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REVIEW

Endoscopic retrograde cholangiopancreatography guided interventions in the management of pancreatic cancer

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Abstract

Pancreatic cancer is the leading cause of cancer-related morbidity and mortality with an overall five-year survival of less than 9% in the United States. At presentation, the majority of patients have painless jaundice, pruritis, and malaise, a triad that develops secondary to obstruction, which often occurs late in the course of the disease process. The technical advancements in radiological imaging and endoscopic interventions have played a crucial role in the diagnosis, staging, and management of patients with pancreatic cancer. Endoscopic retrograde cholangiopancreatography (ERCP)-guided diagnosis (with brush cytology, serial pancreatic juice aspiration cytologic examination technique, or biliary biopsy) and therapeutic interventions such as pancreatobiliary decompression, intraductal and relief of gastric outlet obstruction play a pivotal role in the management of advanced pancreatic cancer and are increasingly used due to improved morbidity

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and complication rates compared to surgical management. In this review, we highlight various ERCP-guided diagnostic and therapeutic interventions for the management of pancreatic cancer.

Key Words: Pancreatic cancer; Endoscopic retrograde cholangiopancreatography; Malignant stricture; Biliary drainage; Biliary stent; Gastric outlet obstruction

Core Tip: Endoscopic retrograde cholangiopancreatography (ERCP)-guided interventions have an important role in the diagnosis, treatment, and palliation of pancreatic cancer. ERCP-guided biliary tissue sampling assists in diagnosing pancreatic cancer and permit therapeutic interventions during the same procedure (if needed). Advanced pancreatic cancers may result in biliary or gastric outlet obstruction. ERCP-guided deployment of either biliary or enteral stents provides effective palliation and improves the quality of life. The selection of biliary stent subtype depends on multiple factors including life expectancy, risk of complications, cost, and the need for ERCP-guided reinterventions. Self-expandable metal stents are preferred over plastic stents because of longer luminal patency, lower rates of stent dysfunction, and overall cost.

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INTRODUCTION

While pancreatic cancer is the 13th most common type of cancer globally, it is the fourth leading cause of cancer-related death in the United States with an estimated 55600 new cases and 47050 deaths in 2020[1]. Despite ongoing advances in the diagnosis and management of pancreatic cancer, its five-year survival rate is less than 9% due to a notable absence of symptoms in the early stages of the disease and relatively late patient presentation at a time when patients already have an advanced disease[1,2]. When symptomatic, the extent of signs and symptoms vary depending on the size and location of the tumor (head, body, or tail)[3]. Painless jaundice secondary to biliary obstruction is one of the most common presenting manifestations of pancreatic cancer involving the head of the pancreas, uncinate process, and occasionally the body of the pancreas in cases of locally advanced malignancy. Other clinical presentations include abdominal/epigastric pain, weight loss, anorexia, and fatigue. Cancers involving the head of the pancreas are detected at an earlier stage (1/3 in stage I) due to obstructive cholestasis, whereas cancer involving the body or tail of the pancreas often remains asymptomatic until stage IV at the time of diagnosis[3].

Pancreatic cancers originate from both exocrine (ductal adenocarcinoma, intraductal papillary mucinous neoplasm (IPMN) with invasive behavior, mucinous cystic neoplasms, and adenosquamous carcinoma) and endocrine components (neuroendocrine cancers). Pancreatic ductal adenocarcinoma is the most common exocrine malignancy, responsible for 83% of cases followed by IPMN, 6% of cases[4]. Pancreatic ductal adenocarcinoma is the most common pancreatic cancer associated with extrahepatic bile duct obstruction, resulting in jaundice during the course of its disease. Progressive biliary obstruction may result in cholestasis, pruritis, and if unchecked may result in malabsorption, liver failure, and premature mortality. Biliary decompression, therefore, has a crucial role in the management of pancreatic cancer. Among patients who have resectable pancreatic cancer, a preoperative biliary decompression is suggested[5]. Palliation with biliary decompression is also critical to relieving symptoms among those with advanced or unresectable cancer[5]. Percutaneous transhepatic or endoscopic retrograde cholangiopancreatography (ERCP)-guided biliary drainage are the most common interventions used in the management of pancreatic cancers associated with biliary obstruction. Endoscopic ultrasound (EUS) is an emerging intervention that is increasingly utilized in the

management of pancreatic cancers. In this review, we specifically focus on the role of ERCP in the diagnosis and management of pancreatic cancer.

ERCP-GUIDED DIAGNOSTIC INTERVENTIONS

ERCP is a commonly performed diagnostic and therapeutic procedure in the management of pancreatobiliary disorders. Endoscopy is often combined with fluoroscopy and contrast medium, permitting a detailed visualization of the anatomy of the pancreatobiliary ductal systems. With the advancement of diagnostic imaging modalities such as high-resolution computed tomography and magnetic retrograde cholangiopancreatography, coupled with the significant risk of post-ERCP pancreatitis, the use of diagnostic ERCP has decreased. Cross-sectional radiological imaging is helpful for the identification and characterization of pancreatobiliary masses. Recently published consensus guidelines recommended ERCP-guided biliary sampling for an unresectable mass when there is a concurrent need for biliary decompression, however, for resectable masses, or when ERCP tissue acquisition unsuccessful, EUS-guided fine needle biopsy is preferred[6]. The capability of EUS in obtaining tissue samples for pathological staining and diagnosis of pancreatic malignancy has shifted the role of ERCP primarily to therapeutic interventions[7-9]. Indeed, the diagnostic yield of EUS is comparable to ERCP and carries a markedly reduced risk of complications. Multiple prospective and retrospective studies focusing on individuals with pancreatic cancer have shown the overall superior diagnostic yield of EUS over ERCP with a range of sensitivity of 43%-94% (median 81%) *vs* 13%-81% (median 52%) and specificity of 93%-100% (median 100%) *vs* 75%-100% (median 100%) (Table 1)[10-17]. In a recent RCT, Lee *et al*[18] showed 96.7% sensitivity for diagnosis of malignancy in extrinsic type biliary stricture (due to pancreatic cancer) by using a combined approach of initial ERCP-guided transpapillary biliary biopsy (ERCP-TPB) followed by EUS-guided fine needle biopsy in those negative for malignancy on initial ERCP-TPB. For intrinsic (biliary tract cancer) biliary stricture, an initial and followed up ERCP-TPB are adequate in diagnosis of malignancy with a 96.6% sensitivity[18]. ERCP, in contrast, allows for the opportunity to perform both intervention and diagnosis in the same procedure – pancreatobiliary drainage and specimen collection for cytopathology. In case of known or suspected pancreatic cancer, ERCP is used in the management of biliary obstruction. Cytological and histological specimens for pathological diagnosis are essential in the management of pancreatic cancer, guiding the selection of chemoradiation therapy, and ERCP-mediated procedures such as ERCP-guided brush cytology, needle aspiration, or forceps biopsy are occasionally utilized. Fluoroscopy guided biliary brush cytology, biliary biopsy, and cholangioscopy-guided biopsy are the most common ERCP techniques for tissue acquisition.

ERCP-guided biliary brush cytology

Biliary brush cytology is obtained by advancing 8 French (Fr) cytology brush over a guidewire beyond the stricture using a specialized catheter. The brush is moved back and forth across the stricture to obtain an adequate sample. The brush is then withdrawn into the catheter before removal of the endoscope and catheter as a unit to improve the diagnostic yield of a sample and prevent contamination. A series of prospective and retrospective studies including 1285 patients with malignant biliary strictures has shown the sensitivity of brush cytology sample obtained from the bile duct ranged from 30% to 78% (median 54%) with a specificity of 97% to 100% (median 100%) for the diagnosis of malignant biliary strictures (Table 2)[10,15,19-37]. To increase the diagnostic yield of brush cytology, various technical modifications have been evaluated. Farrell *et al*[38] compared brushing alone with a combined approach of stricture dilation coupled with endoscopic aspiration with 22-gauge needle and brushing and demonstrated an increased diagnostic yield of cytology with a sensitivity of 57% *vs* 85% ($P < 0.02$) and a specificity of 80% *vs* 100%, with the standard and modified techniques, respectively. Overall, biliary brushing is a safe technique associated with minimal risk of adverse events such as pancreatitis and bile duct perforation.

ERCP-guided endobiliary forceps biopsy

Fluoroscopic-guided biliary biopsy improves the diagnostic yield over simple biliary brush cytology by obtaining biliary tissue sampling deeper to the epithelial layer. It can be performed by passing 5-Fr to 10-Fr biopsy forceps at the lower edge of stricture.

Table 1 Prospective/retrospective studies comparing the overall yield of endoscopic ultrasound and endoscopic retrograde cholangiopancreatography in the diagnosis of pancreatic cancer

Ref.	Year	No. of patients	No. of patients with pancreatic cancer	Diagnostic yield of EUS		Diagnostic yield of ERCP	
				Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Moura *et al*[10]	2018	50	48	94	100	60	100
Weilert *et al*[11]	2014	51	34	94	100	50	100
Oppong *et al*[12]	2010	37	32	53	100	29	100
Ross *et al*[13]	2008	114	68	83	100	13	100
Wakatsuki *et al*[14]	2005	83	68	93	100	33	100
Rösch *et al*[15]	2004	50	16	43	100	54	100
Glasbrenner *et al*[16]	2000	95	50	78	93	81	88
Cellier *et al*[17]	1998	41	41	55	90	78	75
Total	-	521	357	81[1]	100[1]	52[1]	100[1]

Decimal numbers are rounded off.
[1]Median. EUS: Endoscopic ultrasound; ERCP: Endoscopic retrograde cholangiopancreatography.

The specimen can be collected at the level of stricture by opening and closing the biopsy forceps under the guidance of fluoroscopy. While the optimal number of individual biopsy specimens remains a matter of contention, general protocol suggests a minimum of three tissue samples to establish the diagnosis of malignant stricture[30,39,40]. A series of 19 prospective and retrospective studies on 1101 patients with malignant biliary strictures evaluated with endobiliary forceps biopsy have shown that sensitivity ranges from 36% to 81% (median 61%) with specificity from 90% to 100% (median 100%) for the diagnosis of malignant biliary strictures (Table 3)[10,15,26,29,30,34-37,41-51]. The diagnostic yield is much higher with the combination of forceps biopsy and brush cytology with a pooled sensitivity of 63% to 86% and a specificity of 97% to 100%[30,52]. Despite the increased sensitivity and specificity, forceps biopsy remains technically challenging and a user-dependent procedure, and as such is less commonly performed than brush cytology. Indeed, it is related to a number of unique adverse events, such as bleeding and perforation of common hepatic duct, secondary to a variety of factors – forceps size and stiffness, number of biopsy passes, and the technical capability of the endoscopist[20,30,44].

Cholangiopancreatoscopic-guided biopsy

Cholangiopancreatoscopy involves direct luminal visualization of the biliary and pancreatic ductal systems. Conventionally, it was performed by two endoscopists using a mother-daughter per-oral scope setup where one endoscopist handle ERCP scope while other endoscopist operate a fragile scope within biopsy channel of main ERCP scope. The introduction of ultraslim gastroscope loaded with anchoring balloon (a slight modification in this technique) enabled a single operator to perform this procedure without issues of scope fragility. Novel intraductal visualization techniques employing the Spyglass system have augmented diagnostic yield by permitting the endoscopist the opportunity to obtain targeted tissue under direct visualization. This system involves the use of a disposable SpyScope with a tip-deflecting access catheter, working catheter, SpyBite biopsy forceps, and two irrigation channels enabling a single operator to perform the procedure. Cholangioscopy-guided biopsy can be performed by advancing a cholangioscope through the biopsy channel of a duodenoscope, enabling direct visualization and biopsy of a biliary stricture. The classic cholangioscopic features of malignant biliary strictures are cholangioscopic visualization of intraductal nodules surrounded by tortuous, irregularly dilated blood vessels, and the presence of papillary or villous mucosal projections[53,54]. ERCP-guided cholangioscopy has increased the diagnostic yield of bile duct biopsy by allowing the collection of suspected neoplastic tissue under direct visualization. In cases of main pancreatic duct IPMN, a premalignant condition of the pancreas, ERCP-guided pancreatoscopy with biopsy may be helpful in making the diagnosis, particularly due to its classic, pathognomonic features fish egg-like, villous and prominent mucosal

Table 2 Prospective/retrospective studies on the diagnostic yield of endoscopic retrograde cholangiopancreatography guided brush cytology for malignant biliary stricture

Ref.	Year	No. of patients	No of patients with malignant strictures	TP on brush cytology	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Moura *et al*[10]	2018	50	48	40	40	100	100	7
Agarwal *et al*[21]	2018	40	40	27	68	NA	NA	NA
Sethi *et al*[33]	2016	162	106	58	55	100	100	54
Shieh *et al*[22]	2014	32	32	25	78	NA	NA	NA
Weber *et al*[36]	2008	58	58	24	41	NA	NA	NA
Kitajima *et al*[37]	2007	60	NA	NA	72	100	NA	NA
Fogel *et al*[23]	2006	102	94	28	30	NA	NA	NA
Rösch *et al*[15]	2004	50	28	28	46	100	NA	NA
Stewart *et al*[24]	2001	406	246	147	60	98	98	61
Macken *et al*[25]	2000	106	62	35	57	100	100	62
Jailwala *et al*[26]	2000	133	104	31	30	100	100	28
Glasbrenner *et al*[27]	1999	78	57	32	56	91	94	43
Mansfield *et al*[28]	1997	54	52	17	54	100	100	8
Sugiyama *et al*[35]	1996	43	31	25	48	100	NA	NA
Pugliese *et al*[29]	1995	94	64	35	54	100	100	50
Ponchon *et al*[30]	1995	210	128	45	35	97	96	44
Lee *et al*[31]	1995	149	106	40	37	100	100	39
Foutch *et al*[32]	1991	30	17	06	33	100	100	58
Pugliese *et al*[34]	1987	22	12	08	66	88	NA	NA
Total	-	1879	1285	651	54[1]	100[1]	-	-

[1]Median value of available data. TP: True positive; PPV: Positive predictive value; NPV: Negative predictive value; NA: Data not available. Decimal numbers are rounded off.

protrusions which carry a sensitivity of 68% and a specificity of 87%[55-57]. Cholangioscopy is 88% to 100% sensitive and 77% to 92% specific for the diagnosis of pancreatobiliary malignancy[54,58-62]. Common complications with cholangiopancreatoscopy are bile duct perforation, hemorrhage, air embolization, pancreatitis, and cholangitis. The overall risk of complications with this modality is higher than ERCP, therefore, the utility of cholangiopancreatoscopy is reserved for selected cases of inaccessible ductal lesions[63].

ERCP-guided naso-pancreatic drainage

ERCP-guided naso-pancreatic drainage (ENPD) is a method to collect pancreatic juice using a specialized drainage catheter compatible with standard duodenoscope. ENPD was first implemented by Endo *et al*[64] in 1974 for cytodiagnosis of pancreatic cancer. A slight modification of the standard ENPD technique wherein pancreatic juice collection is performed after injection of synthetic secretin, has been shown to provide a dedicated sample with a sufficient number of cells for cytological analysis and has improved the diagnostic sensitivity from 50.9% to 70.4%[65]. Of note, in this study, an additional 13 pancreatic cancer patients were diagnosed using the modified ENPD technique that were missed with EUS-fine needle aspiration (EUS-FNA), making the modified ENPD technique preferred, particularly in instances where tissue collection with EUS-FNA is unsuccessful or impossible[65]. Another modification of ENPD involving placement of a 4 or 5 Fr tube (with 8-12 hole) in the main pancreatic duct and collection of pancreatic juice 2-6 times daily for up to 3 d has increased the diagnostic yield for detection of pancreatic cancer with 80% sensitivity, 100% specificity, 100% positive predictive value, 71% negative predictive value, and 87%

Table 3 Prospective/retrospective studies on the diagnostic yield of fluoroscopic guided endobiliary forceps biopsy for malignant biliary stricture

Ref.	Year	No. of patients	No of patients with malignant strictures	TP on forceps biopsy	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Moura *et al*[10]	2018	50	48	40	44	100	100	7
Tanaka *et al*[47]	2018	123	123	80	65	NA	NA	NA
Naitoh *et al*[48]	2016	208	160	97	61	100	100	43.2
Chen *et al*[49]	2016	79	65	35	54	100	100	31.82
Nishikawa *et al*[50]	2014	72	64	32	50	96	97	40.7
Kawashima *et al*[51]	2012	61	34	26	76	100	NA	NA
Hartman *et al*[41]	2012	81	38	30	76	100	100	81
Draganov *et al*[42]	2012	26	17	5	29	100	100	43
Wright *et al*[43]	2011	133	117	84	72	100	100	36
Weber *et al*[36]	2008	58	58	31	53	NA	NA	NA
Kitajima *et al*[37]	2007	60	NA	NA	62	100	NA	NA
Rösch *et al*[15]	2004	50	28	28	36	100	NA	NA
Jailwala *et al*[26]	2000	133	104	48	43	90	94	31
Schoefl *et al*[44]	1997	103	58	38	65	100	100	69
Sugiyama *et al*[35]	1996	43	31	25	81	100	100	67
Ponchon *et al*[30]	1995	128	82	35	43	97	97	41
Pugliese *et al*[29]	1995	52	36	19	53	100	100	48
Kubota *et al*[45]	1993	41	32	26	81	100	100	75
Pugliese *et al*[34]	1987	22	06	06	100	100	NA	NA
Total	-	1453	1101	685	61[1]	100[1]	-	-

[1]Median value of available data. Decimal numbers are rounded off. TP: True positive; PPV: Positive predictive value; NPV: Negative predictive value; NA: Data not available.

overall accuracy[66]. Iiboshi *et al*[67] reported similar results of ENPD with 100% sensitivity, 83.3% specificity, and 95% accuracy in the diagnosis of in situ pancreatic cancer. For pancreatic cancers smaller than 1 cm, the diagnostic yield of EUS-FNA is limited. ERCP-guided serial pancreatic juice aspiration cytologic examination (SPACE) technique is a promising modality that may be superior to EUS-FNA for diagnosing pancreatic cancer at early stages (stage 0 and stage I)[68]. A multicenter Japanese study on 200 (51 with stage 0 and 149 with stage I) pancreatic cancer patients has shown a better cytological confirmation of stage 0 pancreatic cancer using ERCP-guided SPACE technique as compared to EUS-FNA (72% *vs* 17%). In contrast, for stage I pancreatic cancer, EUS-FNA has been shown to be superior to ENPD (84% *vs* 60%)[69]. Post-ENPD pancreatitis and cholangitis are the commonly reported complications[65].

ENDOSCOPIC RETROGRADE-GUIDED THERAPEUTIC INTERVENTIONS

ERCP-guided biliary decompression

While 15% of pancreatic cancer patients are candidates for surgical resection, preoperative biliary decompression may be required. It is also a commonly employed feature in these individuals for palliation. ERCP-guided biliary drainage or decompression with transpapillary stenting is the mainstay of management for patients with biliary obstruction and its related complications. In patients with advanced pancreatic malignancy, endoscopic and surgical biliary drainage showed

similar success rate and long-term symptomatic relief[70,71]. Endoscopic biliary decompression, however, is minimally invasive, more convenient, and relatively safer than surgical bypass for biliary decompression, especially for patients with unresectable pancreatic cancer[72]. Endoscopic decompression is associated with fewer complications, shorter hospital stays, lower cost, and better quality of life.

Indications

A recent cross-sectional study on 411409 inpatient ERCP procedures revealed that malignant biliary obstruction was the fourth most common indication for ERCP in the past decade, with balloon dilation or stenting of biliary or pancreatic strictures often performed[7]. Indeed, with these interventions, there is a noted improvement of pruritus, jaundice, and known complications of malignant biliary obstruction such as acute cholangitis and renal dysfunction[73]. Preoperative ERCP-guided biliary decompression is a preferred approach for patients who encounter delays in surgical intervention due to a decision to initiate neoadjuvant therapy and in those with severe malnourishment requiring nutritional support[74-76]. In unresectable pancreatic cancer, ERCP-guided transpapillary biliary stenting not only improves patient's symptoms and quality of life but is also associated with reduced mortality and morbidity[77].

Technical accessibility and consideration

The procedural feasibility of ERCP-guided transpapillary biliary stenting is above 90% with a short term efficacy in terms of symptomatic relief of over 80%[78,79]. Sphincterotomy with adjunctive guidewire rather than standard catheter for biliary canalization is associated with rapid access to the bile duct, a higher success rate (85% to 95%), and lower risk of complications[80,81]. ERCP-mediated biliary decompression can be performed by the deployment of either a self-expandable metal stent (SEMS) or plastic stent over the guidewire threaded across a malignant stricture. Stent selection depends on several factors such as the level of biliary dysfunction, the need for reintervention, complication rate, cost, and the likelihood of short- and long-term patient survival[82]. SEMS have a significantly lower risk of complications and stent dysfunction compared with plastic stents[82]. A recent meta-analysis showed a lower rate of stent dysfunction, subsequent rate of reinterventions, and longer median survival for SEMS when compared with plastic stents[83]. Compared to percutaneous and surgical biliary decompressions, ERCP-mediated biliary stenting not only improved patient symptoms and quality of life but was also associated with reduced mortality and morbidity[77]. In cases of unsuccessful ERCP-transpapillary biliary stenting, EUS-guided biliary drainage with transmural stenting has been increasingly used as an alternative option for palliation in malignant biliary obstruction[6]. A recent meta-analysis (10 studies including 3 RCT) compared the efficacy of EUS-guided biliary decompression with ERCP in the palliation of malignant biliary obstruction and demonstrated a similar technical (94.8% *vs* 96.5%) and clinical (93.8% *vs* 95.7%) success rates respectively[84].

Types of biliary stents

Plastic stents: Plastic biliary stents are usually made of polyethylene, polyurethane, or Teflon that are available in different sized diameters including 7, 8.5, 10 and 11.5 Fr and lengths ranging from 5 cm to 15 cm. Large diameter stents are preferable because of better flow rate, infrequent stasis, and decreased incidence of stent occlusion. These stents are designed into various shapes - straight, curved, single, or double pigtails. The introduction of sidewall anchoring flaps and pigtails on either end of the stent prevents stent migration. The choice of stent depends upon multiple factors including the likely etiology of the lesion, as well as location and length of the biliary stricture. Plastic stents are preferred for benign lesions, whereas metal stents are favored in malignant lesions. Plastic stents offer the benefit of ease of deployment, abrogate the need for biliary sphincterotomy, and are less expensive in the management of individuals with shorter life expectancy[85,86]. Plastic stents also have a more limited duration of patency and often require stent exchange every 10 to 12 wk to circumvent stent occlusion, thus making them a relatively unfavorable therapeutic option for the management of malignant biliary obstruction in those with a longer life expectancy. A large RCT has shown an overall superiority of metal stents over plastic stents in managing patients with longer survival times, whereas no differences in the rate of adverse events and mortality were reported[87].

Self-expanding metal stents: Endoscopic biliary SEMS employ a large diameter stent (8-10 mm), which has been shown to significantly reduce the risk of stent occlusion (approximately 50% lower than plastic stents) while not completely eliminating the

risk of complete obstruction[82]. SEMS are manufactured as fully-covered or partially-covered devices. While the original SEMS were comprised of uncovered metal [stainless steel, nitinol (a mixture of titanium and nickel)] or platinol (a combination of the platinum core with encasement of nitinol), which reduced the risk of stent migration, but these were associated with significant stent dysfunction secondary to tumor ingrowth or occlusive biliary sludge, which when coupled with the limited ability to remove these metal stents, created major disadvantages and further complications. To address these issues, second-generation SEMS were manufactured as partially-covered or fully-covered devices with a polyurethane, polycaprolactone, or silicone membrane that resulted in a significantly lower risk of tumor ingrowth and reduced difficulties associated with stent retrieval/removal. Despite these advances, fully-covered biliary SEMS pose several challenges such as higher risks of stent migration, pancreatitis, and cholecystitis. Furthermore, fully-covered SEMS have several specific anatomical restrictions, primarily due to their covered nature. For example, proximal biliary lesions at the level of hilum have unique anatomical considerations specifically related to biliary drainage from intrahepatic side branches. As such in this scenario, partially-covered SEMS are preferred over fully-covered SEMS particularly as lesions become more proximal, as partially-covered SEMS would allow effective drainage of the intrahepatic side branches through fenestrations of uncovered portions of the stent. Multiple RCT and retrospective studies have shown the superiority of uncovered SEMS over covered SEMS for long-term stent patency, however no significant difference in patency between two SEMS after 6 and 12 mo, and no difference in patient survival or complication rates such as pancreatitis, cholangitis, cholecystitis, perforation, bleeding, length of hospital stay, and incidence of recurrent biliary obstruction (Table 4)[47,88-106]. Taken together, uncovered SEMS are associated with higher rates of stent dysfunction due to tumor ingrowth whereas covered SEMS have a higher rate of stent migration and a lower risk of sludge-mediated occlusion (Table 4)[47,88-106]. Overall, no difference was observed in the rates of pancreatitis and cholecystitis between covered and uncovered SEMS[47,88-106].

Compared to plastic stents, metal stents are 15-30 times more expensive and technically difficult to deploy[82]. SEMS provides longer stent patency (6 to 9 mo) than plastic stents (3 to 4 mo). Multiple studies have shown no significant difference in technical or therapeutic success rates, complication rates, and 30 d mortality, however, these studies did show a lower rate of stent occlusion and overall risk of obstruction for uncovered SEMS at four-months[85]. The selection of biliary stent subtype depends on multiple factors including life expectancy, risk of complications, cost, and the need for ERCP-guided reinterventions (if needed) for stent replacement / manipulation.

Safety and complications of ERCP-guided biliary decompression: ERCP-guided biliary drainage is a relatively safe, minimally invasive intervention compared to percutaneous or surgical biliary decompression. It is however associated with several complications including post-ERCP pancreatitis, cholangitis, cholecystitis, biliary ductal perforation, stent migration or obstruction, liver abscess, and hemorrhage[107,108]. Several factors have been associated with higher complication rates such as degree of obstructive jaundice, previous gastrointestinal surgeries, and multiple comorbidities[109-112]. Such high-risk patients have demonstrated an increased risk of post-ERCP complications and are managed conservatively with rectal indomethacin or diclofenac, adequate hydration, nutritional support, and early use of antibiotics. After plastic biliary stenting, close follow up is required for early identification of recurrent biliary obstruction due to stent occlusion. For those patients with a longer life expectancy (more than 3 mo) and when close follow up is impossible, scheduled stent exchange is required[6]. In case of biliary decompression using SEMS, on demand biliary reintervention is recommended based on clinical judgement[6].

ERCP-guided preoperative biliary drainage for resectable pancreatic cancers

The role of preoperative biliary drainage (PBD) in the management of resectable pancreatic cancer is still controversial. Routine PBD is not recommended, however, in cases of pruritus or cholangitis, biliary stenting can be considered following interdisciplinary consultation[6]. Factors such as liver dysfunction, hyperbilirubinemia, coagulopathy, and cholangitis correlate with the severity of biliary obstruction and are associated with deleterious effects on renal or cardiovascular function, malnutrition, and an increased risk of postoperative morbidities[111,112]. Therefore, some surgeons recommend PBD before performing a Whipple procedure for symptomatic relief and associated prevention of complications due to cholestasis in patients with obstructive jaundice. In a retrospective study, Coates *et al*[113] compared the impact of PBD on short

Table 4 Randomized controlled trials and retrospective studies comparing covered with un-covered biliary self-expanding metal stents for malignant distal biliary obstruction

Ref.	Year	Study design	Type of stent	No. of patients	Pancreatic malignancy (%)	Stent patency (d)	Patient survival (d)	No. of stent dysfunction	No. of complications
Seo *et al*[15]	2019	RCT	Uncovered, Covered	60, 59	100	NA, NA	NA, NA	10[1], 0	12, 14
Conio *et al*[88]	2018	RCT	Uncovered, Covered	80, 78	72.5, 75.6	541 (Median)[1], 240 (Median)	112 (Median), 134 (Median)	10, 12	10, 19
Flores-Carmona *et al*[89]	2016	RCT	Uncovered, Covered	46, 22	52.5, 50	NA, NA	NA, NA	4, 3	NA, NA
Mangiavillano *et al*[90]	2015	RCT	Uncovered, Covered	21, 23	NA	194 (Median)[1], 89 (Median)	NA, NA	NA, NA	1, 1
Lee SJ *et al*[91]	2014	RCT	Uncovered, Covered	20, 20	30, 60	413.3 ± 63 (mean ± SD)[1], 207.5 ± 46 (mean ± SD)	359.9 ± 61.5 (mean ± SD), 350.5 ± 43.8 (mean ± SD)	4[1], 10	0, 3
Ung *et al*[92]	2013	RCT	Uncovered, Covered	34, 34	79, 88	127 (Median), 153 (Median)	157 (Median), 154 (Median)	NA, NA	0, 2
Kitano *et al*[93]	2013	RCT	Uncovered, Covered	60, 60	100, 100	166.9 ± 124.9 (mean ± SD)[1], 219.3 ± 159.1 (mean ± SD)	223 (Median), 285(Median)	22, 14	2, 2
Fukuda *et al*[94]	2012	RCT	Uncovered, Covered	71, 72	84.5, 83.3	314 (Median)[1], 552(Median)	NA, NA	23, 17	NA, NA
Krokidis *et al*[95]	2011	RCT	Uncovered, Covered	40, 40	100, 100	166.0 ± 82.8 (mean ± SD)[1], 234.0 ± 132 (mean ± SD)	203.2 ± 74.8 (Median ± SD), 247.0 ± 126.7 (Median ± SD)	12[1], 4	4, 5
Krokidis *et al*[96]	2010	RCT	Uncovered, Covered	30, 30	0, 0	166.0 ± 87.7 (mean ± SD)[1], 227.3 ± 139.7 (mean ± SD)	180.5 ± 82.6 (Median ± SD), 243.5.0 ± 141.1 (Median ± SD)	10[1], 4	4, 3
Kullman *et al*[97]	2010	RCT	Uncovered, Covered	200, 200	77, 76	154 (Mean), 199 (Mean)	174 (Median), 116 (Median)	45, 47	20, 14
Telford *et al*[98]	2010	RCT	Uncovered, Covered	61, 68	77, 86	711 (Median), 357 (Median)	239 (Median), 227 (Median)	12[1], 23	27[1], 48
Cho *et al*[99]	2009	RCT	Uncovered, Covered	38, 39	NA	195 (Median), 227 (Median)	NA, NA	NA, NA	4, 10
Gonzalez-Huix *et al*[100]	2008	RCT	Uncovered, Covered	53, 61	58.5, 52.5	NA, NA	NA, NA	6[1], 8	14[1], 23
Yoon *et al*[46]	2006	Retrospective	Uncovered, Covered	41, 36	68.2, 86	319 (Mean), 398 (Mean)	308 ± 42 (mean ± SD), 392 ± 60 (mean ± SD)	11[1], 15	1, 4
Park *et al*[101]	2006	Retrospective	Uncovered, Covered	108, 98	65.7, 54.1	143.5 (Mean), 148.9 (Mean)	207 (Mean), 209 (Mean)	20, 21	3, 17
Isayama *et al*[102]	2004	RCT	Uncovered, Covered	55, 57	58.2, 59.6	193 (Mean)[1], 225 (Mean)	237 (Mean), 255 (Mean)	21[1], 8	3, 8
Lee *et al*[103]	2004	RCT	Uncovered, Covered	21, 22	38.1, 40.9	127 (Median)[1], 216 (Median)	NA, NA	11, 4	NA, NA
Smith *et al*[105]	1995	RCT	Uncovered, Covered	24, 22	70.1, 77.3	NA, NA	NA, NA	NA, NA	3, 3

[1]Statistically significant data; RCT: Randomized controlled trial; NA: Data not available.

term (90 d) postoperative outcome and demonstrated a need for repeat surgical intervention in patients who underwent pancreatoduodenectomy without preoperative ERCP, with no significant difference in the rate of complications, hospital stay, and 30-90 d mortality between two groups. PBD also prepares the patient for neoadjuvant chemotherapy due to improved liver function test and the relative contraindication to chemotherapy use with hyperbilirubinemia after relieving biliary obstruction. However, PBD was criticized in several studies because of reported increased morbidity, mortality, prolonged hospital stay after preoperative biliary stenting[114-116].

ERCP-PBD using covered SEMS is preferred over uncovered SEMS and plastic stents because of a decreased risk of stent dysfunction and longer stent patency[6]. In a recent RCT, Seo *et al*[106] have shown comparable success rates of covered and uncovered SEMS in pancreatic cancer patients undergoing PBD before and after neoadjuvant therapy, however, covered SEMS were suggested to be superior in cases of diagnosis uncertainty. If a biliary stricture turns out to be malignant, there is no need to replace covered SEMS with uncovered SEMS because risk of stent dysfunction due to tumor ingrowth is negligible. Shorter stent lengths (4 cm as opposed to 6 or 8 cm) and the presence of an in situ gallbladder were significant predictors associated with failure to attain prolonged biliary drainage with a hazard ratio of 2.1 and 6.9[106]. The type of stent selection should be individualized based on these factors. Recent meta-analyses and systematic reviews demonstrated an increased risk of complications without a significant survival difference in patients undergoing PBD *vs* direct surgery[76,117-119]. Severe hyperbilirubinemia was not present in the majority of studies included in meta-analysis, hence the role of PBD in patients with severe biliary obstruction is uncertain. To further investigate the effects of preoperative ERCP on pancreatic cancer survival rates, Rustgi *et al*[120] assessed overall survival among 2890 patients with pancreatic cancers from 2000 through 2011. Of these, 1864 patients underwent ERCP within 6 mo of surgery and 1026 patients underwent surgical resection without preoperative ERCP. After adjustment of confounding factors, patients in the preoperative ERCP group did not demonstrate an increased risk of mortality compared to patients who proceeded directly to surgical resection[121,122]. This study did not comment on ERCP-related adverse events such as biliary sepsis, and thus warrants further analysis. In clinical practice, however, preoperative ERCP is often performed due to issues related to either delay in the definitive surgical resection or the provision of neoadjuvant chemotherapy. Overall, PBD should be avoided in patients undergoing early surgical resection (usually under 2 wk), however, those with persistent symptoms (pruritis), severe jaundice, and delay in surgery for medical optimization, PBD may be justified.

ERCP-guided biliary drainage in neoadjuvant treatment of pancreatic cancer

In patients with borderline resectable pancreatic malignancy, neoadjuvant chemotherapy or chemoradiation is clearly beneficial, whereas their role in outright surgically resectable malignancy remains unclear[76]. Neoadjuvant therapy enables the surgical resection of a borderline resectable disease by downstaging of pancreatic tumors and has shown to improve the outcomes of surgical management in treating patients with metastasis. Furthermore, PBD is a prerequisite for neoadjuvant therapy to prevent chemotherapy-induced hepatotoxicity and may be pursued 3 mo prior to surgical resection[76]. A meta-analysis including six RCT favored the biliary decompression using SEMS in patients with unresectable cancer or those unfit for surgical resection due to multiple comorbidities or advanced disease[75]. Among patients with resectable pancreatic cancer who may undergo surgical resection within three months, the placement of a plastic biliary stent should be adequate as prolonged biliary drainage avoids interruptions of medical treatment by improving symptoms of biliary obstruction or cholangitis. Hence the placement of SEMS appears reasonable to consider in these patients. An RCT on SEMS *vs* surgery to palliate malignant obstructive jaundice in stage IV pancreatic cancer has demonstrated the added benefits of cost-effectiveness, reduced hospital stay, and procedural morbidity in patients palliated with SEMS, a finding that was balanced however by the noted difficulty in SEMS removal during surgery[74].

Role of ERCP in gastric outlet obstruction

Indications: An estimated of 15% of patients with pancreatic cancer experience mechanical gastric outlet obstruction (GOO) during the course of their disease, especially if malignant lesions involve the gastric antrum, proximal or distal duodenum[121,122]. Endoscopic-guided enteral stent placement is an effective palliative option in the management of advanced pancreatic cancer[121]. Endoscopic palliation of

GOO is typically indicated in patients with a shorter life expectancy usually less than 6 mo.

Technical accessibility and consideration: Endoscopic palliation of GOO involves the advancement of a guidewire across the malignant stricture and endoscopic deployment of an enteral stent (covered or uncovered). Simultaneous obstructions of both gastro-duodenal outlet and bile duct are often found in patients with advanced pancreatic cancer. In these cases, the anatomical level of the malignant stricture is classified as obstruction involving proximal duodenum at the level of duodenal bulb or genu (type I), second part of duodenum involving papilla (type II) or distal to papilla in the third part of duodenum (type III)[122]. This anatomical classification is important because the level of obstruction determines the management approach. In type I obstruction, an anatomical consideration that enables the advancement of a scope through the duodenal stricture (often with dilatation), biliary stenting should be performed prior to duodenal stent placement. If there are technical difficulties associated with endoscope passage through a duodenal stricture, then duodenal stenting should be performed first, with subsequent advancement of the scope through the duodenal stent to perform either immediate or delayed (after a few days) biliary stenting. In type II obstruction, ERCP-guided transpapillary stenting may be challenging due to difficulty in finding papillary opening. In this situation, EUS-guided transmural or antegrade biliary stenting is recommended and duodenal stenting could be performed simultaneously[122]. In type III obstruction, the sequence of either biliary or duodenal stent placement is not critical. ERCP-guided transpapillary stenting is associated with poor clinical outcome in patients with combined biliary and GOO because of risk of cholangitis from duodenobiliary reflux of food particles and digestive juice[122]. Endoscopic enteral stenting should be performed in cases of a solitary malignant stricture without evidence of distal obstruction from the site of stent deployment. Palliative gastric decompression with the placement of jejunal feeding tube or total parenteral nutrition should be considered in case of multiple strictures or GOO, especially if distal to the location of planned stent deployment[123]. In patients who fail standard endoscopic management of GOO, there is increasing use of less invasive EUS-guided gastrojejunostomy due to its advantages to establish longer patency, fewer adverse events, and higher clinical and technical success rates[122,124].

Safety and complications: Overall, the placement of SEMS is associated with more favorable results in patients with poor performance status and a relatively shorter life expectancy, whereas gastrojejunostomy (GJJ) may offer more durable results in patients with a more favorable prognosis[123,125]. A systemic review (including 32 studies) and several prospective studies on the endoscopic placement of SEMS studies have shown an overall technical success rate of 97% (91% to 100%) and the clinical success rate of 89% (63% to 95%)[126-134]. Another systemic review (44 studies) has shown a higher clinical success rate (89%) of endoscopically placed enteral stents compared to GJJ[125]. Placement of enteral SEMS is associated with a shorter hospital stay and early resumption of oral intake, with similar major complication rates noted between SEMS and GJJ[126]. Enteral stents are associated with an increased risk of stent migration or malfunction (17%) typically due to tumor ingrowth and/or food impaction, a complication that is managed endoscopically with the clearance of impacted food or stent replacement[123]. More recently, a meta-analysis (including 13 studies) on 1624 patients with malignant GOO showed comparable stent dysfunction and similar clinical and technical success rates of covered *vs* uncovered SEMS. Covered SEMS, however, showed lower rates of luminal occlusion (RR: 0.44; 95%CI: 0.28-0.68) at the expense of higher stent migration (RR: 4.28; 95%CI: 2.89-6.34) and overall adverse events (RR: 1.75; 95%CI: 1.09-2.83)[135]. Covered SEMS are associated with stent migration, usually within 8 wk of placement, requiring endoscopic repositioning or replacement. Other complications of enteral stenting are hemorrhage (1%), enteral perforation (1%), peritonitis, pancreatitis, cholangitis, biliary or intestinal obstruction, and abdominal pain[123].

CONCLUSION

ERCP plays a vital role in the management of pancreatic cancer. ERCP-guided brush cytology and forceps biopsy of malignant biliary strictures provide reasonable tissue for diagnostic confirmation of disease. ERCP-guided SPACE technique is a promising modality that may be superior than EUS-FNA for diagnosing pancreatic case at early stages. The therapeutic interventions of ERCP are helpful in effective preoperative

biliary decompression in those with resectable pancreatic cancer. In patients with unresectable pancreatic cancer, palliation with ERCP-guided biliary decompression by the placement of either plastic or self-expanding metal stents relieves symptoms to improve quality of life. Selection of stents should be individualized depending upon patient's clinical presentation, weighing not only the risks and benefits, but also the physician's clinical judgement. GOO is a common complication of advanced pancreatic cancer, ERCP-guided enteral stenting is preferred modality over surgical gastrojejunostomy in the management of GOO in patients with poor performance and shorter life expectancy.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Assessing the yield and safety of endoscopy in acute graft-*vs*-host disease after hematopoietic stem cell transplant

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Abstract

BACKGROUND

Acute gastrointestinal (GI) graft-*vs*-host disease (aGVHD) is the most complication of hematopoietic stem cell transplant (HSCT) in patients with hematologic malignancy. Limited data exists on endoscopic evaluation of GVHD in post-HSCT patients with differing GI symptoms. Further, the diagnostic value of gross endoscopic findings as well as the safety of endoscopy in this commonly thrombocytopenic and neutropenic patient population remains unclear.

AIM

To understand the diagnostic value of symptoms and gross endoscopic findings as well as safety of endoscopy in aGVHD patients.

METHODS

We analyzed 195 endoscopies performed at City of Hope in patients who underwent allogeneic HSCT less than 100 d prior for hematologic malignancy and were subsequently evaluated for aGVHD *via* endoscopy. The yield, sensitivity, and specificity of diagnosing aGVHD were calculated for upper and lower endoscopy, various GI tract locations, and presenting symptoms.

RESULTS

Combined esophagogastroduodenoscopy (EGD) and flexible sigmoidoscopy (FS)

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demonstrated a greater diagnostic yield for aGVHD (83.1%) compared to EGD (66.7%) or FS (77.2%) alone with any presenting symptom. The upper and lower GI tract demonstrated similar yields regardless of whether patients presented with diarrhea (95.7% *vs* 99.1%) or nausea/vomiting (97.5% *vs* 96.8%). Normal-appearing mucosa was generally as specific (91.3%) as abnormal mucosa (58.7%-97.8%) for the presence of aGVHD. Adverse events such as bleeding (1.0%), infection (1.0%), and perforation (0.5%) only occurred in a small proportion of patients, with no significant differences in those with underlying thrombocytopenia (P = 1.000) and neutropenia (P = 0.425).

CONCLUSION
Combined EGD and FS with biopsies of normal and inflamed mucosa demonstrated the greatest diagnostic yield regardless of presenting symptom and appears to be safe in this population of patients.

Key Words: Graft-*vs*-host disease; Esophagogastroduodenoscopy; Colonoscopy; Endoscopy; Flexible sigmoidoscopy; Stem cell transplant; Hematopoietic stem cell transplant; Thrombocytopenia; Neutropenia; Malignancy

Core Tip: We analyzed a retrospective cohort of 195 endoscopies performed in cancer patients who had a hematopoietic stem cell transplant less than 100 d prior to endoscopy and evaluated the diagnostic value of various endoscopic procedures, gross endoscopic findings, and presenting symptoms. Our findings show that combined esophagogastroduodenoscopy and flexible sigmoidoscopy with biopsies of normal and abnormal-appearing mucosa results in the greatest yield for diagnosing acute gastrointestinal graft-*vs*-host disease independent of symptoms. Additionally, we found no significant difference in adverse events in patients with and without thrombocytopenia and neutropenia.

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INTRODUCTION

Graft-*vs*-host disease (GVHD) is the most common life-threatening complication of allogeneic hematopoietic stem cell transplant (HSCT) with the gastrointestinal (GI) tract commonly involved[1-4]. Classically, acute GVHD (aGVHD) occurs less than 100 d post-HSCT, while chronic GVHD (cGVHD) occurs after day 100[5]. Diagnosing aGVHD relies upon clinical findings and is confirmed with tissue biopsy. Endoscopy with esophagogastroduodenoscopy (EGD), colonoscopy, flexible sigmoidoscopy (FS), or combinations of these procedures are often performed to obtain GI tissue to confirm the diagnosis and assess the severity of GVHD histopathologically[6]. Histopathological evidence of GVHD is defined by the presence of apoptotic bodies in tissue specimens per updated 2014 NIH consensus guidelines[7,8].

Currently, there are limited primary data to guide endoscopic evaluation of aGVHD in the post-HSCT population. Previous studies examining clinical characteristics and endoscopic findings in aGVHD patients were limited to small case series in diverse patient populations (children and adults for a variety of indications)[9-22]. The largest studies focusing specifically on the population at risk for aGVHD included fewer than 175 endoscopic evaluations[9,10,14]. Based upon previous studies, FS with biopsy of the rectosigmoid colon is considered the standard evaluation for patients with symptoms localizing to the lower gut. The evidence supporting the use of EGD in the evaluation of GVHD in patients with upper GI symptoms is scarce. Further, the diagnostic value of gross endoscopic findings and presenting symptoms and their relationship to histopathological evidence of aGVHD remains unclear. To this end, the primary aim of

our study was to characterize clinical symptoms and endoscopic findings in a large set of patients post-HSCT undergoing evaluation of aGVHD. A secondary aim was to understand which anatomical locations in the GI tract were most commonly involved by aGVHD and to assess whether presenting symptoms localized to specific portions of the GI tract histopathologically.

Additionally, there is inconsistent data on the safety of endoscopic evaluation in patients with thrombocytopenia and neutropenia[23-29], especially in those who have undergone HSCT. Intra and post-procedural bleeding are viewed as difficult to manage in thrombocytopenic patients given the perceived notion that it occurs diffusely rather than focally. In light of the higher perceived infectious and bleeding risks of performing endoscopy in this patient population, our final aim was to assess endoscopic safety.

MATERIALS AND METHODS

Study population and oversight

A retrospective review was conducted of all endoscopic procedures performed at City of Hope (COH), an academic, tertiary care cancer center, between December 2017 and July 2019 to identify patients who had undergone allogenic HSCT with clinical suspicion for aGVHD. The institutional review board at COH approved this study. The endoscopic database included data from December 2017 onwards as part of a new electronic health record implemented at COH; endoscopic data prior to this did not interface with the new electronic health record and was not accessible for review.

Study eligibility criteria

Patients from the endoscopic database were included in the study if they: (1) Had a hematologic malignancy such as leukemia, lymphoma, or myelodysplastic or myeloproliferative syndromes; (2) Underwent allogeneic HSCT at COH; and (3) Developed symptoms prompting clinical suspicion for aGVHD leading to referral for endoscopic evaluation. Patients who underwent HSCT for immunodeficiencies, congenital metabolic defects, or hemoglobinopathies were excluded. Further, patients who did not have tissue biopsied during endoscopy or underwent HSCT greater than 100 d prior to endoscopy were excluded. If a single patient underwent multiple endoscopies at different times, each endoscopic evaluation was counted as a separate procedure.

Data sources and variables

Two investigators (Rajan AV, Trieu H) reviewed all endoscopy and corresponding pathology reports, collected data on endoscopic findings as well as interventions performed, and reviewed the medical records. Pathology reports were also reviewed and pathological findings as well as their anatomical location were collected. All biopsy samples were sent for pathologic examination as part of routine clinical care and histology was evaluated by expert GI pathologists at COH. Histological grading of the severity of aGVHD was done on a scale ranging from mild, moderate, to severe as per standard of care at City of Hope Medical Center and in concordance with 2014 NIH Consensus Criteria[8]. Mild aGVHD was defined as rare or few apoptotic cells of individual crypts; moderate aGVHD was defined as apoptosis with crypt microabscesses and crypt cell flattening; and, severe aGVHD was defined as dropout of many crypts or flat mucosa with total denudation. In some instances, a single tissue sample was classified as a range of severities such as both mild and moderate. Illustrative histological images can be seen in Figure 1.

Demographic, clinical, and laboratory data from the electronic health records were collected. Hemoglobin count, platelet count, and absolute neutrophil count (ANC) were obtained from the last complete blood count (CBC) drawn prior to endoscopy and first CBC drawn post-endoscopy. Pre-procedure blood urea nitrogen and creatinine as well as pre and post-procedure international normalized ratio were obtained in a similar manner. Additionally, transfusion data was collected such as number of units of platelets, packed red blood cells (pRBC), and fresh frozen plasma/cryoprecipitate (FFP) transfused within 72 h prior to endoscopy and 72 h after. Thrombocytopenia was defined as a pre-procedure platelet count less than or equal to 50000 per microliter with no platelet transfusions or less than or equal to 75000 per microliter with one or more platelet transfusions. Neutropenia was defined as a pre-procedure ANC of less than 1000 cells per microliter.

Adverse events after endoscopy were defined as overt clinical GI bleeding,

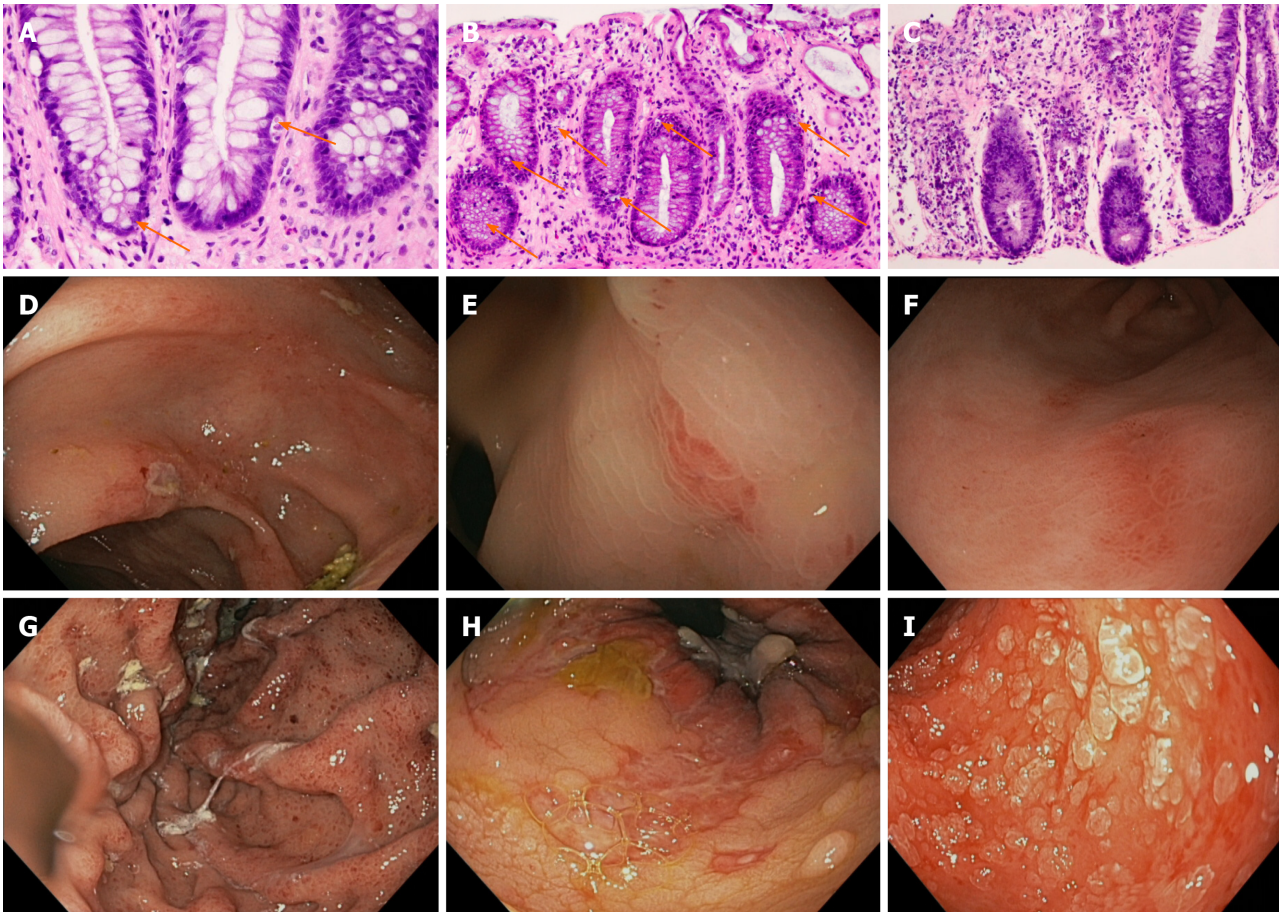

Figure 1 Illustrative images of endoscopic and histopathological views of graft-*vs*-host disease. A: Colon biopsy revealing mild graft-*vs*-host disease (GVHD) with few apoptotic bodies; B: Colon biopsy revealing moderate GVHD with all crypts involved; C: Colon biopsy revealing severe GVHD with gland destruction; D: Colonic ulcer without surrounding colitis; E: Rectal erythema and edema; F: Gastric edema and erosion; G: Severe gastritis; H: Severe colitis; I: Severe duodenitis.

infection, luminal perforation, and/or death due to any cause within 1 wk. When an adverse event occurred, the medical record was reviewed for details related to endoscopic approaches for hemostasis and other interventions required to manage the adverse events.

Statistical analysis

Data were stored using the Research Electronic Data Capture (REDCap) 8.10.2 data management platform (Vanderbilt University, Nashville, Tennessee). Descriptive statistics were computed for demographic, clinical, endoscopic, and pathologic variables. Contingency tables were created to calculate the yield, sensitivity, and specificity of biopsies based on certain endoscopic findings and presenting symptoms for diagnosing aGVHD. Fisher's exact test was performed to compare the incidence of post-endoscopic complications in the thrombocytopenic and neutropenic patients. All statistical analyses were performed using Stata/IC 15.1 (StataCorp, College Station, TX, United States). The statistical methods of this study were reviewed by Trieu H from the University of Southern California.

RESULTS

Identification of study cohort and clinical characteristics

A total of 4023 endoscopies were performed at COH during the examined study period. As shown in Figure 2, 195 endoscopies met inclusion criteria and were included in the analysis. Females accounted for 51.8% of the patients, with a median age of 56 years (range 17-78) as shown in Table 1. Endoscopic evaluation for aGVHD occurred at a median of 27 d (range 9-98 days) following HSCT. The most common primary hematologic malignancy diagnoses were acute myelogenous leukemia in

Table 1 Baseline demographics and clinical characteristics

Demographics and clinical characteristics	*n* = 195
Age (yr), median (range)	56 (17-78)
Female, *n* (%)	101 (51.8)
Time since HSCT in days, median (range)	27 (9-98)
Hematologic disorder, *n* (%)[1]	
AML	80 (41.0)
B-ALL	34 (17.4)
MDS	30 (15.4)
Myelofibrosis	13 (6.7)
Presenting symptoms, *n* (%)[1]	
Diarrhea	144 (73.9)
Nausea/vomiting	107 (54.9)
Abdominal pain	50 (25.6)
Gross endoscopic findings, *n* (%)[1]	
Edema/erythema	108 (55.4)
Gastritis	84 (43.1)
Ulcerations/erosions	56 (28.7)
Colitis	39 (20.0)
Esophagitis	27 (13.9)
Duodenitis	26 (13.3)
Normal	25 (12.8)
Pathologic findings, *n* (%)[1]	
Mild GVHD	133 (68.2)
Chronic inflammation	41 (21.0)
Moderate GVHD	36 (18.5)
Ulceration/erosion	25 (12.8)
Severe GVHD	16 (8.2)
Location of pathologic findings, *n* (%)[1]	
Sigmoid colon	118 (60.5)
Stomach	105 (53.9)
Rectum	103 (52.8)
Duodenum	94 (48.2)
Pre-procedure lab values, median (range)	
Hemoglobin (g/dL)	9.0 (6.7-14.4)
Platelets ($\times 10^3/\mu L$)	80 (16-388)
ANC ($\times 10^3/\mu L$)	2.6 (0.0-23.0)
INR	1.0 (0.9-1.7)
BUN	14 (2-78)
Creatinine	0.70 (0.28-3.32)
Pre-procedure transfusions, *n* (%)	
1 or more units of platelets transfused	78 (40.0)
1 or more units of pRBCs transfused	55 (28.2)

1 or more units of FFP transfused	3 (1.5)
Immunosuppressant use within 1-wk pre-procedure, *n* (%)[1]	
Tacrolimus	164 (84.1)
Sirolimus	115 (59.0)
Mycophenolate	70 (35.9)
Methylprednisone	55 (28.2)
Hydrocortisone	49 (25.1)

[1]Only the most common findings were included in this table. FFP: Fresh frozen plasma/cryoprecipitate; pRBCs: Packed red blood cells; BUN: Blood urea nitrogen; INR: International normalized ratio; ANC: Absolute neutrophil count; AML: Acute myelogenous leukemia; B-ALL: B-cell acute lymphoblastic leukemia; MDS: Myelodysplastic syndromes; GVHD: Graft-*vs*-host disease; HSCT: Hematopoietic stem cell transplant.

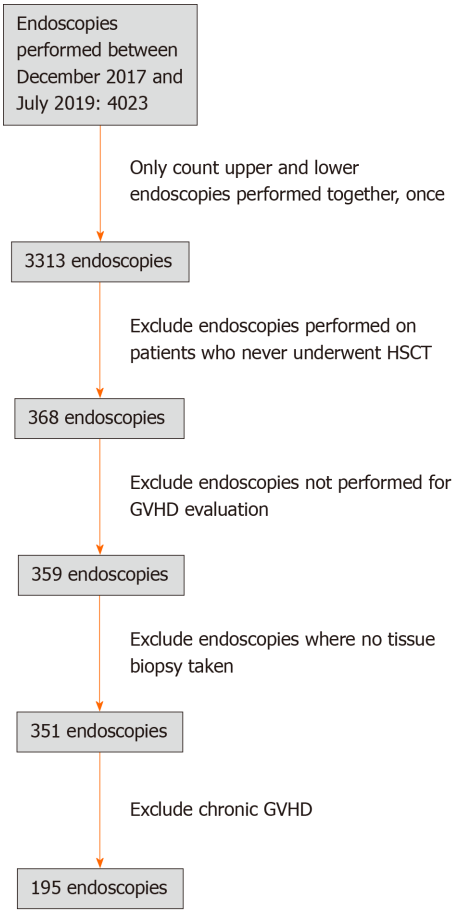

Figure 2 Patient selection flow-chart. GVHD: Graft-*vs*-host disease; HSCT: Hematopoietic stem cell transplant.

41.0% and B-cell acute lymphoblastic leukemia in 17.4%. Acute GVHD was confirmed histologically in 76.4% of patients.

Median pre-procedure hemoglobin count was 9.0 g/dL, platelet count 80 × 10^3/μL, and ANC 2.6 × 10^3/μL as shown in Table 2. The majority (greater than 90%) of pre-procedure hemoglobin and platelet counts were obtained after the last unit of product was transfused. Forty percent of patients required transfusions of 1 or more units of platelets, while 28.2% required 1 or more units of pRBCs, and only 1.5% required 1 or more units of FFP within 72 h prior to endoscopy.

Endoscopic procedures for evaluating aGVHD

Combined EGD and FS (43.0%) was the most common method of evaluation for aGVHD with fewer patients undergoing EGD (23.1%) or FS (29.2%) alone as shown in Table 2. Acute GVHD was confirmed histologically in 83.1% of patients who underwent combined EGD and FS and 77.2% of patients who underwent FS alone.

Table 2 Yield of performing different endoscopic modalities in detecting graft-*vs*-host disease in patients with different presenting symptoms

Endoscopic procedure	Confirmed GVHD in patients with any symptom, % (*n*)	Confirmed GVHD in patients presenting with diarrhea, % (*n*)	Confirmed GVHD in patients presenting with nausea/vomiting, % (*n*)	Confirmed GVHD in patients presenting with abdominal pain, % (*n*)
EGD (*n* = 45)	66.7 (30/45)	85.7 (6/7)[1]	70.6 (24/34)	57.1 (8/14)
FS (*n* = 57)	77.2 (44/57)	76.8 (43/56)	87.5 (7/8)[2]	76.9 (10/13)
Colonoscopy (*n* = 4)	75.0 (3/4)	75.0 (3/4)	-	100.0 (1/1)
EGD + FS (*n* = 83)	83.1 (69/83)	84.9 (62/73)	85.9 (55/64)	90.5 (19/21)
EGD + colonoscopy (*n* = 6)	50.0 (3/6)	50.0 (2/4)	0 (0/1)	100.0 (1/1)

[1]Three of six patients who presented with diarrhea and underwent esophagogastroduodenoscopy with confirmed graft-*vs*-host disease (GVHD) also had nausea/vomiting at time of presentation.
[2]Seven of seven patients who presented with nausea/vomiting and underwent FS with confirmed GVHD also had diarrhea at time of presentation. EGD: Esophagogastroduodenoscopy; FS: Flexible sigmoidoscopy; GVHD: Graft-*vs*-host disease.

When evaluating the diagnostic yield of endoscopic evaluation by presence of symptoms as shown in Table 2, combined EGD and FS provided the highest yield for diagnosing aGVHD in patients presenting with abdominal pain (90.5%). EGD alone and combined EGD and FS demonstrated comparably high yields in patients with diarrhea (85.7% and 84.9% respectively). Three of the six patients who had confirmed GVHD and had underwent EGD alone presented with both diarrhea and nausea/vomiting. FS alone and EGD with FS demonstrated similarly high yields in patients presenting with nausea/vomiting (87.5% and 85.9% respectively). Seven of the seven patients who had confirmed GVHD and had underwent FS alone presented with both nausea/vomiting and diarrhea.

Endoscopic and histologic findings

The most common endoscopic findings were edema/erythema, gastritis, ulcerations/erosions, and colitis as shown in Table 1 and illustrated in Figure 1. Histopathologic examination revealed mild aGVHD in 68.2% of tissue specimens, chronic inflammation without histological evidence of aGVHD in 21.0%, moderate aGVHD in 18.5%, ulceration/erosion in 12.8%, and severe aGVHD in 8.2%.

We assessed the frequency with which endoscopic findings demonstrated histological evidence of aGVHD as well as the utility of endoscopic findings as markers for aGVHD anywhere in the GI tract, which is summarized in Table 3. Eighty-four percent of patients with biopsies of normal endoscopically appearing mucosa demonstrated histological features consistent with aGVHD, with all of these patients demonstrating mild aGVHD on pathology, less than 5% showing concurrent moderate aGVHD and none with severe aGVHD. The sensitivity of a normal endoscopic appearance for aGVHD anywhere in the GI tract was thus 14.1%. As shown in Table 3, the presence of general endoscopic abnormalities (*i.e.*, ulceration, friability, blood clots) were more specific (58.7%-97.8%) than sensitive (2.7%-59.7%) for the presence of aGVHD anywhere along the GI tract on biopsy. Furthermore, the presence of esophagitis, colitis, gastritis, and duodenitis were particularly specific for aGVHD (94.3%, 93.0%, 88.9%, 78.6%, respectively) in biopsies obtained from the respective portions of the GI tract.

Patient symptoms and presence of aGVHD

In this cohort, the most frequent indications for endoscopic evaluation were diarrhea (141/195, 72.3%), nausea/vomiting (94/195, 48.2%), and abdominal pain (42/195, 21.5%) as seen in Table 1. Further, 87.0% (60/69) of patients presenting with both diarrhea and nausea/vomiting had confirmed aGVHD on histopathology. We attempted to identify portions of the GI tract in which a biopsy would provide the greatest yield for diagnosing aGVHD in patients with each of the above presenting symptoms. To this end, we calculated the proportion of patients presenting with one of the above symptoms, a biopsy taken from a specific location, and histological

Table 3 Gross endoscopic findings and concurrent presence of mild, moderate, and severe graft-*vs*-host disease

Endoscopic finding	Patients with GVHD, % (*n*)	Sensitivity (%)	Specificity (%)	Patients with mild GVHD, % (*n*)	Patients with moderate GVHD, % (*n*)	Patients with severe GVHD, % (*n*)
Normal[1]	84.0 (21/25)	14.1	91.3	100.0 (21/21)	4.8 (1/21)	0 (0/21)
General findings[1]						
Edema/erythema	82.4 (89/108)	59.7	58.7	88.8 (79/89)	30.3 (27/89)	12.4 (11/89)
Ulceration/erosion	80.4 (45/56)	30.2	76.1	77.8 (35/45)	40.0 (18/45)	26.7 (12/45)
Friability	90.9 (10/11)	6.7	97.8	80.0 (8/10)	30.0 (3/10)	20.0 (2/10)
Nodule	80.0 (4/5)	2.7	97.8	100.0 (4/4)	50.0 (2/4)	25.0 (1/4)
Specific findings[2]						
Gastritis	84.5 (60/71)	72.3	78.6	95.0 (57/60)	16.7 (10/60)	1.7 (1/60)
Duodenitis	66.7 (14/21)	16.1	88.9	78.6 (11/14)	21.4 (3/14)	21.4 (3/14)
Colitis	97.1 (33/34)	30.3	93.0	57.6 (19/33)	42.4 (14/33)	24.2 (8/33)
Esophagitis	66.7 (14/21)	70.0	94.3	100.0 (14/14)	0 (0/14)	0 (0/14)

[1]We did not localize these endoscopic findings to a particular segment of the gastrointestinal (GI) tract. Diagnostic yield, sensitivity, and specificity calculated were for finding graft-*vs*-host disease (GVHD) anywhere in the GI tract.
[2]Patients in the "Specific Findings" category had endoscopic evidence of inflamed mucosa in a specific segment of the GI tract along with biopsy taken from this segment. Diagnostic yields, sensitivities, and specificities calculated were for finding histopathological evidence of GVHD in this specific segment of the GI tract. GVHD: Graft-*vs*-host disease.

evidence of aGVHD out of all patients presenting with one of the above symptoms, a biopsy taken from a specific location, and histological evidence of aGVHD in tissue taken from any location (Table 4).

In patients presenting with diarrhea, biopsying the lower GI tract demonstrated a slightly greater diagnostic yield compared to biopsying the upper tract (99.1% *vs* 95.7%). When considering specific locations within each tract, the ileum, cecum, and ascending colon all demonstrated 100% yield, however the number of patients who had tissue obtained from these locations were extremely low. Excluding these locations, the rectum and sigmoid colon demonstrated the greatest diagnostic yield. In patients presenting with nausea/vomiting, biopsy from either the upper or lower tract demonstrated similar yields (97.5% and 96.8%). Biopsying the descending colon resulted in 100% yield, however only 6 patients with nausea/vomiting had a biopsy obtained here. Excluding the descending colon, the sigmoid colon and rectum again demonstrated the greatest diagnostic yield. Biopsies from the lower GI tract demonstrated greater yield than biopsies of the upper tract (96.8% *vs* 89.3%) in patients with abdominal pain. Although biopsies taken from the ileum down to the descending colon demonstrated 100% yield, only 4 patients at most had biopsies taken from these locations. Excluding these areas, biopsies from the stomach and sigmoid colon demonstrated the diagnostic greatest yields (89.3% and 87.1%).

Adverse events after endoscopy

Death due to any cause within 1 wk of endoscopy occurred in 0% (0/195) of patients. Bleeding occurred in 1.0% (2/195), infection in 1.0% (2/195), and perforation in 0.5% (1/195). Both of the patients with bleeding required second look endoscopies to manage bleeding not resolved with supportive management and were successfully managed endoscopically.

Thrombocytopenia was identified in 67 patients. Adverse outcomes including death occurred in 1.5% (1/67) of patients in the thrombocytopenic group and 2.3% (3/128) of patients in the non-thrombocytopenic group with the bleeding occurring in 1.5% and 0.8% of patients, respectively. There was no significant difference in these adverse outcomes between the two groups (P = 1.000) (Table 5).

Neutropenia was identified in 25 patients, all of whom were on broad spectrum antibiotics prior to endoscopy. Adverse outcomes including death occurred in 4.0% (1/25) of neutropenic patients and 1.8% (3/170) of non-neutropenic patients, with bleeding occurring in 4.0% and 0.6% of patients, respectively. No cases of infection

Table 4 Utility of biopsying various segments of the gastrointestinal tract in patients presenting with diarrhea, nausea/vomiting, and abdominal pain

Presenting symptom and biopsy location[1]	Histological evidence of GVHD in location, % (*n*)
Diarrhea (*n* = 144)	
Upper GI tract	95.7 (67/70)
Esophagus	51.9 (14/27)
Stomach	82.1 (55/67)
Duodenum	87.1 (61/70)
Lower GI tract	99.1 (109/110)
Ileum	100.0 (2/2)
Cecum	100.0 (1/1)
Ascending colon	100.0 (4/4)
Transverse colon	75.0 (3/4)
Descending colon	91.7 (11/12)
Sigmoid colon	93.5 (101/108)
Rectum	94.0 (94/100)
Nausea/vomiting (*n* = 107)	
Upper GI tract	97.5 (77/79)
Esophagus	51.6 (16/31)
Stomach	84.6 (66/78)
Duodenum	87.3 (69/79)
Lower GI tract	96.8 (60/62)
Ileum	-
Cecum	-
Ascending colon	-
Transverse colon	-
Descending colon	100.0 (6/6)
Sigmoid colon	90.2 (55/61)
Rectum	91.1 (51/56)
Abdominal pain (*n* = 50)	
Upper GI tract	89.3 (25/28)
Esophagus	66.7 (8/12)
Stomach	89.3 (25/28)
Duodenum	85.7 (24/28)
Lower GI tract	96.8 (30/31)
Ileum	100.0 (1/1)
Cecum	100.0 (1/1)
Ascending colon	100.0 (2/2)
Transverse colon	100.0 (1/1)
Descending colon	100.0 (4/4)
Sigmoid colon	87.1 (27/31)
Rectum	86.7 (26/30)

[1]Denominators represent all patients with presenting symptom, biopsy obtained from specified location in the gastrointestinal (GI) tract, and histological evidence of graft-*vs*-host disease in tissue obtained anywhere in the GI tract. GI: Gastrointestinal; GVHD: Graft-*vs*-host disease.

Table 5 Complications in thrombocytopenic and neutropenic patients

Complication	Non-thrombocytopenic patients	Thrombocytopenic patients	Non-neutropenic patients[1]	Neutropenic patients[1]
Any-cause mortality within 1 wk of endoscopy, *n* (%)	0/128 (0)	0/67 (0)	0/170 (0)	0/25 (0)
Adverse outcomes excluding death, *n* (%)	3/128 (2.3)	1/67 (1.5)	3/170 (1.8)	1/25 (4.0)
Bleeding within 1 wk of endoscopy	1/128 (0.8)	1/67 (1.5)	1/170 (0.6)	1/25 (4.0)
Infection within 1 wk of endoscopy	2/128 (1.6)	0/67 (0)	2/170 (1.2)	0/25 (0)
Perforation within 1 wk of endoscopy	1/128 (0.8)	0/67 (0)	1/170 (0.6)	0/25 (0)
Adverse outcomes including death within 1 wk, *n* (%)[2]	3/128 (2.3)	1/67 (1.5)	3/170 (1.8)	1/25 (4.0)

[1]Thrombocytopenia was defined as a pre-procedure platelet count ≤ 50 × 10^3/μL or ≤ 75 × 10^3/μL and ≥ 1 units of platelet transfused. Neutropenia was defined as a pre-procedure absolute neutrophil count < 1000 cells/μL.
[2]P = 1.000 for thrombocytopenic *vs* non-thrombocytopenic patients and P = 0.425 for neutropenic vs non-neutropenic patients.

occurred in the neutropenic patients. No significant difference in adverse outcomes was observed when comparing neutropenic to non-neutropenic patients (P = 0.425).

Intraprocedural bleeding occurred in 10 of 195 (5.1%) non-duplicate endoscopies which required hemostatic interventions such as hemoclips (9/195 or 4.6%), epinephrine injections (1/195 or 0.5%), or argon plasma coagulation (2/195 or 1.0%) during the index procedure. Two of these patients experienced recurrent post-procedure bleeding that was controlled during second look endoscopy. No patient with intraprocedural bleeding experienced other adverse outcomes (infection, perforation, or death) within one week of endoscopy.

DISCUSSION

We report the largest cross-sectional study to date on the management and safety of endoscopic evaluation of aGVHD in patients who have undergone HSCT. A number of prior studies have found that symptoms such as diarrhea often occur in the presence of aGVHD in the lower GI tract, warranting evaluation with FS, while upper GI symptoms such as nausea and vomiting warrant evaluation with EGD[6,14,16,18,19,22]. On the contrary, we found that combined EGD and FS with biopsies resulted in at least an 80% diagnostic yield in patients with any presenting symptom.

Interestingly, EGD alone in patients presenting with diarrhea and FS alone in patients presenting with nausea/vomiting demonstrated greater yields than combined EGD and FS. This finding could be due to the small number of patients presenting with diarrhea or nausea/vomiting who also underwent these modalities of endoscopic evaluation. Further, three of six patients with confirmed aGVHD who underwent EGD alone and all seven patients with confirmed GVHD who underwent FS alone presented with concurrent nausea/vomiting and diarrhea. Taken together, combined EGD and FS may be the most effective endoscopic approach to GVHD evaluation regardless of presenting symptoms.

To explore this concept further, we analyzed anatomical patterns of aGVHD localization for different presenting symptoms. Biopsies taken from either the upper or lower GI tracts demonstrated greater than 90% yield for histological evidence of aGVHD, with the lower GI tract demonstrating slightly greater yields across most presenting symptoms. When considering specific locations within the upper and lower tracts, the rectosigmoid colon demonstrated the greatest diagnostic yield across all symptoms except abdominal pain when excluding locations where fewer than seven patients had biopsies. Our findings are consistent with those of prior studies which

recommend biopsies of the rectosigmoid colon for evaluation of lower GI aGVHD[14,16-18]. Thus, a biopsy approach targeted to the rectosigmoid colon may be ideal for patients who are not candidates for combined EGD with FS.

In addition, we hypothesized that macroscopic features observed on endoscopy may be suggestive of the presence and severity of aGVHD, acknowledging inconsistent findings in the literature[3,9,12,13,20]. We found that endoscopic evidence of inflammation was generally as specific as normal mucosa for the presence of aGVHD, however histological examination of inflamed mucosa more frequently revealed moderate to severe aGVHD. Normal appearing mucosa with aGVHD was typically mild with only one case of moderate grade findings. Our results thus confirm the clinical practice of performing biopsies of normal appearing mucosa (covering multiple segments of the GI tract) to evaluate for histological evidence of aGVHD. Abnormal mucosa should be biopsied to evaluate for actual histological grade of aGVHD.

The safety of endoscopic evaluation for aGVHD in HSCT patients continues to be an ongoing concern, given this population may be at increased risk for bleeding and infection. In our study, adverse events were relatively rare, complicating only 2.1% of all endoscopies. Further, none of the endoscopies that required hemostasis for intra-endoscopic bleeding had subsequent uncontrolled bleeding. Similarly low complication rates have been reported in the literature, including two studies of adult cancer patients with thrombocytopenia and neutropenia which found post-endoscopic complication rates of less than 5%[28,29]. Additionally, we found no significant differences in adverse events when comparing the thrombocytopenic and non-thrombocytopenic groups and the neutropenic and non-neutropenic groups. These findings suggest that endoscopic evaluation for aGVHD in this vulnerable population may be safe regardless of pre-procedure platelet and neutrophil count, challenging the need for thresholds set in place by endoscopy societies. Taken together with the findings of recent papers[28,29], a prospective, controlled study evaluating platelet and neutrophil thresholds for endoscopy should be conducted to potentially limit transfusions and aid in antibiotic and neutrophil-stimulation pharmacological stewardship efforts.

Our study had several limitations. Given the retrospective nature, there may have been confounding by indication accounting for the findings of high yield of FS alone or EGD alone across different symptoms. However, by review of the entire medical record to capture all symptoms, we limited the potential for this bias. Selection bias is also possible since all patients underwent endoscopic evaluation with biopsy, though this was the intent of our study. Our study lacked power for statistical comparisons given the low rate of adverse events – while this impaired our ability to perform multiple logistic regression and limited us to use of Fisher's exact test, we believe the absolute incidence of these events have meaning and can be interpreted clinically and used as part of the risk/benefit calculations in post-HSCT patients referred for endoscopy. We believe that by reporting the largest endoscopic data in this patient population, our results add to the literature on the topic.

CONCLUSION

Determining the optimal endoscopic strategy for acute GVHD evaluation in patients with HSCT is challenging due to the inherent vulnerability of this population. Our findings suggest that combined EGD and FS with biopsy of the stomach and rectosigmoid colon results in the greatest diagnostic yield for most patients referred for evaluation of aGVHD, independent of symptoms. We confirm that biopsy of normal appearing mucosa is warranted and found that endoscopic evidence of severe inflammation is specific for more histologically severe GVHD. In resource limited settings, or in patients with high risk for sedation related complications, FS with rectosigmoid biopsies may be an appropriate approach given reasonable yield for detection of aGVHD. Our study also found no significant difference in adverse events between thrombocytopenic and neutropenic patients, confirming the safety of endoscopy in this patient population. Future, larger, controlled studies are needed to control for confounders and more accurately model the risk associated with endoscopy in the thrombocytopenic and neutropenic groups.

ARTICLE HIGHLIGHTS

Research background

Gastrointestinal (GI) graft-*vs*-host disease (GVHD) is the most common complication of hematopoietic stem cell transplant (HSCT) and is often diagnosed *via* endoscopy with biopsy.

Research motivation

Limited data exists on optimal endoscopic strategy and safety for GVHD evaluation in cancer patients who have had HSCT.

Research objectives

To create a strategy of endoscopic approach based on symptoms, gross endoscopic findings, and biopsy location as well as understand the safety of endoscopy in acute GVHD (aGVHD) patients.

Research methods

We analyzed 195 endoscopies performed at City of Hope in patients who underwent HSCT for hematological malignancy and were evaluated for aGVHD.

Research results

Evaluation using combined esophagogastroduodenoscopy (EGD) and flexible sigmoidoscopy (FS) demonstrated a greater diagnostic yield for aGVHD (83.1%) compared to EGD (66.7%) or FS (77.2%) alone in patients with any presenting symptom. Biopsies obtained from either the upper or lower GI tract, specifically the rectosigmoid colon, demonstrated comparably high yields in patients with diarrhea (95.7% *vs* 99.1%) or nausea/vomiting (97.5% *vs* 96.8%). Normal-appearing mucosa was generally as specific (91.3%) for the presence of aGVHD on biopsy as the presence of endoscopic abnormalities (58.7%-97.8%), however sensitivity was low. Adverse events occurred in a small proportion of patients, including bleeding (1.0%), infection (1.0%), and perforation (0.5%). There was no significant difference in occurrence of adverse events in thrombocytopenic compared to non-thrombocytopenic patients (P = 1.000) and neutropenic compared to non-neutropenic patients (P = 0.425).

Research conclusions

Combined EGD and FS with biopsy of the stomach and rectosigmoid colon results in the greatest diagnostic yield for most patients referred for evaluation of aGVHD, independent of symptoms. Biopsy of normal appearing mucosa is warranted, and endoscopic evidence of severe inflammation is specific for more histologically severe GVHD. In resource limited settings, or in patients with high risk for sedation related complications, FS with rectosigmoid biopsies may be an appropriate approach given reasonable yield for detection of aGVHD. Our study also found no significant difference in adverse events between thrombocytopenic and neutropenic patients, confirming the safety of endoscopy in this patient population.

Research perspectives

Future, larger, controlled studies are needed to control for confounders and more accurately model the risk associated with endoscopy in the thrombocytopenic and neutropenic groups.

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ORIGINAL ARTICLE

Retrospective Study

Role of endoscopic ultrasound in pediatric patients: A single tertiary center experience and review of the literature

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Abstract

BACKGROUND

Although endoscopic ultrasound (EUS) is now widely available and has an established role in adults, the utility of EUS and EUS-guided fine needle aspiration (EUS-FNA) in pediatrics is insufficiently described compared to adults and is supported by only a few studies.

AIM

To report the experience of a single tertiary center in the use of EUS and EUS-FNA in a pediatric population and to further assess its safety, feasibility, and clinical impact on management.

METHODS

A retrospective study of 13 children (aged 18 years or younger) identified from our medical database was conducted. A retrospective review of demographic data, procedure indications, EUS findings, and the clinical impact of EUS on the subsequent management of these patients was performed.

RESULTS

During the 4-year study period, a total of 13 (1.7%) pediatric EUS examinations out of 749 EUS procedures were performed in our unit. The mean age of these 8 females and 5 males was 15.6 years (range: 6-18). Six of the 13 EUS examinations were pancreatobiliary (46.1%), followed by mediastinal 2/13 (15.4%), peri-gastric 2/13 (15.4%), abdominal lymphadenopathy 1/13 (7.7%), tracheal 1/13 (7.7%) and rectal 1/13 (7.7%). Overall, EUS-FNA was performed in 7 patients (53.8%) with a diagnostic yield of 100%. The EUS results had a significant impact on clinical care in 10/13 (77%) cases. No complications occurred in these patients during or after any of the procedures.

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CONCLUSION
EUS and EUS-FNA in the pediatric population are safe, feasible, and have a significant clinical impact on the subsequent management; thus avoiding invasive and unnecessary procedures.

Key Words: Endoscopic ultrasound; Endoscopic ultrasound-guided fine needle aspiration; Pediatric

Core Tip: Although endoscopic ultrasound (EUS) is now widely available and has an established role in adults, the utility of EUS and EUS-guided fine needle aspiration in pediatrics is insufficiently described compared to adults and is supported by only a few studies. More effort is required to increase the awareness of EUS among pediatric gastroenterologists which may have a clinical impact on the subsequent management and minimize unnecessary procedures in children.

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INTRODUCTION

Since the introduction of endoscopic ultrasound (EUS) in 1980, the diagnostic and therapeutic indications, in addition to the scope design, have rapidly grown. The role of EUS in gastrointestinal and pancreatobiliary disorders in adults is well established[1]. EUS, magnetic resonance cholangiopancreatography, and computed tomography (CT) have been considered in many studies to be minimally or non-invasive tools that can be used in the assessment of pancreatobiliary disorders avoiding invasive and unnecessary procedures[2,3].

Although EUS is now widely available and has an established role in adults, the utility of EUS and EUS-guided fine needle aspiration (EUS-FNA) in pediatrics is insufficiently described compared to adults and is supported by only a few studies[3-12]. This could be attributed to many factors including: Low incidence of gastrointestinal tumors and pancreatobiliary disorders in pediatric patients, a lacking of awareness among pediatric gastroenterologists and the absence of dedicated pediatric endosonographers. Certainly, these few pediatric EUS procedures do not allow pediatric endoscopists to gain and maintain competency in EUS and most EUS procedures in pediatrics are performed by adult endoscopists[7,8]. Therefore, more effort is required to increase the awareness of EUS among pediatric gastroenterologists, as it may have a clinical impact on the subsequent management and minimize unnecessary procedures in children[10].

The aim of this study is to report the experience of a single tertiary center in the use of EUS and EUS-FNA in a pediatric population and to assess its safety, feasibility, and clinical impact on subsequent patient management.

MATERIALS AND METHODS

Patients

All EUS procedures performed between January 2016 and January 2020 at the Endoscopy Unit of Mansoura Specialized Medical Hospital, Mansoura University, Egypt, were reviewed. Patients aged 18 years or younger were identified from our medical database. A retrospective review of demographic data, procedure indications, EUS findings, and the clinical impact of EUS on subsequent management of the patients was conducted.

The inclusion criteria were as follows: Patients who required EUS and EUS-guided

tissue acquisition after imaging studies [abdominal ultrasound (US), CT, or magnetic resonance imaging], that shows either mediastinal, pancreatic, or intra-abdominal solid or cystic lesions (size > 1 cm) or patients who required pancreatic EUS to exclude pancreatic insulinoma after negative imaging studies. The exclusion criteria were as follows: Patients or parents who refused participation in the study, patients with a contraindication to interventional endoscopy; such as patients who were unfit for anesthesia or patients with coagulation disorders. Our ethical committee approved the study protocol and written consent was obtained from all patients or parents before the procedure.

Methods

This retrospective study was conducted to assess the safety, feasibility, and clinical impact of EUS and EUS-FNA in a pediatric population. All procedures were performed under intravenous propofol sedation. All EUS examinations were carried out by two experienced endosonographers using a Pentax linear Echoendoscope EG3870UTK (PENTAX Medical, Tokyo, Japan) connected to a Hitachi Avius ultrasound system (Hitachi Medical Systems, Tokyo, Japan).

Technique: Examination of the pancreatic head, Ampulla of Vater, biliary tract, gallbladder, and portal regions was performed from the second part of the duodenum and duodenal bulb; the pancreatic body and tail, left suprarenal gland and the liver were visualized from the stomach; the mediastinum and trachea were examined from the esophagus. For rectal EUS, the scope was advanced to the sigmoid colon, and examination of the rectosigmoid junction, rectum and anal canal was performed after filling the lumen with water during slow withdrawal of the scope.

EUS-FNA was performed using either a 19 or 22 gauge FNA needle (Cook Medical, Bloomington, IN, USA). Color Doppler was used to identify the best position for puncture avoiding interposing blood vessels between the target lesion and the needle. After the solid lesions were penetrated by the needle under EUS guidance, the needle was moved to and fro 10-12 times in different directions while the stylet was slowly removed (slow pull technique). After each pass, tissue material was divided into two parts: The first part was smeared onto slides and fixed with 95% alcohol and the second part was placed in a formalin tube and labelled. Two needle passes were performed for solid lesions to increase the diagnostic yield. EUS elastography was used to differentiate the nature of solid lesions and to target the hardest area of the lesion during sampling. One pass was carried out for cystic lesions with near total aspiration of the fluid content to decrease the risk of infection. Prophylactic intravenous antibiotics were given before aspiration of cystic lesions. All samples were sent to the Pathology Department for evaluation.

Cytopathological examination: All slides were stained with hematoxylin and eosin and all tissue samples fixed in formalin were placed in paraffin and stained with hematoxylin and eosin for evaluation of the presence of a histologic core. Immunohistochemical markers were used when needed. All prepared slides and tissue samples were examined by experienced cytopathologists.

Study outcomes: The patient's medical records were revised for standard data which included patient demographics, initial diagnosis, previous abdominal US, CT, or magnetic resonance imaging, EUS indications, EUS findings, impact of EUS on the patient's clinical care, and adverse events during and for 2 h after the procedure.

RESULTS

During the 4-year study period, a total of 13 (1.7%) pediatric EUS examinations out of 749 EUS procedures were performed in our unit. The mean age of the 8 females and 5 males was 15.6 years (range: 6-18). The procedures performed included 12 (92.3%) upper EUS and 1 (7.7%) lower EUS. Six of the EUS examinations were pancreatobiliary (46.1%), followed by mediastinal 2/13 (15.4%), peri-gastric 2/13 (15.4%), abdominal lymphadenopathy 1/13 (7.7%), tracheal 1/13 (7.7%) and rectal 1/13 (7.7%) (Table 1). Overall, EUS-FNA was performed in 7 patients (53.8%); using a 19G in 4 patients and a 22G needle in 3 patients with a diagnostic yield of 100%. In cystic lesions or lesions with a cystic component [solid pseudopapillary neoplasm (SPN)], a 19G needle was used. In solid lesions, a 22G needle was used with a median of 2 passes except for a rectal gastrointestinal stromal tumor (GIST) where a 19G needle was used to obtain sufficient tissue. No complications occurred during or after any of the procedures,

Table 1 Population characteristics and indications for endoscopic ultrasound

Children	*n* = 13
Females/males	8/5
Age (median)	15.6 yr
Age (range)	6-18 yr
Indications for EUS (*n*)	13
Upper	
Thoracic	
Tracheal mass	1
Mediastinal mass	2
Abdominal	
Pancreatic head mass	1
Retroperitoneal mass	1
Ampullary mass	1
Abdominal lymphadenopathy	1
Peri-gastric mass	2
Suspected insulinoma	3
Lower	
Rectal subepithelial lesion	1
EUS-FNA (*n*)	7
Solid	5
Cystic	2
Adverse events (*n*)	0

EUS: Endoscopic ultrasound; EUS-FNA: Endoscopic ultrasound-guided fine needle aspiration.

which were all technically successful. Details of the indications, EUS findings (Figures 1-3), EUS-FNA, diagnosis and treatment are shown in (Table 2).

EUS had a significant impact on clinical care in 10/13 (77%) cases. In these cases, surgical treatment was carried out after accurate staging by EUS or a definitive diagnosis was reached by EUS-FNA in 4 cases (tracheal fibroma, pancreatic neuroendocrine tumor (NET), SPN, and rectal GIST). Chemotherapy was administered in 2 cases (lymphoma), endoscopic treatment was performed in 2 cases (deroofing of ampullary duplication cyst and aspiration of mediastinal bronchogenic cyst), and follow-up in 2 cases (gastric duplication cyst and peri-gastric postpancreatitis collection which resolved with antibiotics). In 3 cases with suspected insulinoma, EUS did not achieve a definitive diagnosis or therapy; as no pancreatic masses were detected.

DISCUSSION

The role of EUS in the adult population is wellestablished. However, it has not been adequately assessed in the pediatric population with gastrointestinal and pancreaticobiliary disorders. EUS in the pediatric population is most commonly performed for assessment of pancreatic solid/cystic lesions, pancreatitis (recurrent acute, chronic), suspected choledocholithiasis, subepithelial lesions such as duplication cysts and pancreatic rest, and benign/malignant lymphadenopathy. With the gradually increasing number of EUS indications in children, it is likely to gain more acceptance for the pediatric population[13].

The feasibility of EUS in pediatric patients was provided by the ASGE Technology Committee status evaluation report[14]. Based on the size of the echoendoscope,

Table 2 Details of endoscopic ultrasound procedures

N	Age	Sex	Indication	EUS findings	EUS-FNA	Diagnosis	Treatment
1	17	F	Tracheal mass assessment before surgery	Hypoechoic tracheal mass measuring 13 mm × 9.5 mm separable from esophageal wall	Nil	Tracheal fibroma	Surgery
2	15	F	Pancreatic head mass	Isoechoic pancreatic head mass with hypoechoic rim about 30 mm × 25 mm separable from all vessels	22G	Well differentiated NET	Surgery
3	12	F	Retroperitoneal mass	Isoechoic mass with small cystic areas about 60 mm × 60 mm compressing the SMA	19G	SPN	Surgery
4	15	F	Ampullary mass	Ampullary cyst 35 mm × 30 mm with double wall and clear content	Nil	Duplication cyst	Endoscopic deroofing
5	15	F	Peri-gastric mass	Extraluminal cyst arising from the muscularis propria of antral wall with double wall about 40 mm × 35 mm	Nil	Duplication cyst	Follow up
6	18	M	Peri-gastric mass	Hypoechoic ill-defined peri-gastric collection with hyperechoic calcified areas	19G	Postpancreatitis collection	Resolved with antibiotics
7	17	M	Rectal SEL	Exophytic rectal mass about 33 mm × 21 mm mostly arising from the muscularis propria with intact submucosa and mucosa	19G	GIST	Surgery
8	18	M	Mediastinal mass	Large subcarinal cyst 10 cm × 7.6 cm compressing the right atrium and trachea with organized blood inside	19G	Bronchogenic cyst	Full aspiration by EUS with no recurrence
9	18	F	Mediastinal mass	Multiple hypoechoic subcarinal, para-aortic and celiac lymph nodes, largest about 22 mm	22G	Lymphoma	Chemotherapy
10	18	M	Abdominal lymphadenopathy	Multiple hypoechoic lymph nodes at portahepatis, para-aortic, and aorto-caval regions, largest about 55 mm × 34 mm. Splenomegaly with multiple focal lesions	22G	Lymphoma	Chemotherapy
11	18	F	Suspected insulinoma	Normal pancreas with no detected lesions	Nil	Nil	Nil
12	6	M	Suspected insulinoma	Normal pancreas with no detected lesions	Nil	Nil	Nil
13	17	F	Suspected insulinoma	Normal pancreas with no detected lesions	Nil	Nil	Nil

G: Gauge; SMA: Superior mesenteric artery; NET: Neuroendocrine tumor; SPN: Solid pseudopapillary neoplasm; SEL: Subepithelial lesion; GIST: Gastrointestinal stromal tumor; EUS-FNA: Endoscopic ultrasound-guided fine needle aspiration.

standard adult radial echoendoscopes (diameter: 12.7-14.2 mm) and linear echoendoscopes (diameter: 12.1-14.6 mm) can be used with caution in pediatric patients weighing more than 15 kg, given their relatively rigid distal tip. Throughthe scope miniprobes (frequency: 12-30 MHz) may be used safely in patients weighing less than 15 kg through the standard gastroscopes with a 2.8 mm working channel[14].

Herein, we report the experience of a single tertiary center in the use of EUS and EUS-FNA in a pediatric population and compare the findings to the most relevant studies in the literature assessing the role of EUS in children (Table 3). A total of 12 studies[3-12,15,16] were published between 1998 and 2019 including 524 patients and 584 EUS procedures. The age of the enrolled patients ranged between 0.5 and 21 years. Examination of the pancreatobiliary system was the main indication for EUS; which was performed in 396 (67.8%) cases. EUS-FNA was performed in 92 (15.7%) cases achieving a diagnosis in 81 cases with an overall diagnostic accuracy of 88% (7 cases in our study with a diagnostic accuracy of 100%). Therapeutic EUS was performed in 16 cases (7 pancreatic pseudocyst drainage, 7 celiac plexus block, 1 EUS-guided transgastric biliary drainage[4,6-8,15,16] and 1 mediastinal bronchogenic cyst aspiration in our study). The incidence rate of EUS-related complications ranged between 1.96% and 7.1%; which was reported in only 4 studies[3,4,6,16]. Complications included mild pancreatitis after FNA of solid pancreatic lesions, fever and bleeding after EUS-guided cystogastrostomy and anesthesia-related complications (hypoxia due to airway obstruction and laryngospasm). No complications occurred in any of the patients in our study during or after the procedures. With regard to the echoendoscopes, EUS procedures were performed with different echoendoscopes including radial, linear and recently the slim echoendoscope provided by Pentax (insertion tube of 10.8 mm, biopsy channel 2.8 mm; Pentax EG-3270UK, Pentax Hamburg, Germany) which can be used safely in children younger than 10 years. In our study, all EUS procedures were

Table 3 Summary of current literature in comparison to our study

Ref.	Patients, *n*	EUS, *n*	Time frame (yr)	Age range (yr)	Pancreatobiliary indications	Other indications	EUS-FNA
Roseau *et al*[9], 1998	18	23	7	4-16	8	15	0
Varadarajulu *et al*[10], 2005	14	15	3	5-17	15	0	3
Cohen *et al*[5], 2008	32	32	6	1.5-18	19	13	7
Bjerring *et al*[11], 2008	18	18	16	0.5-15	11	7	0
Attila *et al*[8], 2009	38	40	7	3-17	25	15	12
Al-Rashdan *et al*[7], 2010	56	58	8	4-18	42	15	15
Rosen *et al*[12], 2010	25	42	5	NA	0	42	0
Scheers *et al*[4], 2015	48	52	14	2-17	52	0	12
Gordon *et al*[6], 2016	43	51	6	4-18	34	17	13
Mahajan *et al*[3], 2016	121	125	8	3-18	118	7	7
Fugazza *et al*[15], 2017	40	47	6	3-18	28	19	3
Raina *et al*[16], 2017	58	68	5	6-21	38	20	13
Current study	13	13	4	6-18	6	7	7
Total	524	584	3-16	0.5-21	396	177	92

NA: Not available; EUS: Endoscopic ultrasound; FNA: Fine needle aspiration.

performed with the standard linear echoendoscope safely without any complications.

Similar to previous studies, most of our EUS examinations were pancreatobiliary 6/13 (46.1%); mainly for solid pancreatic lesions or suspected insulinomas. EUS-FNA was performed in 7 patients and a definite diagnosis was achieved in all patients allowing them to undergo appropriate management (patients with pancreatic NET, SPN, and rectal GIST underwent surgery, those with mediastinal and abdominal lymphomas started chemotherapy, peri-gastric postpancreatitis collection resolved with antibiotics, and a mediastinal bronchogenic cyst was completely aspirated). A commonly reported therapeutic indication for EUS in pediatrics is the drainage of pancreatic fluid collections[4,15,16]. In the present study, the child who presented with a large mediastinal bronchogenic cyst (10 cm × 7.6 cm) underwent successful EUS-guided aspiration of the cyst content with no recurrence within 6 mo after aspiration. In the 3 cases with suspected insulinomas, one patient subsequently underwent surgical intervention and was diagnosed with nesidioblastosis and 2 patients underwent further evaluation.

In this study, integration of EUS into the management plan had a significant impact on the clinical care in 77% of cases. This was comparable to the study by Varadarajulu *et al*[10], who reported that EUS had a significant impact on the clinical care of 13 out of 14 patients (93%) with pancreaticobiliary disorders. Similarly, Raina *et al*[16] reported a significant impact on clinical care in 88% of cases and AlRashdan *et al*[7] reported a different diagnosis achieved by EUS in 86% of cases. These data suggest that EUS when performed by expert endosonographers is safe, feasible, and has a significant impact on the clinical care of pediatric patients.

Many factors affect the choice of sedation during pediatric EUS procedures including: The expected duration of the procedure, the expected level of patient cooperation particularly during EUS-FNA, the American Standards Association classification of the patient, and the personal preference of the patients and parents, as well as the endoscopists[8]. In our study, all procedures were performed under intravenous propofol sedation. However, the available data in the literature are insufficient to make recommendations about the safety, adequacy, and cost of general anesthesia *vs* intravenously administered moderate sedation for EUS in pediatric patients.

The present study has some limitations. First, the number of patients included in the study was relatively small; with infants and younger children not well represented, limiting the ability to generalize results to all age groups. Second, it was a single tertiary center experience with retrospective data analysis, with possible selection and recall bias. Finally, the rarity of the performed therapeutic EUS procedures does not

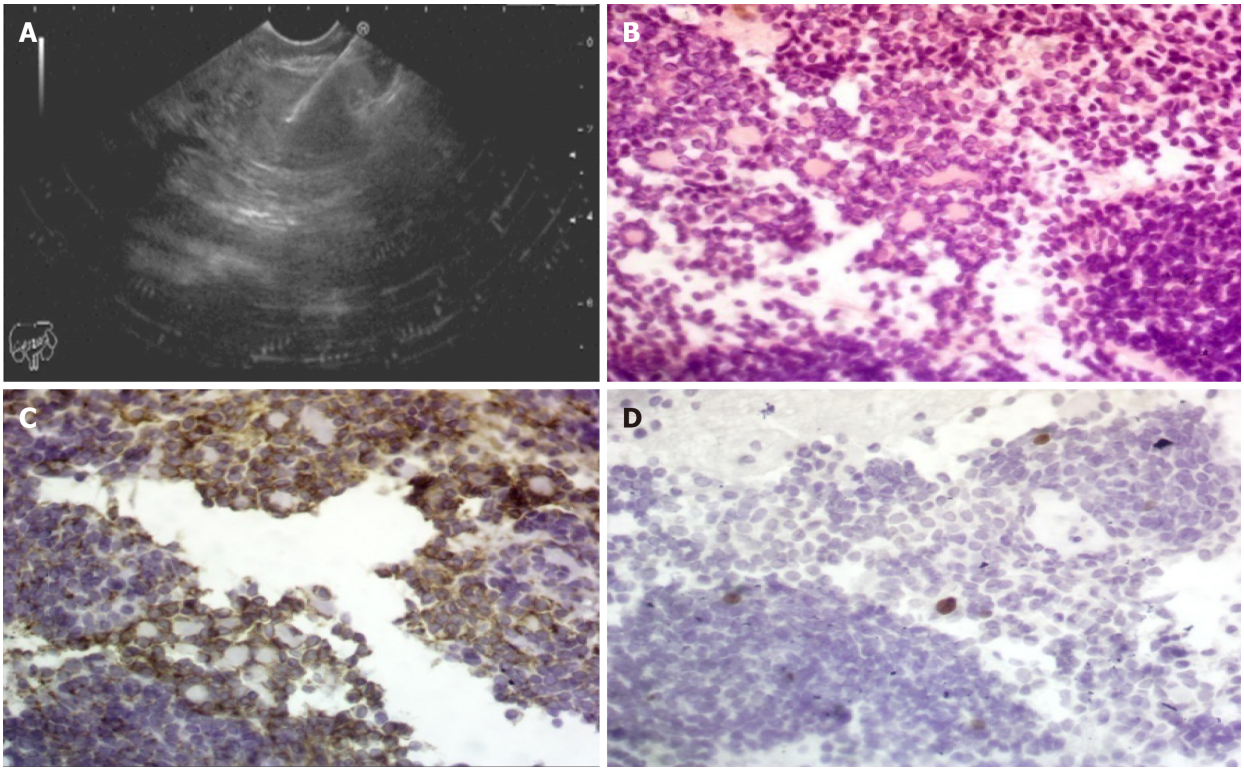

Figure 1 Endoscopic ultrasound and hematoxylin/eosin staining. A: Pancreatic head mass with fine needle aspiration; B: Hematoxylin/eosin staining: Shows cellular tumor tissue formed by small cells with focal resetting and tumor cell nuclei show fine chromatin with a little cytoplasm (Hematoxylin/eosin, 400 ×); C: Shows moderate membranous reaction of the tumor cells (CD56, 400 ×); and D: Show positive nuclear staining in a few tumor cells (< 2%) (Ki-67, 400 ×); consistent with a well-differentiated neuroendocrine tumor.

allow definite conclusions.

CONCLUSION

EUS and EUS-FNA in the pediatric population are safe, feasible, and have a significant clinical impact on subsequent management; thus avoiding more invasive and additional unnecessary procedures. EUS utilization in pediatrics although rare, is expected to increase in the future. Dedicated EUS programs in high volume tertiary centers can ensure that the correct indications are followed, with a high impact on patient management and safety of procedures in the pediatric population.

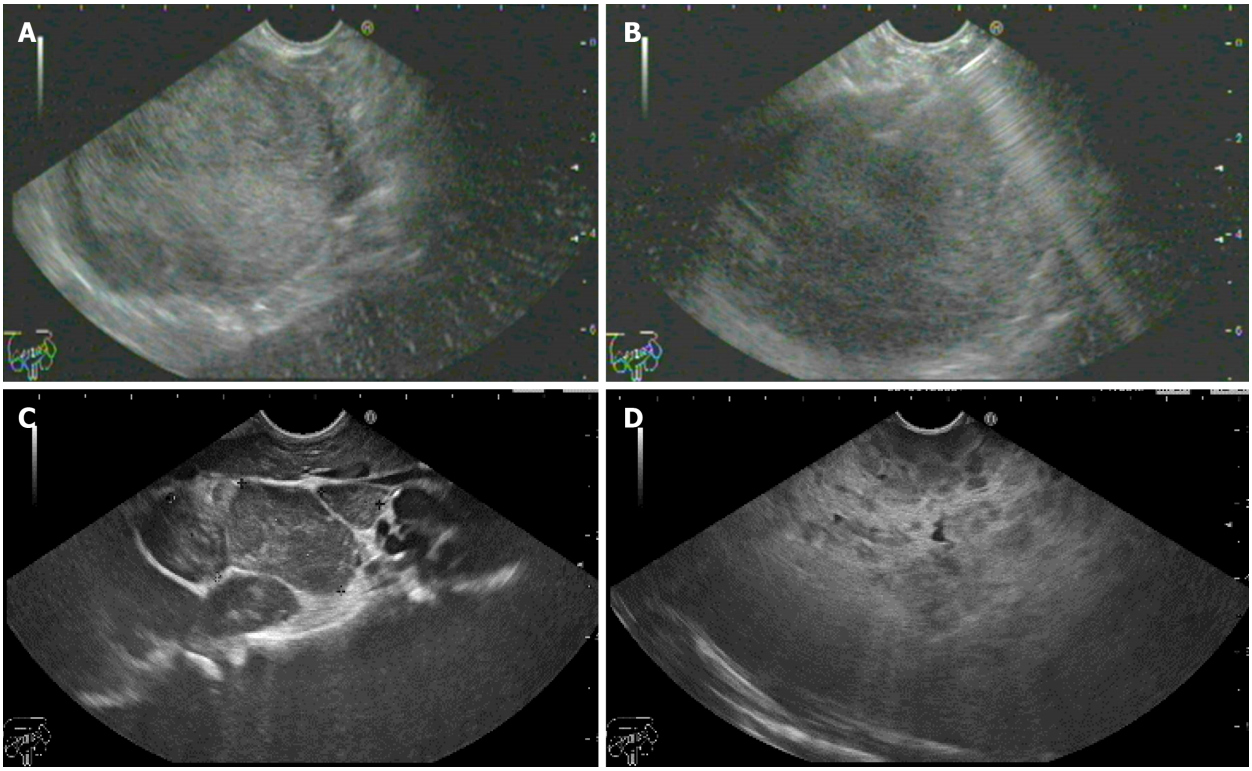

Figure 2 Endoscopic ultrasound. A and B: Solid pseudopapillary neoplasm with fine needle aspiration; C and D: Mediastinal lymph nodes with multiple splenic focal lesions diagnosed as lymphoma.

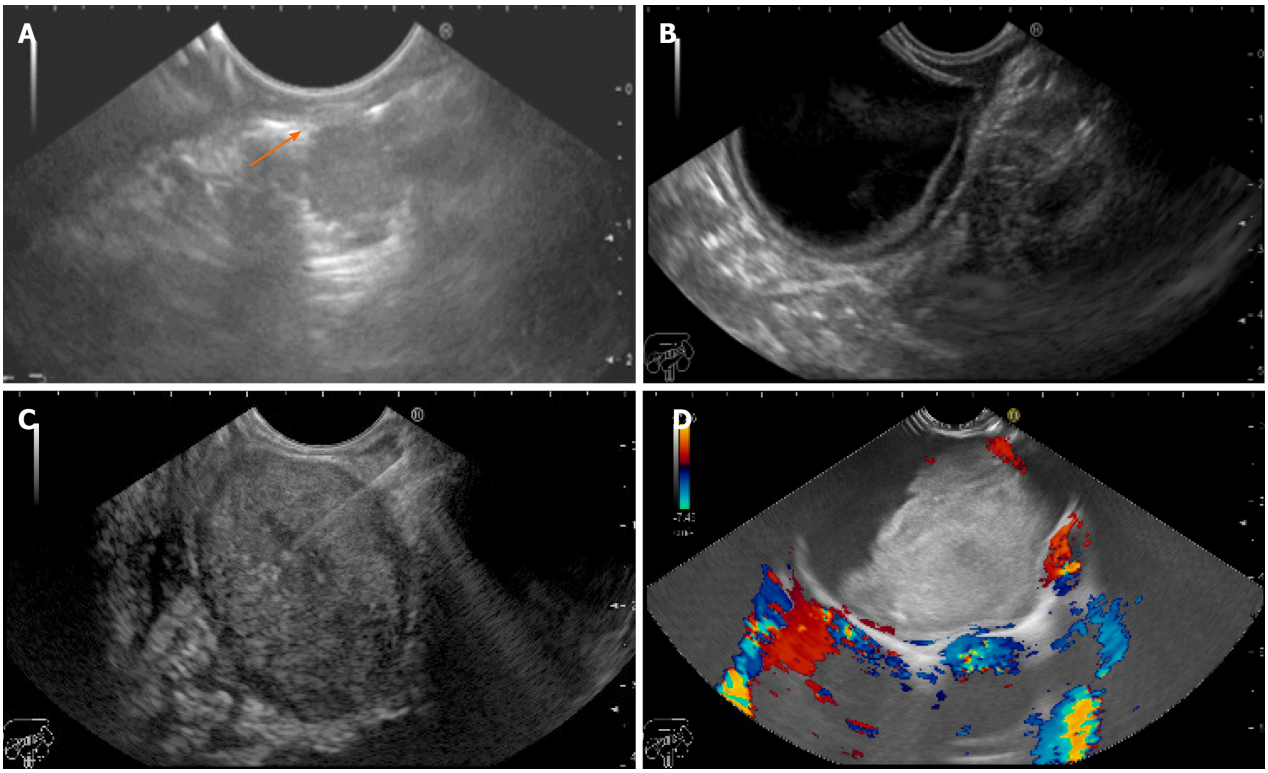

Figure 3 Endoscopic ultrasound. A: Tracheal fibroma separable from the esophageal wall (arrow); B: Antral duplication cyst; C: Rectal gastrointestinal stromal tumor with fine needle aspiration; and D: Mediastinal bronchogenic cyst.

ARTICLE HIGHLIGHTS

Research background

Although endoscopic ultrasound (EUS) is now widely available and has an established role in adults, the utility of EUS and EUS-guided fine needle aspiration (EUS-FNA) in pediatrics is insufficiently described compared to adults and is only supported by a few studies.

Research motivation

More effort is necessary to increase the awareness of EUS among pediatric gastroenterologists, as it may have a clinical impact on the subsequent management and minimize unnecessary procedures in children.

Research objectives

The aim of this study was to report the experience of a single tertiary center in the use of EUS and EUS-FNA in a pediatric population and to further assess its safety, feasibility, and clinical impact on the subsequent management.

Research methods

This was a retrospective study. The patient's medical records were reviewed for standard data which included patient demographics, initial diagnosis, previous abdominal ultrasound, computed tomography, or magnetic resonance imaging, EUS indications, EUS findings, impact of EUS on the patient's clinical care, and adverse events.

Research results

During the 4-year study period, a total of 13 (1.7%) pediatric EUS examinations out of 749 EUS procedures were performed in our unit. The mean age of the 8 females and 5 males was 15.6 years (range: 6-18). Most of EUS examinations were pancreatobiliary. Overall, EUS-FNA was performed in 7 patients (53.8%) with a diagnostic yield of 100%. EUS had a significant impact on clinical care in 10/13 (77%) cases. No complications occurred in our patients during or after any of the procedures.

Research conclusions

EUS and EUS-FNA in the pediatric population are safe, feasible, and have a significant clinical impact on subsequent management; thus avoiding more invasive and additional unnecessary procedures.

Research perspectives

EUS utilization in pediatrics although rare, is expected to increase in the future. Dedicated EUS programs in high volume tertiary centers can ensure that the correct indications are followed, with a high impact on patient management and safety of procedures in the pediatric population.

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ORIGINAL ARTICLE

Observational Study

Defining the advantages and exposing the limitations of endoscopic variceal ligation in controlling acute bleeding and achieving complete variceal eradication

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Author contributions: Krige J, Jonas E and Kotze U devised the study concept and design; Krige J, Kotze U were involved in acquisition of data; Krige J, Jonas E, Kotze U, Kloppers C, Gandhi K, Allam H, Bernon M and Burmeister S analyzed and interpreted the data; Krige J, Jonas E and Kotze U drafted the manuscript; Krige J, Jonas E, Kotze U, Kloppers C, Gandhi K, Allam H, Bernon M, Burmeister S and Setshedi M critically revised the manuscript for important intellectual content; Krige J, Kotze U and Setshedi M carried out the statistical analysis; Krige J and Jonas E provided final approval of the article.

Institutional review board statement: This study was approved by the Human Research Ethics Committee University of

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Abstract

BACKGROUND

Bleeding esophageal varices (BEV) is a potentially life-threatening complication in patients with portal hypertension with mortality rates as high as 25% within six weeks of the index variceal bleed. After control of the initial bleeding episode patients should enter a long-term surveillance program with endoscopic intervention combined with non-selective β-blockers to prevent further bleeding and eradicate EV.

AIM

To assess the efficacy of endoscopic variceal ligation (EVL) in controlling acute variceal bleeding, preventing variceal recurrence and rebleeding and achieving complete eradication of esophageal varices (EV) in patients who present with BEV.

METHODS

A prospectively documented single-center database was used to retrospectively identify all patients with BEV who were treated with EVL between 2000 and 2018. Control of acute bleeding, variceal recurrence, rebleeding, eradication and survival were analyzed using Baveno assessment criteria.

RESULTS

One hundred and forty patients (100 men, 40 women; mean age 50 years; range, 21–84 years; Child-Pugh grade A = 32; B = 48; C = 60) underwent 160 emergency

Cape Town Health Sciences Faculty.

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and 298 elective EVL interventions during a total of 928 endoscopy sessions. One hundred and fourteen (81%) of the 140 patients had variceal bleeding that was effectively controlled during the index banding procedure and never bled again from EV, while 26 (19%) patients had complicated and refractory variceal bleeding. EVL controlled the acute sentinel variceal bleed during the first endoscopic intervention in 134 of 140 patients (95.7%). Six patients required balloon tamponade for control and 4 other patients rebled in hospital. Overall 5-d endoscopic failure to control variceal bleeding was 7.1% (n = 10) and four patients required a salvage transjugular intrahepatic portosystemic shunt. Index admission mortality was 14.2% (n = 20). EV were completely eradicated in 50 of 111 patients (45%) who survived > 3 mo of whom 31 recurred and 3 rebled. Sixteen (13.3%) of 120 surviving patients subsequently had 21 EV rebleeding episodes and 10 patients bled from other sources after discharge from hospital. Overall rebleeding from all sources after 2 years was 21.7% (n = 26). Sixty-nine (49.3%) of the 140 patients died, mainly due to liver failure (n = 46) during follow-up. Cumulative survival for the 140 patients was 71.4% at 1 year, 65% at 3 years, 60% at 5 years and 52.1% at 10 years.

CONCLUSION
EVL was highly effective in controlling the sentinel variceal bleed with an overall 5-day failure to control bleeding of 7.1%. Although repeated EVL achieved complete variceal eradication in less than half of patients with BEV, of whom 62% recurred, there was a significant reduction in subsequent rebleeding.

Key Words: Endoscopy; Variceal ligation; Variceal bleeding; Secondary prophylaxis; Esophageal varices; Variceal recurrence

Core Tip: Control of acute bleeding is crucial in patients with portal hypertension and actively bleeding esophageal varices (BEV). The present study demonstrated that endoscopic variceal ligation (EVL) was highly effective in controlling acute variceal bleeding during the first endoscopic intervention in 95.7% of 140 patients with an overall 5-d failure to control bleeding of 7.1%. Although repeated EVL achieved complete variceal eradication in less than half of patients with BEV, of which 62% recurred, there was a significant reduction in subsequent rebleeding. EVL was effective and safe with a low complication rate in treating BEV.

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INTRODUCTION

Bleeding esophageal varices (BEV) is a potentially life-threatening complication in patients with portal hypertension with mortality rates as high as 25% within six weeks of the index variceal bleed[1]. Although endoscopic intervention provides the optimal emergency method to control actively BEV, the risks of bleeding complications remain substantial and as many as 23% of patients have treatment failure within 5-d due to either uncontrolled or early rebleeding[2]. Approximately 60% of survivors rebleed within two years after the initial bleeding episode with a mortality rate of 30%[3]. Secondary prophylaxis of variceal bleeding is thus crucial and there is a general consensus, supported by the American Association for the Study of Liver Diseases (AASLD), the American Society for Gastrointestinal Endoscopy (ASGE) and the British Society of Gastroenterology (BSG) guidelines that following an initial bleeding episode patients should enter a long-term surveillance program with endoscopic intervention

combined with non-selective β-blockers to pre-empt further bleeding and eradicate EV[1,3-5].

Endoscopic variceal ligation (EVL) has replaced injection sclerotherapy (IST) as the endoscopic interventional procedure of choice for BEV, supported by randomized controlled trial data that show more rapid eradication of varices with lower rates of recurrent bleeding and fewer endoscopic-related complications[6]. However, few studies have specifically evaluated detailed outcomes in relation to the inherent technical constraints of ligating device design which may influence the effectiveness of EVL in controlling acute variceal bleeding and in particular, achieving complete eradication of varices, a problem conceptually more relevant to endoscopic banding than sclerotherapy. This prospective study, based on a protocol-driven standardized EVL technique from a high-volume academic endoscopy referral center, assessed the efficacy of EVL in controlling acute variceal bleeding, preventing early rebleeding and achieving complete and durable variceal eradication to prevent late recurrent bleeding in a cohort of patients who presented with an index variceal bleeding event.

MATERIALS AND METHODS

Patients and methods

Consecutive adult patients with endoscopically proven BEV admitted to a specialist surgical gastroenterology unit with a particular interest in portal hypertension in Groote Schuur Hospital, Cape Town between January 2000 and December 2018 were assessed. Patients who had received sclerotherapy or had endoscopic treatment initiated elsewhere were excluded. The outcome of all endoscopic treatments, both emergency and subsequent elective therapy, was analyzed to assess the efficacy of EVL in acute variceal bleeding control and achieving complete and lasting variceal eradication. The study was a monocentric retrospective analysis following STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statements of all patients. After approval from the institutional Human Research and Ethics Committee, the unit database was searched and filtered for adult patients with endoscopically proven BEV who received EVL as the endoscopic method of treatment.

Data extraction

All data were entered prospectively into a bespoke computer programme by a dedicated research and data manager. Data collected included demographic and clinical information, cause of portal hypertension, Child–Pugh score, hematology and liver function tests, liver biopsy, imaging results, endoscopy information, including variceal size, number of bands placed at each session, the interval between and the number of banding sessions. Outcome data included the efficacy of EVL in controlling the acute index bleed, preventing early rebleeding, achieving complete variceal eradication, minimizing late recurrent bleeding and overall survival. Data were analyzed on January 30, 2020.

Study endpoints

The primary endpoints of the study were (1) effective endoscopic control of the index variceal bleeding event; and (2) success in achieving complete variceal eradication as defined in the analysis criteria. Secondary endpoints included (1) early rebleeding; (2) variceal recurrence and rebleeding; and (3) overall survival.

Acute bleeding management and technique of variceal ligation

Details of the acute bleeding management protocol in our unit have been published previously[7-9]. As soon as the patient was stable, diagnostic endoscopy and EVL were performed[10,11]. Endoscopic banding devices used during the study period included the Saeed Multi-band Ligator (Cook Endoscopy, Winston-Salem, NC, USA), and the Speedband Superview Super 7 Multiple Band Ligator (Boston Scientific Corp., Natick, MA, USA)[11]. Full details of the variceal ligation technique used have been published previously[12-14]. During endoscopy for the sentinel bleed and subsequent bleeds, a band was applied first to the bleeding varix and then proximally in a helical fashion for approximately 10 cm to the remaining varices. In patients in whom bleeding could not be controlled a Sengstaken-Blakemore or Minnesota balloon tube was inserted for immediate tamponade and further endoscopic procedures were performed within 24 h. When endoscopic measures failed transjugular intrahepatic portosystemic shunt (TIPS) was used as rescue treatment.

Patients underwent regular EVL until complete variceal eradication, defined as the absence of varices, was achieved. In a subcategory of patients who had residual varices which were too small or insufficiently pliable to be suctioned into the banding device to allow secure and safe band deployment, complete eradication was not pursued. After the initial EVL session during the index admission to hospital, subsequent variceal ligation procedures were undertaken at two-week intervals as an outpatient until the varices were eradicated or unsuitable for continued ligation. Surveillance endoscopy was performed at 3 and 6 monthly intervals and then annually to identify recurrence or persistent varices and repeat EVL performed whenever technically feasible. All patients were given non-selective β–blockers (NSBB) during follow-up unless specifically contra-indicated.

Rebleeding

Baveno criteria were used to define 5-d and 6 wk failure to control bleeding[5]. Additional variceal ligation was undertaken if bleeding was due to residual or recurrent varices. Other sources of bleeding, such as gastric varices, portal hypertensive gastropathy, peptic ulcers or erosive gastritis were included in the definition of rebleeding and treated on their merits.

Statistical analysis

The Student *t*-test and χ^2 test were used when appropriate and the Kaplan–Meier method was used to estimate the cumulative incidence of re-bleeding and actuarial survival. Multivariate analysis was used to assess risk factors for rebleeding. A P value < 0.05 was considered significant. SAS System Package version 9.2.1 software (SAS Systems International, Cary, NC, USA) was used for statistical analysis. Data were censored at the time of the last clinic or endoscopy visit, TIPS placement or death. Ethical and institutional review board approval (HREC 120/2019) was obtained before study initiation and data analysis.

RESULTS

The 140 patients (100 men, 40 women, median age: 50 years; range: 21-84 years) included 32 Child-Pugh grade A, 48 grade B and 60 grade C patients when assessed on first admission to hospital (Table 1). The underlying diagnoses were alcoholic cirrhosis n = 75 (53.6%), hepatitis B infection n = 13 (9.9%), cryptogenic cirrhosis n = 13 (9.9%), hepatitis and alcohol n = 9 (6.4%), non-alcoholic fatty liver disease n = 8 (5.7%), schistosomiasis n = 7 (5%), and portal vein thrombosis n = 5 (3.6%). The remaining ten patients had autoimmune hepatitis (n = 3), hepatitis C (n = 2), and one each of granulomatous hepatitis, myelofibrosis, Budd-Chiari syndrome, chronic active hepatitis and primary sclerosing cholangitis. The 140 patients received 160 emergency and 298 elective EVL procedures during a total of 928 endoscopy sessions.

Control of bleeding during the index endoscopic procedure

Acute bleeding was successfully controlled by EVL in 134 of 140 patients (95.7%) during the index endoscopic procedure (Figure 1). A balloon tube was used in six patients in whom acute bleeding could not be controlled by EVL, and a further four patients rebled within 5-d, resulting in a cumulative 5-d failure to control bleeding of 7.1% (n = 10; Child-Pugh grade A n = 0, grade B n = 1, grade C n = 9). These ten patients required 11 additional endoscopic banding sessions and four patients with recalcitrant variceal bleeding required a salvage TIPS.

Index admission mortality

The index in-hospital admission mortality was 14.2% (n = 20) with a median survival of 8 d (range 1-44). Ten patients died of multi-organ failure (MOF) including two of the four patients who had a salvage TIPS. A further seven patients died of progressive liver failure, another as a result of advanced hepatocellular carcinoma and two elderly patients with vasculopathy died of a myocardial infarction. The index admission mortality for the 32 Child-Pugh grade A patients was 0, for the 48 Child-Pugh grade B patients was 2.1% and for the 60 Child-Pugh grade C patients was 31.7% (19 of 60 patients).

Rebleeding after index admission

Overall, 26 (21.7%) of the 120 surviving patients had 31 recurrent bleeding episodes

Table 1 Number of banding procedures and time to eradication of varices

Child-Pugh grade	Number of patients	Survival > 90 d	Number eradicated	Number of banding procedures median (range)	Months to eradicate median (range)	Number recurred
A	*n* = 32	32	15	3 (1-13)	15 (1-55)	9
B	*n* = 48	44	18	2 (1-12)	4 (1-29)	12
C	*n* = 60	35	17	2 (1-5)	3 (1-47)	10
Total	*n* = 140	111	50	2 (1-13)	5 (1-55)	13

after discharge from hospital. Two of these patients survived less than 3 mo (Figure 1). Sixteen patients had 21 EV rebleeding episodes which were successfully treated with emergency EVL. The 6-mo EV specific rebleeding incidence was 8.3% (*n* = 10 patients), at 12 mo was 12.5% (*n* = 15), at 2 years was 12.5% (*n* = 15) and beyond 2 years the total cumulative rebleeding rate after initial index control was 13.3% (*n* = 16). The remaining ten patients had bleeding from other sources which included gastric varices (*n* = 3), gastric ulcers (*n* = 4), duodenal ulcer (*n* = 1), esophagitis (*n* = 1), and Mallory Weiss tear (*n* = 1). The 6-mo overall all sources rebleeding incidence was 13.3% (*n* = 16 patients), at 12 mo was 17.5% (*n* = 21), at 2 years was 20.8% (*n* = 25) and beyond 2 years the total cumulative rebleeding rate after initial index control was 21.7% (*n* = 26, Table 2).

Eradication of varices

Eradication was achieved in 50 of 111 patients (45%) who survived longer than 3 mo, after a median of 2 banding procedures (range 1-13), during a median of 6 mo, (range 0.5-55 mo) (Table 1). EV remained eradicated in 19 (Child-Pugh grade A *n* = 6, grade B *n* = 6, grade C *n* = 7) patients with a median follow-up from eradication of 25 mo (range 4-112 mo) (Figure 1). Seven of the 19 patients died after a median survival of 44 mo (range 4-112 mo).

Recurrent bleeding after variceal eradication

Three of the 31 patients with recurrent EV after eradication presented with variceal rebleeding at 3, 4 and 25 mo, respectively, and were successfully treated with EVL.

Varices not eradicated

The 61 patients whose EV were not eradicated had a total of 224 banding procedures (median 5 banding procedures, range 1-11) during a mean of 25 mo (Figure 1). Twenty three of the 61 patients died (18 due to progressive liver failure, 3 with MOF aggravated by recurrent BEV and 2 due to hepatorenal failure) at a median of 23 mo (range 3-103 mo). The remaining 38 patients were followed up for a median of 6 mo (range 0.5-99 mo). In 41 patients who had at least 4 banding sessions, EV reduced in size to either grade 1 (*n* = 25) or grade 2 (*n* = 16) none of whom rebled despite no further EVL. This group in whom EVL was not technically possible was regarded as having "functional eradication" as results were comparable to those with complete eradication.

Esophageal complications

Esophageal stricture at the banding site was noted in 16 patients during a follow-up endoscopy, none of whom required esophageal dilatation for relief of symptoms and resolved after passage of the endoscope.

Survival analysis

During a median follow-up period of 42 mo (range 9-220 mo), 69 (49.3%) of the 140 patients died (mean: 6.7 mo, range 0.03-141.7 mo). Liver failure (*n* = 46) was the most common cause of death followed by MOF in 14 patients. The cumulative overall survival of all 140 patients by life table analysis was 71.4% at 1 year, 65% at 3 years, 60% at 5 years and 52.1% at 10 years. Overall survival according to Child-Pugh grading is presented in Table 3. No significant specific risk factors for rebleeding were evident on multivariate analysis (Table 4).

Table 2 Rebleeding after index admission in 120 surviving patients

	Overall bleeding from all sources		Bleeding from esophageal varices	
	Patients	Bleeding events	Patients	Bleeding events
< 6 mo	16 (13.3%)	22	10 (8.3%)	16
6-12 mo	21 (17.5%)	28	15 (12.5%)	20
1-2 yr	25 (20.8%)	30	15 (12.5%)	20
> 2 yr	26 (21.7%)	31	16 (13.3%)	21
Overall	26 (21.7%)	31	16 (13.3%)	21

Table 3 Cumulative survival by Child-Pugh grade, *n* (%)

Child-Pugh Grade	Number of patients	1-yr survival	3-yr survival	5-yr survival	10-yr survival
A	*n* = 32	30 (93.7)	29 (90.6)	29 (90.6)	25 (78.1)
B	*n* = 48	40 (83.3)	36(75)	34 (70.8)	31 (64.5)
C	*n* = 60	30 (50)	26 (43.3)	21 (35)	17 (28.3)

Table 4 Specific risk factors for rebleeding on multivariate analysis

	Total, *n* = 140	No rebleeding, *n* = 104	Rebleeding, *n* = 36	*P* value
Age				0.149
20-39 yr	36	30	6	
40-59 yr	74	50	24	
> 60 yr	30	24	6	
Gender				0.112
Male	100	78	22	
Female	40	26	14	
Child-Pugh grade				0.965
A	32	24	8	
B	48	35	13	
C	60	45	15	
Cause of varices				0.343
Alcoholic	84	60	24	
Non-Alcoholic	56	44	12	

DISCUSSION

In this prospective study the efficacy of EVL was evaluated in a large cohort of consecutive portal hypertensive patients treated at a specialist endoscopy referral center using specific and validated endpoints including control of the initial bleeding event and subsequent variceal eradication, rebleeding and recurrence. Acute control of active variceal bleeding was highly successful and hemostasis was achieved in 95.7% of patients with minimal banding morbidity. However, varices were completely eradicated in only 45% of patients who survived more than 3 mo. Furthermore, varices recurred in 62% of patients previously eradicated and 9.7% of these had further variceal bleeding. Overall, 81% of patients in this study had bleeding that was effectively controlled during the index banding procedure and, after repeat banding, never bled again from esophageal varices. However, the remaining 19% of the cohort had refractory and complicated variceal bleeding and required either balloon tamponade during the index endoscopy (4%) or rebled during the initial

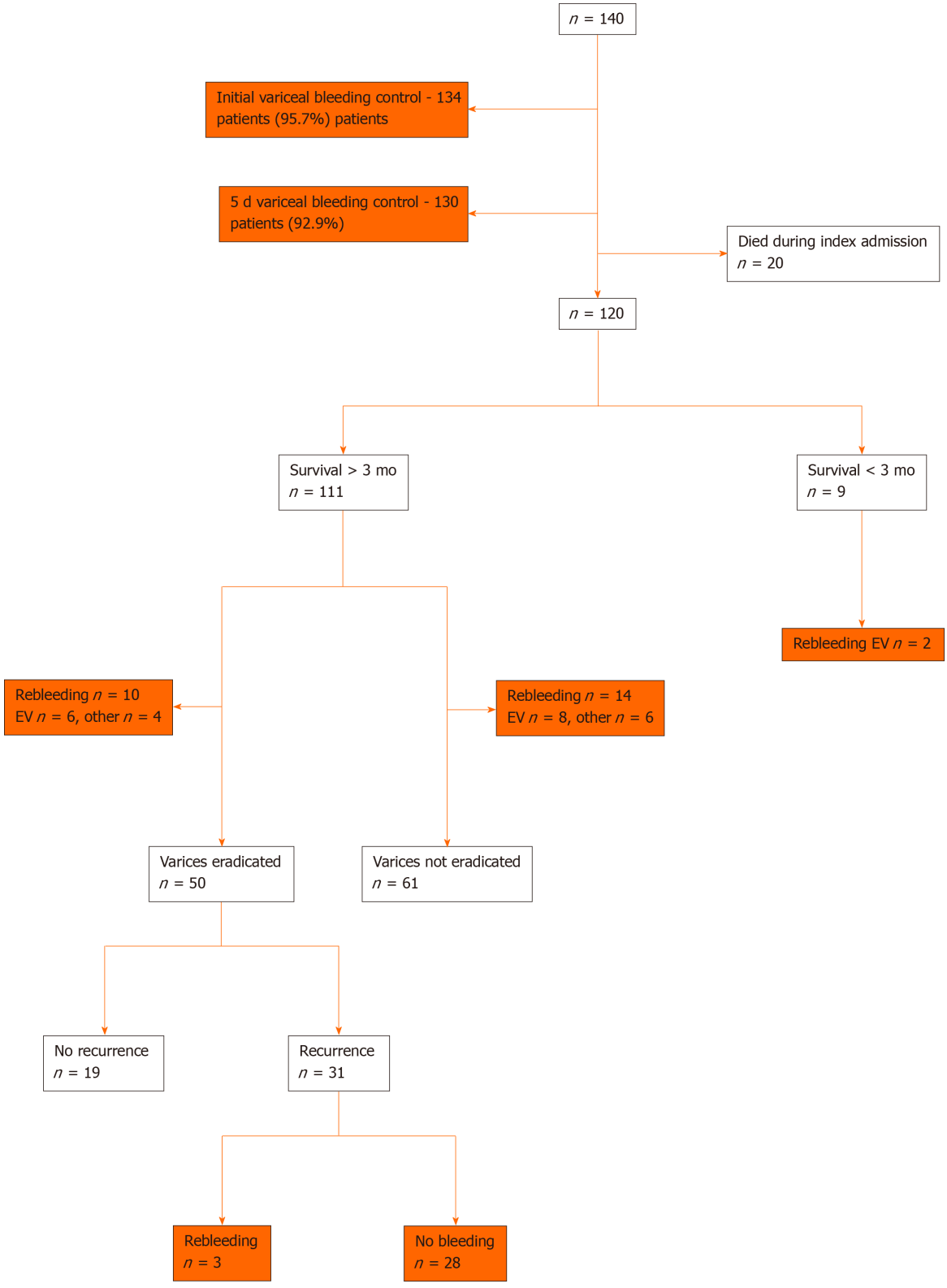

Figure 1 Flow diagram showing outcome after the first variceal bleed in 140 patients treated by emergency endoscopic variceal ligation.
EV: Esophageal varices.

hospitalization (3%) or rebled subsequently (12%) over the next 24 mo from residual or recurrent esophageal varices. As EVL is now universally regarded as the endoscopic method of choice for treating EV[6] the data in this study are relevant and pertinent to current endoscopic variceal management and emphasize several important and unresolved issues related to the role of EVL in achieving hemostasis in actively bleeding varices and variceal eradication to prevent rebleeding[1-4].

Experts agree that EVL requires a high level of manipulative skill and mature

judgement, especially when applying bands during active variceal bleeding[15]. Despite initial scepticism and concerns that EVL would prove less effective than sclerotherapy in achieving control of actively bleeding varices as blood or clot filling the cap during profuse bleeding may obscure vision and limit accurate band deployment, there were very few failures of acute hemostasis in this study. In three small non-randomized studies by El-Saify[16], Saeed[17] and Hou[18], active variceal bleeding control was reported in 100% of patients. Patient numbers in these studies, however, were small and there was no consistency in the definition of duration of control of active bleeding. In an updated analysis of 17 prospective randomized controlled trials (RCTs) comparing EVL with sclerotherapy, bleeding variceal control with EVL ranged from 86% to 100%, and was significantly better than IST in 2[19,20] of 17 RCTs[21-35] (Table 4). However, the reported efficacy of EVL in these RCTs varied widely due to arbitrary and inconsistent definitions of bleeding control[19].

The incidence of variceal rebleeding after EVL in RCTs ranges from 0% to 36% (Table 4). In a meta-analysis[6] of 14 RCTs, the overall rebleeding rate for EVL patients was 21.7% compared to an earlier analysis of RCTs which showed a median rebleeding rate of 32%[36]. However, the calculations and denominators in many papers are not clearly defined and lack adherence to uniform standard definitions of rebleeding including time periods, whether overall or confined to variceal bleeding, or uncontrolled, or during the first admission or during long-term follow-up. In addition, there is non-uniformity among different trials in the definition of recurrent bleeding which may include esophageal, gastric and ectopic varices and non-variceal sources (portal hypertensive gastropathy, treatment-induced or peptic ulcer)[25,26]. In our study we defined these criteria and analyzed the three specific and crucial time periods. The most common source of recurrent bleeding in our patient cohort during the early phase after initiation of endoscopic therapy and before variceal eradication was from patent residual varices which occurred in two-thirds of bleeding episodes, while one-third rebled from other sources.

Current AASLD/ACG guidelines emphasize total eradication of all varices as the desired endpoint of EVL[1]. Similarly, the reported incidence of variceal eradication varies widely, ranging from a high of 95% to a low of 55% in RCTs (Table 5). A plausible explanation is that inconsistent definitions were used and in some reports the definition of variceal eradication included varices too small to be ligated. The wide variation in eradication rates may also be related to different treatment protocols such as different treatment intervals, number of bands applied per session and selective banding of EV in some centers which band only grade 3–4 EV[26,27]. Ultimately, the results of any long-term banding study are influenced by the diligence and regularity of follow-up endoscopy and the meticulousness and reproducibility of the methodology, and the accuracy with which residual variceal size is recorded. There is increasing recognition that two important limitations of long-term EVL are the number of varices that are resistant to complete eradication and the substantial variceal recurrence rate after eradication. Both limitations are influenced by the design and mechanism of ligation. Experienced endoscopists know that EVL becomes increasingly difficult as varices decrease in size[15,37]. Small varices are difficult to ligate effectively for two technical reasons. Grade I and 2 varices do not have sufficient variceal substance to provide purchase and grip for the constricting elastic band. In addition, mucosal fibrosis due to prior banding episodes further limits mucosal pliability and the ability to suck enough tissue into the cap, thus preventing successful band application. Of note are the number of RCTs which report higher variceal recurrence rates in patients undergoing EVL (Table 5).

The number of endoscopy sessions required to achieve variceal eradication has varied considerably within reported series and between centers (Table 5). A number of studies, including a meta-analysis by Ko *et al*[18,38-42] indicated that EVL achieved variceal eradication rates between 79% and 100%. While there is some evidence to suggest that the methodology and technique of EVL might affect the number of sessions necessary to achieve obliteration, this alone does not explain the substantial differences found between patients. Furthermore, the reproducibility, method and accuracy with which residual variceal size is recorded is dependent on the degree of insufflation used during endoscopy as prolonged or over-inflation during endoscopy tends to flatten varices which then appear misleadingly small.

A major drawback of EVL is the higher propensity to variceal recurrence when compared to IST in RCTs (Table 5). Although new varices formed following initial eradication in 31 of 50 (62%) patients in our study, this was associated with rebleeding in only 3 (9.7%) patients. Variceal recurrence in other studies ranged between 8% and 48% after banding[18,35,42]. More recent studies have shown recurrence rates of 12% to 36% (mean 25%) using EVL and NSBB[26-28,30]. Interpretation of these results is

Table 5 Updated summary of published randomized controlled trials of endoscopic variceal ligation *vs* injection sclerotherapy

Ref.	Year	Number of patients	Number in each group		Control of bleeding		Varices eradicated		Eradication sessions		Rebleeding		Major complications		Variceal recurrence		Survival	
			EVL	IST	EVL	IST	EVL	IST	EVL	IST	EVL	IST	EVL	IST	EVL	IST	EVL	IST
Stiegmann *et al*[21]	1992	129	64	65	86%	77%	55%	56%	4	5	36%	48%	2%	22%	33%	50%	72%	55%
Laine *et al*[22]	1993	77	38	39	89%	89%	59%	69%	4.1	6.2	24%	31%	24%	56%	-	-	89%	85%
Gimson *et al*[23]	1993	103	54	49	91%	92%	82%	71%	3.4	4.9	30%	53%	69%	65%	-	-	52%	18%
Lo *et al*[24]	1995	120	61	59	94%	80%	74%	63%	3.8	6.5	11%	36%	3.3%	19%	-	-	84%	68%
Hou *et al*[25]	1995	134	67	67	100%	88%	87%	79%	3.5	4.6	18%	33%	4%	22%	48%	30%	79%	84%
Sarin *et al*[26]	1997	95	47	48	86%	80%	94%	94%	4.1	5.2	6.4%	20.8%	45%	50%	28.7%	7.5%	93%	89%
Baroncini *et al*[27]	1997	111	57	54	-	-	93%	93%	3.5	4.0	16%	19%	11%	31%	30%	13%	79%	78%
Avgerinos *et al*[28]	1997	77	37	40	-	-	95%	98%	3.7	5.8	27%	48%	35%	60%	31%	44%	80%	79%
Lo *et al*[19]	1997	71	37	34	97%	76%	-	-	-	-	17%	33%	5%	29%	-	-	81%	65%
Siqueira *et al*[29]	1998	40	20	20	-	-	90%	100%	3.1	3.7	0%	5%	-	-	0%	0%	100%	95%
De la Pena *et al*[30]	1999	88	42	46	-	-	79%	71%	5.3	6.6	31%	50%	14%	41%	47%	23%	81%	78%
Masci *et al*[31]	1999	100	50	50	-	-	88%	82%	3.4	5.3	12%	42%	18%	38%	32%	27%	80%	78%
Fakhry *et al*[32]	2000	84	43	41	94%	94%	-	-	2.8	4.8	16%	15%	2%	65%	21%	20%	93%	93%
Zargar *et al*[33]	2005	73	37	36	100%	83%	95%	92%	3.7	7.7	3%	19%	3%	22%	11%	9%	-	-
Villanueva *et al*[20]	2006	179	90	89	96%	85%	-	-	-	-	7%	12%	4%	13%	-	-	87%	79%
Luz *et al*[34]	2011	100	50	50	92%	96%	-	-	-	-	22%	14%	-	-	-	-	77%	80%
Ali *et al*[35]	2017	124	60	64	100%	100%	87%	80%	-	-	23%	28%	10%	27%	-	-	78%	72%

EVL: Endoscopic variceal ligation; IST: Injection sclerotherapy. Bold color highlighted comparisons are significant, $P < 0.05$.

complicated by the differences in length of follow up, definitions of variceal recurrence, different medications and dosage used and the etiology of portal hypertension. Accumulated evidence suggests that patent para-esophageal and peri-esophageal variceal feeder vessels predispose to variceal recurrence. Data from RCTs show lower recurrence rates after IST, probably because sclerotherapy induces fibrosis and eradication of perforating veins in contrast to band ligation, which does not affect collateral vessels in the deeper esophageal wall layers[18,42].

The current study has several limitations. Firstly, as the study was conducted in a single center academic tertiary referral hospital with experienced on-call endoscopists

and staff available around the clock, patient selection and treatment bias may occur as similar advanced interventions may not be available or replicated in smaller hospitals. Secondly, half the patients in the study were Child-Pugh grade C with hepatic decompensation associated with the highest mortality and our results cannot be generalized to all other patient populations. The use of an inclusive "all-cause" definition for rebleeding was applied to minimize bias found in previous definitions which often excluded non-variceal causes of re-bleeding.

The strengths of this study are derived from the implementation of a modern protocol-driven and standardized EVL technique in a specialist endoscopy center. In order to provide the highest possible level of uniformity and to minimize differences in the zero-time entry, only patients who received their initial and subsequent treatment in our unit were included. The study design minimized possible biases that may arise from patient selection, referral practices and local variations in treatment strategies. The use of rebleeding and death as the main outcomes provided robust, consistent and objective end-points in the study. Unlike other studies which included non-consecutive patients, incomplete reporting of inclusion and exclusion criteria and have incomplete follow-up or inclusion of patients at differing disease stages without separate analyses, our study design avoided these pitfalls by excluding non-measurable biases.

CONCLUSION

In conclusion, this study confirms that EVL provides the optimal endoscopic method both for control of acute bleeding and for the long-term treatment of varices despite the higher tendency for recurrence. Consistent with previous reports, EVL in this study was safe with low procedure-related complication rates. While complete visual eradication of varices is more frequently achievable with IST and has consistently been used as the desired endpoint for endoscopic variceal intervention, this goal is not always attainable in EVL. As alluded to above, the inherent attributes of EVL and IST are dissimilar and complete eradication may not be achievable in all patients undergoing EVL. Overall four-fifths of patients in this study had EV that were easily managed and responded to β-blockers and EVL with no further bleeding after the initial index intervention. However, the remaining one-fifth of patients were complicated and had bleeding that was difficult to control in the short and long-term despite being on combination therapy. We have identified a subgroup of patients with small (Grade 1 and 2) varices where size and mucosal scarring preclude further safe banding. Importantly we have shown that these patients have "stable varices" with no rebleeding or progression which resulted in "functional eradication" despite the presence of residual small visible varices. The results of this study should stimulate further research to optimize robust and objective endpoints for reporting of EVL which are likely to differ from the historical outcomes reported in previous RCTs. The elusive Holy Grail of endoscopic variceal banding remains the attainment of long-term bleed-free survival.

ARTICLE HIGHLIGHTS

Research background

Bleeding esophageal varices (BEV) is a potentially life-threatening complication in patients with portal hypertension with mortality rates as high as 25% within six weeks of the index variceal bleed. Although endoscopic intervention provides the optimal emergency method to control actively BEV, the risks of bleeding complications remain substantial and as many as 23% of patients have treatment failure within 5-d due to either uncontrolled or early rebleeding. Approximately 60% of survivors rebleed within two years after the initial bleeding episode with a mortality rate of 30%. Secondary prophylaxis to prevent further variceal bleeding is thus crucial.

Research motivation

Endoscopic variceal ligation (EVL) has replaced injection sclerotherapy (IST) as the endoscopic interventional procedure of choice for BEV, supported by randomized controlled trial data that show more rapid eradication of varices with lower rates of recurrent bleeding and fewer endoscopic-related complications. However, few studies have specifically evaluated detailed outcomes in relation to the inherent technical

constraints of ligating device design which may influence the effectiveness of EVL in controlling acute variceal bleeding and in particular, achieving complete eradication of varices, a problem conceptually more relevant to endoscopic banding than sclerotherapy.

Research objectives

This analysis, based on a protocol-driven standardized EVL technique from a high-volume academic endoscopy referral center, used STROBE guidelines to assess the efficacy of EVL in controlling acute variceal bleeding, preventing early rebleeding and achieving complete and durable variceal eradication to prevent late recurrent bleeding in a cohort of patients who presented with an index variceal bleeding event.

Research methods

Consecutive adult patients with endoscopically proven BEV between January 2000 and December 2018 were assessed. The outcome of all endoscopic treatments, both emergency and subsequent elective therapy, was analyzed to assess the efficacy of EVL in acute variceal bleeding control and achieving complete and lasting variceal eradication. Data collected included demographic and clinical information, cause of portal hypertension, Child–Pugh score, hematology and liver function tests, liver biopsy, imaging results, endoscopy information, including variceal size, number of bands placed at each session, the interval between and the number of banding sessions. Outcome data included the efficacy of EVL in controlling the acute index bleed, preventing early rebleeding, achieving complete variceal eradication, minimizing late recurrent bleeding and overall survival. The primary endpoints of the study were (1) effective endoscopic control of the index variceal bleeding event and (2) success in achieving complete variceal eradication as defined in the analysis criteria. Secondary endpoints included (1) early rebleeding; (2) variceal recurrence and rebleeding and (3) overall survival.

Research results

Acute control of active variceal bleeding in the 140 patients was highly successful and hemostasis was achieved in 95.7% of patients with minimal banding morbidity. However, varices were completely eradicated in only 45% of patients who survived more than 3 months. Furthermore, varices recurred in 62% of patients previously eradicated and 9.7% of these had further variceal bleeding. Overall, 81% of patients in this study had bleeding that was effectively controlled during the index banding procedure and, after repeat banding, never bled again from esophageal varices. However, the remaining 19% of the cohort had refractory and complicated variceal bleeding and required either balloon tamponade during the index endoscopy (4%) or rebled during the initial hospitalization (3%) or rebled subsequently (12%) over the next 24 months from residual or recurrent esophageal varices.

Research conclusions

In conclusion, this study confirms that EVL provides the optimal endoscopic method both for control of acute bleeding and for the long-term treatment of varices despite the higher tendency for recurrence. Consistent with previous reports EVL in this study was safe with low procedure-related complication rates. While complete visual eradication of varices is more frequently achievable with IST and has consistently been used as the desired endpoint for endoscopic variceal intervention, this goal is not always attainable in EVL.

Research perspectives

In this study we have identified a subgroup of patients with small varices where size and mucosal scarring preclude further safe banding. Importantly we have shown that these patients have "stable varices" with no rebleeding or progression which resulted in "functional eradication" despite the presence of residual small visible varices. The results of this study should stimulate further research to optimize robust and objective endpoints for reporting of EVL which are likely to differ from the historical outcomes reported in previous randomized controlled trials. The elusive Holy Grail of endoscopic variceal banding remains the attainment of long-term bleed-free survival.

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ORIGINAL ARTICLE

Observational Study

Predictor of respiratory disturbances during gastric endoscopic submucosal dissection under deep sedation

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Abstract

BACKGROUND

Sedation is commonly performed for the endoscopic submucosal dissection (ESD) of early gastric cancer. Severe hypoxemia occasionally occurs due to the respiratory depression during sedation.

AIM

To establish predictive models for respiratory depression during sedation for ESD.

METHODS

Thirty-five adult patients undergoing sedation using propofol and pentazocine for gastric ESDs participated in this prospective observational study. Preoperatively, a portable sleep monitor and STOP questionnaires, which are the established screening tools for sleep apnea syndrome, were utilized. Respiration during sedation was assessed by a standard polysomnography technique including the pulse oximeter, nasal pressure sensor, nasal thermistor sensor, and chest and abdominal respiratory motion sensors. The apnea-hypopnea index (AHI) was obtained using a preoperative portable sleep monitor and polysomnography during ESD. A predictive model for the AHI during sedation

2014.

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

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was developed using either the preoperative AHI or STOP questionnaire score.

RESULTS

All ESDs were completed successfully and without complications. Seventeen patients (49%) had a preoperative AHI greater than 5/h. The intraoperative AHI was significantly greater than the preoperative AHI (12.8 ± 7.6 events/h *vs* 9.35 ± 11.0 events/h, $P = 0.049$). Among the potential predictive variables, age, body mass index, STOP questionnaire score, and preoperative AHI were significantly correlated with AHI during sedation. Multiple linear regression analysis determined either STOP questionnaire score or preoperative AHI as independent predictors for intraoperative AHI ≥ 30/h (area under the curve [AUC]: 0.707 and 0.833, respectively) and AHI between 15 and 30/h (AUC: 0.761 and 0.778, respectively).

CONCLUSION

The cost-effective STOP questionnaire shows performance for predicting abnormal breathing during sedation for ESD that was equivalent to that of preoperative portable sleep monitoring.

Key Words: Deep sedation; Respiratory depression; Polysomnography; Endoscopic submucosal dissection; Sleep apnea syndrome; STOP questionnaire

Core Tip: Risk factors for sedation during endoscopic submucosal dissection (ESD) have not been systematically explored. Our study demonstrated that the preoperative portable sleep monitor and STOP questionnaire scores accurately predict abnormal breathing during sedation and the cost-effective questionnaire can be clinically used for risk stratification of respiratory depression during ESD, leading to a safe ESD procedure.

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INTRODUCTION

Recently, endoscopic mucosal dissection (ESD) has been widely used to treat early gastric cancer. ESD is a highly difficult and often lengthy surgical procedure[1]. Appropriate sedation improves the quality of treatment and increases patient satisfaction[2-6]. The levels of sedation are divided into several stages, from minimal to deep[7]. The dangers of respiratory and circulatory system failures increase with moderate and deep sedation[8]. Moreover, the occurrence of sedation-related complications in gastrointestinal endoscopy can lead to significant morbidity and occasional mortality in patients[8]. Further, the risks can be high especially for procedures performed outside the operating room, such as the endoscopic laboratory[9]. When administering sedatives, careful attention must be paid to the respiratory status during sedation. Continuous respiratory and oxygen monitoring is critical, which is clearly stated in the guidelines on gastrointestinal endoscopy[10]. However, the required components of monitoring have not been defined yet. Additionally, respiratory monitoring often comprises only oxygen administration and pulse oximetry measurements[11,12]. In our previous study, apnea or hypopnea was not well detected by the pulse oximeter alone; it was proven that polysomnography (PSG), which is usually used for sleep apnea diagnosis, was useful for the accurate detection of abnormal breathing during sedation for ESD[13]. However, the PSG technique is a laborious and costly procedure to be used as a clinical tool for monitoring during sedation. Therefore, the preoperative identification of patients at high risk of intraoperative respiratory depression can help to ensure the optimal environment for practical sedation.

Sleep apnea syndrome (SAS) is an independent factor for postoperative respiratory complications following general anesthesia[14-17]. We previously demonstrated the occurrence of SAS-like respiration disorders during the sedation for ESDs[13].

In this study, we examined whether abnormal breathing is more frequent during sedation than during sleep and aimed to develop a clinically useful prediction model for abnormal breathing during the sedation for ESD.

MATERIALS AND METHODS

Patients

We performed this prospective observational study after obtaining approval from the Institutional Ethics Committee (No. 1902-2014; Graduate School of Medicine, Chiba University, Chiba, Japan). Written informed consent was obtained from each patient. Inclusion criteria was the adult patient during ESD for early gastric cancer under propofol sedation with expected < 2 h. Exclusion criteria were patients with severe heart disease and renal failure, including high aspiration risks and drug allergy to propofol. In total, 35 patients (24 men and 11 women; mean age, 73.2 years) were enrolled between 2014 and 2016.

Patient preparation before ESD

Preoperatively, the patients underwent a portable sleep study during natural sleep and answered the STOP questionnaire. The portable sleep study (PS) was performed using a portable sleep monitor (PSS, SAS-2100; Nihon Kohden, Tokyo, Japan), which measures the airflow *via* a nasal pressure cannula and oxygen saturation (SaO_2). PS data were analyzed using dedicated computer software (QP-021 W; Nihon Kohden). Apnea and hypopnea were determined by absence of airflow for 10 s or more and more than 50% decrease of the nasal pressure signal for 10 s or more independently of SaO_2 change, respectively. The apnea-hypopnea index (AHI) was determined as the frequencies of apneas and hypopneas/hour of monitoring period and the AHI measured by the PS before ESD was considered to be preoperative AHI. The STOP questionnaire was originally designed to preoperatively screen obstructive sleep apnea patients using four yes/no questions including habitual snoring, daytime fatigue/tiredness, observed apnea during sleep, and high blood pressure. The score is based on the number of "yes" answers and ranges from 0 to 4[19]. When two or more questions are answered with "yes," the result is considered positive.

Sedation and polysomnography measurements during ESD

Prior to sedation for the ESD procedure, standard PSG electrodes were attached (PSG-1100; Nihon Kohden), in addition to routine monitors used during gastrointestinal endoscopy including those for pulse oximetry, electrocardiogram, and intermittent blood pressure measurements. Airflow measurements were obtained *via* a nasal pressure cannula and oronasal thermistors. Thoraco-abdominal wall motions with piezo-respiratory effort sensors, SaO_2, and snoring monitored by a microphone were recorded and stored.

Oxygen at the rate of 2 L/min was administered *via* the nasal cannula while the patients were on their left side. Propofol (1-2 mg/kg) was carefully administered until patients lost consciousness and continuously infused at a rate of 1-4 mg/kg per hour to maintain Ramsey scores of 5-6 (loss of responses to verbal commands and light tapping on the shoulder, but arousable by painful stimulation)[18]. Pentazocine (7.5 mg) was intravenously administered for analgesia about every 30 min. Unstable cardiorespiratory abnormalities detected by patient monitors were used for decision making regarding the propofol infusion rates and airway maneuvers to restore breathing.

After the completion of measurements, a certified sleep technician (RK) and investigators manually analyzed the PSG data with using dedicated computer software (Polysmith; Nihon Kohden, Tokyo, Japan). We focused on two sensors: Nasal cannula and oro-nasal thermistor for airflow measurement; and Piezo-respiratory effort sensors (RIP-chest and/or RIP-abdomen) for thoraco-abdominal wall motion assessment. Apneic and hypopneic events were systematically classified based on the presence or absence of thoraco-abdominal respiratory movements and divided into obstructive and central.

Statistical analyses

The values are presented as means and standard deviations for continuous data and numbers of cases and proportions for categorical data. Univariate correlations between the intraoperative AHI and other variables (STOP questionnaire score, dosage of propofol, age, sex, and body mass index [BMI]) were performed using Pearson's correlation analysis; additionally, the results were presented using coefficients and *P* values. Two multiple linear regression analysis models: Model 1, multiple linear regression analysis explaining the intraoperative AHI (objective variable) with all potential explanatory variables except for the STOP questionnaire score; model 2, multiple linear regression analysis explaining the intraoperative AHI (objective variable) with all explanatory variables except for preoperative AHI. We calculated the cutoff values for the pre-AHI and STOP questionnaire scores. By setting the threshold values for intraoperative AHI ≥ 30/h (severe SAS) and AHI ≥ 15 and < 30/h (moderate SAS), we converted each variable into a binary outcome. We performed logistic regression analysis using binary data as objective variables and preoperative AHI and STOP questionnaire scores as exploratory variables, deriving cutoff values for each. We plotted receiver operating characteristic curves, calculated sensitivities and specificities, and determined Youden's Indexes. We calculated areas under the curves (AUCs) for preoperative AHI and STOP questionnaire scores to evaluate the predictive abilities of the cutoff values. We also calculated *P* values for the difference between the AUCs. *P* value < 5% was considered statistically significant. SAS Version 9.4 (SAS Institute; Cary, NC, United States) was used for all statistical analyses.

RESULTS

The patient background data are shown in Table 1. All procedures were performed successfully and no patient required treatment discontinuation. The average age of the patients was 73.2 years (24 men and 11 women). There were 3 patients with mild respiratory comorbidity, none of which had subjective symptoms. Fourteen patients (45.1%) were suspected to have SAS (total scores ≥ 2) using the STOP questionnaire. Seventeen patients (48.6%) were diagnosed preoperatively with SAS (preoperative AHI ≥ 5) with the aid of PS. Among those, 6 patients (35.3%) had moderate SAS (preoperative AHI ≥ 15 and < 30) and 2 patients (11.8%) had severe SAS (preoperative AHI ≥ 30). The mean preoperative AHI was 9.25 ± 11.03/h. The average intraoperative AHI was 12.76 ± 7.59/h (central: 3.2 ± 2.8/h, obstructive: 9.6 ± 6.5/h), which was significantly higher than the preoperative AHI (P = 0.049). The mean intraoperative AHI in patients with SAS was significantly higher than in those without SAS (SAS-positive: 16.44 ± 7.99/h, SAS-negative: 9.29 ± 5.37/h, P = 0.017) (Table 2). Intraoperative AHI was significantly elevated by sedation in SAS-negative and mild SAS patients, but not in moderate and severe SAS patients. Thirty-one patients (88.6%) had intraoperative AHIs ≥ 5 according to the SAS. Among these, eleven patients (35.5%) had intraoperative AHIs ≥ 15 and < 30. Additionally, it was observed that AHIs exceeded 30 in 2 patients (6.5%; not shown in table). Based on these intraoperative AHI measurements, we attempted to determine the predictors of respiratory disturbances under sedation.

Single regression analysis was performed with intraoperative AHI as the objective variable and preoperative AHI, STOP questionnaire score, propofol dose/hour, age, sex, and BMI as the explanatory variables. A significant association was observed between the preoperative AHI (P = 0.0068), STOP questionnaire score (P = 0.0375), age (P = 0.0272), and BMI (P = 0.0299) (Table 3). In the multiple regression analysis, a significant difference was observed in preoperative AHI (P = 0.0296) when the STOP questionnaire score was removed from the above variables (Table 4). Age was included as an influential variable; however, no significant difference was found (P = 0.1240). Similarly, a significant difference was found between the STOP questionnaire score (P = 0.0069) and age (P = 0.0040) in the multiple regression analysis when preoperative AHI was excluded from the above variables (Table 5).

Receiver operating characteristic curves were created to evaluate the relationship between the preoperative screening tests and intraoperative AHI as the outcome. When the outcome was intraoperative AHI ≥ 15 and < 30 (SAS: Moderate criteria), if a preoperative AHI of 5.9 was considered as a cutoff, the sensitivity was 76.9%, the specificity was 68.2%, and the Youden's index was 0.451, which was then defined as the optimum cutoff. Similarly, if a STOP questionnaire score of 2 was taken as the cutoff value, the sensitivity was 75%, the specificity was 73.7%, and the Youden's index was 0.4868 (Figure 1). When the outcome was intraoperative AHI ≥ 30 (SAS: Severe

Table 1 Patient characteristics and details of endoscopic submucosal dissection

	n	%
Gender		
Male	24	68.6
Female	11	31.4
Age in yr	73.2 ± 10.2	
BMI in kg/m^2	23.0 ± 3.7	
Score of STOP questionnaire		
0	6	19.4
1	11	35.5
2	9	29
3	4	12.9
4	1	3.2
Total dose of propofol in mg/h	9.8 ± 3.8	
Sedation period in min	107.6 ± 44.0	

Data are presented as mean ± standard deviation unless otherwise indicated. BMI: Body mass index.

Table 2 Relationship between preoperative apnea-hypopnea index and intraoperative apnea-hypopnea index

	n (%)	Preoperative AHI	Intraoperative AHI	*P* value
All patients	35	9.25 ± 11.03	12.76 ± 7.59	0.049
SAS				
Negative	18 (51.4)	2.55 ± 1.40	9.29 ± 5.37[b]	< 0.001
Positive	17 (48.6)	16.34 ± 12.35	16.44 ± 7.99	NS
Mild	9 (52.9)	8.41 ± 2.37	15.21 ± 8.08	0.042
Moderate	6 (35.3)	18.55 ± 3.35	15.58 ± 7.60	NS
Severe	2 (11.8)	45.40 ± 7.35	24.57 ± 7.67	NS

Data are presented as mean ± standard deviation unless otherwise indicated.
[b]P = 0.017, SAS negative *vs* positive. AHI: Apnea-hypopnea index; SAS: Sleep apnea syndrome; NS: Not significant.

criteria), if a preoperative AHI of 8.3 was taken as a cutoff value, the sensitivity was 100%, the specificity was 69.7%, and the Youden's index was 0.6970, which was then defined as the optimum cutoff value. Similarly, if a STOP questionnaire score of 2 was taken as the cutoff value, the sensitivity was 100%, the specificity was 58.6%, and the Youden's index was 0.5862 (Figure 2). Moreover, we compared the preoperative AHI and STOP questionnaire scores as potential preoperative screening tests to determine which would have a higher diagnostic ability. For intraoperative AHI ≥ 15 and < 30, the preoperative AHI showed an AUC of 0.778 and the STOP questionnaire score showed an AUC of 0.761, which were nearly equivalent; however, the difference was not statistically significant (P = 0.8921) (Figure 1). For intraoperative AHI ≥ 30, the preoperative AHI showed an AUC of 0.833, and the STOP questionnaire score showed an AUC of 0.707. Thus, the estimates of preoperative AHI were higher and the diagnostic ability was greater; however, these differences were not statistically significant (P = 0.4450) (Figure 2).

DISCUSSION

The establishment of predictive models for respiratory depression during sedation for

Table 3 Intraoperative apnea-hypopnea index and single regression analysis of each item

	P value	R^2
Preoperative AHI	0.0068	0.2016
Age	0.0272	0.1393
BMI	0.0299	0.1350
STOP questionnaire	0.0375	0.1408
Dose of propofol	0.0783	0.0910
Gender	0.2048	0.0483

AHI: Apnea-hypopnea index; BMI: Body mass index.

Table 4 Multiple regression analysis comparing intraoperative apnea-hypopnea index and each item (excluding STOP questionnaire score)

	Partial regression coefficient		Standardized regression coefficient		
	B	Standard error	*β*	*t*	*P* value
Intercept	24.273	9.215	0	2.63	0.0129
Preoperative AHI	0.252	0.111	0.366	2.28	0.0296
Age	-0.189	0.120	-0.254	-1.58	0.1240

AHI: Apnea-hypopnea index.

Table 5 Multiple regression analysis comparing intraoperative apnea-hypopnea index and each item (excluding preoperative apnea-hypopnea index)

	Partial regression coefficient		Standardized regression coefficient		
	B	Standard error	*β*	*t*	*P* value
Intercept	34.319	8.401	0	4.09	0.0003
STOP questionnaire	3.306	1.134	0.444	2.92	0.0069
Age	-0.364	0.116	-0.477	-3.13	0.0040

ESD may increase the safety and comfort of the ESD procedure. In this prospective observational study, we found that (1) half of the patients undergoing ESD surgery experienced SAS preoperatively; (2) intraoperative AHI was significantly greater than the preoperative AHI, although these variables were significantly correlated with each other; and (3) both preoperative AHI and STOP questionnaire score were independent predictors of respiratory depression during sedation.

High prevalence of SAS in patients undergoing ESD

In the United States, among patients aged between 30 and 60 years, the prevalence of SAS is defined as AHI ≥ 5, and the clinical symptoms suggesting SAS are reported to be noted in 4% of men and 2% of women. Notably, when the asymptomatic patients are included, the incidence increases up to 24% in men and 9% in women[24]. This suggests that several patients undergoing ESD surgery remain undiagnosed. In fact, we found that about half of the patients were diagnosed with SAS based on preoperative PS. Obesity and aging are well-known risk factors for SAS and these were increasingly common in our ESD patients. Accordingly, preoperative SAS screening should be stressed more such that clinicians can predict and prepare for the risk of respiratory depression during ESD under sedation.

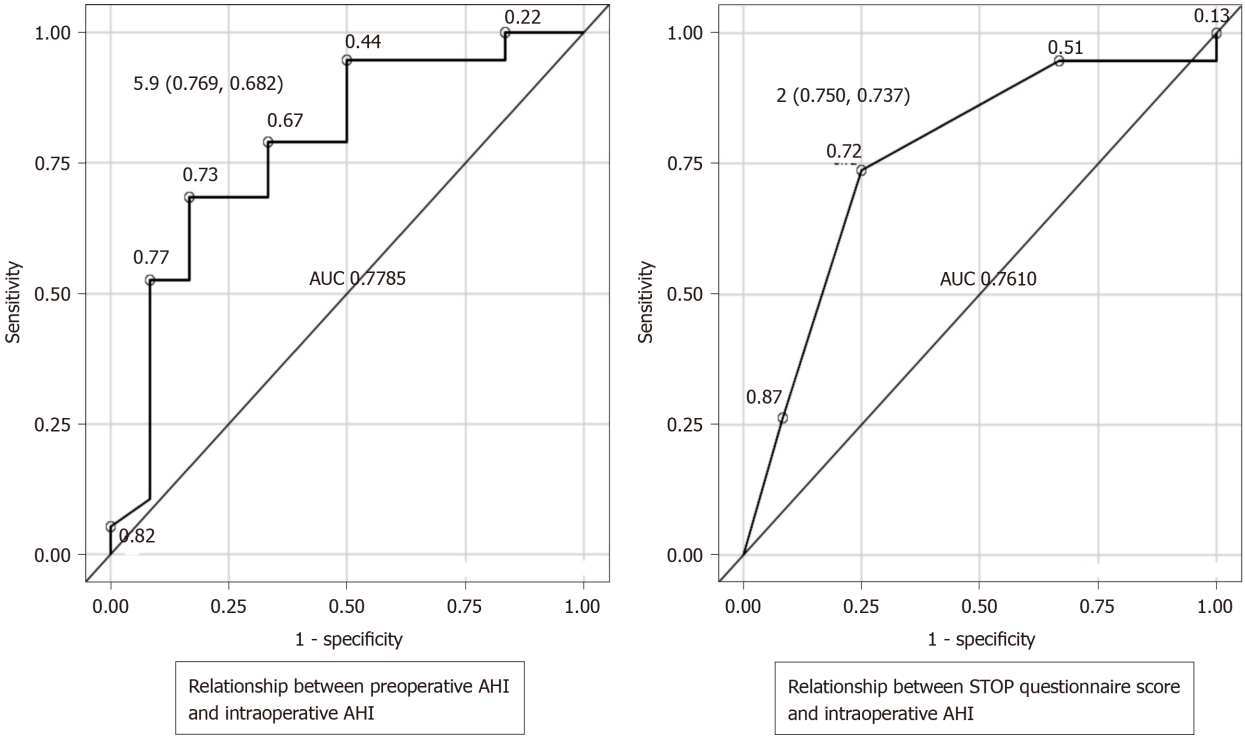

Figure 1 Receiver operating characteristic curves. When the intraoperative apnea-hypopnea index (AHI) outcome was < 30 and ≥ 15 (sleep apnea syndrome: Moderate criteria), if a preoperative AHI of 5.9 is taken as the cutoff value, the sensitivity is 76.9% and the specificity is 68.2%. Similarly, for a STOP questionnaire score of 2 used as the cutoff value, the sensitivity was 75% and the specificity was 73.7%. Preoperative AHI showed an area under the curve of 0.778 and the STOP questionnaire score showed a nearly equivalent area under the curve of 0.761; the difference was not statistically significant (P = 0.8921). AUC: Area under the curve.

Nature and mechanisms of respiratory depression during sedation

Preoperative SAS is an independent risk factor for postoperative respiratory complications[14-17]. However, whether preoperative SAS is a risk factor for hypoxemia during endoscopic procedures under sedation still remains controversial[20,21]. PSG is a standard diagnostic technique for evaluating the presence and severity of SAS. We previously demonstrated that PSG can detect respiratory disturbances under deep sedation more accurately and in more detail than pulse oximetry[13,22]. In this study, using the same PSG technique, we detected more episodes of respiratory depression during sedation than during natural sleep, particularly in patients without preoperative SAS and those with mild preoperative SAS. Notably, the severity of intraoperative SAS did not differ from the preoperative SAS severity in patients with preoperative moderate and severe SAS. Additional profound suppression of the upper airway muscle tone during deep sedation than that during natural sleep might account for the increased severity of SAS during sedation. The lateral decubitus position commonly used for gastric ESD procedure, which is known to improve the upper airway patency and AHI in SAS patients, might have prevented worsening of AHI in patients with moderate to severe SAS in this study[23]. In any case, it is advised to use adequate respiratory monitoring such as that involving capnogram, thermistor, and nasal pressure.

Screening of SAS using STOP questionnaire prior to ESD under sedation

Our results indicate that both preoperative portable sleep monitor and STOP questionnaire are equally effective for predicting the occurrence of respiratory depression during sedation for gastric ESD. Although portable sleep monitoring is a simple clinical test that can be performed at the patient's home, the device for the sleep study is costly and is not available at all medical facilities where endoscopic surgery is performed under sedation. In contrast, the STOP questionnaire consists of only four simple questions and can be used without special devices and laborious setting and analysis. In the original STOP questionnaire study[19], two patterns of the questionnaire (STOP with four questions and STOP-BANG with eight questions) were proposed and tested. Although STOP-BANG had better predictive performance, it requires additional measurements of BMI and neck circumference as well as information on age

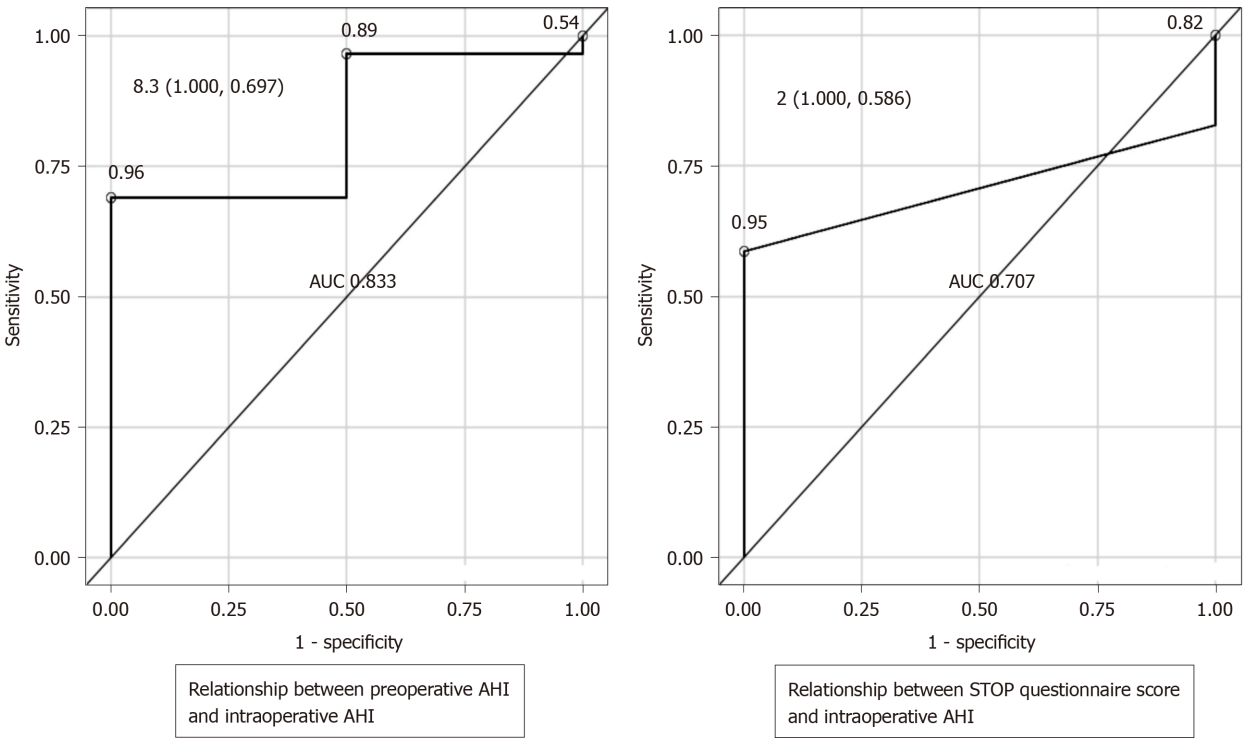

Figure 2 Receiver operating characteristic curves. When the intraoperative apnea-hypopnea index (AHI) outcome was ≥ 30 (sleep apnea syndrome: Severe criteria) and if a preoperative AHI of 8.3 was taken as the cutoff value, the sensitivity was 100% and the specificity was 69.7%. Similarly, for a STOP questionnaire score of 2 used as the cutoff value, the sensitivity was 100% and the specificity was 58.6%. Preoperative AHI showed an area under the curve of 0.833 and the STOP questionnaire score showed an area under the curve of 0.707. Preoperative AHI showed higher estimates and the diagnostic ability was greater; however, the difference was not statistically significant (P = 0.4450). AUC: Area under the curve.

and sex. In an original study testing a general surgery population, the AUCs for predicting AHI ≥ 15 and AHI ≥ 30 during natural sleep were 0.722 and 0.769, respectively, when a STOP questionnaire score of 2 was used as the cutoff value. Using the same STOP questionnaire score cutoff value, we found that the AUCs for predicting intraoperative AHI ≥ 15 and AHI ≥ 30 were 0.761 and 0.707, respectively, in patients undergoing ESD surgery in agreement with the original STOP study. Accordingly, we consider the STOP questionnaire as a clinically relevant tool for predicting moderate to severe respiratory depression during sedation for ESD procedures in contrast to preoperative portable sleep monitoring. However, it should be noted that the performance of the STOP questionnaire is limited. A positive STOP questionnaire result may indicate that the patient may have respiratory depression during sedation, but it does not accurately predict the severity of respiratory depression. In contrast, a negative STOP questionnaire result may indicate that the patient would not develop severe respiratory depression; nevertheless, it does not guarantee stable respiration during sedation.

Limitations of this study

This study had several limitations. First, the total number of study patients was relatively small. Therefore, there is a possibility of bias in patient selection. In future studies, it will be necessary to expand the patient population and include more cases. Second, there were differences in the analysis method for AHI in PSG and PS. While the PSG was analyzed manually by a certified sleep technician, PS data were automatically analyzed by computer software. Thus, the AHI values might be different if the PS data are manually scored.

CONCLUSION

In conclusion, respiratory depression, characterized by obstructive apnea and hypopnea, commonly develops during ESD surgery under sedation. Additionally, the preoperative portable sleep monitor and STOP questionnaire scores accurately predict abnormal breathing. From the viewpoint of cost-effectiveness, the STOP questionnaire

is a clinically useful tool for risk stratification of respiratory depression during ESD, leading to safe ESD procedures.

ARTICLE HIGHLIGHTS

Research background

Recently, endoscopic treatments often take a long time under deep sedation. In these cases, there are many respiratory disturbances that cannot be detected.

Research motivation

In our previous study, polysomnography (PSG) could accurately identify the respiratory disturbances during endoscopic submucosal dissection (ESD) under deep sedation. We wanted to know the preoperative characteristics of patients who experienced intraoperative respiratory disturbances.

Research objectives

We established predictive models for respiratory depression during sedation for ESD.

Research methods

Thirty-five adult patients undergoing sedation for gastric ESDs were studied. Preoperatively, a portable sleep monitor and STOP questionnaires were used. Respiration during sedation was assessed using a standard PSG. The apnea-hypopnea index (AHI) was obtained using a preoperative portable sleep monitor and PSG during ESD. A predictive model for the AHI during sedation was developed using either the preoperative AHI or STOP questionnaire score.

Research results

Half of the patients had a preoperative AHI greater than 5 /hour. The intraoperative AHI was significantly greater than the preoperative AHI (12.8 ± 7.6 events/h *vs* 9.4 ± 11.0 events/h, $P = 0.049$). Multiple linear regression analysis determined either STOP questionnaire score or preoperative AHI as an independent predictor for moderate to severe respiratory depression during sedation.

Research conclusions

The cost-effective STOP questionnaire has performance for predicting abnormal breathing during sedation for ESD that is equivalent to that of preoperative portable sleep monitoring, and can be used as a routine screening tool prior to the ESD procedure.

Research perspectives

The results of this study could increase the safety of ESD under sedation through the development of a clinically useful screening tool for predicting respiratory depression, which possibly leads to fatal outcomes during the procedure.

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SYSTEMATIC REVIEWS

Fluorescence guided intraluminal endoscopy in the gastrointestinal tract: A systematic review

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Author contributions: Mortensen OE, Achiam MP, Nerup N, Shiwaku H, and Svendsen MBS contributed to the idea, conceptualized, and designed the review; Mortensen OE, Achiam MP, and Thorsteinsson M carried out the screening process and data extraction; Mortensen OE drafted the initial manuscript; all authors reviewed and approved the final manuscript as submitted.

Conflict-of-interest statement: All authors state that they have no conflict of interest.

PRISMA 2009 Checklist statement: The guidelines of the PRISMA 2009 statement have been adopted.

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Abstract

BACKGROUND

Conventional endoscopy is based on full spectrum white light. However, different studies have investigated the use of fluorescence based endoscopy systems where the white light has been supplemented by infrared light and the use of relevant fluorophores. Fluorescence endoscopy utilizes the fluorescence emitted from a fluorophore, visualizing what is not visible to the naked eye.

AIM

To explore the feasibility of fluorescence endoscopy and evaluate its use in diagnosing and evaluating gastrointestinal disease.

METHODS

We followed the PRISMA guidelines for this systematic review. The research covered five databases; PubMed, Scopus, Web of Science, Embase, and the Cochrane Collection, including only studies in English and Scandinavian languages. Authors screened title and abstract for inclusion, subsequently full-text for inclusion according to eligibility criteria listed in the protocol. The risk of bias was assessed for all studies according to the Newcastle-Ottawa Scale. The authors extracted the data and reported the results in both text and tables.

RESULTS

We included seven studies in the systematic review after screening a total of 2769 papers. The most prominent fluorophore was indocyanine green (n = 6), and

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whereas one study (n = 1) used Bevacizumab 800-CW. Three studies investigated fluorescence endoscopy in detecting varices, adenomas in patients with familial adenomatous polyposis and neoplasms in the gastrointestinal tract. Four studies evaluated the usefulness of fluorescence endoscopy in assessing tumor invasion. Three of the four studies reported an exceptional diagnostic accuracy (93%, 89% and 88%) in assessing tumor invasion, thus representing better visualization and more correct diagnosis by fluorescence endoscopy compared with the conventional endoscopy. The relationship between the endoscopic findings, tumor invasion, and tumor vascularity was evaluated in two studies showing a significant correlation ($^{d}P < 0.05$ and $^{b}P < 0.01$).

CONCLUSION
The use of fluorescence endoscopy is a promising method adding diagnostic value in the detection of neoplasia, adenomas, and assessment of tumor invasion within the gastrointestinal tract. More studies are needed to utilize the feasibility of fluorescence endoscopy compared with other endoscopic methods.

Key Words: Fluorescence endoscopy; Gastroscopy; Gastrointestinal tract; Gastrointestinal diseases; Infrared light; Fluorophore; Indocyanine green

Core Tip: In the evaluation of tumor invasion, detection of neoplasia and adenomas, studies on fluorescence endoscopy reports promising results.

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INTRODUCTION

Gastrointestinal diseases are the third most common cause of death with gastrointestinal cancer as the leading cause; in 2018 gastric cancer was estimated to cause 738000 deaths worldwide[1]. The high prevalence is, among others, correlated to multifactorial reasons like lifestyle, physical inactivity, stress, and genetics[2,3]. Conventional endoscopy is widely used for gastrointestinal diseases because it is a minimally invasive and potentially curative procedure, facilitating diagnosis, staging, and treatment. The method of flexible conventional endoscopy is based on the visualization by white light. Thus, allowing the surgeon to visualize the gastrointestinal tract from the inside[4,5]. Recently, studies have examined flexible endoscopy in combination with infrared light, and administration of a fluorophore[6].

Fluorescence arises when a fluorophore is in circulation, and the tissue of interest is exposed to light in a wavelength, that the fluorophore absorbs. When the fluorophore absorbs the photons from the light, an excitation happens where the electrons are shifted to a higher state of energy. Spontaneously, the electrons will shift back to their state of energy releasing the extra energy (emission) as light at another wavelength seen as fluorescence[7,8] (Figure 1). Fluorescence guided flexible intraluminal endoscopy is based on the principle of fluorescence and the spectrum of infrared (IR) light, including near-infrared light. IR light has a wavelength of about 780 nm to 1000 nm. IR light has a limited scattering when it reaches the tissue and a low absorption by water and hemoglobin, thus facilitating a less obstructed penetration through tissue compared with standard white light[9]. The mucosal and submucosal vessels are not visible to the naked eye (in white light), but after intravenous injection of a fluorophore and illumination by IR light, profound structures can be visualized. As angiogenesis and neovascularization are essential factors in carcinogenesis and tumor invasion, visualization of mucosal and submucosal vessels may increase the diagnostic value of the endoscopy[10,11].

Conceptually, the endoscope consists of a light source and an imaging plane–light

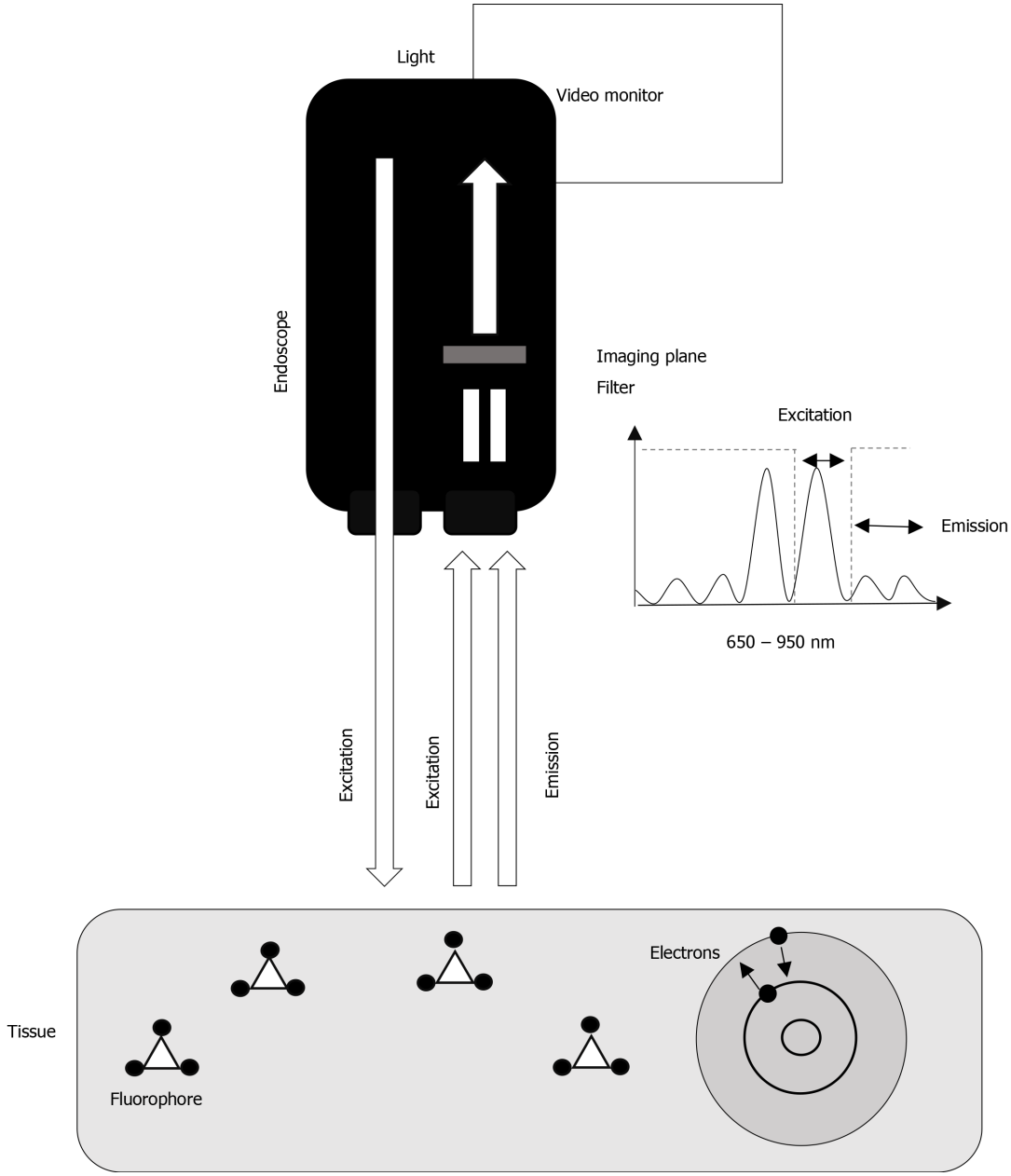

Figure 1 The endoscope emits light in the excitation spectrum of the fluorophore injected. The electrons of the fluorophore will shift from one state of energy to another (excitation), and back, releasing energy as light (fluorescence) at another wavelength (emission). The imaging plane and the filter receive the signal and separate the signals of excitation and emission, only allowing the excitation light to pass.

fibers within the endoscope, with an external camera chip on the tip of the distal end of the camera. The light entering the endoscope for illumination can be white light for standard visualization, whereas when in fluorescence mode, the light primarily consists of the excitatory wavelengths of the fluorophore used. Still in fluorescence mode, after reaching the tissue, the total amount of light reenters the endoscope at the tip. Before reaching the camera chip, the excitatory light needs to be filtered by an optical filter (Figure 1)[12,13]. A frequently used fluorophore is Indocyanine green (ICG), which is excited at the wavelength at 805 nm. Intravenously administered ICG binds to the lipoproteins in the circulation[7]; however, several kinds of other fluorophores exist. The IRDye-800CW is another cyanine fluorophore used for specific protein labeling *e.g.*, Bevacizumab-800CW[13-15]. The aim of this systematic review was to evaluate the diagnostic and therapeutic value of fluorescence-guided flexible intraluminal endoscopy.

MATERIALS AND METHODS

The protocol, flow diagram, and the present manuscript adhered to the PRISMA guidelines for systematic reviews[16]. The protocol was submitted for PROSPERO with the registration number CRD42020147516[17].

Criteria and outcomes

The eligibility criteria for this systematic review was made according to the principals of participants, interventions, comparison, and outcome. Only human studies examining gastrointestinal diseases and surgical advantages, in general, were included. The studies should use fluorescence endoscopy and compare this method with the use of standard endoscopy or endoscopic expert knowledge, or histopathological examinations. Outcomes of interest were a result representing an increase or decrease in the diagnostic or therapeutic value of fluorescence endoscopy. According to the study design, animal studies and other reviews were excluded. We included randomized controlled trials, case-series with more than five subjects, and prospective/retrospective cohort studies independent of the year of publication and the publication status. Only studies written in English or Scandinavian languages were included.

Search strategy

The search string was built in PubMed (Table 1) and adapted to Scopus, Web of Science, Embase, and the Cochrane Collection to identify all the relevant articles for this systematic review. The search string covers all organs from the mouth to the anus, but it does not include the accessory glandular organs. The key words used in the search strategy is shown in Table 1. The database search was performed on June 9th, 2019. Titles and abstracts were screened using an online tool Rayyan[18,19] by four authors (Mortensen OE, Achiam MP, Nerup N, and Thorsteinsson M) to meet the inclusion and exclusion criteria. Consecutively, with two of the authors performing a full-text screening. Subsequently, the reference lists of the included studies were screened to find additional studies. If any discrepancies about inclusion or exclusion, the full-text studies were brought to a meeting and re-examined until consensus. The authors used the web application Rayyan to manage all the data in the screening process. Two authors (Mortensen OE and Thorsteinsson M) performed a data extraction. The handling of data and data from the studies have been extracted from the studies without any modifications and statistical measurements. We extracted data about patients, patient characteristics, diagnosis, fluorophores and dosage used, adverse events, endoscopic findings, diagnostic accuracy, vessel count, and conclusions. No additional analyses were performed.

Quality assessment

The Newcastle-Ottawa scale for cohort studies was used to assess the risk of bias of the included studies[20]. The risk of bias assessment focused on the three main subjects; selection, comparability, and outcome (Table 2).

RESULTS

The authors screened 2769 articles in Rayyan and added one study from the reference lists of other studies. The authors screened 2069 articles after the removal of duplicates, of those 2052 articles were excluded after the screening of title and abstract. Seventeen articles were assessed for full-text screening, where additional ten studies were excluded due to wrong study design or if full-text versions were not available. Finally, seven studies were included comprising a total of 190 patients (Table 3), selected according to the criteria listed. The full screening process is shown in the PRISMA flow diagram (Figure 2).

Quality assessment

The studies were rated for bias according to the Newcastle-Ottawa scale and reported according to their quality (Table 2). All studies were assessed as poor quality due to the lack of comparability and missing control groups. No risk of bias was made across the studies because of the limited number of studies included.

Table 1 Search string in PubMed, Embase, Scopus, Web of Science and Cochrane

Classification
(Endoscop OR Esophagoscop OR Gastroscop OR Gastroscopic Surgical Procedure OR Gastroscopic Surgical Procedures OR Colonoscop OR Colonoscopic Surgical Procedure OR Colonoscopic Surgical Procedures OR Surgery Gastroscopic OR Surgery Colonoscopic) AND (Indocyanine green fluorescence OR Indocyanine Green OR ICG OR fluorescent OR fluorescent dye OR fluorescence OR fluorescein OR near-infrared OR near infrared) AND (Upper Gastrointestinal Tract OR Lower Gastrointestinal Tract OR Upper gastrointestinal disease OR Lower gastrointestinal disease OR Upper gastrointestinal diseases OR Lower gastrointestinal diseases OR gastrointestinal tract OR gastrointestinal diseases OR GI diseases OR GI-diseases OR Upper GI-Diseases OR Lower GI-diseases)

ICG: Indocyanine green; GI: Gastrointestinal.

Table 2 Newcastle Ottawa quality assessment scale

Ref.	Selection					Comparability		Outcome				Total score
	1	2	3	4	Score	1	Score	1	2	3	Score	
Iseki *et al*[25], 2000	a	b	a	a	●○●●	-	○○	a	a	a	●●●	Poor quality
Mataki *et al*[21], 2003	a	b	a	b	●○●○	-	○○	a	a	a	●●●	Poor quality
Okamoto *et al*[22], 2005	a	b	a	b	●○●○	-	○○	c	a	a	○●●	Poor quality
Ishihara *et al*[12], 2006	a	b	a	a	●○●●	-	○○	a	a	a	●●●	Poor quality
Kimura *et al*[23], 2007	a	b	a	b	●○●○	-	○○	a	a	a	●●●	Poor quality
Ortiz- Fernandez-Sordo *et al*[24], 2018	a	b	a	a	●○●●	-	○○	a	a	a	●●●	Poor quality
Hartmans *et al*[15], 2018	a	b	a	a	●○●●	-	○○	c	a	a	○●●	Poor quality

●/a: One star rewarded; ○/b/c: No star rewarded.

Studies and definitions

All the included studies used a system from Olympus (Tokyo, Japan). Intravenous injection of the fluorophore was done in all included studies visualizing the vascularity of the tissue of interest. Six of the seven studies investigated the diagnostic value of fluorescence endoscopy in patients with previously diagnosed adenomas, neoplasms, or cancer (n = 170)[12,15,21], and one study investigated the use in detecting esophageal varices (n = 20)[22-25].

All studies categorized and evaluated the endoscopic findings differently according to the observed fluorescence appearance. Two studies classified the fluorescence staining as no tumor stain, homogeneous tumor stain, inhomogeneous tumor stain, or pooling of the dye[12,25], while another study categorized the staining as no stain, faint stain, dense stain, homogeneous stain, and pooling of the dye. The definitions were as

Table 3 Included studies

Ref.	Study design	Patients (*n*)	Age (yr)	Gender (M/W)	Diagnosis	Contrast	Dosage (mg/kg)	Adverse events	Endoscopic findings	Diagnostic accuracy (%)	Vessel count	Applicability
Iseki *et al*[25], 2000	Retrospective	37	59 (me)	25/12	Gastric cancer	ICG	2-5	N/A	16/18 M tumors: No stain or homogeneous stain. 17/19 SM or more invasive tumors: Inhomogeneous stain or pooling of the dye	89	Yes	Tumor invasion
Mataki *et al*[21], 2003	Retrospective	33	N/A	N/A	Early stage gastric cancer and gastric adenoma	ICG	1	None	0/8 adenomas: + fluorescence. 9/14 M tumors: + fluorescence. 11/11 SM tumors: + fluorescence	N/A	N/A	Tumor invasion
Okamoto *et al*[22], 2005	Retrospective	20	65 (me)	12/8	Varices	ICG	2, 0.1, 0.01, 0.005 or 0.001	None	Clear fluorescence with doses of ICG in 0.005 to 0.01 mg/kg	N/A	N/A	Detection of varices
Ishihara *et al*[12], 2006	Retrospective	30	N/A	N/A	Gastriccancer	ICG	2	N/A	21/23 M or SM tumors < 1 mm: No stain or homogeneous stain. 7/7 SM tumors > 1 mm: Inhomogeneous stain or pooling of the dye	93	N/A	Tumor invasion
Kimura *et al*[23], 2007	Retrospective	30	71.5 (me)	20/10	Early stage gastric cancer and gastric adenoma	ICG	0.01	None	1/20 M tumors: + fluorescence. 8/10 SM tumors: + fluorescence	N/A	Yes	Tumor invasion
Ortiz-Fernandez-Sordo *et al*[24], 2018	Pilot study	23	69 (49-85) (med)	20/3	Early neoplastic lesions within Barrett's esophagus	ICG	2	None	7/23 tumors: No stain (5/7 were less than HGD) 18/23 tumors: Stain (17/18 were at least HGD, MC or SMC)	88	N/A	Detection of neoplasms
Hartmans *et al*[15], 2018	Retrospective	17	42 (20-65) (med)	5/12	FAP	Bevacizumab800CW	4.5, 10 or 25 mg	None	Colorectal adenomas detected at all doses by fluorescence	N/A	N/A	Detection of colorectal adenomas

N/A: Not applicable; FAP: Familial adenomatous polyposis; M: Mucosal; SM: Submucosal; me: Mean; med: Median; No stain: Decreased dye accumulation in the tumor compared to surrounding mucosa; Homogeneous stain: Diffuse increased dye accumulation in the tumor compared to surrounding mucosa; Inhomogeneous stain: Scattered dye accumulation in the tumor; Pooling of the dye: Strong dye accumulation in the tumor; HGD: High grade dysplasia; MC: Mucosal carcinoma; SMC: Submucosal carcinoma.

follows; no stain: A decreased dye accumulation in the tumor compared to surrounding mucosa, homogeneous stain: A diffusely increased dye accumulation in the tumor compared with the surrounding mucosa, inhomogeneous stain: A scattered dye accumulation in the tumor, and pooling of the dye: A substantial dye accumulation in the tumor[24]. In another two studies, they categorized the pooling of the dye/fluorescence categorized as positive or negative[21,23]. The staining definitions and diagnostic values accordingly are shown in Table 3.

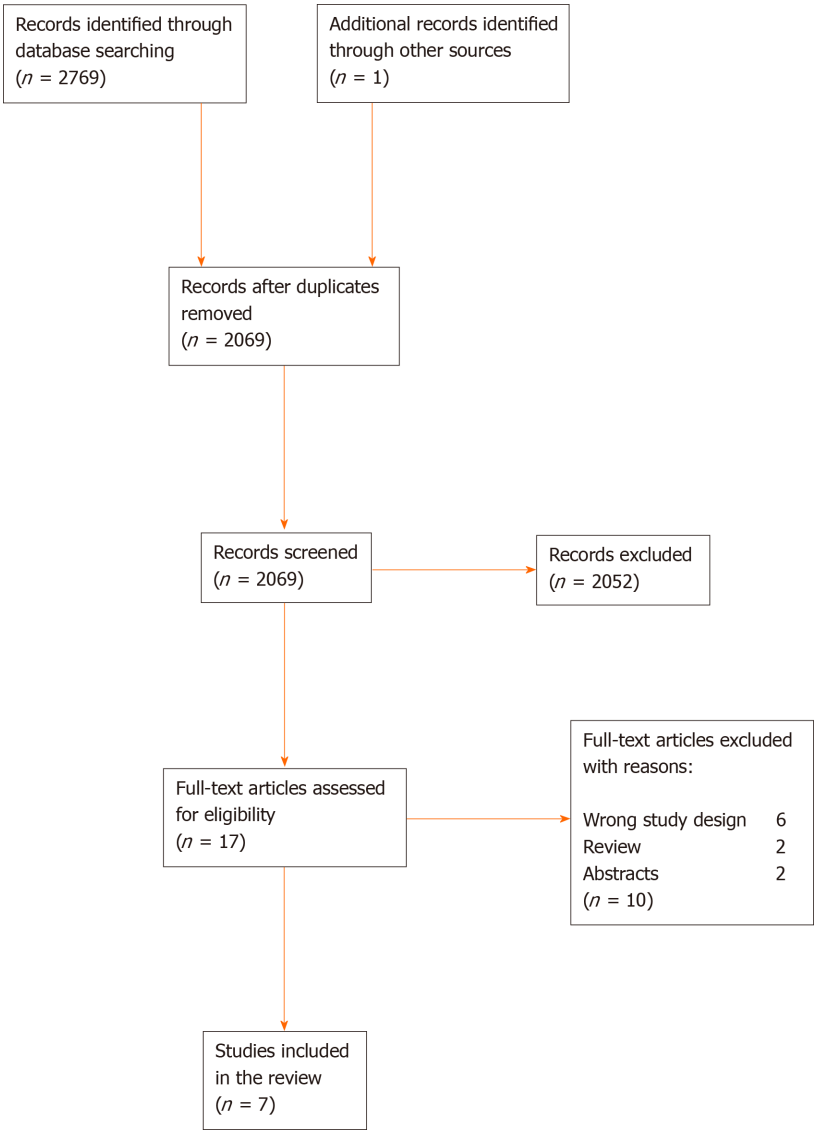

Figure 2 The screening process for the systematic review according to the PRISMA flow diagram.

Fluorophores

Six of seven studies used ICG as a fluorophore[12,21-25]. The dose of ICG ranged from 0.001 to 5 mg/kg bodyweight varying between a fixed dose or different doses of ICG. Four studies reported no adverse events according to ICG[21-24], and the remaining two did not report the frequency or absence of adverse events[12,25]. One study made a dose-response test for Bevacizumab-800CW, which was used as a fluorophore labeling Vascular Endothelial Growth Factor A present in colorectal adenomas and reported no adverse events according to the injections and doses (Table 3)[15].

Inter- and intraobserver examination

Three studies assessed inter- or intraobserver agreement in the infrared fluorescence endoscopic examination. One study reported 90% in interobserver agreement[23], while another study reported a 97% interobserver agreement[21]. The third study reported 97% (kappa 0.97) in intraobserver agreement and a 85% (kappa 0.85) in interobserver agreement[25].

Tumor invasion and neoplasms

Five studies reported infrared fluorescence endoscopy as useful to assess tumor invasion or detect neoplasia[12,21,23-25]. In a retrospective study of 30 patients with depressed gastric cancers, the authors reported that 21 of 23 intramucosal and submucosal tumors smaller than 1 mm were observed with no stain or faint stain. Seven of seven submucosal tumors larger than 1 mm and more invasive tumors were observed with dense staining or pooling of the dye. Consequently, 28 of 30 both

mucosal and submucosal tumors were correctly diagnosed (diagnostic accuracy 93%, Table 3). Additionally, 18 of 19 (accuracy 95%) of tumors with ulcerative changes were correctly diagnosed. Diagnostic accuracy was described as the level of compliance for endoscopic findings by using IR-light and a fluorophore compared with the histopathological examinations[12].

Iseki *et al*[25] (n = 37) reported that 16 of 18 mucosal tumors were observed with no stain or homogeneous tumor stain. Seventeen of 19 submucosal or deeper tumors were observed with inhomogeneous tumor stain or pooling of the dye. Consequently, 33 of 37 mucosal and submucosal tumors correctly diagnosed (diagnostic accuracy 89%, Table 3). Additionally, 33 of 37 (accuracy 89%) tumors correctly diagnosed as depressed or ulcerative. The study compared the diagnostic accuracy of fluorescence endoscopy and chromoendoscopy in assessing tumor invasion. Chromoendoscopy had a diagnostic accuracy at 68%, compared with fluorescence endoscopy (89%, $^{a}P < 0.02$). Furthermore, the authors reported that tumor invasion assessed by fluorescence endoscopy was strongly correlated to the degree of tumor vascularity ($^{b}P < 0.01$).

The study of Mataki *et al*[21] (n = 33) reported all eight gastric adenomas (accuracy 100%) negative for pooling of dye as in contrast to 20 of 25 (80%) for both mucosal and submucosal tumors which were positive for pooling of dye (Table 3) ($^{c}P < 0.03$ for mucosal and submucosal). The authors suggested the fluorescence endoscopy as a diagnostic staging tool to determine if a tumor was eligible to make an endoscopic mucosal resection.

Kimura *et al*[23] (n = 30) reported one of 20 gastric adenomas or intramucosal tumors as being positive in fluorescence, and eight of ten submucosal tumors as being positive in fluorescence. The study did not state diagnostic accuracy, but the numbers correspond to a sensitivity of 80% and specificity of 95%. Also, a significant correlation between the invasiveness of the tumor, fluorescence, and vessel count was found ($^{d}P < 0.05$).

One study examined early neoplastic lesions within Barrett's esophagus in 23 cases[24]. Seven cases showed no stain, and histology showed less than high-grade dysplasia in five of those seven cases. Eighteen of 23 showed staining, and histology showed at least high-grade dysplasia, intramucosal carcinoma or submucosal carcinoma. Diagnostic accuracy was 88% (Table 3), sensitivity 90%, specificity 83%, and negative predictive value 71% in identifying the high-grade dysplasia or more advanced histopathology.

Dose-response

Two studies made a dose-response examination[15,22]. Okamoto *et al*[22] investigated esophageal varices (n = 20) with two studies-a clinical study, and an experimental study to evaluate tissue permeability. The clinical study suggested the optimal dose range of ICG between 0.005-0.01 mg/kg bodyweight based on their evaluation of the fluorescent signal to differentiate between normal mucosa and varices.

One study made a dose-response study with another fluorophore, Bevacizumab-800CW, investigating patients with Familial Adenomatous Polyposis (n = 17). Colorectal adenomas were detected with all doses of the fluorophore; 4.5 mg, 10 mg, and 25 mg, whereas normal mucosa showed no fluorescence[15].

DISCUSSION

In this systematic review, we identified seven studies using fluorescence endoscopy to assess and evaluate tumor invasion, detect neoplasms, adenomas and esophageal varices. Although fluorescence endoscopy was first described many years ago, this method with interesting results has become even more promising for therapeutic and diagnostic purposes with the recent advances within the field of fluorescence-guided surgery and cancer-specific imaging[26].

Tumor development and invasion

Six studies evaluated fluorescence endoscopy according to tumor development and invasion. In one study, fluorescence endoscopy was compared with chromoendoscopy, which is another method used to visualize and detect neoplasia in the gastrointestinal tract. The authors found a significantly higher diagnostic accuracy using fluorescence endoscopy (68% *vs* 89%, $^{a}P < 0.02$)[25]. Furthermore, the authors reported a significant correlation between tumor invasion and tumor vascularity when using fluorescence endoscopy ($^{b}P < 0.01$) as tumors with a tumor stain had significantly more vessels than did tumors without a tumor stain[25-27]. Additionally, the

vessels were more varied in size in tumors showing inhomogeneous stain than tumors with a homogeneous stain. The authors suggested that tumor invasion to the submucosa will induce new, permeable vessels, which will result in extravasation of blood observed as pooling of the dye. The association between tumor invasion, fluorescence and vessel count was reproduced in another study with a significant correlation ($^{d}P < 0.05$)[23]. The association of vascularity and tumor invasion was also demonstrated in a study of 44 patients which reported a color change in the endoscopic findings based on the tumor vascularity. The study assessed the tumor vascularity with an endoscopic quantitative analysis of the hemoglobin index[28]. Additionally, another study of 25 specimens from resections of early gastric cancer investigated color changes appearing during endoscopy. They suggested that blood flow, angiogenesis, and the microvasculature in tumors as factors responsible for the endoscopic findings[29]. Nevertheless, these mechanisms are not fully understood and need further assessment.

Indocyanine green

For evaluating vascularity, ICG has been used for many years, first for photography, later for angiography in 1969[30]. The contrast has been commercially available for many years, as it has a high level of safety and a very low incidence of adverse events has been reported[31,32]. In this systematic review, four of six included studies (n = 106) using ICG specifically reported that no adverse effects occurred[21-24], while the remaining two studies reporting nothing on adverse events. Usually, the recommended dosage of ICG is 0.2-0.25 mg/kg, which must not exceed 2 mg/kg in total[33]. One study included in this review reported an optimal dose of ICG at 0.005 to 0.01 mg/kg body weight[22], while another study reported a very high dosage of ICG at 2-5 mg/kg body weight[25]. However, no consensus about the ICG dosage exists in the studies.

Cancer-specific probes

Another subject of emerging clinical interest is the potentially cancer-specific fluorescent probes. Studies investigating the cancer-specific probes reflect the need for developing cancer-specific, optically detectable imaging agents to detect cancers and to add diagnostic and therapeutic value to fluorescence endoscopy. Both cancer-specific probes and the fluorescence endoscopy has been validated by several studies[15,34-37].

Recently, several studies have investigated the urokinase-type plasminogen activator receptor (uPAR) as a cancer-specific probe[38-41]. Using uPAR as a probe, one study subsequently demonstrated the feasibility of uPAR-coupled fluorescent probes. The promising results pointed towards a future using ICG-coupled uPAR probes for imaging and image-guided surgery as the tumor-targeted fluorophores may improve the discrimination between normal and neoplastic tissue. Cancer-specific fluorescent probes may also enable fluorescence-guided endoscopic resection with real-time assessment of the tumor margins, as well as prove to be a novel tool in response evaluation of tumors after chemoradiotherapy. The latter being possible by evaluation of fluctuations in fluorescence intensity caused by changes in tumor vascularity[42].

Quantitative examination

Fluorescence endoscopy is still lacking a method to quantify the fluorescent signal to decrease the subjectivity and increase objectivity, sensitivity, and specificity of the method. Some studies have investigated methods to quantitate the fluorescent signal. In the studies included in this review, the fluorescent signal was judged qualitative, meaning visually subjectively, except for one study which quantified the fluorescent signal *ex vivo*[15]. In a series of animal studies[43-45], a new method named quantitative-ICG for quantification of perfusion using ICG fluorescence was presented and validated. The quantification of the fluorescent signal will add an important factor to all technologies using fluorescence as a diagnostic marker.

Limitations

This systematic review with a focus on human studies using fluorescence endoscopy led to 2769 articles screened, but only seven studies included in the final review, which reflects the limited research within the field. Notwithstanding the limited number of studies, seven of seven studies were rated as poor quality in the Newcastle Ottawa Scale for bias assessment. The low score reflects potential unreliability within the studies, as they all lacked control groups and non-exposed cohorts, thus indicating that this method needs further investigation. However, less strict criteria may have led to more heterogeneous studies included and a more challenging comparison of the

endoscopic findings. The exclusion criteria were to keep a homogeneity in the studies and to reflect high clinical applicability of this systematic review.

CONCLUSION

In conclusion, this systematic review found that fluorescence endoscopy may add both diagnostic and therapeutic value within the field of gastrointestinal diseases. The majority of the studies included investigated the value within tumor staging, and the detection of adenomas, and neoplasms, thus indicating this method as an opportunity for a more precise diagnosis in the early development of neoplasms and tumors. More studies are needed to examine the usefulness of fluorescence endoscopy compared with other endoscopic methods. Furthermore, the combination of fluorescence endoscopy, quantification of the fluorescent signal, and cancer-specific fluorescent probes has the potential to improve the endoscopic diagnosis, monitoring and therapy of gastrointestinal diseases.

ARTICLE HIGHLIGHTS

Research background

Different studies have investigated the use of fluorescence based endoscopy systems where the white light has been supplemented by infrared light and the use of relevant fluorophores. Fluorescence endoscopy is among the recent advances within the field of fluorescence-guided surgery and cancer-specific imaging.

Research motivation

The aim of this systematic review was to evaluate both the diagnostic and therapeutic value of fluorescence-guided flexible intraluminal endoscopy. Angiogenesis and neovascularization are important factors in tumor invasion, and as mucosal and submucosal vessels are not visible to the naked eye, but after intravenous injection of a fluorophore and illumination by infrared light, profound structures can be visualized.

Research objectives

Fluorescence endoscopy can be used within the detection the early development of neoplasms and tumors, adenomas, assessment of tumor invasion within the gastrointestinal tract. Those qualities are a part of the recent advances within the field of fluorescence-guided surgery and cancer-specific imaging.

Research methods

The research method was a data analysis. We followed the PRISMA guidelines for this systematic review. The research covered five databases; PubMed, Scopus, Web of Science, Embase, and the Cochrane Collection. Authors screened title and abstract for inclusion, subsequently full-text for inclusion according to eligibility criteria listed in the protocol. The risk of bias was assessed for all studies according to the Newcastle-Ottawa Scale. The authors extracted the data and reported the results in both text and tables.

Research results

We included seven studies in the systematic review after screening a total of 2769 papers. Four studies evaluated the usefulness of fluorescence endoscopy in assessing tumor invasion. Three of the four studies reported an exceptional diagnostic accuracy in assessing tumor invasion, thus representing better visualization and more correct diagnosis by fluorescence endoscopy compared with the conventional endoscopy. The relationship between the endoscopic findings, tumor invasion, and tumor vascularity was evaluated in two studies showing a significant correlation. The use of fluorescence endoscopy is a promising method.

Research conclusions

This systematic review explored the diagnostic and therapeutic value of fluorescence endoscopy. This study proposes fluorescence endoscopy as a method, which can increase those values, in the context of what is already known. This systematic review reflects a high clinical applicability, and fluorescence endoscopy is a method, that

builds on the approach of tumor vascularity. This is the hypothesis of this systematic review and how this cooperate with the diagnostic and therapeutic value.

Research perspectives

More studies are needed to utilize the feasibility of fluorescence endoscopy compared with other endoscopic methods exploring the diagnostic and therapeutic value in different clinical issues.

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LETTER TO THE EDITOR

Real-world clinical data of endoscopy-based cancer detection during the emergency declaration for COVID-19 in Japan

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Abstract

The impact of the coronavirus disease 2019 (COVID-19) pandemic is widespread throughout the world, causing serious damage to healthcare systems. Therefore, we examined the significance of endoscopy based on the recommendation of Asian-Pacific Society for Digestive Endoscopy and Japan Gastroenterological Endoscopy Society during the COVID-19 pandemic by evaluating the details of gastrointestinal endoscopy performed during the declaration of emergency in Japan. We have continued performing gastrointestinal endoscopy at an outpatient clinic that specialized in endoscopic medical care in Tokyo, Japan. During the emergency declaration period, 544 patients underwent gastrointestinal endoscopy. As a control, we investigated 1327 patients who underwent gastrointestinal endoscopy during the same period in 2019. Although the total number of endoscopies during the emergency declaration was halved, the advanced cancer detection rate during the emergency declaration was significantly higher than that in 2019 (P = 0.04). Additionally, no COVID-19 infection was observed in healthcare workers, staff, or patients during this period. It is possible that an outpatient endoscopy units can contribute to the detection of advanced cancer, while the hospital in charge for patients with COVID-19 infection could not perform endoscopy during the declaration of emergency.

Key Words: COVID-19; Pandemics; Gastrointestinal; Endoscopy; Neoplasms; Personal protective equipment

Core Tip: It is possible that an outpatient endoscopy units can contribute to the detection of

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advanced cancer, while the hospital in charge for patients with coronavirus disease 2019 (COVID-19) infection could not perform endoscopy during the declaration of emergency. Gastrointestinal endoscopy may be one of the safety nets in the COVID-19 pandemic to not delay the diagnosis of advanced, life-threatening cancers.

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TO THE EDITOR

We read with interest the recent paper by Olszewski *et al*[1] reporting their best practice outline for endoscopy during the coronavirus disease 2019 (COVID-19) outbreak. As the authors describe, we strongly feel the need to change our practice to incorporate these factors to improve the safety of patients, health care providers, and community as a whole during this disaster.

Our facility is an outpatient clinic that specialized in endoscopic medical care in Tokyo, Japan. We have continued performing gastrointestinal endoscopy according to the recommendations of Asian-Pacific Society for Digestive Endoscopy (APSDE)[2] and Japan Gastroenterological Endoscopy Society (JGES)[3]. We would like to introduce our successful approach.

First, patients were categorized as high-risk or low-risk using the ASPDE and JGES risk assessment at reception and endoscopy was only performed in low-risk patients. Endoscopy was not applicable when any of the following criteria were met: (1) Patients with respiratory infection; (2) Patients with a body temperature ≥ 37.5 °C; (3) Patients who were in close contact with subjects in an endemic area within the last 2 wk; (4) Patients who traveled to endemic areas within the last 2 wk; and (5) Patients complaining of symptoms due to COVID-19 infection.

Second, the indications for endoscopy were limited as follows: Symptomatic patients, patients with abnormalities in other tests, patients with previous appointments, and patients who strongly wished for investigation. A new reservation for asymptomatic patients or surveillance endoscopy was not accepted.

We were focused on preventing COVID-19 infection in healthcare workers using personal protective equipment, including gloves, hairnets, protective eyewear (goggles or face shield), and waterproof gowns. To prevent the inhalation of airborne droplets and aerosolized virus[4,5], we wore a surgical mask or N95 during the endoscopy procedure. We also applied a surgical mask with a handmade scope insertion port (Figure 1) for patients during the upper-endoscopy procedure. The patients changed their shoes to slippers at the entrance, measured their body temperature, washed their hands and gargled in the washroom, wore a mask, and maintained social distancing.

To improve the environment of the endoscopic room, we ventilated the examination room and the waiting rooms about 6 times/h (about 2 times/h of the outside air volume), installed an air purifier, and employed specialized staff to clean the clinic.

During the emergency declaration period (between April 7th and May 26th in 2020), 544 patients (311 for upper endoscopy and 233 for colonoscopy) underwent gastrointestinal endoscopy. Table 1 shows the comparison of gastrointestinal endoscopy performed in 2020 and the same period in 2019. The total number of endoscopies during the emergency declaration was halved. There was no significant difference in the cancer detection rate between 2019 and 2020. For advanced cancer, the detection rate during the emergency declaration period was higher than that during the same period in the last year ($P = 0.04$). As a result of the above precautions, no COVID-19 infection was observed in healthcare workers, staff, or patients during this period.

As one of the factors of this higher detection rate in advanced lesion, it may have been possible to enrich cases with findings based on strict adaptation criteria of the endoscope. It is possible that an outpatient endoscopy units can contribute to the detection of advanced cancer, while the hospital in charge for patients with COVID-19 infection could not perform endoscopy during the declaration of emergency.

Gastrointestinal endoscopy based on the recommendations of APSDE and JGES

Table 1 Comparison of gastrointestinal endoscopy performed in 2019 and 2020

	2020	2019	*P* value
Upper endoscopy, *n*	311	790	
Colonoscopy, *n*	233	537	
Total, *n*	544	1327	
Age (yr ± SD)	55.2 ± 13.4	55.8 ± 13.2	0.34
Sex, male (%)	53.9	47.3	0.01
All malignancies, *n* (%)	6 (1.1)	8 (0.6)	0.40
Advanced lesion, *n* (%)	5 (0.9)	2 (0.2)	0.04
Early lesion, *n* (%)	1 (0.2)	6 (0.5)	0.66

Figure 1 A surgical mask for patient during procedure with a handmade scope insertion port.

may be one of the safety nets in the COVID-19 pandemic to not delay the diagnosis of advanced, life-threatening cancers. Our clinic was able to play an important role even during the declaration of emergency.

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LETTER TO THE EDITOR

Endotracheal intubation in patients with COVID-19 using an ultrathin flexible gastrointestinal endoscope

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Abstract

Pneumonia caused by severe acute respiratory syndrome coronavirus 2 occasionally becomes severe and requires endotracheal intubation. Endotracheal intubation is usually performed using a laryngoscope; however, the operator needs to be in close proximity to the patient's face during the procedure, which increases the risk of droplet exposure. Therefore, we simulated fiberoptic endotracheal intubation on a mannequin representing the patient, using an ultrathin flexible gastrointestinal endoscope as an alternative to the bronchoscope, in order to maintain distance from the patient during the procedure. We performed this procedure 10 times and measured the time required; the median procedure time was 6.4 s (interquartile range, 5.7-8.1 s). The advantage of this method is the short procedure time and distance maintained from the patients. The flexible tip-steerable control and length of the gastrointestinal endoscope contributed to shortening the procedure time and maintaining distance from the patients. In addition, this method can handle difficult airways without risk of misplacement of the endotracheal tube. However, it is necessary to consider the risk of aerosol generation associated with this procedure. In the pandemic setting of coronavirus disease 2019, this approach may be useful when a gastrointestinal endoscopist is in charge of endotracheal intubation of patients with coronavirus disease 2019.

Key Words: Endotracheal intubation; SARS-CoV-2; COVID-19; Laryngoscopes; Bronchoscopes; Gastrointestinal endoscopes

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Core Tip: Proximity of the operators to the patient is inevitable with conventional endotracheal intubation procedures. In this endotracheal intubation method, the gastrointestinal endoscope is used as an alternative to the bronchoscope. Thus, endotracheal intubation can be performed while keeping a relatively safe distance from the patient, as the gastrointestinal endoscope has a long effective length. Furthermore, the flexible tip-steerable control of the gastrointestinal endoscope enables quick and reliable endotracheal intubation.

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TO THE EDITOR

Endotracheal intubation is performed in patients with severe respiratory failure induced by severe acute respiratory syndrome coronavirus 2[1]. These patients are usually intubated using a laryngoscope[2]. Coronavirus disease 2019 (COVID-19) is highly contagious; thus, preventing the propagation of infection requires maintaining a safe distance and avoiding direct exposure to droplets from infected patients[3]. However, it is difficult for healthcare professionals to maintain distance while intubating patients using a laryngoscope because operators need to stand in close proximity to patients' faces.

Here, we report the use of an ultrathin flexible gastrointestinal endoscope with a tip outer diameter of 5.0 mm (GIF-XP260N; Olympus, Tokyo, Japan) to perform endotracheal intubation on a mannequin representing the patient. The purpose of this simulation-based study was to evaluate the feasibility and usefulness of using a gastrointestinal endoscope as an alternative to the bronchoscope in endotracheal intubation. This procedure included four steps (Figures 1 and 2) as follows: First, the operator holding an endoscope over which a 7.0 mm endotracheal tube was mounted stood to the left of the supine patient; second, the endoscope was inserted into the trachea; third, we ensured instant insertion of the endotracheal tube into the trachea using the endoscope as a guide; and finally, the endoscope was withdrawn. We repeatedly performed the procedure 10 times and recorded the corresponding time taken for each procedure. The procedure time was defined as the total time elapsed between the insertion of the endoscope into the mouth and the final withdrawal of the endoscope. The median procedure time was 6.4 s (interquartile range, 5.7-8.1 s; Table 1).

Bronchoscope-guided endotracheal intubation in patients with COVID-19 has already been reported[4,5]. In our method, an ultrathin gastrointestinal endoscope was used as an alternative to the bronchoscope. This method is advantageous owing to the short procedure time. This can be attributed to the flexible tip-steerable control of the gastrointestinal endoscope because the gastrointestinal endoscope has angulation control knobs for up, down, left, and right movements, whereas the bronchoscope has an angulation control knob only for up and down movements[6]. Hence, the gastrointestinal endoscope may serve as a better alternative to the bronchoscope for endotracheal intubation. This technique will also be useful in patients with difficult airways in order to avoid the risk of misplacement of the endotracheal tube[7]. Furthermore, the effective length of the gastrointestinal endoscope used was 1.1 meters allowing the operator to maintain a relatively safe distance by standing to the left of the patient, minimizing direct exposure to droplets from patients.

However, our method has a few limitations. Conventionally, endotracheal intubation is performed by anesthesiologists familiar with techniques used in intubation[1]. Notably, gastrointestinal endoscopes are not usually available in the emergency room or intensive care unit where endotracheal intubation is often performed. Furthermore, owing to the potential for generating aerosols, it is unlikely that flexible bronchoscope-guided intubation will be the first choice in conscious patients with COVID-19[1,2].

During this COVID-19 pandemic, there may be occasions when a gastrointestinal endoscopist is in charge of endotracheal intubation in patients with confirmed or

Table 1 The procedure time

	Time (s)
1st	10.2
2nd	7.9
3rd	8.1
4th	10.0
5th	6.5
6th	5.6
7th	4.5
8th	5.8
9th	5.6
10th	6.2
	Median, 6.4 (interquartile range, 5.7–8.1)

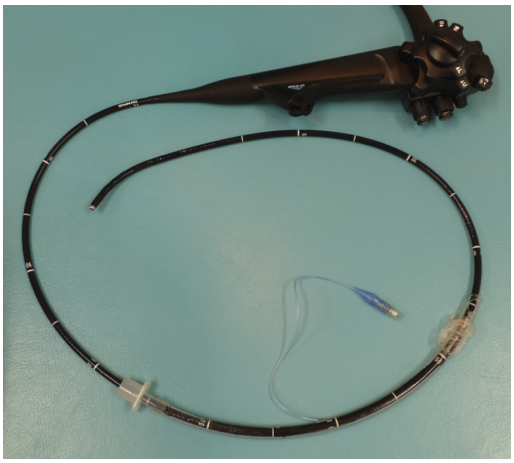

Figure 1 The ultrathin gastrointestinal endoscope mounted into an endotracheal tube.

suspected COVID-19. If the gastrointestinal endoscopist is not familiar with endotracheal intubation using a laryngoscope, the intubation procedure is expected to be time-consuming, thus increasing the risk of direct exposure to droplets from patients. Therefore, endotracheal intubation using this method may be useful in reducing the risk of exposure to severe acute respiratory syndrome coronavirus 2.

CONCLUSION

Endotracheal intubation using an ultrathin flexible gastrointestinal endoscope is a quick and reliable procedure that can be performed while maintaining distance from the patient. Therefore, this method may be useful in endotracheal intubation in patients with COVID-19.

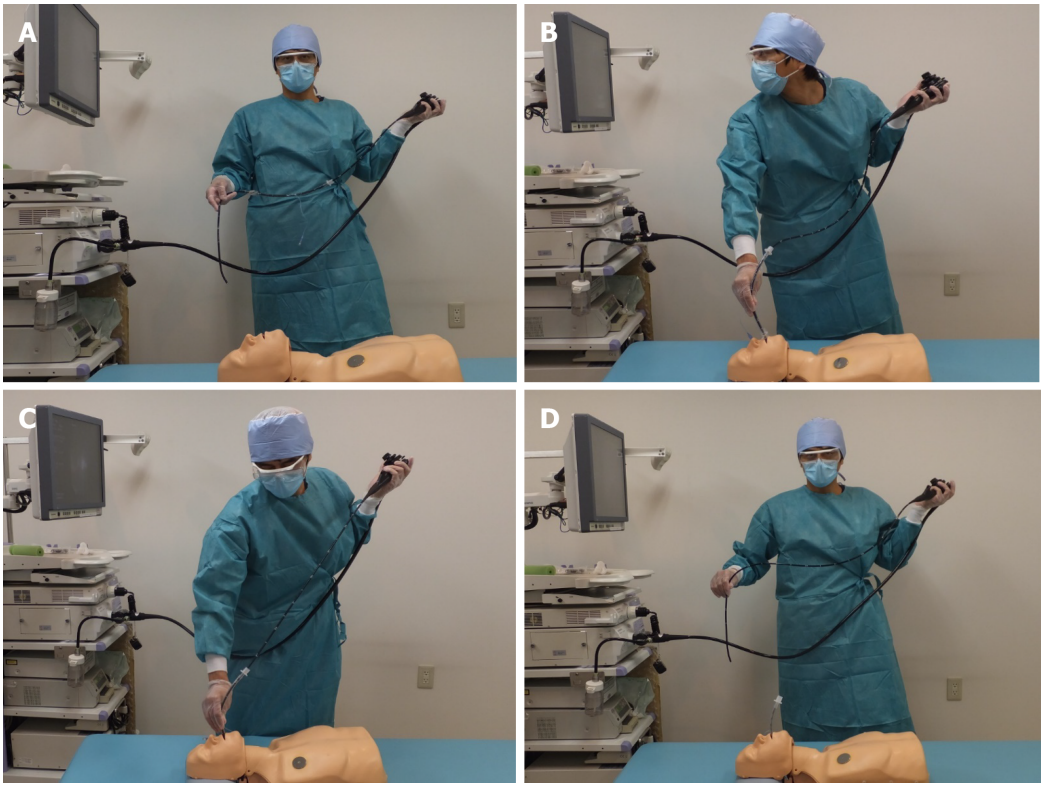

Figure 2 Gastrointestinal endoscope-guided endotracheal intubation. A: The operator standing to the left of the patient; B: Inserts the endoscope into the trachea; C: Endoscope-guided endotracheal intubation is performed; and D: The endoscope is withdrawn.

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