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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

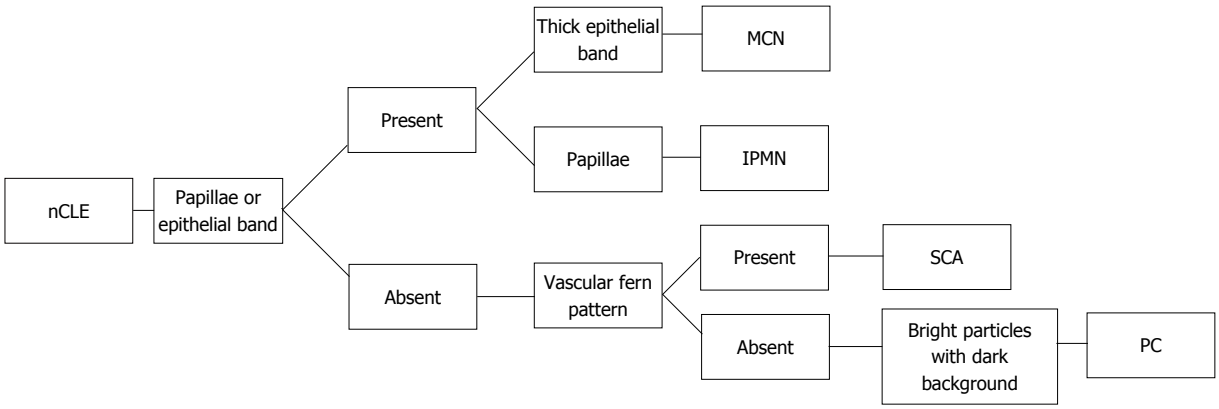

Figure 1 Algorithm for endoscopic ultrasound-guided needle-based confocal laser endomicroscopy imaging biomarker analysis for the evaluation of pancreatic cystic lesions. nCLE: Needle-based confocal laser endomicroscopy; IPMN: Intraductal papillary mucinous neoplasm; MCN: Mucinous cystic neoplasm; SCA: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

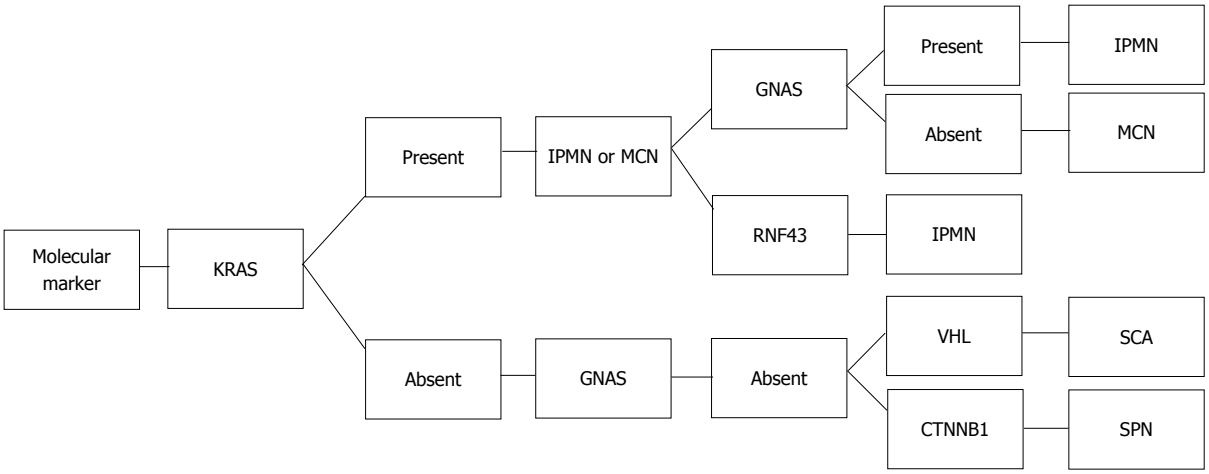

Figure 2 Proposed algorithm for cyst fluid molecular biomarker for the evaluation of pancreatic cystic lesions. IPMN: Intraductal papillary mucinous neoplasm; MCN: Mucinous cystic neoplasm; SPN: Solid pseudopapillary neoplasm; SCA: Serous cystadenoma.

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.

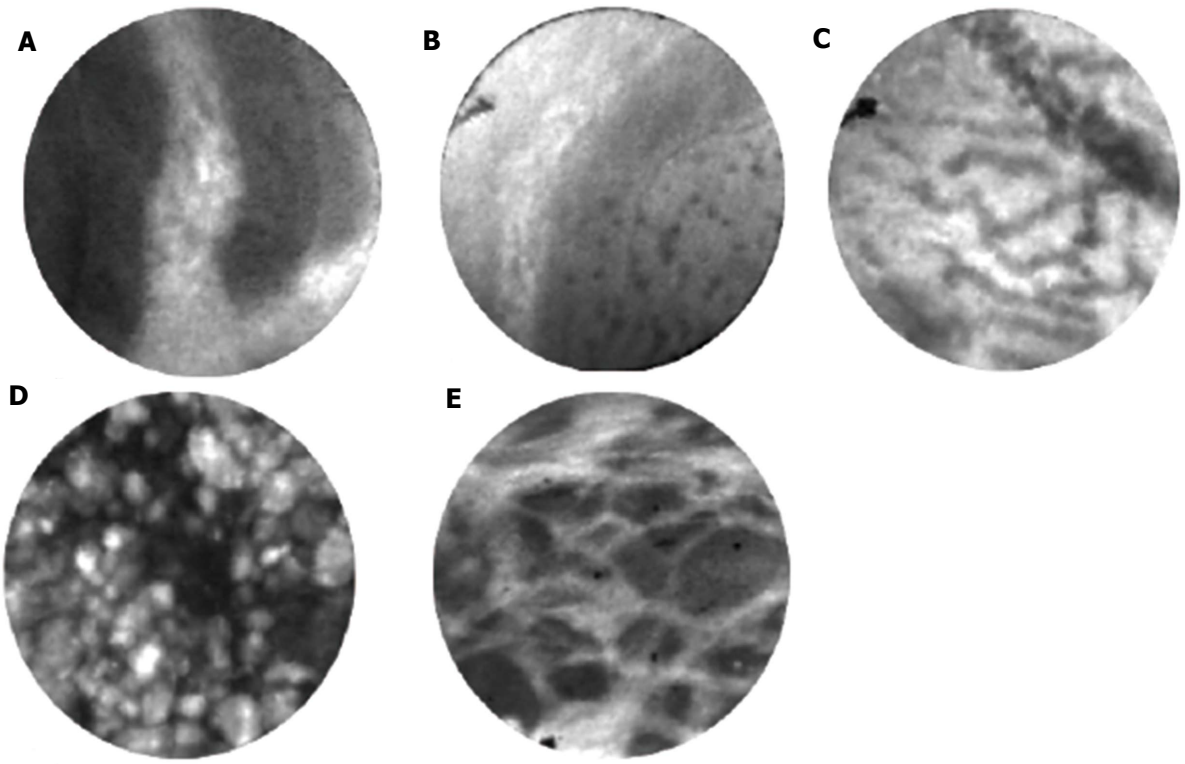

Figure 3 Confocal endomicroscopy findings of various types of pancreatic cystic lesions. A: Papillae of intraductal papillary mucinous neoplasm; B: Epithelial bands of mucinous cystic neoplasm; C: Fern pattern of serous cystadenoma; D: Bright particles against a dark background of pseudocyst; E: Trabecular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

REFERENCES

1 **de Jong K**, Nio CY, Hermans JJ, Dijkgraaf MG, Gouma DJ, van Eijck CH, van Heel E, Klass G, Fockens P, Bruno MJ. High prevalence of pancreatic cysts detected by screening magnetic resonance imaging examinations. *Clin Gastroenterol Hepatol* 2010; **8**: 806-811 [PMID: 20621679 DOI: 10.1016/j.cgh.2010.05.017]

2 **Laffan TA**, Horton KM, Klein AP, Berlanstein B, Siegelman SS, Kawamoto S, Johnson PT, Fishman EK, Hruban RH. Prevalence of unsuspected pancreatic cysts on MDCT. *AJR Am J Roentgenol* 2008; **191**: 802-807 [PMID: 18716113 DOI: 10.2214/AJR.07.3340]

3 **Zhang XM**, Mitchell DG, Dohke M, Holland GA, Parker L. Pancreatic cysts: depiction on single-shot fast spin-echo MR images. *Radiology* 2002; **223**: 547-553 [PMID: 11997566 DOI: 10.1148/radiol.2232010815]

4 **Matthaei H**, Schulick RD, Hruban RH, Maitra A. Cystic precursors to invasive pancreatic cancer. *Nat Rev Gastroenterol Hepatol* 2011; **8**: 141-150 [PMID: 21383670 DOI: 10.1038/nrgastro.2011.2]

5 **Zamboni G,** Klöppel G, Hruban R, Longnecker D, Adler G. Mucinous cystic neoplasms of the pancreas: IARC Press, 2000

6 **Brugge WR**, Lewandrowski K, Lee-Lewandrowski E, Centeno BA, Szydlo T, Regan S, del Castillo CF, Warshaw AL. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. *Gastroenterology* 2004; **126**: 1330-1336 [PMID: 15131794 DOI: 10.1053/j.gastro.2004.02.013]

7 **Gaddam S**, Ge PS, Keach JW, Mullady D, Fukami N, Edmundowicz SA, Azar RR, Shah RJ, Murad FM, Kushnir VM, Watson RR, Ghassemi KF, Sedarat A, Komanduri S, Jaiyeola DM, Brauer BC, Yen RD, Amateau SK, Hosford L, Hollander T, Donahue TR, Schulick RD, Edil BH, McCarter M, Gajdos C, Attwell A, Muthusamy VR, Early DS, Wani S. Suboptimal accuracy of carcinoembryonic antigen in differentiation of mucinous and nonmucinous pancreatic cysts: results of a large multicenter study. *Gastrointest Endosc* 2015; **82**: 1060-1069 [PMID: 26077458 DOI: 10.1016/j.gie.2015.04.040]

8 **Tanaka M**, Chari S, Adsay V, Fernandez-del Castillo C, Falconi M, Shimizu M, Yamaguchi K, Yamao K, Matsuno S; International Association of Pancreatology. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. *Pancreatology* 2006; **6**: 17-32 [PMID: 16327281 DOI: 10.1159/000090023]

9 **Tanaka M**, Fernández-del Castillo C, Adsay V, Chari S, Falconi M, Jang JY, Kimura W, Levy P, Pitman MB, Schmidt CM, Shimizu M, Wolfgang CL, Yamaguchi K, Yamao K; International Association of Pancreatology. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatology* 2012; **12**: 183-197 [PMID: 22687371 DOI: 10.1016/j.pan.2012.04.004]

10 **Vege SS**, Ziring B, Jain R, Moayyedi P; Clinical Guidelines Committee; American Gastroenterology Association. American gastroenterological association institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. *Gastroenterology* 2015; **148**: 819-822; quize12-13 [PMID: 25805375 DOI: 10.1053/j.gastro.2015.01.015]

11 **Pelaez-Luna M**, Chari ST, Smyrk TC, Takahashi N, Clain JE, Levy MJ, Pearson RK, Petersen BT, Topazian MD, Vege SS, Kendrick M, Farnell MB. Do consensus indications for resection in branch duct intraductal papillary mucinous neoplasm predict malignancy? A study of 147 patients. *Am J Gastroenterol* 2007; **102**: 1759-1764 [PMID: 17686073 DOI: 10.1111/j.1572-0241.2007.01224.x]

12 **Tang RS**, Weinberg B, Dawson DW, Reber H, Hines OJ, Tomlinson JS, Chaudhari V, Raman S, Farrell JJ. Evaluation of the guidelines for management of pancreatic branch-duct intraductal papillary mucinous neoplasm. *Clin Gastroenterol Hepatol* 2008; **6**: 815-819; quiz 719 [PMID: 18602036 DOI: 10.1016/j.cgh.2008.04.005]

13 **Kaimakliotis P**, Riff B, Pourmand K, Chandrasekhara V, Furth EE, Siegelman ES, Drebin J, Vollmer CM, Kochman ML, Ginsberg GG, Ahmad NA. Sendai and Fukuoka Consensus Guidelines Identify Advanced Neoplasia in Patients With Suspected Mucinous Cystic Neoplasms of the Pancreas. *Clin Gastroenterol Hepatol* 2015; **13**: 1808-1815 [PMID: 25818077 DOI: 10.1016/j.cgh.2015.03.017]

14 **Singhi AD**, Zeh HJ, Brand RE, Nikiforova MN, Chennat JS, Fasanella KE, Khalid A, Papachristou GI, Slivka A, Hogg M, Lee KK, Tsung A, Zureikat AH, McGrath K. American Gastroenterological Association guidelines are inaccurate in detecting pancreatic cysts with advanced neoplasia: a clinicopathologic study of 225 patients with supporting molecular data. *Gastrointest Endosc* 2016; **83**: 1107-1117.e2 [PMID: 26709110 DOI: 10.1016/j.gie.2015.12.009]

15 **Konda VJ**, Meining A, Jamil LH, Giovannini M, Hwang JH, Wallace MB, Chang KJ, Siddiqui UD, Hart J, Lo SK, Saunders MD, Aslanian HR, Wroblewski K, Waxman I. A pilot study of in vivo identification of pancreatic cystic neoplasms with needle-based confocal laser endomicroscopy under endosonographic guidance. *Endoscopy* 2013; **45**: 1006-1013 [PMID: 24163192 DOI: 10.1055/s-0033-1344714]

16 **Modi RM,** Kamboj AK, Swanson B, Conwell DL, Krishna SG.

Novel technique for diagnosis of mucinous cystic neoplasms: in vivo and ex vivo confocal laser endomicroscopy. *VideoGIE* 2017; **2**: 55-56 [DOI: 10.1016/j.vgie.2016.12.003]

17 **Napoleon B**, Lemaistre AI, Pujol B, Caillol F, Lucidarme D, Bourdariat R, Morellon-Mialhe B, Fumex F, Lefort C, Lepilliez V, Palazzo L, Monges G, Poizat F, Giovannini M. In vivo characterization of pancreatic cystic lesions by needle-based confocal laser endomicroscopy (nCLE): proposition of a comprehensive nCLE classification confirmed by an external retrospective evaluation. *Surg Endosc* 2016; **30**: 2603-2612 [PMID: 26428198 DOI: 10.1007/s00464-015-4510-5]

18 **Krishna SG**, Swanson B, Conwell DL, Muscarella P 2nd. In vivo and ex vivo needle-based confocal endomicroscopy of intraductal papillary mucinous neoplasm of the pancreas. *Gastrointest Endosc* 2015; **82**: 571-572 [PMID: 26005013 DOI: 10.1016/j.gie.2015.04.021]

19 **Napoléon B**, Lemaistre AI, Pujol B, Caillol F, Lucidarme D, Bourdariat R, Morellon-Mialhe B, Fumex F, Lefort C, Lepilliez V, Palazzo L, Monges G, Filoche B, Giovannini M. A novel approach to the diagnosis of pancreatic serous cystadenoma: needle-based confocal laser endomicroscopy. *Endoscopy* 2015; **47**: 26-32 [PMID: 25325684 DOI: 10.1055/s-0034-1390693]

20 **Modi RM**, Swanson B, Muscarella P 2nd, Conwell DL, Krishna SG. Novel techniques for diagnosis of serous cystadenoma: fern pattern of vascularity confirmed by in vivo and ex vivo confocal laser endomicroscopy. *Gastrointest Endosc* 2017; **85**: 258-259 [PMID: 27449195 DOI: 10.1016/j.gie.2016.07.015]

21 **Kamboj AK**, Swanson B, Dillhoff ME, Conwell DL, Krishna SG. Cystic pancreatic neuroendocrine tumors: correlation of in vivo needle-based confocal endomicroscopic findings by ex vivo analysis. *Gastrointest Endosc* 2017; **85**: 259-260 [PMID: 27492715 DOI: 10.1016/j.gie.2016.07.055]

22 **Modi RM**, Kamboj AK, Swanson B, Conwell DL, Krishna SG. Epidermoid cyst within an intrapancreatic accessory spleen: endosonography and confocal endomicroscopy of an unusual pancreatic cystic lesion. *Endoscopy* 2016; **48**: E332-E333 [PMID: 27741530 DOI: 10.1055/s-0042-117506]

23 **Nakai Y**, Iwashita T, Park DH, Samarasena JB, Lee JG, Chang KJ. Diagnosis of pancreatic cysts: EUS-guided, through-the-needle confocal laser-induced endomicroscopy and cystoscopy trial: DETECT study. *Gastrointest Endosc* 2015; **81**: 1204-1214 [PMID: 25634486 DOI: 10.1016/j.gie.2014.10.025]

24 **Krishna SG**, Swanson B, Hart PA, El-Dika S, Walker JP, McCarthy ST, Malli A, Shah ZK, Conwell DL. Validation of diagnostic characteristics of needle based confocal laser endomicroscopy in differentiation of pancreatic cystic lesions. *Endosc Int Open* 2016; **4**: E1124-E1135 [PMID: 27853737 DOI: 10.1055/s-0042-116491]

25 **Springer S**, Wang Y, Dal Molin M, Masica DL, Jiao Y, Kinde I, Blackford A, Raman SP, Wolfgang CL, Tomita T, Niknafs N, Douville C, Ptak J, Dobbyn L, Allen PJ, Klimstra DS, Schattner MA, Schmidt CM, Yip-Schneider M, Cummings OW, Brand RE, Zeh HJ, Singhi AD, Scarpa A, Salvia R, Malleo G, Zamboni G, Falconi M, Jang JY, Kim SW, Kwon W, Hong SM, Song KB, Kim SC, Swan N, Murphy J, Geoghegan J, Brugge W, Fernandez-Del Castillo C, Mino-Kenudson M, Schulick R, Edil BH, Adsay V, Paulino J, van Hooft J, Yachida S, Nara S, Hiraoka N, Yamao K, Hijioka S, van der Merwe S, Goggins M, Canto MI, Ahuja N, Hirose K, Makary M, Weiss MJ, Cameron J, Pittman M, Eshleman JR, Diaz LA Jr, Papadopoulos N, Kinzler KW, Karchin R, Hruban RH, Vogelstein B, Lennon AM. A combination of molecular markers and clinical features improve the classification of pancreatic cysts. *Gastroenterology* 2015; **149**: 1501-1510 [PMID: 26253305 DOI: 10.1053/j.gastro.2015.07.041]

26 **Khalid A**, Brugge W. ACG practice guidelines for the diagnosis and management of neoplastic pancreatic cysts. *Am J Gastroenterol* 2007; **102**: 2339-2349 [PMID: 17764489 DOI: 10.1111/j.1572-0241.2007.01516.x]

27 **Khalid A**, Zahid M, Finkelstein SD, LeBlanc JK, Kaushik N, Ahmad N, Brugge WR, Edmundowicz SA, Hawes RH, McGrath KM. Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PANDA study. *Gastrointest Endosc* 2009; **69**: 1095-1102 [PMID: 19152896 DOI: 10.1016/j.gie.2008.07.033]

28 **Khalid A**, Pal R, Sasatomi E, Swalsky P, Slivka A, Whitcomb D, Finkelstein S. Use of microsatellite marker loss of heterozygosity in accurate diagnosis of pancreaticobiliary malignancy from brush cytology samples. *Gut* 2004; **53**: 1860-1865 [PMID: 15542529 DOI: 10.1136/gut.2004.039784]

29 **Wu J**, Matthaei H, Maitra A, Dal Molin M, Wood LD, Eshleman JR, Goggins M, Canto MI, Schulick RD, Edil BH, Wolfgang CL, Klein AP, Diaz LA Jr, Allen PJ, Schmidt CM, Kinzler KW, Papadopoulos N, Hruban RH, Vogelstein B. Recurrent GNAS mutations define an unexpected pathway for pancreatic cyst development. *Sci Transl Med* 2011; **3**: 92ra66 [PMID: 21775669 DOI: 10.1126/scitranslmed.3002543]

30 **Nikiforova MN**, Khalid A, Fasanella KE, McGrath KM, Brand RE, Chennat JS, Slivka A, Zeh HJ, Zureikat AH, Krasinskas AM, Ohori NP, Schoedel KE, Navina S, Mantha GS, Pai RK, Singhi AD. Integration of KRAS testing in the diagnosis of pancreatic cystic lesions: a clinical experience of 618 pancreatic cysts. *Mod Pathol* 2013; **26**: 1478-1487 [PMID: 23743931 DOI: 10.1038/modpathol.2013.91]

31 **Wu J**, Jiao Y, Dal Molin M, Maitra A, de Wilde RF, Wood LD, Eshleman JR, Goggins MG, Wolfgang CL, Canto MI, Schulick RD, Edil BH, Choti MA, Adsay V, Klimstra DS, Offerhaus GJ, Klein AP, Kopelovich L, Carter H, Karchin R, Allen PJ, Schmidt CM, Naito Y, Diaz LA Jr, Kinzler KW, Papadopoulos N, Hruban RH, Vogelstein B. Whole-exome sequencing of neoplastic cysts of the pancreas reveals recurrent mutations in components of ubiquitin-dependent pathways. *Proc Natl Acad Sci USA* 2011; **108**: 21188-21193 [PMID: 22158988 DOI: 10.1073/pnas.1118046108]

32 **Crippa S**, Fernández-Del Castillo C, Salvia R, Finkelstein D, Bassi C, Domínguez I, Muzikansky A, Thayer SP, Falconi M, Mino-Kenudson M, Capelli P, Lauwers GY, Partelli S, Pederzoli P, Warshaw AL. Mucin-producing neoplasms of the pancreas: an analysis of distinguishing clinical and epidemiologic characteristics. *Clin Gastroenterol Hepatol* 2010; **8**: 213-219 [PMID: 19835989 DOI: 10.1016/j.cgh.2009.10.001]

33 **Machado NO**, Al Qadhi H, Al Wahibi K. Intraductal Papillary Mucinous Neoplasm of Pancreas. *N Am J Med Sci* 2015; **7**: 160-175 [PMID: 26110127 DOI: 10.4103/1947-2714.157477]

34 **Singhi AD**, Nikiforova MN, McGrath K. DNA testing of pancreatic cyst fluid: is it ready for prime time? *Lancet Gastroenterol Hepatol* 2017; **2**: 63-72 [PMID: 28404017 DOI: 10.1016/S2468-1253(16)30084-X]

35 **Biankin AV**, Biankin SA, Kench JG, Morey AL, Lee CS, Head DR, Eckstein RP, Hugh TB, Henshall SM, Sutherland RL. Aberrant p16(INK4A) and DPC4/Smad4 expression in intraductal papillary mucinous tumours of the pancreas is associated with invasive ductal adenocarcinoma. *Gut* 2002; **50**: 861-868 [PMID: 12010891 DOI: 10.1136/gut.50.6.861]

36 **Kanda M**, Sadakari Y, Borges M, Topazian M, Farrell J, Syngal S, Lee J, Kamel I, Lennon AM, Knight S, Fujiwara S, Hruban RH, Canto MI, Goggins M. Mutant TP53 in duodenal samples of pancreatic juice from patients with pancreatic cancer or high-grade dysplasia. *Clin Gastroenterol Hepatol* 2013; **11**: 719-730.e5 [PMID: 23200980 DOI: 10.1016/j.cgh.2012.11.016]

37 **Sasaki S**, Yamamoto H, Kaneto H, Ozeki I, Adachi Y, Takagi H, Matsumoto T, Itoh H, Nagakawa T, Miyakawa H, Muraoka S, Fujinaga A, Suga T, Satoh M, Itoh F, Endo T, Imai K. Differential roles of alterations of p53, p16, and SMAD4 expression in the progression of intraductal papillary-mucinous tumors of the pancreas. *Oncol Rep* 2003; **10**: 21-25 [PMID: 12469138 DOI: 10.3892/or.10.1.21]

38 **Schoedel KE**, Finkelstein SD, Ohori NP. K-Ras and microsatellite marker analysis of fine-needle aspirates from intraductal papillary mucinous neoplasms of the pancreas. *Diagn Cytopathol* 2006; **34**: 605-608 [PMID: 16900481 DOI: 10.1002/dc.20511]

39 **Pea A**, Yu J, Rezaee N, Luchini C, He J, Dal Molin M, Griffin JF, Fedor H, Fesharakizadeh S, Salvia R, Weiss MJ, Bassi C, Cameron

JL, Zheng L, Scarpa A, Hruban RH, Lennon AM, Goggins M, Wolfgang CL, Wood LD. Targeted DNA Sequencing Reveals Patterns of Local Progression in the Pancreatic Remnant Following Resection of Intraductal Papillary Mucinous Neoplasm (IPMN) of the Pancreas. *Ann Surg* 2017; **266**: 133-141 [PMID: 27433916 DOI: 10.1097/SLA.0000000000001817]

40 **Garcia-Carracedo D**, Chen ZM, Qiu W, Huang AS, Tang SM, Hruban RH, Su GH. PIK3CA mutations in mucinous cystic neoplasms of the pancreas. *Pancreas* 2014; **43**: 245-249 [PMID: 24518503 DOI: 10.1097/MPA.0000000000000034]

41 **Yu J**, Sadakari Y, Shindo K, Suenaga M, Brant A, Almario JAN, Borges M, Barkley T, Fesharakizadeh S, Ford M, Hruban RH, Shin EJ, Lennon AM, Canto MI, Goggins M. Digital next-generation sequencing identifies low-abundance mutations in pancreatic juice samples collected from the duodenum of patients with pancreatic cancer and intraductal papillary mucinous neoplasms. *Gut* 2017; **66**: 1677-1687 [PMID: 27432539 DOI: 10.1136/gutjnl-2015-311166]

42 **Garcia-Carracedo D**, Turk AT, Fine SA, Akhavan N, Tweel BC, Parsons R, Chabot JA, Allendorf JD, Genkinger JM, Remotti HE, Su GH. Loss of PTEN expression is associated with poor prognosis in patients with intraductal papillary mucinous neoplasms of the pancreas. *Clin Cancer Res* 2013; **19**: 6830-6841 [PMID: 24132918 DOI: 10.1158/1078-0432.CCR-13-0624]

43 **Schönleben F**, Qiu W, Ciau NT, Ho DJ, Li X, Allendorf JD, Remotti HE, Su GH. PIK3CA mutations in intraductal papillary mucinous neoplasm/carcinoma of the pancreas. *Clin Cancer Res* 2006; **12**: 3851-3855 [PMID: 16778113 DOI: 10.1158/1078-0432.CCR-06-0292]

44 **Singhi AD**, McGrath K, Brand RE, Khalid A, Zeh HJ, Chennat JS, Fasanella KE, Papachristou GI, Slivka A, Bartlett DL, Dasyam AK, Hogg M, Lee KK, Marsh JW, Monaco SE, Ohori NP, Pingpank JF, Tsung A, Zureikat AH, Wald AI, Nikiforova MN. Preoperative next-generation sequencing of pancreatic cyst fluid is highly accurate in cyst classification and detection of advanced neoplasia. *Gut* 2017; Epub ahead of print [PMID: 28970292 DOI: 10.1136/gutjnl-2016-313586]

45 **Al-Haddad M**, DeWitt J, Sherman S, Schmidt CM, LeBlanc JK, McHenry L, Coté G, El Chafic AH, Luz L, Stuart JS, Johnson CS, Klochan C, Imperiale TF. Performance characteristics of molecular (DNA) analysis for the diagnosis of mucinous pancreatic cysts. *Gastrointest Endosc* 2014; **79**: 79-87 [PMID: 23845445 DOI: 10.1016/j.gie.2013.05.026]

46 **Shen J**, Brugge WR, Dimaio CJ, Pitman MB. Molecular analysis of pancreatic cyst fluid: a comparative analysis with current practice of diagnosis. *Cancer* 2009; **117**: 217-227 [PMID: 19415731 DOI: 10.1002/cncy.20027]

47 47 **Lennon AM**, Wolfgang C. Cystic neoplasms of the pancreas. *J Gastrointest Surg* 2013; **17**: 645-653 [PMID: 23340991 DOI: 10.1007/s11605-012-2072-6]

48 **Jais B**, Rebours V, Malleo G, Salvia R, Fontana M, Maggino L, Bassi C, Manfredi R, Moran R, Lennon AM, Zaheer A, Wolfgang C, Hruban R, Marchegiani G, Fernández Del Castillo C, Brugge W, Ha Y, Kim MH, Oh D, Hirai I, Kimura W, Jang JY, Kim SW, Jung W, Kang H, Song SY, Kang CM, Lee WJ, Crippa S, Falconi M, Gomatos I, Neoptolemos J, Milanetto AC, Sperti C, Ricci C, Casadei R, Bissolati M, Balzano G, Frigerio I, Girelli R, Delhaye M, Bernier B, Wang H, Jang KT, Song DH, Huggett MT, Oppong KW, Pererva L, Kopchak KV, Del Chiaro M, Segersvard R, Lee LS, Conwell D, Osvaldt A, Campos V, Aguero Garcete G, Napoleon B, Matsumoto I, Shinzeki M, Bolado F, Fernandez JM, Keane MG, Pereira SP, Acuna IA, Vaquero EC, Angiolini MR, Zerbi A, Tang J, Leong RW, Faccinetto A, Morana G, Petrone MC, Arcidiacono PG, Moon JH, Choi HJ, Gill RS, Pavey D, Ouaïssi M, Sastre B, Spandre M, De Angelis CG, Rios-Vives MA, Concepcion-Martin M, Ikeura T, Okazaki K, Frulloni L, Messina O, Lévy P. Serous cystic neoplasm of the pancreas: a multinational study of 2622 patients under the auspices of the International Association of Pancreatology and European Pancreatic Club (European Study Group on Cystic Tumors of the Pancreas). *Gut* 2016; **65**: 305-312 [PMID: 26045140 DOI: 10.1136/gutjnl-2015-309638]

49 **Krishna SG**, Brugge WR, Dewitt JM, Kongkam P, Napoleon B, Robles-Medranda C, Tan D, El-Dika S, McCarthy S, Walker J, Dillhoff ME, Manilchuk A, Schmidt C, Swanson B, Shah ZK, Hart PA, Conwell DL. Needle-based confocal laser endomicroscopy for the diagnosis of pancreatic cystic lesions: an international external interobserver and intraobserver study (with videos). *Gastrointest Endosc* 2017; **86**: 644-654.e2 [PMID: 28286093 DOI: 10.1016/j.gie.2017.03.002]

50 **Law JK**, Ahmed A, Singh VK, Akshintala VS, Olson MT, Raman SP, Ali SZ, Fishman EK, Kamel I, Canto MI, Dal Molin M, Moran RA, Khashab MA, Ahuja N, Goggins M, Hruban RH, Wolfgang CL, Lennon AM. A systematic review of solid-pseudopapillary neoplasms: are these rare lesions? *Pancreas* 2014; **43**: 331-337 [PMID: 24622060 DOI: 10.1097/MPA.0000000000000061]

51 **Banks PA**, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS; Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; **62**: 102-111 [PMID: 23100216 DOI: 10.1136/gutjnl-2012-302779]

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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

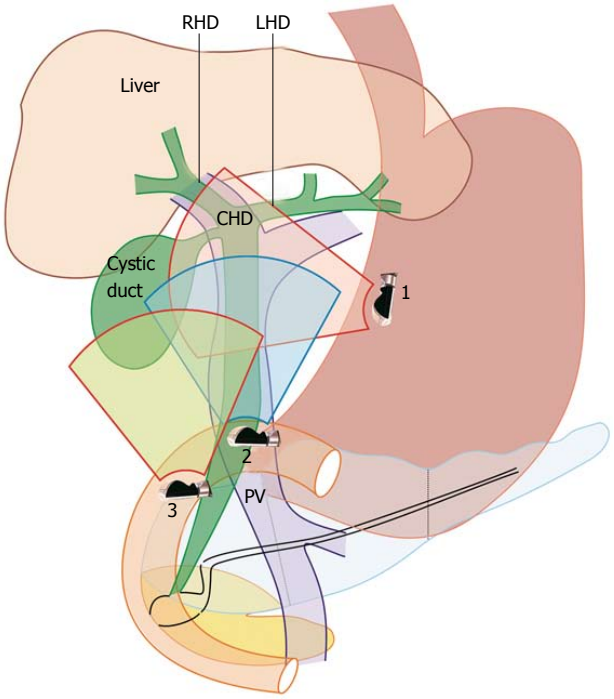

Figure 1 Station 1 shows the gall bladder at around 6 o'clock position; station 2 shows the gall bladder at around 3 o'clock position; and station 3 shows the gall bladder at around 9 o'clock position. RHD: Right hepatic duct; LHD: Left hepatic duct; CHD: Common hepatic duct; PV: Portal vein.

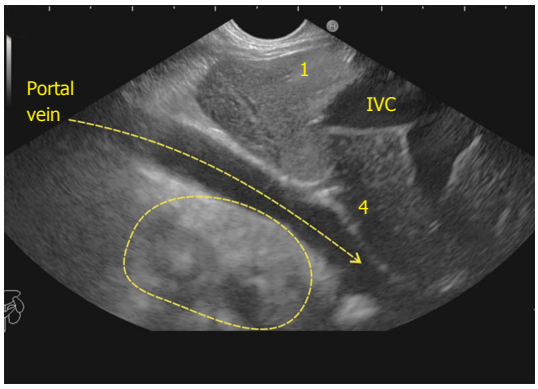

Figure 2 The supraduodenal part of portal vein is seen as a curving vessel going from 5/6 o'clock position to 9/10 o'clock position. The yellow arrow points to the curving part of portal vein. The area marked with yellow outline shows the area in which the CBD and Gall Bladder can be seen. 1: Segment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

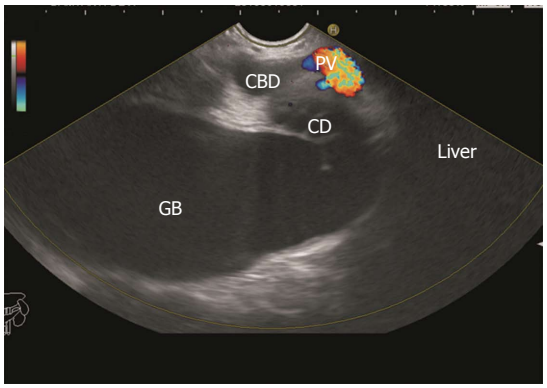

Figure 3 The upper part of common bile duct is first identified beyond the curving part of portal vein. With slight rotation of the scope the cystic duct and gall bladder can be traced in the area beyond the portal vein between 5 o'clock position to 10 o'clock position. CBD: Common bile duct; GB: Gall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

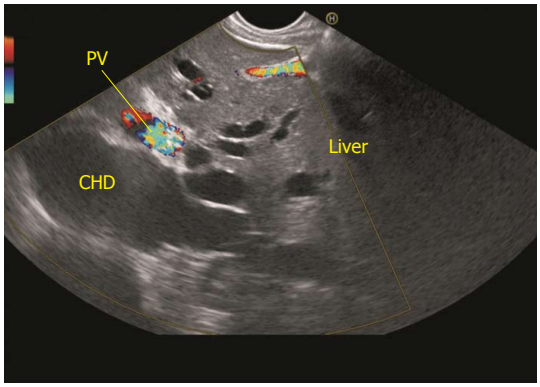

Figure 4 The dilated ducts of segment 2 and 3 can be followed to formation of left hepatic duct. The left hepatic duct joins the right hepatic duct to form common hepatic duct. The common hepatic duct (CHD) lies beyond the supraduodenal part of portal vein. PV: Portal vein.

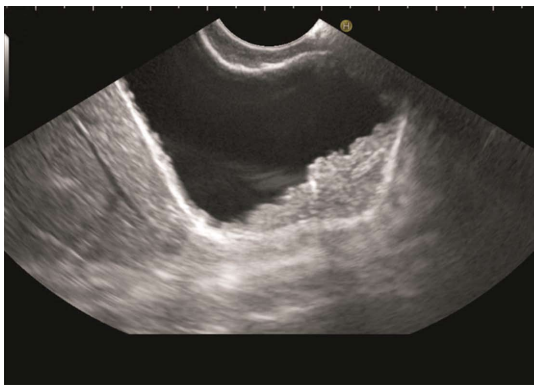

Figure 5 The gall bladder imaging is done from duodenal bulb. The layers of GB can be seen. The irregular polypoidal mass occupying the lumen is due to adenomyomatosis of GB. GB: Gall bladder.

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

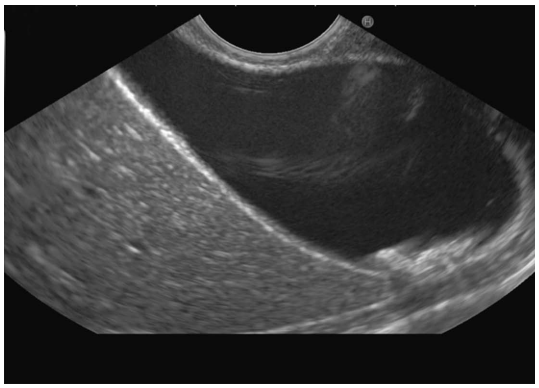

Figure 6 Gall bladder imaging from the duodenal bulb. The stones are present in the lumen of GB. The neck of the Gall Bladder is present at 11 o'clock position and the fundus is present at 3 o'clock position. GB: Gall bladder.

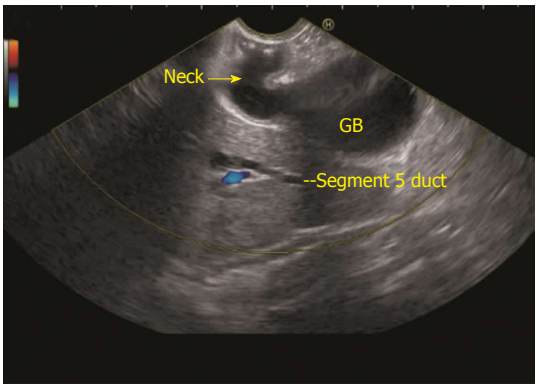

Figure 9 The neck of the gall bladder is present just below the probe and the fundus is present at 3 o'clock position. The segment 5 duct is seen beyond the GB. GB: Gall bladder.

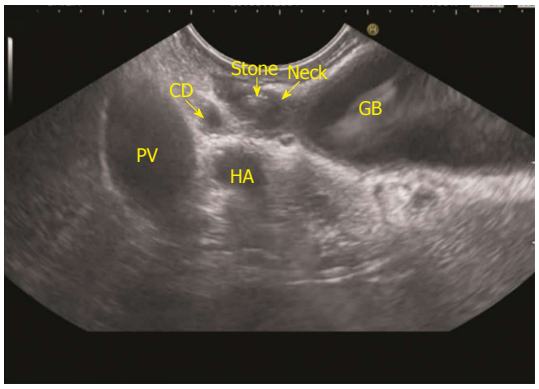

Figure 7 A stone is seen in the neck of gall bladder. These stones can be missed by routine abdominal ultrasound. The neck of the gall bladder is present just below the probe and the fundus is present at 3 o'clock position. PV: Portal vein; GB: Gall bladder.

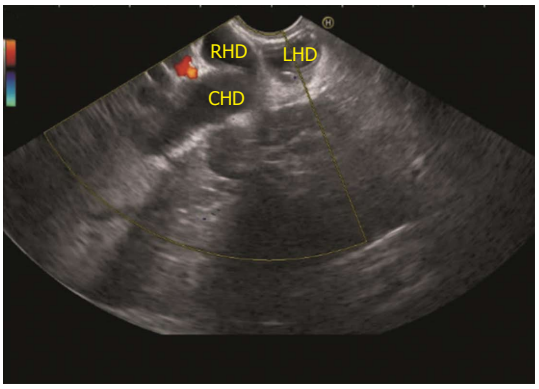

Figure 10 Once the gall bladder imaging is done from duodenal bulb an anticlockwise rotation can trace the common bile duct towards the hilum of liver. The CHD is seen to be dividing into right and left hepatic duct. RHD: Right hepatic duct; LHD: Left hepatic duct; CHD: Common hepatic duct.

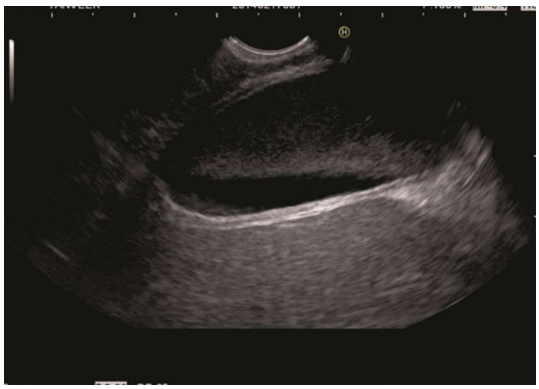

Figure 8 The segment 5 of liver is seen beyond the gall bladder. A layer of gall bladder (GB) sludge is seen in the lumen of GB.

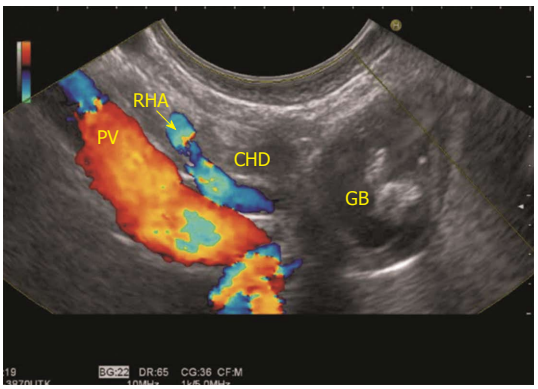

Figure 11 The imaging is done from duodenal bulb and the portal vein is identified going from 5 o'clock position to 10 o'clock position in a long axis. The CHD is identified between the probe and portal vein. The CHD is followed up by anticlockwise rotation and the remnant of gall bladder is seen in 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

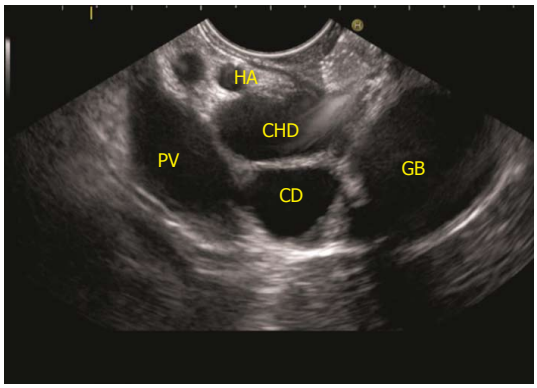

Figure 12 The imaging is done from duodenal bulb and the portal vein is identified going from 5 o'clock position to 10 o'clock position in a long axis. The CHD is identified between the probe and portal vein. The CHD is followed up by anticlockwise rotation and the continuity into cystic duct and gall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

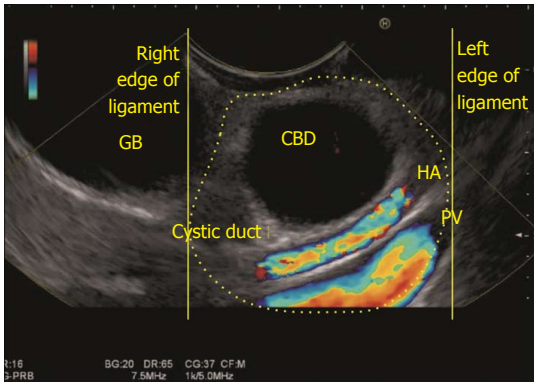

Figure 13 The gall bladder imaging is done from descending duodenum with up deflection and anti-clockwise rotation. The hepatoduodenal ligament is identified as a bean shaped structure between the probe and liver (shown in dotted yellow area). The CBD can be traced along the cystic duct and the gall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

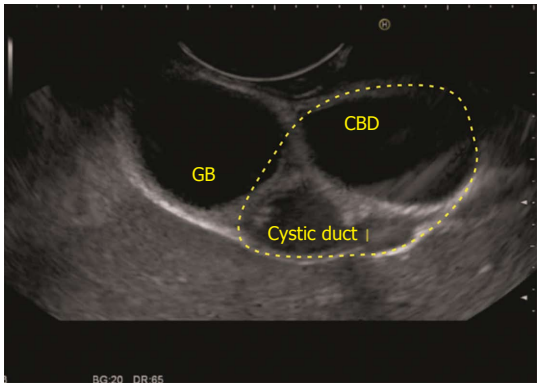

Figure 14 The gall bladder imaging is done from descending duodenum. The hepatoduodenal ligament is identified between the probe and liver (shown in dotted yellow area). The CBD, the cystic duct and the gall bladder are visualized on the under surface of liver. CBD: Common bile duct; GB: Gall bladder.

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

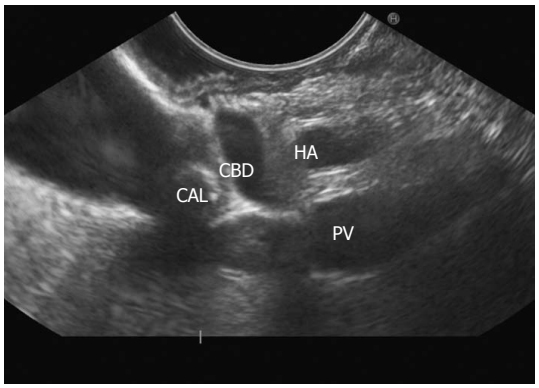

Figure 15 The gall bladder imaging is done from descending duodenum with up deflection and anti-clockwise rotation. The CBD can be traced and a stone is seen in the Cystic duct. The distended gall bladder is also visualized. PV: Portal vein; CBD: Common bile duct.

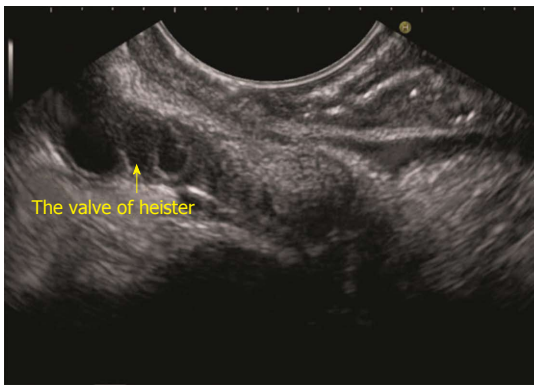

Figure 16 The gall bladder imaging is done from descending duodenum with up deflection and anti-clockwise rotation. The tortuous cystic duct with a spiral valve of Heister is seen.

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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REFERENCES

1 **Dietrich CF**. Endoscopic Ultrasound: An Introductory manual and Atlas. New York: Thieme, 2006 [DOI: 10.1055/b-002-52057]
2 **Van Dam S**, Sivak MV. Gastrointestinal Endosonography. Philadelphia, Pennsylvania: Saunders, 1999
3 **Rosch T**, Will U, Chang KJ. Logitudianl Endosonography: Atlas and Manual for Use in the Upper Gastrointestinal Tract. Germany, 2001
4 **Gress FG**, Ishan B. Endoscopic Ultrasonography. Massachusetts: Wiley-Blackwell, 2001
5 **Al-Haddad M**. EUS in Bile Duct, Gallbladder, and Ampullary Lesions. In: Robert H. Hawes, Paul Fockens, Shyam Varadarajulu. Endosonography. Philadelphia: Saunders, 2015: 226-255. Available from: URL: https://www.us.elsevierhealth.com/endosonography-9780323221511.html
6 **Rameshbabu CS**, Wani ZA, Rai P, Abdulqader A, Garg S, Sharma M. Standard imaging techniques for assessment of portal venous system and its tributaries by linear endoscopic ultrasound: a pictorial essay. *Endosc Ultrasound* 2013; **2**: 16-34 [PMID: 24949362 DOI: 10.7178/eus.04.005]
7 **Sharma M**, Rai P, Rameshbabu CS, Arya S. Imaging of the pancreatic duct by linear endoscopic ultrasound. *Endosc Ultrasound* 2015; **4**: 198-207 [PMID: 26374577 DOI: 10.4103/2303-9027.162997]
8 **Sharma M**, Pathak A, Rameshbabu CS, Rai P, Kirnake V, Shoukat A. Imaging of pancreas divisum by linear-array endoscopic ultrasonography. *Endosc Ultrasound* 2016; **5**: 21-29 [PMID: 26879163 DOI: 10.4103/2303-9027.175878]
9 **Sharma M**, Rai P, Rameshbabu CS, Senadhipan B. Imaging of peritoneal ligaments by endoscopic ultrasound (with videos). *Endosc Ultrasound* 2015; **4**: 15-27 [PMID: 25789280 DOI: 10.4103/2303-9027.151317]
10 **Sharma M**, Rai P, Mehta V, Rameshbabu CS. Techniques of imaging of the aorta and its first order branches by endoscopic ultrasound (with videos). *Endosc Ultrasound* 2015; **4**: 98-108 [PMID: 26020043 DOI: 10.4103/2303-9027.156722]
11 **Sharma M**, Rameshbabu CS, Dietrich CF, Rai P, Bansal R. Endoscopic ultrasound of the hepatoduodenal ligament and liver hilum. *Endosc Ultrasound* 2016; Epub ahead of print [PMID: 27824022 DOI: 10.4103/2303]
12 **Pathak A**, Shoukat A, Thomas NS, Mehta D, Sharma M. Seagulls of endoscopic ultrasound. *Endosc Ultrasound* 2017; **6**: 231-234 [PMID: 28663526 DOI: 10.4103/2303-9027.190919]
13 **Owen CC**, Bilhartz LE. Gallbladder polyps, cholesterolosis, adenomyomatosis, and acute acalculous cholecystitis. *Semin Gastrointest Dis* 2003; **14**: 178-188 [PMID: 14719768]
14 **Sun XJ**, Shi JS, Han Y, Wang JS, Ren H. Diagnosis and treatment of polypoid lesions of the gallbladder: report of 194 cases. *Hepatobiliary Pancreat Dis Int* 2004; **3**: 591-594 [PMID: 15567752]
15 **Mitake M**, Nakazawa S, Naitoh Y, Kimoto E, Tsukamoto Y, Asai T, Yamao K, Inui K, Morita K, Hayashi Y. Endoscopic ultrasonography in diagnosis of the extent of gallbladder carcinoma. *Gastrointest Endosc* 1990; **36**: 562-566 [PMID: 2279643 DOI: 10.1016/S0016-5107(90)71164-9]
16 **Vijayakumar A**, Vijayakumar A, Patil V, Mallikarjuna MN, Shivaswamy BS. Early diagnosis of gallbladder carcinoma: an algorithm approach. *ISRN Radiol* 2012; **2013**: 239424 [PMID: 24959553 DOI: 10.5402/2013/239424]
17 **Kapoor A**, Kapoor A, Mahajan G. Differentiating malignant from benign thickening of the gallbladder wall by the use of acoustic radiation force impulse elastography. *J Ultrasound Med* 2011; **30**: 1499-1507 [PMID: 22039022 DOI: 10.7863/jum.2011.30.11.1499]
18 **Sugiyama M**, Atomi Y, Yamato T. Endoscopic ultrasonography for differential diagnosis of polypoid gall bladder lesions: analysis in surgical and follow up series. *Gut* 2000; **46**: 250-254 [PMID: 10644321 DOI: 10.1136/gut.46.2.250]
19 **Azuma T**, Yoshikawa T, Araida T, Takasaki K. Differential diagnosis of polypoid lesions of the gallbladder by endoscopic ultrasonography. *Am J Surg* 2001; **181**: 65-70 [PMID: 11248179 DOI: 10.1016/S0002-9610(00)00526-2]
20 **Yang HL**, Sun YG, Wang Z. Polypoid lesions of the gallbladder: diagnosis and indications for surgery. *Br J Surg* 1992; **79**: 227-229 [PMID: 1555088 DOI: 10.1002/bjs.1800790312]
21 **Gallahan WC**, Conway JD. Diagnosis and management of gallbladder polyps. *Gastroenterol Clin North Am* 2010; **39**: 359-367, x [PMID: 20478491 DOI: 10.1016/j.gtc.2010.02.001]
22 **Yang LP**, Yang ZL, Tan XG, Miao XY. [Expression of annexin A1 (ANXA1) and A2 (ANXA2) and its significance in benign and malignant lesions of gallbladder]. *Zhonghua Zhongliu Zazhi* 2010; **32**: 595-599 [PMID: 21122411]

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

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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.

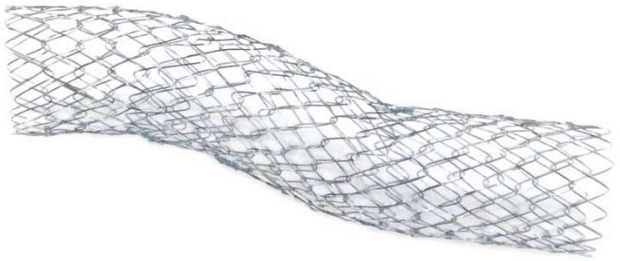

Figure 1 Niti-S 14 appearance with a braided structure made from nitinol, and a large diameter of 14 mm with a length of 60 or 80 mm.

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

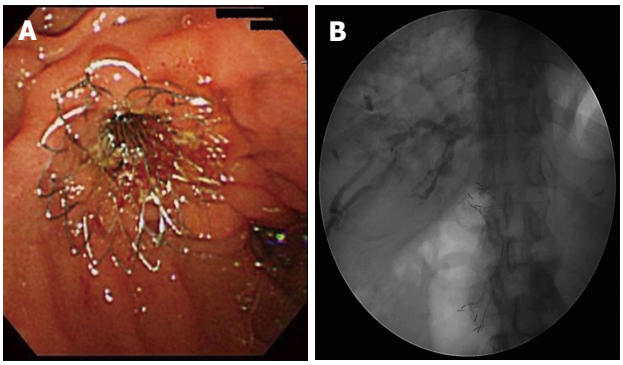

Figure 2 Stent placement of Niti-S 14 after sphincterotomy in pancreatic cancer. A: Endoscopic view; B: Picture of endoscopic retrograde pancreatocholangiography.

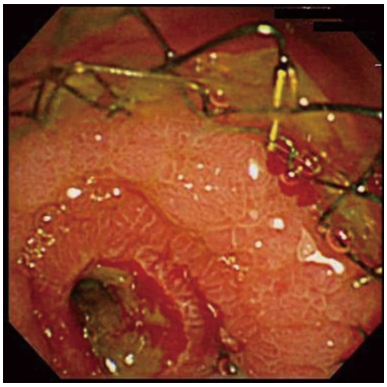

Figure 3 Endoscopic view of the duodenal major papilla after Niti-S 14 placement. The bile duct cavity is maintained despite bile duct mucosa or tumor growth into the stent.

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

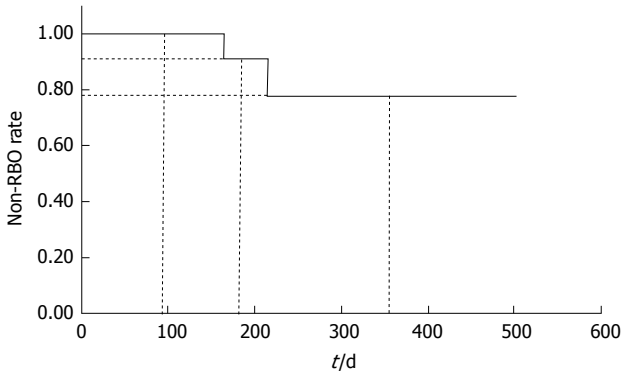

Figure 4 Kaplan-Meier analysis of stent patency. The non-RBO rates of 3, 6 and 12 mo were 100%, 91% and 78%, respectively. RBO: Recurrent biliary obstruction.

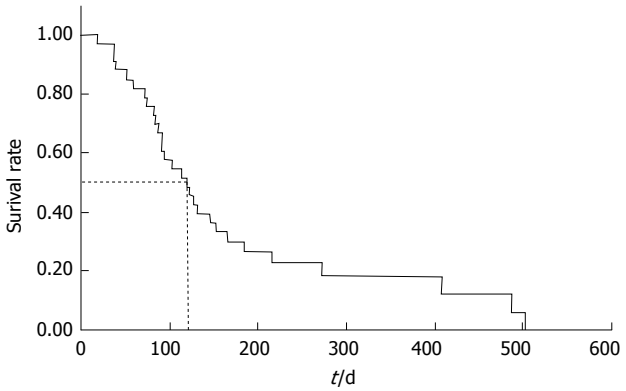

Figure 5 Kaplan-Meier analysis of survival. The median survival time was 120 d.

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.

REFERENCES

1 **Kozarek RA**. Endoscopically placed biliary drains and stents. *Am Fam Physician* 1982; **26**: 189-192 [PMID: 7102497]

2 **Davids PH**, Groen AK, Rauws EA, Tytgat GN, Huibregtse K. Randomised trial of self-expanding metal stents versus polyethylene stents for distal malignant biliary obstruction. *Lancet* 1992; **340**: 1488-1492 [PMID: 1281903 DOI: 10.1016/0140-6736(92)92752-2]

3 **Knyrim K**, Wagner HJ, Pausch J, Vakil N. A prospective, randomized, controlled trial of metal stents for malignant obstruction of the common bile duct. *Endoscopy* 1993; **25**: 207-212 [PMID: 8519239 DOI: 10.1055/s-2007-1010294]

4 **Prat F**, Chapat O, Ducot B, Ponchon T, Pelletier G, Fritsch J, Choury AD, Buffet C. A randomized trial of endoscopic drainage methods for inoperable malignant strictures of the common bile duct. *Gastrointest Endosc* 1998; **47**: 1-7 [PMID: 9468416 DOI: 10.1016/S0016-5107(98)70291-3]

5 **Kaassis M**, Boyer J, Dumas R, Ponchon T, Coumaros D, Delcenserie R, Canard JM, Fritsch J, Rey JF, Burtin P. Plastic or metal stents for malignant stricture of the common bile duct? Results of a randomized prospective study. *Gastrointest Endosc* 2003; **57**: 178-182 [PMID: 12556780 DOI: 10.1067/mge.2003.66]

6 **Isayama H**, Komatsu Y, Tsujino T, Sasahira N, Hirano K, Toda N, Nakai Y, Yamamoto N, Tada M, Yoshida H, Shiratori Y, Kawabe T, Omata M. A prospective randomised study of "covered" versus "uncovered" diamond stents for the management of distal malignant biliary obstruction. *Gut* 2004; **53**: 729-734 [PMID: 15082593 DOI: 10.1136/gut.2003.018945]

7 **Saleem A**, Leggett CL, Murad MH, Baron TH. Meta-analysis of randomized trials comparing the patency of covered and uncovered self-expandable metal stents for palliation of distal malignant bile duct obstruction. *Gastrointest Endosc* 2011; **74**: 321-327.e1-e3 [PMID: 21683354 DOI: 10.1016/j.gie.2011.03.1249]

8 **Almadi MA**, Barkun AN, Martel M. No benefit of covered vs uncovered self-expandable metal stents in patients with malignant distal biliary obstruction: a meta-analysis. *Clin Gastroenterol Hepatol* 2013; **11**: 27-37.e1 [PMID: 23103324 DOI: 10.1016./j.cgh.2012.10.019]

9 **Yang Z**, Wu Q, Wang F, Ye X, Qi X, Fan D. A systematic review and meta-analysis of randomized trials and prospective studies comparing covered and bare self-expandable metal stents for the treatment of malignant obstruction in the digestive tract. *Int J Med Sci* 2013; **10**: 825-835 [PMID: 23794946 DOI: 10.7150/ijms.5969]

10 **Speer AG**, Cotton PB, MacRae KD. Endoscopic management of malignant biliary obstruction: stents of 10 French gauge are preferable to stents of 8 French gauge. *Gastrointest Endosc* 1988; **34**: 412-417 [PMID: 2460394 DOI: 10.1016/S0016-5107(88)71407-8]

11 **Siegel JH**, Pullano W, Kodsi B, Cooperman A, Ramsey W. Optimal palliation of malignant bile duct obstruction: experience with endoscopic 12 French prostheses. *Endoscopy* 1988; **20**: 137-141 [PMID: 2460332 DOI: 10.1055/s-2007-1018158]

12 **Loew BJ**, Howell DA, Sanders MK, Desilets DJ, Kortan PP, May GR, Shah RJ, Chen YK, Parsons WG, Hawes RH, Cotton PB, Slivka AA, Ahmad J, Lehman GA, Sherman S, Neuhaus H, Schumacher BM. Comparative performance of uncoated, self-expanding metal biliary stents of different designs in 2 diameters: final results of an international multicenter, randomized, controlled trial. *Gastrointest Endosc* 2009; **70**: 445-453 [PMID: 19482279 DOI: 10.1016/j.gie.2008.11.018]

13 **Mukai T**, Yasuda I, Isayama H, Iwashita T, Itoi T, Kawakami H, Kogure H, Nakai Y. Pilot study of a novel, large-bore, fully covered self-expandable metallic stent for unresectable distal biliary malignancies. *Dig Endosc* 2016; **28**: 671-679 [PMID: 26927207 DOI: 10.1111/den.12643]

14 **Kullman E**, Frozanpor F, Söderlund C, Linder S, Sandström P,

Lindhoff-Larsson A, Toth E, Lindell G, Jonas E, Freedman J, Ljungman M, Rudberg C, Ohlin B, Zacharias R, Leijonmarck CE, Teder K, Ringman A, Persson G, Gözen M, Eriksson O. Covered versus uncovered self-expandable nitinol stents in the palliative treatment of malignant distal biliary obstruction: results from a randomized, multicenter study. *Gastrointest Endosc* 2010; **72**: 915-923 [PMID: 21034892 DOI: 10.1016/j.gie.2010.07.036]

15 **Telford JJ**, Carr-Locke DL, Baron TH, Poneros JM, Bounds BC, Kelsey PB, Schapiro RH, Huang CS, Lichtenstein DR, Jacobson BC, Saltzman JR, Thompson CC, Forcione DG, Gostout CJ, Brugge WR. A randomized trial comparing uncovered and partially covered self-expandable metal stents in the palliation of distal malignant biliary obstruction. *Gastrointest Endosc* 2010; **72**: 907-914 [PMID: 21034891 DOI: 10.1016/j.gie.2010.08.021]

16 **Isayama H**, Hamada T, Yasuda I, Itoi T, Ryozawa S, Nakai Y, Kogure H, Koike K. TOKYO criteria 2014 for transpapillary biliary stenting. *Dig Endosc* 2015; **27**: 259-264 [PMID: 25209944 DOI: 10.111/den.12379]

17 **Costamagna G**, Tringali A, Reddy DN, Devière J, Bruno M, Ponchon T, Neuhaus H, Mutignani M, Rao GV, Lakhtakia S, Le Moine O, Fockens P, Rauws EA, Lepilliez V, Schumacher B, Seelhoff A, Carr-Locke D. A new partially covered nitinol stent for palliative treatment of malignant bile duct obstruction: a multicenter single-arm prospective study. *Endoscopy* 2011; **43**: 317-324 [PMID: 21360423 DOI: 10.1055/s-0030-1256294]

18 **Kahaleh M**, Talreja JP, Loren DE, Kowalski TE, Poneros JM, Degaetani M, Raijman I, Sejpal DV, Patel S, Rosenkranz L, McNamara KN, Brijbassie A, Wang AY, Gaidhane M, Sethi A, Stevens PD. Evaluation of a fully covered self-expanding metal stent with flared ends in malignant biliary obstruction: a multicenter study. *J Clin Gastroenterol* 2013; **47**: e96-100 [PMID: 23933803 DOI: 10.1097/MCG.0b013e3182951a32]

19 **Petersen BT**, Kahaleh M, Kozarek RA, Loren D, Gupta K, Kowalski T, Freeman M, Chen YK, Branch MS, Edmundowicz S, Gluck M, Binmoeller K, Baron TH, Shah RJ, Kinney T, Ross W, Jowell P, Carr-Locke D. A multicenter, prospective study of a new fully covered expandable metal biliary stent for the palliative treatment of malignant bile duct obstruction. *Gastroenterol Res Pract* 2013; **2013**: 642428 [PMID: 23606835 DOI: 10.1155/2013/642428]

20 **Isayama H**, Mukai T, Itoi T, Maetani I, Nakai Y, Kawakami H, Yasuda I, Maguchi H, Ryozawa S, Hanada K, Hasebe O, Ito K, Kawamoto H, Mochizuki H, Igarashi Y, Irisawa A, Sasaki T, Togawa O, Hara T, Kamada H, Toda N, Kogure H. Comparison of partially covered nitinol stents with partially covered stainless stents as a historical control in a multicenter study of distal malignant biliary obstruction: the WATCH study. *Gastrointest Endosc* 2012; **76**: 84-92 [PMID: 22482918 DOI: 10.1016/j.gie.2012.02.039]

21 **Kawakubo K**, Isayama H, Nakai Y, Togawa O, Sasahira N, Kogure H, Sasaki T, Matsubara S, Yamamoto N, Hirano K, Tsujino T, Toda N, Tada M, Omata M, Koike K. Risk factors for pancreatitis following transpapillary self-expandable metal stent placement. *Surg Endosc* 2012; **26**: 771-776 [PMID: 22011943 DOI: 10.1007/s00464-011-1950-4]

22 **Shimizu S**, Naitoh I, Nakazawa T, Hayashi K, Miyabe K, Kondo H, Yoshida M, Yamashita H, Umemura S, Hori Y, Ohara H, Joh T. Predictive factors for pancreatitis and cholecystitis in endoscopic covered metal stenting for distal malignant biliary obstruction. *J Gastroenterol Hepatol* 2013; **28**: 68-72 [PMID: 23020651 DOI: 10.111/j.1440-1746.2012.07283.x]

23 **Shimizu E**, Kikuyama M, Hirai R, Matsumura K, Kin H, Nagasawa M, Ogawa K. Acute cholecystitis after expandable metal stent placement for malignant biliary obstruction (in Japanese). *J Jp Bil Assoc* 2006; **20**: 142-146

24 **Sofi AA**, Nawras A, Alaradi OH, Alastal Y, Khan MA, Lee WM. Does endoscopic sphincterotomy reduce the risk of post-endoscopic retrograde cholangiopancreatography pancreatitis after biliary stenting? A systematic review and meta-analysis. *Dig Endosc* 2016; **28**: 394-404 [PMID: 26636754 DOI: 10.1111/den.12584]

25 **Dong Q**, Yang XH, Zhang Y, Jing W, Zheng LQ, Liu YP, Qu XJ. Elevated serum CA19-9 level is a promising predictor for poor prognosis in patients with resectable pancreatic ductal adenocarcinoma: a pilot study. *World J Surg Oncol* 2014; **12**: 171 [PMID: 24890327 DOI: 10.1186/1477-7819-12-171]

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ORIGINAL ARTICLE

Retrospective Study

Post-endoscopic procedure satisfaction scores: Can we improve?

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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.

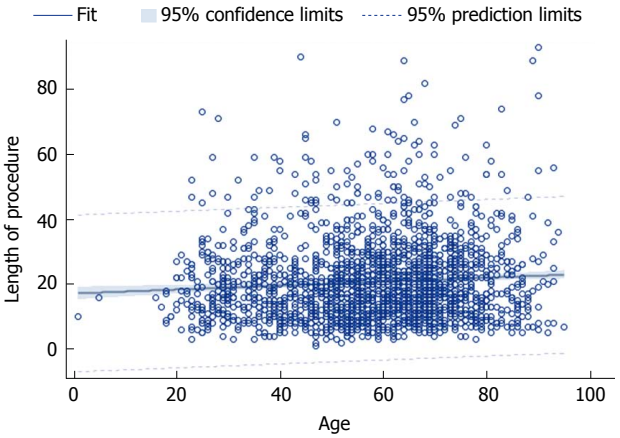

Figure 1 Fit Plot of the relationship between age and procedure length.

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.

REFERENCES

1 **Rizk MK**, Sawhney MS, Cohen J, Pike IM, Adler DG, Dominitz JA, Lieb JG 2nd, Lieberman DA, Park WG, Shaheen NJ, Wani S. Quality indicators common to all GI endoscopic procedures. *Gastrointest Endosc* 2015; **81**: 3-16 [PMID: 25480102 DOI: 10.1016/j.gie.2014.07.055]

2 **Eckardt AJ**, Swales C, Bhattacharya K, Wassef WY, Phelan NP, Zubair S, Martins N, Patel S, Moquin B, Anwar N, Leung K, Levey JM. Open access colonoscopy in the training setting: which factors affect patient satisfaction and pain? *Endoscopy* 2008; **40**: 98-105 [PMID: 18253904 DOI: 10.1055/s-2007-995469]

3 **Allen JI**. Quality assurance for gastrointestinal endoscopy. *Curr Opin Gastroenterol* 2012; **28**: 442-450 [PMID: 22759591 DOI: 10.1097/MOG.0b013e3283561f0d]

4 **Rasool S**, Ahmed S, Siddiqui S, Salih M, Jafri W, Hamid S. Evaluation of quality and patient satisfaction during endoscopic procedure: a cross sectional study from south Asian country. *J Pak Med Assoc* 2010; **60**: 990-995 [PMID: 21381548]

5 **Trujillo-Benavides OE**, Altamirano-García AA, Baltazar-Montúfar P, Maroun-Marun C, Méndez-Del Monte R, Torres-Rubí D. [Level of satisfaction from patients who undergone an endoscopic procedure and related factors]. *Rev Gastroenterol Mex* 2010; **75**: 374-379 [PMID: 21169103]

6 **Qureshi MO**, Shafqat F, Ahmed S, Niazi TK, Khokhar N. Factors affecting patient satisfaction during endoscopic procedures. *J Coll Physicians Surg Pak* 2013; **23**: 775-779 [PMID: 24169383 DOI: 11.2013/JCPSP.775779]

7 **Del Río AS**, Baudet JS, Fernández OA, Morales I, Socas Mdel R. Evaluation of patient satisfaction in gastrointestinal endoscopy. *Eur J Gastroenterol Hepatol* 2007; **19**: 896-900 [PMID: 17873615 DOI: 10.1097/MEG.0b013e3281532bae]

8 **Salmon P**, Shah R, Berg S, Williams C. Evaluating customer satisfaction with colonoscopy. *Endoscopy* 1994; **26**: 342-346 [PMID: 8076565 DOI: 10.1055/s-2007-1008988]

9 **Bernstein C**, Thorn M, Monsees K, Spell R, O'Connor JB. A prospective study of factors that determine cecal intubation time at colonoscopy. *Gastrointest Endosc* 2005; **61**: 72-75 [PMID: 15672059 DOI: 10.1016/S0016-5107(04)02461-7]

10 **Anderson JC**, Messina CR, Cohn W, Gottfried E, Ingber S, Bernstein G, Coman E, Polito J. Factors predictive of difficult colonoscopy. *Gastrointest Endosc* 2001; **54**: 558-562 [PMID: 11677470 DOI: 10.1067/mge.2001.118950]

11 **Kim WH**, Cho YJ, Park JY, Min PK, Kang JK, Park IS. Factors affecting insertion time and patient discomfort during colonoscopy. *Gastrointest Endosc* 2000; **52**: 600-605 [PMID: 11060182 DOI: 10.1067/mge.2000.109802]

12 **Cirocco WC**, Rusin LC. Factors that predict incomplete colonoscopy. *Dis Colon Rectum* 1995; **38**: 964-968 [PMID: 7656745 DOI: 10.1007/BF02049733]

13 **Anderson JC**, Gonzalez JD, Messina CR, Pollack BJ. Factors that predict incomplete colonoscopy: thinner is not always better. *Am J Gastroenterol* 2000; **95**: 2784-2787 [PMID: 11051348 DOI: 10.1111/j.1572-0241.2000.03186.x]

14 **Church JM**. Complete colonoscopy: how often? And if not, why not? *Am J Gastroenterol* 1994; **89**: 556-560 [PMID: 8147359]

15 **Krishnan P**, Sofi AA, Dempsey R, Alaradi O, Nawras A. Body mass index predicts cecal insertion time: the higher, the better. *Dig Endosc* 2012; **24**: 439-442 [PMID: 23078436 DOI: 10.1111/j.1443-1661.2012.01296.x]

16 **Liang CM**, Chiu YC, Wu KL, Tam W, Tai WC, Hu ML, Chou YP, Chiu KW, Chuah SK. Impact factors for difficult cecal intubation during colonoscopy. *Surg Laparosc Endosc Pecutan Tech*. 2012; **22**: 443-446 [PMID: 230470390 DOI: 10.1097/SLE.0b013e3182611c69]

17 **Hsu CM**, Lin WP, Su MY, Chiu CT, Ho YP, Chen PC. Factors that influence cecal intubation rate during colonoscopy in deeply sedated patients. *J Gastroenterol Hepatol* 2012; **27**: 76-80 [PMID: 21649720 DOI: 10.1111/j.1440-1746.2011.06795.x]

18 **Hsieh YH**, Kuo CS, Tseng KC, Lin HJ. Factors that predict cecal insertion time during sedated colonoscopy: the role of waist circumference. *J Gastroenterol Hepatol* 2008; **23**: 215-217 [PMID: 18289354 DOI: 10.1111/j.1440-1746.2006.04818.x]

19 **Hansen JJ**, Ulmer BJ, Rex DK. Technical performance of colonoscopy in patients sedated with nurse-administered propofol. *Am J Gastroenterol* 2004; **99**: 52-56 [PMID: 14687141 DOI: 10.1046/j.1572-0241.2003.04022.x]

20 **Mui LM**, Ng EK, Chan KC, Ng CS, Yeung AC, Chan SK, Wong SK, Chung SC. Randomized, double-blinded, placebo-controlled trial of intravenously administered hyoscine N-butyl bromide in patients undergoing colonoscopy with patient-controlled sedation. *Gastrointest Endosc* 2004; **59**: 22-27 [PMID: 14722542 DOI: 10.1016/S0016-5107(03)02377-0]

21 **Yoshikawa I**, Honda H, Nagata K, Kanda K, Yamasaki T, Kume K, Tabaru A, Otsuki M. Variable stiffness colonoscopes are associated with less pain during colonoscopy in unsedated patients. *Am J Gastroenterol* 2002; **97**: 3052-3055 [PMID: 12492189 DOI: 10.1111/j.1572-0241.2002.07100.x]

22 **Saunders BP**, Fukumoto M, Halligan S, Jobling C, Moussa ME, Bartram CI, Williams CB. Why is colonoscopy more difficult in women? *Gastrointest Endosc* 1996; **43**: 124-126 [PMID: 8635705 DOI: 10.1016/Soo16-5107(06)80113-6]

23 **Sadahiro S**, Ohmura T, Yamada Y, Saito T, Taki Y. Analysis of length and surface area of each segment of the large intestine according to age, sex and physique. *Surg Radiol Anat* 1992; **14**: 251-257 [PMID: 1440190 DOI: 10.1007/BF01794949]

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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

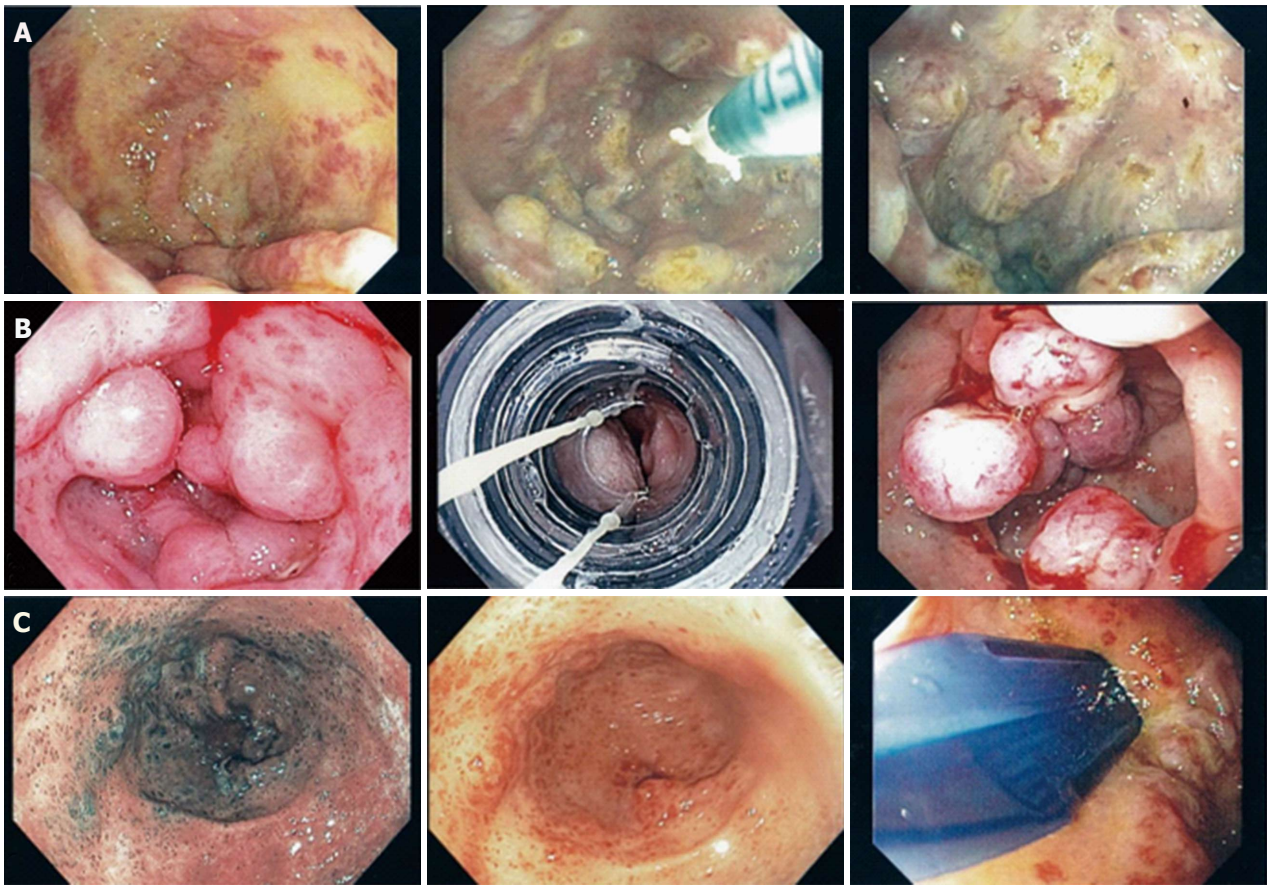

Figure 1 Argon plasma coagulation (A), endoscopic band ligation (B) and TTS- radiofrequency ablation (C).

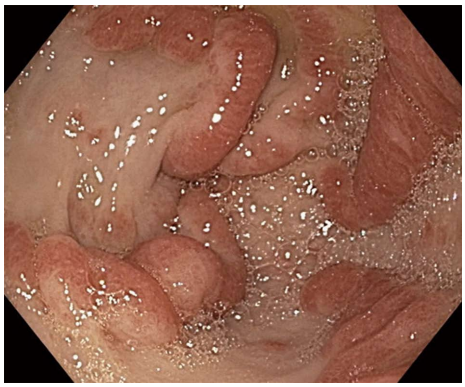

Figure 2 White light endoscopy.

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.

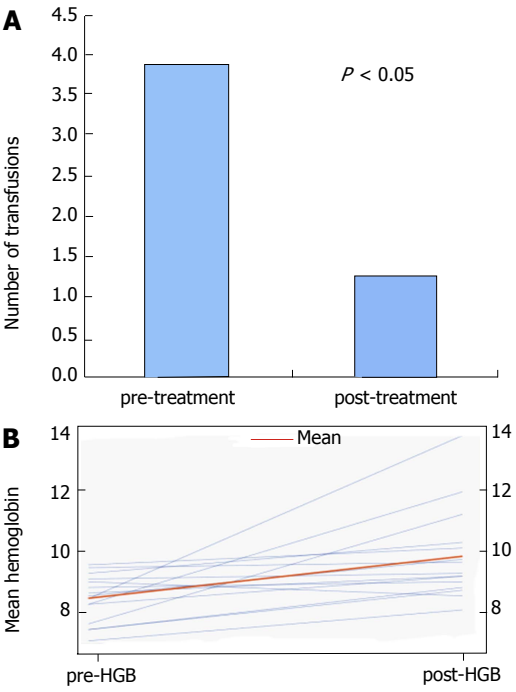

Figure 3 Number of transfusions (A) and mean hemoglobin (B) in 6-mo period pre- and post-treatment for gastric antral vascular ectasia. HGB: Hemoglobin.

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[25]. 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

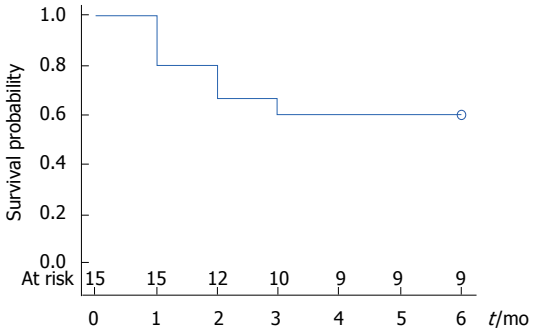

Figure 4 Transfusion free survival curve.

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

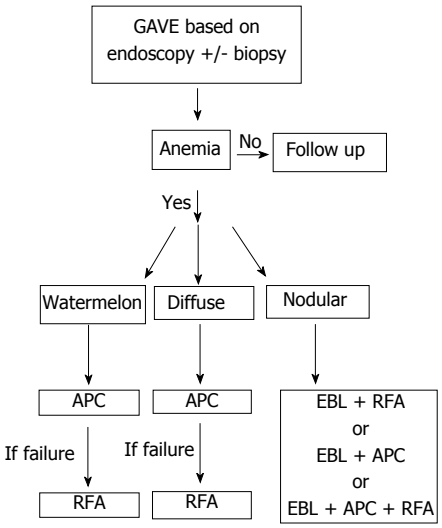

Figure 5 Suggested flow chart for treatment algorithm. GAVE: Gastric antral vascular ectasia; APC: Argon plasma coagulation; RFA: Radiofrequency ablation; EBL: Endoscopic band ligation. Can consider radiofrequency ablation as first line therapy as well for watermelon and diffuse type.

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.

REFERENCES

1 **Rider JA**, Klotz AP, Kirsner JB. Gastritis with veno-capillary ectasia as a source of massive gastric hemorrhage. *Gastroenterology* 1953; **24**: 118-123 [PMID: 13052170]

2 **Dulai GS**, Jensen DM, Kovacs TO, Gralnek IM, Jutabha R. Endoscopic treatment outcomes in watermelon stomach patients with and without portal hypertension. *Endoscopy* 2004; **36**: 68-72 [PMID: 14722858 DOI: 10.1055/s-2004-814112]

3 **Ito M**, Uchida Y, Kamano S, Kawabata H, Nishioka M. Clinical comparisons between two subsets of gastric antral vascular ectasia. *Gastrointest Endosc* 2001; **53**: 764-770 [PMID: 11375585 DOI: 10.1067/mge.2001.113922]

4 **Payen JL**, Calès P, Voigt JJ, Barbe S, Pilette C, Dubuisson L, Desmorat H, Vinel JP, Kervran A, Chayvialle JA. Severe portal hypertensive gastropathy and antral vascular ectasia are distinct entities in patients with cirrhosis. *Gastroenterology* 1995; **108**: 138-144 [PMID: 7806035 DOI: 10.1016/0016-5085(95)90018-7]

5 **Westerhoff M**, Tretiakova M, Hovan L, Miller J, Noffsinger A, Hart J. CD61, CD31, and CD34 improve diagnostic accuracy in gastric antral vascular ectasia and portal hypertensive gastropathy: An immunohistochemical and digital morphometric study. *Am J Surg Pathol* 2010; **34**: 494-501 [PMID: 20351488 DOI: 10.1097/PAS.0b013e3181d38f0a]

6 **Patwardhan VR**, Cardenas A. Review article: the management of portal hypertensive gastropathy and gastric antral vascular ectasia in cirrhosis. *Aliment Pharmacol Ther* 2014; **40**: 354-362 [PMID: 24889902 DOI: 10.1111/apt.12824]

7 **Fuccio L**, Mussetto A, Laterza L, Eusebi LH, Bazzoli F. Diagnosis and management of gastric antral vascular ectasia. *World J Gastrointest Endosc* 2013; **5**: 6-13 [PMID: 23330048 DOI: 10.4253/wjge.v5.i1.6]

8 **Alkurdi B**, Monkemuller K, Khan AS, Council L, McGuire BM, Peter S. Gastric antral vascular ectasia: a rare manifestation for gastrointestinal bleeding in left ventricular assist device patients--an initial report. *Dig Dis Sci* 2014; **59**: 2826-2830 [PMID: 24821465 DOI: 10.1007/s10620-014-3200-9]

9 **Allamneni C**, Alkurdi B, Naseemuddin R, McGuire BM, Shoreibah MG, Eckhoff DE, Peter S. Orthotopic liver transplantation changes the course of gastric antral vascular ectasia: a case series from a transplant center. *Eur J Gastroenterol Hepatol* 2017; **29**: 973-976 [PMID: 28520574 DOI: 10.1097/MEG.0000000000000908]

10 **Jana T**, Thosani N, Fallon MB, Dupont AW, Ertan A. Radiofrequency ablation for treatment of refractory gastric antral vascular ectasia (with video). *Endosc Int Open* 2015; **3**: E125-E127 [PMID: 26135652 DOI: 10.1055/s-0034-1391323]

11 **Elhendawy M**, Mosaad S, Alkhalawany W, Abo-Ali L, Enaba M, Elsaka A, Elfert AA. Randomized controlled study of endoscopic band ligation and argon plasma coagulation in the treatment of gastric antral and fundal vascular ectasia. *United European Gastroenterol J* 2016; **4**: 423-428 [PMID: 27403309 DOI: 10.1177/2050640615619837]

12 **Becq A**, Camus M, Rahmi G, de Parades V, Marteau P, Dray X. Emerging indications of endoscopic radiofrequency ablation. *United European Gastroenterol J* 2015; **3**: 313-324 [PMID: 26279839 DOI: 10.1177/2050640615571159]

13 **Naidu H**, Huang Q, Mashimo H. Gastric antral vascular ectasia: the evolution of therapeutic modalities. *Endosc Int Open* 2014; **2**: E67-E73 [PMID: 26135263 DOI: 10.1055/s-0034-1365525]

14 **Bhatti MA**, Khan AA, Alam A, Butt AK, Shafqat F, Malik K, Amin J, Shah W. Efficacy of argon plasma coagulation in gastric vascular ectasia in patients with liver cirrhosis. *J Coll Physicians Surg Pak* 2009; **19**: 219-222 [PMID: 19356335 DOI: 04.2009/JCPSP.219222]

15 **Naga M**, Esmat S, Naguib M, Sedrak H. Long-term effect of argon plasma coagulation (APC) in the treatment of gastric antral vascular ectasia (GAVE). *Arab J Gastroenterol* 2011; **12**: 40-43 [PMID: 21429455 DOI: 10.1016/j.ajg.2011.01.012]

16 **Kantsevoy SV**, Cruz-Correa MR, Vaughn CA, Jagannath SB, Pasricha PJ, Kalloo AN. Endoscopic cryotherapy for the treatment of bleeding mucosal vascular lesions of the GI tract: a pilot study. *Gastrointest Endosc* 2003; **57**: 403-406 [PMID: 12612530 DOI: 10.1067/mge.2003.115]

17 **Farooq FT**, Wong RC, Yang P, Post AB. Gastric outlet obstruction as a complication of argon plasma coagulation for watermelon stomach. *Gastrointest Endosc* 2007; **65**: 1090-1092 [PMID: 17451706 DOI: 10.1016/j.gie.2006.10.006]

18 **Sato T**, Yamazaki K, Akaike J. Endoscopic band ligation versus argon plasma coagulation for gastric antral vascular ectasia associated with liver diseases. *Dig Endosc* 2012; **24**: 237-242 [PMID: 22725108 DOI: 10.1111/j.1443-1661.2011.01221.x]

19 **Baudet JS**, Salata H, Soler M, Castro V, Díaz-Bethencourt D, Vela M, Morales S, Avilés J. Hyperplastic gastric polyps after argon plasma coagulation treatment of gastric antral vascular ectasia (GAVE). *Endoscopy* 2007; **39** Suppl 1: E320 [PMID: 18273773 DOI: 10.1055/s-2007-966802]

20 **Dray X**, Repici A, Gonzalez P, Fristrup C, Lecleire S, Kantsevoy S, Wengrower D, Elbe P, Camus M, Carlino A, Pérez-Roldán F, Adar T, Marteau P. Radiofrequency ablation for the treatment of gastric antral vascular ectasia. *Endoscopy* 2014; **46**: 963-969 [PMID: 25111135 DOI: 10.1055/s-0034-1377695]

21 **McGorisk T**, Krishnan K, Keefer L, Komanduri S. Radiofrequency ablation for refractory gastric antral vascular ectasia (with video). *Gastrointest Endosc* 2013; **78**: 584-588 [PMID: 23660565 DOI: 10.1016/j.gie.2013.04.173]

22 **Gutkin E**, Schnall A. Gastroesophageal junction tear from HALO 90 System: A case report. *World J Gastrointest Endosc* 2011; **3**: 105-106 [PMID: 21772942 DOI: 10.4253/wjge.v3.i5.105]

23 **Islam RS**, Pasha SF, Fleischer DE. Refractory gastric antral vascular ectasia treated by a novel through-the-scope ablation catheter. *Gastrointest Endosc* 2014; **80**: 896-897 [PMID: 24731266 DOI: 10.1016/j.gie.2014.02.1026]

24 **Zepeda-Gómez S**, Sultanian R, Teshima C, Sandha G, Van Zanten S, Montano-Loza AJ. Gastric antral vascular ectasia: a prospective study of treatment with endoscopic band ligation. *Endoscopy* 2015; **47**: 538-540 [PMID: 25650636 DOI: 10.1055/s-0034-1391395]

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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.

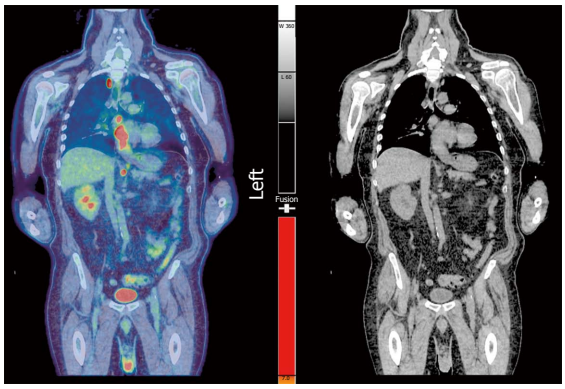

Figure 1 Positron emission tomography-computed tomography image. Positron emission tomography (PET)-computed tomography image of PET positive lower oesophageal tumour with uptake in the primary tumour and also in high paratracheal and coeliac nodes.

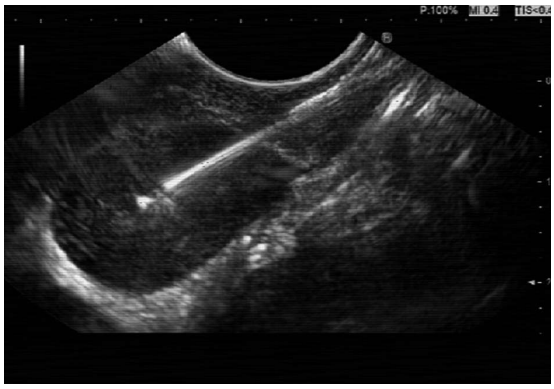

Figure 2 Endoscopic ultrasound-guided fine-needle aspiration image. Endoscopic ultrasound-guided fine-needle aspiration of a high mediastinal node in upper Gastrointestinal cancer.

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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REFERENCES

1 **Allum WH**, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. *J Clin Oncol* 2009; **27**: 5062-5067 [PMID: 19770374 DOI: 10.1200/JCO.2009.22.2083]

2 **Hulscher JB**, van Sandick JW, de Boer AG, Wijnhoven BP, Tijssen JG, Fockens P, Stalmeier PF, ten Kate FJ, van Dekken H, Obertop H, Tilanus HW, van Lanschot JJ. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med* 2002; **347**: 1662-1669 [PMID: 12444180 DOI: 10.1056/NEJMoa022343]

3 **Shapiro J**, van Lanschot JJB, Hulshof MCCM, van Hagen P, van Berge Henegouwen MI, Wijnhoven BPL, van Laarhoven HWM, Nieuwenhuijzen GAP, Hospers GAP, Bonenkamp JJ, Cuesta MA, Blaisse RJB, Busch ORC, Ten Kate FJW, Creemers GM, Punt CJA, Plukker JTM, Verheul HMW, Bilgen EJS, van Dekken H, van der Sangen MJC, Rozema T, Biermann K, Beukema JC, Piet AHM, van Rij CM, Reinders JG, Tilanus HW, Steyerberg EW, van der Gaast A; CROSS study group. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *Lancet Oncol* 2015; **16**: 1090-1098 [PMID: 26254683 DOI: 10.1016/S1470-2045(15)00040-6]

4 **Allum WH**, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R; Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, the British Society of Gastroenterology and the British Association of Surgical Oncology. Guidelines for the management of oesophageal and gastric cancer. *Gut* 2011; **60**: 1449-1472 [PMID: 21705456 DOI: 10.1136/gut.2010.228254]

5 **National Oesophago-Gastric Cancer Audit**. 2013, Annual Report. Available from: URL: http://www.hscic.gov.uk

6 **Smith BR**, Chang KJ, Lee JG, Nguyen NT. Staging accuracy

of endoscopic ultrasound based on pathologic analysis after minimally invasive esophagectomy. *Am Surg* 2010; **76**: 1228-1231 [PMID: 21140689]
7 **Puli SR**, Reddy JB, Bechtold ML, Antillon D, Ibdah JA, Antillon MR. Staging accuracy of esophageal cancer by endoscopic ultrasound: a meta-analysis and systematic review. *World J Gastroenterol* 2008; **14**: 1479-1490 [PMID: 18330935 DOI: 10.3748/wjg.14.1479]
8 **van Vliet EP**, Heijenbrok-Kal MH, Hunink MG, Kuipers EJ, Siersema PD. Staging investigations for oesophageal cancer: a meta-analysis. *Br J Cancer* 2008; **98**: 547-557 [PMID: 18212745 DOI: 10.1038/sj.bjc.6604200]
9 **Catalano MF**, Alcocer E, Chak A, Nguyen CC, Raijman I, Geenen JE, Lahoti S, Sivak MV Jr. Evaluation of metastatic celiac axis lymph nodes in patients with esophageal carcinoma: accuracy of EUS. *Gastrointest Endosc* 1999; **50**: 352-356 [PMID: 10462655 DOI: 10.1053/ge.1999.v50.98154]
10 **Bhutani MS**, Hawes RH, Hoffman BJ. A comparison of the accuracy of echo features during endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration for diagnosis of malignant lymph node invasion. *Gastrointest Endosc* 1997; **45**: 474-479 [PMID: 9199903]
11 **Chen VK**, Eloubeidi MA. Endoscopic ultrasound-guided fine needle aspiration is superior to lymph node echofeatures: a prospective evaluation of mediastinal and peri-intestinal lymphadenopathy. *Am J Gastroenterol* 2004; **99**: 628-633 [PMID: 15089893 DOI: 10.1111/j.1572-0241.2004.04064.x]
12 **Saftoiu A**, Vilman P. Endoscopic ultrasound elastography-- a new imaging technique for the visualization of tissue elasticity distribution. *J Gastrointestin Liver Dis* 2006; **15**: 161-165 [PMID: 16802011]
13 **Janssen J**, Dietrich CF, Will U, Greiner L. Endosonographic elastography in the diagnosis of mediastinal lymph nodes. *Endoscopy* 2007; **39**: 952-957 [PMID: 18008203 DOI: 10.1055/s-2007-966946]
14 **Faige DO**. EUS in patients with benign and malignant lymphadenopathy. *Gastrointest Endosc* 2001; **53**: 593-598 [PMID: 11323584]
15 **Paterson S**, Duthie F, Stanley AJ. Endoscopic ultrasound-guided elastography in the nodal staging of oesophageal cancer. *World J Gastroenterol* 2012; **18**: 889-895 [PMID: 22408347 DOI: 10.3748/wjg.v18.i9.889]
16 **Yuan S**, Yu Y, Chao KS, Fu Z, Yin Y, Liu T, Chen S, Yang X, Yang G, Guo H, Yu J. Additional value of PET/CT over PET in assessment of locoregional lymph nodes in thoracic esophageal squamous cell cancer. *J Nucl Med* 2006; **47**: 1255-1259 [PMID: 16883002]
17 **Choi J**, Kim SG, Kim JS, Jung HC, Song IS. Comparison of endoscopic ultrasonography (EUS), positron emission tomography (PET), and computed tomography (CT) in the preoperative locoregional staging of resectable esophageal cancer. *Surg Endosc* 2010; **24**: 1380-1386 [PMID: 20033712 DOI: 10.1007/s00464-009-0783-x]
18 **Salahudeen HM**, Balan A, Naik K, Mirsadraee S, Scarsbrook AF. Impact of the introduction of integrated PET-CT into the preoperative staging pathway of patients with potentially operable oesophageal carcinoma. *Clin Radiol* 2008; **63**: 765-773 [PMID: 18555034 DOI: 10.1016/j.crad.2008.02.002]
19 **Williams RN**, Ubhi SS, Sutton CD, Thomas AL, Entwisle JJ, Bowrey DJ. The early use of PET-CT alters the management of patients with esophageal cancer. *J Gastrointest Surg* 2009; **13**: 868-873 [PMID: 19184245 DOI: 10.1007/s11605-009-0812-z]
20 **Noble F**, Nolan L, Bateman AC, Byrne JP, Kelly JJ, Bailey IS, Sharland DM, Rees CN, Iveson TJ, Underwood TJ, Bateman AR. Refining pathological evaluation of neoadjuvant therapy for adenocarcinoma of the esophagus. *World J Gastroenterol* 2013; **19**: 9282-9293 [PMID: 24409055 DOI: 10.3748/wjg.v19.i48.9282]
21 **Noble F**, Bailey D; SWCIS Upper Gastrointestinal Tumour Panel, Tung K, Byrne JP. Impact of integrated PET/CT in the staging of oesophageal cancer: a UK population-based cohort study. *Clin Radiol* 2009; **64**: 699-705 [PMID: 19520214 DOI: 10.1016/j.crad.2009.03.003]
22 **van Westreenen HL**, Westerterp M, Sloof GW, Groen H, Bossuyt PM, Jager PL, Comans EF, van Dullemen HM, Fockens P, Stoker J, van der Jagt EJ, van Lanschot JJ, Plukker JT. Limited additional value of positron emission tomography in staging oesophageal cancer. *Br J Surg* 2007; **94**: 1515-1520 [PMID: 17902092 DOI: 10.1002/bjs.5708]
23 **Torrance AD**, Almond LM, Fry J, Wadley MS, Lyburn ID. Has integrated 18F FDG PET/CT improved staging, reduced early recurrence or increased survival in oesophageal cancer? *Surgeon* 2015; **13**: 19-33 [PMID: 24206935 DOI: 10.1016/j.surge.2013.09.002]
24 **Han D**, Yu J, Zhong X, Fu Z, Mu D, Zhang B, Xu G, Yang W, Zhao S. Comparison of the diagnostic value of 3-deoxy-3-18F-fluorothymidine and 18F-fluorodeoxyglucose positron emission tomography/computed tomography in the assessment of regional lymph node in thoracic esophageal squamous cell carcinoma: a pilot study. *Dis Esophagus* 2012; **25**: 416-426 [PMID: 21951837 DOI: 10.1111/j.1442-2050.2011.01259.x]
25 **Blencowe NS**, Whistance RN, Strong S, Hotton EJ, Ganesh S, Roach H, Callaway M, Blazeby JM. Evaluating the role of fluorodeoxyglucose positron emission tomography-computed tomography in multi-disciplinary team recommendations for oesophago-gastric cancer. *Br J Cancer* 2013; **109**: 1445-1450 [PMID: 23963146 DOI: 10.1038/bjc.2013.478]
26 **Karashima R**, Watanabe M, Imamura Y, Ida S, Baba Y, Iwagami S, Miyamoto Y, Sakamoto Y, Yoshida N, Baba H. Advantages of FDG-PET/CT over CT alone in the preoperative assessment of lymph node metastasis in patients with esophageal cancer. *Surg Today* 2015; **45**: 471-477 [PMID: 24969050 DOI: 10.1007/s00595-014-0965-6]
27 **Yamada H**, Hosokawa M, Itoh K, Takenouchi T, Kinoshita Y, Kikkawa T, Sakashita K, Uemura S, Nishida Y, Kusumi T, Sasaki S. Diagnostic value of 18F-FDG PET/CT for lymph node metastasis of esophageal squamous cell carcinoma. *Surg Today* 2014; **44**: 1258-1265 [PMID: 24077997 DOI: 10.1007/s00595-013-0725-z]
28 **Redondo-Cerezo E**, Martínez-Cara JG, Esquivias J, de la Torre-Rubio P, González-Artacho C, García-Marín Mdel C, de Teresa-Galván J. Endoscopic ultrasonography-fine needle aspiration versus PET-CT in undiagnosed mediastinal and upper abdominal lymphadenopathy: a comparative clinical study. *Eur J Gastroenterol Hepatol* 2015; **27**: 455-459 [PMID: 25874521 DOI: 10.1097/MEG.0000000000000302]
29 **Yoon YC**, Lee KS, Shim YM, Kim BT, Kim K, Kim TS. Metastasis to regional lymph nodes in patients with esophageal squamous cell carcinoma: CT versus FDG PET for presurgical detection prospective study. *Radiology* 2003; **227**: 764-770 [PMID: 12773680 DOI: 10.1148/radiol.2281020423]
30 **Kneist W**, Schreckenberger M, Bartenstein P, Grünwald F, Oberholzer K, Junginger T. Positron emission tomography for staging esophageal cancer: does it lead to a different therapeutic approach? *World J Surg* 2003; **27**: 1105-1112 [PMID: 12917769 DOI: 10.1007/s00268-003-6921-z]
31 **Okada M**, Murakami T, Kumano S, Kuwabara M, Shimono T, Hosono M, Shiozaki H. Integrated FDG-PET/CT compared with intravenous contrast-enhanced CT for evaluation of metastatic regional lymph nodes in patients with resectable early stage esophageal cancer. *Ann Nucl Med* 2009; **23**: 73-80 [PMID: 19205841 DOI: 10.1007/s12149-008-0209-1]
32 **Kato H**, Kimura H, Nakajima M, Sakai M, Sano A, Tanaka N, Inose T, Faried A, Saito K, Ieta K, Sohda M, Fukai Y, Miyazaki T, Masuda N, Fukuchi M, Ojima H, Tsukada K, Oriuchi N, Endo K, Kuwano H. The additional value of integrated PET/CT over PET in initial lymph node staging of esophageal cancer. *Oncol Rep* 2008; **20**: 857-862 [PMID: 18813827]
33 **Oesophageal cancer incidence statistics**. Available from: URL: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer/incidence#heading-Zero
34 **Stomach cancer incidence statistics**. Available from: URL: http://

www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/stomach-cancer/incidence#heading-Zero

35 **Flechsig P**, Frank P, Kratochwil C, Antoch G, Rath D, Moltz J, Rieser M, Warth A, Kauczor HU, Schwartz LH, Haberkorn U, Giesel FL. Radiomic Analysis using Density Threshold for FDG-PET/CT-Based N-Staging in Lung Cancer Patients. *Mol Imaging Biol* 2017; **19**: 315-322 [PMID: 27539308 DOI: 10.1007/s11307-016-0996-z]

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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.

REFERENCES

1 **Hochberger J**, Tex S, Maiss J, Hahn EG. Management of difficult common bile duct stones. *Gastrointest Endosc Clin N Am* 2003; **13**: 623-634 [PMID: 14986790 DOI: 10.1016/S1052-5157(03)00102-8]

2 **Tohda G**, Ohtani M, Dochin M. Efficacy and safety of emergency endoscopic retrograde cholangiopancreatography for acute cholangitis in the elderly. *World J Gastroenterol* 2016; **22**: 8382-8388 [PMID: 27729744 DOI: 10.3748/wjg.v22.i37.8382]

3 **ASGE Technology Assessment Committee**. Pfau PR, Pleskow DK, Banerjee S, Barth BA, Bhat YM, Desilets DJ, Gottlieb KT, Maple JT, Siddiqui UD, Tokar JL, Wang A, Song LM, Rodriguez SA. Pancreatic and biliary stents. *Gastrointest Endosc* 2013; **77**: 319-327 [PMID: 23410693 DOI: 10.1016/j.gie.2012.09.026]

4 **Khashab MA**, Kim K, Hutfless S, Lennon AM, Kalloo AN, Singh VK. Predictors of early stent occlusion among plastic biliary stents. *Dig Dis Sci* 2012; **57**: 2446-2450 [PMID: 22573343 DOI: 10.1007/s10620-012-2178-4]

5 **Ang TL**, Fock KM, Teo EK, Chua TS, Tan J. An audit of the outcome of long-term biliary stenting in the treatment of common bile duct stones in a general hospital. *J Gastroenterol* 2006; **41**: 765-771 [PMID: 16988765 DOI: 10.1007/s00535-006-1849-3]

6 **Weickert U**, Venzke T, König J, Janssen J, Remberger K, Greiner L. Why do bilioduodenal plastic stents become occluded? A clinical and pathological investigation on 100 consecutive patients. *Endoscopy* 2001; **33**: 786-790 [PMID: 11558033 DOI: 10.1055/s-2001-16519]

7 **Wada K**, Takada T, Kawarada Y, Nimura Y, Miura F, Yoshida M, Mayumi T, Strasberg S, Pitt HA, Gadacz TR, Büchler MW, Belghiti J, de Santibanes E, Gouma DJ, Neuhaus H, Dervenis C, Fan ST, Chen MF, Ker CG, Bornman PC, Hilvano SC, Kim SW, Liau KH, Kim MH. Diagnostic criteria and severity assessment of acute cholangitis: Tokyo Guidelines. *J Hepatobiliary Pancreat Surg* 2007; **14**: 52-58 [PMID: 17252297]

8 **Kanda Y**. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant* 2013; **48**: 452-458 [PMID: 23208313 DOI: 10.1038/bmt.2012.244]

9 **Di Giorgio P**, Manes G, Grimaldi E, Schettino M, D'Alessandro A, Di Giorgio A, Giannattasio F. Endoscopic plastic stenting for bile duct stones: stent changing on demand or every 3 months. A prospective comparison study. *Endoscopy* 2013; **45**: 1014-1017 [PMID: 24288221 DOI: 10.1055/s-0033-1344556]

10 **Li KW**, Zhang XW, Ding J, Chen T, Wang J, Shi WJ. A prospective study of the efficacy of endoscopic biliary stenting on common bile duct stones. *J Dig Dis* 2009; **10**: 328-331 [PMID: 19906114 DOI: 10.1111/j.1751-2980.2009.00404.x]

11 **Slattery E**, Kale V, Anwar W, Courtney G, Aftab AR. Role of long-term biliary stenting in choledocholithiasis. *Dig Endosc* 2013; **25**: 440-443 [PMID: 23808949 DOI: 10.1111/j.1443-1661.2012.01399.x]

12 **Bergman JJ**, Rauws EA, Tijssen JG, Tytgat GN, Huibregtse K. Biliary endoprostheses in elderly patients with endoscopically irretrievable common bile duct stones: report on 117 patients. *Gastrointest Endosc* 1995; **42**: 195-201 [PMID: 7498682 DOI: 10.1016/S0016-5107(95)70091-9]

13 **Pisello F**, Geraci G, Li Volsi F, Modica G, Sciumè C. Permanent stenting in "unextractable" common bile duct stones in high risk patients. A prospective randomized study comparing two different stents. *Langenbecks Arch Surg* 2008; **393**: 857-863 [PMID: 18679709 DOI: 10.1007/s00423-008-0388-1]

14 **Horiuchi A**, Nakayama Y, Kajiyama M, Kato N, Kamijima T, Graham DY, Tanaka N. Biliary stenting in the management of large or multiple common bile duct stones. *Gastrointest Endosc* 2010; **71**: 1200-1203.e2 [PMID: 20400079 DOI: 10.1016/j.gie.2009.12.055]

15 **Fan Z**, Hawes R, Lawrence C, Zhang X, Zhang X, Lv W. Analysis of plastic stents in the treatment of large common bile duct stones in 45 patients. *Dig Endosc* 2011; **23**: 86-90 [PMID: 21198923 DOI: 10.1111/j.1443-1661.2010.01065.x]

16 **Hong WD**, Zhu QH, Huang QK. Endoscopic sphincterotomy plus endoprostheses in the treatment of large or multiple common bile duct stones. *Dig Endosc* 2011; **23**: 240-243 [PMID: 21699568 DOI: 10.1111/j.1443-1661.2010.01100.x]

17 **Han J**, Moon JH, Koo HC, Kang JH, Choi JH, Jeong S, Lee DH, Lee MS, Kim HG. Effect of biliary stenting combined with ursodeoxycholic acid and terpene treatment on retained common bile duct stones in elderly patients: a multicenter study. *Am J Gastroenterol* 2009; **104**: 2418-2421 [PMID: 19568225 DOI: 10.1038/ajg.2009.303]

18 **Leung JW**, Sung JY, Costerton JW. Bacteriological and electron microscopy examination of brown pigment stones. *J Clin Microbiol* 1989; **27**: 915-921 [PMID: 2745700]

19 **Speer AG**, Cotton PB, Rode J, Seddon AM, Neal CR, Holton J, Costerton JW. Biliary stent blockage with bacterial biofilm. A light and electron microscopy study. *Ann Intern Med* 1988; **108**: 546-553 [PMID: 2450501 DOI: 10.7326/0003-4819-108-4-546]

20 **Moesch C**, Sautereau D, Cessot F, Berry P, Mounier M, Gainant A, Pillegand B. Physicochemical and bacteriological analysis of the contents of occluded biliary endoprostheses. *Hepatology* 1991; **14**: 1142-1146 [PMID: 1959864 DOI: 10.1002/hep.1840140631]

21 **Sohn SH**, Park JH, Kim KH, Kim TN. Complications and management of forgotten long-term biliary stents. *World J Gastroenterol* 2017; **23**: 622-628 [PMID: 28216968 DOI: 10.3748/wjg.v23.i4.622]

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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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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 ($n = 0$)	$P = 0.685$ ($n = 6$)

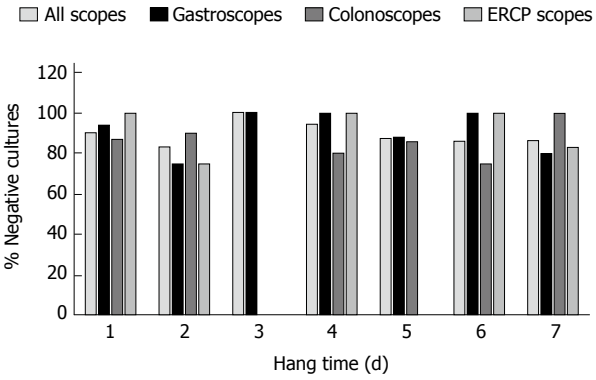

Figure 1 Percentage of negative cultures obtained for all endoscopes throughout the test period. The large percentage of negative cultures is consistent from 1 to 7 d of hang time and between the different types of scopes. ERCP: Endoscopic retrograde cholangiopancreatography.

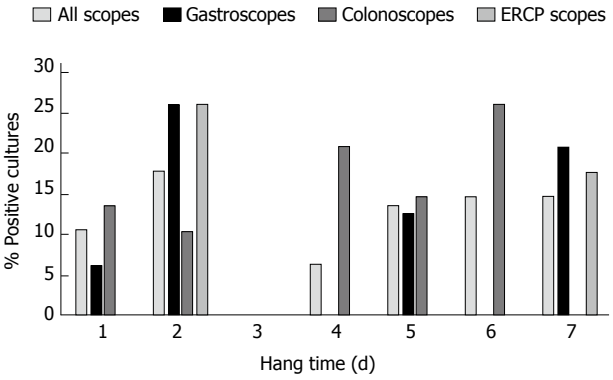

Figure 2 Percentage of positive cultures obtained for all endoscopes throughout the test period. ERCP: Endoscopic retrograde cholangiopancreatography.

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

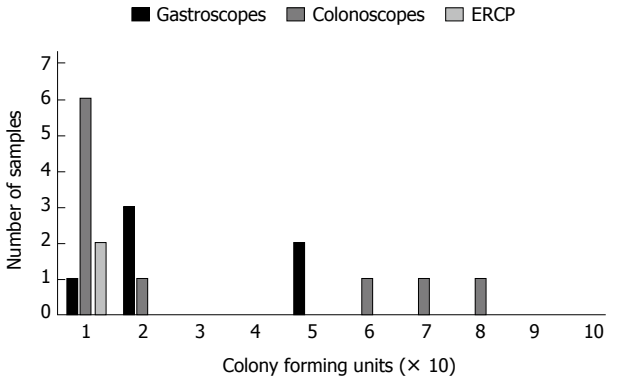

Figure 3 Number of positive culture samples at each level of colony forming units for each endoscope type, where the number of negative cultures for gastroscopes was 67 ($n = 73$), for colonoscopes 67 ($n = 78$) and endoscopic retrograde cholangiopancreatography scopes was 12 ($n = 14$). ERCP: Endoscopic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

1 **ASGE Quality Assurance In Endoscopy Committee**. Petersen BT, Chennat J, Cohen J, Cotton PB, Greenwald DA, Kowalski TE, Krinsky ML, Park WG, Pike IM, Romagnuolo J; Society for Healthcare Epidemiology of America, Rutala WA. Multisociety guideline on reprocessing flexible gastrointestinal endoscopes: 2011. *Gastrointest Endosc* 2011; **73**: 1075-1084 [PMID: 21628008 DOI: 10.1016/j.gie.2011.03.1183]

2 **ASGE Standards of Practice Committee**. Banerjee S, Shen B, Nelson DB, Lichtenstein DR, Baron TH, Anderson MA, Dominitz JA, Gan SI, Harrison ME, Ikenberry SO, Jagannath SB, Fanelli RD, Lee K, van Guilder T, Stewart LE. Infection control during GI endoscopy. *Gastrointest Endosc* 2008; **67**: 781-790 [PMID: 18355826 DOI: 10.1016/j.gie.2008.01.027]

3 Cleaning and disinfection of equipment for gastrointestinal endoscopy. Report of a Working Party of the British Society of Gastroenterology Endoscopy Committee. *Gut* 1998; **42**: 585-593 [PMID: 9616326 DOI: 10.1136/gut.42.4.585]

4 **Association of periOperative Registered Nurses**. Recommended practices for cleaning and processing endoscopes and endoscope accessories. *AORN J* 2003; **77**: 434-438, 441-442 [PMID: 12619857 DOI: 10.1016/S0001-2092(06)61212-X]

5 **Nelson DB**. Recent advances in epidemiology and prevention of gastrointestinal endoscopy related infections. *Curr Opin Infect Dis* 2005; **18**: 326-330 [PMID: 15985829 DOI: 10.1097/01.qco.0000171925.47452.8f]

6 **Burdick JS**, Hambrick D. Endoscope reprocessing and repair costs. *Gastrointest Endosc Clin N Am* 2004; **14**: 717-724, ix-ix [PMID: 15363776 DOI: 10.1016/j.giec.2004.05.002]

7 **Vergis AS**, Thomson D, Pieroni P, Dhalla S. Reprocessing flexible gastrointestinal endoscopes after a period of disuse: is it necessary? *Endoscopy* 2007; **39**: 737-739 [PMID: 17661250 DOI: 10.1055/s-2007-966644]

8 **Rejchrt S**, Cermák P, Pavlatová L, McKová E, Bures J. Bacteriologic testing of endoscopes after high-level disinfection. *Gastrointest Endosc* 2004; **60**: 76-78 [PMID: 15229429 DOI: 10.1016/S0016-5107(04)01313-6]

9 **Epstein L**, Hunter JC, Arwady MA, Tsai V, Stein L, Gribogiannis M, Frias M, Guh AY, Laufer AS, Black S, Pacilli M, Moulton-Meissner H, Rasheed JK, Avillan JJ, Kitchel B, Limbago BM, MacCannell D, Lonsway D, Noble-Wang J, Conway J, Conover C, Vernon M, Kallen AJ. New Delhi metallo-β-lactamase-producing carbapenem-resistant Escherichia coli associated with exposure to duodenoscopes. *JAMA* 2014; **312**: 1447-1455 [PMID: 25291580 DOI: 10.1001/jama.2014.12720]

10 **Manitoba Health, Manitoba Advisory Committee on Infectious Disease, Infection Control Subcommittee EWG**. Guidelines for Infection Prevention and Control in Endoscopy. *Infect Control* 2000: 1-12

11 **Higa JT**, Gluck M, Ross AS. Duodenoscope-Associated Bacterial Infections: A Review and Update. *Curr Treat Options Gastroenterol* 2016; **14**: 185-193 [PMID: 27020265 DOI: 10.1007/s11938-016-0088-9]

12 **Centers for Disease Control and Prevention**. Interim Protocol for Healthcare Facilities Regarding Surveillance for Bacterial Contamination of Duodenoscopes after Reprocessing [Internet]. Atlanta: CDC; 2015. [updated 2015 Mar 11]. [cited 2017 May 02]. Available from: URL: https://www.cdc.gov/hai/organisms/cre/cre-duodenoscope-surveillance-protocol.html

13 **Rutala WA**, Weber DJ. Gastrointestinal endoscopes: a need to shift from disinfection to sterilization? *JAMA* 2014; **312**: 1405-1406 [PMID: 25291575 DOI: 10.1001/jama.2014.12559]

14 **Reasoner DJ**, Geldreich EE. A new medium for the enumeration and subculture of bacteria from potable water. *Appl Environ Microbiol* 1985; **49**: 1-7 [PMID: 3883894]

15 **Centers for Disease Control and Prevention**. Interim culture method for the duodenoscope - distal end and instrument channel [Internet]. Atlanta: CDC; 2015. [updated 2015 Aug 19]. [cited 2017 May 02]. Available from: URL: https://www.cdc.gov/hai/settings/lab/lab-duodenoscope-culture-method.html

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