2 mg/kg) until loss of consciousness, propofol was continuously infused at a rate of 1–4 mg/kg per hour so as to maintain a Ramsey score of 5-6 (loss of responses to verbal commands and light tapping on the shoulder, but arousable by painful stimulation)[13]. Pentazocine (7.5 mg) was intravenously administered for analgesia. Cardiorespiratory abnormalities or instabilities detected by the patient monitors were treated by altering the propofol infusion rate and/or using airway maneuvers following standard institutional protocols.

Measurements

PSG data were manually analyzed by a certified sleep technician (Kunii R) and investigators using dedicated computer software (Polysmith, Nihon Kohden, Tokyo, Japan). For the PSG data, we focused on the following two sensors: (1) airflow measurement using the nasal pressure prong and the oro-nasal thermistor; and (2) thoraco-abdominal wall motion uses piezo-respiratory effort sensors (RIP-chest and/or RIP-abdomen). Apnea was defined as the absence of airflow for ⩾ 10 s, determined using the nasal pressure signal. Hypopnea was defined as a ⩾ 50% reduction in the nasal pressure signal for ⩾ 10 s. State of consciousness (awake or sleep) was determined from the 30-s PSG recording using criteria defined by Rechtschaffen and Kales[14]. Apnea and hypopnea episodes were systematically classified based on the presence or absence of hypoxemia, which was defined as a ⩾ 3% reduction in SaO2 from baseline, conscious states (awake and/or sleep), and presence or absence of thoraco-abdominal respiratory movements (obstructive and/or central). Apnea hypopnea index (AHI), the primary outcome variable, was defined as the frequency of apnea and hypopnea episodes per hour of sedation.

Table 1 Patient characteristics and endoscopic submucosal dissection indications

Characteristic/indication	Value (mean ± SD)
Age (yr)	71.4 ± 6.6
Sex (male/female)	6/4
Height (cm)	159.9 ± 8.9
Body weight (kg)	59.2 ± 8.2
Body mass index (kg/m^2)	23.6 ± 3.5
Histological type	
Well differentiated tubular adenocarcinoma	*n* = 7
Moderately differentiated tubular adenocarcinoma	*n* = 1
Signet-ring cell carcinoma	*n* = 2
Invasion depth: mucosa	*n* = 10
Ulceration: none	*n* = 10
Longer axis of resected specimen size (mm)	35.1 ± 10.2

Statistical analyses

In primary analysis, the hypothesis was tested by comparing the AHI detected using PSG and pulse oximetry. The predominant pattern of respiratory disturbance was determined by comparing obstructive AHI and central AHI using the paired *t*-test. Summary statistics were calculated as frequencies and proportions for categorical data and as means and SD for continuous variables. $P < 0.05$ was considered statistically significant, and all p-values were two sided. All statistical analyses were performed using the SigmaPlot software (ver.12.0; Systat Software Inc., Point Richmond, CA).

RESULTS

Table 1 presents the patient characteristics and ESD indications. Majority of the patients were non-obese and elderly. All ESD procedures were completed without

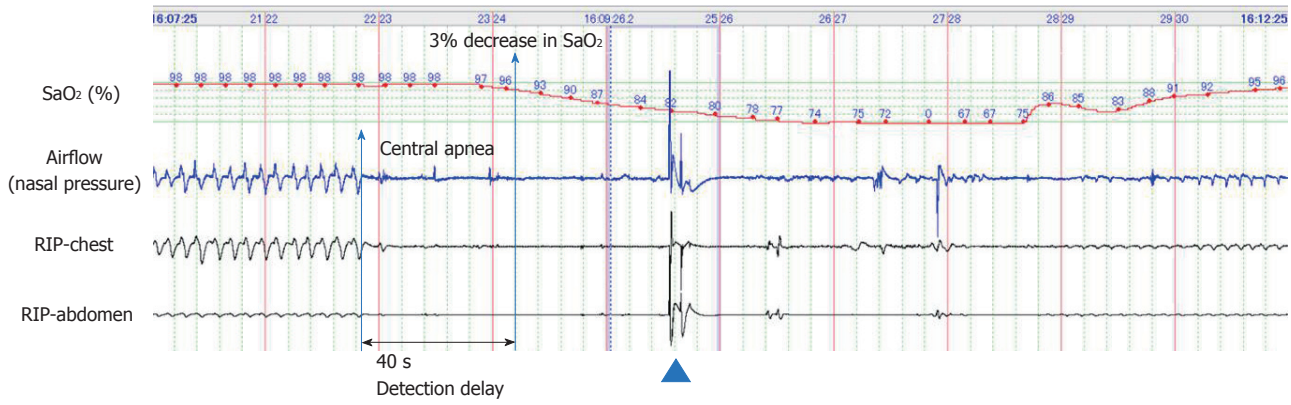

Figure 1 Representative polysomnographic recording of a long central apnea episode occurring soon after a bolus injection of propofol (2 mg/kg) and pentazocine (7.5 mg), followed by continuous infusion of propofol (2 mg/kg per hour) in a 67-year-old female. Chin-lift airway maneuver (shown by an arrowhead) restored breathing once; however, central apnea redeveloped, resulting in severe hypoxemia (SaO_2, 67%); the hypoxemia reversed gradually with improvement in breathing efforts. Polysomnography could detect apnea 40 s before the observed decrease in SaO_2 levels.

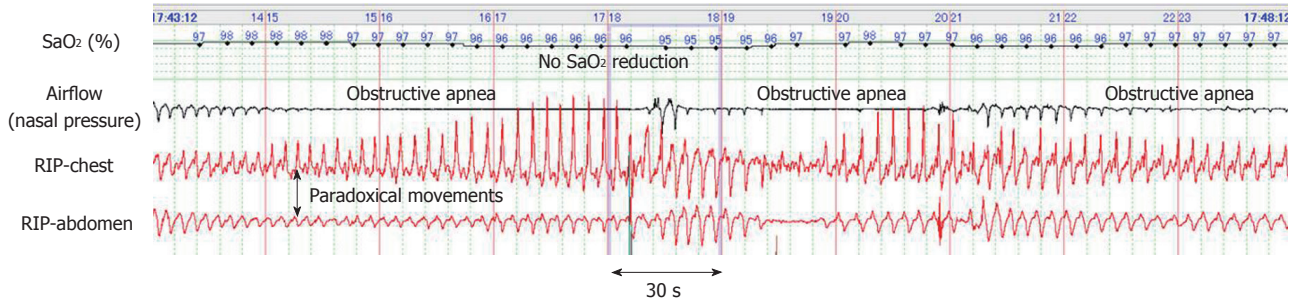

Figure 2 Representative polysomnograph of periodic obstructive apnea that occurred during endoscopic submucosal dissection under propofol sedation. Thoraco-abdominal respiratory movements showed obstructive disturbance represented by paradoxical movements. Despite these long apneas lasting more than one minute, SaO_2 levels remained > 95%.

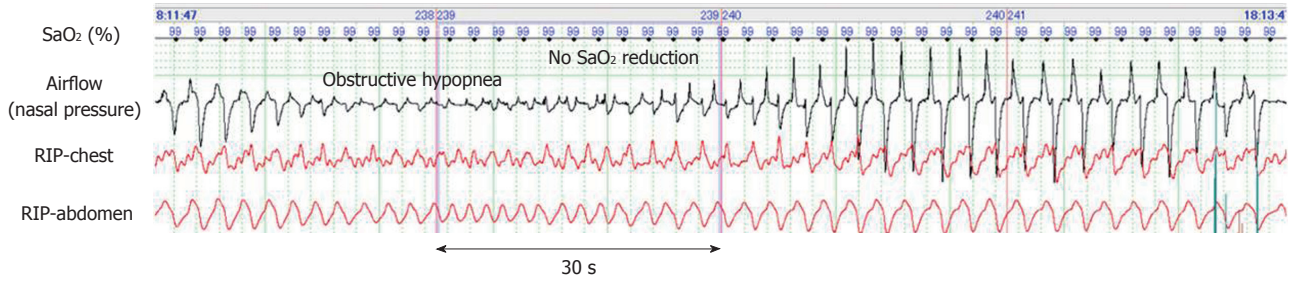

Figure 3 Typical polysomnograph of an obstructive hypopnea that occurred during endoscopic submucosal dissection under propofol sedation. Obstructive hypopnea episodes were diagnosed based on paradoxical thoraco-abdominal wall movements and flattened nasal pressure waves and resolved spontaneously with gradual increase in airflow caused by an increase in breathing effort.

complications.

Figures 1, 2 and 3 represent polysomnographic recordings obtained during propofol sedation. Figure 1 depicts a long episode of central apnea that occurred immediately after initiation of the propofol sedation in a 67-year-old female. The chin-lift airway maneuver (arrowhead) restored breathing once; however, central apnea recurred, resulting in severe hypoxemia (SaO_2, 67%). The hypoxemia gradually reversed along with recovery of breathing efforts. Notably, detection of central apnea by the nasal pressure signal preceded the 3% decrease in oxygen saturation by 40 s.

Figure 2 depicts a typical example of obstructive apnea periodically occurring in sleep state. Despite these long apnea episodes lasting for more than one minute, the SaO_2 level remained > 95%. Similarly, periodic obstructive hypopnea occurred during the sleep state and without resulting in hypoxemia (Figure 3). Further, obstructive hypopnea diagnosed based on paradoxical thoraco-abdominal wall movements and flattened nasal pressure waves resolved spontaneously. Unlike such an abrupt resolution of obstructive hypopnea during natural sleep, obstructive hypopneas during sedation-induced sleep only improved gradually with an increase

Table 2 Details of propofol sedation and results of polysomnography analysis

	Value (mean ± SD)
Initial dose of propofol (mg/kg)	1.2 ± 0.4
Total dose of propofol (mg/kg)	9.8 ± 3.8
Sedation period (min)	113.8 ± 35.8
Total apnea hypopnea index (AHI) (/h)	10.4 ± 5.7
Mean duration of apnea hypopnea (s)	38.1 ± 48.9
Longest apnea and hypopnea (s)	159.1 ± 147.9
Patients with SaO_2 < 70% event (s)	20%
Patients with SaO_2 < 90% event (s)	50%
Cumulative time spent SaO_2 less than 90%	3.7% ± 9.1%
Detection earlier than SaO_2 less (s)	107.4 ± 67.0

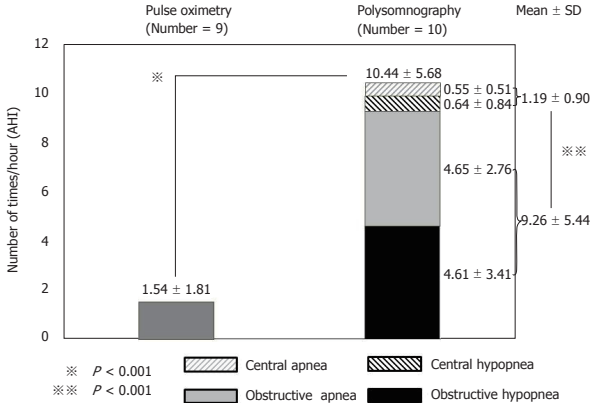

Figure 4 Frequency of respiratory disturbances detected by pulse oximetry and polysomnography. All patients experienced respiratory disturbances during propofol sedation (total AHI: 10.44 ± 5.68/h). Total apnea hypopnea index (AHI) was significantly greater with polysomnography than with pulse oximetry (1.54 ± 1.81/h, $P < 0.001$). Obstructive AHI (9.26 ± 5.44/h) was significantly greater than central AHI (1.19 ± 0.90/h, $P < 0.001$).

in breathing effort.

Severity and patterns of respiratory disturbances during propofol sedation

The results of PSG analysis are presented in Table 2 and Figure 4, and 207 respiratory disturbances were identified in total. While the frequency of the events in individual patients varied, all patients showed respiratory disturbance(s) during propofol sedation (total AHI: 10.44 ± 5.68/h). Based on the classification of the severity of sleep disordered breathing, 9 patients were categorized as having mild respiratory disturbances (AHI > 5 and AHI < 15), whereas 1 patient had moderate (AHI ⩾ 15 and AHI < 30) respiratory disturbance. Although the average duration of apnea and hypopnea episodes was 38 s, the longest episode lasted for > 120 s. Even though the SaO_2 level predominantly remained at >90% during sedation, 5 of 10 patients (50%) had respiratory disturbances that led to SaO_2 levels falling to <90% at least once.

Comparison of abnormal breathing frequencies with and without hypoxemia

Among the 207 respiratory disturbances identified by PSG, 87.9 % did not result in hypoxemia, whereas 12.1 % did, as detected by pulse oximetry. Total AHI, detected by PSG (10.44 ± 5.68/h), was significantly greater than that detected by pulse oximetry (1.54 ± 1.81/h, $P < 0.001$), thereby supporting our primary hypothesis that pulse oximetry alone underestimates respiratory disturbances during propofol sedation in patients undergoing ESD surgery (Figure 4).

Types of respiratory disturbances

While obstructive apnea and hypopnea episodes were common during propofol sedation (Figures 2 and 3), central apnea and hypopnea typically occurred immediately after a bolus injection of propofol and during the initial half of sedation, as depicted in Figure 1. The incidence of obstructive AHI (9.26 ± 5.44/h) was significantly greater than that of central AHI (1.19 ± 0.90/h, $P < 0.001$), thereby indicating the predominance of obstructive respiratory disturbances during propofol sedation (Figure 4).

PSG can detect apnea before decrease in SaO_2

Figure 1 depicts that PSG could detect apnea 40 s earlier than a manifest reduction in the SaO_2 levels. Respiratory disturbance with hypoxemia occurred 25 times in 9 patients, and all such instances were detected by PSG. Importantly, these 25 instances of respiratory disturbances were, on average, detected by PSG 107.4 ± 67.0 s earlier than that by pulse oximetry (Table 2).

DISCUSSION

We measured consciousness, breathing, and oxygenation using PSG during propofol sedation for ESD surgery and observed that respiratory disturbances with SaO_2 falling to < 90% occurred in 50% of the patients. Importantly, a majority of the respiratory disturbances were episodes of non-hypoxemic obstructive apneas and hypopneas, and our data indicate that pulse oximetry underestimates the incidence of respiratory disturbances. To the best of our knowledge, this is the first study of its kind.

Nature and severity of respiratory disturbances during propofol sedation

We used AHI as an index to characterize severity and nature of respiratory disturbances during propofol sedation. AHI was calculated using the incidence of apnea and hypopnea identified based on their standard definitions widely used in PSG studies[15]. Contrary to a previous prospective study that assessed the incidence of respiratory disturbances or hypoxemia and reported a value of 12.8%[11], the incidence of SaO_2 of < 90% was higher in our study (50%). This divergence can be attributed to older age, longer sedation period, and different body position adopted by us. Further, the use of AHI allowed us to quantify the number of apnea and hypopnea episodes in individual

patients; thus, obstructive and central events could be clearly distinguished. Notably, although the severity of respiratory disturbance differed among patients, they all occurred during propofol sedation. Further, apnea and hypopnea episodes were predominantly obstructive in nature, and central events were also observed. These results indicate that devising a uniform strategy to prevent respiratory disturbances during sedation may be difficult and imply that reliable respiratory monitoring that can identify respiratory disturbances without delay and categorize them as either obstructive or central are essential for choosing appropriate treatment strategies. We demonstrated that combined monitoring of nasal pressure and thoraco-abdominal movement is both reliable and accurate; however, the clinical usefulness of this combination is questionable owing to its complexity and the level of respiratory physiology knowledge required. Thus, the nasal pressure waveform alone also reflects inspiratory flow limitation caused by airway obstruction[16], and unlike capnography, this parameter is not affected by carbon dioxide insufflation. Also, the nasal pressure waveform can detect not only the respiratory rate but can also identify the decrease in ventilation, like hypopnea. Therefore, we believe that nasal pressure measurement is potentially useful for respiratory monitoring during sedation and that it must be tested in future clinical studies.

Clinical implications of the results of this study

Our results corroborate with those of previous studies wherein pulse oximetry was found to underestimate apnea and hypopnea incidence during propofol sedation[11,17]. However, this does not imply that pulse oximetry is not a suitable cardiorespiratory monitor during sedation for GI endoscopy. In fact, we found that hypoxemic episodes were accurately identified by pulse oximetry alone (Figure 1). Further, it should be noted that severe desaturation was caused by long duration of central apnea in association with a deeper level of sedation immediately after a bolus injection of propofol, and it has been shown during propofol sedation that, a higher loading dose, rather than total propofol dose, is associated with severe sedation-related adverse events[18]. Although more evidence is necessary, it is possible that unexpected deeper sedation during propofol sedation for GI endoscopy can impair respiratory compensatory mechanisms and lead to rare but critical cardiorespiratory complications that require intensive intervention or treatment[19]. Furthermore, our results indicate that critical events constitute a small proportion of the greater incidence of non-hypoxemic apnea and hypopnea episodes observed here, and currently, we lack an understanding about the pathological significance of these non-hypoxemic apneas and hypopneas. Unlike hypoxic events caused by long duration of central apnea just after a bolus injection of propofol, non-hypoxemic obstructive events tended to happen during continuous infusion of propofol. Therefore, they could be early markers for effective prevention of critical events during and/or immediately after sedation. More severe hypoxemia can develop when oxygen therapy is immediately terminated after endoscopy, because residual sedatives could worsen respiratory disturbances. In fact, deaths in patients undergoing GI endoscopy during and after propofol sedation have been reported[20]. Clearly, future studies need to explore the clinical significance of non-hypoxemic respiratory disturbances.

Pulse oximetry monitors oxygenation rather than ventilation, and several physicians use pulse oximetry alone for monitoring respiration during ESD. Specifically, in patients requiring oxygenation, oxygen saturation is often used as a delayed index for ventilation, and it has been reported that when respiratory arrest occurs, it takes 1-2 min for the decrease in oxygen saturation to become evident[21]. This time lag can be crucial in patients requiring prompt medical intervention.

In ambient air, decreased ventilation increases the partial pressure of carbon dioxide in arterial blood, thereby gradually decreasing oxygen saturation. However, oxygen saturation does not immediately reflect changes in supplemental oxygen provided. In cases of hypercapnia caused by hypoventilation, the oxygen saturation level is usually between 90%–99%, and it is possible that by the time the oxygen saturation decreases, the patient may have entered a state of respiratory arrest[22-24]. Importantly, cardiac arrest usually occurs 4-5 min after respiratory arrest, with a gap of only 1-2 min between the decrease in SaO_2 and the occurrence of cardiac arrest. Thus, the key to safely performing endoscopy in patients under deep sedation is to quickly detect and address respiratory disturbances. Finally, the fact that PSG can detect respiratory disturbances approximately 107.4 s before the decrease in oxygen saturation is important. Therefore, in procedures performed with the patient under sedation, real-time respiration monitoring, such as using PSG based on respiration management for general anesthesia, is considered necessary.

Study limitations

There are several limitations in this study. First, the sample size is small and the patient population is limited to the elderly; thus, generalizing the findings presented here is difficult. Further randomized controlled trials need to be confirmed. However, we believe that our primary hypothesis has been quantitatively tested using AHI rather than just the number of episodes during the sedation. Second, propofol sedation was performed by a trained physician; however, he was not an anesthesiologist. Although whether the involvement of an anesthesiologist increases the safety during sedation for GI endoscopy is unknown[1,18,25,26], we did not aim to test the safety of propofol sedation. However, it was actually difficult to keep the patient's Ramsey score at all times during ESD. The depth of sedation

may have influenced the outcome. Third, this study did not assess in detail patient risks for developing upper airway obstruction when unconscious. Particularly, the greater number of participants with obstructive sleep apnea might have increased the rate of respiratory disturbance with severe hypoxemia, and this aspect should have been addressed before initiating the study. Thus, it would be interesting to explore the differences in the nature of respiratory disturbances during sedation for GI endoscopy between patients with and without obstructive sleep apnea[27].

In conclusion, episodes of non-hypoxemic obstructive apnea and hypopnea, which are undetectable by pulse oximetry, are common in elderly patients undergoing ESD under propofol-induced sedation. Careful respiratory monitoring using both pulse oximetry and nasal pressure monitors may be helpful for preventing critical cardiorespiratory events during relatively deep sedation for advanced GI endoscopy.

ARTICLE HIGHLIGHTS

Research background

Endoscopic treatments often take long time, however procedures are better tolerated in terms of patient satisfaction and safety when sedation is administered.

Research motivation

Recent guidelines on gastrointestinal endoscopy strongly recommend pulse oximetry and careful monitoring of breathing during sedation. But it is unclear as to how many non-critical respiratory disturbances occurred in addition to critical events.

Research objectives

The objectives are to reveal that polysomnography (PSG) can accurately evaluate respiratory disturbance incidence during sedation for gastric endoscopic submucosal dissection (ESD) compare to pulse oximetry alone and to characterize breathing patterns.

Research methods

This study included 10 elderly patients with early gastric cancer undergoing ESD under propofol sedation. PSG measurements were acquired. The comparison of respiratory disturbances between PSG and pulse oximetry was tested by the apnea hypopnea index (AHI), defined as the number of apnea and hypopnea instances per hour during sedation, with and without hypoxemia. The breathing pattern was characterized by the waveform of PSG.

Research results

PSG detected 207 respiratory disturbances in the 10 patients. PSG yielded a significantly greater AHI (10.44 ± 5.68/h) compared with pulse oximetry (1.54 ± 1.81/h, $P < 0.001$). Obstructive AHI (9.26 ± 5.44/h) was significantly greater than central AHI (1.19 ± 0.90/h, $P < 0.001$). Compared with pulse oximetry, PSG detected the 25 instances of respiratory disturbances with hypoxemia 107.4 s earlier on average.

Research conclusions

PSG can better detect respiratory irregularities in detail compared with pulse oximetry and thus provide superior AHI values, leading to distinguish between obstructive and central events clearly.

Research perspectives

It is not necessary to take all kinds of PSG monitoring for the patients under sedation. Among PSG monitoring, nasal pressure measurement is potentially useful for respiratory monitoring and that it must be tested in future clinical studies. Moreover, we will clarify what characters of patients require strict monitoring before endoscopic procedures under sedation.

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ORIGINAL ARTICLE

Prospective Study

Submucosal injection of platelet-rich plasma in endoscopic resection of large sessile lesions

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Author contributions: Lorenzo-Zúñiga V, Moreno de Vega V and Boix J contributed to the design of the study and performed the colonoscopies; Lorenzo-Zúñiga V and Bartolí R performed the data analysis and wrote the document; Marín I, Caballero N, and Bon I have revised the manuscript.

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Abstract

AIM

To prospectively evaluate the efficacy of submucosal injection of platelet-rich plasma (PRP) on endoscopic resection of large sessile lesions.

METHODS

Eleven patients were submitted to endoscopic mucosal resection (EMR) with prior injection of PRP, obtained at the time of endoscopy. Patients were followed during 1 mo. The incidence of adverse events (delayed bleeding or perforation) and the percentage of mucosal healing (MHR) after 4 wk were registered.

RESULTS

EMR was performed in 11 lesions (46.4 mm ± 4 mm, range 40-70 mm). Delayed bleeding or perforation was not observed in any patient. Mean ulcerated area at

baseline was 22.7 cm^2 ± 11.7 cm^2 whereas at week 4 were 2.9 cm^2 ± 1.5 cm^2. Patients treated with PRP showed a very high MHR after 4 wk (87.5%).

CONCLUSION

PRP is an easy-to-obtain solution with proven and favourable biological activities that could be used in advanced endoscopic resection.

Key words: Platelet-rich plasma; Endoscopic mucosal resection; Submucosal injection; Large lesions

Core tip: This was a prospective single-center study to evaluate the efficacy of submucosal injection of platelet-rich plasma (PRP) on 11 patients submitted to endoscopic resection of large lesions. PRP as lifting solution proved absence of delayed bleeding or perforation and strong healing activity.

Lorenzo-Zúñiga V, Moreno de Vega V, Bartolí R, Marín I, Caballero N, Bon I, Boix J. Submucosal injection of platelet-rich plasma in endoscopic resection of large sessile lesions. *World J Gastrointest Endosc* 2018; 10(11): 348-353 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i11/348.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i11.348

INTRODUCTION

Submucosal injection of fluid solutions is crucial to prevent of delayed perforation (DP) in advanced resection techniques, endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), by avoiding deep thermal injury. The perforation rate is traditionally considered as a quality of standard practice. It has a rate of 0.03%-0.8% during diagnostic procedures and 0.15%-3% during therapeutic procedures[1]. Otherwise, delayed bleeding (DB) is a well-known and the most frequent adverse event after these resections, with an incidence of 2.6%–9.7%, not prevented by adding adrenaline to the submucosal fluid cushion or applying argon plasma coagulation, because these methods only decrease the incidence of early bleeding[2-4]. There is no scientific evidence to recommend the systematic closure of the eschars with hemostatic clips to prevent DB because they are ineffective in large mucosal defects and increase procedure costs[5].

The ideal submucosal solution should provide a sustained lift, facilitate en-bloc or oligopiecemeal resection, be inexpensive, widely available and have few adverse effects[1]. The optimal fluid to lift the lesion is still a matter of debate. Platelet-rich plasma (PRP), as autologous concentrated in plasma, has demonstrated strong healing properties as a shield over the eschars after EMR in preclinical models[6,7]. PRP solution has showed the best electrical and rheological properties to perform safety endoscopic resections[8].

Therefore, we aim to evaluate the efficacy of submucosal injection of PRP on EMR of large sessile lesions.

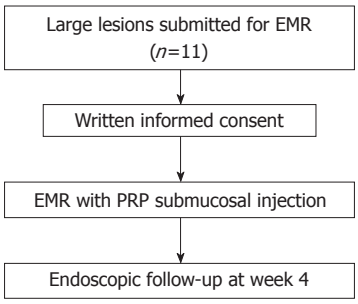

Figure 1 Patient flow-chart. EMR: Endoscopic mucosal resection; PRP: Platelet-rich plasma.

MATERIALS AND METHODS

Subjects

This study was registered at ClinicalTrials.gov under the identifier NCT02931149 (EndoPRP study), was conducted from August 2016 to March 2017. Subjects eligible for the study were men and women aged 18 and older who were submitted for EMR of sessile lesions larger than 35 mm. We obtained a written informed consent in all participants. The Healthcare Ethics Committee of our institution (University Hospital Germans Trias i Pujol) approved the study protocol (IRB approval PT-16-002 on July 8, 2016), and was performed in accordance with the Declaration of Helsinki.

Study design

This was a non-randomized prospective single-center study. We performed an expanded access study (compassionate use) of PRP outside of a clinical trial because we wanted to generate information with a small number of individual patients. Patients were allocated to receive PRP as submucosal injection of PRP prior to EMR (Figure 1). After the procedure, all patients were followed during 4 wk. EMR was performed with blended current controlled by a microprocessor (ME 402 maxium KLS martin, Tuttlingen. Germany). The device used in all patients was a circular polyfilament snare 25 mm in diameter (SnareMaster, Olympus. Tokyo). After the procedure coagulation of the base with APC was performed in all cases.

We obtained PRP with OLIN-1 kit (a single-use sterile product), that comes in both a 20 mL and 40 mL format, from a sample of patient's blood (18-36 mL) drawn at our Endoscopy Unit prior to perform the EMR (Figure 2). Peripheral blood was centrifuged (2500 rpm/8 min at room temperature). Depending on the size of the lesions, smaller or larger than 40

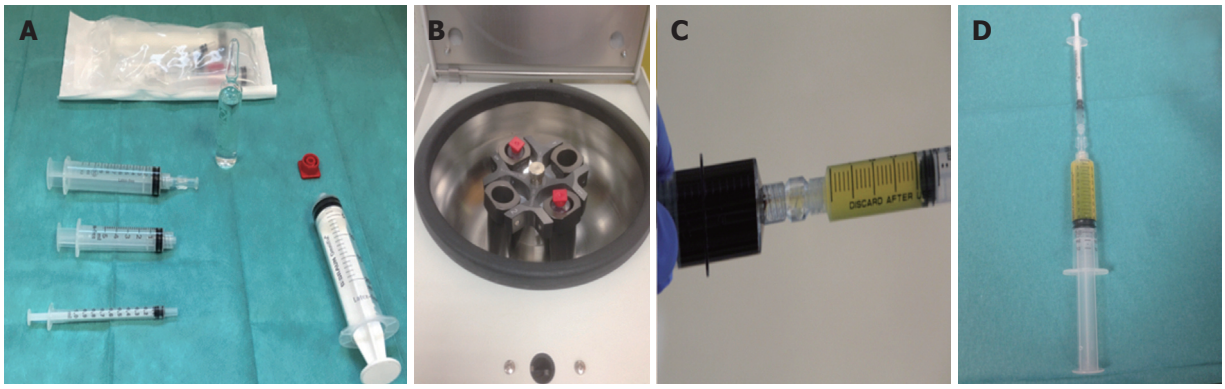

Figure 2 Preparation of platelet-rich plasma. A: Olin-1 Kit; B: Centrifugation of peripheral blood; C: PRP; D: Activation of PRP. PRP: Platelet-rich plasma.

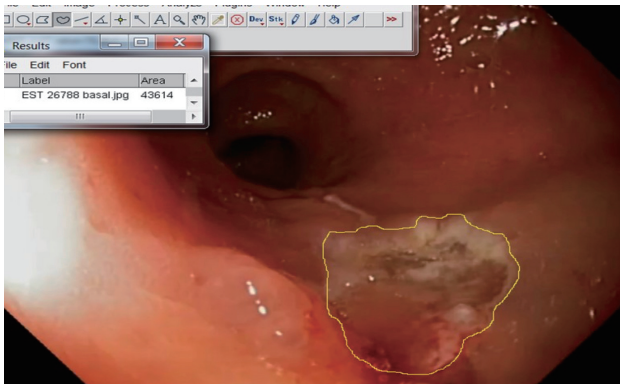

Figure 3 Mean ulcerated area and mucosal healing rate were calculated by the use of ImageJ public software (Image Processing and Analysis in Java. https://imagej.nih.gov/ij).

mm, we used 18 or 36 mL of blood (1 or 2 kits). A 20-mL syringe prefilled with 2 mL acid citrate dextrose (15% vol./vol.) was used for the standardized blood draw. Syringes were centrifuged obtaining two different layers; erythrocytes (± 45% of volume) placed at the bottom, and PRP (55% vol., around 8 mL) on the top. PRP was activated with the addition of 20 mmol/L $CaCl_2$ just before the administration. A sample of 10 μL of blood and plasma were used to take a measurement of baseline blood platelet count and platelet count in PRP.

Assessments

The primary outcome was the assessment of the incidence of adverse events (DB or DP). Secondary objective was the evaluation of mucosal healing rate (MHR), calculated as a percentage of mucosal restoration after 1 mo. Measurement of mucosal lesion and mucosal defect was carried out as comparison with opened forceps (7 mm) or by direct measurement with the specimen before pinning the specimen. We calculated the mean ulcerated and mucosal healing rate by the use of ImageJ public software (Image Processing and Analysis in Java; https://imagej.nih.gov/ij/)(Figure 3).

Statistical analysis

Unless otherwise indicated, results are expressed as mean ± SE or proportions as required. Statistical analyses were carried out with SPSS for Windows version 14.0 (SPSS Inc., Chicago, IL, United States).

RESULTS

Patient characteristics

A total of 11 EMRs large colorectal or gastric lesions were performed in 11 patients (Table 1). There were 6 (54.5%) females and their mean age was 68.3 years (range 53 to 84 years). More than half were located in rectum or in left colon, mean basal platelet count was of 175 × 10^9/L, whereas obtained PRP was 2 times the basal value. The mean lesion size was 46.4 mm (SD, 11.4 mm; range 40-70 mm). Oligopiecemeal technique with complete resection was reached in all cases. Histology showed absence of deep submucosal involvement in all patients.

Assessments

Patient outcomes are summarized in Table 2. DP or DB was not observed in any case. PRP does not prolong EMR time. No evidence of stricture was found during the follow-up. Mean ulcerated area at baseline was 22.7 cm^2 ± 11.7 cm^2 whereas after 4 wk was 2.9 cm^2 ± 1.5 cm^2. The percentage of mucosal healing at week 4 was of 87.5% (Figure 4).

DISCUSSION

In this prospective study, we found that submucosal injection of PRP has proven efficacy in EMR of lesions larger than 35 mm, showing strong healing activity. Otherwise, the use of a submucosal fluid cushion rich in platelets prevents the incidence of DB or DP.

EMR and ESD as resection techniques can produce adverse events, such as perforation or bleeding. Post-EMR bleeding occurs in 5%-7% lesions ⩾ 20 mm, whereas perforation is an uncommon event with an

Table 1 Patient characteristics

	EMR with PRP
No. of patients	11
Mean age (yr)	68.3 ± 9.48
Men/women	5/6
Mean size of lesions (mm)	46.4 ± 11.4
Basal platelet count (10^9/L)	175.4 ± 47.2
PRP count (10^9/L)	362.8 ± 98.7
Site, *n* (%)	
Antrum	2 (18.2)
Rectum	4 (36.4)
Left colon	3 (27.2)
Right colon/cecum	2 (18.2)
Histology, *n* (%)	
Tubular adenoma	3 (27.3)
Tubulovillous adenoma	1 (9.1)
Villous adenoma	0 (0)
Serrated adenoma	4 (36.3)
Intramucosal adenocarcinoma	3 (27.3)

EMR: Endoscopic mucosal resection; PRP: Platelet-rich plasma.

Table 2 Patient outcomes

	EMR with PRP
Delayed perforation, *n* (%)	0 (0)
Delayed bleeding, *n* (%)	0 (0)
Mean ulcerated area at baseline (cm^2)	22.7 ± 11.7
Mean ulcerated area at 4 wk (cm^2)	2.9 ± 1.5
Mucosal healing rate (%)	87.5

EMR: Endoscopic mucosal resection; PRP: Platelet-rich plasma.

incident of 1.4%-1.5%[1]. Mucosal elevation through the injection of a solution into the submucosal space can reduce the incidence of these events and improve the technical feasibility of the procedure[9]. Normal saline is the most widely used solution but is not the most convenient for large lesions due to the maintenance of the fluid cushion. According to this, we should use other biocompatible lifting solutions easy to prepare and to administrate.

Use of PRP involves taking a sample of a patient's blood prior to the endoscopic procedure and concentrating autologous platelets by centrifugation. PRP fluid contains at least 2 times peripheral blood platelets value and high levels of growth factors essential for mucosal healing, which are released from the alpha granules of activated platelets[10,11]. The rationale for use PRP as solution to perform submucosal injection in endoscopic resection techniques lies in the exponential release of multiple bioactive factors, and subsequently, enhances the natural healing process, as well as in its haemostatic properties, with very low risk of fibrotic healing or strictures. In gastrointestinal disorders PRP has demonstrated efficacy in the prevention of DP[7] and wound healing in primary colonic anastomosis[12]. Previous reports have confirmed that surgical sites enhanced with PRP heal at rates two to three times those of untreated surgical sites and anabolic effects are directly correlated to platelet number[13].

Our study has tested the efficacy to use PRP in EMR of lesions large lesions, obtained through an inexpensive kit, showing strong anabolic effects. Otherwise, PRP has favourable biological and rheological properties as compared with other solutions as hyaluronic acid[14]. This faster and stronger healing activity acts as mechanical defense that prevents the appearance of delayed adverse events. Regarding DB, PRP by mimicking the last step of the coagulation cascade, the formation of a fibrin clot, submucosal injection develops a more stable shield than prevent this complication.

Our study has some limitations because with this small number of patients we need larger studies to validate these findings and to perform a comparison study with other lifting solutions. PRP is an easy-to-obtain solution with proven favourable biological activities that could be applied as submucosal injection prior to endoscopic resection of large lesions. These data emphasize the need for continuing research in this topic.

ARTICLE HIGHLIGHTS

Research background

Submucosal injection of fluid solutions is crucial to prevent of adverse events in endoscopic resections. Platelet-rich plasma (PRP) has demonstrated strong healing properties in preclinical models.

Research motivation

PRP solution proved excellent electrical and rheological properties to perform safety endoscopic resections. PRP could be an ideal lifting solution in therapeutic endoscopy.

Research objectives

The primary outcome was the assessment of the incidence of adverse events (delayed bleeding or delayed perforation). Secondary objective was the evaluation of mucosal healing rate (MHR), calculated as a percentage of mucosal restoration after 1 mo.

Research methods

This was a non-randomized prospective single-center study (ClinicalTrials.gov NCT02931149). Subjects eligible for the study were men and women aged 18 and older who were submitted for endoscopic resection (EMR) of sessile lesions larger than 35 mm. Patients were allocated to receive PRP as submucosal injection of PRP prior to EMR.

Research results

EMR was performed in 11 lesions (46.4 mm± 4 mm, range 40-70 mm). Delayed bleeding or perforation was not observed in any patient. Mean ulcerated area at baseline was 22.7 cm^2 ± 11.7 cm^2 whereas at week 4 were 2.9 cm^2 ± 1.5 cm^2. Patients treated with PRP showed a very high MHR after 4 wk (87.5%).

Research conclusions

The new finding of this study is that PRP is lifting solution with proven and favourable biological activities that could be used in advanced endoscopic resection.

Research perspectives

We need larger studies to validate these findings and to perform a comparison

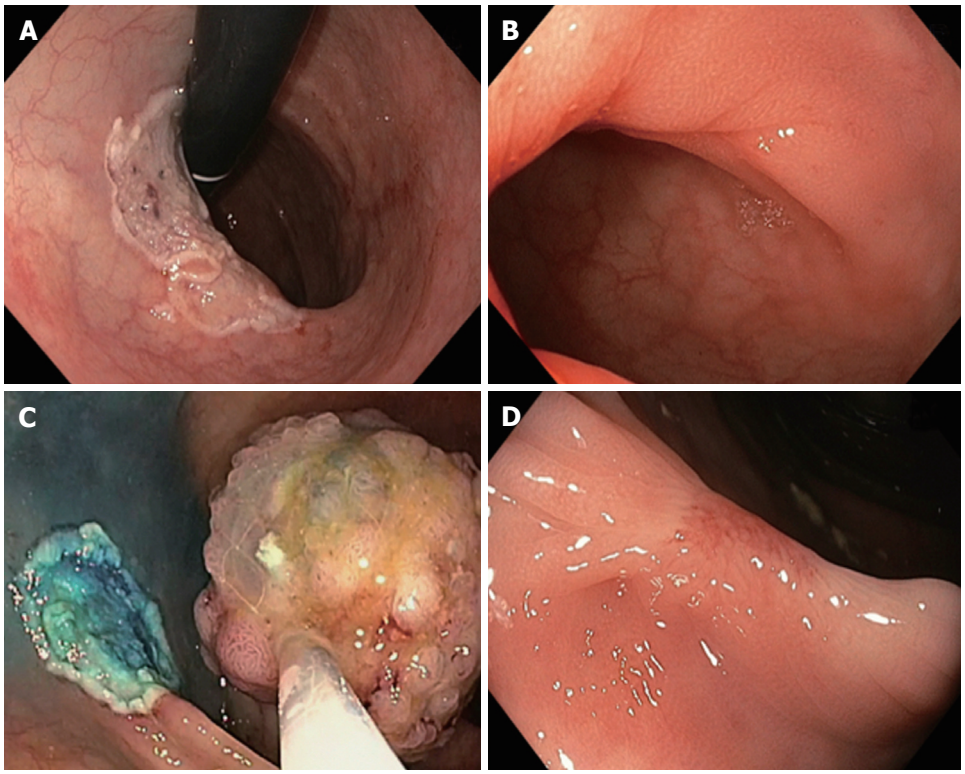

Figure 4 Mucosal healing after endoscopic resection in two patients treated with submucosal injection of platelet-rich plasma at baseline and after 4 wk. A: Patient 1 at baseline; B: Patient 1 at week 4; C: Patient 2 at baseline; D: Patient 2 at week 4.

study with other lifting solutions.

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META-ANALYSIS

Endoscopic retrograde cholangiopancreatography in cirrhosis - a systematic review and meta-analysis focused on adverse events

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Abstract

AIM

To investigate indications and outcomes of endoscopic retrograde cholangiopancreatography (ERCP) in cirrhotics, especially adverse events. Patients with cirrhosis undergoing ERCP are believed to have increased risk. However, there is a paucity of literature describing the indications and outcomes of ERCP procedures in patients with cirrhosis, especially focusing on adverse events.

METHODS

We performed a systematic appraisal of major literature databases, including PubMed and EMBASE, with a manual search of literature from their inception until April 2017.

RESULTS

A total of 6,505 patients from 15 studies were analyzed (male ratio 59%, mean age 59 years), 11% with alcoholic and 89% with non-alcoholic cirrhosis, with 56.2% Child-Pugh class A, and 43.8% class B or C. Indications for ERCP included choledocholithiasis 60.9%, biliary strictures 26.2%, gallstone pancreatitis 21.1% and cholangitis 15.5%. Types of interventions included endoscopic sphincterotomy 52.7%, biliary stenting 16.7% and biliary dilation 4.6%. Individual adverse events included hemorrhage in 4.58% (95%CI: 2.77-6.75%, I^2 = 85.9%), post-ERCP pancreatitis (PEP) in 3.68% (95%CI: 1.83-6.00%, I^2 = 89.5%), cholangitis in 1.93% (95%CI: 0.63-3.71%, I^2 = 87.1%) and perforation in 0.00% (95%CI: 0.00-0.23%, I^2 = 37.8%). Six studies were used for comparison of ERCP-related complications in cirrhosis *vs* non-cirrhosis, which showed higher overall rates of complications in cirrhosis patients with pooled OR of 1.63 (95%CI: 1.27-2.09, I^2 = 65%): higher rates of hemorrhage with OR of 2.05 (95%CI: 1.62-2.58, I^2 = 2.1%) and PEP with OR of 1.33 (95%CI: 1.04-1.70, I^2=65%), but similar cholangitis rates with OR of 1.23 (95%CI: 0.67-2.26, I^2 = 44.3%).

CONCLUSION

There is an overall higher rate of adverse events related to ERCP in patients with cirrhosis, especially hemorrhage and PEP. A thorough risk/benefit assessment should be performed prior to undertaking ERCP in patients with cirrhosis.

Key words: Meta-analysis; Endoscopic retrograde cholangiopancreatography; Systematic review; Adverse events; Cirrhosis

Core tip: Patients with cirrhosis undergoing endoscopic retrograde cholangiopancreatography (ERCP) are considered to have increased risk. However, there is a paucity of literature describing the indications and outcomes of ERCP procedures in these patients. Our meta-analysis included 6,505 patients from 15 studies, with indications including choledocholithiasis, biliary strictures, gallstone pancreatitis and cholangitis. Types of interventions included sphincterotomy, stenting and dilation. Individual adverse events included hemorrhage, post-ERCP pancreatitis (PEP), and cholangitis. Comparison of ERCP-related complications in cirrhosis *vs* non-cirrhosis suggested higher overall rates of complications in cirrhosis patients with pooled (especially hemorrhage and PEP) but similar cholangitis rates.

Mashiana HS, Dhaliwal AS, Sayles H, Dhindsa B, Yoo JW, Wu Q, Singh S, Siddiqui AA, Ohning G, Girotra M, Adler DG. Endoscopic retrograde cholangiopancreatography in cirrhosis - a systematic review and meta-analysis focused on adverse events. *World J Gastrointest Endosc* 2018; 10(11): 354-366 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i11/354.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i11.354

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is one of the most commonly performed endoscopic procedures and is known for its high-risk nature[1]. Performing ERCP in patients with cirrhosis is not only challenging, but may even be a high-risk procedure in this setting[2]. There is a known increased incidence of gallstones and choledocholithiasis in patients with cirrhosis, potentially requiring frequent ERCP procedures[2,3]. ERCP inherently carries risks of usual adverse events, including post-ERCP pancreatitis (PEP), hemorrhage, infection, perforation, and anesthesia-related events[4]. In addition, risks of adverse events in patients are believed to be higher in patients with cirrhosis requiring ERCP due to a poor synthetic function of the liver and resulting portal hypertension, ascites, varices, coagulopathy, and encephalopathy[5].

Surgery may not always be an option for pancreatobiliary disorders in patients with cirrhosis because of the high rates of morbidity and mortality due to underlying liver disease. As a general rule, minimally-invasive approaches, including ERCP, are favored in these patients[6]. Even though the increased risk of ERCP-related adverse events in cirrhosis patients is recognized, there is a relative paucity of literature, as well as some conflicting literature, describing the indications and outcomes of ERCP procedures in patients with cirrhosis.

We thus performed the present systematic review to evaluate the ERCP indications and characteristics, as well as a meta-analysis of ERCP outcomes in patients with cirrhosis. The important outcomes that we focused upon include pooled incidence rates of patient characteristics, ERCP indications, ERCP-related interventions and individual ERCP-related adverse events: (1) hemorrhage; (2) PEP; (3) cholangitis; and

(4) perforation. The secondary outcomes included a comparison of ERCP complications in cirrhosis *vs* non-cirrhosis patients with pooled odds ratio (OR).

MATERIALS AND METHODS

The preferred reporting items for systematic reviews and meta-analyses statement and the meta-analysis of observational studies in epidemiology guidelines were followed[7,8]. The objectives, primary outcomes, search strategy, inclusion criteria, and methods for study selection, data extraction, and data synthesis of this meta-analysis were defined in a protocol in advance. Data fields were pre-defined, and sensitivity analysis and subgroup analysis were also pre-specified in the protocol.

Search strategy

We performed a literature search using the keywords "endoscopic retrograde cholangiopancreatography", "ERCP", "cirrhosis", "adverse events", or "complications" in various combinations to identify original studies published from MEDLINE using both Ovid and PubMed without language restrictions. Other databases that were explored included EMBASE and Scopus. The reference lists of included papers and related review articles were manually searched. A literature search was conducted by two authors (HSM and ASD) in consultation with an experienced medical librarian.

Inclusion and exclusion criteria

We included original prospective, cohort, retrospective, case-control and, when possible, randomized control studies that evaluated the ERCP complications in cirrhosis patients. We also included the studies that provided a comparison of ERCP complications in cirrhosis and non-cirrhosis patients. We included the studies in English and any studies in other languages found through the manual search of references from inception until April 2017. We excluded studies that described the ERCP complications only in non-cirrhosis patients, and did not define clearly the number of ERCPs or their outcomes.

Study selection and data extraction

In the initial screening stage, simple relevance criteria were employed for study selection: (1) human participants; and (2) ERCP complications in cirrhosis patients as an outcome measure. Each title and abstract of the articles obtained through the electronic search was independently reviewed by two investigators (HSM and ASD). Citations were excluded only if deemed to be obviously irrelevant by both reviewing investigators, however those with reviewer disagreement were included for full review.

In the second stage of study selection, the full content of each article obtained during the screening stage was reviewed and evaluated. Using predetermined selection criteria and assessment methods, two investigators (HSM and ASD) independently evaluated the full content of each English language article. Articles in other languages were reviewed and evaluated by multilingual investigators as well as google translation tools using the same criteria and assessment methods.

We included studies that reported the ERCP complications in cirrhosis patients and that described hazard ratio (HR), relative risk (RR), or OR of comparison of ERCP complications in cirrhosis and non-cirrhosis patients. In addition, cohort and case-control studies that reported data on ERCP complications in cirrhosis patients were included if no related randomized controlled trials were found.

Twenty-one studies relevant to the inclusion criteria were identified. The actual numbers of ERCP cases were collected from tables and manuscript text in each study. Since data was from previously published studies, an institutional review board approval was waived. Figure 1 presents the study selection process in accordance with the preferred reporting items for systematic reviews and meta-analyses statement[7]. A summary of studies is shown in Table 1. After excluding six studies for various reasons, including unclear information on a number of ERCPs, outcomes, consensus statements or ERCP in congenital malformation patents, 15 studies were selected for final analysis. These 15 studies included the six studies that were separately used to perform a subset analysis to compare ERCP adverse events in cirrhosis and non-cirrhosis patients.

Data from the eligible studies were independently abstracted by the two investigators (HSM and BD) using the Microsoft Excel program. Any disagreement or uncertainty was resolved by discussion and rechecking original articles, and, if still unresolved, then contacting the authors and consulting external experts. Information such as authors, title, published year, country of study, study design, sample size, and sampling methods, socio-demographic characters such as age, sex, race, exposures and their measurement methods, outcomes and their validation methods, duration of follow-up, adjusted risk factors, and HR or RR of ERCP in cirrhosis and non-cirrhosis patients were duly recorded.

Data synthesis and analysis

The overall proportions of patients experiencing any post-procedure adverse events or specific complications were estimated using random effects methods designed for the pooling of proportions. The actual proportions were estimated after the Freeman-Tukey double arcsine transformation had been applied to the individual study proportions and standard errors were calculated using the scoring method[9,10]. For the subset of studies that provided separate reports of adverse events for patients with or without cirrhosis, we combined individual study results to calculate the pooled OR and 95% confidence intervals (CI) using random-effects meta-analysis for a dichotomous outcome[11]. Between-study heterogeneity

Table 1 Description of 15 studies used in the final analysis

Ref.	Yr of publication	Country	Study type	Cohort/ Case-control	Yr	No. of patients
Navaneethan *et al*[5]	2017	United States	Retrospective	Case-control	2010	3228
Jagtap *et al*[20]	2017	India	Retrospective	Cohort	2014-2016	134
Adler *et al*[16]	2016	United States	Retrospective	Cohort	2003-2014	328
Inamdar *et al*[13]	2016	United States	Retrospective	Case-control	2009	1930
Gill *et al*[14]	2016	Pakistan	Retrospective	Case-control	2008-2014	100
Churrango *et al*[24]	2016	United States	Retrospective	Cohort	2008-2015	194
Leal *et al*[19]	2015	Spain	Retrospective	Case-control	2002-2014	158
Zhang *et al*[2]	2015	China	Retrospective	Cohort	2000-2014	77
Li *et al*[17]	2014	China	Retrospective	Cohort	2000-2008	46
Ma *et al*[22]	2013	China	Retrospective	Cohort	2002-2013	41
Artifon *et al*[21]	2011	Brazil	Prospective	Case-control	Not specified	105
Park *et al*[18]	2004	South Korea	Prospective/Retrospective	Case-control	1998-2003	41
Prat *et al*[25]	1996	France	Retrospective	Cohort	1988-1993	52
Freeman *et al*[23]	1995	United States	Prospective	Case-control	Not specified	64
Sugiyama *et al*[15]	1993	Japan	Prospective	Cohort	Not specified	7

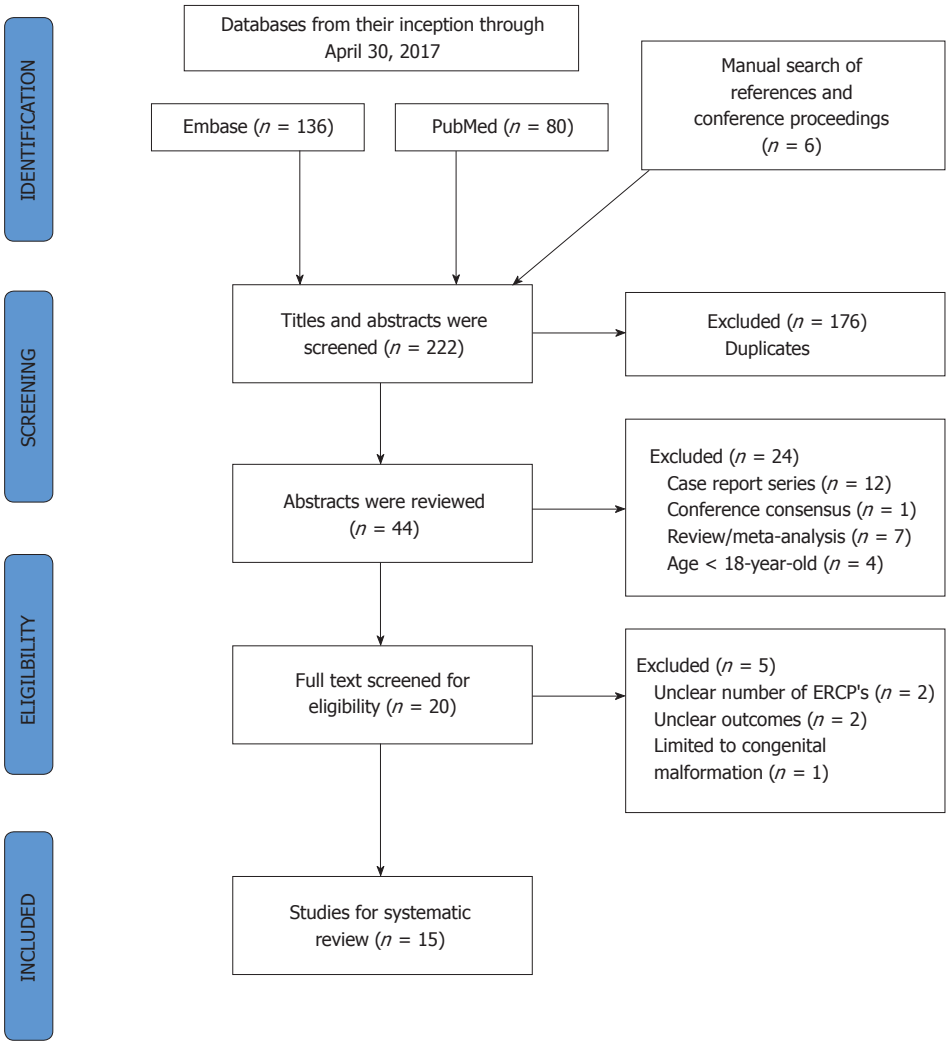


Figure 1 Study selection process in accordance with preferred reporting items for systematic reviews and meta-analysis statement.

was assessed using the I^2 statistic, which is an estimate of the percentage of variation across studies that is due to true heterogeneity and not due to chance[12]. Baseline characteristics of study participants were aggregated from 15 analyzed studies as shown in Table 2. All analyses were performed using STATA version 14.2 (StataCorp, College Station, TX). A two-sided *P*-value < 0.05 was considered statistically significant.

Table 2 Description of studies used for comparison meta-analysis

Ref.	Yr published	Country	Study period	Study type
Navaneethan *et al*[5]	2017	United States	2010	Retrospective (NIS), Multicenter
Inamdar *et al*[13]	2016	United States	2009	Retrospective (NIS), Multicenter
Gill *et al*[14]	2016	Pakistan	2008-2014	Retrospective, Single center
Leal *et al*[19]	2015	Spain	2002-2014	Retrospective, Single center
Li *et al*[17]	2014	China	2000-2008	Retrospective, Single center
Freeman *et al*[23]	1995	United States	NS	Retrospective, Multicenter

Table 3 Endoscopic retrograde cholangiopancreatography-related adverse events in cirrhosis patients

Ref.	Total no. of patients (cirrhotics)	Number of ERCPs	PEP	Hemorrhage	Cholangitis	Perforation	% of complications
Navaneethan *et al*[5]	3228	3228	387[1]	68[1]	10	6	14.5
Jagtap *et al*[20]	134	134	2[1]	4[1]	10	0	11.9
Adler *et al*[16]	328	538	25[1]	6[1]	15	2	14.6
Inamdar *et al*[13]	1930	1930	160[1]	44[1]	15	N/A	11.3
Gill *et al*[14]	100	100	3[1]	6[1]	3	0	12
Churrango *et al*[24]	194	194	3[1]	5[1]	N/A	0	4.1
Leal *et al*[19]	158	158	7[1]	9[1]	10	1	17
Zhang *et al*[2]	77	77	4[2]	24[2]	1	0	37.6
Li *et al*[17]	46	46	4[3]	2[3]	3	0	19.5
Ma *et al*[22]	41	41	0[4]	2[4]	0	0	4.8
Artifon *et al*[21]	105	105	3[5]	7[5]	0	5	14.2
Park *et al*[18]	41	41	3[6]	6[6]	4	0	31.7
Prat *et al*[25]	52	52	0[1]	3[1]	3	1	13.4
Freeman *et al*[23]	64	64	N/A[1]	5[1]	N/A	N/A	7.8
Sugiyama *et al*[15]	H/B	7	0*	0*	0	0	0

[1]PEP and bleeding definitions not clear. Most authors used standard accepted criteria for both; [2]PEP: typical pancreatic pain without perforation and the level of amylase increased to ⩾ 3 ULN after the procedure. Bleeding: hematemesis and/or melena, level of postoperative hemoglobin decreased by > 2 g/dL, or requirement of transfusion therapy; [3]PEP: (1) new or worsened abdominal pain; (2) new or prolongation of hospitalization for at least 2 d; and (3) serum amylase ⩾ 3 ULN, measured more than 24 h after the procedure. Bleeding: melena and/or hematemesis; [4]PEP: Symptoms + Amylase > 500. Bleeding same as [2]; [5]PEP: (1) New or worse typical pain (epigastric radiating to the back) associated with tenderness to palpation; (2) Elevation of serum amylase or lipase ⩾ 3 ULN; (3) Both (1) and (2) persist for 24 h after the ERCP. Bleeding: Not adequately defined; [6]PEP: Amylase ⩾ 3 ULN the morning after procedure + Symptoms. Bleeding: presence of clinical (not just endoscopic) evidence of bleeding, such as melena or hematemesis, with an associated decrease of at least 2 g/dL in the Hb concentration, or the need for a blood transfusion. ERCP: Endoscopic retrograde cholangiopancreatography; PEP: Post-ERCP pancreatitis; N/A: Not available.

Quality assessment

The Newcastle–Ottawa score was used to assess the quality of nonrandomized studies by two authors (BD and HSM). Any discrepancies were resolved by a third reviewer (DGA).

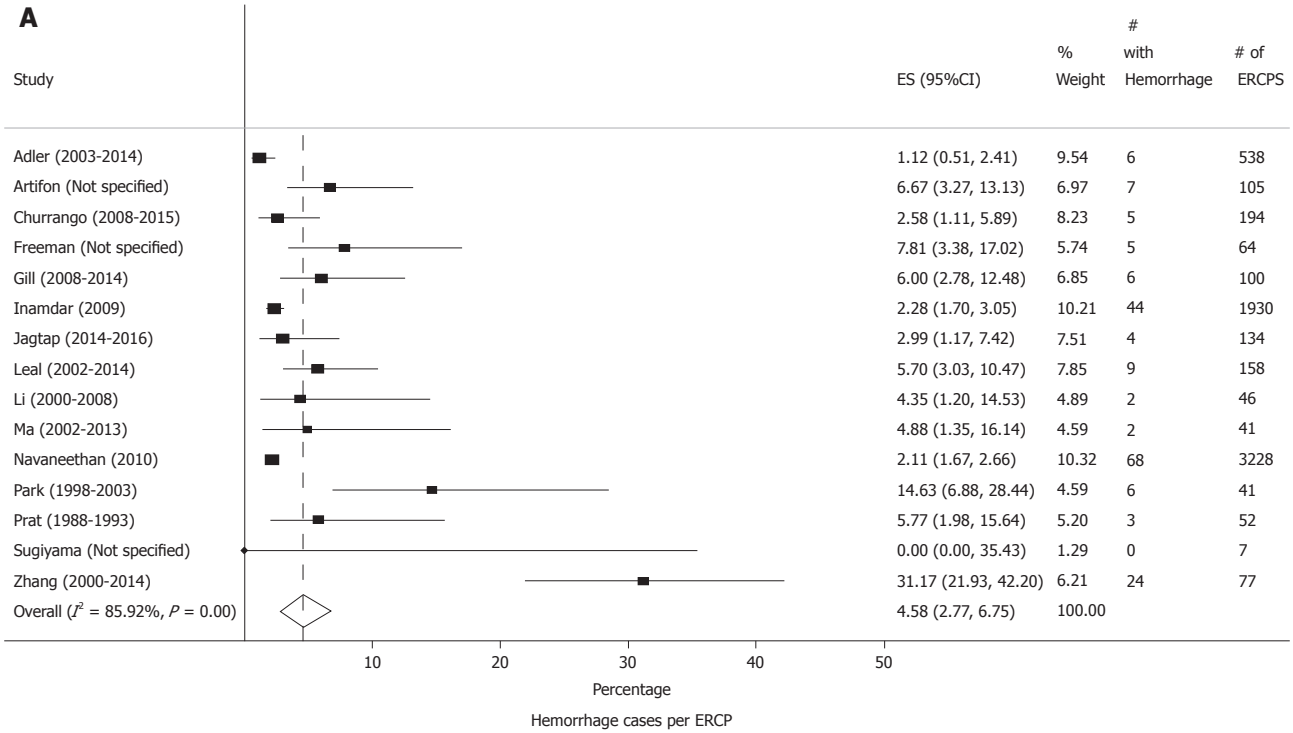
RESULTS

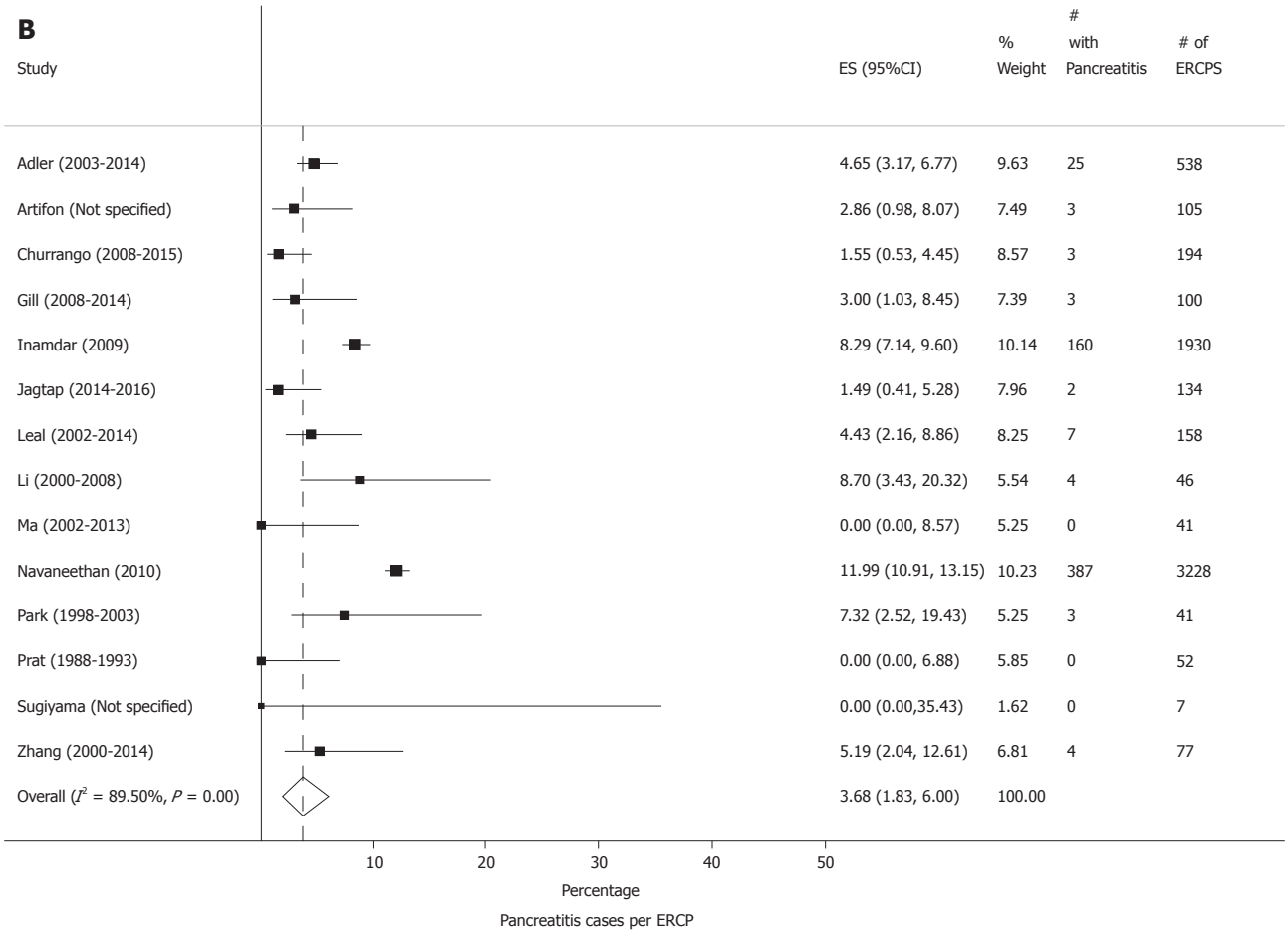
A total of 6505 patients from 15 studies were analyzed. A description of the studies is reported in Table 1. Adverse events secondary to ERCP in these patients are reported in Table 3. From the demographic information that was provided in various studies, male ratio was 59% and mean age was 59.26 years in ten studies. Out of the nine studies that described the etiology of cirrhosis, 11% had alcoholic cirrhosis and 89% had non-alcoholic causes. Data from 13 studies described 56.2% of the patients belonging to Child-Pugh class A, and the remaining 43.8% were Child-Pugh class B or C.

A total of 6735 ERCP procedures were performed. The indications for the ERCP included choledocholithiasis in 60.9% (4006/6571) of the procedures in 13 studies, cholangitis 15.5% (1021/6571) in 13 studies, biliary strictures 26.2% (1740/6635) in 14 studies and gallstone pancreatitis 21.1% (916/4338) in nine studies. The type of intervention during the ERCP was described in ten studies, which included endoscopic sphincterotomy in 52.7% of the procedures, biliary stenting in 16.7% and biliary dilation in 4.6% of the cases.

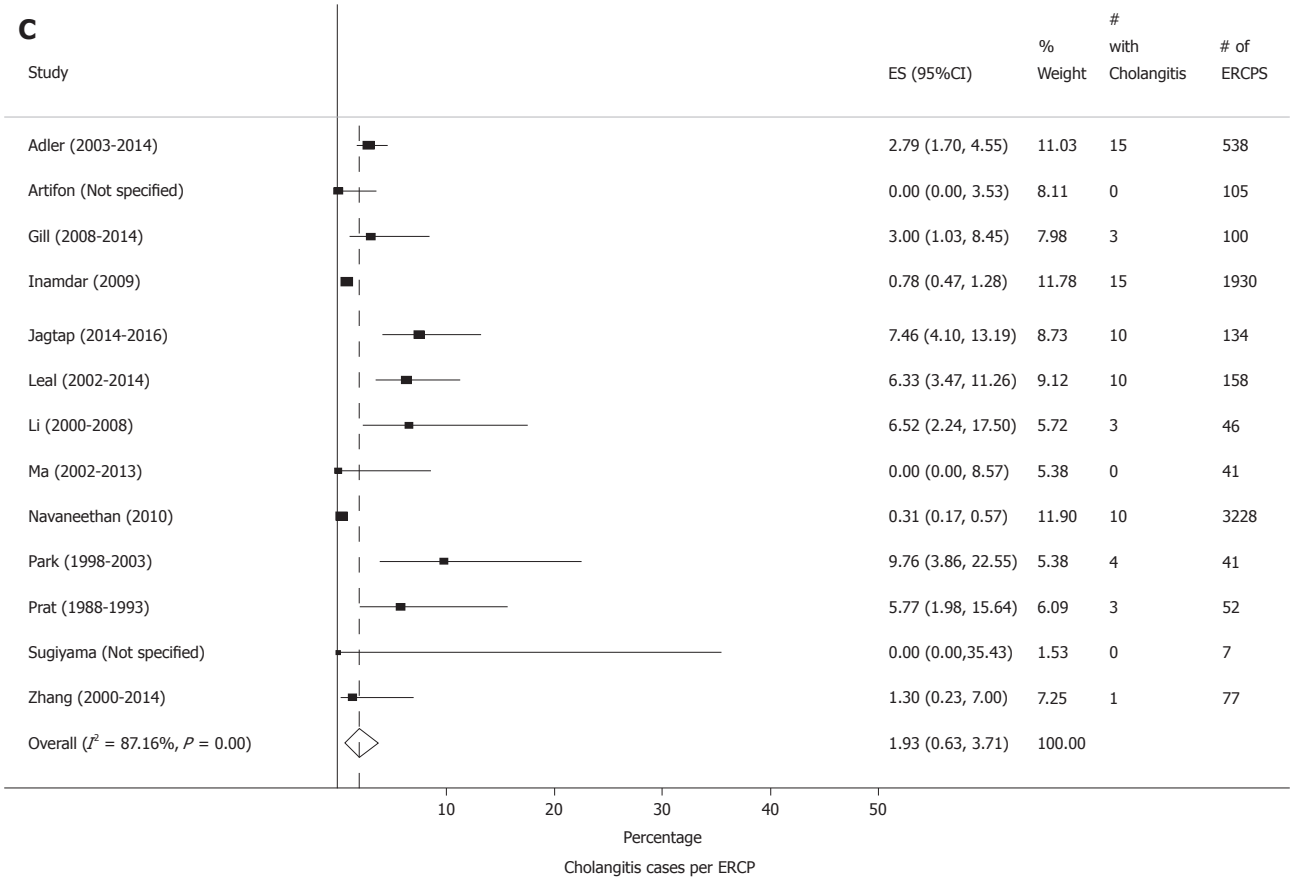
The individual adverse event rates were as follows: incidence of ERCP-related hemorrhage in 15 studies was 4.58% (95%CI: 2.77-6.75%, $P < 0.01$, $I^2 = 85.92\%$) (Figure 2A), PEP in 14 studies was 3.68% (95%CI: 1.83-6.00%, $P < 0.01$, $I^2 = 89.50\%$) (Figure 2B), cholangitis in 13 studies was 1.93% (95%CI: 0.63-3.71%, $P < 0.01$) (Figure 2C) and perforation in 13 studies was 0.00% (95%CI: 0.00-0.23%, $P = 0.08$, $I^2 = 37.8\%$) (Figure 2D).

Six out of 15 studies also compared adverse events in cirrhosis *vs* non-cirrhosis patients. Table 3 provides a description of the studies used for comparing the adverse events. Figure 2E looks at the meta-analysis of the comparison of overall complications in these six studies. Patients with cirrhosis had higher overall rates of complications compared to non-cirrhosis

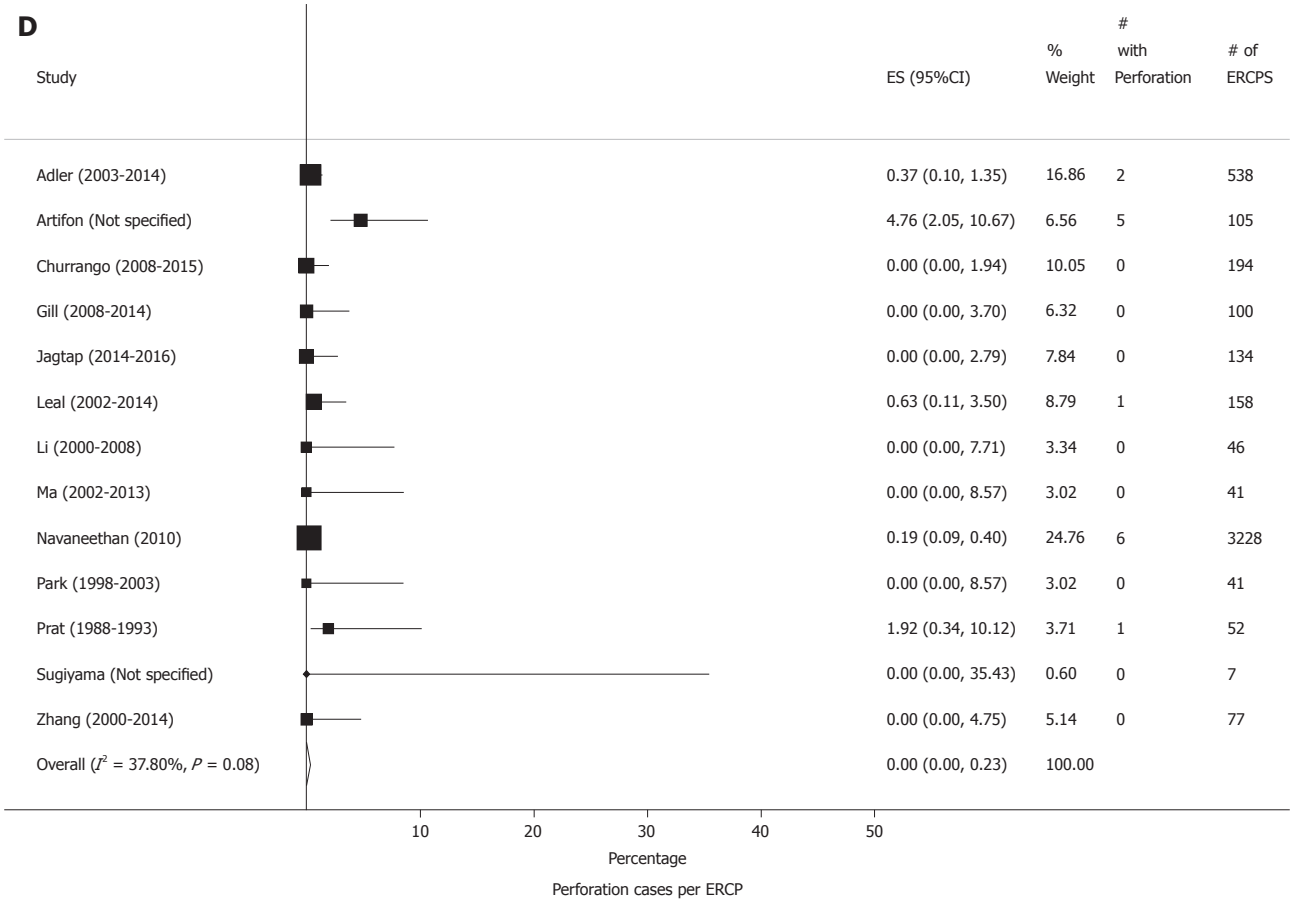

A
Study
ES (95%CI)
% Weight
# with Hemorrhage
# of ERCPS
Adler (2003-2014) 1.12 (0.51, 2.41) 9.54 6 538
Artifon (Not specified) 6.67 (3.27, 13.13) 6.97 7 105
Churrango (2008-2015) 2.58 (1.11, 5.89) 8.23 5 194
Freeman (Not specified) 7.81 (3.38, 17.02) 5.74 5 64
Gill (2008-2014) 6.00 (2.78, 12.48) 6.85 6 100
Inamdar (2009) 2.28 (1.70, 3.05) 10.21 44 1930
Jagtap (2014-2016) 2.99 (1.17, 7.42) 7.51 4 134
Leal (2002-2014) 5.70 (3.03, 10.47) 7.85 9 158
Li (2000-2008) 4.35 (1.20, 14.53) 4.89 2 46
Ma (2002-2013) 4.88 (1.35, 16.14) 4.59 2 41
Navaneethan (2010) 2.11 (1.67, 2.66) 10.32 68 3228
Park (1998-2003) 14.63 (6.88, 28.44) 4.59 6 41
Prat (1988-1993) 5.77 (1.98, 15.64) 5.20 3 52
Sugiyama (Not specified) 0.00 (0.00, 35.43) 1.29 0 7
Zhang (2000-2014) 31.17 (21.93, 42.20) 6.21 24 77
Overall (I^2 = 85.92%, P = 0.00) 4.58 (2.77, 6.75) 100.00
10
20
30
40
50
Percentage
Hemorrhage cases per ERCP

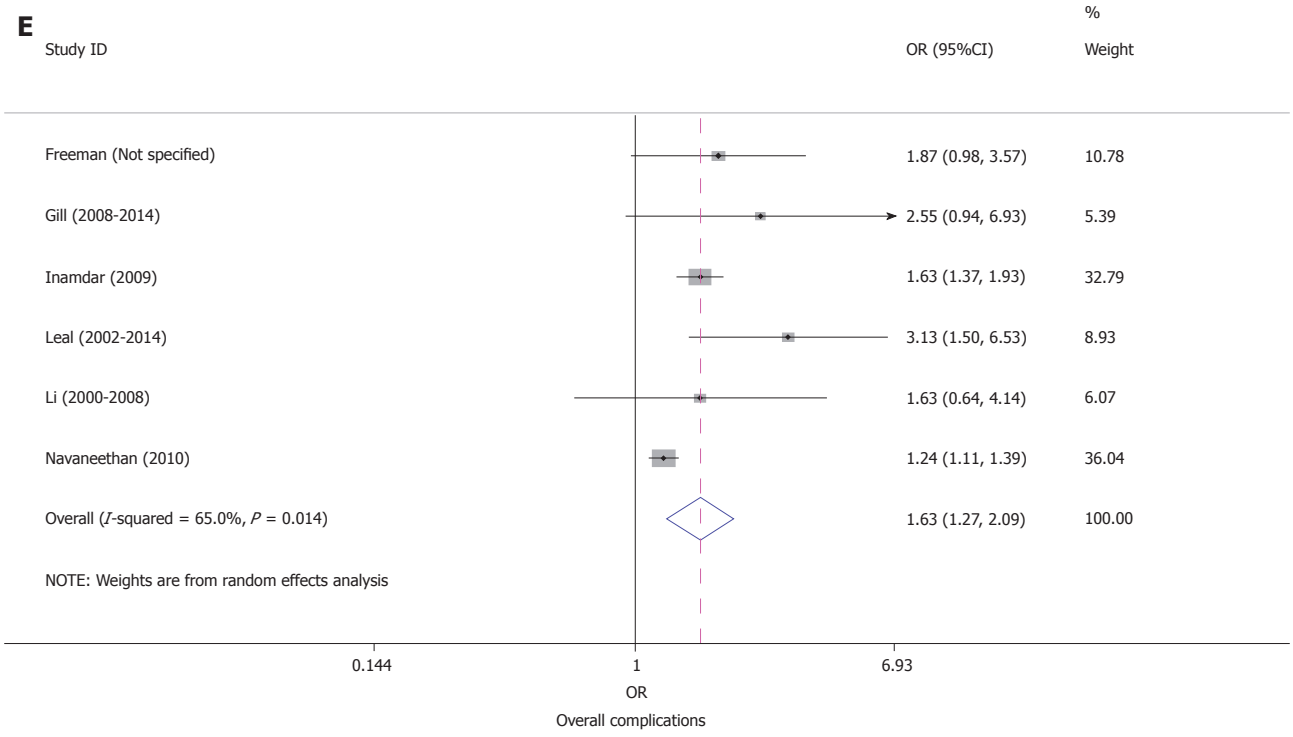

B
Study
ES (95%CI)
% Weight
# with Pancreatitis
# of ERCPS
Adler (2003-2014) 4.65 (3.17, 6.77) 9.63 25 538
Artifon (Not specified) 2.86 (0.98, 8.07) 7.49 3 105
Churrango (2008-2015) 1.55 (0.53, 4.45) 8.57 3 194
Gill (2008-2014) 3.00 (1.03, 8.45) 7.39 3 100
Inamdar (2009) 8.29 (7.14, 9.60) 10.14 160 1930
Jagtap (2014-2016) 1.49 (0.41, 5.28) 7.96 2 134
Leal (2002-2014) 4.43 (2.16, 8.86) 8.25 7 158
Li (2000-2008) 8.70 (3.43, 20.32) 5.54 4 46
Ma (2002-2013) 0.00 (0.00, 8.57) 5.25 0 41
Navaneethan (2010) 11.99 (10.91, 13.15) 10.23 387 3228
Park (1998-2003) 7.32 (2.52, 19.43) 5.25 3 41
Prat (1988-1993) 0.00 (0.00, 6.88) 5.85 0 52
Sugiyama (Not specified) 0.00 (0.00,35.43) 1.62 0 7
Zhang (2000-2014) 5.19 (2.04, 12.61) 6.81 4 77
Overall (I^2 = 89.50%, P = 0.00) 3.68 (1.83, 6.00) 100.00
10
20
30
40
50
Percentage
Pancreatitis cases per ERCP

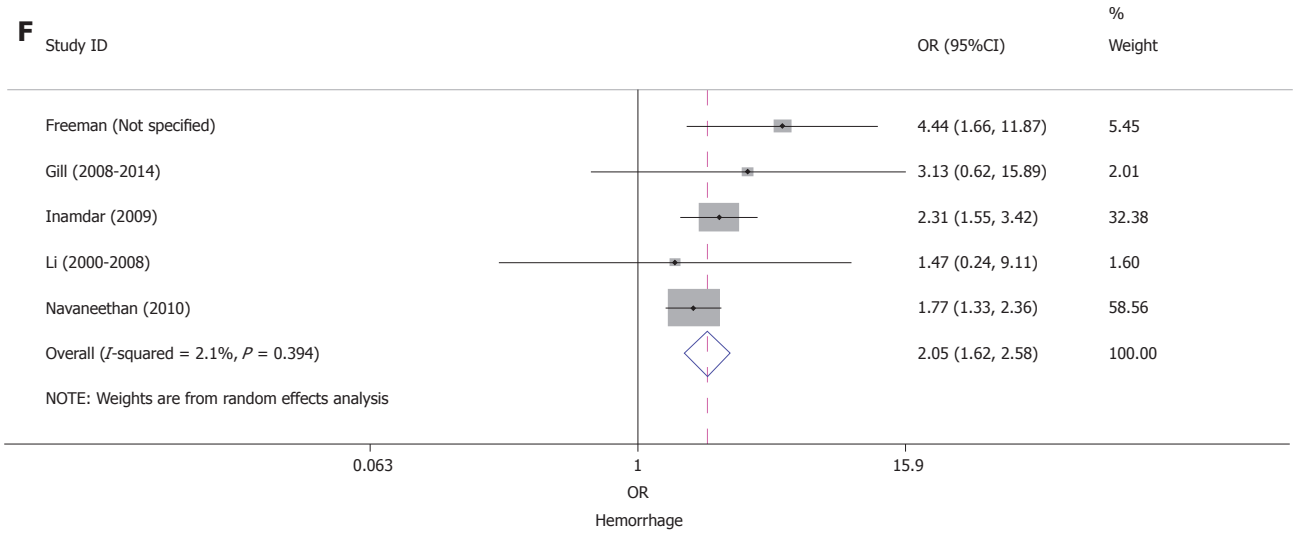
C

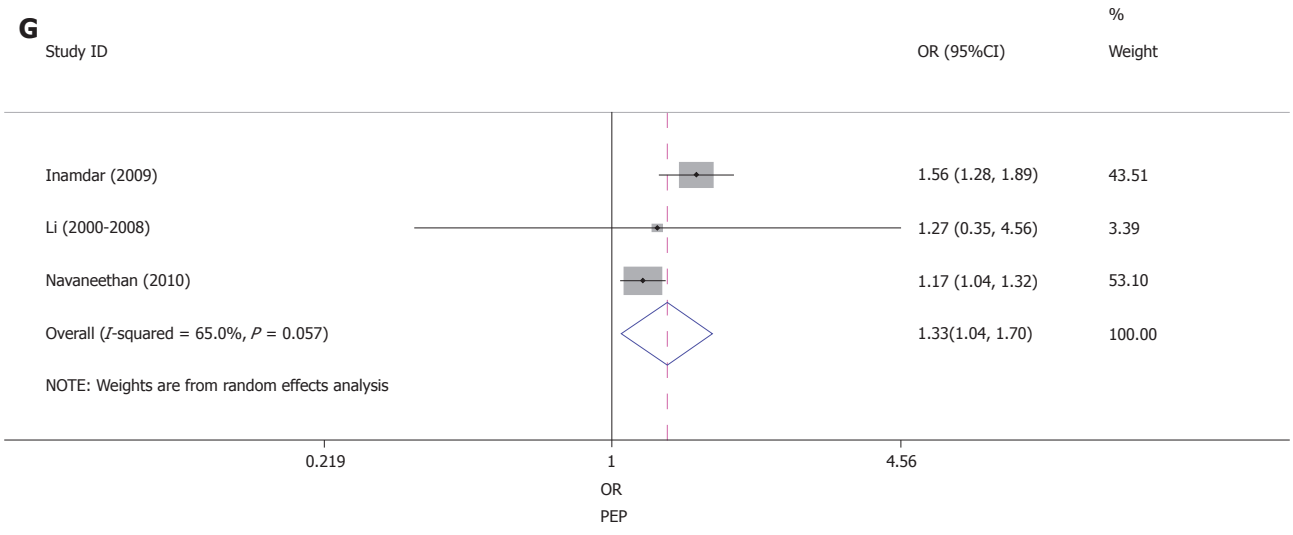

Study
ES (95%CI)
% Weight
# with Cholangitis
# of ERCPS
Adler (2003-2014) 2.79 (1.70, 4.55) 11.03 15 538
Artifon (Not specified) 0.00 (0.00, 3.53) 8.11 0 105
Gill (2008-2014) 3.00 (1.03, 8.45) 7.98 3 100
Inamdar (2009) 0.78 (0.47, 1.28) 11.78 15 1930
Jagtap (2014-2016) 7.46 (4.10, 13.19) 8.73 10 134
Leal (2002-2014) 6.33 (3.47, 11.26) 9.12 10 158
Li (2000-2008) 6.52 (2.24, 17.50) 5.72 3 46
Ma (2002-2013) 0.00 (0.00, 8.57) 5.38 0 41
Navaneethan (2010) 0.31 (0.17, 0.57) 11.90 10 3228
Park (1998-2003) 9.76 (3.86, 22.55) 5.38 4 41
Prat (1988-1993) 5.77 (1.98, 15.64) 6.09 3 52
Sugiyama (Not specified) 0.00 (0.00,35.43) 1.53 0 7
Zhang (2000-2014) 1.30 (0.23, 7.00) 7.25 1 77
Overall (I^2 = 87.16%, P = 0.00) 1.93 (0.63, 3.71) 100.00
10
20
30
40
50
Percentage
Cholangitis cases per ERCP

D


Study
ES (95%CI)
% Weight
# with Perforation
# of ERCPS
Adler (2003-2014) 0.37 (0.10, 1.35) 16.86 2 538
Artifon (Not specified) 4.76 (2.05, 10.67) 6.56 5 105
Churrango (2008-2015) 0.00 (0.00, 1.94) 10.05 0 194
Gill (2008-2014) 0.00 (0.00, 3.70) 6.32 0 100
Jagtap (2014-2016) 0.00 (0.00, 2.79) 7.84 0 134
Leal (2002-2014) 0.63 (0.11, 3.50) 8.79 1 158
Li (2000-2008) 0.00 (0.00, 7.71) 3.34 0 46
Ma (2002-2013) 0.00 (0.00, 8.57) 3.02 0 41
Navaneethan (2010) 0.19 (0.09, 0.40) 24.76 6 3228
Park (1998-2003) 0.00 (0.00, 8.57) 3.02 0 41
Prat (1988-1993) 1.92 (0.34, 10.12) 3.71 1 52
Sugiyama (Not specified) 0.00 (0.00, 35.43) 0.60 0 7
Zhang (2000-2014) 0.00 (0.00, 4.75) 5.14 0 77
Overall (I^2 = 37.80%, P = 0.08) 0.00 (0.00, 0.23) 100.00
10
20
30
40
50
Percentage
Perforation cases per ERCP


E
Study ID
OR (95%CI)
%
Weight
Freeman (Not specified)
1.87 (0.98, 3.57)
10.78
Gill (2008-2014)
2.55 (0.94, 6.93)
5.39
Inamdar (2009)
1.63 (1.37, 1.93)
32.79
Leal (2002-2014)
3.13 (1.50, 6.53)
8.93
Li (2000-2008)
1.63 (0.64, 4.14)
6.07
Navaneethan (2010)
1.24 (1.11, 1.39)
36.04
Overall (I-squared = 65.0%, P = 0.014)
1.63 (1.27, 2.09)
100.00
NOTE: Weights are from random effects analysis
0.144
1
6.93
OR
Overall complications


F
Study ID
OR (95%CI)
%
Weight
Freeman (Not specified)
4.44 (1.66, 11.87)
5.45
Gill (2008-2014)
3.13 (0.62, 15.89)
2.01
Inamdar (2009)
2.31 (1.55, 3.42)
32.38
Li (2000-2008)
1.47 (0.24, 9.11)
1.60
Navaneethan (2010)
1.77 (1.33, 2.36)
58.56
Overall (I-squared = 2.1%, P = 0.394)
2.05 (1.62, 2.58)
100.00
NOTE: Weights are from random effects analysis
0.063
1
15.9
OR
Hemorrhage


G
Study ID
OR (95%CI)
%
Weight
Inamdar (2009)
1.56 (1.28, 1.89)
43.51
Li (2000-2008)
1.27 (0.35, 4.56)
3.39
Navaneethan (2010)
1.17 (1.04, 1.32)
53.10
Overall (I-squared = 65.0%, P = 0.057)
1.33(1.04, 1.70)
100.00
NOTE: Weights are from random effects analysis
0.219
1
4.56
OR
PEP

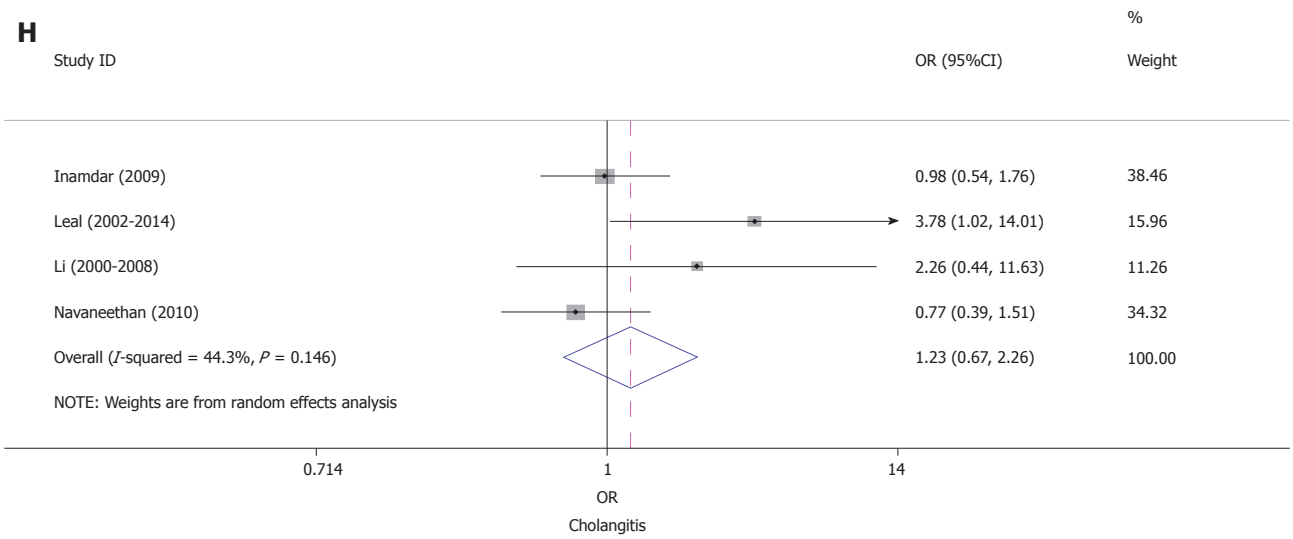


Figure 2 Forest plot. A: Incidence of ERCP-related hemorrhage = 4.58% (95%CI: 2.77-6.75%, $P < 0.01$, $I^2 = 85.92\%$); B: Incidence of ERCP-related pancreatitis = 3.68% (95%CI: 1.83%-6.00%, $P < 0.01$, $I^2 = 89.50\%$); C: Incidence of ERCP-related cholangitis = 1.93% (95%CI: 0.63%-3.71%, $P < 0.01$); D: Incidence of ERCP-related perforation = 0.00% (95%CI: 0.00%-0.23%, $P = 0.08$, $I^2 = 37.8\%$); E: Meta-analysis of overall complications in six studies comparing cirrhosis and non-cirrhosis patients; F: Comparison of post-ERCP hemorrhage rates between cirrhosis and non-cirrhosis patients; G: Comparison of post-ERCP pancreatitis (PEP) rates between cirrhosis and non-cirrhosis patients; H: Comparison of post-ERCP cholangitis rates between cirrhosis and non-cirrhosis patients. ERCP: Endoscopic retrograde cholangiopancreatography.

patients, and this difference was statistically significant. Pooled OR for overall complications was 1.63 (95%CI: 1.27-2.09, $P < 0.0001$, $I^2 = 65\%$). Hemorrhage rate for patients with cirrhosis was higher than non-cirrhosis, from a comparison in five studies, with a pooled OR 2.05 (95%CI: 1.62-2.58, $P < 0.0001$, $I^2 = 2.1\%$) (Figure 2F). PEP rate comparison from three studies showed a higher incidence in patients with cirrhosis, with a pooled OR 1.33 (95%CI: 1.04-1.70, $P = 0.021$, $I^2 = 65\%$) (Figure 2G). Cholangitis rate comparison between patients with or without cirrhosis, as evaluated from four studies was not statistically significant, with a pooled OR of 1.23 (95%CI: 0.67-2.26, $P = 0.511$, $I^2 = 44.3\%$) (Figure 2H). A perforation rate comparison was described in only two studies, and hence comparison analysis could not be obtained.

The power to detect publication bias is low due to the small number of studies for comparison. Nevertheless, the *P*-values were found to be statistically significant for overall complications, hemorrhage and PEP. Figure 3 presents a symmetrical funnel plot for the studies used in comparing overall complications. Heterogeneity is high due to the different sizes of the studies, with some studies being small and others being large. The actual percentage of I^2 is described in the results above. The details regarding the methodological quality of studies using the Newcastle-Ottawa scale are provided in Table 4.

DISCUSSION

In this meta-analysis of studies describing ERCP-related adverse events in patients with cirrhosis, we observed a statistically significant higher rate of overall adverse events related to ERCP, particularly of PEP and hemorrhage. Similar results were observed in the subset analysis of studies, which allowed a comparison of ERCP-related adverse events in cirrhosis *vs* non-cirrhosis patients. Additionally, the subset analysis showed a trend towards higher rates of post-procedure cholangitis in patients with cirrhosis, although that was not significantly higher than that in non-cirrhosis patients.

Prior studies have presented variable results when evaluating adverse events in patients with cirrhosis undergoing ERCP. Most of the studies in the past have shown higher rates of hemorrhage in patients with cirrhosis compared to non-cirrhosis, likely due to a poor synthetic function of the liver, portal hypertension, prolonged coagulation times, *etc.*[5,13-15]. The lowest rates of hemorrhage (1.1%) in cirrhosis patients were reported by Adler *et al*[16] in a large retrospective study performed at two large centers, including over 500 ERCP procedures, as compared to 4.58% seen in our meta-analysis. Two major factors potentially contributing to those lower rates are 1) a smaller percentage (15%) of patients receiving sphincterotomy when compared with other studies that could have confounded the results, and 2) performance of ERCP by very experienced operators with a particularly long history of performing these complicated procedures in patients with advanced liver disease.

A retrospective matched cohort study of the 2009 National Inpatient Sample with 3228 patients by Inamdar *et al*[13] showed an overall ERCP–related hemorrhage rate of 2.3% in cirrhosis patients, which is once again lower than the rate demonstrated in our meta-analysis. However, on the subset analysis, ERCP-associated hemorrhage for decompensated cir-

Table 4 Methodological quality of included studies using the Newcastle-Ottawa scale

Ref.	Country	Study type	Cohort/ Case-control	Yr	No. of patients	Newcastle-Ottawa Scale		Outcome
						Selection	Comparability	
Navaneethan *et al*[5]	United States	Retrospective	Case-control	2010	3228	A	C	***
Jagtap *et al*[20]	India	Retrospective	Cohort	2014-2016	134	A		**
Adler *et al*[16]	United States	Retrospective	Cohort	2003-2014	328	A	C	***
Inamdar *et al*[13]	United States	Retrospective	Case-control	2009	1930	A	B	**
Gill *et al*[14]	Pakistan	Retrospective	Case-control	2008-2014	100	A	C	**
Churrango *et al*[24]	United States	Retrospective	Cohort	2008-2015	194	A	C	**
Leal *et al*[19]	Spain	Retrospective	Case-control	2002-2014	158	A	C	***
Zhang *et al*[2]	China	Retrospective	Cohort	2000-2014	77	A	C	***
Li *et al*[17]	China	Retrospective	Cohort	2000-2008	46	A	C	***
Ma *et al*[22]	China	Retrospective	Cohort	2002-2013	41	B	C	**
Artifon *et al*[21]	Brazil	Prospective	Case-control	Not specified	105	B	C	***
Park *et al*[18]	South Korea	Prospective/Retrospective	Case-control	1998-2003	41	A	C	***
Prat *et al*[25]	France	Retrospective	Cohort	1988-1993	52	A+	C	***
Freeman *et al*[23]	United States	Prospective	Case-control	Not specified	64	A	C	***
Sugiyama *et al*[15]	Japan	Prospective	Cohort	Not specified	7	B	C	***

A+: Excellent; A: Very good; B: Good; C: Fair.

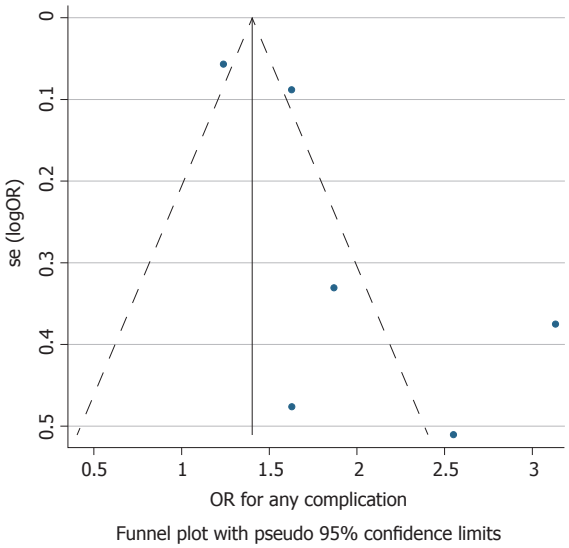


Figure 3 Symmetrical funnel plot for the studies used in comparing overall complications to understand publication bias.

rhosis was 4.3% when compared to 1.3% in patients with compensated cirrhosis, and 1% in non-cirrhosis patients. Another retrospective matched case-control study by Navaneethan *et al*[5] using the 2010 National Inpatient Sample database showed an ERCP-associated hemorrhage of 2.1% in cirrhosis *vs* 1.2% in non-cirrhosis patients. The results from our meta-analysis clearly demonstrate higher rates of hemorrhage in cirrhosis patients than previously reported, with a pooled OR of 2.05.

Li *et al*[17] reported no statistically significant difference between ERCP-associated hemorrhage in cirrhosis (4.3%) and non-cirrhosis (3%) patients, but those with Child-Pugh class C had statistically significant higher rates of hemorrhage at 25%. Nevertheless, further information on whether these bleeds were clinically significant or not was provided. Similarly, a study by Park *et al*[18] described higher rates of ERCP-related hemorrhage in patients with Child-Pugh class C (35%) as compared to class A (0%) and B (16%).

Endoscopic sphincterotomy (EST) has been shown to independently increase the risk of hemorrhage in cirrhosis as well as non-cirrhosis patients[5,14,19]. The Navaneethan *et al*[5] study showed that performing EST in both compensated and decompensated cirrhosis patients was an independent risk factor of post-ERCP bleeding. In the study by Park *et al*[18], the rates of bleeding were significantly lower for endoscopic papillary balloon dilation in comparison to EST. In addition, one study also observed lower rates of bleeding when the ERCPs in cirrhosis patients were performed in medium- and large-sized hospitals[5]. Since only a limited number of studies have described hemorrhage or other adverse events in terms of Child-Pugh class or the type of intervention, no separate analysis could be obtained in our meta-analysis[16-18,20].

In terms of PEP, our meta-analysis shows the overall incidence of cirrhosis to be 3.68% (95%CI: 1.83-6%), as evaluated from 14 studies. The comparative meta-analysis using three available studies reveal a higher rate of PEP in cirrhosis when compared to non-cirrhosis patients, with a pooled OR of 1.33, which was statistically significant as well. While some of the comparison studies failed to demonstrate a statistically significant difference for PEP in cirrhosis *vs* non-cirrhosis patients, the study by Navaneethan *et al*[5] described a higher rate of PEP in cirrhosis patients on univariate analysis, although this difference fell away once they adjusted other factors that increased the risk of PEP. These authors did demonstrate that performing EST was associated with an increased risk of PEP, although the cause was unclear, while at the same time placing prophylactic pancreatic stents was associated with a decreased risk of PEP[5,14,17,19]. Notably, cirrhosis alone did not increase the risk of PEP. Patients with alcoholic

cirrhosis were noted to have a higher rate of PEP *vs* non-alcoholic cirrhosis[5]. Similarly, increased rates of PEP with EST were seen by Adler *et al*[16]. Artifon *et al*[21] showed that the risk of PEP was decreased with supra-papillary technique (0%) in comparison with standard cannulation technique (4.8%). Park *et al*[18] suggested lower rates of PEP with endoscopic papillary balloon dilation in comparison to EST, but the results did not reach statistical significance. A possible argument explaining the higher rates of PEP is the conservative intravenous hydration approach adopted by physicians, due to concerns of volume overload in decompensated cirrhosis patients[13].

The rate of post-ERCP cholangitis in cirrhosis patients from our meta-analysis of 13 studies was 1.93% (95%CI: 0.63-3.71%), and the comparison analysis from four studies showed an OR of 1.23 in cirrhosis patients when compared to non-cirrhosis patients, but it was not statistically significant. In the study by Adler *et al*[16], the overall rate of post-ERCP cholangitis was 2.8%. However, on the sub-group analysis, the rate was 5.8% in patients receiving EST as compared to 2.3% in patients with no sphincterotomy, although the difference was not statistically significant. There was no comparison group of patients without cirrhosis in this study. When looking at literature that included a comparison group of non-cirrhosis patients, the study by Navaneethan *et al*[5] demonstrated lower rates of post-ERCP cholangitis in cirrhosis when compared to non-cirrhosis, although the difference was not statistically significant. The reason for this trend is believed to be the consistent use of prophylactic antibiotics in cirrhosis patients for spontaneous bacterial peritonitis or other indications. No statistically significant difference in cholangitis rates was appreciated in any other studies[13,14,18,22]. The only study showing higher rate of cholangitis in the cirrhosis (6.3%) *vs* non-cirrhosis group (1.8%) was by Leal *et al*[19], however the authors could not provide a plausible explanation for their observation, and suggested performing further studies that implement preventive strategies to avoid cholangitis in patients with cirrhosis.

The perforation rate per our meta-analysis of 13 studies was 0% (95%CI: 0.00-0.23%), and, as described above, there was no comparison analysis between the cirrhosis and non-cirrhosis group due to the small number of studies describing it. Adler *et al*[16] reported an overall perforation rate of 0.4%, and Navaneethan *et al*[5] reported a perforation rate of 0.2% in patients with cirrhosis and 0.1% in patients without cirrhosis, although with no statistically significant difference.

A small number of studies have described the relationship of adverse events with the Child-Pugh score. These studies consistently demonstrated that the patients with higher Child-Pugh class scores had more complications overall[16-18,20]. Inamdar *et al*[13] demonstrated a similar risk of adverse events between the non-cirrhosis group and patients with compensated cirrhosis. However, higher rates of adverse events were observed in patients with decompensated cirrhosis. Similarly, Adler *et al*[16] described the post-procedure adverse events to be lower in Child-Pugh class A (6.1%) as compared to class B and C combined (11.3%), which was statistically significant. Zhang *et al*[2] noted no association between the rates of adverse events when correlated to Child-Pugh class, but elucidated that patients with higher MELD scores had higher rates of adverse events.

Higher rates of adverse events have also been reported depending on maneuvers performed during the ERCP. Performing EST has been associated with higher rates of adverse events in comparison to performing stenting alone or endoscopic papillary balloon dilation[5,14,19,23]. Adler *et al*[16] described the overall post-ERCP adverse events to be higher after EST (23.3%), when compared to patients who did not undergo sphincterotomy (5.6%). Moreover, Freeman *et al*[23] indicated EST in cirrhosis patients was associated with excess morbidity and mortality related to bleeding, with poor outcomes primarily reported in Child-Pugh class C patients. Freeman further suggested that ERCP-related mortality could be reduced by avoiding EST where dilation or stenting alone is adequate.

Even with the higher rates of overall adverse events seen in patients with cirrhosis, as described in our comparison meta-analysis of six studies with an OR of 1.63 (95%CI: 1.27-2.09), the cholangitis rates surprisingly did not show a statistically significant difference amongst the two groups as has been described above.

Our present meta-analysis has a few limitations. First is that the maximum number of cases are derived from only three studies by Navaneethan *et al*[5], Inamdar *et al*[13] and Adler *et al*[16]. Secondly, only a few studies describe adverse events in terms of indications, the severity of cirrhosis or the type of ERCP-related interventions. Due to these reasons, we were unable to obtain a separate sub-group analysis based in relation to these. The heterogeneity of the overall complication comparison in cirrhosis *vs* non-cirrhosis patients is high, which makes it hard to draw specific conclusions from the meta-analysis when combined with the low power to detect bias. This suggests the need for better-controlled prospective studies in the future for improved clarity of post-ERCP adverse events in cirrhosis patients. Based on our experience with ERCP in cirrhosis, we believe that the adverse events seen in patients with cirrhosis are similar overall to those seen among unselected patients undergoing ERCP, although patients with Childs classes B and C have higher adverse event rates when compared with those with Childs class A. Patients with cirrhosis without PSC have significantly greater adverse event rates when compared with patients with PSC, which runs somewhat counter to prevailing thought.

In summary, our meta-analysis clearly demonstrates

that there is a higher rate of adverse events related to ERCP (particularly of hemorrhage and PEP) in patients with cirrhosis than that of patients without cirrhosis, especially in patients with Child-Pugh class B or C, and when receiving interventions like EST. Despite the increased adverse event rates, ERCP remains the least invasive therapeutic approach for appropriate indications in pancreatobiliary pathologies for patients with cirrhosis[13]. A thorough risk/benefit assessment should be performed in cirrhosis patients prior to ERCP.

ARTICLE HIGHLIGHTS

Research background

Patients with cirrhosis undergoing endoscopic retrograde cholangiopancreatography (ERCP) are believed to have increased risks. However, there is a paucity of literature describing the indications and outcomes of ERCP procedures in patients with cirrhosis, especially focusing on adverse events.

Research motivation

ERCP is one of the most commonly performed endoscopic procedures and is known for its high-risk nature. Performing ERCP in patients with cirrhosis is not only challenging, but may even be a high-risk endeavor in this setting. There was therefore a need for a meta-analysis to estimate adverse events associated with ERCP in cirrhosis patients.

Research objectives

To assess the adverse events associated with ERCP in cirrhosis patients.

Research methods

The preferred reporting items for systematic reviews and meta-analyses statement and the meta-analysis of observational studies in epidemiology guidelines were followed. The overall proportion of patients experiencing any post-procedure adverse events or experiencing specific complications were estimated using random effects methods designed for the pooling of proportions. The actual proportions were estimated after the Freeman-Tukey double arcsine transformation had been applied to the individual study proportions and standard errors were calculated using the scoring method.

Research results

Individual adverse events included hemorrhage in 4.58% (95%CI: 2.77-6.75%, I^2 = 85.9%), post-ERCP pancreatitis (PEP) in 3.68% (95%CI: 1.83-6.00%, I^2 = 89.5%), cholangitis in 1.93% (95%CI: 0.63-3.71%, I^2 = 87.1%) and perforation in 0.00% (95%CI: 0.00-0.23%, I^2 = 37.8%).

Research conclusions

There is an overall higher rate of adverse events related to ERCP in patients with cirrhosis, especially hemorrhage and PEP.

Research perspectives

In the future, a thorough risk/benefit assessment should be performed in cirrhosis patients prior to ERCP.

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CASE REPORT

Tight near-total corrosive strictures of the proximal esophagus with concomitant involvement of the hypopharynx: Flexible endoscopic management using a novel technique

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Author contributions: Dhaliwal HS designed and performed the research, reviewed the literature and wrote the paper; Kumar N, Siddappa PK and Garg S critically reviewed the paper for intellectual content; Singh R, Sekhon JS, Masih J and Abraham J collected the data.

Informed consent statement: Informed consent was obtained prior to the procedure from the included patients.

Conflict-of-interest statement: We, all authors, declare no conflict of interest relevant to this work.

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Abstract

AIM

To investigate the role of a novel minimally invasive endoscopic technique in the management of tight near-total corrosive strictures of the proximal esophagus involving the hypopharynx.

METHODS

Two patients with near-total corrosive strictures of the proximal esophagus involving the hypopharynx were managed with the novel endoscopic technique. The technique involved passing a 0.025-inch flexible guide-wire across the stricture, and stricture dilatation, using 10F coaxial diathermy and balloon dilators, followed by

electro-incision of the proximal aspect of the residual eccentric stricture by means of a novel approach using a wire-guided sphincterotome.

RESULTS

Both patients were successfully managed on an outpatient department basis with the complete relief of symptoms and resolution of strictures on endoscopy and an esophagogram. No adverse events were seen during or after the procedure. There was no recurrence of symptoms at a follow-up of over a year in both cases. There was a significant improvement in the body mass index of both patients after the procedure.

CONCLUSION

We report a novel flexible endoscopic technique for the management of complex hypopharyngo-esophageal strictures. In experienced hands, the procedure is relatively simple, safe and effective with a durable response.

Key words: Cricopharyngeal strictures; Electroincision; Corrosive injury; Benign esophageal strictures; Stricture dilatation

Core tip: In this study, we evaluated the minimally invasive endoscopic management of near-total benign fibrotic strictures of the proximal esophagus involving the hypopharynx across the pharyngo-esophageal junction. Both patients were successfully treated using a novel approach: stricture dilatation (with a 10F co-axial diathermic dilator and through-the-scope balloon) followed by the electroincision of residual adhesions at the hypopharyngeal base with a wire-guided sphincterotome. To the best of our knowledge, this report represents the tightest esophageal or hypopharyngeal strictures ever opened endoscopically and reported in the literature.

Dhaliwal HS, Kumar N, Siddappa PK, Singh R, Sekhon JS, Masih J, Abraham J, Garg S. Tight near-total corrosive strictures of the proximal esophagus with concomitant involvement of the hypopharynx: Flexible endoscopic management using a novel technique. *World J Gastrointest Endosc* 2018; 10(11): 367-377 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i11/367.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i11.367

INTRODUCTION

The ingestion of corrosives leading to severe gastrointestinal (GI) injury is a common problem in India due to the relatively easy access to acids[1]. After acute ingestion, progressive cicatrisation sets in over the next 4-6 wk in cases with a severe injury, leading to benign fibrotic strictures of the upper GI tract[2]. Fibrotic strictures after acid ingestion affect both the esophagus and the stomach in almost equal proportions, with esophageal involvement mostly limited to the mid and distal esophagus[1]. Because of the socio-economic conditions prevailing in India, occasional neglected cases of acid ingestion may present late with tight near-total strictures of the esophagus. The situation is even more challenging if the near-total stricture afflicts the proximal esophagus with contiguous involvement of the hypopharynx. Surgery remains the only viable management option in this difficult scenario; however, because of extreme malnutrition, many patients may even be unfit for the surgery. The surgical options include a muscle flap inlay, gastric pull-up and esophageal substitute (colon or ileo-colon) interposition, all of which are associated with high morbidity and mortality[3,4,5]. The surgical outcomes are particularly worse if there is hypopharyngo-esophageal involvement, compared to the scenario if both hypopharynx and cervical esophagus are spared[4]. We report for the first time the successful flexible endoscopic management of near-total corrosive strictures of the proximal esophagus involving the hypopharynx, using a novel technique.

MATERIALS AND METHODS

Study design

This study was a retrospective analysis of the prospectively collected records of the demographic data, radiological findings, endoscopic procedural details, post-procedural course and follow-up of 2 patients with one or more near-total strictures of the proximal esophagus along with hypopharyngeal involvement (as defined below). These cases were managed by us between January 2016 and December 2017.

Definitions and anatomical considerations

A near-total stricture was defined as a very thin streak of oral contrast crossing the stricture on an esophagogram, and endoscopically, while a flexible guide-wire could be negotiated with difficulty across the stricture, a balloon dilator could not be entered into the stricture over the guide-wire even with best efforts.

The hypopharynx, the most inferior part of the pharynx, extends from the level of the upper border of the epiglottis to the lower border of the cricoid cartilage and comprises 3 parts: the piriform sinuses, the post-cricoid region and the posterior pharyngeal wall (Figure 1A and 1B). The cricopharyngeus muscle (CP) is a circular muscle attached anteriorly to the cricoid cartilage (Figure 1B); within the 2-4 cm long upper esophageal sphincter (UES), the CP constitutes the zone of maximal UES pressure, which is approximately 1 cm in length. The apices of the piriform sinuses open into the proximal esophagus across the relaxed CP. The CP normally lies at the level of the C5-C6 vertebrae on a lateral neck X-ray film; while the piriform sinuses lie

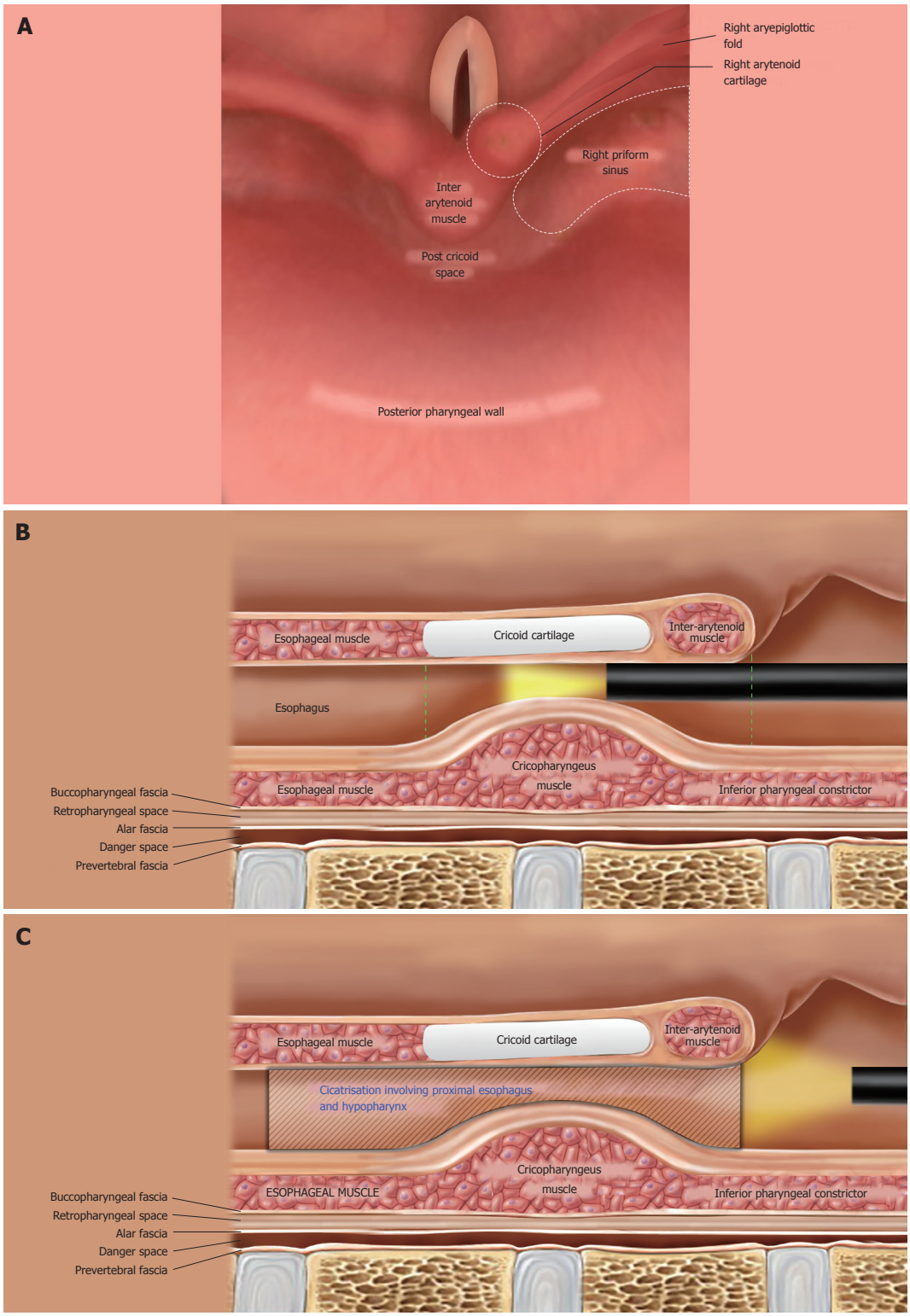

Figure 1 Anatomical consideration while addressing hypopharyngo-esophageal strictures endoscopically. A: The normal anatomy of the adult hypopharynx as seen during flexible endoscopy, with the scope tip behind the epiglottis. The piriform sinuses are 2 inverted pyramids on either side of the larynx with their apex inferiorly at the level of cricopharyngeus muscle (CP); they are bounded medially by the aryepiglottic folds and laterally by the pharyngeal wall; B: Post-cricoid region extends from the level of arytenoid cartilages (joined by the inter-arytenoid muscle in the midline) superiorly to the inferior border of cricoid cartilage (vertical dashed green lines); C: The strictured proximal esophagus and hypopharynx in both of our cases. The fibrotic process in both extended cranially till the proximal aspect of the post-cricoid region; there was an involvement of the apical parts of piriform sinuses as well (not shown here).

immediately above this level. The esophagus begins at the level of the C6 vertebra.

The cicatrisation in our cases had sufficient hypopharyngeal involvement such that it extended almost to the proximal (cranial) aspect of the post-cricoid region (Figure 1C) and the adjoining parts of the apices of both

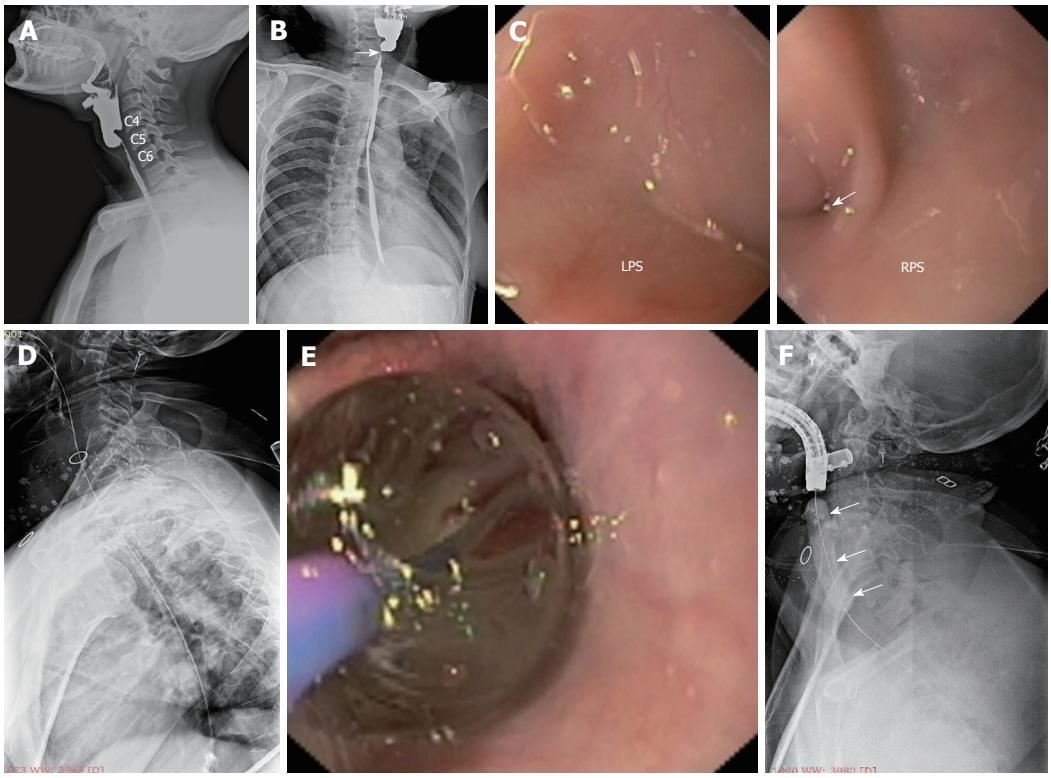

Figure 2 Near-total stricture in case 1 and its endoscopic management. A: Lateral view of barium esophagogram showing the near-total stricture of the proximal esophagus involving the hypopharynx; B: On AP view, the near-total stricture has an eccentric proximal appearance (white arrow) and it is communicating with the right piriform sinus; C: During flexible endoscopic evaluation, the left piriform sinus (LPS) was completely obliterated in its apical region, while the right piriform sinus (RPS) showed a tiny opening (white arrow) which represents the beginning of the near-total stricture; D: A flexible guide-wire was passed across the stricture with difficulty, its correct placement was confirmed under fluoroscopy and the stricture was dilated with a 10F diathermy dilator (video 1); E, F: Subsequently, the stricture was dilated with a TTS balloon (white arrows).

piriform sinuses (in other words, the stricture involved the CP and extended a few millimeters proximal to the CP as well). Furthermore (based on our previous experience as well), near-total strictures with such a proximal extension communicate with only one of the 2 piriform sinuses (generally the right piriform sinus) while the post-cricoid region and the contralateral piriform sinus are completely obliterated. As a result, the proximal part of the stricture appeared eccentric on the antero-posterior (AP) view of an esophagogram.

Initial management

Both patients presented to us with absolute dysphagia. The initial management at presentation consisted of administration of intravenous fluids to correct the dehydration, basic blood investigations including complete blood counts, serum electrolytes, renal function tests, chest radiographs and correction of any underlying dyselectrolytemia or acid-base imbalance**.** Any history of chronic cough, hoarseness of voice and respiratory distress was probed and an otolaryngology (ENT) evaluation was performed to rule out any significant tracheal involvement or airway compromise.

Ethical considerations and informed consent

Both patients underwent multidisciplinary discussion, and a minimally invasive endoscopic therapy was suggested for the relief of absolute dysphagia. The therapeutic procedures were carried out in accordance with the Helsinki declaration. Institutional review board approval was not obtained due to the "time-sensitive nature" of the endoscopic therapy; any further delay while obtaining approval was likely to allow the conversion of the near-total stricture (Figure 2A, 2B) into a total stricture and, hence, potentially depriving the patients of life-saving minimally invasive therapy. Furthermore, both patients were severely malnourished and were also at risk of aspiration pneumonitis due to oro-pharyngeal secretions; hence an immediate action was highly desirable. As part of the informed consent process, the investigational nature of the endoscopic procedure and the potential complications (as discussed below) were explained to the patients. The discussion and the patient's understanding that the endoscopic therapy was being utilized in an off-label fashion were documented in the medical records.

Description of the endoscopic procedure

Both patients were severely malnourished at presentation and were considered high risk candidates for deep sedation. The procedure was performed under conscious sedation in the left lateral position with

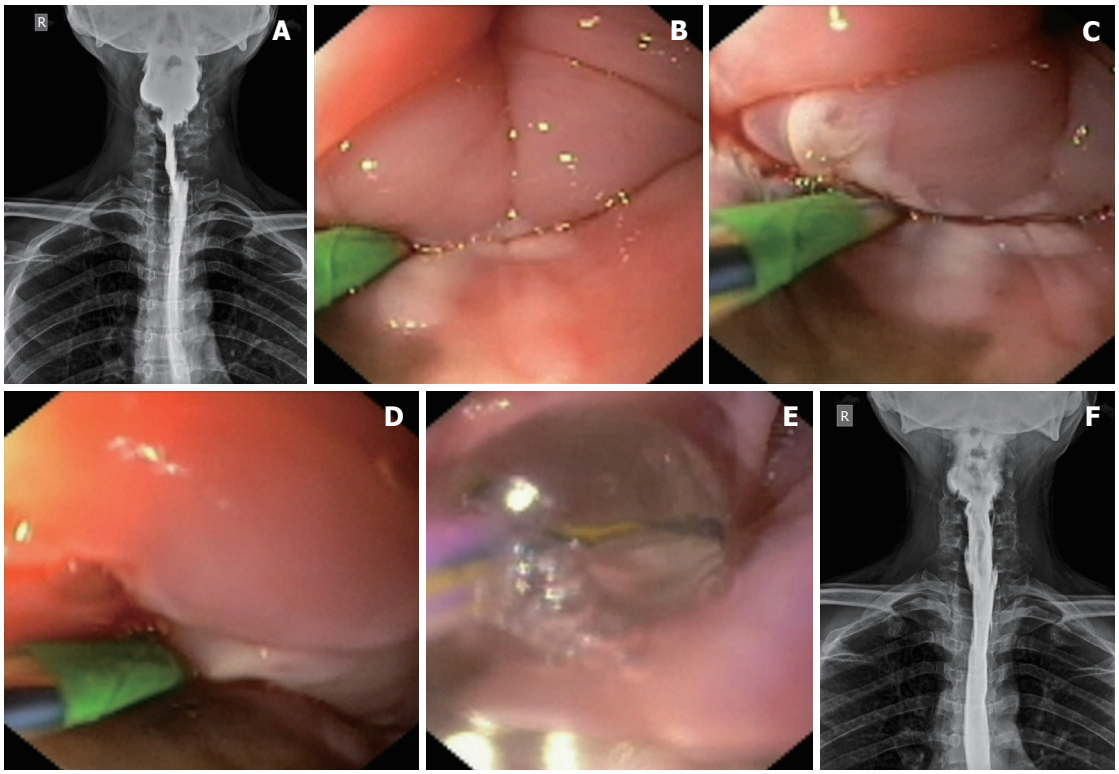

Figure 3 Near-total stricture in case 1 and its endoscopic management. A: The esophagogram after dilatation in case 1 showed a residual eccentric stricture, suggestive of persistent adhesions in the post-cricoid space and left piriform sinus; B-D: Serial endoscopic images of electroincision procedure in case 1, as the wire-guided sphincterotome was progressively moving towards the left pharyngeal wall after cutting the adhesions in the post-cricoid space and left piriform sinus; E: After electro-incision, a dilatation was given with the dilating balloon placed in the left piriform sinus; F: Follow-up esophagogram showing the completely opened-up stricture along its entire length.

oxygen supplementation *via* nasal prong and the careful monitoring of vital parameters. The oropharyngeal secretions were adequately suctioned to prevent aspiration and to gain a clear view. Intermittent suctioning of oropharyngeal secretions with a catheter was also performed by a nurse during the procedure. Once the minute opening was identified at the apex of a piriform sinus (Figure 2C, arrow), a 0.025-inch flexible guide-wire with a straight tip (Jagwire; Boston Scientific, Natick, MA, the United States) was passed across the stricture (Figure 2D). The correct placement of the guide-wire was confirmed fluoroscopically. Subsequently, an attempt was made to pass a 6-8 mm, wire-guided, through-the-scope (TTS) balloon dilator over the wire. When this was not possible, the stricture was defined as near-total.

Stricture dilatation: The near-total strictures were dilated using a co-axial diathermic dilator, followed by a balloon dilator. Under endoscopic guidance, a 10F co-axial diathermic dilator (Cysto-Gastro-Set, Endo-Flex, Voerde, Germany) was threaded over the guide-wire [taken within the channel of a therapeutic gastroscope (GIF1TQ140 or GIF1TQ160, Olympus, Tokyo, Japan)] to the proximal part of the stricture. At this point, an intermittent diathermy current (cut mode, 50W, ERBE electrosurgical unit, Tubingen, Germany) was applied in steps while the endoscopist gently pushed forward the diathermic dilator under fluoroscopic guidance (Video 1) and the assistant held the wire in traction. In this way, the whole stricture segment was traversed by the tip of the diathermic dilator. Subsequently, the diathermic dilator was removed and a 6-8 mm, wire-guided, TTS balloon (CRE; Boston Scientific, Natick, MA, the United States) was passed over the guide-wire to further dilate the strictured segment (Figure 2E, 2F). A nasogastric tube was placed to initiate feeding and subsequent dilatations were attempted every week in an incremental manner with the wire-guided balloon dilators (up to 14 mm).

The strictures in both cases were felt undilatable as the balloon dilators could not open up the adhesions in the post-cricoid space and in the blocked piriform sinus (Video 2). A repeat esophagogram was performed to evaluate the status of the residual stricture (Figure 3A). In both cases, the esophagogram showed (as expected) the passage of oral contrast from one piriform sinus, while the other piriform sinus was still blocked. Both cases were subsequently subjected to electroincision therapy using a wire-guided sphincterotome, as described below.

Electroincision therapy: The platelet count and coagulation parameters were checked before the

procedure. A flexible guide-wire was passed across the stricture into the stomach, and a sphincterotome (Ultratome XL, Boston Scientific, MA, the United States) was threaded over it such that the cutting-wire of the instrument faced the side of the blocked piriform sinus and few millimeters of the cutting-wire were left above the proximal aspect of the residual stricture. At this point, a current (Endocut I, effect 2, 60W, VIO 300D; ERBE, Tubingen, Germany) was applied in steps to cut the adhesions, beginning at the adhesioned post-cricoid space and slowly cutting towards the blocked piriform sinus until the lateral pharyngeal wall was encountered (Figure 3B-D; Video 3). Care was taken to cut along the line of the expected endoluminal space without hitting the anterior laryngeal structures or the posterior pharyngeal wall. The scope (along with sphincterotome) was also pushed distally through the electroincised piriform sinus to cut the deeper (distal) adhesions (of the proximal esophagus) under vision (shown in the last part of Video 3). Subsequently, a balloon dilator (12-15 mm) was inflated within the electroincised piriform sinus (Figure 3E) to disrupt any residual fibrotic strands, followed by the removal of both the wire and balloon.

The scope could now be easily pushed into the esophagus from both piriform sinuses. A careful evaluation of the hypopharynx, vocal cords and proximal esophagus was done to rule out any complication arising from the procedure. The patients were observed in the hospital until evening. They were kept nil per oral for 6 h and were given intravenous fluids and antibiotics. In the absence of any complication, they were discharged from the hospital the same evening. Repeat endoscopic evaluation (Video 4) and esophagography (Figure 3F) were performed after 2 wk to confirm the disappearance of the stricture. An ENT evaluation was also performed at this visit to rule out any injury to the laryngeal nerves during the procedure.

Risk of potential complications and their prevention

The dilatation and electroincision of GI strictures can potentially result in several complications, such as perforation, bleeding, pulmonary aspiration and pain. The standard measures used to prevent these complications have been elaborately discussed elsewhere[6] and were followed in this study. Besides the aforesaid complications, there is an additional concern while addressing hypopharyngeal strictures with the technique described above. As shown in Figure 4A, the laryngeal nerves and vessels lie submucosally in the anterior aspect of the piriform sinuses. The internal branch of the superior laryngeal nerve lies cranially (proximally), while the recurrent laryngeal nerve lies caudally (inferiorly). An injury to the former may result in anesthesia of the laryngeal mucous membrane as far inferiorly as the vocal cords. An injury to the recurrent laryngeal nerve may lead to ipsilateral vocal cord paralysis. Hence, as shown in Figure 4B, the line of electro-incision should stop several millimeters before reaching the anterior aspect of the piriform sinus.

RESULTS

The critical step was to pass the guide-wire across the stricture under combined endoscopic and fluoroscopic guidance. Because the strictures were very tight, this was a cumbersome step and required multiple attempts in both the cases. The guide-wire could not be passed in the first session in the first patient; the procedure was deferred for 3 d so that the tissue edema (because of multiple attempts) could resolve before a repeat attempt was made.

After the initial dilatation with the diathermy dilator and TTS balloon, the esophagograms showed residual eccentric stricture in both of the patients. Hence both of them were subjected to electro-incision. However, the distal esophageal stricture in case 2 was concentric (Figure 5) and hence was managed with dilatation alone (no electroincision was employed). There were no intra-procedural or post-procedural complications. The patients were followed up through regular outpatient department visits (every 3-4 mo) and various outcome measures were noted (Table 1). There was no recurrence of symptoms during the follow-up (22 mo in the first case and 14 mo in the second case). The body mass index improved in both of these patients after the endoscopic intervention.

DISCUSSION

The tight near-total corrosive stricture of the proximal esophagus with hypopharyngeal involvement is a uniquely challenging situation. Surgical intervention, the only viable management option to date, is associated with high morbidity and mortality. Minimally invasive therapeutic options, including endoscopic techniques, are an unmet yet highly desirable need for such difficult-to-treat patients. In this study, we evaluated the minimally invasive endoscopic management of near-total benign fibrotic strictures of the proximal esophagus involving the hypopharynx across the pharyngo-esophageal junction. Both patients were successfully treated using a novel approach: stricture dilatation (with a 10F co-axial diathermic dilator and TTS balloon) followed by the electroincision of residual adhesions at the hypopharyngeal base with a wire-guided sphincterotome. To the best of our knowledge, this report represents the tightest esophageal or hypopharyngeal strictures ever opened endoscopically and reported in the literature.

A diathermic dilator (with an 8.5F or 10F tip) was first used for cysto-gastrostomy or cysto-duodenostomy[7]. Subsequently, Kawakami *et al*[8] reported the successful management of severe biliary or pancreatic strictures using a 6F diathermic dilator. Siddappa *et al*[9] used a 6F diathermic dilator for negotiating near-total antropyloric corrosive strictures in 3 patients. The

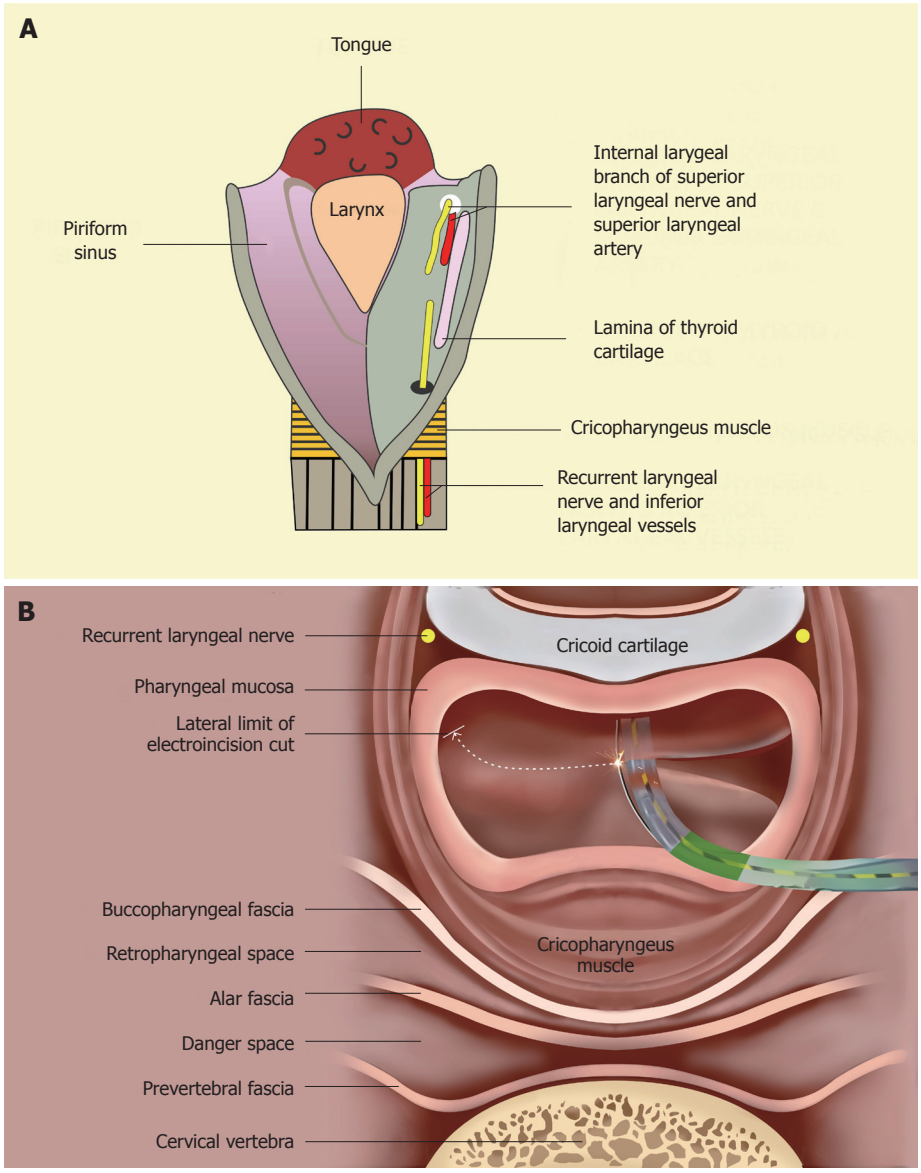

Figure 4 Anatomical considerations to prevent complications while performing the sphincterotome-assisted electroincision of the hypopharyngo-esophageal strictures. A: An opened posterior view of the hypopharynx showing the submucosal location of the nerves and vessels within the anterior aspect of piriform sinuses. The internal branch of the superior laryngeal nerve lies cranially (proximally) while the recurrent laryngeal nerve lies caudally (inferiorly). An injury to the former may result in anesthesia of the laryngeal mucous membrane as far inferiorly as the vocal cords. An injury to the recurrent laryngeal nerve may lead to ipsilateral vocal cord paralysis. These neuro-vascular structures are important to be protected during the electroincision; B: Cross-sectional view at the level of cricopharynx showing the electro-incision of adhesions with a wire-guided sphincterotome. The sphinterotome is progressively moved laterally towards the pharyngeal wall (along the curved dashed line) with its wire cutting the adhesions in the post-cricoid space and then in the left piriform sinus. Care should be taken to stop few millimetres away from the anterior aspect of piriform sinus to avoid damage to the recurrent laryngeal nerve lying submucosally in this region. Similarly, the internal laryngeal nerve and vessel lie at the same location (in a more cranial cross-section) and need to be protected.

present study is the first report on managing near-total esophageal or hypopharyngeal strictures using a diathermic dilator. In contrast to Siddappa *et al*[9], we used a 10F diathermic dilator (instead of a 6F size), as we believe that this is quite safe for GI tract strictures and that a larger diameter diathermic dilator ensures the easy performance of subsequent balloon dilatation. In our opinion, a 6F diathermic dilator is only to be preferred for strictures of thin-walled structures such as the pancreatic or bile ducts.

In both cases, dilatation (with a diathermic dilator followed by a balloon dilator) did not completely open up the stricture, especially the proximal part of the stricture. The residual adhesions obliterating the post-cricoid space and the apex of the contralateral piriform sinus needed to be addressed to prevent the recurrence of symptoms as well as the pooling of secretions (which may lead to aspiration pneumonitis). These adhesions were electroincised using a wire-guided sphincterotome. Both the endoscopic electroincision of strictures in the pharyngo-esophageal region as well as the use of the wire-guided sphincterotome for the electroincision of GI strictures are described for the first time in this report. The electroincision of short-

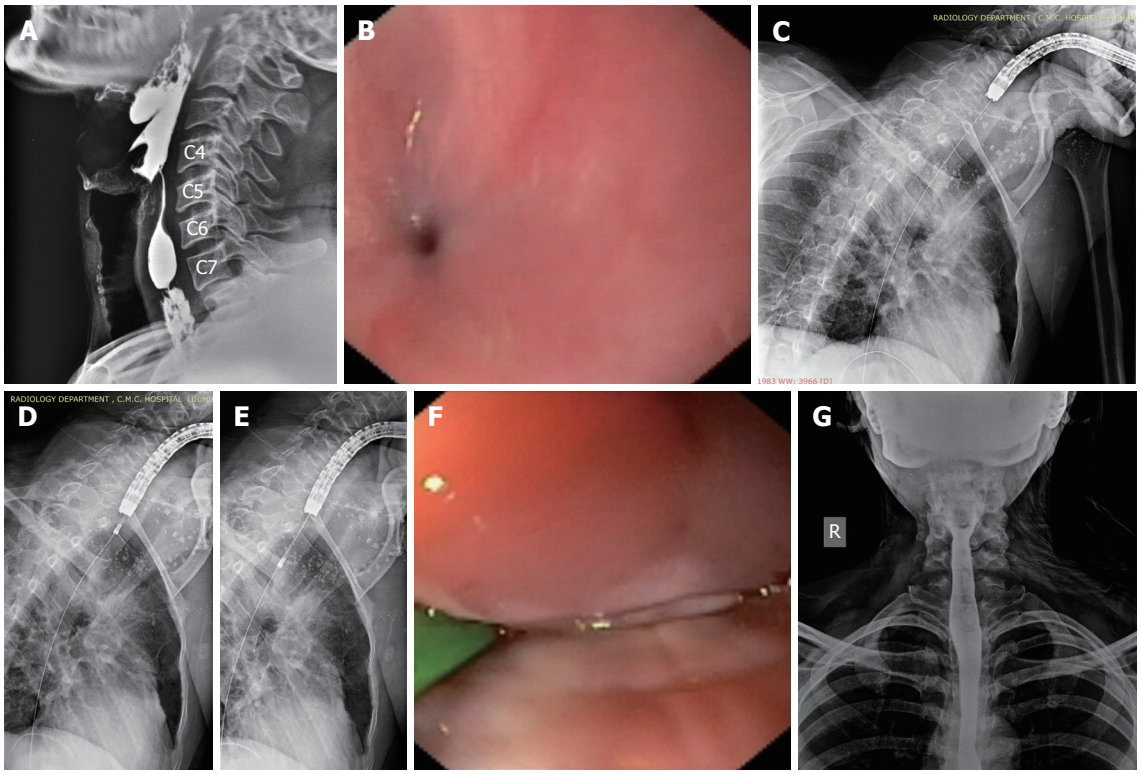

Figure 5 Near-total strictures in case 2 and their management. A: Lateral view of the esophagogram showing the 2 near-total strictures; B: Endoscopic view through the right piriform sinus showing the tiny opening of the proximal near-total stricture. C: A flexible guide-wire was successfully passed across both the strictures; D, E: A 10F diathermic dilator being passed over the guide-wire to dilate the strictures. This was followed by balloon dilatation; F: Endoscopic view of electroincision (with a wire-guided sphincterotome) of the residual adhesions in the proximal stricture; G: The follow-up esophagogram at 2 wk of the completion of endoscopic therapy.

segment benign strictures in the more distal locations of the GI tract using a needle-knife has been extensively described[10,11,12]. The electroincision of adhesions in the pharyngo-esophagus is more challenging because of the surrounding vital structures and the lack of adequate space and visualization. At this location, we preferred electroincision with the wire-guided sphincterotome over a free-hand incision with a needle-knife. The guide-wire helps to orient the sphincterotome so that the plane of incision takes the right vertical (cranio-caudal) path [the curve of the horizontal path (Figure 4B) being assessed while looking down from the unfibrosed proximal hypopharynx] without inadvertently injuring the undesired tissue, which is quite possible with a needle-knife. The guide-wire also provides better control over the movement of the cutting-wire than does a free-hand technique. More-over, the longer length of the cutting-wire of the sphincterotome helps in cutting the deeper (distal) adhesions as well, compared to the relatively small length of a needle-knife. Both of our patients required only 1 session of electroincision with the wire-guided sphincterotome, despite the relatively long length of the strictures (Table 1). Hordijk *et al*[10] previously showed that with a needle-knife, anastomotic strictures 1.5-5 cm in length required a mean of 3 electroincision sessions to become symptom-free. It remains to be seen based on future randomized prospective studies whether the sphincterotome actually has an edge over a needle-knife in reducing the number of electroincision sessions for longer strictures.

Strictures of the proximal esophagus with concomitant hypopharyngeal involvement are challenging to manage endoscopically and are associated with a high recurrence rate. Tharavej *et al*[13] reported a favorable outcome in only 1 out of 28 such patients. One possible explanation for such high failure rates could be the lack of instituting electroincision after dilatation. Dilatation alone is insufficient to completely open up the hypopharyngeal strictures due to the interposition of laryngeal structures at the medial aspect of the dilating balloon placed in one of the piriform sinuses during dilatation (Figure 6). In that study[13], the detailed information on the appearance of the hypopharyngeal strictures was not provided; therefore the length and severity of the single case of hypopharyngeal stricture that responded to dilatation alone are not clear.

For the anatomical reasons illustrated in Figure 4, injury to the laryngeal nerves (particularly the recurrent laryngeal nerve) remains a potential complication of the technique described in this report. In the literature, there are isolated reports of recurrent laryngeal nerve injury after endoscopic procedures[14,15]. The placement of a self-expanding metal stent in the upper esophagus led to bilateral nerve injury by causing persistent compression of the bilateral nerves in the tracheo-esophageal groove[14]. However, injury to this nerve in

Table 1 Demographic details, radiological and endoscopic findings, and outcomes of the 2 patients with near-total strictures of the pharyngo-esophagus treated by the flexible endoscopic technique

		Case 1	Case 2
Demographic details	Age/Sex	37/F	42/M
	BMI (kg/m^2) at presentation	13.2	15.6
	Acid consumed	Sulphuric acid	Nitric acid
	Time since acid was consumed	4 mo	11 mo
	No. of strictures on esophagogram	1	2
	Approximate length of stricture	3.5 cm	4 cm (proximal stricture) 5 mm (distal stricture)
	Near-total stricture communicated with which piriform sinus	Right piriform sinus	Right piriform sinus
	Concomitant gastric stricture	No	No
	Whether feeding jejunostomy was performed?	No	No
Endoscopic procedural details	Time taken for the passage of guide-wire across the stricture	First session: Failed Second session: 22 min	14 min
	Dilatation details		
	First balloon dilatation till	6 mm	6 mm
	No. of dilatations to reach 14 mm	3	4
	Residual stricture after dilatation on esophagogram	Yes	Proximal stricture: Yes Distal stricture: No
	Time taken for electro-incision	12 min	10 min
Primary outcome	Complete relief of dysphagia along with the resolution of stricture(s) on esophagogram and endoscopy, performed after 2 wk of full endoscopic therapy	Yes	Yes
Secondary outcomes	Intraprocedural complication	None	None
	Post-procedural complication	None	None
	Duration of the follow-up	22 mo	14 mo
	Improvement in activities after the procedure	Yes	Yes
	Recurrence of dysphagia during the follow-up or any need of additional therapy	No	No
	Any regurgitation episode during the follow-up	No	No
	Any aspiration episode during the follow-up	No	No
	BMI at last follow-up (kg/m^2)	21.6	23.8

BMI: Body mass index; F: female; M: Male.

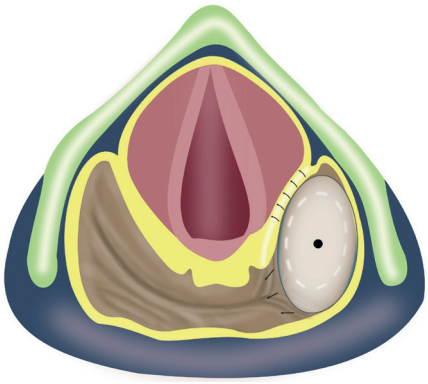

Figure 6 Graphical illustrations to depict the limitations of balloon dilatation for addressing the near-total hypopharyngeal strictures. As the hypopharyngeal stricture is dilated with the balloon placed in one of the piriform sinuses, there is an interposition of laryngeal structures on its medial aspect. The dilating balloon cannot reach the adhesions in the post-cricoid space and the contralateral piriform sinus, which remain undisrupted. Hence, electeroincision is required to completely open-up the stricture and to prevent the recurrence of symptoms.

the piriform sinus during dilatation is unlikely as there is only transient compression on the nerve for a few minutes. There is only one recent report of recurrent nerve injury in the piriform sinus after a bougie dilator (Savary Gillard dilator) was used[15]; the bougie dilator might have caused a longitudinal shearing force to avulse the mucosa of the piriform sinus and, subsequently, caused submucosal injury to the nerve. On the other hand, a balloon dilator only produces a transient radial force which should not avulse the mucosa, and nerve injury after balloon dilatation has never been reported, thus justifying the approach used by us to prevent injury to the laryngeal nerves, without leaving any residual stricture behind. The electro-incision cut was stopped a few millimeters before reaching the anterior aspect of the piriform sinus, and the remaining adhesions in this region were disrupted using a balloon dilator through the electroincised piriform sinus.

Traditionally, open surgical techniques had been the only viable management option for near-total hypopharyngo-esophageal strictures. However, surgery is associated with unacceptable morbidity and mortality. Wu *et al*[4] described the results of the surgical reconstruction of corrosive hypopharyngo-esophageal strictures in their retrospective series of 50 patients. The esophageal substitute was pulled up and anastomosed to the hypopharynx. One patient died intraoperatively and 8 patients (16%) had major early post-operative complications (leakage of the anastomosis, intestinal obstruction, obstruction of the esophageal substitute, graft failure and pneumonia). There were 10 major late complications: 6 had late stenosis of the hypopharyngeal anastomosis, 3 had intestinal obstruction and 1 had failure of the transplanted ileo-colon. Post-operatively, the swallow functions were unsatisfactory

Table 2 Comparison of the open surgical, rigid endoscopic and flexible endoscopic techniques for the management of the near-total hypopharyngeal strictures

	Surgery	Rigid Endoscopy	Flexible Endoscopy
Hospital admission	Required	Required	Not required
Performed by	Gastro-surgeons in the operation theatres	ENT surgeons in the operation theatres	Gastroenterologists or surgical endoscopists in the endoscopy suites
Hyper-extension of the patient's neck	Not required	Required	Not required
Type of anesthesia given	General anesthesia	General anesthesia	Conscious sedation
Anesthetic and procedural time	Longest	Long	Short
External incision over the neck or chest wall	External incision is given. This predisposes to post-operative complications like fistula, wound infection and hematoma formation	Not given	Not given
Concomitant esophageal cicatrisation	Can be tackled	Cannot be tackled	Can be tackled
Clinical recovery after the procedure	Slow	Intermediate	Quick
Morbidity and mortality associated with the technique	High	Low	Least
Contraindications	Elderly patients with comorbidities Severe malnutrition Inability to give general anesthesia	Short neck Retrognathia Inability to give general anesthesia	None
Experience with the procedure till date	Maximum	Limited	Limited

in 16% of the patients. The authors compared these results with another retrospective cohort of 102 patients of corrosive ingestion with an unstenosed hypopharynx who underwent esophageal substitute anastomosis with the cervical esophagus. The surgical outcomes in the 50 patients with hypopharyngeal involvement were significantly worse; on the other hand, among the patients with an unstenosed hypopharynx, only 6.8% (7/102) had major early complications and 93% (95/102) had normal swallow functions post-operatively.

In the past, short-segment cricopharyngeal strictures have also been managed by the endoscopic surgical techniques (rigid endoscopy) employed by ENT surgeons[16,17]. Similar to the endoscopic cricopharyngeal myotomy for Zenker's diverticulum, there are important differences in the management of cricopharyngeal strictures as well, using flexible versus rigid endoscopic techniques. The potential advantages of flexible endoscopy over rigid endoscopy in this context have been discussed in detail elsewhere[18]. Moreover, the rigid endoscopic technique requires expensive equipment (*e.g.*, a CO2 laser), while flexible endoscopy utilizes the routine accessories used for stricture dilatation and endoscopic retrograde cholangiopancreatography (ERCP). The post-operative recovery period is a few days to weeks in rigid endoscopy, while the patient can be discharged the same day after flexible endoscopic management. Lastly, ENT surgeons can only handle cricopharyngeal strictures; cases with adjacent esophageal cicatrisation (as was seen in both of our cases) would be best managed by gastroenterologists using the flexible endoscopic technique. Table 2 enumerates the important differences between the open surgical, rigid endoscopic and flexible endoscopic techniques for the management of hypopharyngeal strictures.

The main limitations of our study are the limited number of patients included and the retrospective nature of the study. Given the rarity of near-total strictures of the pharyngo-esophagus, a large sample size for conducting a prospective study is not expected. We have shown that the minimally invasive endoscopic management of this complex problem is feasible and can be offered to such patients, rather than blindly subjecting them to surgery.

ARTICLE HIGHLIGHTS

Research background

The ingestion of corrosives may lead to tight near-total strictures of the esophagus with concomitant involvement of the hypopharynx. This is an extremely challenging situation for the clinicians and there are limited treatment options for addressing such complex strictures.

Research motivation
The only viable management option for complex hypopharyngo-esophageal strictures is surgery. However, surgical interventions are associated with high morbidity and mortality. Moreover, patients may even be unfit for undergoing surgery due to extreme malnutrition. Because of these reasons, many patients ultimately succumb to their illness. The development of minimally invasive endoscopic techniques would be a highly desirable step to salvage this subset of patients.

Research objectives
In this study, we evaluated a novel flexible endoscopic technique for the management of tight near-total corrosive strictures of the esophagus with concomitant involvement of the hypopharynx.

Research methods
Two patients with near-total hypopharyngo-esophageal strictures were managed by the novel technique, under conscious sedation. A flexible 0.025-inch guide-wire was passed across the stricture, followed by dilatation of the stricture with a 10F coaxial diathermy and balloon dilators. The residual eccentric stricture was electroincised by a novel approach, using a wire-guided sphincterotome.

Research results
Both patients were successfully managed on an OPD basis with the complete relief of symptoms and resolution of strictures on endoscopy and an esophagogram. No complication was seen during or after the procedure. In the follow-up, patients remained symptom-free, along with a significant improvement in the body mass index.

Research conclusions
The complex hypopharyngo-esophageal strictures were successfully opened up with the novel flexible endoscopic technique, without any complications.

Research perspectives
We report a novel minimally invasive flexible endoscopic technique for addressing the tight near-total hypopharyngo-esophageal strictures. The technique is relatively simple, safe and effective with a durable response. But larger studies are required to validate the efficacy and safety of the technique across different endoscopic set-ups.

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EDITORIAL

Management of local recurrence after endoscopic resection of neoplastic colonic polyps

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Abstract

A proportion of neoplastic polyps are incompletely resected, resulting in local recurrence, especially after resection of large polyps or piecemeal resection. Local recurrences that develop after endoscopic resection of intramucosal neoplasms that lacked risk factors for lymph node metastasis or positive vertical margins are usually treated endoscopically. Endoscopic submucosal dissection (ESD) is indicated for local residual or recurrent early carcinomas after endoscopic resection. However, ESD for such recurrent lesions is technically difficult and is typically a lengthy procedure. Underwater endoscopic mucosal resection (UEMR), which was developed in 2012, is suitable for recurrent or residual lesions and reportedly achieves superior *en bloc* resection rates and endoscopic complete resection rates than conventional EMR. However, a large recurrent lesion is a negative independent predictor of successful *en bloc* resection and of complete endoscopic removal. We therefore perform UEMR for relatively small (≤ 10-15 mm) recurrent lesions and ESD for larger lesions.

Key words: Recurrence; Endoscopic management; Colon; Endoscopic submucosal dissection; Underwater endoscopic mucosal resection; Polyp; Endoscopic resection; Fibrosis; Non-lifting sign

Core tip: Local recurrences of neoplastic colonic polyps can occur, especially after resection of large polyps or piecemeal resection. Local recurrences that develop after endoscopic resection of intramucosal neoplasms that lacked risk factors for lymph node metastasis or positive vertical margins are usually treated endoscopically. We perform underwater endoscopic mucosal resection for relatively small (≤ 10-15 mm) recurrent lesions and endoscopic submucosal dissection for larger lesions.

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INTRODUCTION

Adenomatous polyps are the commonest neoplasms found during colorectal cancer screening[1]. Detection and removal of these cancer precursors may prevent many cancers and reduce mortality[2]. However, a proportion of neoplastic polyps are incompletely resected[3], resulting in local recurrence, especially after resection of large polyps (≥ 20 mm), in 4.3% to 36.7% of cases[4-10]. Not only size[4,6,8-10], but also piecemeal resection[7,9-11], histology of adenoma (compared with serrated polyp)[5,10], and intraprocedural bleeding[6,10] are also reportedly risk factors for local recurrence. A systematic review found that local recurrence after endoscopic mucosal resection (EMR) of non-pedunculated colorectal lesions occurs in 3% of *en bloc* resections and 20% of piecemeal resections; more than 90% of recurrences are detected 6 mo after EMR[12]. Periodic inspection by colonoscopy is desirable for early detection of local residual tumors/recurrences, and endoscopic management measures being suitable for many such lesions that are detected early[13]. The European Society of Gastrointestinal Endoscopy guideline recommends endoscopic follow-up within 6 mo of piecemeal resection of adenomas larger than 10 mm[14]. Local recurrences that develop after endoscopic resection of intramucosal neoplasms that lacked risk factors for lymph node metastasis or positive vertical margins are usually treated endoscopically. Here we review and summarize the management of local recurrence after endoscopic resection.

MANAGEMENT OF LOCAL RECURRENCE AFTER ENDOSCOPIC RESECTION

Several groups have reported their management of local recurrences. Hotta *et al*[11] reported performing additional endoscopic resection in 32 of 34 recurrent lesions (94%), the remaining two patients (6%) undergoing additional surgery. In a multicenter prospective study of 1000 consecutive wide-field EMRs, 93% (135 of 145) of local recurrences were successfully resected endoscopically, the remaining 10 being referred for surgery[6]. Knabe *et al*[7] reported a prospective two-center study of 243 consecutive patients with 252 adenomas resected endoscopically. Seventy-seven residual tumors and recurrences were all treated by endoscopic resection and/or argon plasma coagulation. Sakamoto *et al*[15] have reported a retrospective study of 60 consecutive patients with locally recurrent or residual tumors after endoscopic resection. Of 69 lesions in 60 patients, 67 were treated endoscopically, whereas two required surgical treatment. *En bloc* resection rates were 39% (23/58) with EMR (39%) and 56% (5/9) with endoscopic submucosal dissection (ESD)[15].

According to the Japan Gastroenterological Endoscopy Society guidelines for colorectal ESD/EMR[13], ESD (Figure 1) is indicated for local residual or recurrent early carcinomas after endoscopic resection. Although most local recurrences can be treated endoscopically, additional endoscopic resection is technically challenging because of severe fibrosis at the original resection site because such fibrosis results in the non-lifting sign with submucosal fluid injection. Thus, ESD for such recurrences is technically difficult and typically a lengthy procedure.

Underwater EMR (UEMR) was developed and described by Binmoeller *et al*[16] in 2012. In this procedure, air is evacuated from the affected segment of lumen and water infused until the lumen is complete full, at which stage hot snare polypectomy is performed without submucosal injection. This procedure is reportedly effective for resecting large polyps[16,17]. It is also suitable for recurrent or residual lesions. Kim *et al*[18] reported a retrospective, cross-sectional study of patients with recurrent adenoma after piecemeal EMR of colorectal laterally spreading tumor (≥ 2 cm). The *en bloc* resection rate (47% *vs* 16%, $P = 0.002$) and complete resection rate (89% *vs* 32%, $P < 0.001$) were significantly higher in the UEMR group ($n = 36$) than that of the conventional EMR ($n = 44$)[18]. Argon plasma coagulation of visible residual lesions during the salvage procedure was less frequently required in the UEMR than the EMR group (11% *vs* 66%, $P < 0.001$). The recurrence rate at follow-up colonoscopy was significantly lower in the UEMR group (10% *vs* 39%, $P = 0.02$). In this trial, UEMR was an independent predictor of *en bloc* resection and complete resection, whereas a large recurrent lesion is a negative independent predictor of successful *en bloc* resection and complete endoscopic removal. We therefore perform UEMR for relatively small (≤ 10-15 mm) recurrent lesions (Figure 2) and ESD for larger lesions.

Even with the technical advances of ESD and development of UEMR, endoscopic treatment of recurrent lesions is still challenging. We therefore recommend precise diagnosis of the extent of naïve lesions by careful examination using indigo carmine and/or narrow band imaging endoscopy. We also recommend close follow-up after

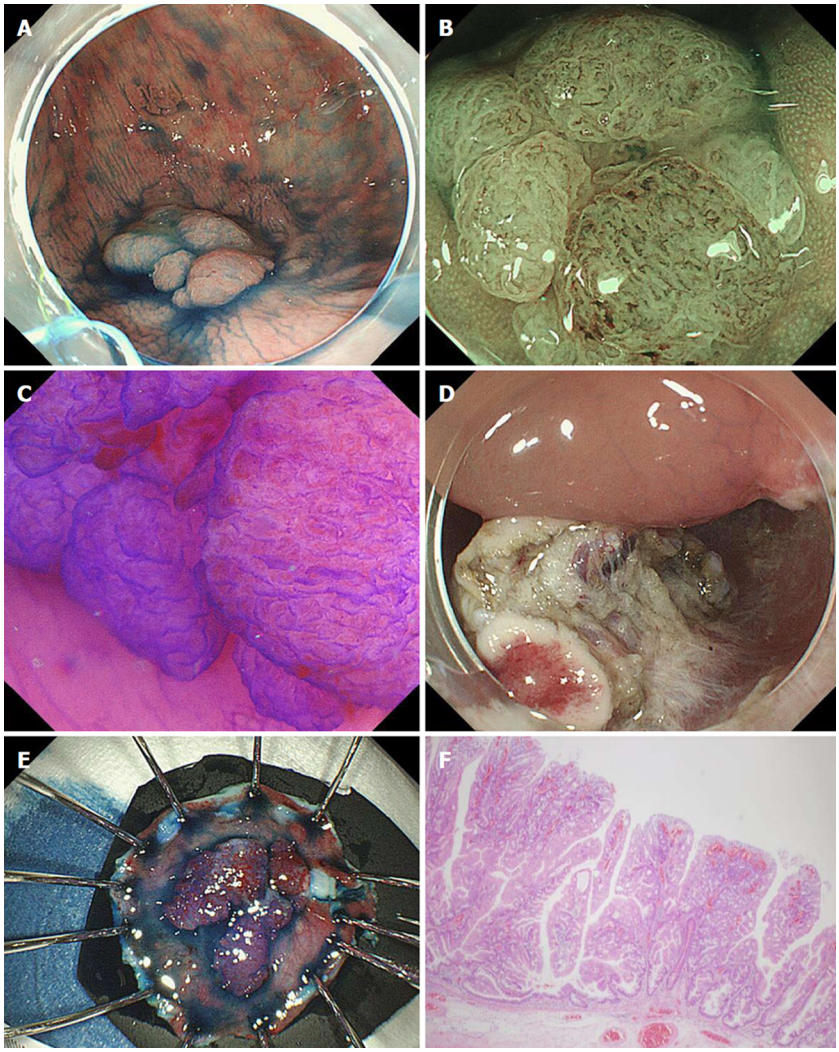

Figure 1 Endoscopic submucosal dissection of recurrent lesion in the cecum. A: A Local recurrence (laterally spreading tumor, granular type) was identified in the cecum 18 mo after piecemeal endoscopic mucosal resection; B: The Japan Narrow-band imaging Expert Team classification was type 2B[19]; C: Kudo's pit pattern was V_I[20]. The laterally spreading tumor was diagnosed as an intramucosal lesion and ESD performed; D, E: Although there was severe fibrosis in the submucosal layer, *en bloc* resection was achieved; F: The pathological diagnosis was adenocarcinoma arising from a sessile serrated adenoma/polyp, type 0-IIa, 16 × 15 mm, pTis, pHM0, pVM0; ER0, Cur EA; pap > tub1, ly0, v0.

piecemeal resection or resection of large polyps.

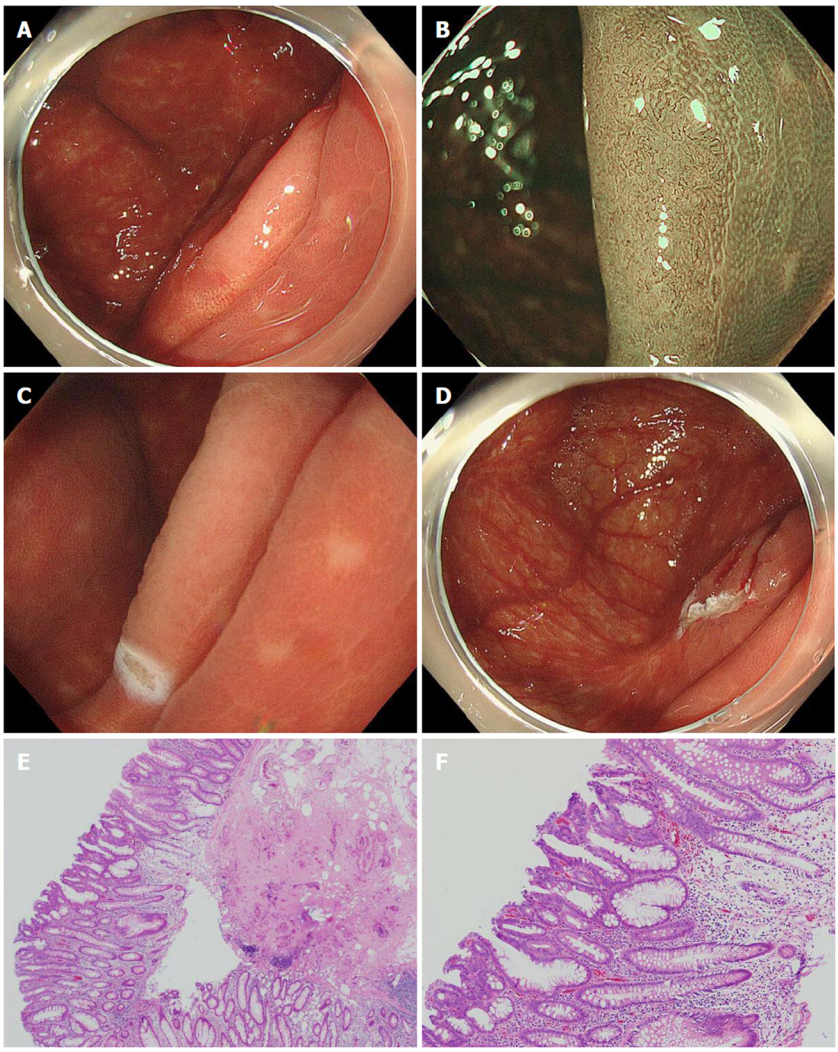

Figure 2 Underwater endoscopic mucosal resection of a recurrent lesion in the cecum. A: A local recurrence was identified in the cecum 12 mo after *en bloc* endoscopic mucosal resection; B: Magnified endoscopy with narrow band imaging revealed Japan Narrow-band imaging Expert Team classification type 2A; C: Underwater endoscopic mucosal resection was performed after marking; D: Complete resection was achieved. E, F: The pathological diagnosis was low grade adenoma.

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MINIREVIEWS

Long term oncological outcome of laparoscopic techniques in pancreatic cancer

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Abstract

The laparoscopic technique in distal pancreatic resection (LDP) has been widely accepted, and outcome data support the hypothesis that survival is improved, partly due to improved postoperative safety and recovery, thus optimizing treatment with adjuvant chemotherapy. But laparoscopic pancreaticoduodenectomy (LPD or Whipple-procedures) has spread more slowly, due to the complexity of the procedure. Surgical safety has been a problem in hospitals with low patient volume, resulting in raised postoperative mortality, requiring careful monitoring of outcome during the surgical learning curve. Robotic assistance is expected to improve surgical safety, but data on long term oncological outcome of laparoscopic Whipple procedures with or without robotic assistance is scarce. Future research should still focus surgical safety, but most importantly long term outcome, recorded as recurrence at maximal follow up or - at best - overall long term survival (OS). Available data show median survival above 2.5 years, five year OS more than 30% after LDP even in series with suboptimal adjuvant chemotherapy. Also after LPD, long term survival is reported equal to or longer than open resection. However, surgical safety during the learning curve of LPD is a problem, which hopefully can be facilitated by robotic assistance. Patient reported outcome should also be an endpoint in future trials, including patients with pancreatic ductal adenocarcinoma.

Key words: Chemotherapy; Endpoint; Imaging; Laparoscopic surgery; Long term outcome; Overall survival; Pancreatic cancer; Robotic assistance

Core tip: Laparoscopic techniques have profoundly altered oncological gastrointestinal surgery, also resectional treatment of pancreatic ductal adenocarcinoma. Long term outcome of distal resections has been gradually improved. Median survival is more than 2.5 years, five year overall survival above 30%, whereas outcome of laparoscopic

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pancreaticoduodenectomy needs further evaluation before the technique can be widespread. It is an open question how wide this spread ought to be, but robotic assistance is expected to improve surgical safety.

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INTRODUCTION

Improved survival after laparoscopic resection of gastrointestinal carcinoma was expected after elimination of the initial failures in surgical performance during the nineties. A randomized controlled trial (RCT) from Barcelona[1], comparing survival after laparoscopic and open colectomy (n = 219) supported this concept. But subsequent multicenter RCTs with comprehensive patient numbers could not verify any survival difference[2]. In patients with ductal pancreatic adenocarcinoma (PDAC), no RCT comparing long term outcome of laparoscopic and open distal resection was identified in the Cochrane review 2016[3]. In 2017, a small series from India was published with shorter hospital stay after laparoscopic resection[4]. Nevertheless, laparoscopic distal pancreatectomy (LDP) has become a widespread technique, and selection of relevant clinical parameters for assessment of long term oncological outcome is ever more underlined[5]. Also increasing numbers of laparoscopic pancreaticoduodenectomy (LPD/Whipple procedures) have been reported with good outcome[6], and oncological advantages over an open approach have been suggested[7].

The clinical benefit of adjuvant chemotherapy after open resectional surgery in pancreatic cancer (PC) patients is well documented[8,9], whereas the question of upfront surgery *vs* neoadjuvant chemotherapy is unsettled. These questions have never been investigated, focusing only laparoscopically operated patients, but fair rationales indicate that evidence generated from PC patients operated openly, is transferable to laparoscopic practice. This minireview updates current evidence on long term oncological outcome of laparoscopic resection combined with applied chemotherapy in PDAC patients. The intention of the analysis is first to improve selection of endpoints in future clinical trials, second to guide the choices of surgical methodological development.

Methods (search strategy and data management)

Search in PubMed was performed with the key words: PC, combined with chemotherapy, laparoscopy, morbidity, outcome, safety, survival. Reports were selected, based on publication date and comprehended internal validity in each paper. Cochrane reviews, meta-analyses and review articles, relevant to the scope of this review were prioritized. Data on long term survival was particularly focused. Core information from the most relevant publications was selected for presentation in two summary tables.

DISTAL RESECTIONS

The laparoscopic technique was introduced in distal resections during the nineties, concurrent with ongoing diagnostic improvements generated from increasing use of abdominal CT, MRI and ultrasound examination. Concomitantly, awareness of the malignancy potential of mucinous cysts[10] enables surgical removal of premalignant tumors/early invasive carcinoma, thus improving postoperative survival after any surgical technique. In the first report from our department on 50 PDAC patients, undergoing LDP[11], five year survival was above 30%, which was very much better than in our previous series, obviously due to earlier diagnosis, but the early skepticism aligned with laparoscopic techniques in PDAC patients was opposed by those data. In 2012, Mitchem, Strasberg *et al*[12] published a modified open technique for resection of adenocarcinoma of the body/tail of the pancreas; the Radical Antegrade Modular Pancreaticosplenectomy Procedure (RAMPS), underlining new technical aspects, including the necessity of removal also of the left adrenal gland in numerous cases; "posterior RAMPS". In 47 patients, operated by the RAMPS

technique, median postoperative survival was 26 mo, 5 year overall actuarial survival (OS) 35.5%, mean lymph node count was 18 and rate of R0 resection (free margin) 81%. Survival in the 50 PDAC patients, operated with LDP in our department, was similar but lymph node count in our specimens was significantly lower. This observation initiated investigation of the putative impact on lymph node count of improved pathology examination, focusing specimens from patients undergoing LDP during ten years (January 2007-January 2017). The lymph node count and the number of positive glands increased significantly when specimens underwent a strictly, standardized examination[13]. Accordingly, comparison of lymph node count in the specimens from different centers is associated with significant uncertainty, thus also comparison of oncological outcome of surgical methods, based on lymph node count. Also the rate of R0 resections is an unsafe oncological quality indicator, first because of various R0 definitions[14,15], second because neoadjuvant chemotherapy is used increasingly and R0 status has not been clearly defined in this situation. Due to spot wise death of tumor tissue during chemotherapy in PDAC, the R0 concept must be redefined. Overall survival/cancer related death rate are the most appropriate clinical parameters for evaluation of long term oncological outcome of resectional surgical methods, subsidiary, recurrence rate at maximal follow up.

In a Pan-European, retrospective study (DIPLOMA), oncological outcome was compared between LDP and open distal pancreatectomy (ODP). Among 1212 patients, operated from 2007-2015 in 34 centers, distributed between 11 countries, propensity score matching was possible in 340. Postoperative survival was median 31 and 28 mo after ODP and LDP respectively[16]. Data registration was not standardized between the participating 34 centers, and the uncertainty of these data is substantial. In another recent report from two centers (Oslo/Norway and Seoul/South Korea) who standardized their registration, 207 patients with histologically confirmed PDAC underwent LDP from 2002-2016. Median overall and recurrence-free survival were 32 and 16 mo, five year OS and recurrence-free survival was 38, 2% and 35, 9% respectively[17]. Adjuvant chemotherapy was given according to national guidelines in Norway and Korea during the inclusion period, which later has been shown to be suboptimal, as the ESPAC 4 study documented improved survival of Gemcitabine plus Capecitabine[9]. Accordingly, even better long term oncological outcome of LDP is probably achievable, when the procedure is combined with the best adjuvant regimen. These data are in line with comparative studies from single centers in Asia. Shin *et al*[18] compared median OS and recurrence rate at maximal follow-up in PDAC patients, 70 operated with LDP, 80 ODP between December 2006 and August 2013. Five year OS was 32.5% *vs* 27.6%, recurrence after maximal follow-up was found in 50% *vs* 60%, respectively, but there was no statistically significant difference after propensity score matching. Hu *et al*[19] reported recurrence after maximal follow-up in 18% after LDP *vs* 48% after ODP, but total patient number was only 34, and hence no significant difference. In a Cochrane review 2016[3], the authors conclude that short time outcome (hospital stay, recovery, postoperative morbidity, *etc*.) seems improved after LDP (medium strong evidence), whereas evidence favoring better long term oncological outcome is still weak.

PANCREATICODUODENECTOMY (WHIPPLE PROCEDURES)

The first international State-of-the-Art conference on Minimally Invasive Pancreatic Resection took place in Sao Paulo, Brazil on April 20th, 2016, and a comprehensive summary of the proceedings have been published[20]. A systematic review on best-evidence of outcome after LPD identified 582 publications, 26 comparative studies[21]. Information from the National Cancer Data Base (NCDB) comparing short term outcome of LPD with open pancreaticoduodenectomy (OPD) describes 4421 patients, operated 2010-2011; 4037 (91%) underwent OPD, 384 (9%) LPD, and no difference was found in 30 day mortality, 5.2% *vs* 3.7% respectively[22]. This report gives no information on long term oncological outcome. Another paper based on the Nationwide Inpatient Sample Database identified 15574 Whipple procedures performed from 2000-2010; 681 of these (4.4%) laparoscopically[23]. The main conclusion is that even during the learning curve of laparoscopic surgeons, safety seems acceptable, short term outcome is equal or better than OPD, but no information on long term oncological outcome is given. A report from the Mayo Clinic on outcome in 108 patients after LPD, compared to 214 after OPD found no significant survival difference[7], but delay of recovery due to postoperative morbidity resulted of no adjuvant chemotherapy in 12% after OPD *vs* 4% after LPD (P = 0.04). However, at a national level, this difference could not be verified, in a report from NCDB in 7967 subjects[24]. Kendrick[21] mentions number of lymph nodes retrieved and margin status

as relevant endpoint parameters for assessment for oncological outcome and lists five publications with this information, but only two of these reports have information on local recurrence and survival at the time of maximal follow up. A comparative study from France[25], gives only data on short term outcome, but in a recent combined report from the United States and France, favorable survival was found after LPD[26]. After propensity score matching median OS was 35.5 mo after LPD *vs* 29.6 after OPD; 1-, 3 and 5-year survival was 80.5% *vs* 49.2%, 77.7% *vs* 39.7%, and 46.4% *vs* 30% respectively. However, a recent metaanalysis shows that the immediate risk of postoperative morbidity may influence OS, as introduction of LPD in hospitals with low patient volume, resulted in more than doubling of postoperative mortality, 7.5% *vs* 3.4%[27]. Also a Pan European report from 14 centers having performed more than ten LPD, found increased morbidity after minimally invasive procedures[28]. All centers should obviously not introduce this procedure. Information from core papers on oncological long term outcome of distal resections is put together in Table 1, pancreaticoduodenectomy in Table 2.

ROBOTIC ASSISTANCE

Robotic surgery was first utilized for pancreatic resection in 2003[29], and is becoming increasingly utilized[30], even though the number of operated patients is still limited. Robotic assistance in distal resections has been evaluated in a metaanalysis from 2016[31], reporting nine comparative studies with all together 246 robotic *vs* 391 laparoscopic procedures. Short term outcome in terms of postoperative morbidity, hospital stay and recovery were similar. An updated metaanalysis 2017[32], including 813 patients, verified this but conversion rate was lower in RDP than LDP. Information about long term oncological outcome is missing in both these papers, but is reported in two small series: In ten PDAC patients median OS was 15, range 7-29 mo[33], in 72 other patients[34] mean OS was 15.6 mo ± 5.8 mo, and only 26% of the latter cases received adjuvant chemotherapy, *i.e.*, there is a potential for further increased survival.

Safety aspects

The complexity of Whipple procedures and the resulting risk of postoperative severe morbidity and mortality are well known. Robot-assistance may possibly result in more precise dissection and safer construction of anastomoses. Institutions gaining experience with robot assisted pancreaticoduodenectomy (RPD)[31], underline that standardization of key element of the learning curve of RPD is mandatory[35]. A good model for this has been published from Pittsburgh, where quality outcomes of the first consecutive 200 RPD procedures have been monitored in subgroups of 20 cases, reviewing the learning curve during the implementation phase[36]. This program was developed also to adjust the introduction of a robotic platform to the ongoing paradigm shift in healthcare; a move from fees for service to payment for performance, thus achieving better value from available resources[37]. This is particularly relevant for RPD-procedures, as a major downside is high costs. Nevertheless, a recent comparative study found comparable surgical and oncological safety, median OS was 23 mo *vs* 22 mo after RDP and ODP respectively, and even costs were equal[38]. The robotic platform is expected to improve recovery significantly after major pancreatic surgery, thus obtaining better patient outcome/satisfaction for used resources.

ADJUVANT AND NEOADJUVANT CHEMOTHERAPY

Adjuvant chemotherapy has been utilized in PC patients for more than twenty years, and selection of regimens is continuously improving, based on well accomplished RCTs. In Scandinavia, Gemcitabine plus capecitabine have been standard of care in unselected cases after the ESPAC 4 trial[9], but it has already been documented that Folfirinox is more potent[39]. Selection of patients tolerating regimens with significant toxicity leads to five year survival far above 30% after open pancreatic surgery - this probably applies also for laparoscopic techniques. So far, no prospective trials have been conducted, investigating these questions. Current knowledge stem from observational studies of patients, receiving regimens which were inferior to the present standard of care. Accordingly, a reasonable presumption is that there is room for further improvement of postoperative survival after laparoscopic pancreatic surgery, when combined with updated adjuvant treatment.

Neoadjuvant chemotherapy attracts increasing interest, and numerous RCTs are

Table 1 Core information on distal pancreatic resection in pancreatic cancer patients

Ref.	No. of patients reported	Study	Median survival (mo)	
			Open	Laparoscopic
Van Hilst *et al*[16], 2017	680	Comparative, 34 centers (propensity score matching) retrospective	28	31
Mitchem *et al*[12], 2012	47	Non comparative, single center retrospective	26	NA
Sahakyan *et al*[17], 2017	207	Non comparative, two centers retrospective	NA	32
Shin *et al*[18], 2015	150	Comparative, single center (propensity score matching) retrospective	29	33
Grossman *et al*[40], 2016	78	Non comparative, single center retrospective	25	NA

NA: Not applicable.

ongoing, including resectable and borderline resectable patients undergoing open pancreatic resections. Also considerations on putative benefit and/or harm of neoadjuvant treatment algorithms in laparoscopic pancreatic surgery have to await results from these trials.

DISCUSSION

Five year OS above 30%-35% after LDP has recently been reported from numerous centers, illustrating that increasing evidence show good long term oncological outcome. Comparison with outcome of ODP favors the laparoscopic technique, even though data from RCTs are still lacking. In recent reports, five year OS is 25% after the RAMPS procedure[40,41]. Patients with PDAC in the pancreatic body or tail should therefore be offered laparoscopic resection if the HepatoPancreaticoBiliary (HPB) center possesses the required expertize. But pancreatic head tumors are still resected openly in most HPB-centers, as the role of LPD is not at all clear and long term oncological outcome is mostly unknown. The international State-of-the-Art conference on Minimally Invasive Pancreatic Resection in 2016 concluded that the small number of comparative studies of LPD *vs* OPD is also of low quality, Newcastle-Ottawa score (NOS) < 6[21]. This score is a risk of bias assessment tool for observational studies[42]. During the State-of-the-Art conference 2016, a specific session evaluated what would be the future most essential scientific contributions in this field, underlining that numerous important questions need valid answers[43]. Even though RCT is the reference standard for clinical comparative research according to the traditional pyramid of evidence level, the applicability of this study design is limited and numerous clinical questions cannot be solved by any randomized trial. A critical question in any trial is selection of primary and secondary outcome variables (clinical endpoints). The importance of adequate choice of endpoint is clearly illustrated by finalized or ongoing RCTs comparing outcome of open and laparoscopic techniques in pancreatic surgery. The PLOT trial[4] randomized 60 Whipple operated patients, focusing hospital stay, and found median 13 d after OPD *vs* 7 d after LPD, $P = 0.001$, which is relevant and interesting, but marginally important. In the Netherlands, the LEOPARD 1 study[44] includes patients in need of distal resection, randomizing between open and laparoscopic technique with time to functional recovery as primary endpoint. Similarly, the LEOPARD 2 studies[45] randomize upfront resectable patients between OPD and LPD with the same endpoint. These studies represent relevant clinical research, and valid answers might be generated, but it is already well known from numerous prospective observational studies that LPD is associated with rapid recovery in most centers, and it would be more interesting to investigate whether or not robotic assistance could further improve recovery, safety and particularly long term OS.

In trials focusing outcome of any Whipple procedures focus on safety aspects, especially postoperative mortality, is critically important. This is emphasized in comprehensive registry studies[22] and single center reports[46]. In the State-of-the-Art conference 2016[21], an important "take home messages" to HPB-centers on their way to introduce LPD was; "Surgeons should assess their level of commitment with a clear understanding of the procedure complexity, expected learning curve, and requirements to achieve proficiency". This message is further underlined by recent information from the Leopard 2 study. The data monitoring board has recommended early termination of the trial because of too high 90-d complication-related mortality

Table 2 Core information on pancreaticoduodenectomy/Whipple-procedures in pancreatic cancer patients

Ref.	No. of patients reported	Study	Overall survival		
			Open	Laparoscopic	*P* value
Croome *et al*[7], 2014	322 LPD 108 OPD214	Comparative, retrospective single center	Median 21.8 mo	Median 25.3 mo	0.22
Nussbaum *et al*[24], 2016	7967 LPD 1191 OPD 6776	Comparative Registry (NCDB) Retrospective	Two year 47%	Two year 43%	NS
Conrad *et al*[26], 2017	65 LPD 40 OPD 25	Comparative, retrospective two centers	Median 29.6 mo	Median 35.5 mo	NS

LPD: Laparoscopic pancreaticoduodenectomy; OPD: Open pancreaticoduodenectomy; NCDB: National Cancer Data Base; NS: Not significant.

in the laparoscopic arm, *i.e*., 10% *vs* 2% in the open arm[47] .

The implementation of laparoscopic techniques in oncological surgery has put focus on the traditional pyramid of evidence level, raising the question: how should surgical methods be developed, evaluated and broadened? Both internal and external validity of published investigations are highly relevant, as prospective data, documenting increased survival will probably be reproducible in the publishing center. However, the same outcome data cannot be presupposed transferable to other centers if core conditions differ. Methodological considerations should also be developed across surgical subspecialties, illustrated by a recent report on 10597 patients with lung cancer stage 1, included in a propensity match study, comparing long term oncological outcome of minimally invasive (MI) and open lung resection[48]. Four year survival was 68.6% after MI procedures *vs* 64.8% after open lung resection (P = 0.003). For patients with lung cancer, these data is a significant contribution to evidence based guidance of surgical methodological development.

Finally, the lack of patient reported outcome (PRO) in the literature is a major problem, raising the uncertainty concerning short- and long term outcome in patients with PDAC. There are numerous explanations for the scarcity of data on health related quality of life (HQoL) in this group of patients. One important problem is that disease specific QoL measures are comprehensive, including irrelevant questions which result in low response rates from patients included in prospective trials[49]. This problem has recently been solved by development of the PC Disease Impact (PACADI) score[50]. This is a brief, disease specific measure, and item selection was based on the patients' priorities of which dimensions of PRO had greatest impact on their everyday QoL. In our opinion, every trial evaluating laparoscopic techniques in PC patients should also include PRO as an endpoint. Prospective comparative studies with long follow-up of OS as primary outcome parameter, longitudinally recorded PRO as secondary endpoint, are strongly warranted.

CONCLUSION

The potential for clinical benefit from laparoscopic techniques in pancreatic surgery is great, but available evidence is still limited. Outcome of LPD and RPD is associated with great uncertainty. For all Whipple procedures, surgical safety is a particular concern, which probably can be improved by robotic assistance.

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MINIREVIEWS

Endoscopic evaluation of immunotherapy-induced gastrointestinal toxicity

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Abstract

Immunotherapy is any treatment aimed at boosting or enhancing the immune system. It includes a wide range of options, from vaccines to treatment for conditions such as allergy and cancer. In the case of cancer, unlike other available treatments, immunotherapy is not aimed at destroying the tumor cells but at stimulating the patient's immune system so that it attacks the tumor. In cancer, immunotherapy provides a series of advantages. Nevertheless, immunotherapy administered for treatment of cancer is associated with immune-mediated enterocolitis. Colitis mediated by monoclonal anti-cytotoxic T lymphocyte–associated antigen 4 and to programmed cell death protein 1 and its ligand PDL1 shares characteristics with chronic inflammatory bowel disease (IBD), and similar findings have been reported for both the endoscopy images and the segment involved. The most frequent lesions on endoscopy are ulcer and erythema, and the most frequently affected site is the sigmoid colon. A segmental pattern has been reported to be slightly more frequent than a continuous pattern. In addition, upper gastrointestinal lesions have been reported in up to half of patients, with the most frequent findings being gastritis and erosive duodenitis. As is the case in IBD, systemic corticosteroids and immunosuppressive treatment (anti-TNF agents) are the approaches used in patients with a more unfavorable progression. Immunotherapy must be suspended completely in some cases.

Key words: Enterocolitis; Ipilimumab; Immunotherapy; Immune-related adverse event; Nivolumab; Toxicity; Endoscopy

Core tip: Widespread use of immunotherapy in various types of cancer has led to reports of new associated adverse effects resulting from increased stimulation of the immune system, which can confuse the body's own tissues and organs with foreign matter, thus leading it to attack the body's healthy tissue. The most frequent immune-mediated adverse effects include asthenia, general malaise, fever, gastrointestinal toxicity (abdominal pain, diarrhea, and colitis), cutaneous toxicity, hypothyroidism and

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hepatitis. This review of the endoscopic evaluation of immunotherapy-induced toxicity presents the most typical endoscopic images, the differential diagnosis based on these images, and the initial management.

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WHAT DO WE UNDERSTAND BY THE TERM "IMMUNOTHERAPY"?

Immunotherapy is any treatment aimed at boosting or enhancing the immune system. It includes a wide range of options, from vaccines to treatment for conditions such as allergy and cancer. In the case of cancer, unlike other available treatments, immunotherapy is not aimed at destroying the tumor cells but at stimulating the patient's immune system so that it attacks the tumor. In cancer, immunotherapy provides a series of advantages, such as targeted treatment, which only acts on tumor cells without damaging healthy cells, and immunological memory, which can subsequently be reactivated to recognize and attack the tumor once the immune system is stimulated. Immunotherapy is also subject to disadvantages, such as the time necessary for it to take effect-the immune response is not immediate but gradual- and the associated adverse effects. There are 2 main types of immunotherapy: Specific immunotherapy, which causes a response to a specific cell or antigen and includes vaccines and adaptive cell therapy; and nonspecific immunotherapy, which is aimed at stimulating the whole immune system and includes cytokines and regulatory proteins such as antibodies to cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) or the programmed cell death protein 1 and its ligand PDL1 (PD1/PDL1) pathway. Also of interest are monoclonal antibodies, which are included in another group, known as passive immunotherapy, and comprise molecules designed to recognize tumor cells or substances that the tumor needs for growth. These are administered intravenously and can destroy tumor cells or deprive them of the essential components they require for growth. They are sometimes combined with other treatments in order to enhance their effect[1,2].

Ipilimumab is a monoclonal anti-CTLA-4 immunoglobulin 1 (IgG1) antibody that activates destruction of regulatory T cells by stimulating antibody-mediated cytotoxicity, thus halting the immunosuppressive effect. Ipilimumab is currently approved for the treatment of advanced melanoma (unresectable or metastatic) in monotherapy or in combination with nivolumab (anti-PD1)[3-8].

The most advance therapy attempts to inhibit the PD-1/PD-L1 checkpoint pathway. The PD1 receptor is found in lymphocytes and acts as an inhibitory-type checkpoint by interacting with its ligands PDL1 and PDL2. Tumor cells are capable of expressing PDL1, thus inhibiting the action of the cytotoxic T cell on them and generating tolerance. In this way, anti-PD1 drugs (nivolumab, pembrolizumab, durvalumab) and anti-PDL1 drugs (avelumab, atezolizumab) overcome tumor immune tolerance and enable the action of cytotoxic T cells. Anti-PD1 and anti-PDL1 agents have several indications in various scenarios, both in monotherapy and in combination therapy in patients with melanoma, lung cancer, renal cell carcinoma, urothelial carcinoma, classic Hodgkin lymphoma, and head and neck tumors[9].

PATHOPHYSIOLOGY OF GASTROINTETINAL TOXICITY

Toxicity of the various types of immunotherapy, or immune-related adverse effects, is closely associated with the mechanism of action of the different treatments, for example, the toxicity of interleukin 2 (IL-2) results from release of nitric oxide, IL-1, tumor necrosis factor alpha, and interferon gamma. In adoptive cell therapy, the initial toxicity is caused by lymphodepleting chemotherapy. After T-cell infusion, immunotoxicity manifests as fever, tachycardia, vascular hyperpermeability followed by multiorgan failure. In the most severe cases, this is due to cytokine release syndrome[10]. Blockade of CTLA-4 suppresses the function of regulatory T cells, which

contribute to local inflammation in the gastrointestinal mucosa. It has been suggested that colitis associated with CTLA4 could result, in part, from this immunosuppressive function[11]. PD-1 and CTLA-4 blockade can generate toxicity that mimics autoimmune diseases[12].

HOW TOXIC IS IMMUNOTHERAPY FOR THE GASTROINTESTINAL TRACT?

Adverse effects involving the digestive system are recorded in around one-third of all patients receiving immunotherapy, specifically monoclonal anti-CTLA-4 IgG1 and anti-PD1 IgG4 antibodies[13].

Immune-mediated enterocolitis is one of the most common adverse effects, especially with ipilimumab. Up to one-third of patients treated with ipilimumab experience diarrhea, and immune-mediated colitis is observed in 7%-22% of cases[14]. In contrast, immune-mediated enterocolitis associated with nivolumab is less common, affecting around 10% of all patients who receive it[15]. The combination of ipilimumab and nivolumab is even more toxic than when each agent is used separately[8].

ENDOSCOPY

When should it be performed?

Colonoscopy with biopsies is the standard diagnostic approach for patients with lower digestive symptoms (*e.g.*, diarrhea, hematochezia). It is recommended in patients who receive immunotherapy and have persistent diarrhea or associated poor prognostic factors (hospitalization due to oral intolerance or absence of response to corticosteroids). Upper gastrointestinal symptoms (*e.g.*, dysphagia, gastroesophageal reflux, epigastralgia) are not uncommon and necessitate gastroscopy[16].

Which are the main endoscopy findings?

In the colon: In their series of 39 patients receiving anti-CTLA-4, Marthey *et al*[17] reported the most common lesions in endoscopy to be ulcer (79%) (Figures 1 and 2), erosion (13%), and erythema (8%) (Figure 3). The rectum and/or sigmoid colon were involved in 97% of cases, with extensive colitis being observed in 66% of patients. The distribution of the lesions was patchy in 55% of cases. The ileum was affected in only 5 patients.

In their study of 40 patients receiving treatment with anti-CTLA-4 agents who developed diarrhea and underwent flexible sigmoidoscopy or colonoscopy, Beck *et al*[18] reported findings for 36 cases. Again, the most common findings were erythema and ulcer (in 63% of patients). Endoscopy revealed inflammation several months after onset of enterocolitis, thus suggesting that in some cases, enterocolitis induced by anti-CTLA-4 agents can progress to inflammatory bowel disease (IBD).

We can find similar results for the type of involvement in immune-mediated colitis caused by anti-PD1 agents, which is less frequent than that associated with anti-CTLA-4 agents. Collins *et al*[15] studied a series of 20 patients with diarrhea who were receiving treatment with anti-PD1 agents and in 12 of whom colonoscopy findings were abnormal. The most frequent location was the descending colon (83%), and a patchy pattern, rather than a continuous pattern, was the most common (found in approximately 73% of patients). The most common lesions are also the same as those described above, namely, erythema, erosion, and ulceration.

Esophagus-stomach-duodenum: In their study of 22 patients who underwent gastroscopy, Marthey *et al*[17] found lesions in 13 (60%), the most common being gastritis (Figures 4 and 5) and erosive duodenitis.

Similar results were reported by Collins *et al*[15], who found that 63% of patients also presented upper gastrointestinal lesions. Erythematous gastritis was reported in most cases.

Biliary tract: The scientific literature also contains references to biliary involvement, more specifically in cases of extrahepatic cholangitis[19] and toxic hepatitis[20]. In such cases, endoscopy can be based on retrograde cholangiopancreatography or cholangioscopy. To our knowledge, no endoscopic images of the biliary tract obtained by cholangioscopy have been reported.

Small intestine: To our knowledge, there are no published capsule endoscopy-based

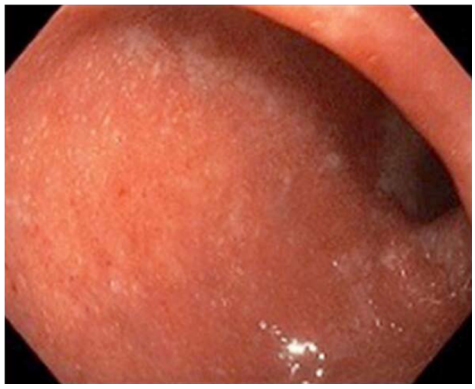

Figure 1 Mucosa at the rectosigmoid junction with mild erythematous spots and no erosions or ulcers.

data on involvement of the small intestine as a result of toxicity induced by immunological therapy.

Other aspects associated with endoscopy

Other lesions seen in endoscopy include exudates, granularity, and loss of vascular pattern. These findings are similar to those of IBD (ulcerative colitis and Crohn disease). Endoscopy findings from the first 2 wk of treatment with the drug and before the onset of symptoms have not been shown to predict the development of immune-mediated colitis. Endoscopy-confirmed involvement and the need for infliximab are not more common in patients receiving high-dose anti-CTLA-4 agents, thus suggesting that the severity of enterocolitis is not dose-dependent[21,22].

WHICH DIFFERENTIAL DIAGNOSIS SHOULD BE MADE?

Suspicion of toxicity due to immunotherapy should be based on the presenting complaints, of which diarrhea is the most common. Therefore, immune-mediated colitis should be taken into consideration in any patient receiving treatment with anti-CTLA-4 and/or anti-PD1 agents and who presents compatible symptoms. Other possible presenting complaints are abdominal pain, vomiting, hematochezia, weight loss, and/or fever. Onset of symptoms may be at any time during treatment and even several months after the last dose. The main conditions in the differential diagnosis are tumor progression, the infectious causes of diarrhea, and the development of IBD (Table 1). Therefore, imaging tests should also form part of the extension study for the primary tumor. Feces should also be tested for parasites and *Clostridium difficile*, and other tests, such as diagnostic colonoscopy, should be performed[21].

The main laboratory abnormalities in patients receiving immunotherapy are anemia, increased C-reactive protein, and low levels of serum albumin, all of which are nonspecific and play no role in the differential diagnosis. Therefore, endoscopy is the key to diagnosis. However, the result of a macroscopically normal endoscopy does not rule out the diagnosis, and biopsy specimens should be taken throughout the colon and assessed according to the segment they came from. Furthermore, infection by cytomegalovirus should also be ruled out by immunohistochemical staining of the biopsy specimens.

Histopathology findings are compatible with acute colitis, which is characterized by a marked inflammatory cellular infiltrate in the lamina propria consisting of neutrophils, lymphocytes, plasma cells, and eosinophils. Occasional findings include foci of neutrophilic cryptitis, crypt abscess, gland destruction, and erosions of the mucosal surface[23].

The histological characteristics of immune-mediated colitis are often nonspecific and may mimic those of other types of colitis. However, a variety of histologic characteristics that can act as useful pointers have been reported. Active colitis, together with major apoptosis of the epithelial cells in the crypt, has been recognized as the most useful characteristic. Other, less common associated patterns include lymphocytic and collagenous colitis. The correlation with the clinical history and, in particular, exposure to the drug plays an essential role in enabling the pathologist to differentiate immune-mediated colitis from infectious colitis, IBD, and drug-related colitis[24].

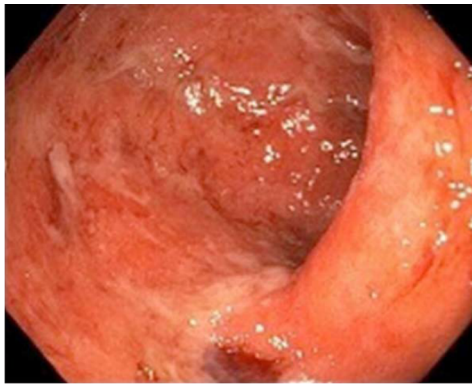

Figure 2 Mucosa at the rectosigmoid junction with erythema and fibrin-covered superficial erosions.

HOW SHOULD THE DISEASE BE TREATED?

Management of the patient with suspected immune-mediated enterocolitis should be multidisciplinary, involving oncologists, gastroenterologists, endoscopists, and the intensive care unit.

Treatment is mainly medical, and endoscopy is used only for diagnosis. Treatment of mild diarrhea (fewer than 3 watery stools per day) is based initially on oral antidiarrheal drugs together with fluid-electrolyte replacement. In moderate cases or absence of response, treatment should be started with oral corticosteroids (prednisone or equivalent at 0.5-1 mg/kg per day). In cases of severe diarrhea (more than 6 watery stools per day), treatment with anti-CTLA-4 and/or anti-PD1 agents should be suspended permanently, and intravenous corticosteroids should be started (methylprednisolone or equivalent 1-2 mg/kg per day). Patients who do not have a clinical response to intravenous corticosteroids after 3 d of treatment should start biologics (infliximab in a single dose of 5 mg/kg). The response to infliximab is generally fast, although some patients may require a second dose after 2 wk[21,25]. Marthey *et al*[17] reported that 37% of patients were treated successfully with corticosteroids. Biologic therapy was necessary owing to resistance to corticosteroids in 30% of cases (12 of 39 patients); infliximab was successful in 83% of cases (10 of 12 patients). Given the favorable response to infliximab, this therapy should be intensified rapidly in patients who do not respond to corticosteroids and whose clinical course is indolent. Treatment with corticosteroids during the first 5 d after onset of symptoms can enable more rapid resolution of symptoms than later initiation of treatment[26].

Perforation of the colon, while potentially fatal, is uncommon (< 1%). However, when surgery is necessary, colectomy should be subtotal and not segmental, since in most cases, enterocolitis induced by anti-CTLA-4 agents affects the whole colon[27-29].

CONCLUSION

Immune-mediated colitis is an emerging condition, given that the indications for immunotherapy, specifically anti-CTLA-4 and anti-PD1 agents, are expected to increase over time and for different types of tumor. Therefore, it is important to know the symptoms and determine the degree of involvement of immune-mediated colitis using endoscopy in order to initiate appropriate treatment early. The differential diagnosis should be based on infection, tumor progression, and IBD, with which the disease shares symptoms, endoscopy-confirmed lesions, and treatment.

The most common endoscopy-confirmed lesions of immune-mediated colitis are ulcers and erosions on edematous and erythematous mucosa. The most common location is the sigmoid colon, and a segmental pattern is slightly more common than a continuous pattern. Although histopathology is not specific in immune-mediated colitis, a biopsy must be taken to rule out other diseases and make a definitive diagnosis. Treatment includes systemic corticosteroids, although biologic therapy with infliximab may be necessary in some cases. Lastly, we believe that it is of the utmost importance to perform new studies that provide a detailed description of the adverse effects of regulatory proteins and of new, forthcoming agents in order to improve recognition and treatment of immune-mediate colitis in daily clinical practice.

Table 1 Differential diagnosis

Disease	Endoscopy findings	Clinical characteristics
IBD	UC: Continuous and circumferential mucosal inflammation starting in the rectum	Rectal bleeding, abdominal pain, diarrhea, chronic anemia
	CD: Deep fissures, cobblestoning, segmental distribution, relative rectal sparing, and terminal ileal involvement	
Radiation colitis	Similar to IBD	Rectal bleeding, chronic anemia
Infectious colitis	Diffuse effects on the colon	Dysentery-like diarrhea, different agents, *Clostridium difficile* and CMV to be ruled out
Colitis associated with diverticulosis	Segmental distribution, peridiverticular, sigmoid colon affected, rectum and proximal colon are normal	Rectal bleeding, abdominal pain, diarrhea
NSAID-induced colitis	Any part of the intestine, isolated lesions	Recurrent abdominal pain, obstruction, perforation, hemorrhage, chronic anemia
Microscopic colitis	Normal endoscopy findings	Watery diarrhea
Ischemic colitis	Segmentary colitis (sigmoid /left colitis)	Acute onset of abdominal pain and rectal bleeding

IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's disease; CMV: Cytomegalovirus; NSAID: Nonsteroidal anti-inflammatory drug.

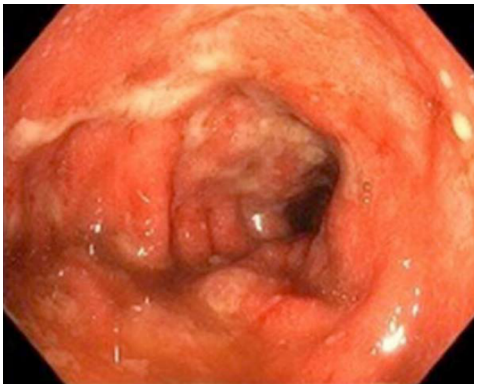

Figure 3 Mucosa in the descending colon with extensive erythema and deep fibrin-covered ulcers.

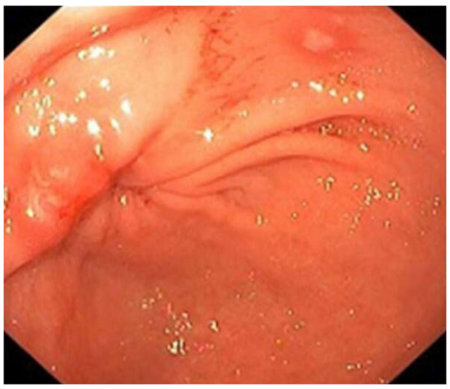

Figure 4 Erosion on the mucosa of the gastric antrum with generalized erythema.

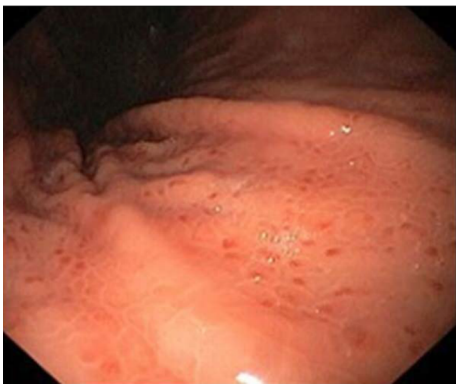

Figure 5 Petechiae on the mucosa of the gastric fold.

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META-ANALYSIS

Video capsule endoscopy *vs* double-balloon enteroscopy in the diagnosis of small bowel bleeding: A systematic review and meta-analysis

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Abstract

AIM

To compare the diagnostic accuracy of video capsule endoscopy (VCE) and double-balloon enteroscopy (DBE) in cases of obscure gastrointestinal bleeding (OGIB) of vascular origin.

METHODS

MEDLINE (*via* PubMed), LILACS (*via* BVS) and Cochrane/CENTRAL virtual databases were searched for studies dated before 2017. We identified prospective and retrospective studies, including observational, cohort, single-blinded and multicenter studies, comparing VCE and DBE for the diagnosis of OGIB, and data of all the vascular sources of bleeding were collected. All patients were subjected to the same gold standard method. Relevant data were then extracted from each included study using a standardized extraction form. We calculated study variables (sensitivity, specificity, prevalence, positive and negative predictive values and accuracy) and performed a meta-analysis using Meta-Disc software.

RESULTS

In the per-patient analysis, 17 studies (1477 lesions) were included. We identified 3150 exams (1722 VCE and 1428 DBE) in 2043 patients and identified 2248 sources of bleeding, 1467 of which were from vascular lesions. Of these lesions, 864 (58.5%) were diagnosed by VCE, and 613 (41.5%) were diagnosed by DBE. The pretest probability for bleeding of vascular origin was 54.34%. The sensitivity of DBE was 84% (95%CI: 0.82-0.86; heterogeneity: 78.00%), and the specificity was 92% (95%CI: 0.89-0.94; heterogeneity: 92.0%). For DBE, the positive likelihood ratio was 11.29 (95%CI: 4.83-26.40; heterogeneity: 91.6%), and the negative

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likelihood ratio was 0.20 (95%CI: 0.15-0.27; heterogeneity: 67.3%). Performing DBE after CE increased the diagnostic yield of vascular lesion by 7%, from 83% to 90%.

CONCLUSION
The diagnostic accuracy of detecting small bowel bleeding from a vascular source is increased with the use of an isolated video capsule endoscope compared with isolated DBE. However, concomitant use increases the detection rate of the bleeding source.

Key words: Small bowel bleeding; Hemorrhage; Upper gastrointestinal bleeding; Obscure hemorrhage; Enteroscopy

Core tip: We performed a systematic review and meta-analysis comparing the diagnostic accuracy of video capsule endoscopy and double-balloon enteroscopy (DBE) in cases of obscure gastrointestinal bleeding of vascular origin. This is the first systematic review in this setting. We observed that the diagnostic accuracy of detecting small bowel bleeding from a vascular source is increased with the use of an isolated video capsule endoscope compared with isolated DBE. However, concomitant use increases the detection rate of the bleeding source.

Brito HP, Ribeiro IB, de Moura DTH, Bernardo WM, Chaves DM, Kuga R, Maahs ED, Ishida RK, de Moura ETH, de Moura EGH. Video capsule endoscopy *vs* double-balloon enteroscopy in the diagnosis of small bowel bleeding: A systematic review and meta-analysis. *World J Gastrointest Endosc* 2018; 10(12): 400-421
URL: https://www.wjgnet.com/1948-5190/full/v10/i12/400.htm
DOI: https://dx.doi.org/10.4253/wjge.v10.i12.400

INTRODUCTION

Approximately 5% of gastrointestinal bleeding occurs between the ligament of Treitz and the ileocecal valve[1-3] and can be classified as occult when there is no overt bleeding or overt bleeding with melena or hematochezia. Obscure gastrointestinal bleeding (OGIB) includes both definitions[1,2,4].

The most common sources of OGIB in older patients are small bowel angioectasias (30% to 40%), whereas tumors (17%) are more frequent in patients under 50 years old[5,6]. Other causes include Meckel's diverticula, radiation enteropathy, Dieulafoy's lesions, small-bowel varices, nonsteroidal anti-inflammatory drug enteropathy and inflammatory bowel disease[7-10].

Although prior evaluation of proximal and distal parts of small bowel with upper and lower endoscopy is recommended, it is occasionally not possible to identify the bleeding source with these methods. In these cases, newer endoscopic evaluation techniques are recommended, such as video capsule endoscope (VCE) and deep enteroscopy [which encompasses spiral, single, and double-balloon enteroscopy (DBE)].

The advent of VCE in 1998 enabled direct and painless visualization of small-bowel mucosa[4,11]. DBE, which has been on the market since 2003, allows for the endoscopic scrutiny of the entire small intestine, but it has the disadvantage of being an invasive procedure.

The diagnostic and therapeutic yield of these technologies has been compared with conventional approaches of push enteroscopy (PE), intraoperative enteroscopy and radiologic methods, revealing greater diagnostic yield[12]. Few studies comparing the diagnostic success of VCE and DBE are inconclusive in determining which of these two methods is superior. Thus, we decided to compare these methods in this review.

Although numerous meta-analyses have compared the efficacy of VCE and DBE in detecting an OGIB, this is the first systematic review and meta-analysis comparing OGIBs specifically in vascular origins. The objective of this study is to compare the diagnostic accuracy of VCE and DBE in cases of OGIB of vascular origin.

MATERIALS AND METHODS

Protocols and registration

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) recommendations and registered on PROSPERO international database (www.crd.york.ac.uk/prospero/) under number CRD42017078046.

Eligibility criteria

Types of studies: transversal studies from which it was possible to extract information necessary to calculate using only directly or indirectly supplied data. No abstracts or data from unpublished research were accepted. There were no restrictions in terms of language or date of publication.

Types of participants: patients with overt or occult OGIB from a vascular source. There were no restrictions regarding sex, age, risk factors, or anemia level in the study participants.

Types of interventions: VCE and DBE. Only studies that completed both exams, *i.e.*, VCE followed by DBE, were included regardless of where the procedure was performed, the type of colon cleaning, and the brand of the capsule or enteroscope.

Outcome measures: the main outcomes were sensitivity, specificity, pretest and posttest probabilities, positive and negative predictive values, and the accuracy of DBE.

Information sources

To identify articles, searches were conducted using MEDLINE (*via* PubMed), LILACS (*via* BVS) and Cochrane/CENTRAL virtual databases. Databases were searched from March 2017 to April 2018 with no restriction regard the idiom or the year of publication.

Search

The search used varied strategies depending on the database, and these strategies are specified below: (A) PubMed/MEDLINE: (angiodysplasias OR arteriovenous OR malformation OR hemorrhage OR gastrointestinal OR hemorrhages OR hematochezia OR angioectasia OR intestines OR small bowel bleeding OR intestine OR duodenum OR duodenal OR jejunum OR jejunal OR ileum OR ileal OR bleeding OR intestinal OR occult OR obscure phlebectasias) AND (double balloon OR enteroscopy OR enteroscopes OR enteroscopies OR double balloon endoscopy OR capsule endoscopy OR capsule endoscope OR full enteroscopy OR deep enteroscopy) AND (diagnosis/broad[filter]); and (B) LILACS and Cochrane/CENTRAL: enteroscopy AND capsule endoscopy AND obscure bleeding.

Study selection

Articles were initially selected after an assessment of the titles and abstracts to assess the relevance of the full text. Then, abstracts were read, and those that did not fit the inclusion criteria were excluded. Two independent reviewers performed eligibility assessment and study selection. Disagreements between reviewers were resolved by consensus.

Data collection process

The method of data extraction from each included study consisted of completing information sheets after the paper was read. Relevant data were then extracted from each included study using a standardized extraction form. One review author extracted data from the included studies, and a second author checked the extracted data. Disagreements were resolved by discussion between the two review authors.

Data items

The selected data included age, gender, total number of patients, study design, VCE and DBE models, intestinal preparation, interval time between VCE and DBE, number of patients with diagnoses of small-bowel bleeding using VCE and DBE and number of vascular lesions found. Only bleeding from vascular lesions was considered true positive diagnostically. We classified "vascular lesions" as angiodysplasias, varices, hemangiomas, red spots, and Dieulafoy lesions. Bleeding from tumor, ulcer, erosions, polyps and masses were not classified as vascular lesions but were considered bleeding from alternative sources.

Risk of bias in individual studies

To evaluate the risk of bias and the applicability of primary diagnostic accuracy studies, we used the QUADAS-2 tool (Table 1), which is structured in four domains.

The first domain is patient selection, which we described in terms of risk of bias. The second domain is a description of the index test, including analysis of how it was conducted and interpreted. The third domain is the reference standard, namely its description, conduction and interpretation. The fourth domain is flow and timing, where we recorded any patient who did not receive the index test(s) and/or reference standard, patients who were excluded from the analysis, and the time interval or any interventions that occurred between the index test(s) and the reference standard.

Summary measures

The sensitivity, specificity, pretest probability, positive and negative predictive values, and accuracy of DBE were the primary outcome measures and calculated using data provided from the original papers. Analysis was performed using capsule endoscopy as the gold standard for detection of small bowel lesions. We also created a summary receiver operating characteristic curve (sROC). All of these variables were subjected to per-lesion analyses. I-square was used to evaluate heterogeneity. Studies that remained under 50% of the sROC curve were removed.

Data were organized, and averages and standard deviations were calculated using Microsoft Excel Software 2013. Analysis was performed using the Meta-Disc 1.4 software.

RESULTS

In the per-patient analysis, 17 studies (1477 lesions) were included (Figure 1). In 3150 exams (1722 VCE and 1428 DBE) performed in 2043 patients, 2248 sources of bleeding were identified, of which 1467 were found to be vascular lesions and 781 were related to other sources, including tumor, ulcer, erosions, polyps and mass. Eight hundred and sixty-four (58.5%) lesions were diagnosed by VCE, and 613 (41.5%) by DBE. Of these, 605 (40.9%) were angiodysplasia; 5 (0.33%) were varices; 160 (10.8%) were described as blood and clots/bleeding, active bleeding or bleeding; 11 (0.74%) were red spots; 45 (3.04%) were described as arteriovenous malformation; 10 (0.67%) Dieulafoy lesions; 7 (0.47%) angiomas; and 74 (5.01%) were described generically as vascular lesions. Some patients were subjected to the same exam twice, and some of the sources of bleeding were identified by both exams.

The sensitivity of DBE was 84% [95% confidence interval (CI): 0.82-0.86; heterogeneity: 78.00%] (Figure 2), and the specificity was 92% (95%CI: 0.89-0.94; heterogeneity: 92.0%) (Figure 3). The positive likelihood ratio was 11.29 (95%CI: 4.83-26.40; heterogeneity: 91.6%) (Figure 4), and the negative likelihood ratio was 0.20 (95%CI: 0.15-0.27; heterogeneity: 67.3%) (Figure 5).

The posttest probability was 41.6% for DBE in the studied population and 85% for VCE. The area under the sROC curve was 0.9469 for DBE (Figure 6) and 0.9526 for VCE (Figure 7). The difference between the areas under independent ROC curves was 0.006, and the *P*-value was 0.41 (two-tailed).

Performing DBE after CE increased the diagnostic yield to vascular lesion by 7% from 83% to 90%

STUDY CHARACTERISTICS

Information extracted from each paper included characteristics of trial participants (including age, gender), study design, VCE and DBE models, intestinal preparation, interval time between VCE and DBE, number of patients with diagnoses of small-bowel bleeding using VCE and DBE, number of vascular lesions found, and the source of obscure gastrointestinal bleeding (Table 2).

All studies had similar characteristics; they studied the use of VCE and DBE in the diagnoses of OGIB sources, listing the sources separately. None of the studies classified vascular lesions according to the Yano[13] or Saurin[14] classification for vascular lesions of the small bowel.

A retrograde and/or anterograde route was decided based on VCE findings. Full enteroscopy using DBE was not always performed. The interval time was different in all studies based on institutional protocols. There were different definitions for vascular lesions. Every study reported a positive predictive value greater than 90%, except Fujimori[2] (33.33%) and Zhang[15] (53.31%).

Fujimori[2] exhibited high heterogeneity in poll specificity and sensitivity in addition to a poll accuracy under the medium media on SROC curve. Therefore, we excluded this paper.

Table 1 QUADAS-2. Risk of bias in individual studies

Study	Hadithi *et al*, 2006[4]	Hermans *et al*, 2017[11]	Hollerman *et al*, 2014[37]	Kaffes *et al*, 2007[34]	Kalra *et al*, 2015[16]	Kamalapor *et al*, 2008[30]	Kameda *et al*, 2008[27]	Li *et al*, 2010[35]	Lin *et al*, 2007[40]	Maeda *et al*, 2015[32]	Marmo *et al*, 2009[23]	TianMin, *et al*, 2013[39]	Nakamura *et al*, 2006[29]	Rahmi *et al*, 2013[33]	Chu *et al*, 2016[17]	Zhang, *et al*, 2015[15]
Was a consecutive or random sample of patients enrolled?	YES	UNCLEAR	UNCLEAR	YES	UNCLEAR	UNCLEAR	YES	YES	YES	YES	YES	YES	YES	YES	YES	UNCLEAR
Was a case-control design avoided?	YES	YES	NO	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Did the study avoid inappropriate exclusions?	YES	YES	YES	YES	UNCLEAR	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO
Could the selection of patients have introduced bias?	LOW	MODERATE	HIGHT	LOW	HIGH	HIGH	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	HIGH
Are there concerns that the included patients do not match the review question?	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	HIGH

Were the index test results interpreted without knowledge of the results of the reference standard?	YES	NO	YES	NO	YES	NO	YES	UNCLEAR	UNCLEAR	UNCLEAR	YES	NO	YES	NO	NO	UNCLEAR
If a threshold was used, was it prespecified?	YES LOW	YES MODERATE	YES LOW	YES MODERATE	NO MODERATE	YES MODERATE	YES LOW	YES MODERATE	NO MODERATE	YES MODERATE	YES LOW	NO HIGH	YES LOW	YES MODERATE	YES MODERATE	YES MODERATE
Could the conduct or interpretation of the index test have introduced bias?	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	HIGH
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	UNCLEAR
Is the reference standard likely to correctly classify the target condition?																

Were the reference standard results interpreted without knowledge of the results of the index test?	YES	NO	YES	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	UNCLEAR
Could the reference standard, its conduct, or its interpretation have introduced bias?	LOW	MODERATE	LOW	MODERATE	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	HIGH	HIGH
Are there concerns that the target condition as defined by the reference standard does not match the review question?	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	HIGH	HIGH
Was there an appropriate interval between index test(s) and reference standard?	YES	NO	NO	NO	NO	NO	YES	YES	YES	YES	YES	YES	YES	NO	YES	UNCLEAR

Did all patients receive a reference standard?	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Did all patients receive the same reference standard?	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Were all patients included in the analysis?	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Could the patient flow have introduced bias?	MODERATE	LOW	LOW	LOW	LOW	MODERATE	LOW	LOW	LOW	LOW	LOW	LOW	LOW	MODERATE	LOW	LOW

Risk of bias within studies

Most studies (thirteen) had a low risk of bias. In 3 studies, DBE was performed after VCE, which could introduce bias in the route used (antegrade/retrograde). QUADAS-2 revealed that most studies did not exhibit bias. All studies followed the same pattern of inclusion: positive findings for VCE with posterior use of DBE performed in the same center.

Kalra[16] used Medtronic, Duluth, and the United States VCE, whereas Chu[17] used the OMOM capsule endoscopic device. All other studies were performed using the given imaging device.

Complementary analysis

Analyzing DBE as the standard procedure resulted in the following metrics for VCE: sensitivity of 93% (95%CI: 0.91-0.95; heterogeneity: 89.0%); specificity of 82% (95%CI: 0.79-0.84; heterogeneity: 87.3%); positive likelihood ratio of 5.44 (95%CI: 3.22-9.21; heterogeneity: 88.0%); negative likelihood ratio of 0.07 (95%CI: 0.03-0.18; heterogeneity: 91.3%) and accuracy of 86.75%.

DISCUSSION

VCE and DBE were developed as new examination techniques for the small intestine and have the potential to overcome conventional enteroscopy[11]. The small bowel is difficult to inspect with endoscopic methods. Prior to evaluation of the small bowel, it is recommended to repeat an upper digestive endoscopy and a colonoscopy[18]. Although intraoperative enteroscopy is the best for observing the entire small bowel, it is the most invasive procedure.

This is the first systematic review with meta-analysis to analyze the accuracy of DBE combined with VCE in diagnosing vascular lesions as a source of small bowel bleeding. The studies selected exhibited homogeneous intervention in a large number of patients. Eligibility criteria were strict, and selection and analysis were performed using international recognized protocols to avoid bias.

Saurin *et al*[14] divided the small bowel lesions into three distinct groups:

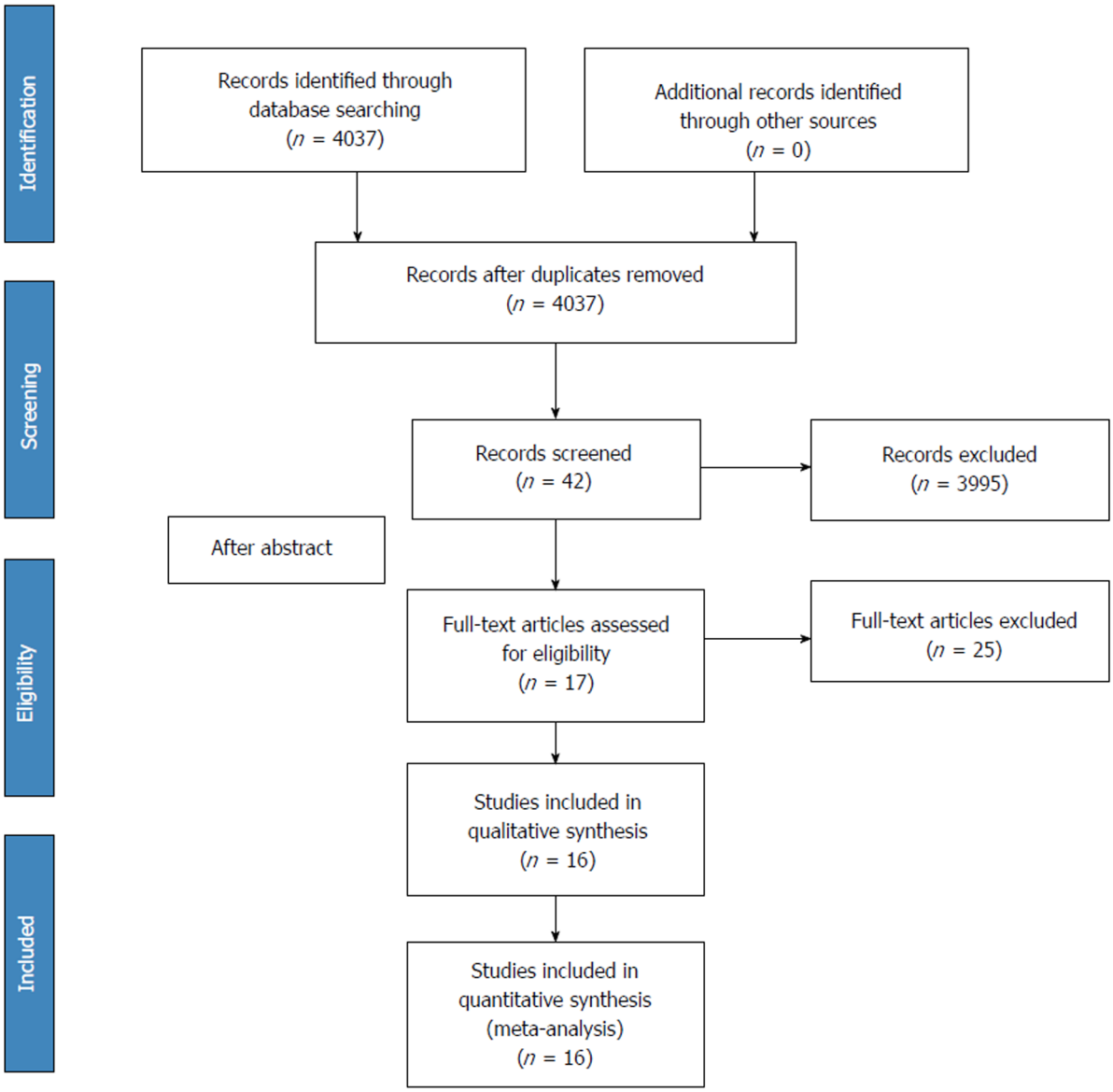

Figure 1 Flow diagrams - PRISMA[36].

submucosal veins, diverticula and nodules are included in the P0 lesions group; red spots and small or isolated erosions are considered P1 lesions; and angioectasias, varices, ulcerations and tumors represent P2 lesions. Yano *et al*[13] divided vascular small bowel lesions into 4 types depending on their characteristics and the presence or absence of bleeding. None of the studies in this meta-analysis divided the vascular lesions according to these classifications. Many sources of obscure bleeding were of vascular origin. When an endoscopic capsule or enteroscopy examination is performed and a source of bleeding is not identified, the cause is considered to be vascular by default. Thus, flash blood and clots/bleeding, active bleeding, and bleeding were considered as vascular sources in our study.

The benefits of VCE include the noninvasive nature of the test, patient acceptance, safety and diagnostic yield. However, it is limited by the inability to perform conventional endoscopic procedures, such as air insufflation, local reexamination, rinsing, biopsy, therapeutic intervention and precise identification of lesions. However, in DBE, a complete small bowel examination is typically not possible using only one route, so it often requires combined oral and rectal approaches. Diagnostic algorithms to identify gastrointestinal bleeding have suggested that VCE is best used initially to identify the lesion. DBE is best used for performing a therapeutic procedure after VCE. Thus, VCE was chosen as the gold standard in this review.

The diagnostic yield of VCE, DBE and single balloon enteroscopy (SBE) appears highest for patients with ongoing overt bleeding[19-21]. Comparing VCE and SBE, Shiani *et al*[19] reported a strong degree of concordance between VCE and SBE for active

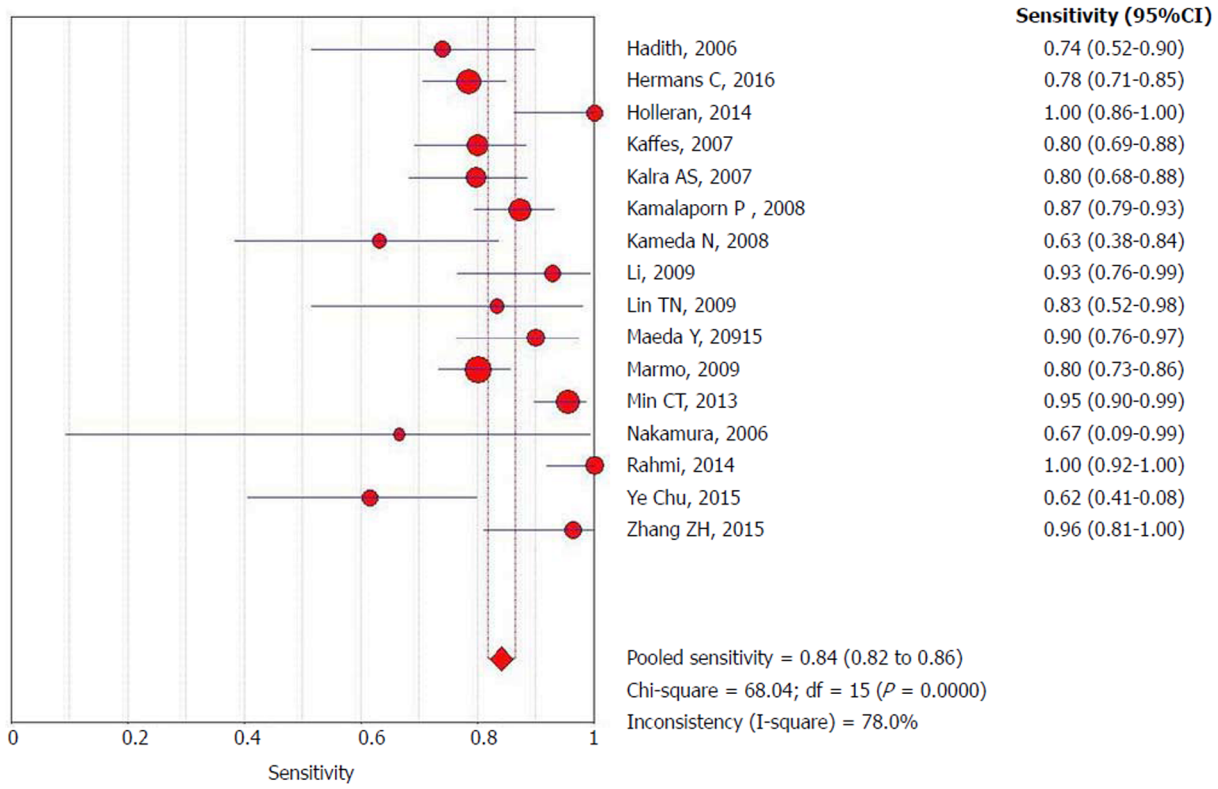

Figure 2 Forrest plot: Double-balloon enteroscopy sensitivity per-lesion analysis.

bleeding and clots but only moderate concordance for vascular lesions and fair concordance for ulcers. The diagnostic yield of VCE is increased if performed within 2 wk (greatest in 48 to 72 h). The timing of capsule endoscopy can influence the diagnosis and outcomes in patients with small bowel bleeding by identifying patients for early intervention, leading to endoscopic or surgical interventions or changes in medical management[22]. A study reported a high diagnostic and therapeutic yield (90%) with early (within 24 h) DBE in 10 patients with overt small bowel bleeding[23].

Regarding emergency ongoing overt OGIB, European Society of Gastrointestinal Endoscopy suggests that small bowel capsule endoscopy or device-assisted enteroscopy should be considered as a first-line approach[24]. Studies included in this meta-analysis did not differentiate the cause of bleeding as emergency or nonemergency. However, our results revealed increased accuracy of VCE to identify the vascular source of bleeding compared with DBE. This result demonstrates the ability of VCE to exclude lesions and to demonstrate the direction of the DBE. These results allow us to recommend the capsule as the first-line approach in these cases.

In the evaluation of OGIB, Martínez *et al*[25] demonstrated that the overall diagnostic yield of antegrade DBE is roughly equivalent to VCE; however, the diagnostic yield of DBE is increased when pre-DBE imaging is positive. A lesion source is frequently identified when pre-DBE imaging is negative or not performed. In a systematic review with 9 articles, Westerhof *et al*[26] reported that the diagnostic yields of CE and DBE for OGIB varied between 38% and 83% for CE and between 43% and 75% for DBE. The concordance between findings of CE with those of DBE varied between 29% and 92%, and the most frequent diagnosis was angiodysplasias. Our review reveals that DBE is reasonably sensitive and exhibits high specificity; however, it performs worse than VCE. Performing DBE after the CE increases the vascular lesion detection index by 7% from 83% to 90%.

This study is helpful for selecting the best initial diagnostic procedure in patients in whom vascular bleeding is suspected, such as cases of vascular syndromes, elderly patients and patients using anticoagulants. In many locations, these procedures are associated with high costs and are not always available at the same center. Although suggestions for the use of DBE as the first choice in obscure bleeding are reported, we have demonstrated that VCE would be the best and safest choice based on a 7% increase in diagnostic yield of DBE regardless of the severity of the case.

Variables that have been associated with an increased detection rate includes earlier VCE, inpatient status, overt GI bleeding with transfusion requirement, male sex, increasing age, use of warfarin and liver comorbidity[24]. Unfortunately, the articles

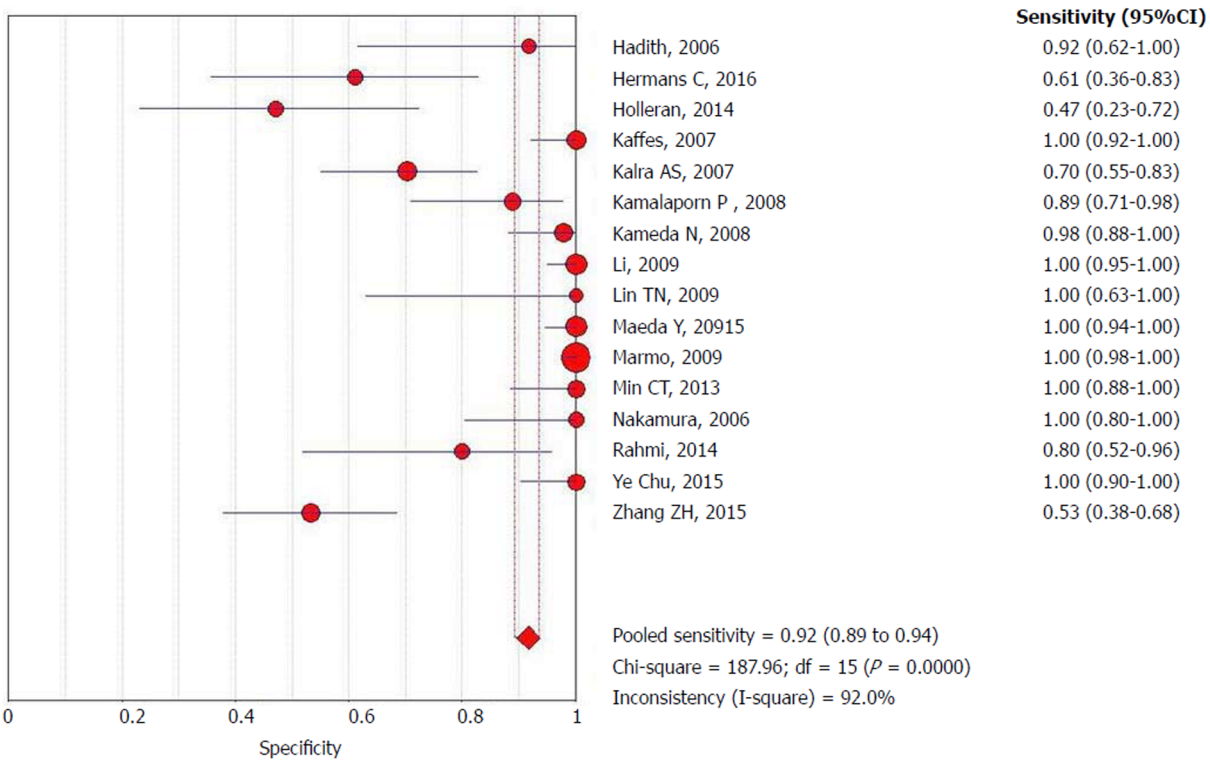

Figure 3 Forrest plot: Double-balloon enteroscopy specificity per-patient analysis.

did not stratify the findings according to these variables but according to the findings of the examinations, preventing very interesting data from being collected and analyzed.

A greater sensitivity of DBE in small bowel OGIB after using the VCE as the initial examination was observed. Considering the high sensibility of VCE in relation to DBE (93% × 84%), we suggest its use for suspicion of vascular lesions. Despite the low specificity noted when using VCE after DBE, its posttest result is double that of DBE (85% × 41.6%), prompting us to suggest using this feature after DBE with a negative finding. In this meta-analysis, we included studies in which VCE was performed before enteroscopy, and the route was chosen according to the possible location of the finding in the VCE. This procedure leads to an increased probability of finding the lesion with DBE. On the other hand, some enteroscopies were not completed because they only used one of the insertion pathways.

In one study[27] that attempted complete small bowel examination, all patients underwent both an antegrade and retrograde DBE procedure, whereas the DBE strategy varied in the other studies. In two studies, the antegrade or retrograde approach of DBE was chosen based on the VCE findings[2,28]. One study[29] chose the route of DBE based on the medical history. One study[4] chose the antegrade route of DBE in all cases followed by an alternate approach if considered necessary. In many studies, the decision to perform an additional DBE using the alternate route was made after considering several factors, including the results of the initial procedure, clinical indication, and patient consent. Two studies[29,30] had a single-blinded design.

The mean age of our study was 57.2 years. Angiectasias accounts for 20% to 30% of small bowel bleeding and are more commonly observed in older patients. In addition, bleeding in those who use nonsteroidal anti-inflammatory drugs and proper intestinal preparation facilitates lesion identification. The analyzed studies did not stratify the findings in the examinations regarding age, use of medications (nonsteroidal anti-inflammatory drugs), urgency/emergency indications, and bowel preparation, which prevents us from analyzing more data that would provide valuable information[31].

Although studies have assessed the diagnostic yield of VCE, PE, and device-assisted enteroscopy in OGIB, the precise significance of lesions identified and the impact on clinical outcome have not been consistently evaluated for those modalities. In the case of OGIB, a positive patient outcome should be either cessation of bleeding or resolution of anemia. Several studies have demonstrated a change in patient management and improved outcomes following VCE and device-assisted enteroscopy[32].

Of the included manuscripts, seven included patient follow-up. The mean duration

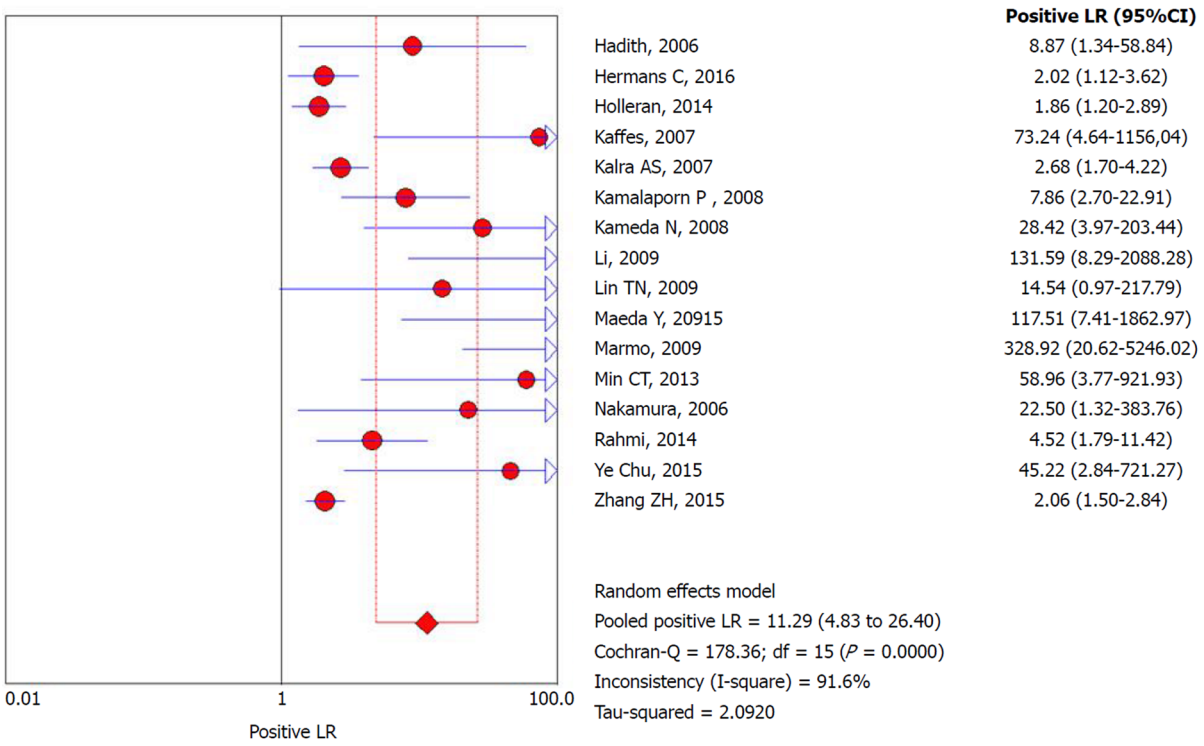

Figure 4 Forrest plot: Double-balloon enteroscopy positive likelihood ratio per-patient analysis.

of follow-up varied from 5 to 12 mo. Patients continued to exhibit bleeding in most of these studies, ranging from 65% to 81% including those whose findings were external of the small bowel[4,25,27,31,33-35].

Our study has some limitations, including nonstandardized follow-up of the patients after the exams, no standardized bowel preparation between the studies and no standard interval time between the exams. Additionally, performing DBE after a VCE exam facilitates the decision of the insertion route for enteroscopy (Figure 8). All of these limitations appear to favor DBE. The analyzed studies did not stratify the findings in the examinations regarding age, use of medications (nonsteroidal anti-inflammatory drugs), urgency/emergency of the indication, and the preparation, which prevents us from analyzing more data that would provide valuable information. These are data that would enrich the revision; however, they depend on the particularities of conduct of each author.

In conclusion, the diagnostic accuracy of detecting small bowel bleeding from a vascular source is greater with the use of an isolated VCE compared with isolated DBE. However, concomitant use increases the detection rate of the bleeding source.

Table 2 Studies characteristics

	Median age; range	Patient total	Study design	VCE Model	DBE Model	Preparation	Interval CE × DBE	No. of patients with diagnoses of SBB by CE/total CE performed	No. of patients with diagnoses of SBB by DBE/total DBE performed
Fujimoto *et al*[28], 2007	64 (38-93)	45 M: 25 F: 20	Prospective study	Pillcam (Given Imaging, Yoqneam, Israel).	EN-450P5 DBE diagnostic model and/or the EN-450T5	CE: 12 h fast + 1 L sodium sulfate/sodium bicarbonate DBE: 72 h after CE in 36 pct	72 h	18/45 Angiodysplasia: 6 Varices: 2 jejunal	18/36
Hadithi *et al*[4], 2006	63.2 (19-86)	35 M:22 F: 13	Prospective blinded study	Given M2A, Given Imaging Ltd., Yoqneam, Israel	Fuji Photo Optical Incorporated Company Fujinon Inc., Japan	CE: fast overnight after the ingestion of 1 L of sodium sulfate/sodium bicarbonate solution DBE: fast overnight after ingestion of 1 L clean prep. for the antegrade approach and bowel cleansing as for colonoscopy (4 L Klean prep)	7 to 14 d	21/35 AVM: 19 Fresh blood and clots: 5	28/35 AVM: 16 Fresh blood and clots: 2
Hermans *et al*[11], 2017	69 (18-91)	146 M: 91 F: 55	Retrospective observational study.	Olympus VC (Olympus EndoCapsule; Tokyo, Japan) and Pillcam VC (Covidien plc, Dublin, Ireland)	Fujinon Double-Balloon Enteroscopy System (Fujinon GMBH, Germany), EN-450T5	CE: 2 L PEG in a single or split dose DBE: 1 L PEG divided into two doses to be used twice	111 (1–1091) days	105/134 Angiodysplasias: 70 active bleedings without visible focus : 35	93/146 Angiodysplasias: 19
Holleran *et al*[37], 2013	54 (16-90)	246 M: 130 F: 116	Retrospective comparative study	SB1 or SB2 pillcam (Given imaging, Yokneam, Israel)	Fujinon double-balloon enteroscope (EN-450P5/20, Fujinon, Inc., Saitama, Japan)	CE: No preparation was required other than an overnight fast. Anterograde DBE: overnight fast Retrograde DBE: PEG the day prior	NR*	40/46 Angiodysplasia: 10 Active bleeding: 3	116/246 Angiodysplasias: 44
Kaffes *et al*[34], 2007	62 ± 18	60	Prospective cohort study	M2A; Given Imaging Ltd, Yoqneam, Israel)	Fujinon	CE, DBE: fasting period of 8 h before the oral procedure and a bowel preparation with a sodium (Picoprep; Pharmatel, Thornleigh, Australia)	NR*	45/60 Angiectasia:28 Red spots: 9 Blood: 8	45/60 Angioectasia: 21 Red spots: 9 Blood: 8

Kalra, A *et al*[16], 2015	66.6 ± 13.2	116 M:65 F: 51	Retrospective review	Medtronic, Duluth, GA, the United States	Fujifilm Medical System, Stanford, CT, the United States	Retrograde DBE: bowel preparation the night before the procedure.	1 yr	/69	29/69 AVM: 29
Kamalaporn *et al*[30], 2008	64.1 (34-83)	195 M: 26 F:25	Retrospective review	Given M2A CE system (Given Imaging Ltd, Israel)	Fujinon DBE system (Fuji Photo Optical Incorporated Company, Fujinon Inc., Japan)	CE: 2 to 4 L PEG and fasted overnight, at least 8 h before the procedure DBE: 4 L PEG and fasted overnight	139 (40 to 335) d	181/202 studies Angiodysplasia: 33 Bleeding: 22	56/56 Angiodysplasia: 36 Bleeding: 9
Kameda *et al*[27], 2008	62.4 (27-84)	32 M: 13 F: 19	Prospective single-blind trial	Pill Cam capsule (M2A, Given Imaging, Yoqneam, Israel)	DBE system (FujinonToshiba ES System, Saitama, Japan)	CE: fasting after midnight on the evening before the examination (minimum 8 h) DBE: overnight fasting and ingestion of 1 l of electrolyte lavage preparation (Niflec, Ajinomoto Pharma, Tokyo, Japan) in the morning.	1-7 d	29/32 Angiodysplasia: 8 bleeding: 6	21/32 Angiodysplasia: 7 bleeding: 6
Li *et al*[35], 2010		190	Prospective study	M2A, Given Imaging, Ltd. (Yoqneam, Israel)	Fujinon EN-450P5/ 20 and EN-450P5/28 (Fujinon Inc., Saitama, Japan)	CE: 1 L of PEG electrolyte 12 h before the procedure Anterograde DBE: fasted for 8 h. Retrograde DBE: PEG electrolytes preparation 4 h before the examination	5.8 d (1-18)	165/190 AVM: 7 Fresh blood or clots: 8	34/51 AVM: 9 Bleeding: 0 Angioma: 4
Lin *et al*[40], 2007	63.5 ± 22.7 (11-87)	10 M:3 F:7	Prospective study	Pill Cam SB capsule (Given Imaging, Yoqneam, Israel)	DBE: EN-450P5 and the EN-450T5	CE: fast overnight for 8-12 h Anterograde DBE: fasting for 6-8 h Retrograde DBE: bowel cleansing as in a colonoscopy.	7 d	9/10 Angiodysplasias: 3 Bleeding: 3	8/10 Angiodysplasias: 3 Varices: 1 Dieulafoy's lesion: 1
Maeda *et al*[32], 2010	70 (30-92)	89 M: 48 F: 41	Retrospective analysis	PilCam SB® (SB1, SB2, or SB3) (Covidien, Irvine, CA, the United States).	(EN-450 T5/W or EN-580 T, Fujinon Inc., Saitama, Japan)	NR*	24 h	58/89 Angioectasia: 8 AVM : 3 Dieulafoy lesion: 9 Varices: 2	29/37 Angioectasia: 8 AVM: 3 Dieulafoy lesion:6 Varice: 1
Marmo R *et al*[23], 2008	61.6 ± 16.2	193 M: 119 F: 74	Prospective study	Pillcam SB	Fujinon Double-Balloon Enteroscopy System	Anterograde DBE: fasting period of 8 h Retrograde DBE: 4 L PEG-based preparation	2 wk	175/193 Vascular lesions: 74 Blood or clot: 34	132/193 Vascular lesions: 72

Tian Min *et al*[39], 2013	55.4 (23-78)	62 M: 34 F:28	Prospective study	Pill Cam SB capsule	EN-450P5 and the EN-450T5 (Fujinon)	CE: 2 L to 4 L PEG and fasted overnight Anterograde DBE: fasting for 6-8 h before the procedure. Retrograde DBE: bowel cleansing as in a colonoscopy.	15 (4-60) d	44/62 Angiodysplasia: 26 Bleeding: 26	48/62 Angiodysplasia: 27 Bleeding: 30
Nakamura *et al*[29], 2006	58.5 (25 ± 85)	32 M: 21 F: 11	Prospective and blinded	M2A, Given Imaging,	Fuji EN−450 T5/20	CE: fluid diet for 12 h and observed a fasting period starting at midnight Anterograde DBE: fasted for 12 h Retrograde DBE: clear liquid diet on the day before the examination and PEG electrolyte lavage solution on the morning of the examination	48 h	19/32 Angiodysplasias: 4 Red spots: 2	12/28 Angiodysplasias: 2 Red spots: 2
Rahmi *et al*[33], 2013	67 ± 11	383 M: 114 F: 269	Prospective, multicenter study	PillCam SB device	EN-450P5 and EN-450T5; Fujinon	CE: residue-free diet 2 d before VCE ingestion; 2 L PEG solution the night before the examination; patients then fasted overnight Anterograde DBE: No bowel preparation Retrograde DBE: 4 L of a PEG solution was given the day before the procedure	4.1 ± 6.3 mo	266/383 Angiodysplasia: 266	205/266 Angiodysplasia: 190
Chu *et al*[17], 2016	51.1 ± 17.1	121 M: 60 F: 61	Study Cohorts	OMOM capsule endoscopic device (Jinshan Science and Technology Group Co., Ltd, Chongqing, China)	Fujinon EN-450P5/20	CE: 2 L polyethylene glycol-based electrolyte solution 12 h prior to the test, followed by an overnight fast for bowel preparation fast Retrograde DBE: bowel preparation used for CE procedure the day before the examination	1 wk	115/121 Angiodysplasia: 86% Active bleeding: 6	29/46 Angiodysplasia: 9

Zhang *et al*[15], 2015	47.19 (16-78)	88 M: 64 F: 24	Prospective study	Pill Cam SB	Fuji DBE system	CE: 3 liters of PEG (2 liters at 10:00 pm the night before the procedure, and 1 L with the simethicone at 4:00 am on the morning of the procedure) Anterograde DBE: fast for 6-8 h Retrograde DBE: 2 L of PEG	NR	53/88 MAV: 14 Hemangioma: 0 Diverticulum with a Bleeding: 1	52/88 MAV: 10 Hemangioma: 3 Diverticulum with a Bleeding: 7

M: Male; F: Female; SBB: Small bowel bleeding; PEG: Polyethylene glycol solution; AVM: Arteriovenous malformation; VC: Video capsule; NR: Not related; DBE: Double-balloon enteroscopy; VCE: Video capsule endoscope.

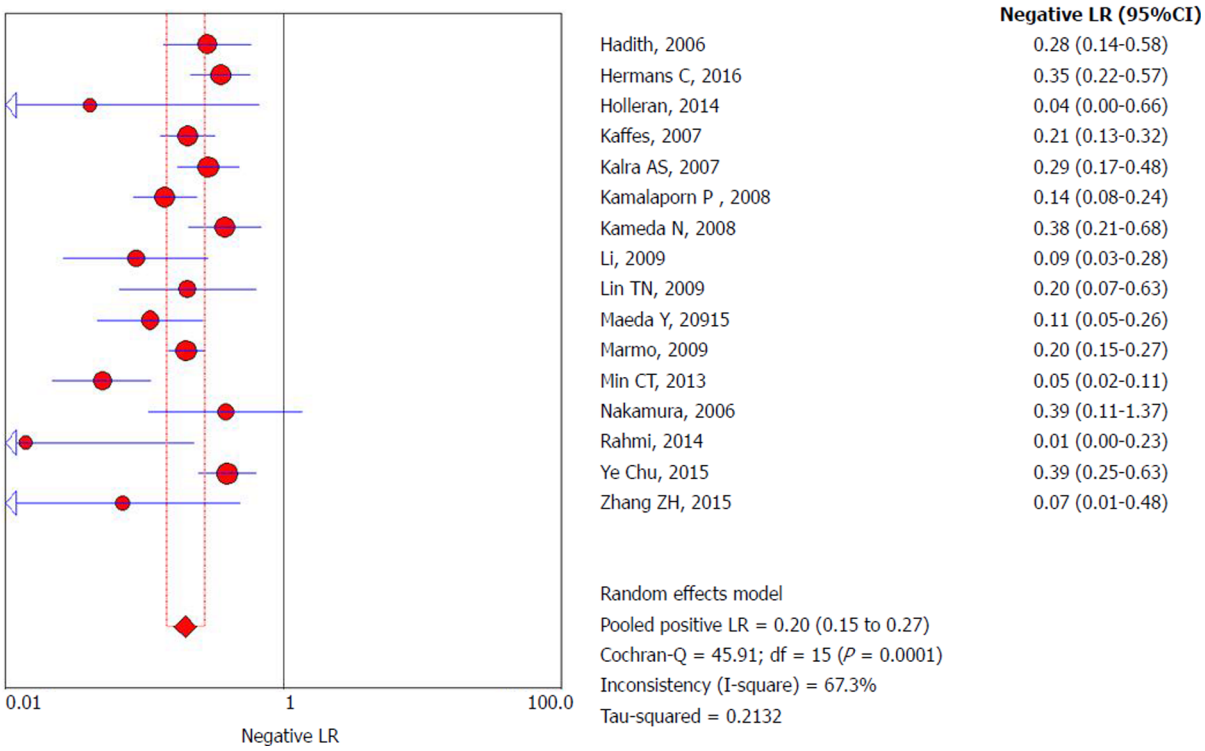

Figure 5 Forrest plot: Double-balloon enteroscopy negative likelihood ratio per-patient analysis.

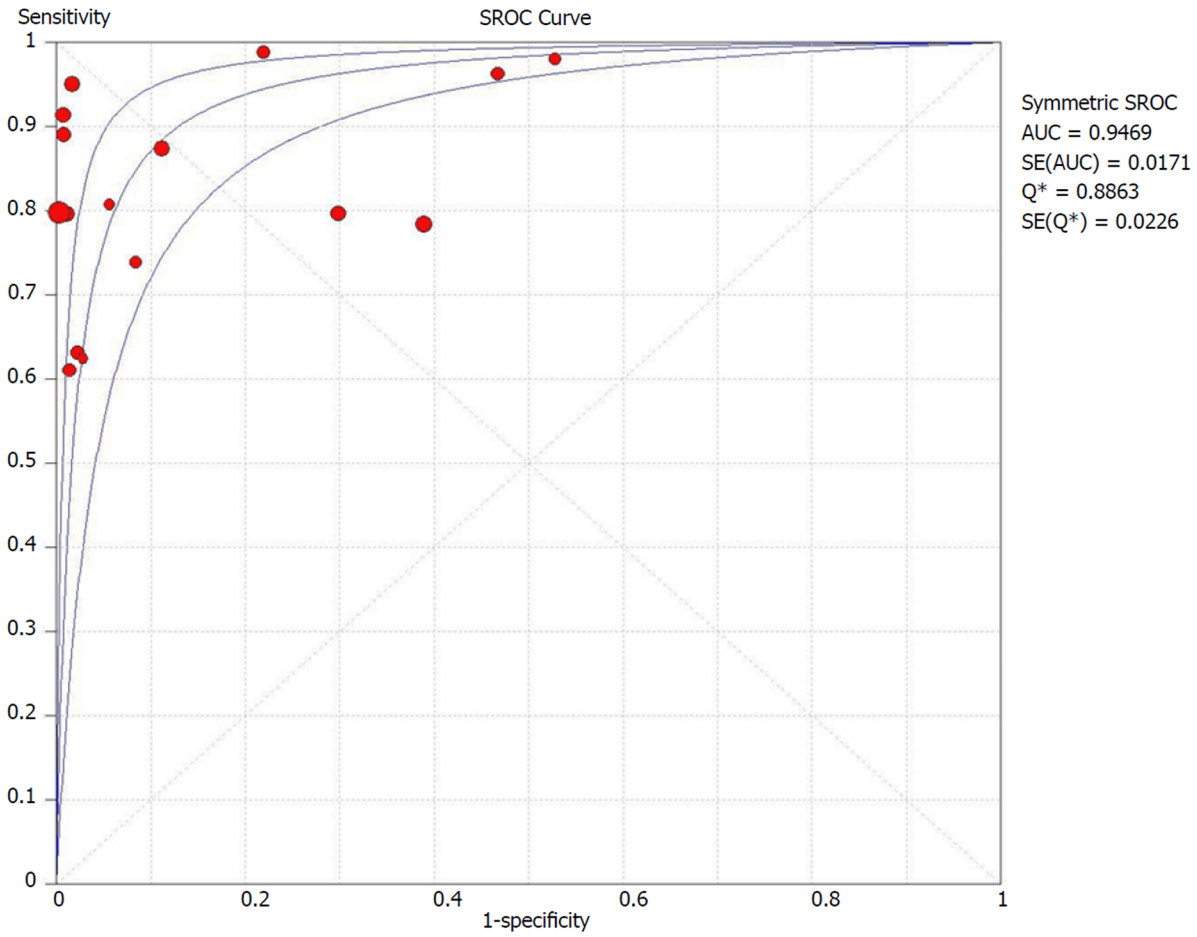

Figure 6 Summary receivers operating characteristic curve for double-balloon enteroscopy in per-patient analysis. sROC: Summary receiver operating characteristic.

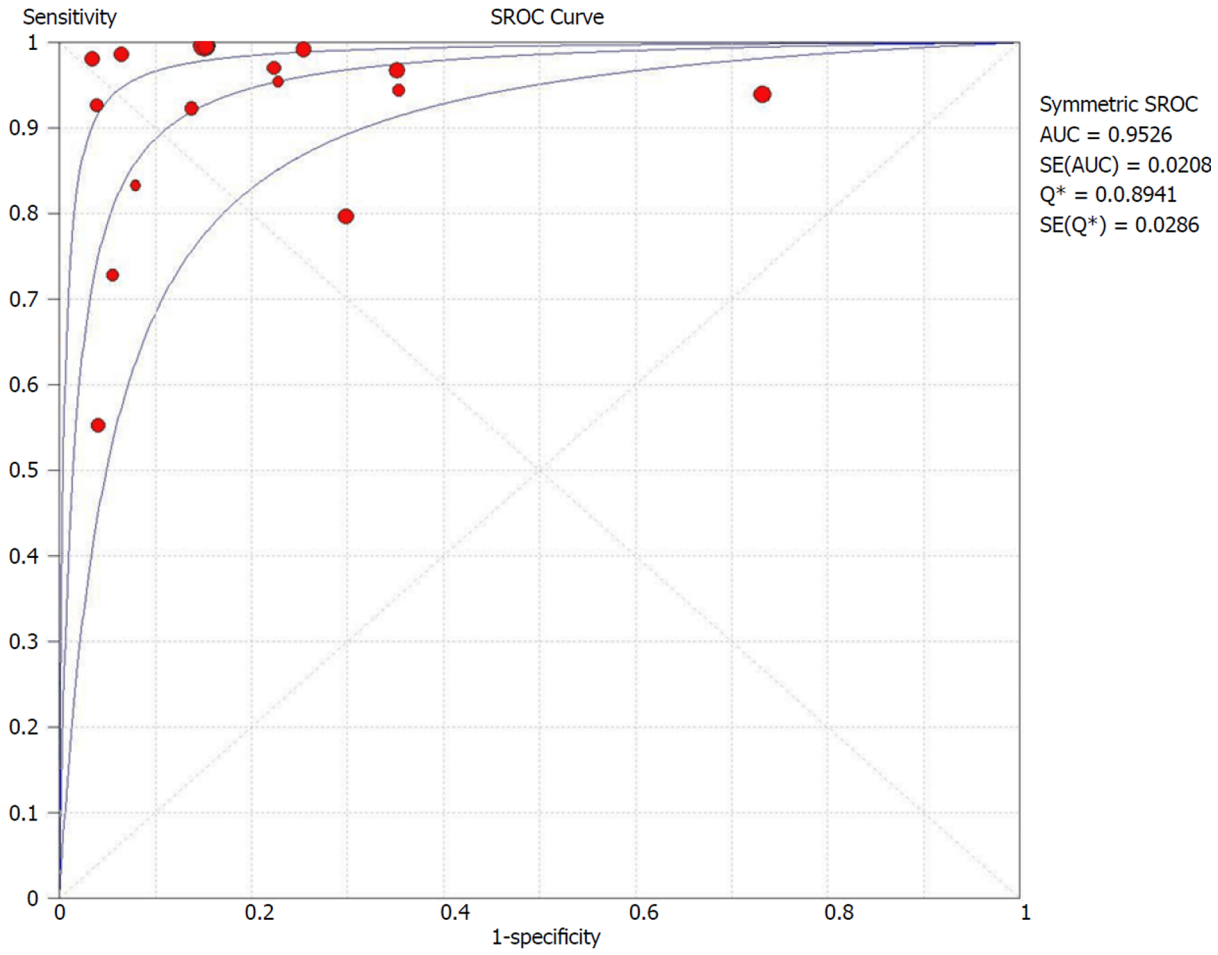

Figure 7 Summary receiver operating characteristic curve for video capsule endoscopy in per-patient analysis. sROC: Summary receiver operating characteristic.

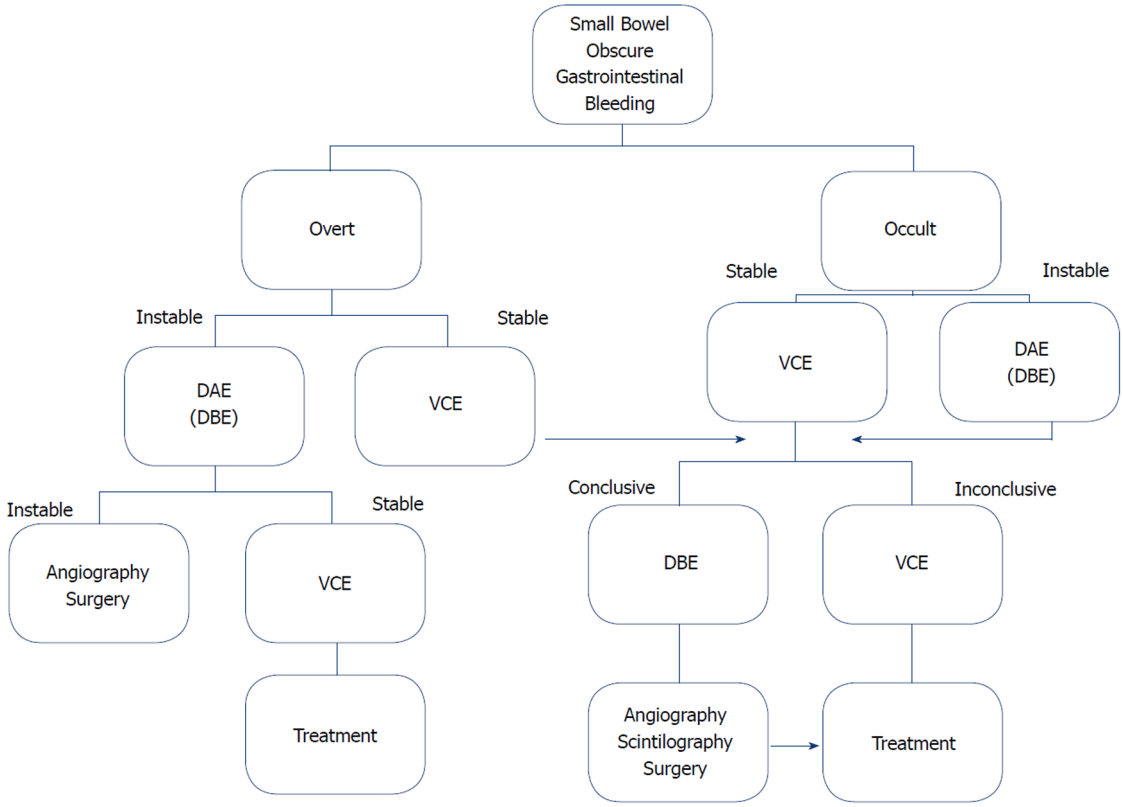

Figure 8 Suggested management approach to overt and occult small-bowel bleeding after upper endoscopy and colonoscopy did not identify vascular bleeding origin. Positive test results should direct specific therapy. When video capsule endoscopy is contraindicated or unavailable, device-assisted endoscopy may serve as the initial test for small-bowel evaluation. VCE: Video capsule endoscopy; DAE: Device-assisted endoscopy; DBE: Double-balloon enteroscopy.

ARTICLE HIGHLIGHTS

Research background

Obscure gastrointestinal bleeding (OGIB) is a challenge to the professional who faces this occurrence. Although only a small part of these bleeds occurs in the midgut, the difficulty in accessing it implies a longer interval between the onset of symptoms and diagnosis and therapy. Initially, we used enteroscopes with single balloon, including spiral and double balloon overtubes, which is the most commonly used. Subsequently, the endoscopic capsule was introduced, allowing a greater index of complete observation of the small intestine with greater comfort to the patient. A weakness includes the therapeutic impossibility present in balloon enteroscopy. Due to the particularities of each of the methods, we should seek data in the available scientific literature to support our most appropriate diagnostic decision.

Research motivation

Video capsule endoscopy (VCE) and double-balloon enteroscopy (DBE) are recognized endoscopic diagnostic approaches for OGIB, for which vascular origins represent the most common source. Our initial motivation was to determine whether there is a preferential diagnostic approach in OGIB by vascular origin that maintains high accuracy. From the literature review about the subject, we realized some characteristics that we interpreted as important limitations in the previous works. Thereafter, this study sought to remove these limitations and to follow a rigorous methodological approach in the selection and analysis to enhance knowledge about accuracy data.

Research objectives

We want to compare accuracy data between the two most widespread indicated endoscopic approach methods in OGIB: VCE and DBE. It was possible to obtain a large sample of patients submitted to both methods from the literature. We believe that future systematic reviews on this issue can be based on our selection and analysis methodology. In addition, new studies that will be published can be added to update and provide a greater dimension to the theme.

Research methods

This systematic review was conducted according to the PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and registered on PROSPERO international database. The search was performed in the electronic databases MedLine (*via* PubMed), LILACS

(*via* BVS) and Cochrane/CENTRAL virtual databases. The QUADAS-2 tool was used to evaluate the risk of bias and the applicability of primary diagnostic accuracy studies and the incorporation of recent studies on the OGIB approach. All articles were read and chosen based on common consensus among three authors, and restricted inclusion criteria provide greater magnitude and accuracy.

Research results

Seventeen studies were included with 3150 exams performed in 2043 patients, resulting in the identification of 1467 vascular lesions. The specificity found for DBE is greater than that of VCE (92% *vs* 82%) possibly because the examiner is able to examine in more detail the alterations found when performing DBE. In contrast, the sensitivity of the VCE is greater than that of the DBE (93% *vs* 84%) perhaps due to the natural increase in the capacity of the lens of the capsule and the fact that the insufflation of air in the small intestine during the examination with DBE greatly increases the pressure in the organ above the capillary pressure, which prevents the lesions from being observed in this exam. The increase in the diagnostic yield to the vascular lesion is greater when the DBE is performed after VCE.

Research conclusions

Through direct meta-analysis of the largest sample ever collected, we compared in isolation the diagnostic methods studied. The diagnostic accuracy of detecting small bowel bleeding from a vascular source is greater with VCE despite reduced specificity. This study sought to remove the bias from the lack of methodological rigor applied in the restrict inclusion criteria with the use of more than two authors for study selection and rigorous protocols accepted worldwide for the choice these studies, thus obtaining more purified results. This study also proposes that in addition to contributing to a greater specificity intrinsic to the examination, performing DBE after the use of VCE contributes to increased accuracy.

Research perspectives

The comparison between these two methods through meta-analyses always could be influenced by the technical differences applied in each study. A pertinent study design would include multicentric study with standardized protocols of care, including initial care, standard interval time between onset of symptoms and the first exam, standardized time between the exams, and standardized patient follow-up and bowel preparation.

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META-ANALYSIS

Sodium picosulphate or polyethylene glycol before elective colonoscopy in outpatients? A systematic review and meta-analysis

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Abstract

AIM

To determine the best option for bowel preparation [sodium picosulphate or polyethylene glycol (PEG)] for elective colonoscopy in adult outpatients.

METHODS

A systematic review of the literature following the PRISMA guidelines was performed using Medline, Scopus, EMBASE, Central, Cinahl and Lilacs. No restrictions were placed for country, year of publication or language. The last search in the literature was performed on November 20th, 2017. Only randomized clinical trials with full texts published were included. The subjects included were adult outpatients who underwent bowel cleansing for elective colonoscopy. The included studies compared sodium picosulphate with magnesium citrate (SPMC) and PEG for bowel preparation. Exclusion criteria were the inclusion of inpatients or groups with specific conditions, failure to mention patient status (outpatient or inpatient) or dietary restrictions, and permission to have unrestricted diet on the day prior to the exam. Primary outcomes were bowel cleaning success and/or tolerability of colon preparation. Secondary outcomes were adverse events, polyp and adenoma detection rates. Data on intention-to-treat were extracted by two independent authors and risk of bias assessed through the Jadad scale. Funnel plots, Egger's test, Higgins' test (I^2) and sensitivity analyses were used to assess reporting bias and heterogeneity. The meta-analysis was performed by computing risk difference (RD) using Mantel-Haenszel (MH) method with fixed-effects (FE) and random-effects (RE) models. Review Manager 5 (RevMan 5) version 6.1 (The Cochrane Collaboration) was the software chosen to perform the meta-analysis.

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RESULTS

662 records were identified but only 16 trials with 6200 subjects were included for the meta-analysis. High heterogeneity among studies was found and sensitivity analysis was needed and performed to interpret data. In the pooled analysis, SPMC was better for bowel cleaning [MH FE, RD 0.03, IC (0.01, 0.05), $P = 0.003$, $I^2 = 33\%$, NNT 34], for tolerability [MH RE, RD 0.08, IC (0.03, 0.13), $P = 0.002$, $I^2 = 88\%$, NNT 13] and for adverse events [MH RE, RD 0.13, IC (0.05, 0.22), $P = 0.002$, $I^2 = 88\%$, NNT 7]. There was no difference in regard to polyp and adenoma detection rates. Additional analyses were made by subgroups (type of regimen, volume of PEG solution and dietary recommendations). SPMC demonstrated better tolerability levels when compared to PEG in the following subgroups: "day-before preparation" [MH FE, RD 0.17, IC (0.13, 0.21), $P < 0.0001$, $I^2 = 0\%$, NNT 6], "preparation in accordance with time interval for colonoscopy" [MH RE, RD 0.08, IC (0.01, 0.15), $P = 0.02$, $I^2 = 54\%$, NNT 13], when compared to "high-volume PEG solutions" [MH RE, RD 0.08, IC (0.01, 0.14), $I^2 = 89\%$, $P = 0.02$, NNT 13] and in the subgroup "liquid diet on day before" [MH RE, RD 0.14, IC (0.06,0.22), $P = 0.0006$, $I^2 = 81\%$, NNT 8]. SPMC was also found to cause fewer adverse events than PEG in the "high-volume PEG solutions" [MH RE, RD -0.18, IC (-0.30, -0.07), $P = 0.002$, $I^2 = 79\%$, NNT 6] and PEG in the "low-residue diet" subgroup [MH RE, RD -0.17, IC (-0.27, 0.07), $P = 0.0008$, $I^2 = 86\%$, NNT 6].

CONCLUSION

SPMC seems to be better than PEG for bowel preparation, with a similar bowel cleaning success rate, better tolerability and lower prevalence of adverse events.

Key words: Sodium picosulphate; Polyethylene glycol; Bowel cleaning success; Tolerability; Colonoscopy; Randomized clinical trials; Meta-analysis

Core tip: Previous meta-analyses did not consider patient status (if inpatient or outpatient) for inclusion in the studies and grouped different types of patients. They also failed to conduct analyses by subgroups (regimen schedule, volume of polyethylene glycol solution, dietary restriction) in order to elucidate confounding factors. This is the first systematic review and meta-analysis for this specific group of patients and the first to communicate effectiveness by NNT.

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INTRODUCTION

Colonoscopy is the gold-standard method for polyp and adenoma detection and can reduce both incidence and mortality for colorectal cancer[1,2]. Different devices and tools were created to improve mucosal exposure and the detection of neoplastic lesions[3] and carbon dioxide insufflation used to increase tolerance to colonoscopy[4]. Even so, bowel cleaning is still the cornerstone for optimizing colonoscopy.

Cleaning efficacy is the most important characteristic of bowel cleansers as the quality of cleaning directly impacts on evaluation, difficulty, speed, and completeness of colonoscopy[5,6]. As inadequate bowel preparation results in missing pre-cancerous lesions and increases the costs related to repetition of colonoscopy, the choice of the product should aim to achieve high-quality bowel preparation and optimize the evaluation[7,8].

Polyethylene glycol (PEG)-based solutions are the most widely used and studied bowel cleansers. PEG is an isosmotic laxative which achieves high-quality bowel preparations through the ingestion of large volumes of the solution (approximately four liters). Their poor palatability and the volume to be ingested increase the

incidence of adverse events and decrease full intake of the medication[9-11].

Among purgatives that have been recently developed to overcome these limitations is sodium picosulphate with magnesium citrate (PICO or SPMC), a low-volume dual laxative which may cause less gastrointestinal symptoms. It promotes colon cleansing by retaining fluids in the colon and by increasing the frequency and the force of peristalsis; however, due to electrolyte exchanges it can cause dehydration and biochemical impairments[12,13].

PEG solutions trials date from 1982 and have contributed to their consolidation as the most widely used solutions[14]. Although sodium picosulphate has been used for several years in the United Kingdom and Australia, large randomized clinical trials evaluating its efficacy are recent and usually compare it to PEG solution[13,15]. Other solutions that have already been compared to SPMC are oral sulfate solution and mannitol[16,17].

The highest level of evidence for medical practice is found in meta-analyses of randomized clinical trials. Among meta-analyses that compared PEG and sodium picosulphate for bowel preparation before colonoscopy[18-20], the largest one (Jin *et al*[20]) included 21 studies and showed no difference in bowel cleaning efficacy between them. Unfortunately, inclusion criteria for population did not specify patient status (their condition of inpatient or outpatient), which impaired the quality of the results obtained to be applied in medical practice as inpatient status is an independent risk factor for inadequate bowel preparation[11,21].

As most colonoscopies are performed in outpatients and there is no established evidence comparing sodium picosulphate and PEG cleaning efficacy and tolerability in this subset of patients, we therefore conducted this meta-analysis. Regimens adopted for bowel preparation were also considered for analysis since there are studies demonstrating differences in cleaning efficacy depending on the kind of the regimen adopted[22].

MATERIALS AND METHODS

Protocol and registration

Strategies for the search, selection and analysis were pre-specified as stated in Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and documented in a protocol registered in International Prospective Register of Systematic Reviews (PROSPERO) database (CRD 42016050059)[23].

Eligibility criteria

Eligibility criteria were based on PICOS (population, intervention, comparison, outcomes and study design) strategy. Only randomized clinical trials with full texts published were included irrespective of language or time of publication. The subjects included were adult outpatients who underwent bowel cleaning for elective colonoscopy. The included studies compared sodium picosulphate/magnesium citrate and PEG. Exclusion criteria were inpatient status, groups with specific comorbidities, combination of different products for the preparation of the solution, association with enema or enteroclysis and the absence of dietary restrictions on the day prior to the exam. Primary outcomes evaluated were efficacy and tolerability. Secondary outcomes were prevalence of adverse events, and polyp and adenoma detection rates.

Search strategy and study selection

Two independent authors identified records in the following electronic databases: Medline, Scopus, EMBASE, Central, Cinahl and Lilacs. No limits were applied for country, year of publication or language. The last search in the literature was performed on November 20th, 2017. Search keywords were "colonoscopy", "colonosc*", "sodium picosulphate", "sodium picosulfate", "polyethylene glycol", "polyethylene glycols" and "random*". Full search strategy for each database is shown in Supplementary material (Appendix 1). Medline was the main database for the development of the search strategy, as follows: "(colonoscopy OR colonoscopies OR bowel preparation OR bowel prep* OR bowel cleansing OR bowel clean* OR colon preparation OR colon prep* OR colon cleansing OR colon clean' AND (sodium picosuffate OR sodium picosulphate OR picosulfate OR picosulphate) AND (polyethylene OR polyethylene glycol OR polyethylene glycols OR polyethylene glicol OR polyethylene glicols)".

Two independent authors performed eligibility assessment and studies selection. Duplicated references were excluded and the remaining ones were screened by title and abstract. Those that met any of the exclusion criteria were disregarded. The full

texts of the remaining records were assessed and the studies that met the eligibility criteria were included for the meta-analysis. The gray literature search was made in the references of the included studies and a third author solved disagreements between the other two.

Data collection process

Data available in texts, charts or tables were extracted by two independent authors using a previously devised form. Data presented in percentage were converted into frequency and rounded up if the number obtained was not an integer.

Data items: The following data were collected for each trial: (1) characteristics of participants; (2) type of intervention; (3) outcomes; and (4) type of outcome measurement (including definition, score adopted, bowel cleansing success, tolerability, adverse events prevalence, polyp and adenoma detection rate).

The following definitions standardizations were previously established for outcomes: (1) bowel cleaning success, defined as the number of patients with successful cleaning by either the study or by the assessment score as "excellent, adequate, good or clean"; (2) tolerability, defined as the number of patients who ingested the entire bowel cleaning preparation or the minimum established by the study as acceptable; (3) adverse events prevalence, defined as the number of patients affected by at least one adverse event; (4) polyp detection rate (PDR), defined as the number of patients with at least one polyp detected during colonoscopy; (5) adenoma detection rate (ADR), defined as the number of patients with at least one adenoma detected during colonoscopy.

Risk of bias in individual studies

As treatment effect size may differ due to selection, performance, detection and attrition bias, the methodological evaluation of the studies was performed. Two authors working independently determined the adequacy of randomization, adequacy of blinding, and the description of withdrawals and dropouts using the Jadad scale[24] for the evaluation of the randomized clinical trials.

Summary measures

Meta-analysis was preferably performed using intention-to-treat (ITT) data. Per-protocol (PP) data were only used when ITT data were not available. Outcomes evaluated were dichotomous (bowel cleansing success, tolerability, adverse events prevalence, polyp and adenoma detection rate). Risk difference (RD) with 95% confidence intervals (CI) was calculated for each outcome.

Synthesis of results

Meta-analyses were performed by computing RD for dichotomous outcomes using Mantel-Haenszel method (MH) with fixed-effects (FE) and random-effects (RE) models. Heterogeneity was assessed by Cochran's Q test (*P* value), which examines the null hypothesis that all studies are evaluating the same effect, and by Higgins' test (I^2), which quantifies inconsistency across studies and describes the percentage of the variability in effect estimates that is due to heterogeneity[25]. FE model was used in the presence of null or low heterogeneity ($I^2 < 50\%$) assuming the true effect size did not differ across studies. However, an I^2 value equal to or greater than 50% was considered substantial heterogeneity and RE model was preferred to FE as true effect size varied from one study to another and a more conservative approach for statistical significance was needed. The number needed to treat (NNT) for each outcome with statistical difference was also calculated. Review Manager 5 (RevMan 5) Version 6.1 (by the Cochrane Collaboration, 2015) was the software chosen to run the meta-analysis.

Risk of bias across studies

Reporting bias across studies was evaluated by a graphic diagnostic tool named funnel plot. For each trial, the treatment effect was plotted against the measure of study precision (represented by the inverse of its standard error) and the symmetry of scatter plot assessed by Egger's test[26]. Asymmetrical funnel plot suggests the presence of reporting bias (absence of low-precision studies that have negative or non-significant results), methodological bias or true heterogeneity between smaller and larger studies.

Additional analysis

In the presence of an asymmetrical funnel plot or high heterogeneity, ($I^2 \geq 50\%$) a sensitivity analysis was conducted to explore how the results of the meta-analysis change under different assumptions[27]. Heterogeneity and funnel plot before and after the removal of each study from the meta-analysis was assessed to identify the study

accounting for the inconsistency among trials (usually due to a markedly different intervention effect or an undue influence on the summary results). If heterogeneity was reduced to below 50% after the removal of the outlier, the corrected intervention effect estimate was applied and the interpretation of results made with caution. If inconsistency did not decrease, it was considered true heterogeneity.

Subgroup analyses were performed for variables that could knowingly influence the effect sizes: (1) types of regimen [(A) full intake on the day prior the exam; (B) intake split into the day prior and the same day of the exam; and (C) intake only on the same day of the exam); (2) volume of PEG-based solution [(A) low-volume group - 2L or less; and (B) high-volume group - more than 2L]; (3) dietary restrictions on day before [(A) low fiber or low residue diet; and (B) liquid diet].

RESULTS

Search and study selection

A total of 662 records were identified through a search in the databases (57 in MEDLINE, 128 in EMBASE, 384 in Scopus, 85 in CENTRAL, 8 in CINAHL and none in LILACS) (Figure 1). After adjusting for duplicates, 457 records remained and were evaluated by title and abstract. 390 records were excluded because they met one or more exclusion criteria. Of the 67 remaining, 28 were then excluded (2 were short communications and 26 were congress abstracts). The full texts of the remaining 39 records were examined and 23 were rejected. Reasons are presented in Supplementary material (Appendix 2). At the end, 16 studies were included in the meta-analysis[9,11,23-36].

Studies characteristics

All 16 studies selected were RCTs, with full text available, published in English between 1996 and 2017. Included studies involved 6200 participants, from 18 to 86 years of age. Main patient exclusion criteria were age, renal insufficiency, congestive heart failure, recent myocardial infarction, constipation, gastrointestinal or colon disorders, and previous colorectal surgery (Table 1).

Thirteen of 16 studies were multicenter. Six studies were conducted in South Korea, two in the United States and eight in different countries. Brand names of sodium picosulphate based products were CitraFleet®, Pico®, Pico-Salax®, Picolax®, Picoprep®, Picolight powder® and Prepopik®, while polyethylene glycol-based products were Colyte®, ColonLytely®, Coolprep powder®, Endofalk®, Half-Lytely®, Kleanprep®, Moviprep®, New Meroken® and Fortrans™.

Seven studies compared split dose regimens[28-30,32,33,38,40] and 4 studies compared day-before dose[13,33,34,41]. None of the included studies compared same-day dose. Four studies compared different regimens of bowel cleaning between the two products[15,31,39,40] and three others[35-37] according to the interval time to colonoscopy.

Two different adjuvants were used in 5 studies. Four studies[13,15,36,41] used Bisacodyl with PEG and 2 studies used it with SPMC[29,41]. Magnesium citrate was also used separated from sodium picosulphate in one study[36].

Dietary restrictions on the day prior to the procedure were considered in all studies. In four studies, patients were given liquid diet[13,15,34,36] and in twelve studies a low-fiber or low-residue diet[23-26,28,30,32-36] was allowed.

Outcomes

Sixteen studies evaluated bowel cleaning success. Efficacy was measured by five different bowel preparation scales: a 4-point scale[42], Boston bowel preparation scale[29,30,32,37,38], Aronchick scale[13,15,32,33,40,41], Harefield scale[32] and Ottawa bowel preparation scale[15,35,36,39,40]. Tolerability was evaluated in 12 studies[9,11,23,24,28-30,32-36], adverse events prevalence in 13 studies[13,15,28,29,31,34,37-39,41], PDR in seven[28,31,37-41] and ADR in five studies[31,32,38,39,41].

Risk of bias within studies

The maximum Jadad score obtained was three, since patient blinding was not possible due to the different characteristics of cleaning protocols (Table 2). Eleven studies scored three points[9,11,26-28,30-34,36], four studies scored two points[28-30,34] and one study scored just one point[40]. All of them were randomized, but Kim *et al*[40] did not describe the randomization method and Regev *et al*[34] randomized patients inappropriately. Kim *et al*[40], Leitao *et al*[28], Kim *et al*[29] and Munsterman *et al*[30] also failed to describe losses.

Results of individual studies

Raw data of included studies are presented in Supplementary material (appendix 3).

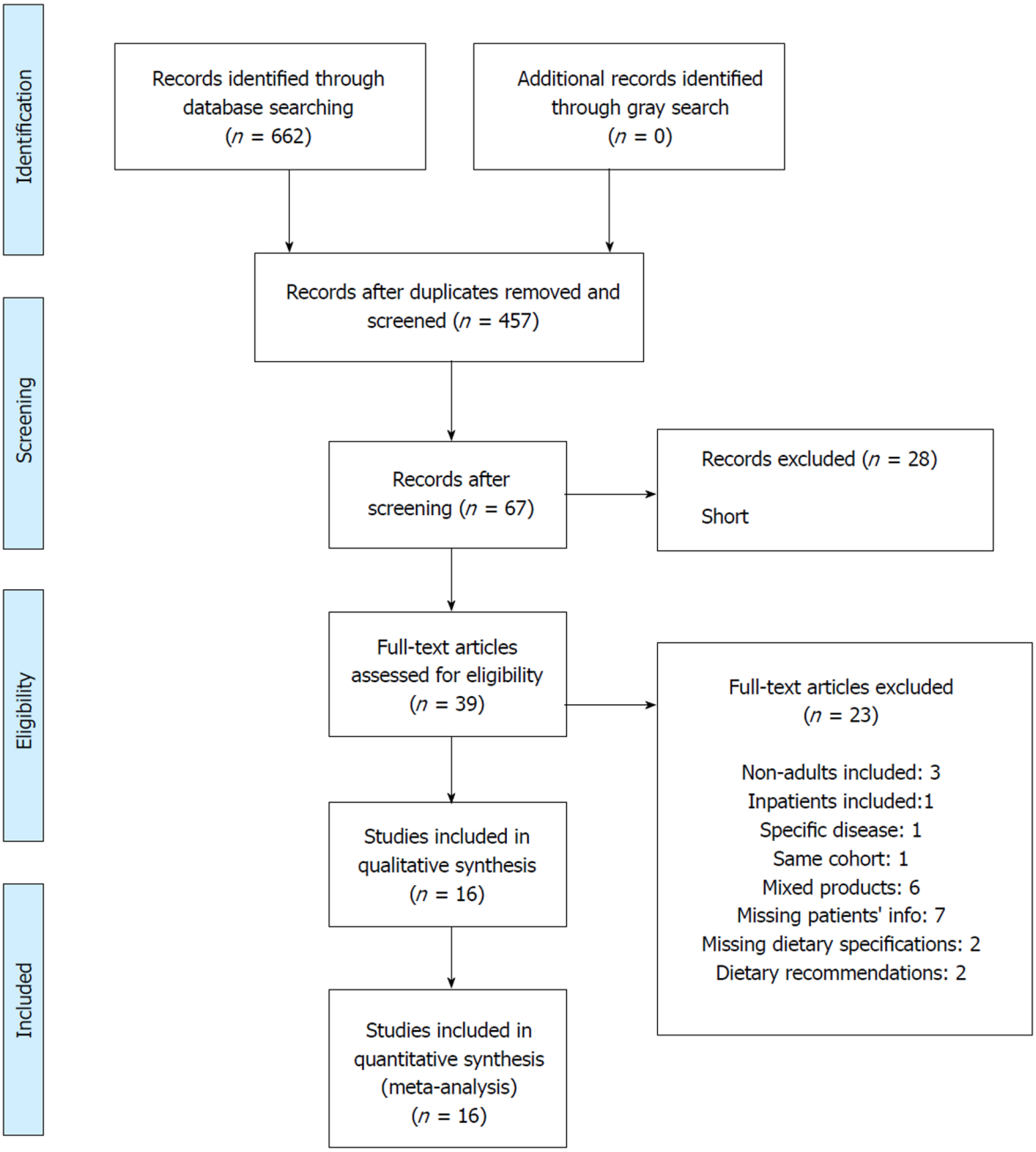

Figure 1 Flow diagram of included studies.

One study (Kim *et al*[40]) presented four different treatment arms, two of which were SPMC arms (with 2 or 3 sachets in split dose regimen) and two others of PEG arms (4 L of solution in a split or in a same-day dose regimen). For the analysis, the study was dismembered into two based on treatment regimens (Kim *et al*[40], SPMC split dose arms *vs* PEG split dose; and Kim *et al*[40], SPMC split dose *vs* PEG same-day dose).

Another study (Kojecky *et al*[33]) presented three different treatment arms (PEG, PEG plus ascorbic acid and SPMC) with two subgroups each (day-before dose and split dose). PEG and PEG-A treatment arms were grouped and the study dismembered into two according to the regimen (Kojecky *et al*[33], day-before dose; and Kojecky *et al*[33], split dose).

Bowel cleansing success: Twelve studies (corresponding to fourteen comparisons) demonstrated that sodium picosulphate and PEG had the same efficacy in bowel cleaning[13,29,33-40], two studies demonstrated that sodium picosulphate was better[15,41] and one study demonstrated that PEG was better[31].

Tolerability: Three studies (four comparisons) demonstrated that both obtained the same tolerability level[37,39,40], seven demonstrated that SPMC was better

Table 1 Studies characteristics

STUDY	SITE	POPULATION	INTERVENTION (ITT/PP)	COMPARISON (ITT/PP)	OUTCOMES
Regev *et al*[34]	1	29 to 86 y	Pico-Salax (1+1+1)/0 sachets	New-Meroken® 3/0 L	Bowel cleansing quality
	Israel		+ (200/h for 16h)/0 mL of water		Cecal intubation
		ITT: 68	+ clear liquid diet	+ clear liquid diet	General discomfort
		PP: 68	39/39	29/29	Medication Intake
					Adverse events
Lawrance *et al*[35]	1	18 to 75 y	Pico® (1+1)/0 sachets for morning procedure or	ColonLytely® 4/0 L for morning procedure or	Bowel cleansing quality
	Australia		Pico 1/1 sachets for afternoon procedure	ColonLytely® 4/0 L for afternoon procedure	
			+ liquid	+ clear liquid 2/0	
		ITT: 634	+ low residue diet	284/279	Medication Intake
		PP: 625	171/169		
			CB fleet® (45+45)/0 mL		
			+ (750+750)/0 mL of water for morning procedure or		Mucosal inflammation
			CB fleet® 45/45 mL		
			+ 750/750 mL of water for afternoon procedure		
			+ low residue diet		
			179/177		
Kao *et al*[36]	1	18 to 75 y	SPMC (1+1+MC)/0 sachets for morning procedure or	PEG 4/0 L for morning procedure or	Bowel cleansing quality
	Canada		SPMC (1+1)/MC sachets for afternoon procedure	PEG 2/2 L for afternoon procedure	Bowel cleansing quality according to the procedure time
		ITT: 834	+ liquid	+ liquid	Tolerability
		PP: 790	+ clear liquid diet	+ clear liquid diet	
			194/194	218/210	Adherence
			NaP 45/45/0 mL for morning procedure or	PEG 2/0 L + bisacodyl 20/0 mg for morning procedure or	Sleeping hours
			NaP 0/45/45 mL for afternoon procedure	PEG 0/2 L + bisacodyl 20/0 mg for afternoon procedure	Willingness to reuse
			+ liquid	+ liquid	Safety
			+ clear liquid diet	+ clear liquid diet	
			164/164	214/210	Ischemic colitis
Katz *et al*[15]	12	18 to 80 y	Prepopik® (1+1)/0 sachets	Half-Lytely e bisacodyl Tablets® 2/0 L	Bowel cleansing quality
	USA		+ (1200+720)/0 mL of liquid	+ 10/0 mg bisacodyl	Acceptability
					Tolerability
		ITT: 603	+ clear liquid diet	+ clear liquid diet	Medication Intake
		PP: 598			Ease to use medication
			300/296	303/302	General experience
					Taste
					Willingness to reuse
					Adverse events
Manes *et al*[37]	3	18 to 85 y	CitraFleet® (1+1)/0 sachets	Moviprep® 2/0 L	Bowel cleansing quality
	Italy		+ 3/0 L of liquid for morning procedure or	+ 1/0 L of liquid for morning procedure or	Bowel cleansing quality of right colon
		ITT: 293	CitraFleet® 1/1 sachets	Moviprep® 1/1 L	Polyps detected

		PP: 285	+ 1.5/1.5 L of liquid for afternoon procedure	+ 500/500 mL of liquid for afternoon procedure	Acceptance
			+ low-fiber diet	+ low-fiber diet	Tolerability
			145/140	148/145	Adherence
					Adverse events
Rex *et al*[15]	10	18 to 80 y	Prepopik® 1/1 sachets	Half-Lytely e bisacodyl Tablets® 2/0 L	Bowel cleansing quality
	USA		+ 1200/720 mL of liquid	+ bisacodyl 10/0 mg	Acceptability
				+ clear liquid diet	Tolerability
		ITT: 608	+ clear liquid diet		Ease to use medication
		PP: 601			Medication Intake
					Taste
			NA/305	NA/298	Willingness to reuse medication
					Adverse events
					Colonoscopy before
Jeon *et al*[38]	1	20 to 80 y	Picolight powder® (1+1)/1 sachet	Coolprep powder® 1/1 L	Bowel cleansing quality
	South Korea		+ (1+1)/1 L of water	+ 500/500 mL of water	Cecal intubation
			+ low-fiber diet	+ low-fiber diet	Withdrawal time
		ITT: 430			ADR
		PP: 388			PDR
					Tolerability
			215/195	215/193	Satisfaction
					Adverse events
Kang *et al*[39]	1	18 to ou mais	Picolight® 0/(1+1)	Colyte® 2/2 L	Bowel cleansing quality
	South Korea		+ 0/≥ 1 L of water	+ low-fiber diet	Tolerability
		ITT: 197	+ low-fiber diet	99/99	Adverse events
		PP: 197	98/98		Sleep time quantity
					PDR
					ADR
Kim *et al*[40]	1	18 to 75 y	SPMC 1/1 sachets	PEG 0/4 L	Bowel cleansing quality
	South Korea		+ 1/1 L of liquid		Adherence
			+ low-fiber diet	+ low-fiber diet	Medication Intake
		ITT: 200	50/50	50/50	
		PP: 200	SPMC (1+1)/1 sachets	PEG 2/2 L	Tolerability
			+ (1+1)/1 L of liquid		Taste
			+ low-fiber diet	+ low-fiber diet	Biochemical changes
			50/50	50/50	Adverse events
Kim *et al*[41]	1	18 to 80 y	Picolight (1+1)/0 sachets	Standard PEG 4/0 L	Acceptability
	South Korea		+ 2L of water		Adherence to instructions
		ITT: 194	+ bisacodyl 10/0 mg	+ bisacodyl 10/0 mg	Bowel cleansing quality
		PP: 184	+ low-fiber diet (ZeroCol)	+ semi-fluid diet	Adverse events
			97/94	97/90	Willingness to reuse medication
Leitao *et al*[28]	3	18 to 80 y	CitraFleet® 1/1 sachets	Enddealk® 2/1L	Bowel cleansing quality
	Norway		+ 2/2 L of water	+ 0/1 L of liquid	Tolerability
		ITT: 368	+ no-grains diet	+ diet without crops	Adherence
		PP: 368			PDR
			179/179	189/189	Cecal intubation time
					Cecal intubation
Kim *et al*[29]	13	20 to 75 y	sachets	Standard PEG 2/2 L	Bowel cleansing quality
	South Korea		+ 2/2 L of water	no bisacodyl	Satisfaction
			+ bisacodyl 10/0 mg	+ low-fiber diet	Tolerability
			+ low-fiber diet		Medication Intake

		ITT: 387	193/181	194 / 184	Ease to use
		PP: 365			Taste
					Willingness to reuse
					Adverse events
Munsterman *et al*[30]	1	18 to 80 y	Picoprep® 1/1 sachets for morning procedure or	Kleanprep® 3/1 L for morning procedure or	Bowel cleansing quality
	Netherlands	ITT: 173	Picoprep® 1/1 sachets for afternoon procedure	Kleanprep® 2/2 L for afternoon procedure	
		PP: 172	+ 2/2 L of water	+ additional liquid	Tolerability
			+ low-fiber diet	+ low-fiber diet	
			88/87	85/85	
Pohl *et al*[31]	17	40 to 80 y	CitraFleet® (1+1)/0 sachets	Moviprep® 1/1 L	Patients with at least one polyp or flat lesion
	Germany	ITT: 399	+ 250mL/h of water after sachet	+ 500/500 mL of liquid	Patients with at least one adenoma
		PP: 398			Cancer detection rate
			+ fibers restriction diet	+ fibers restriction diet	Flat lesion detection rate
			NA/197	NA/201	Advanced lesions detection rate
Yoo *et al*[32]	1	18 to 80 y	Picolight® 1/1 sachets	Coolprep® 1/1 L	Bowel cleansing quality
	South Korea		+ 1/1 L of water	+ 500/500 mL of water	Bubble score
		ITT: 200	+ low-fiber diet	+ low-fiber diet	Tolerability
		PP: 200			
			100/100	100/100	Satisfaction
Kojecky *et al*[33]	3	18 to 99 y	Picoprep® 2/0 sachets	Fortrans™ 4/0 L	Length of preparation
	Czech Republic		+ 2L of water	94/102	
		ITT: 612	92/102	Fortrans™ 3/1 L	Time to colonoscopy
				87/102	
		PP: 584	OR	Moviprep™ 2/0 L	
				+ 1/0 L of fluids	
			Picoprep® 1/1 sachets	96/102	Bowel cleansing quality
			+ 1/1 L of water		
			86/102	Moviprep™ 1/1	
				+ 0.5/0.5 L of fluids	
				93/102	Tolerability score
			+ low residue diet	+ low residue diet	

* In intervention and control columns, slash separates different days and plus sign separates different doses on the same day; * ITT: number of randomized patients (intention to treat); * PP: number of treated patients (per protocol); * NR: not reported in full-text; * PDR: polyp detection rate; * ADR: adenoma detection rate.

tolerated[13,15,28,34,35,40,41] and one that PEG was better than SPMC[39].

Adverse events prevalence: Eight studies reported adverse events prevalence as a dichotomous outcome. Five of them showed that both products regimens presented the same adverse events prevalence[13,15,28,34,38] and three of them that SPMC regimens achieved fewer adverse events[29,31,41].

PDR: Five studies (corresponding to six comparisons) demonstrated that PDR was the same with both products regimens[31,37,38,40,41]. In one study there was statistical difference in favor of SPMC[28].

ADR: Only five studies assessed ADR and none of them showed difference between SPMC and PEG[31,32,38,39,41].

Syntheses of results

The overall meta-analysis for each outcome was performed with heterogeneity assessment and cumulative treatment effect.

Bowel cleaning success: An asymmetrical funnel plot and high heterogeneity (I^2 = 91%, P < 0.00001) were observed among the 15 studies included. An outlier study

Table 2 Assessment of risk of bias by JADAD scale

#	STUDY	Randomized? (1 pt)	Randomization method	Adequate randomization? (1 pt)	Double blind? (1 pt)	Masking method	Adequate masking? (1 pt)	Loss description? (1 pt)	Jadad (0-5 pts)	GENERAL QUALITY
1	Regev *et al*[34]	Yes	Randomization per patients' ID (odd or even numbers)	No	No	Endoscopist blind for the preparation regimen	No	Yes	2	Intermidiate
2	Lawrance *et al*[35]	Yes	Randomized using Generator Pro 1.69 (Segobit software) in ratio 2:1:1 (PEG:NaP:Pi-co)	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
3	Kao *et al*[36]	Yes	Randomization in blocks of 8 and stratified per AM/PM using a computer-generated table	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
4	Katz *et al*[15]	Yes	Randomization numbers allocated sequentially by voice system	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
5	Manes *et al*[37]	Yes	Randomization by computer-generated sequence	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
6	Rex *et al*[15]	Yes	Randomization numbers allocated sequentially by voice system	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
7	Jeon *et al*[38]	Yes	Randomization by computer-generated table	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
8	Kang *et al*[39]	Yes	Randomization in blocks using website randomization.com	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
9	Kim *et al*[40]	Yes	Not described	No	No	Endoscopist blind for the preparation regimen	No	No	1	Low
10	Kim *et al*[41]	Yes	Randomization by computer-generated sequence	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
11	Leitao *et al*[28]	Yes	Randomization 1:1 with blocks of 10 by endoscopy-unit secretary	Yes	No	Endoscopist blind for the preparation regimen	No	No	2	Intermidiate

12	Kim *et al*[29]	Yes	Randomization by computer-generated table	Yes	No	Not described	No	No	2	Intermidiate
13	Munsterman *et al*[30]	Yes	Randomization by computer-generated 1:1 stratified by age (18-64) or (65-80)	Yes	No	Endoscopist blind for the preparation regimen	No	No	2	Intermidiate
14	Pohl *et al*[31]	Yes	Randomization 1:1 in blocks of 4 by statistician list-generated	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
15	Yoo *et al*[32]	Yes	Randomization 1:1 in blocks of 4 by a a computer-generated list	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
16	Kojecky *et al*[33]	Yes	Randomization 1:1 using a software generated random table	Yes	No	Endoscopist blind for the preparation regiment	No	Yes	3	High

responsible for reporting bias was identified through sensitivity analysis (Pohl *et al*[31]). After its exclusion (I^2 = 35%, P = 0.09) and through the use of FE model, there was statistical difference in favor of SPMC. More cases of success were obtained with SPMC compared to PEG [MH FE, RD 0.03, IC (0.01, 0.05), P = 0.003, I^2 = 33%] with a NNT of 34 (34 people need to be treated with SPMC to obtain 1 additional benefit over PEG) (Figures 2 and 3).

Patient tolerability: Sensitivity analysis of the eleven included studies revealed true heterogeneity (I^2 = 88%, P < 0.00001) and RE model was adopted. SPMC was better tolerated than PEG [MH RE, RD 0.08, IC (0.03, 0.13), P = 0.002, I^2 = 88%], with a NNT of 13 (Figure 4). As Manes *et al*[37] and Jeon *et al*[38] criteria for completion of intake were different from other studies (failure was defined as lower than 70% and 50% of ingestion of the solutions, respectively), additional analysis was performed without them. The result still favored SPMC [MH RE, RD 0.09, IC (0.03, 0.15), P = 0.002, I^2 = 91%] and lower NNT (NNT of 11).

Adverse events prevalence: A RE model analysis was conducted due to the high heterogeneity among the ten included studies (I^2 = 88%, P < 0.00001). Fewer adverse events occurred using SPMC [MH RE, RD 0.13, IC (0.05, 0.22), P = 0.002, I^2 = 88%], and the NNT obtained was 7 (7 people need to be treated with SPMC to avoid 1 adverse event over PEG) (Figure 5).

PDR: An asymmetric funnel and inconsistency in the upper limit (I^2 = 50%, P = 0.06) were observed among the seven included studies. Sensitivity analysis identified the study responsible for the heterogeneity (Leitao *et al*[28]). The study was not excluded due to the small number of studies included (fewer than 10) and a RE model analysis was conducted. There was no difference between SPMC and PEG for polyp detection [MH RE, RD -0.03, IC (-0.09, 0.02), P = 0.30, I^2 = 50%] (Figure 6).

ADR: Heterogeneity was null among the five studies included and a FE model analysis showed no statistical difference between SPMC and PEG, but a trend in favor of PEG was present [MH FE, RD -0.05, IC (-0.11, -0.00), P = 0.05, I^2 = 0%] (Figure 7).

Subgroups analyses

Additional analyses were performed by subgroups based on type of regimen, volume of PEG solution and dietary recommendations for the day prior to colonoscopy.

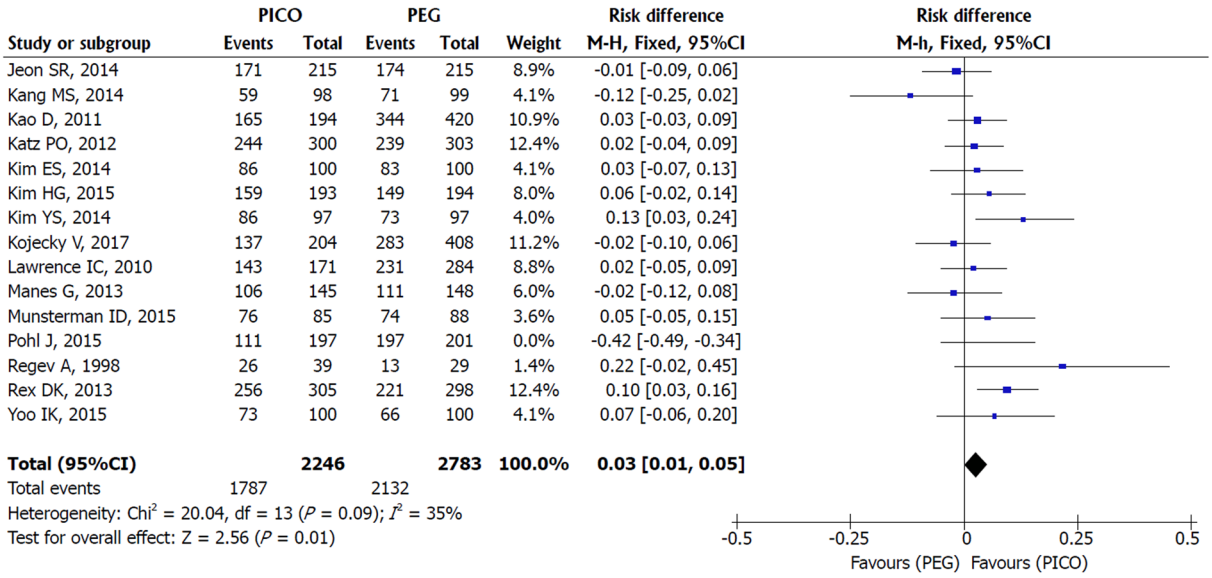

Figure 2 Metanalysis forest plot of bowel cleaning success.

Per type of regimen: Studies were divided into four subgroups according to regimens compared: day-before dose[13,33,34,41]; split dose[28-30,32,33,38,40]; according to interval time for colonoscopy[35-37]; and comparison of different regimens[15,31,39].

Bowel cleansing success: SPMC was better than PEG for bowel cleaning in day-before dose comparison [MH RE, RD 0.06, IC (0.01, 0.11), P = 0.02, I^2 = 38%], with an NNT of 17. No difference was observed in the split dose regimen [MH FE, RD 0.01, IC (-0.03, 0.05), P = 0.56, I^2 = 29%], in the according-to-interval-time regimens [MH FE, RD 0.02, IC (-0.03, 0.06), P = 0.45, I^2 = 0%] and in the different regimens subgroup [MH RE, RD -0.14, IC (-0.50, 0.21), P = 0.42, I^2 = 98%].

Additional sensitivity analysis by subgroups showed that inconsistency among all studies included in the overall meta-analysis decreased from 91% to 19% after the removal of different regimens subgroup, in which the previous outlier study for the outcome was identified (Pohl *et al*[31]). Without this subgroup, the statistical difference disappeared and there was only a trend in favor of SPMC [MH FE, RD 0.03, IC (0.00, 0.05), P = 0.03, I^2 = 19%] (Appendix 4 - Figure 1).

Patient tolerability: No difference was observed in tolerability in the split dose regimen (MH RE, RD 0.04, IC [-0.05, 0.14], P = 0.38, I^2 = 86%) and in the different regimens subgroup [MH RE, RD 0.04, IC (-0.09, 0.17), P = 0.54, I^2 = 97%]. In the day-before dose regimen [MH FE, RD 0.17, IC (0.13, 0.21), P < 0.0001, I^2 = 0%] and in the according-to-interval-time subgroups [MH RE, RD 0.08, IC (0.01, 0.15), P = 0.02, I^2 = 54%], SPMC was better tolerated than PEG, with an NNT of 6 and 13, respectively. Sensitivity analysis by subgroups did not change the overall meta-analysis results either (Appendix 4 - Figure 2).

Adverse events: Three subgroups were available (day-before dose, split dose and different regimens). No difference was found in day-before dose [MH RE, RD -0.18, IC (-0.50, 0.14), P = 0.26, I^2 = 96%] and in split dose subgroups [MH RE, RD -0.07, IC (-0.16, 0.02), P = 0.15, I^2 = 62%], but there were fewer adverse events with SPMC in the different regimens subgroup [MH RE, RD -0.10, IC (-0.19, -0.02), P = 0.01, I^2 = 60%], with a NNT of 10(Appendix 4 - Figure 3).

PDR: The analysis showed no difference in PDR in the split dose subgroup [MH FE, RD 0.04, IC (-0.03, 0.10), P = 0.28, I^2 = 43%] and superiority of PEG over SPMC in the different regimens subgroup [MH FE, RD -0.09, IC (-0.17, -0.01), P = 0.02, I^2 = 0%], with a NNT of 12 (Appendix 4 - Figure 4).

ADR: Only two subgroups (split dose and different regimens) with 2 studies each were available. There was no statistical difference in ADR between them [split dose: MH FE, RD -0.02, IC (-0.11, 0.07), P = 0.70, I^2 = 0%; different regimens: MH FE, RD -0.06, IC (-0.14, 0.01), P = 0.09, I^2 = 0%] (Appendix 4 - Figure 5).

Per volume of PEG solution: Eight studies were included in low-volume subgroup[13,15,31-33,36-38] and nine in high-volume subgroup[29,30,33-36,39-41].

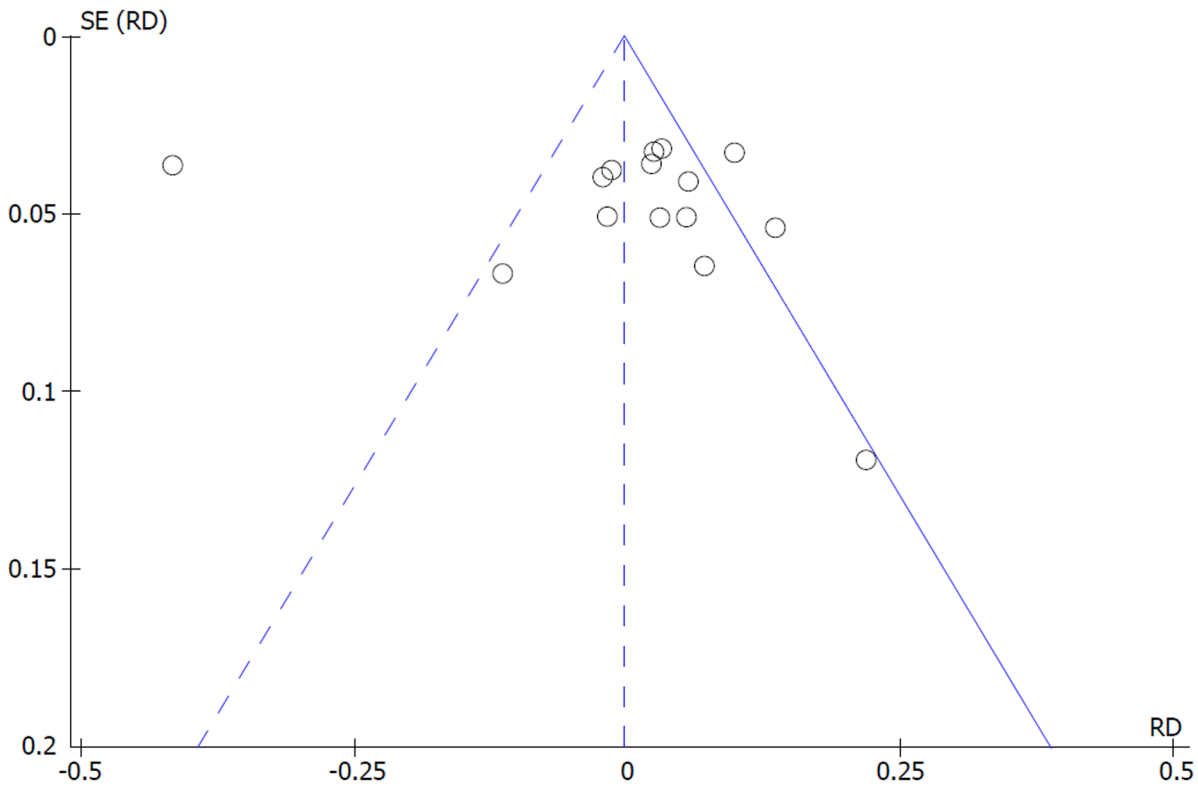

Figure 3 Metanalysis funnel plot of bowel cleaning success.

Bowel cleansing success: Low-volume PEG subgroup presented high heterogeneity (I^2 = 96%, P < 0.00001) and sensitivity analysis identified one study (Pohl *et al*[31]) as the responsible for funnel asymmetry and high heterogeneity. Considering the small number of studies, it was maintained for the analysis and RE model was adopted. No difference was observed in bowel cleaning between SPMC and low-volume PEG [MH RE, RD -0.03, IC (-0.16, 0.09), P = 0.61, I^2 = 95%]. High-volume subgroup analysis also showed no difference between them [MH FE, RD 0.03, IC (-0.01, 0.06), P = 0.09, I^2 = 42%] (Appendix 4 - Figure 6).

Patient tolerability: SPMC was better tolerated than high-volume PEG solution [MH RE, RD 0.08, IC (0.01, 0.14), I^2 = 89%, P = 0.02], with a NNT of 13, and a trend in favor of SPMC was observed in the low-volume PEG subgroup [MH RE, RD 0.08, IC (0.00, 0.16), I^2 = 87%, P = 0.05]. (Appendix 4 - Figure 7).

Adverse events: After the performance of a sensitivity analysis, a study responsible for the heterogeneity in the high-volume subgroup was identified (Kim *et al*[41]), but was not excluded due to the small number of studies (fewer than 10 studies). RE model analysis showed SPMC caused fewer adverse events than PEG in the high-volume subgroup [MH RE, RD -0.18, IC (-0.30, -0.07), P = 0.002, I^2 = 79%], with a NNT of 6. There was no difference in adverse events prevalence in the low-volume subgroup [MH RE, RD 0.09, IC (-0.02, 0.20), P = 0.12, I^2 = 91%] (Appendix 4 - Figure 8).

PDR: Sensitivity analysis was carried out for high-volume subgroup and the study responsible for the inconsistency was identified (Leitao *et al*[28]). It was not removed due to the small number of included studies. There was no difference in PDR in the low-volume subgroup [MH FE -0.05, IC (-0.11, 0.01), P = 0.11, I^2 = 0] or in the high-volume subgroup [MH RE, RD -0.03, IC (-0.14, 0.09), P = 0.65, I^2 = 71%] (Appendix 4 - Figure 9).

ADR: No difference was observed between SPMC and PEG in both subgroups [low-volume: MH FE, RD -0.04, IC (-0.11, 0.02), P = 0.17, I^2 = 0%; high-volume: MH FE, RD -0.07, IC (-0.17, 0.02), P = 0.12, I^2 = 0%] (Appendix 4 - Figure 10).

Per dietary recommendations: Four studies were included in liquid diet subgroup[13,15,34,36] and twelve studies[23-28,30,32-36] in the low residue diet subgroup.

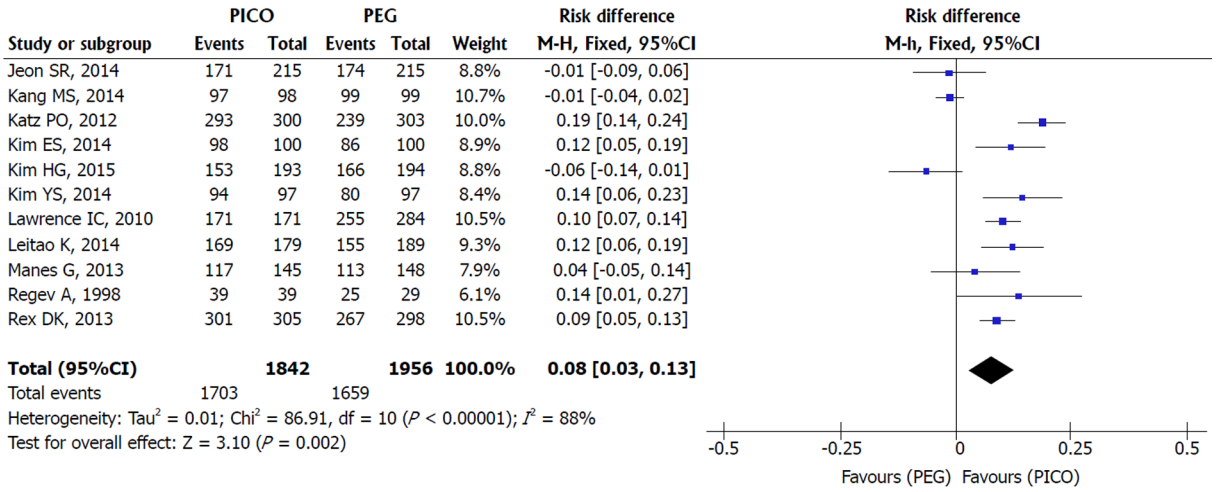

Figure 4 Metanalysis forest plot of tolerability.

Bowel cleansing success: The analysis showed that SPMC was better than PEG for bowel cleaning in the liquid diet subgroup [MH FE, RD 0.06, IC (0.02, 0.09), $P = 0.002$, $I^2 = 40\%$], with a NNT of 17. In the low residue diet subgroup, high heterogeneity and an asymmetrical funnel plot were initially observed ($I^2 = 93\%$, $P < 0.00001$). After sensitivity analysis, one study (Pohl *et al*[31]) was identified as the responsible for reporting bias. After its exclusion, heterogeneity decreased to an acceptable level ($I^2 = 31\%$) and analysis using FE model showed that SPMC and PEG were similar in the low residue subgroup [MH FE, RD 0.01, IC (-0.02, 0.04), $I^2 = 30\%$, $P = 0.38$] (Appendix 4 – Figure 11).

Patient tolerability: SPMC was better tolerated than PEG in the liquid diet group [MH RE, RD 0.14, IC (0.06, 0.22), $I^2 = 81\%$, $P = 0.0006$], with an NNT of 8, and a trend in favor of SPMC was identified in the low residue subgroup [MH RE, RD 0.06, IC (0.00, 0.11), $I^2 = 86\%$, $P = 0.05$] (Appendix 4 - Figure 12).

Adverse events: There was low heterogeneity ($I^2 = 43\%$, $P = 0.17$) among the three studies included in the liquid diet subgroup and high heterogeneity ($I^2 = 86\%$, $P < 0.00001$) among the seven studies included in the low residue subgroup. FE and RE models were used for liquid diet and low residue subgroups, respectively. There was no difference between SPMC and PEG in the liquid diet subgroup [MH FE, RD -0.02, IC (-0.08, 0.05), $P = 0.59$, $I^2 = 43\%$], but the low residue subgroup SPMC presented fewer adverse events than PEG [MH RE, RD -0.17, IC (-0.27, -0.07), $P = 0.0008$, $I^2 = 86\%$], with a NNT of 6 (Appendix 4 - Figure 13).

Polyp and adenoma detection rates: PDR and ADR subgroups were the same for SPMC *vs* PEG comparison because all the included trials in this comparison recommended only low residue diet on the day before.

DISCUSSION

Summary of evidence

Results from the meta-analysis of the 16 included studies (with 6200 subjects from ten different countries) indicate that for adult outpatients before elective colonoscopy, SPMC is at least similar to PEG in bowel cleaning efficacy, better in tolerability and in adverse events prevalence and similar in polyp and adenoma detection rate.

As high inconsistency and true heterogeneity were present among the included studies despite the strict inclusion criteria adopted, caution for interpretation of data is recommended. Populations of different countries with different dietary patterns, different options of dosage and schedule for bowel preparation and different scales and different instruments to measure outcomes may have contributed to increase heterogeneity. As bowel cleaning protocols vary between different institutions worldwide, variations across trials are inherent and expected.

As this meta-analysis provided an overall impression by grouping different bowel cleaning protocols and did not consider confounding factors, such as type of regimen, volume of solution ingested and dietary restrictions, additional analyses by subgroups were conducted to elucidate these aspects and to help decision-making in

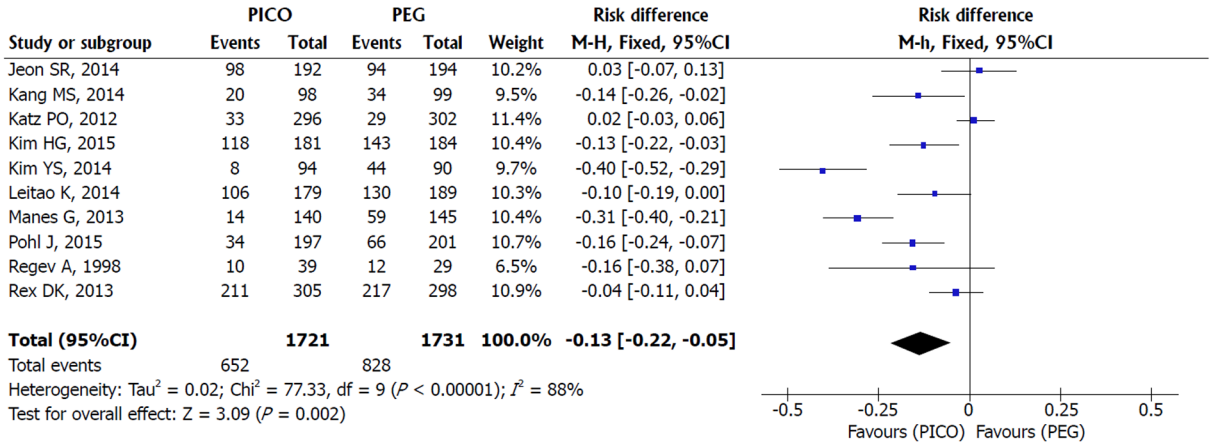

Figure 5 Metanalysis forest plot of adverse events.

daily clinical practice.

Sensitivity analyses provided additional information on the influence of the studies in the meta-analysis, helping with the confounding factors. Pohl *et al*[31] was identified as the main outlier study for bowel cleaning due to its methodological bias of treatment: the comparison of different regimens of bowel preparation.

As previously known in a meta-analysis by Bucci *et al*[43], the interval time between the last drink of bowel preparation and the beginning of colonoscopy (also known as "runway time") is a key factor for cleaning quality. When Pohl *et al*[31] compared different regimens (a split regimen of PEG and a day-before regimen of SPMC), the difference between treatment effects was increased and favored that one with the shorter "runway time" (PEG).

The sensitivity analysis by subgroups of regimen confirmed the impact of including trials comparing different regimens. Through the exclusion of this subgroup (Rex *et al*[15], Kang *et al*[39], Kim *et al*[40] and Pohl *et al*[31]), a more reliable analysis with less heterogeneity was obtained and the difference in bowel cleaning and the trend in favor of PEG for adenoma detection disappeared. Hence, the more rational approach was to assume SPMC and PEG were similar for both outcomes.

Statistical difference in favor of SPMC was also identified in the sub-analysis in the following situations: (1) bowel preparation was made on the day before (better bowel cleaning success and better tolerability); (2) bowel preparation was made based on the interval time to colonoscopy (also better tolerability); (3) when compared to high-volume solution of PEG (better tolerability and fewer adverse events); (4) liquid diet was the option on the day before (with better bowel cleaning success and better tolerability); and (5) low residue diet was the option on the day before (fewer adverse events).

Although there was statistical difference in these outcomes, it is also important to observe the number needed to treat to evaluate treatment effectiveness properly and to help deciding about changes in daily clinical practice. If the NNT is high, there is low chance of benefits for the patient with the alternative treatment, which might not justify its adoption.

The high NNTs of SPMC for bowel cleaning (NNT of 34) and for tolerability (NNT of 13) result in a small chance of benefit for the patient (2.9% and 7.6%, respectively). However, the small NNT for adverse events (NNT of 7) reveals a significant reduction of 14.2% when SPMC is used, this being its main advantage and the reason for its adoption over PEG.

Benefits of using SPMC are also obtained in day-before preparations (16.6% more chance of tolerability), against high-volume solutions of PEG (reduction of 16.6% in chance of adverse events) and with prior-day dietary restrictions (a 12.5% greater chance of tolerability with the use of liquid diet and a 16.6% reduction in the chance of adverse events with low residue diet).

Despite the potential benefits of SPMC demonstrated in this meta-analysis, care should be taken in regard to some of the product faults. Because of the potential electrolyte shifts, SPMC is not recommended in patients with renal insufficiency, end-stage liver disease, heart failure and electrolyte abnormalities[44,45]. PEG is the product of choice for those patients as it is an inert molecule and isosmotic solution, which also induces less mucosal damage (inflammation or ulceration) by ten times when compared to SPMC[35].

The main disadvantage of PEG consists in the amount of solution to be ingested as

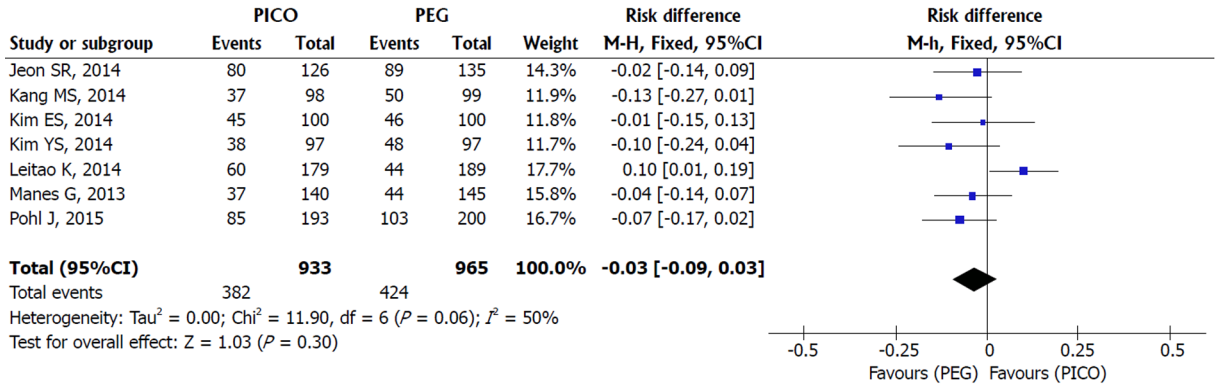

Figure 6 Metanalysis forest plot of polyp detection rate.

observed in the meta-analysis by Xie *et al*[46]. Further sub-analyses by volume of PEG solution presented in this meta-analysis reinforce this drawback. High-volume PEG presented less tolerability and more adverse events than SPMC whereas no difference was found between low-volume PEG and SPMC. As tolerability and adverse events are correlated factors that can affect bowel cleaning, SPMC appears as an interesting alternative.

An extensive search strategy, well-defined eligibility criteria, careful inclusion of the studies and analyses based on "intention-to-treat" data are the strength of this study. Results obtained by additional analyses focusing on subgroups based on regimen schedule, volume of PEG solution and dietary restriction bring new information and complement two recent meta-analyses.

Jin *et al*[20] and van Lieshout *et al*[47] showed that SPMC was equally effective or slightly superior to PEG in terms of bowel cleaning efficacy and that it was better tolerated than PEG. However, they did not consider patient status (if inpatient or outpatient) for studies selection and grouped different types of patients. This is the first meta-analysis for this specific group of patients and the first communicating effectiveness of bowel preparation using NNT.

Limitations

Nine full-text trials identified in the search were not included in this meta-analysis due to the lack of essential information concerning eligibility criteria[48-56]. Their absence may have contributed to borderline results in some sub-analyses with few included studies, but it assured the assertiveness of the results for this specific population.

Quality of bowel cleaning measured by different cleanliness scores and patients' preferences and impressions of the products are other important outcomes that were not evaluated. Due to the different instruments to collect data used by trials, matching these data is prejudiced.

The type and severity of adverse events were also not explored. Owing to the methodological feature of RCTs and the characteristics of those products, the events are generally mild to moderate gastrointestinal symptoms (nausea, vomiting, abdominal pain, bloating and dizziness). Serious adverse events after bowel preparation are rare[57].

In addition, results obtained by this meta-analysis should be only inferred to healthy patients or those with mild disease as the included trials excluded other types of patients. This is especially important for the use of SPMC, as it is known for the occurrence of electrolyte disturbances which could have a repercussion in moderately or severely diseased patients.

Finally, although all the included studies were randomized clinical trials, five of them presented problems regarding randomization and masking, the description of losses and failure in reporting the outcomes, which compromised the quality of the evidence. Therefore, the quality of the evidence obtained was moderate for bowel cleaning efficacy, tolerability and adverse events prevalence, and low for polyp and adenoma detection rates[58]. Future studies might influence some outcomes and sub-analyses, especially those with borderline differences, with high NNTs or few studies included.

Conclusion

According to data published until now, SPMC seems to be a better product than PEG for bowel preparation in healthy or mildly diseased adult outpatients before

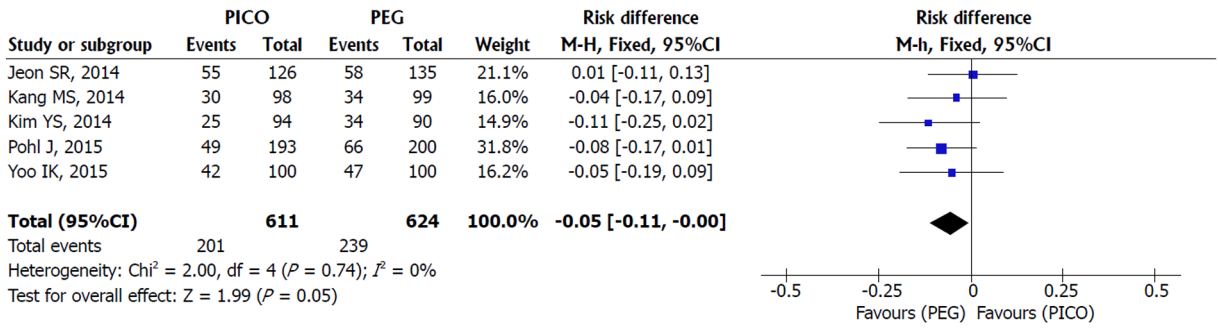

Figure 7 Metanalysis forest plot of adenoma detection rate.

colonoscopy as its bowel cleaning efficacy is at least equal to that of PEG, its tolerability is better and adverse events prevalence is lower. The latter corresponds to the main advantage of using SPMC instead of PEG. Both SPMC and PEG can be used for split preparations as there are no difference in bowel cleaning success, tolerability and adverse events prevalence, but SPMC should be the choice for day-before preparations because of its better tolerability.

ARTICLE HIGHLIGHTS

Research background

Colonoscopy reduces the incidence and mortality for colorectal cancer. Bowel preparation is the cornerstone for colonoscopy as the quality of bowel cleaning directly affects the effectiveness for detecting neoplastic lesions. Different options of purgatives exist as a result of the search for the ideal product and none of them have all the ideal features. PEG solutions are the most widely used and studied bowel cleanser, while SPMC is a recently developed one to overcome PEG's poor palatability and large volume of solution to be ingested. Meta-analyses of RCTs are the best evidence for medical practice, but none of them compared SPMC and PEG for outpatients before colonoscopy, leaving a gap in the literature.

Research motivation

Most of elective colonoscopies are performed in outpatients and inpatient status is an independent risk factor for inadequate bowel preparation. As previous meta-analyses comparing SPMC and PEG before elective colonoscopy did not consider patient status for inclusion criteria, there is no established evidence for this subset of patients.

Research objectives

To determine the best option for bowel preparation in adult outpatients before elective colonoscopy by comparing cleaning efficacy, tolerability, AE prevalence, PDR and ADR between SPMC and PEG. This is the first meta-analysis to include only outpatients and to communicate effectiveness using NNT.

Research methods

Systematic review and meta-analysis followed PRISMA Statement. Eligibility criteria were based on PICOS strategy. Search was performed in MEDLINE, Scopus, EMBASE, CENTRAL/Cochrane, CINAHL and LILACS. Jadad scale was the tool adopted to evaluate the methodological quality of included RCTs and heterogeneity among studies was assessed by Higgins' test (I^2). Meta-analysis was preferably performed using intention-to-treat data by computing risk difference (RD) for dichotomous outcomes using Mantel-Haenszel (MH) method and NNT calculated for each outcome with statistical difference.

Research results

Sixteen RCTs with 6200 subjects were included for the meta-analysis and high heterogeneity was found among them. Sensitivity analysis and sub analysis by type of regime, volume of PEG solution and dietary recommendations were performed to interpret data. In the overall analysis, SPMC was better for bowel cleaning [RD 0.03, IC (0.01, 0.05), NNT 34], for tolerability [RD 0.08, IC (0.03, 0.13), NNT 13] and for adverse events [RD 0.13, IC (0.05, 0.22), NNT 7]. The small NNT for adverse events (NNT of 7) reveals a reduction of 14.2% when SPMC is used. Better tolerability for SPMC was also found in "Day-before preparations" [RD 0.17, IC (0.13, 0.21), NNT 6], "According to interval time" [RD 0.08, IC (0.01, 0.15), NNT 13], "Against high-volume of PEG" [RD 0.08, IC (0.01, 0.14), NNT 13] and "Liquid diet subgroup" [RD 0.14, IC (0.06,0.22), NNT 8].

Research conclusions

Data from published RCTs suggests SPMC is a better bowel cleanser than PEG before elective colonoscopy for healthy and mildly diseased adult outpatients because of its better tolerability,

lower AE prevalence and cleaning efficacy at least equal to that of PEG. For split preparations, SPMC and PEG can be equally use, but for day-before preparations SPMC should be the standard choice.

Research perspectives

Future RCTs might influence the outcomes of this meta-analysis with few studies included and/or with borderline differences obtained (*e.g.*, PDR, ADR, per type of regimen and per dietary recommendations) since Meta-analyzes are limited by the number of studies available and by the quality of the studies included. More homogeneous and definitive results should be obtained through a large intercontinental multi-center RCT, with the same bowel preparation protocol and tools for evaluating results. Although expensive and hard-working, it would be the best study format to compare purgatives and determine the best conditions for each of the available purgatives.

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