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REVIEW

Choledochoscopy: An update

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Abstract

Choledochoscopy, or cholangioscopy, is an endoscopic procedure for direct visualization within the biliary tract for diagnostic or therapeutic purposes. Since its conception in 1879, many variations and improvements are made to ensure relevance in diagnosing and managing a range of intrahepatic and extrahepatic biliary pathologies. This ranges from improved visual impression and optical guided biopsies of indeterminate biliary strictures and clinically indistinguishable pathologies to therapeutic uses in stone fragmentation and other ablative therapies. Furthermore, with the evolving understanding of biliary disorders, there are significant innovative ideas and techniques to fill this void, such as nuanced instances of biliary stenting and retrieving migrated ductal stents. With this in mind, we present a review of the current advancements in choledochoscopy with new supporting evidence that further delineates the role of choledochoscopy in various diagnostic and therapeutic interventions, complications, limitations and put forth areas for further study.

Key Words: Choledochoscopy; Cholangioscopy; Indeterminate biliary strictures; Difficult bile stones; Primary sclerosing cholangitis; Cholangiocarcinoma

Core Tip: The role of choledochoscopy (for extrahepatic biliary procedures) and cholangioscopy (for intrahepatic biliary procedures) is one and a half centuries old. It is a reliable tool in the visualization of indeterminate strictures and subsequent biopsy for diagnostic purposes. Furthermore, it serves as the "safety net" in therapeutic measures where endoscopic retrograde cholangiopancreatography cannot manage, such as biliary stone fragmentation and retrieving migrated equipment. With the advent of new

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techniques and adjuncts, its potential has further evolved to improve the procedure's accuracy. We provide a comprehensive update on the current and future potential of choledochoscopy.

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INTRODUCTION

Choledochoscopy, or cholangioscopy, refers to an endoscopic procedure for direct visualization within the biliary tract for diagnostic or therapeutic purposes. Attempts to directly visualize the bile duct lumen began as early as 1879. However, it was only with the Wildegans choledochoscope in 1953 that choledochoscopes started having some interventional capabilities. Other milestones in choledochoscopy include developing a flexible choledochoscope by Shore and Lipman in 1965, improved imaging quality with the Hopkins rod lens system in 1975, and cameras attached to the choledochoscopes to televise images for simultaneous viewing in 1985[1].

Regarding currently available choledochoscopes, peroral choledochoscopy was introduced in 1976 using the dual-operator "mother-baby" scope. Subsequently, single-operator choledochoscopes such as the direct peroral choledochoscopes (D-POC) and SpyGlass Direct Visualisation system choledochoscopes (Boston Scientific Corporation, Natick, MA, United States) were introduced[2]. Table 1 enlists technical specifications and details of commonly available choledochoscopes. Spurred by an improved understanding of biliary disorders and innovative technological advances, choledochoscopy remains an evolving field. Choledochoscopy and cholangioscopy are used interchangeably in the literature. However, for this review, choledochoscopy refers to the extrahepatic biliary tree procedure, and cholangioscopy refers to the intrahepatic biliary tree procedure. This review aims to update the technical advances in choledochoscopy, new evidence that further delineates the role of choledochoscopy in various diagnostic and therapeutic interventions, complications, limitations, and put forth areas for further study.

LITERATURE RESEARCH

An electronic search of PubMed was conducted in February 2021 for literature published in English. The following terms were used, and relevant articles were considered: [(choledochoscopy) OR (cholangioscopy)]. The last date of the search was 28th February 2021.

TYPES OF CHOLEDOCHOSCOPY

Choledochoscopy can be performed by peroral, percutaneous transhepatic, percutaneous transenteric *via* access loop, intra-operative transcystic, or intra-operative transcholedochal access (Figure 1). Table 2 summarizes types of choledochoscopy according to access routes, with each route's advantages and limitations. Peroral and percutaneous transhepatic access are the most widely discussed in the literature and are further elaborated on in this section.

Peroral choledochoscopes (POC) are further categorized into dual-operator or single-operator systems. Dual-operator systems require two endoscopists to operate "mother-baby" scopes, where a choledochoscope is inserted through the instrumentation channel of a duodenoscope. This includes original fibreoptic scopes and newer videocholangioscopes with Narrow Band Imaging (NBI) capacity. The original fibreoptic scopes were necessary for peroral choledochoscopy but have limited use currently due to its disadvantages: requires two endoscopists, low image quality with fibreoptic imaging, suboptimal working or irrigation channels, poor maneuverability

Table 1 Technical specifications of commonly discussed choledochoscopes

Type of choledochoscope	Fibreoptic or digital-based imaging systems1	Outer diameter (mm)	Accessory working channel diameter (mm)	Tip deflections
Percutaneous				
CHF-CB30 L/S (Olympus Medical Systems, Tokyo, Japan)[13]	Digital	2.8	1.2	2-way (up-down)
Peroral – dual-operator				
Mother-baby[4]	Fibreoptic	"Mother": 12.6 mm "Baby": 2.8–3.4 mm	0.8 – 1.2	2-way (up-down)
Short-access-mother-baby (Karl Storz, Tuttlingen, Germany)[4]	Fibreoptic	"Mother": 12.6 mm "Baby": 3.4 mm	1.5	2-way (up-down)
Videocholangioscope (CHF-B290; Olympus Medical Systems, Tokyo, Japan)[6]	Digital	3.3	1.3	2-way (up-down)
Peroral – Single-Operator				
SpyGlass Legacy 2007 (Boston Scientific Corporation, Natick, MA, United States)[5]	Fibreoptic	3.3	1.2	4-way (up-down, left-right)
SpyGlass Direct Visualisation 2015 (Boston Scientific Corporation, Natick, MA, United States)[5]	Digital	3.6	1.2	4-way (up-down, left-right)
SpyGlass Direct Visualisation II 2018 (Boston Scientific Corporation, Natick, MA, United States)	Digital	Data has not been published yet		
Direct peroral choledochoscopy using variety of ultra-thin endoscopes[5]	Digital	5.0 – 5.9	2.0	4-way (up-down, left-right)

Fibreoptic and digital catheters differ in the modality used to illuminate, acquire and transmit endoscopic images back to the camera. Fibreoptic catheters utlitise multiple individual fibre-optic bundles to reflect light off cable walls and into a camera. Digital catheters use imaging chips to convert reflected light into a digital signal, to produce a higher resolution digital image.

Table 2 Types of choledochoscopy

Type of choledochoscopy	Advantages	Disadvantages
Peroral (endoscopic)	Natural orifice	(1) Technical expertise; (2) Sedation or anesthesia; and (3) Not possible in patients with previous gastric resections or Roux-en-Y gastric bypass
Percutaneous transhepatic (interventional radiology)	(1) Shorter scope length; (2) Repeated with ease; and (3) Therapeutic interventions	(1) Need dilated intra-hepatic ducts; and (2) Risk of bleeding, bile leak, tumor seeding, biliary fistula and skin excoriation
Percutaneous transenteric *via* access loop (interventional radiology, surgical)	(1) Shorter scope length; (2) Repeated with ease; (3)Therapeutic interventions; (4) Ductal dilatation not necessary; and (5) In patients with RPC	(1) Previous access loop creation; and (2) Risk of small bowel injury, peritonitis, biliary fistula and skin excoriation
Intra-operative transcystic (surgical)	(1) Avoid CBD incision; (2) Therapeutic interventions; (3) Can document CBD clearance; and (4) It can be done laparoscopically	(1) The spiral valve of Heister; (2) Anatomy of the cystic duct; (3) Size of the cystic duct; (4) Need thin scopes (3 mm); (5) Technical expertise; and (6) Risks of bleeding, bile leak
Intra-operative transcholedochal (surgical)	Most direct access	(1) Need dilated extra-hepatic biliary system; (2) Risk of bleeding, bile leak; (3) Can put an internal stent; and (4) Can put T tube

RPC: Recurrent pyogenic cholangitis; CBD: Common bile duct.

with two-way tip deflection, and scope fragility[3,4]. In contrast, interest in video-cholangioscopes (CHF-B260, latest version: CHF-B290; Olympus Medical Systems, Tokyo, Japan) remains despite the need for two endoscopists. Advantages include using NBI for improved image quality, the stability of baby scope positioning in bile ducts, and a small outer diameter for use in intrahepatic bile ducts[5,6]. However, its role, especially considering the latest CHF-B290 model, is still being defined and is not currently available for clinical use.

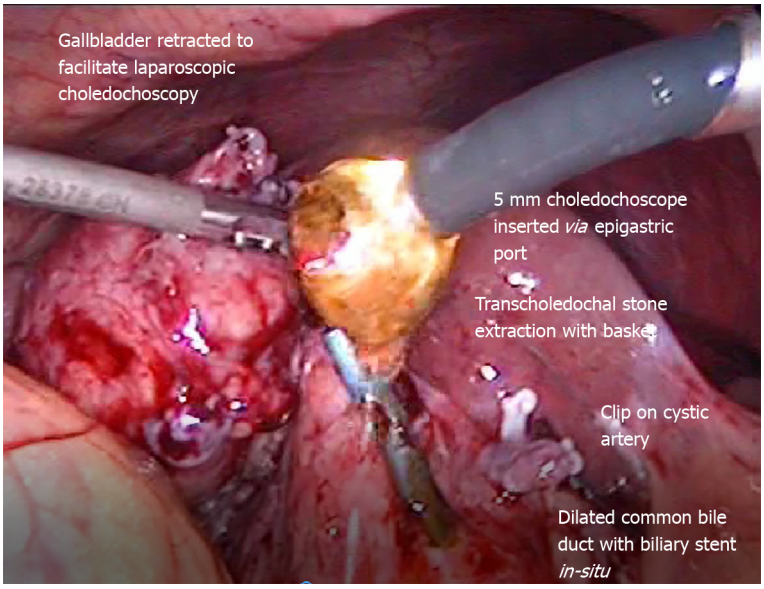

Figure 1 Laparoscopic transcholedochal common bile duct stone extraction by operative choledochoscopy.

To minimize drawbacks associated with the dual-operator technique, single-operator systems such as the SpyGlass Direct Visualisation peroral choledochoscopy system and D-POC using ultra-thin endoscopes were developed. Currently, three versions of SpyGlass are available – the first-generation SpyGlass Legacy 2007 (Fibre-optic) (FSOC), second-generation SpyGlass Digital System delivery, and access catheter 2015 (Digital) (DSOC) and third-generation SpyGlass Digital System II delivery and access catheter 2018 (Digital). Advantages of FSOC include a four-way deflectable tip for better maneuverability and a dedicated irrigation channel for continuous irrigation. It is limited by the inferior image quality and field-of-view (70˚), poor durability of the reusable fibreoptic probe, small therapeutic channel, and cumbersome setup[7]. Thus, DSOC improved on FSOC by having digital images with 400% greater resolution and 60% wider field-of-view (110˚), improved accessory channel, and easy "plug and play" set up[8]. The third-generation SpyGlass Direct Visualisation II delivery and access catheter 2018 (Digital) is touted to have 250% better resolution than DSOC and adjusted lighting to reduce flare. However, clinical data on its efficacy is not yet available[9].

D-POC utilizes a variety of ultra-slim endoscopes designed initially for pediatric and transnasal use. Key advantages are the variety of endoscopes already available, four-way deflectable tip, and the ability to use NBI for improved image quality. Disadvantages include relatively large outer diameters (5.0-5.9 mm), which may complicate scope insertion and advancement in smaller bile ducts, requiring prior large sphincterotomy to accommodate scope diameters gastric and duodenal looping [5].

Novel multi-bending choledochoscopes are developed to improve the ease of bile duct cannulation. This avoids accessory devices as two bending sections allow more acute angulation and control the choledochoscope while preventing choledochoscope dislodgement. Three prototype models exist. For the first two prototypes, freehand insertion had a 0% technical success rate in a study by Itoi *et al*[10] involving seven patients. Compared to the second prototype, the third prototype has more excellent distal tip angulation (200˚ *vs* 160˚) and a smaller outer diameter distal end (4.9 mm *vs* 5.2 mm) to improve the scope's pushability to minimize loop formation. This translated into improved technical success rates and shorter procedure time with reduced radiation exposure than conventional choledochoscopes and previous generations of multi-bending choledochoscopes. In a randomized controlled trial by Lee *et al*[11] involving 92 patients, while efficacy in diagnostic and therapeutic interventions was equivalent, multi bending choledochoscope had high technical success rates of freehand biliary insertion (89.1% *vs* 30.4%, $P < 0.001$) and shorter mean procedure time with reduced radiation exposure (3.2 ± 1.8 *vs* 6.0 ± 3.0 min, $P = 0.004$) than conventional D-POC.

Percutaneous transhepatic choledochoscopy (PTCS) is reserved for cases when peroral choledochoscopy is unsuitable, such as in complicated anatomy. This percutaneous approach permits shorter endoscopes with better maneuverability to

reach areas that are less accessible perorally[12]. A variety of endoscopes can be used, such as those used for other indications (*e.g.*, nephroscope, ureteroscope, bronchoscope) and those specifically designed for choledochoscopy (*e.g.*, CHF-CB30 L/S; Olympus Medical Systems, Tokyo, Japan)[13]. However, it remains second-line to peroral choledochoscopy due to the invasive and time-consuming need to create and mature a large-diameter percutaneous tract several days before choledochoscopy and complications such as bile leak and bleeding metastatic spread to the peritoneum or sinus tract[14].

CHOLEDOCHOSCOPE ADJUNCTS AND ACCESSORIES

This section will discuss the advancements in accessories that facilitate choledochoscope advancement, optimize view, improve image quality and efficacy in specific interventions.

Choledochoscope advancement

Devices are developed to guide the advancement of D-POC into bile ducts. An example is how in a study by Yang *et al*[15] involving 79 patients, the use of D-POC enabled high rates of scope insertion (72.0%). Another device to increase choledochoscope stability is a hybrid balloon catheter anchoring device using a 0.021-inch guidewire attached to a balloon catheter's distal end. In a single-center retrospective study by Li *et al*[16] involving 55 patients, this device-guided D-POC achieved significantly higher technical success rates compared to the conventional wire-guided method (92.7% *vs* 47.1%, $P < 0.05$). Another anchoring technique is advancing D-POC over a reusable guide probe of the Kautz device (MTW, Wesel, Germany), designed initially for non-transendoscopic placement of biliary stents. This method increases probe stiffness to prevent choledochoscope looping and had an 85% technical success rate[17].

Optimize view by medications

Ways to optimize view across various modes of choledochoscopy have been described. In D-POC, intraductal simethicone reduces the surface tension of gas bubbles and improves mucosal visualization by anti-foaming action. This is particularly useful in the presence of pneumobilia following a sphincterotomy for choledochoscope access [18].

Optimize view by structural modification

In percutaneous choledochoscopy, Demmert *et al*[19] devised a novel choledochoscopy expander using microwires to create a flexible whisk-like shape to distend the gallbladder lumen before visualization by choledochoscopy mechanically. A case report showed its use improved gallbladder visualization with reduced infolding of gallbladder lumen and minimal mucosal injury. Other accessories include a transparent cap to the choledochoscope in gallbladder-preserving surgery. According to Jian *et al*[20] in a retrospective study of 50 patients, the addition of a transparent cap for patients undergoing laparoscopic choledochoscopy significantly reduced gallbladder exploration time (12.04 ± 6.01 min *vs* 27.96 ± 12.24 min). Reasons put forth include eliminating blind spots as the transparent cap promoted distance between the lens and mucosa, allowing complete visualization. Other benefits include protection of the scope. Sometimes direct visualization by choledochoscopy is not possible due to complete ductal obstruction. In such instances, microcatheters made of the 3-French outer sheath of a basket catheter (MicroCatch; MTW Endoskopie, Düsseldorf, Germany) and 3-French endoscopic nasobiliary drainage tube (Daimon-PTCD set, Hanaco Medical, Saitama, Japan) can aid injection of contrast medium to facilitate guidewire manipulation[21].

Image-enhanced function systems

To improve direct visualization capabilities, choledochoscopy can harness various preexisting image-enhanced function systems, such as NBI, probe-based confocal laser endomicroscopy, i-Scan, chromocholangioscopy, and autofluorescence imaging. NBI utilizes filtered light to improve visualization of ductal mucosa and vessels compared to conventional white-light imaging. It is compatible with videocholangioscopes and D-POC[5]. NBI can improve visual differentiation of benign from malignant strictures [22]. However, improved visualization *via* NBI may not translate into improved rates of malignancy detection. Dysplasia detection rate did not increase even when 48%

more suspicious lesions were biopsied when using NBI in patients with primary sclerosing cholangitis (PSC)[23]. i-Scan, a computed virtual chromoendoscopy system, may also improve visualization of ductal mucosa and vasculature compared to conventional white-light imaging. While diagnostic accuracy using i-Scan was not significantly better, surface structure, surface microvascular architecture, and margins were significantly better visualized[24]. Probe-based confocal laser endomicroscopy captures microscopic images of living tissue for real-time histological tissue assessment under direct visualization. Compatibility with DSOC was demonstrated in a study by Tanisaka *et al*[25] involving 30 patients with indeterminate biliary strictures (IBS). While probe-based confocal laser endomicroscopy during DSOC had lower sensitivity compared to DSOC alone (94.1% *vs* 100%), higher specificity (92.3% *vs* 76.9%) and accuracy [93.3% (95%CI: 78.7%-98.8%) *vs* 90% (95%CI: 74.4%-96.5%)] was reported. Chromocholangioscopy can show differences between inflamed, ischaemic, and dysplastic biliary lesions based on different gross surface staining patterns using methylene blue injections during choledochoscopy[26]. However, data on the efficacy of chromocholangioscopy in IBS are limited. Lastly, autofluorescence imaging, which compares colors of lesions when blue excitation light and green and red field cameras, are utilized to distinguish between normal and neoplastic mucosa. Itoi *et al*[27] evaluated autofluorescence imaging as an adjunctive imaging technique during PTCS. Amongst 65 biliary tract lesions, PTCS with autofluorescence imaging had higher specificity (87.5% *vs* 52.5%) and accuracy (87.7% *vs* 70.8%) than PTCS alone, though sensitivity decreased (88% *vs* 100%).

Nevertheless, most image-enhanced function systems have not yet been validated for clinical use in choledochoscopy. Further studies need to evaluate different choledochoscopes with these current imaging systems and if better biliary visualization indeed translates into improved diagnostic and therapeutic accuracy.

Tissue diagnosis

For the acquisition of larger tissue samples, the SpyBite Max biopsy forceps acquire twice the amount of tissue than the SpyBite biopsy forceps[9]. This is particularly promising given how the diagnostic accuracy of biopsy samples of IBS obtained *via* the legacy SpyBite biopsy forceps has been hampered by inadequate tissue samples[28].

Stone retrieval and fragmentation

For stone retrieval, a variety of equipment is available for the retrieval of stones. Commonly, stone retrieval baskets are the foremost choice, as there are many variable shapes and sizes that can suit most situations. These include Dormia baskets, SpyGlass Retrieval Basket (SpyBasket), and SpyGlass Retrieval Snare (SpySnare)[29]. However, the baskets require expansion and retraction to securely surround the stones, which may be difficult due to limited space[13]. In those cases, open-ended graspers such as alligator forceps are an option.

When the stone is too large to fit into a retrieval basket or difficult to remove after securing the forceps, fragmentation of the stones is possible[30]. Lithotripsy, either electrohydraulic lithotripsy (EHL), extracorporeal shockwave lithotripsy (ESWL), or laser lithotripsy (LL), can aid fragmentation. Traditionally, mechanical lithotripsy is less commonly used due to its limitations in breaking large pigment stones and challenging maneuverability[31]. In addition, EHL has a higher risk of duct damage due to relative imprecision. Furthermore, the probe's caliber may be too large to enter more miniature endoscopes if needed[13]. LL probes are small caliber and allow accurate and precise fragmentation. Commonly, pulse and non-pulsed lasers are available depending on the penetration depth required. However, LL is notably more expensive than EHL.

Migrated hardware retrieval

Choledochoscopic visualization of the hepatobiliary ducts is also valuable for retrieving migrated hardware such as stents using SpyBasket and SpySnare[32], broken baskets[33,34], and migrated coils[35]. However, such instances have yet to be reported on a larger scale and currently lack power. With the garnering of more reported cases, it would then be possible to truly delineate the potential of choledochoscopy in therapeutic interventions and other instances.

Stricture ablation

Choledochoscopy can perform therapeutic interventions like ablation of cholangiocarcinoma (CCA) *via* photodynamic therapy or radiofrequency ablation. Choledochoscopy can confirm successful radiofrequency ablation administration and

immediate post-procedure complications. Novel choledochoscopy-guided balloon-radiofrequency ablation techniques demonstrated in animal models also show potential for clinical use[36]. Case reports by Chandrasekar *et al*[37] and Brunaldi *et al*[38] describe the use of digital cholangioscopy to evaluate photodynamic therapy.

Scope handling techniques

The use of different techniques when handling the choledochoscope has also been proposed in lithotripsy. For example, Zhang *et al*[39] proposed the J maneuver when performing choledochoscopy in a freehand technique, described as retroflection of the upper endoscope while in the second part of the duodenum, simultaneous rotation and retraction of the endoscope towards the papilla. Zhang *et al*[39] claimed that this maneuver would eliminate the need for surgical bile duct exploration.

CLINICAL APPLICATIONS

Choledochoscopy can be used for diagnostic and therapeutic indications (Table 3), with main indications in diagnosing IBS and lithotripsy. This section will discuss the efficacy of choledochoscopy compared to conventional methods and recent advances in various diagnostic and therapeutic indications.

IBS

IBS is defined as biliary strictures with aetiologies that cannot be established after standard diagnostic investigations such as laboratory tests, imaging (such as computed tomography or magnetic resonance cholangiopancreatography), or procedures (such as endoscopic retrograde cholangiopancreatography (ERCP)-guided tissue biopsy)[40]. This section will discuss the role of choledochoscopy in diagnosing IBS, specifically when along with the diagnostic algorithm it should be done, optimal choledochoscope choice, the two main ways choledochoscopy can be used, and factors affecting its diagnostic accuracy.

The imperative in biliary strictures is to exclude malignancies, where ERCP with brush cytology is the initial modality of choice. However, despite its high specificity with brush cytology (> 95%), sensitivity remains low. In a review of 16 studies involving 1556 patients, Burnett *et al*[41] reported that ERCP brush cytology had a sensitivity of 41.6% ± 3.2% (99%CI) and a negative predictive value (NPV) of 58.0% ± 3.2% (99%CI). Thus, adjunctive diagnostic modalities such as choledochoscopy are required. Per the 2018 Asia-Pacific ERCP Club consensus guidelines, choledochoscopy-guided biopsies are recommended to improve diagnostic accuracy in situations where conventional ERCP-based brush cytology and forceps biopsy are inconclusive despite clinical suspicion[42].

Choledochoscopy is a valuable diagnostic modality as it can affect the aggressiveness of management. In a multicentre study by Prat *et al*[43] involving 61 IBS patients, choledochoscopy prevented unnecessary surgical resection in 33 out of 57 patients with initially-suspected carcinoma, and significantly improved management adequacy rates ($P < 0.001$) than before choledochoscopy despite a moderate overall diagnostic sensitivity (52%-63.6%). Hence given differences in morbidity in surgical compared to conservative management, there is value in choledochoscopy for patients with unclear diagnoses.

Stricture location determines if choledochoscopy should be done at all and, if done, when along with the diagnostic algorithm after ERCP-based sampling[42]. Firstly, strictures can be intrinsic (*e.g.*, cholangiocarcinoma, periampullary bile duct cancer) or extrinsic to bile duct (*e.g.*, pancreatic cancer, gallbladder cancer, metastatic disease)[44]. Peroral choledochoscopy is more helpful in evaluating intrinsic than extrinsic strictures. The sensitivity for diagnosing malignancy in intrinsic strictures was higher than extrinsic strictures in both FSOC visual impression and FSOC-guided biopsy[44]. Secondly, strictures are either proximal or distal strictures. Martinez *et al*[45] recommend that peroral choledochoscopy can be used immediately after the first inconclusive ERCP-based sampling for proximal biliary strictures. On the contrary, for distal biliary strictures, peroral choledochoscopy is recommended only if both ERCP-based sampling and endoscopic ultrasound-guided fine-needle aspiration are negative.

Choledochoscopy should be used in both ways for the diagnosis of IBS – visual impression and choledochoscopy-guided biopsies. Direct visualization by choledochoscopy permits the identification of mucosal features suspicious for malignancy and targeted biopsies. In a recent meta-analysis by Wen *et al*[40] involving

Table 3 Diagnostic and therapeutic indications for choledochoscopy

Diagnostic indications	Therapeutic indications
Visual impression and visually-guided biopsies of: (1) Indeterminate biliary strictures (IBS); (2) Dominant strictures in primary sclerosing cholangitis (PSC); and (3) IgG4-related sclerosing cholangitis (IgG4-SC)	Stone fragmentation: (1) Electrohydraulic lithotripsy (EHL); and (2) Laser lithotripsy (LL)
Precise preoperative mapping of the extent of tumor involvement in CCA	Ablative therapies in cholangiocarcinoma (CCA): (1) Radiofrequency ablation; (2) Photodynamic therapy; (3) Nd:YAG laser ablation; and (4) Argon plasma coagulation
Choledochal cysts	Cystic duct stent placement
Intraductal papillary neoplasms of the bile duct	Guidewire passage through strictures, surgically altered anatomy
Cholangioadenoma	Resection of ductal masses
Biliary papillomatosis	Retrieval of migrated ductal stents
Eosinophilic cholangitis	Gallbladder stenting and drainage
Biliary varices	
Right Hepatic Artery Syndrome	
Congenital pancreaticobiliary maljunction	
Post-liver transplant ductal ischemia	
Tissue sampling and visual evaluation for infections: (1) Cytomegalovirus; and (2) HIV	
Evaluation of intrahepatic biliary tracts during minimally invasive surgery	

HIV: Human immunodeficiency virus.

356 patients across 11 studies, the visual impression was more sensitive than choledochoscopy-guided biopsy across DSOC, FSOC, and D-POC (95% *vs* 74%, 84.5% *vs* 60.1%, 83%-92% *vs* 43%-89.5%). However, specificity was higher in choledochoscopy-guided biopsy than visual impression across DSOC, FSOC and D-POC (98% *vs* 92%, 98% *vs* 82.6%, 97% *vs* 84%-92%)[40]. Furthermore, the lack of a standardized visual classification system necessitates that biopsy results confirm visual findings. Thus, it is insufficient to use either visual impression or biopsy findings alone.

Various choledochoscopes have been studied in the diagnosis of IBS. However, an ideal choledochoscope has not yet been established for IBS diagnosis in clinical practice. POC are more frequently used in IBS. However, PTCS can also be used when POC instability prevents adequate bile duct visualization[46]. When comparing POC without the use of image-enhanced function systems, DSOC has an excellent diagnostic yield in both visual impression and choledochoscopy-guided biopsies[40,47,48]. In a study by Mizrahi *et al*[47] involving 324 patients, DSOC had a significantly higher diagnostic yield of visual impression for malignancy than FSOC (78% *vs* 37%, $P = 0.004$). However, studies comparing the efficacy of different choledochoscopes when image-enhanced function systems are used are lacking. For instance, NBI, which is compatible only with videocholangioscopes and D-POC, may significantly improve the efficacy of these two choledochoscopes compared to others.

Several factors confound the diagnostic accuracy of choledochoscopy in IBS. This section will explore these confounders in visual impression and choledochoscopy-guided biopsies and advances made to mitigate them.

For both visual impression and biopsies, the diagnostic accuracy of choledochoscopy may decrease with increasing hyperbilirubinemia levels[49] and in specific patient populations such as patients with PSC[50]. This highlights the importance of patient optimization pre-procedure and identification of other confounding patient factors. Other factors include inadequate experience amongst endoscopists (< 25 cases performed)[49].

A major drawback of visual impression using choledochoscopy is the lack of a standardized visual classification system[40], especially because diagnostic accuracy is experience and operator-dependent. Several studies have proposed novel classification systems. However, there is a lack of comparative studies to standardize one classification system. Tumor vessels, which are dilated and tortuous vessels, are markers of malignancy that provide moderate diagnostic accuracy when coupled with biopsy

[51]. Other malignant characteristics include nodular mucosa, neovascularization, friability, and papillary characteristics[52]. More recently, in 2018, a new classification system by Robles-Medranda *et al*[53] classified lesions based on morphological and vascular characteristics (*i.e.*, polypoid, ulcerated, honeycomb, *etc.*). This had a high sensitivity (96.3%) and specificity (92.3%) amongst 106 patients. However, there was a discrepancy in an inter-observer agreement between experts and non-experts ($\kappa > 80\%$ and 64.7%-81.9% respectively). Better inter- and intra-observer agreement between both expert and non-expert operators ($\kappa > 80\%$; $P < 0.001$) was seen in the use of neovasculature morphology, defined as irregular or 'spider' vascularity as proposed by Robles-Medranda *et al*[53] in 2020. This had a sensitivity of 94%, a specificity of 63%, a positive predictive value (PPV) of 75%, NPV of 90% amongst the 95 patients studied[54]. In 2020, Sethi *et al*[55] proposed the Monaco Classification, which combined eight observable criteria (presence of stricture, lesion, mucosal features, papillary projections, ulcerations, abnormal vasculature, scarring, pronounced pit pattern). A fair diagnostic accuracy (70%) and inter-observer agreement ($\kappa = 0.31$, SE = 0.02) was reported, with ulceration (OR = 10.3, $P = 0.01$) and papillary projections (OR = 7.2, $P = 0.02$) being most associated with malignancy.

Two main issues limit the use of choledochoscopy-guided biopsies in IBS – challenges in analyzing small biopsy samples obtained during choledochoscopy and lack of consensus on the optimum number of sample sizes required.

Firstly, choledochoscopy-guided tissue samples are often too small for accurate offsite histopathological examination and thus decrease sensitivity. Adequate tissue acquisition is primarily limited by the technical ability of choledochoscopy forceps jaw [28]. Other factors include age less than 65 years old (OR = 0.170, 95%CI: 0.044–0.649, $P = 0.010$) and previous biliary stenting before POC (OR = 0.199, 95%CI: 0.053–0.756, $P = 0.017$)[56]. Thus, one approach improves the choledochoscopy forceps jaw's technical ability to acquire large tissue samples per bite, such as in the SpyBite Max biopsy forceps[57]. Alternatively, specimen processing techniques that can process smaller tissue samples have been proposed as adjuncts to conventional histopathological examination. One method is rapid onsite evaluation of touch imprint cytology (ROSE-TIC) during choledochoscopy-guided biopsies. Touch imprint cytology is useful as an adjunct in cases where clinical suspicion for malignancy is high, but offsite sampling is negative or indeterminate[58]. In a study by Varadarajulu *et al*[59] involving 31 FSOC- and DSOC-guided biopsy procedures, ROSE-TIC provided an additional opportunity for onsite specimen processing and demonstrated sensitivity (100%), specificity (88.9%), PPV (86.7%), NPV (100%), and diagnostic accuracy (93.5%). However, the use of ROSE-TIC in the context of choledochoscopy has yet to be validated in large-size trials. Another method already used for processing smaller specimens is cell block cytology. A study by Baars *et al*[60] involving 240 SpyBite specimens from the upper gastrointestinal tract in 10 patients found that cellblock cytology results in fewer crush artifacts and requires a significantly smaller specimen to achieve equivalent diagnostic accuracy (1.49 mm *vs* 2.02 mm, $P < 0.001$) compared to standard histopathology. However, as this comparative analysis was performed using gastrointestinal samples, a pilot study involving six IBS patients was performed. All 20 SpyBite samples were successfully processed by cell block cytology[60].

Secondly, the optimum number of biopsies to be taken during choledochoscopy remains unestablished. This may depend on specimen processing techniques (onsite *vs* offsite) and stricture location (intrinsic *vs* extrinsic). In a randomized control trial using DSOC by Bang *et al*[58] involving 62 patients, three biopsies were recommended for offsite specimen processing and one biopsy for onsite specimen processing to achieve equivalent diagnostic accuracy (90%). Additional biopsies for offsite specimen processing did not improve diagnostic accuracy. However, other retrospective studies by Onoyama *et al*[28] and Varadarajulu *et al*[59] recommend minimally four biopsies when using offsite and onsite[60] processing techniques, respectively. Furthermore, Varadarajulu *et al*[59] observed that extrinsic strictures required more biopsies than intrinsic strictures for onsite processing techniques.

PSC

Diagnosis of current studies on choledochoscopy in PSC has focused on identifying CCA in PSC strictures and subtyping PSC through visual impression and choledochoscopy-guided biopsies. While the accuracy of visual impression and choledochoscopy-guided biopsies have been well-studied in IBS, the same conclusions cannot simply be applied to PSC. Underlying ductal inflammation and scarring may mimic CCA visually and complicate the passage of choledochoscopes through bile ducts to evaluate strictures[61]. However, large-scale studies specifically on PSC patients are limited.

The ability to accurately exclude CCA in PSC is critical as PSC patients have an increased CCA risk[61]. Various investigations such as imaging and serological tumor markers such as carbohydrate antigen 19-9 are possible but lack sufficient sensitivity and specificity when used alone[62]. Tissue diagnosis is thus crucial in this workup. A meta-analysis by Njei *et al*[61] across 21 studies found that single-operator choledochoscopy-guided biopsies are the most accurate in diagnosing CCA in PSC patients as compared to brush cytology, fluorescence in situ hybridization, and probe-based confocal laser endomicroscopy, with a sensitivity of 65% (95%CI: 35%-87%) and specificity of 97% (95%CI: 87%-99%). A study by Majeed *et al*[63] involving 225 PSC patients found that the use of DSOC in addition to second brush cytology improved sensitivity than second brush cytology alone (100% *vs* 82%) in detecting CCA in PSC. However, another retrospective study by Kaura *et al*[64] involving 36 PSC patients found that the addition of SpyGlass choledochoscopy-guided biopsy to fluorescence in situ hybridization did not significantly increase sensitivity compared to brush cytology alone. Hence, there remains uncertainty on whether choledochoscopy with other diagnostic investigations can improve CCA detection in PSC.

Furthermore, choledochoscopy findings on visual inspection can subtype PSC into early or late stages of the disease. Sandha *et al*[65] proposed the novel Edmonton Classification, which categorizes PSC's visual impression features on FSOC and DSOC into three phenotypes – "inflammatory type", "fibrostenotic type", and "nodular or mass-forming type". Fujisawa *et al*[66] further correlated these findings with time course – "'inflammatory type" correlated to active phase and early-stage PSC, "fibrostenotic type" with chronic phase and late-stage PSC, and "nodular or mass-forming type" in either phase. Stratification into the disease stages is vital in informing each patient's disease and guiding targeted treatment[65].

In the management of PSC, the role of POC has also been considered, specifically when managing patients with dominant strictures. A dominant stricture is defined as a stricture of ≤ 1.5 mm in the common bile duct or ≤ 1 mm in the hepatic duct within 2 cm of the intrahepatic confluence. In a prospective study by Awadallah *et al*[67] involving 55 patients with PSC, POC was able to help with the diagnosis of PSC-associated biliary strictures and discovered the presence of choledocholithiasis, which was missed in 30.0% of similar patients undergoing cholangiography, improving therapeutic yield. In bacterial cholangitis superimposed, temporary drainage and flushing measures to keep the biliary ducts patent can be performed. This includes the use of naso-biliary tubes for drainage, biliary lavage for decanting and flushing[68], as well as percutaneous transhepatic cholangioplasty for relief of jaundice[69].

IgG4-sclerosing cholangitis

Choledochoscopy is primarily used to visually differentiate IgG4-related sclerosing cholangitis (IgG4-SC) from PSC and CCA. Accurate differentiation is essential as the prognosis and management of the three conditions differ[66]. A study by Itoi *et al*[70] using peroral videocholangioscopes on 33 patients found a significant discrepancy in the incidence of visual findings such as the presence of dilated and tortuous vessels, scarring, and pseudodiverticula between patients with IgG4-SC and PSC (P = 0.015, P = 0.001, P = 0.0007 respectively). There is a significant discrepancy in the incidence of partially enlarged vessels and dilated vessels between IgG4-SC patients and distal CCA (P = 0.004) and hilar CCA (P = 0.015)[70]. Another study by Ishii *et al*[71] using peroral videocholangioscopes on 17 IgG4-SC and 53 CCA patients reported that the use of vessel morphology seen on choledochoscopy could distinguish IgG4-SC patients from CCA patients with sensitivity (96%), specificity (89%), interobserver agreement (κ = 0.719), and the intraobserver agreement (κ = 0.768 and 0.754).

CCA

Choledochoscopy may be helpful in the precise preoperative mapping of CCA before surgical resection. This section will discuss the utility of choledochoscopy regarding its rate of adequate tissue acquisition, diagnostic accuracy in mapping the lateral extent of tumor involvement, ability to impact management, therapeutic interventions, and caveats to its use in CCA.

Choledochoscopy allows good access laterally along the bile duct to reach lateral margins of CCA. For example, in a study by Ogawa *et al*[72] involving 118 target sites along the extrahepatic bile duct, DSOC-guided mapping biopsies could reach 100% of target sites compared to fluoroscopy-guided mapping biopsy (78%).

Diagnostic accuracy of the preoperative mapping of CCA using choledochoscopy requires further validation, owing to the small sample sizes studied[73]. In a study by Pereira *et al*[74] involving 43 patients, the accuracy of DSOC-guided visual impression and DSOC-guided biopsy was 95% and 81% respectively in the diagnosis of CCA. To

further increase diagnostic accuracy in identifying the superficial spread of CCA based on visual impression, Fukasawa *et al*[75] proposed the novel Form-Vessel Classification (F-V scores), stratifying the form of biliary surface and vessel structure seen on peroral choledochoscopy into four and three grades, respectively. Amongst the 30 biopsy samples from 11 patients, higher F-V scores corresponded with a higher histological malignancy rate and frequency of mutant alleles[75].

Furthermore, choledochoscopy has been shown to alter management. Tyberg *et al*[76] reported that DSOC-guided mapping biopsy altered the surgical plan in 32 out 105 patients, where six patients required less extensive surgery, 12 had more extensive disease precluding surgery, and 14 were found to have the benign disease.

Caveats to the use of choledochoscopy in the preoperative mapping of CCA include suboptimal rates of successful biopsies attributable to inadequate sample size[72] and limited ability to visualize proximal tumor margin and submucosal tumor extension in all patients[77].

The use of choledochoscopy to perform therapeutic interventions in CCA has also been explored. As mentioned in the section on adjuncts to choledochoscopes above, the use of radiofrequency ablation, photodynamic therapy, and modalities like Nd-YAG laser ablation or Argon plasma coagulation in treating hemobilia have been explored in recent years[78]. However, further studies should be reported to broaden the currently lacking literature as therapies like photodynamic therapy are currently rarely used due to their complex logistical requirements and unclear role in managing biliary pathologies such as malignant biliary strictures[12].

Extrahepatic stones

The primary use of the choledochoscopy resides as an option in managing large or complicated extrahepatic stones in the biliary tree after endoscopic measures have been considered or found unsuitable. Endoscopic treatment *via* ERCP with standard sphincterotomy or endoscopic papillary large balloon dilatation (EPLBD) is currently recognized as the first-line treatment for extrahepatic bile duct stones, using a combination of basket or balloon catheterization for the exploration and then extraction[79].

Choledochoscopy can be considered for the removal of difficult extrahepatic bile stones. POC-guided clearance is was highly effective in clearing difficult bile stones defined as large stones ≥ 15 mm in diameter and with a prior attempt at stone clearance or impacted multiple stones[80]. Any stones in the hepatic duct or above a stricture were also considered difficult. Choledochoscopy has also been touted to have surpassed the previous second-line therapy of mechanical lithotripsy. In a study involving 32 patients with huge common bile duct stones, defined as stones not cleared by endoscopic sphincterotomy and EPLBD or not amenable to EPLBD, Angsuwatcharakon *et al*[81] claimed a higher success rate in choledochoscopy-guided laser lithotripsy over mechanical lithotripsy in the first session (63.0% *vs* 100%, $P < 0.01$) and lower radiation exposure (20989 *vs* 40745 mGycm^2).

Additionally, the use of EHL and LL assisted by POC also has excellent duct clearance rates. Both EHL and LL had higher ductal clearance rates when compared to ESWL in dealing with retained biliary stones[82]. However, complications and length of hospital say were similar between the two. In a meta-analysis of 49 studies, Korrapati *et al*[83] noted the accuracy of POC to be 89.0% (95%CI: 84%-93%) for the visualization of the pathology and a clearance rate of 88.0% (95%CI: 85%-91%).

The safety and reduced radiation exposure make choledochoscopy an excellent alternative to conventional management of extrahepatic biliary stones. In a study by Franzini *et al*[4] involving 100 patients, the use of choledochoscopy-guided EHL was non-inferior to ERCP with EPLBD in the removal of complex biliary stones (defined as > 15 mm, > 10 stones, the disproportion of ≥ 2 mm between stone and distal common bile duct or biliary stricture with a stone upstream)[84]. However, some still consider POC to be relatively complicated and time-consuming despite its safety and benefits compared to the conventional and more straightforward mechanical lithotripsy technique[85]. In a study by Buxbaum *et al*[86] consisting of 60 patients comparing POC-assisted lithotripsy and conventional therapy (defined as mechanical lithotripsy), the duration for lithotripsy procedure was significantly longer (120.7 *vs* 81.2 min, $P = 0.0008$). In contrast, Angsuwatcharakon *et al*[81] claimed that there was no significantly different procedure time (66 *vs* 83 min, $P = 0.23$) between POC-assisted lithotripsy and mechanical lithotripsy in stone management after the failure of EPLBD. While more trials with higher power should be performed to establish the significance of this disparity in procedural time, the efficacy and non-inferior complications rate of POC-assisted lithotripsy against manual lithotripsy in the management of large bile duct stones has been established. Therefore, it can be used as a standard of care after failing

endoscopic treatment with ERCP and sphincterotomy.

The efficacy of different types of POC in stone removal is also a consideration. In a retrospective study involving 32 patients who failed conventional ERCP for stone removal, Murabayashi *et al*[87] noted that both DSOC and videocholangioscope (CHF-B260) achieved a 100% complete stone removal with similar adverse event rates. However, DSOC was noted to have significantly shorter procedural time (67 ± 30 minutes *vs* 107 ± 64 min), and a lesser number of endoscopic sessions were needed (1.35 ± 0.49 *vs* 2.00 ± 0.85)[87].

Alternative therapeutic options like ESWL, where direct contact with the stone is unnecessary, are valuable when patients cannot undergo endoscopic therapy[88]. However, the risk of recurrence was notably higher when compared to POC. A prospective study of 58 patients by Aljebreen *et al*[89] compared ESWL and SpyGlass-guided EHL. Bile duct stone clearance rate was 100% in the SpyGlass-guided EHL group and 64.4% in the ESWL group. Historically, the role of chemical dissolution (such as methyl) of stones had been entertained by perfusing the common bile duct with solvents. However, the success rate remains low (66%-74%), with high complication rates (67%), including haemorrhage, duodenal ulceration, acute pancreatitis, and anaphylaxis[90].

Intrahepatic stones

The use of cholangioscopy for hepatolithiasis is limited due to relatively smaller hepatic ducts and strictures within the intrahepatic lumens[12]. Consequently, the literature is scarce, with few large patient studies. In a case series involving 190 patients, Cheng *et al*[91] reported a high intrahepatic stone clearance rate *via* POC (88.4%). However, a higher recurrence rate is reported with such an approach. In a retrospective study by Huang *et al*[92] of 245 patients undergoing PTCS to treat hepatolithiasis, recurrence rates was 63.2% overall, depending on the type of hepatolithiasis. Cholangioscopy *via* a percutaneous transenteric approach *via* access loop is another alternative for hepatolithiasis extraction. Access loops are preemptively created during hepaticojejunostomy for ease of future biliary interventions. This is particularly relevant for patients with intrahepatic strictures, predisposed to recurrent hepatolithiasis and cholangitis requiring repeated biliary intervention[93]. In cases with altered surgical anatomy, the use of cholangioscopy is valuable, allowing access to pathology sites without a choledochotomy, hence sparing the patient from a T-tube insertion. This helps lower complication rates and operative duration, and the length of hospital stay[94].

Other indications

In terms of diagnostic indications, choledochoscopy has also been used in diseases with a higher probability of malignant transformation, such as in the detection of dysplasia[95] and intraoperative determination of resection planes[96] in choledochal cysts, or diagnosis of malignant lesions such as intraductal papillary neoplasms of the bile duct[97]. In addition, recent reports demonstrate a role in the diagnosis of benign biliary pathologies such as cholangioadenoma[98], biliary papillomatosis[99], eosinophilic cholangitis[100], choledochal varices[101], right hepatic artery syndrome[102], congenital pancreaticobiliary maljunction[103], post-transplant ductal ischemia[104], infections such as cytomegalovirus and human immunodeficiency virus-associated cholangiopathy[105,106] and intraoperative evaluation for intrahepatic biliary duct injury during surgery[107].

For therapeutic interventions, choledochoscopy is useful in visualization and subsequent guidewire placement in the context of surgically altered anatomy. One example is PTCS in severe biliary-enteric strictures that have failed conventional fluoroscopic techniques[108]. Other examples include DSOC-guided direct visualization of late fibrotic strictures of anastomotic regions after deceased donor transplantation. This enabled guidewire placement, followed by subsequent dilation and stent placement[109,110]. Other surgically altered anatomy to which choledochoscopy is used successfully includes strictures in hepaticojejunostomy, afferent loop syndrome[111], and other complex biliary strictures that previously failed conventional guidewire placement[112]. Treatment of haemobilia has also been reported[78].

Choledochoscopy-assisted endoscopic transpapillary gallbladder stenting (ETGS) and subsequent drainage in acute cholecystitis is a potential use that has been recently explored. ETGS is an alternative for acute cholecystitis patients with significant comorbidity who are at prohibitive risk for cholecystectomy or even percutaneous cholecystostomy[113]. However, ETGS is commonly limited by poor cystic duct cannulation rates. In a retrospective study by Cao *et al*[114] of 226 patients with acute cholecystitis requiring ETGS, the use of single-operator choledochoscope guidance

increased the overall technical success of cannulation rates to 75%-86.4%.

COMPLICATIONS

Complications arising from choledochoscopy can be divided into procedure-related complications (including preparatory and intra-procedure complications) as well as technical complications of choledochoscopy. We will discuss a possible preventive measure that can be taken.

Procedure-related

For percutaneous choledochoscopy, complications occur during preparatory procedures such as percutaneous transhepatic biliary drainage and tract dilation than during choledochoscopy itself[115]. Regarding mild complications, a study by Wang *et al*[116] on 826 patients reported bleeding (1.9%), T-tube dislodgement (0.8%), infection (0.7%), basket incarceration (0.6%), and bile leaks (0.4%). Additionally, post-operative choledochoscopy could result in damage to T-tube systems, preventing extraction of retained stones, and causing bleeding and intestinal fistulas[117]. Severe complications include severe haemobilia, haemoperitoneum, sinus tract rupture, and ductal injury [115].

Peroral choledochoscopy is generally regarded as a low-risk procedure. Complications such as cholangitis, pancreatitis, haemobilia, bile leak, air embolization, bile duct perforation have been reported[44]. A meta-analysis by Korrapati *et al*[83] involving 2193 patients across 49 studies who underwent peroral choledochoscopy reported an overall adverse event rate of 7% (95%CI: 6%–9%), where complications primarily included cholangitis, followed by pancreatitis and perforation. However, Lenze *et al*[118], reported a 16.4% adverse event rate (pancreatitis, cholangitis, or significant bleeding) amongst 67 patients who underwent DSOC. While all complications in this study were successfully treated conservatively, it reinforces that choledochoscopy should only be used in patients failing conventional procedures.

Technical-related

Rates of adverse events arising from choledochoscopy have been compared against conventional procedures used in biliary disorders. A large retrospective study by Sethi *et al*[119] compared the adverse event rates occurring in 3475 ERCP procedures and 402 ERCP with additional choledochoscopy. It was found that the additional choledochoscopy contributed to a significantly higher rate of cholangitis than when the only ERCP was done (1.0% *vs* 0.2%; OR = 4.98; 95%CI: 1.06-19.67), which is postulated to be secondary to intermittent intraductal irrigation during choledochoscopy[119]. A caveat when comparing adverse events rates across procedures is the selection bias in patients undergoing choledochoscopy. They are likely to have failed conventional methods like ERCP, possibly due to underlying complicated anatomy or lesions, which in itself may predispose to complications[83].

Prevention of complications

Risks of complications can be mitigated. A retrospective multicentre study by Ang *et al*[120] analyzing 250 DSOC procedures found that prophylactic pre-procedural antibiotics significantly decreased the rate of cholangitis in patients who received antibiotics (n = 102) than those who did not (n = 148) (1% *vs* 12.8% respectively, P < 0.001).

Special considerations

Choledochoscopy has demonstrated good safety profiles in diverse patient groups – the elderly, pregnant women, and children. In a multicentre study by Bernica *et al*[121] across 209 patients, there was no significant difference in adverse events rates even in patients above 75 years old when compared with younger patients (7.30% for patients aged below 65 years, 6.98% for patients aged 65–75 years, and 7.79% for patients aged above 75 years; P < 0.17). Choledochoscopy is a promising alternative procedure for choledocholithiasis in pregnant women who require minimal radiation exposure. Pregnant women with choledocholithiasis have significant radiation exposure when treated conventionally *via* ERCP. A case report demonstrated the ability to completely reduce radiation exposure during choledocholithiasis identification and removal using DSOC. This combination of DSOC with ERCP was not associated with adverse maternal and fetal outcomes[122]. Case series have also reported successful choledochoscopy with no significant complications in children for indications such as

intrahepatic lithotripsy[123], evaluation of biliary strictures, and management before and after liver transplant[124]. While choledochoscopy in children is beyond the scope of this review, it can be extrapolated to be a safe and effective modality used in pediatric biliary pathologies such as Caroli disease, biliary atresia, and monitoring post-Kasai procedure.

In summary, choledochoscopy is generally a low-risk procedure that can be used even in the elderly, pregnant women, and children when indicated. However, given that patients undergoing choledochoscopy have a higher risk of complications than conventional biliary procedures, choledochoscopy should only be used in patients failing conventional procedures.

LIMITATIONS

Overall limitations of choledochoscopy include operator-dependency, cost, and technical limitations in choledochoscopes and accessories.

Firstly, the accuracy of choledochoscopy is highly operator-dependent and may be affected by insufficient endoscopy experience (< 25 cases performed)[49]. Increased choledochoscopy volume could result in a less steep learning curve. This is supported by the concept that repetition allows for accurate anatomical recognition and more straightforward instrumentation guidance[125]. Simulated training models are proposed to improve inter-operator discrepancy. A randomized control trial by Li *et al*[126] involving 20 resident trainees found that the use of physical three-dimensional printed models for simulated choledochoscopy led to significantly higher accurate anatomical structure identification ($P < 0.05$) and reduction in time taken to complete simulated choledochoscopy. Other training models include a three-dimensional printed model of a biliary tree integrated with augmented reality by Tang *et al*[127]. This allows for spatially accurate real-time simulated choledochoscopy. A training model for the freehand double-bending D-POC technique is also reported[128]. The advent of artificial intelligence to aid in customized, individualized learning should also be considered in surgery[129]. Larger studies are needed to validate these training models, determine optimum training time to achieve competency in choledochoscopy and compare if training translates to reduced inter-operator discrepancy in clinical practice.

Another limitation lies in the cost-benefit analysis of choledochoscopy compared to conventional procedures. High capital costs for the initial purchase of processors, scopes, and repair costs are cited as factors against choledochoscopy. For recurring costs for performing a single procedure, Loras *et al*[130] found that additional choledochoscopy use during ERCP in 2018 can increase procedural costs alone by $3662.71 and $2637.02 for stone extraction and stricture diagnosis, respectively. ERCP with choledochoscopy was the most expensive among advanced endoscopic procedures studied, even though ERCP alone was not more expensive than most other procedures[130]. However, there is an argument for cost-efficacy in choledochoscopy. Choledochoscopy may reduce the need to perform costlier procedures. In a study by Sandha *et al*[131] across 51 patients with difficult-to-access choledocholithiasis, choledochoscopy-guided lithotripsy circumvented the need for laparoscopic and open surgical bile duct exploration. This decreased costs per procedure by $1619 and $3210 respectively[131]. However, it is essential to consider the potential reusability of the equipment. While it is thought that reusable devices are more cost-effective and environmentally less damaging[132], the use of disposable equipment in other laparoscopic surgeries is noted to be associated with more significant intraoperative problems caused by technical difficulties[133]. Thus, proper handling and technical maintenance of reusable equipment should be emphasized and taught to benefit financially, economically, and technically.

Other limitations include the technical aspects of fiberoptics and accessories. Suboptimal image quality, size of therapeutic channels of current systems, ease of use, and various accessories still limit choledochoscopy use[12]. However, given how new technology could overcome previous models' limitations and develop new accessories quickly, it is promising that current technical limitations can similarly be overcome.

FUTURE DIRECTIONS

Future studies can develop quality indicators to prove the adequacy of choledochoscopy, validate technological advances, and identify factors affecting

choledochoscopy efficacy and methods to overcome limitations in specific indications such as IBS diagnosis and preferred management of complex bile stone disease.

First, future studies can focus on ways to improve the accuracy of choledochoscopy. Other than hyperbilirubinemia and endoscopists' experience, patient and procedural factors should be identified[49]. This can guide ways to optimize patients pre-procedure and improve the quality of choledochoscopy. Specifically, studies are still needed to determine the optimal number of biopsies for IBS diagnosis while considering technical improvements in choledochoscopy forceps jaws (*e.g.*, SpyBite Max). Regarding visual impression, many studies have developed novel visual classification systems such as the "tumor vessel sign"[51], characterization of mucosal and vascular features[52-54], and the Monaco Classification[55]. However, these are done using specific choledochoscopes like DSOC. Given how different choledochoscopes have variable imaging quality, studies need to determine if such visual classification systems can be accurately applied even when using choledochoscopes with lower imaging quality. Subsequently, comparative studies are needed to determine a standardized classification system with the highest accuracy and least inter-observer variability.

Secondly, there is a lack of quality indicators to demonstrate the biliary system's complete visualization in real-time during each choledochoscopy. Good advancement of the choledochoscope for complete visualization is often presumed[134]. Zimmer *et al*[134] proposed the visualization of the "bilio-papillary Z line" as a quality indicator. As it represents the distal-most end of the common bile duct at the bilio-papillary junction, visualization of the "bilio-papillary Z line" is thought to confirm visualization of the entire common bile duct. However, this marker is limited due to occasional difficult access and prolapsing papillary mucosa at this junction[134]. Future studies should evaluate this marker's accuracy and develop other quality indicators easily adaptable in clinical use.

Thirdly, studies can further clarify the role of novel enhanced imaging systems and new video display techniques. Some studies involving NBI and i-Scan reported no increase in diagnostic accuracy rate despite improved duct visualization[23,24]. Future studies need to explore if improved biliary visualization correlates to improved diagnostic or therapeutic efficacy.

To further improve image quality, studies can explore the use of new display techniques during choledochoscopy, which may negate any loss of three-dimensionality and poor spatial orientation associated with choledochoscopy. These include three-dimensional (3D) and two-dimensional-4K ultra-high definition (2D-4K), which has four-fold more pixels than two-dimensional high definition (2D-HD)[135]. While 3D and 2D-4K display techniques have not been studied in choledochoscopy, advantages are reported in laparoscopic surgery. The 3D display enables better laparoscopic performance compared to conventional 2D-HD monitors[136]. However, it is less clear whether 3D or 2D-4K display is better. Some studies demonstrated significantly better laparoscopic performance in 3D display than 2D-4K display, lower operative time, error rates[136], and increased precision in tasks[137]. Other studies found no significant difference in either operative time or error rates[138]. Nevertheless, given that 3D and 2D-4K displays may optimize scope-guided procedures, studies can consider evaluating these new display techniques in choledochoscopy.

Lastly, the role of artificial intelligence in chole-dochoscopy can be explored. Artificial intelligence has shown good accuracy in automating the detection of polyps, neoplasia, and blind spots and documentation of the procedure's technical details when used for colonoscopy and oesophagogastroduodenoscopy[139]. Given how it has shown potential in improving efficiency, particularly in gastrointestinal endoscopy, future studies may consider applying machine learning models to automate certain aspects of choledochoscopy.

CONCLUSION

Choledochoscopy (for extrahepatic biliary procedures) and cholangioscopy (for intrahepatic biliary procedures) is a dynamic instrument, adapting to a myriad of different circumstances. While the two phrases are used interchangeably, a distinction has to be acknowledged. It serves a diagnostic purpose in the evaluation of biliary pathologies and aids in histology sampling. It also serves a therapeutic purpose in stone fragmentation and extraction and manages malignant lesions in the biliary tree. Collectively, the utility of this instrument has advanced tremendously in recent years,

potentially overtaking conventional methods of diagnosis and treatment in the near future. Choledochoscopy is complementary to other endoscopic, interventional radiology, and operative techniques for biliary intervention as well. With the increasing ability of artificial intelligence to automate the detection of pathologies and individualise training for endoscopists, a future pioneered by choledochoscopy and cholangioscopy is promising.

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MINIREVIEWS

Composite intestinal adenoma-microcarcinoid: An update and literature review

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Abstract

Composite intestinal adenoma-microcarcinoid (CIAM) is a rare intestinal lesion consisting of conventional adenoma and small, well differentiated carcinoid [microcarcinoid (MC)] at its base. The incidence of CIAM is 3.8% in surgically resected colorectal polyps. While its pathogenesis is unknown, studies support the role of Wnt/β-catenin pathway in the tumorigenesis of CIAM. CIAMs have been primarily reported in the colon wherein they present as polyps with well-defined margins, similar to conventional adenomatous polyps. MC is usually found in adenomatous polyps with high-risk features such as large size, villous architecture, or high grade dysplasia. Histologically, the MC component is often multifocal and spans 3.9 to 5.8 millimeters in size. MC is usually confined within the mucosa but occasional CIAM cases with MC extending to the submucosa have been reported. MC of CIAM demonstrates bland cytology and inconspicuous proliferative activity. The lesional cells are positive for synaptophysin and 60% to 100% of cases show nuclear β-catenin positivity. MC poses a diagnostic challenge with its morphologic and immunohistochemical resemblance to both benign and malignant lesions, including squamous morules/metaplasia, adenocarcinoma, squamous cell carcinoma, sporadic neuroendocrine tumor and goblet cell adenocarcinoma. CIAM is an indolent lesion with a favorable outcome. Complete removal by polypectomy is considered curative. Awareness and recognition of this rare entity will help arrive at correct diagnosis and improve patient care. Currently, CIAM is not recognized as a subtype of mixed neuroendocrine-non-neuroendocrine neoplasm by WHO.

Key Words: Composite; Adenoma; Microcarcinoid; Composite intestinal adenoma-microcarcinoid; Wnt/β-catenin; Mixed neuroendocrine-non-neuroendocrine neoplasm

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Core Tip: Composite intestinal adenoma-microcarcinoid (CIAM) is a rare intestinal lesion consisting of adenoma and well differentiated microcarcinoid components. While it is a form of mixed neoplasm with both neuroendocrine and non-neuroendocrine elements, CIAM is currently not recognized as a distinct subtype of mixed neoplasm by WHO. It is found incidentally during the pathologic examination of adenomatous polyps. Altered Wnt/β-catenin pathway appears to play a role in its pathogenesis. Other benign and malignant lesions need to be distinguished from CIAM given differing therapeutic implications. CIAM is an indolent disease with a favorable outcome.

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INTRODUCTION

Composite intestinal adenoma-microcarcinoid (CIAM) is a rare intestinal lesion consisting of conventional adenoma and associated microscopic well-differentiated neuroendocrine cell clusters [microcarcinoid (MC)] at its base. The adenoma component presents as a typical polyp, which is removed either endoscopically or surgically[1-3]. The MC component does not form grossly evident nodules or masses [1,3] and is typically located at the base of the polyp, usually within the mucosa. Occasional cases of CIAM with the MC component extending into the submucosa have been reported[1,4,5]. As MC occupies only a minute area and forms small nests or clusters microscopically, the overall architecture of the polyp is preserved[2,3].

CIAM was first described by Moyana *et al*[6] in 1988. In this report, the authors described two adenomas co-existing with carcinoids: One was in the center of a dome-shaped polyp, and the other was at the base of a sessile villous adenoma. The authors also noticed a transition zone between the two components. It is unclear how much of the lesion was composed of carcinoid component in their report. However, based on the illustrations provided in the report, the carcinoid components do not appear subtle [6]. Since its first description, CIAM have been sporadically documented as case reports or small case series[2,5,7,8].

Although CIAM is a rare entity, endocrine cell "differentiation" is not uncommon in colorectal adenomas, wherein the cells of neuroendocrine phenotype are considered to originate from the endoderm[9,10]. For example, argyrophil cells have been reported in 59% to 85% of adenomatous polyps[10,11]. In Iwashita's study, argyrophil cells and argentaffin cells were found in 76.4% and 60.4% of 212 colorectal adenomas, respectively. These cells were usually located in the lower third portion of the adenomatous glands[9]. In 8% to 10% of these cases, the density of the neuroendocrine cells may be higher than usual[9,10]. Therefore, it is not surprising that endocrine cell neoplasia may arise within adenomas and that it localizes preferentially at the base of the adenoma[2].

CIAM is distinct from mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN). MiNEN is an umbrella term referring to a neoplasm with both neuroendocrine and non-neuroendocrine components[4,12]. It is required that each component constitutes at minimum 30% of the neoplasm to qualify for MiNEN[12-14]. The terms "low grade" MiNEN and mixed adenoma well-differentiated neuroendocrine tumor (MANET) have been interchangeably used in the literature for a subset of CIAM meeting the required criterion of 30% for each component[4,12]. However, not all CIAMs described in the literature are necessarily low grade MiNEN. Moreover, recent WHO did not officially endorse a composite tumor consisting of an adenoma (a precursor of invasive adenocarcinoma) and well-differentiated neuroendocrine tumor as a subtype of MiNEN in the gastrointestinal tract and hepatopancreatobiliary organs [14].

Although this rare entity is not recognized by the current WHO classification, its recognition will allow for more efficient pathological diagnosis and more detailed clinicopathologic studies, thus leading to better patient care. CIAM may be under-recognized given its rarity and occasional morphologic subtlety. Moreover, it can resemble other benign and malignant lesions and can be mis-diagnosed. Its prognosis is vastly different from that of malignant composite tumors with expansile growth. We summarize the current state of knowledge on CIAM and provide an overview on its pathogenesis, microscopic features, differential diagnosis, as well as prognosis and treatment options. The differences in terminologies–CIAM, collision tumor and MiNEN–are also briefly discussed.

DEMOGRAPHICS

CIAM is identified in middle-aged to elderly patients, with a reported mean age of 60 years[1-4]. Slight male predilection has been reported[1,4,15], while another study found no gender predilection[3]. It is unknown whether there is a demographic divergence between CIAM and typical adenomatous polyps.

INCIDENCE

Recently we reported that the incidence of CIAM is 3.8% in surgically resected colorectal polyps. Our cohort consisted of consecutive, surgically resected 158 colorectal polyps from one tertiary care center over a span of 16 years[1]. Its incidence in endoscopically removed polyps is unknown.

To date, the largest series of colorectal CIAM has been reported by Kim *et al*[3] in South Korea, consisting of 24 cases. In their series, the polyps were excised endoscopically (91.7%) or surgically (8.3%) over a span of 7 years[3]. In the United States, the largest series of intestinal (to include 4 cases in the duodenum) CIAM was reported by Estrella *et al*[15] in a Cancer Center, consisting of 25 cases over a span of nearly 18 years[15]. However, the incidence of CIAM was not reported in these studies.

ASSOCIATED CONDITIONS

Colorectal MC is likely exceedingly rare and no minimum size criterion is currently available. MC has been observed in patients with chronic colitis, such as diversion colitis[16] and inflammatory bowel disease (IBD), especially in ulcerative colitis[17-21]. Likewise, Weyant *et al*[22] described a case of colonic MC and diffuse neuroendocrine cell hyperplasia following long-term cystoplasty[22]. These associations suggest that MC may represent an exaggerated proliferative response of gut mucosa to chronic inflammation.

On the other hand, it is largely unknown whether these patients with inflammatory conditions actually have a higher incidence of CIAM. Most reported CIAMs are sporadic, and it appears to be a much rarer condition than solitary MC[3]. Sigel and Goldblum[17] described a well differentiated neuroendocrine tumor adjacent to high grade glandular dysplasia in the setting of IBD. The authors postulated that the neuroendocrine tumor might have originated from multipotential dysplastic cells in the adjacent mucosa[17]. Alternatively, the MC component may reflect a metaplastic phenomenon related to chronic injury of the overlying adenomatous component[7].

Genetic predisposition may account for some cases of CIAM. Carcinoids at the base of duodenal adenomas have been reported in association with familial adenomatous polyposis (FAP)[15,23]. These observations support a role of the adenomatous polyposis coli (APC)/β-catenin pathway in the pathogenesis of CIAM (to be discussed below), although the risk of CIAM is probably explained by the risk of adenoma in this cohort.

PATHOGENESIS

The mechanism for the development of MC component in CIAM is not well understood. Earlier, authors postulated that CIAM represents a form of collision

tumor wherein the two components arise from two different clones and they coincidentally occur adjacent to one another[8]. However, evolving knowledge regarding the multipotent stem cells in the gut and their role in tumorigenesis has shed light on the possible histogenesis of tumors with different histologic components such as CIAM. Indeed, *in vitro* studies of the ileal epithelial cells (IEC-18) of rat have shown that these cells can transform into differing cell types with one type showing neuroendocrine-like morphology and expressing serotonin receptor gene, and the other with adenoma-like mRNA transcription and protein expression[24].

Likewise, a morphologic "transition zone" has been observed in several studies of CIAM[2,4,6,25]. In Pulitzer *et al*[2]'s study, the MC appeared to arise directly from the basal epithelium of adenomatous crypts, penetrating the basement membrane and infiltrating the lamina propria[2]. La Rosa *et al*[4] also observed numerous cells with both morphologic and immunohistochemical neuroendocrine differentiation along the base of the adenomatous glands. In addition, these cells demonstrated the same mutational and microsatellite instability profile as the adenomatous components, further supporting the hypothesis that these two components most likely represent divergent differentiation of a common precursor[4]. Interestingly, unlike conventional adenomas without MC, no *KRAS* mutation was identified in either component of CIAM. These findings suggested that the adenoma component of CIAM may develop through an alternative *KRAS*-independent pathway[4].

The finding of CIAM in FAP patients suggests the involvement of the Wnt/β-catenin pathway in the tumorigenesis of CIAM, as expected based on the canonical pathway by which normal mucosa becomes adenomatous. The MC components of CIAMs frequently display strong and diffuse nuclear β-catenin reactivity by immunohistochemistry[1,2,7,15]. In Estrella *et al*[15] study, the level of nuclear β-catenin expression was higher in the MC component of CIAM when compared with either the sporadic neuroendocrine tumors without associated adenoma, or neuroendocrine carcinomas associated with adenoma. Moreover, there was no difference in the level of β-catenin expression between CIAM patients with and without FAP[15].

This plausible hypothesis, though, requires confirmation by additional molecular studies as neither the presence nor absence of nuclear β-catenin expression by immunohistochemistry appears to be a true reflection of an activated Wnt signaling pathway[15,26-29]. For example, Su *et al*[29] found that carcinoid tumors can show nuclear β-catenin immunohistochemical staining without mutations in the *β-catenin* and *APC* genes[29].

In summary, CIAM appears to represent a true composite tumor with a common origin for the MC and adenoma components, and is not a collision tumor. Further molecular studies are needed to better understand the mechanisms driving its tumorigenesis.

PRESENTATION

CIAMs have been reported in the stomach, duodenum, ileum, colon, and rectum[4]. They are predominantly found in the colon, usually in the cecum and right colon[1-3]. They present as polyps with well-defined margins, similar to conventional adenomatous polyps. The reported mean size of the polyps is 2.4 cm[3]. As the MC component is microscopic, it is incidentally found during the pathologic examination of otherwise typical adenomatous polyps.

To the best of our knowledge, no definite clinical symptoms related to the MC component of CIAM have been established, however, one case report of rectal "collision tumor" consisting of adenoma and carcinoid tumor presented with carcinoid syndrome (elevated serum serotonin and chromogranin A, elevated urine 5-hydroxyindoleacetic acid level, and moderate tricuspid regurgitation). The patient's symptoms subsided following the endoscopic removal of the polyp with wide margins[30]. It is unclear whether this case represents a composite tumor (CIAM) or a collision tumor, as the author did not provide detailed histologic examination and classified the lesion as "collision" tumor[30].

MICROSCOPIC EXAMINATION AND IMMUNOHISTOCHEMISTRY

Adenomas with a MC component are usually high-risk adenomas (size ≥ 10 mm, villous components and/or high grade dysplasia)[1,3,5,7,15]. Therefore, the adenomatous components of CIAM tend to be large. For example, the mean size of

polyps was 24 mm in Kim *et al*[3]'s study. In our study, the average size of the polyps was 42 mm (probably because our cohort consisted of surgically removed polyps that were deemed endoscopically unresectable), all of the adenomas showed villous components and 50% had high grade dysplasia (Figure 1). However, no statistically significant differences in terms of polyp size, polyp location (right *vs* left) or the frequency of associated high grade dysplasia between the adenomas with and without MC were found[1]. In contrast, in Kim *et al*[3]'s study where most of CIAMs were detected in endoscopically resected polyps, 86% of CIAMs had conventional adenoma with low grade dysplasia[3]. In Salaria *et al*[7]'s study, high grade glandular dysplasia was seen in 4 (36%) of 11 CIAMs[7].

Microscopically, the MC component is found at the base of full-thickness adenomatous glands. The background lamina propria is myxoinflammatory with sometimes conspicuous eosinophils. The MC components are oftentimes connected to the overlying glandular components[3]. These small nests, irregular cords or clusters of neuroendocrine cells are sparsely distributed and do not form grossly evident nodules or masses (Figure 1). Occasional acinar structures may be seen[1-3,7].

In Salaria *et al*[7]'s study, the MC component extended over an average length of 3.9 mm. Also 64% (7/11) of the MCs were multifocal[7]. In Kim *et al*[3]'s and La Rosa *et al*[4]'s studies, the mean size of the MC components was 4.7 mm and 3.2 mm, respectively[3,4]. In our study, MCs were distributed over a mean area of 5.8 mm and were multifocal in 83% of the cases. In a majority of CIAMs, the MC components are confined within the mucosa, though extension into the submucosa can be seen[1,4,15] (Figure 2).

Cytologically, the neuroendocrine cells constituting MC are bland and monotonous (Figure 1). The cells show scant to abundant granular or eosinophilic cytoplasm and round central nuclei with salt and pepper-pattern chromatin. They are devoid of nuclear atypia, hyperchromasia, nuclear pleomorphism, conspicuous mitotic activity, and apoptosis. In other words, they are typical well-differentiated neuroendocrine cells.

By immunohistochemistry, the MC components are positive for synaptophysin (Figure 2B), supporting their neuroendocrine differentiation[1,3,15]. Chromograinin-A and CD56 show variable staining[4,5]. Variable immunolabeling with squamous markers such as p63 and CK5/6 can be seen[1,7]. They are well-differentiated with a low Ki-67 proliferation index (usually < 1%-2%) (Figure 2D), although sometimes the total number of neuroendocrine cells in MC may be insufficient (< 500 cells in total) for reliable Ki-67 index measurement[1,3,7]. The MC component shows nuclear β-catenin positivity (Figure 2C) in 60% to 100% of the cases, suggesting the role of Wnt/β-catenin pathway in the CIAM tumorigenesis[1,7,15].

MOLECULAR ANALYSIS

La Rosa *et al*[4] carried out mutational analysis for *KRAS, BRAF, PIK3CA* and microsatellite instability analysis on 6 CIAMs. No mutations were identified, and all cases were microsatellite stable in both adenoma and MC components[4].

DIFFERENTIAL DIAGNOSIS

MCs in CIAM may pose diagnostic challenge and may lead to misdiagnosis or overdiagnosis. MC can resemble squamous morules/metaplasia, invasive adenocarcinoma, squamous cell carcinoma (SCC), sporadic neuroendocrine tumor, and goblet cell adenocarcinoma (GCA). Awareness and recognition of this entity is crucial for accurate diagnosis and patient care.

Squamous morules/metaplasia

Squamous morules/metaplasia is an incidental histologic lesion that can be seen in colorectal adenomas[13,31]. The reported incidence of squamous morules in colonic adenoma is about 0.4%[11,32,33]. In our study, the incidence of squamous morules was 5.1% in surgically resected large colonic polyps[1].

Microscopically, squamous morules are characterized by a proliferation of immature squamoid or spindled cells forming nests and nodules without definitive keratinization or intercellular bridges[11,13,32]. Usually the nests protrude into the lumen of adenomatous glands (Figure 3), or may be identified at the base of the polyps especially in the cases of torsion and prolapse[1,13,32]. Immunohistochemically,

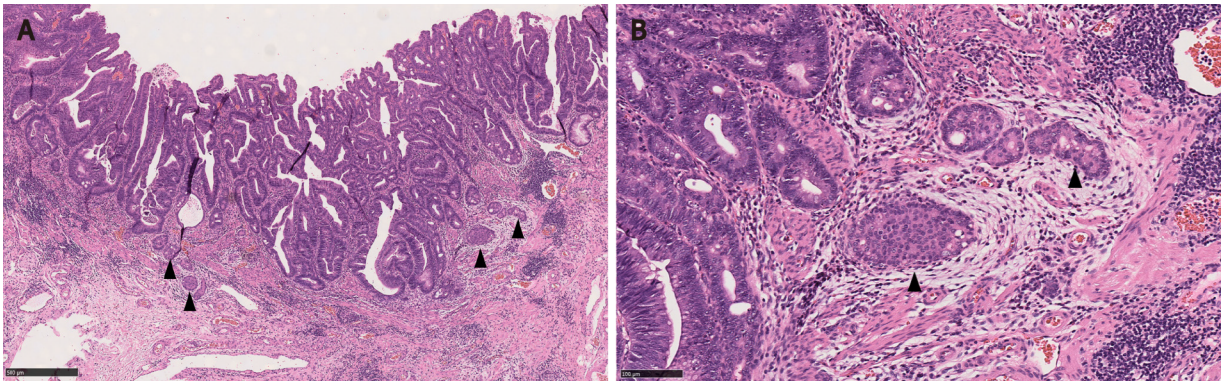

Figure 1 Composite intestinal adenoma-microcarcinoid consisting of tubulovillous adenoma with high grade dysplasia and microcarcinoid components (arrowheads) at its base. A: The overall polyp architecture is preserved (Hematoxylin and eosin, 50 ×); B: Microcarcinoid component shows bland cytology, within edematous stroma with conspicuous eosinophils, resembling desmoplasia (Hematoxylin and eosin, 200 ×).

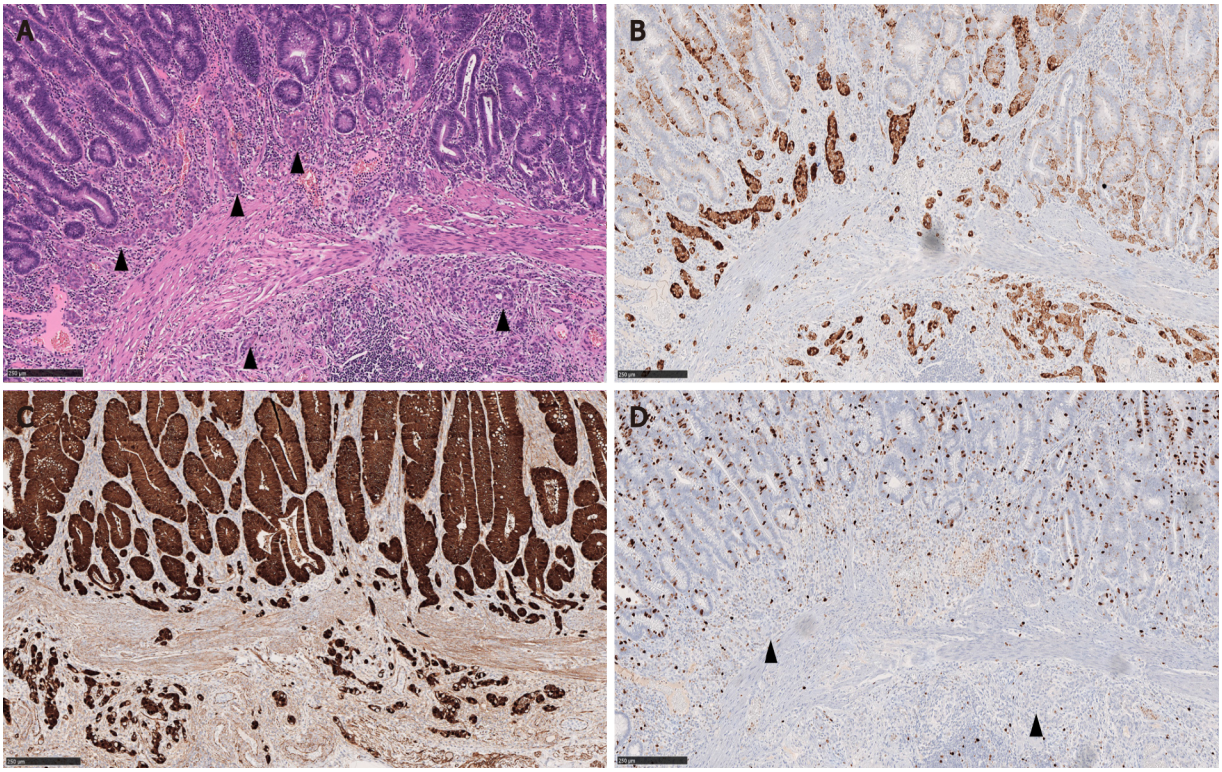

Figure 2 Composite intestinal adenoma-microcarcinoid with submucosal invasion of the microcarcinoid component. A: The microcarcinoid (MC) components (arrowheads) form small nests that are sparsely distributed at the polyp base. No nodules or masses are grossly evident (Hematoxylin and eosin, 100 ×); B-D: The MC components are positive for synaptophysin and beta-catenin (nuclear stain) with low proliferative rate (arrowheads) (B: Synaptophysin immunostain, 100 ×; C: Beta-catenin immunostain, 100 ×; D: Ki 67 immunostain, 100 ×).

squamous morules are positive for pan cytokeratin, CK5/6, cyclin D1 and β-catenin (nuclear staining)[1,13,34,35] (Figure 4) and show variable staining for p63[15,32]. Focal synaptophysin and chromogranin positivity can be seen[32].

There can be significant histomorphologic overlap between the MC component of CIAM and squamous morules**.** Both can present as solid nests around the bottom of adenomatous glands or myxoinflammatory stroma[1,32]. Indeed, in Kim *et al*[3]'s study, 6 CIAM cases were initially diagnosed as adenoma with squamous morules/metaplasia[3]. In Pulitzer *et al*[2]'s study, one CIAM was originally interpreted as adenoma with focal squamous metaplasia owing to the presence of abundant eosinophilic cytoplasm in MC[2]. In Salaria *et al*[7]'s study, MC was initially interpreted as squamous morules in 5 of 10 CIAMs[7].

In addition, there is immunophenotypic resemblance between the MC component of CIAM and squamous morules. Squamous morules may show focal positivity for

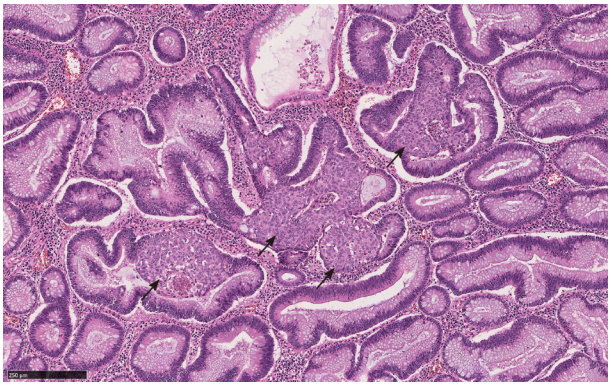

Figure 3 Squamous morules (arrows) with associated tubulovillous adenoma (Hematoxylin and eosin, 100 ×).

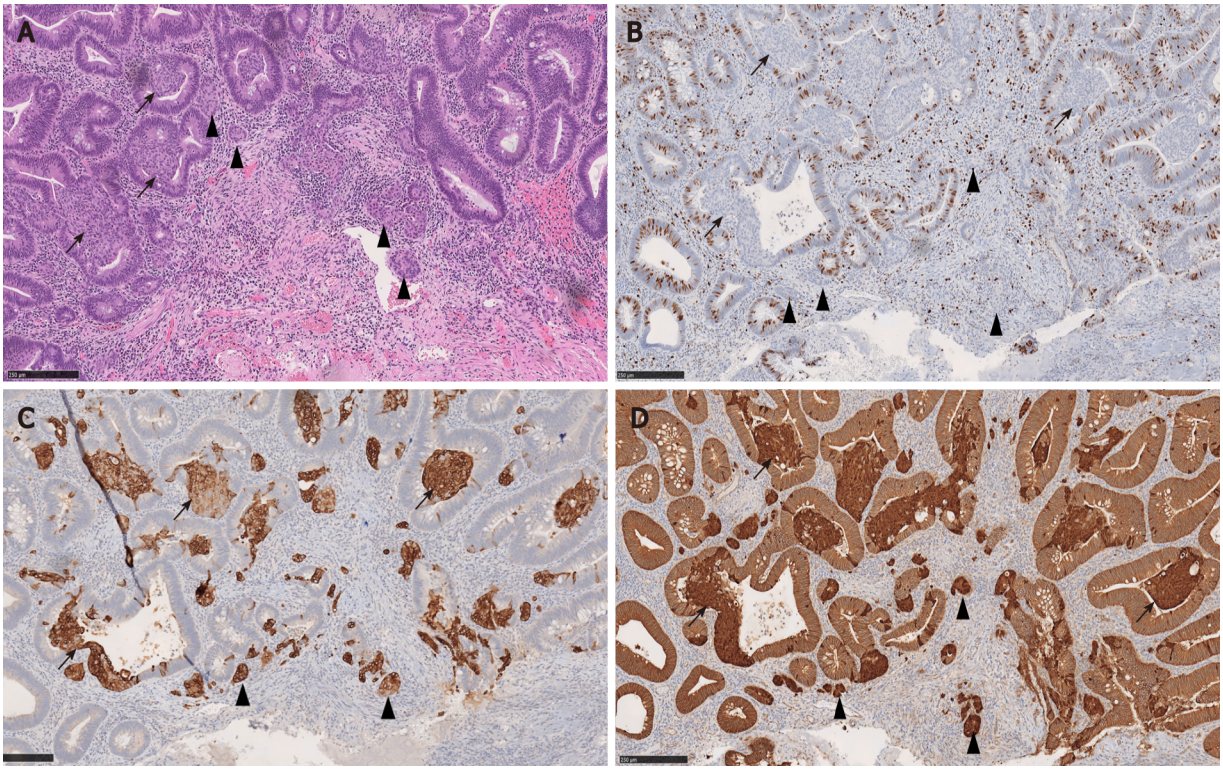

Figure 4 Composite intestinal adenoma-microcarcinoid with associated squamous morules (arrows). Both microcarcinoid (arrowheads) and squamous morules (arrows) show low proliferative rate and positivity for CK5/6 and beta-catenin (nuclear staining), suggestive of a shared pathogenesis. A: Hematoxylin and eosin, 100 ×; B: Ki 67 immunostain, 100 ×; C: CK5/6 immunostain, 100 ×; D: Beta-catenin immunostain, 100 ×.

neuroendocrine markers such as synaptophysin and chromogranin[32]. Conversely, the MC components of CIAM are variably immunoreactive with p63 and/or CK5/6 (Figure 4), suggesting squamous differentiation. In Salaria *et al*[7]'s study, 2 of 6 MC were focally positive for p63, and 5 of 6 MC were positive for CK5/6[7].

Given the morphologic and immunohistochemical overlap between squamous morules and the MC component of CIAM, we hypothesized that these two entities may be related. Interestingly, 33.3% (2 of 6) of CIAM showed concurrent squamous morule (Figure 4), compared to 4.0% (6 of 152) of adenomas without MC in our cohort, suggesting shared pathogenesis between the two ($P < 0.05$)[1]. Similarly, Estrella *et al* [15] reported that 4 (16%) of 25 CIAMs had squamous metaplasia in the adjacent adenomatous component[15].

Nevertheless, given that squamous morules/metaplasia is benign and the MC of CIAM is likely indolent, misdiagnosing MC as squamous morules/metaplasia may not have a significant clinical impact. In fact, it may be nearly impossible to distinguish these two in some cases.

SCC

As stated above, 16 to 33% of CIAMs can co-exist with squamous morules/metaplasia [1,15]. Moreover, MC components can demonstrate squamous differentiation with variable p63 and/or CK5/6 immunoreactivity (Figure 4) in a myxoinflammatory background mimicking desmoplasia. Therefore, SCC is considered a differential consideration for MC component of CIAM.

Primary colorectal SCC is a rare malignancy with an incidence of 0.1%-0.25%[36]. To date, less than 100 cases of colorectal SCC have been reported in the literature[37].

Usually, SCC of colon presents late in the disease course and shows an aggressive behavior with early metastasis and poor overall survival[38,39]. Thus, it is important not to overdiagnose the MC of CIAM as SCC. It will be helpful to be aware that MC can show immunohistochemical squamous differentiation to avoid this misinterpretation.

Invasive adenocarcinoma

MC components of CIAM may be misdiagnosed as invasive adenocarcinoma or tumor budding. Possible and reasonable explanations for this are: First, MC may show infiltrative or single-cell patterns at the polyp base, mimicking invasive disease[2] (Figure 5). Second, the background myxoinflammatory lamina propria associated with MC may resemble the edema and fibroblastic proliferation of desmoplasia that is usually associated with invasive disease[5,7]. Third, MC is commonly found at the base of full-thickness adenomatous mucosa frequently with high grade glandular dysplasia[1,5]. In fact, one of the CIAM cases reported by Lin *et al*[5] had been initially misinterpreted as adenocarcinoma[5].

Awareness of this entity and the recognition of bland cytoarchitecture and negligible mitotic activity of MC will be helpful to avoid misclassification[2]. Confirming neuroendocrine differentiation can be a useful diagnostic tool in challenging cases[7] (Figure 5).

Conventional sporadic neuroendocrine tumor

CIAMs and sporadic neuroendocrine tumors are treated differently. The MC components in CIAMs are usually situated at the polyp base in the mucosa, therefore complete polypectomy may suffice to remove the MC component with negative margin. On the other hand, the usual epicenter of sporadic neuroendocrine tumors is the submucosa. Therefore, additional surgery may be required to achieve complete resection with negative margin when the initial endoscopic biopsy shows sporadic neuroendocrine tumor[3].

For example, sporadic rectal neuroendocrine tumors are relatively common and oftentimes present as nodules or polyps on endoscopy[14,40-43]. They are usually small (over 50% of the cases < 1.0 cm in diameter), low grade, and located in the mucosa or submucosa[14] (Figure 6). Moreover, 79% to 84% of rectal neuroendocrine tumors are L-cell type that is known to be associated with rather indolent biologic behavior[44,45]. Therefore, rectal neuroendocrine tumors have an excellent overall prognosis especially after an endoscopic resection[41,42,45]. However, tumor stage and grade are still important prognosticators[41,43,46]. Large tumor size [(≥ 1.0 cm), high grade (WHO grade 2 to 3)], and the presence of muscular and lymphovascular invasion are often associated with metastatic disease, requiring aggressive treatment [43].

Nevertheless, MCs of CIAMs may also invade the submucosa[1,4,5,15]. Thus, to ensure complete removal of the MC component, further surgery may still be required following polypectomy[47]. Therefore, from a management standpoint, the tumor size and depth appear to be more relevant than their classifications.

Few studies have explored the biological differences between the MC components in CIAMs and sporadic intestinal carcinoid tumors without associated adenomatous components. Estrella *et al*[15] observed significantly higher β catenin expression score in CIAMs compared with sporadic neuroendocrine tumors, suggesting that CIAM may develop *via* a distinct pathway from the latter (*i.e.*, the adenoma pathway). In this study the overall 3- and 5-year survival of CIAM patients was significantly lower than those with sporadic NET[15]. This likely is due to the co-existing adenoma in CIAM as no CIAM patients died of neuroendocrine tumor in this study.

GCA

GCA, previously known as goblet cell carcinoid, adenocarcinoid, crypt cell carcinoma and microglandular carcinoma, is a subtype of appendiceal neoplasm. GCA is a mixed tumor with both glandular and neuroendocrine elements, and contains goblet cells

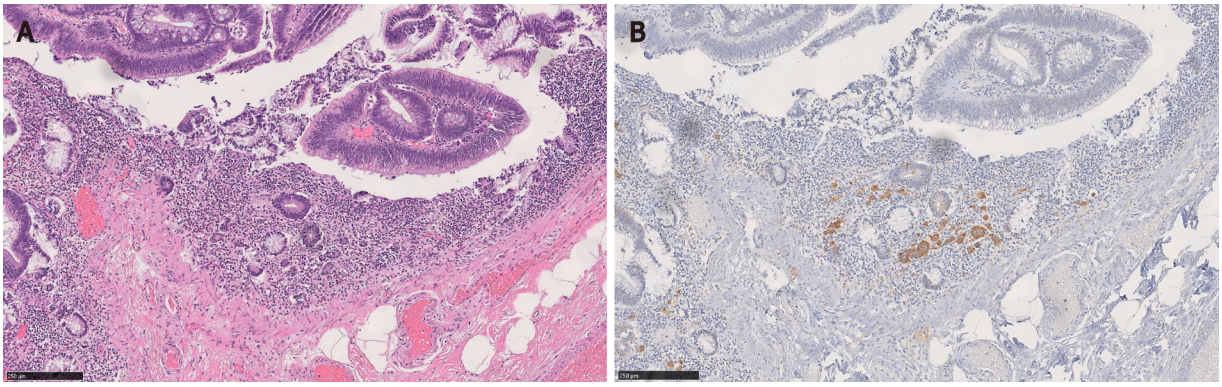

Figure 5 Microcarcinoid component of composite intestinal adenoma-microcarcinoid may mimic invasive adenocarcinoma. A: The microcarcinoid component is found at the base of full-thickness adenomatous glands (Hematoxylin and eosin, 100 ×); B: However, the constituting cells are positive for synaptophysin immunostain (Hematoxylin and eosin, 100 ×).

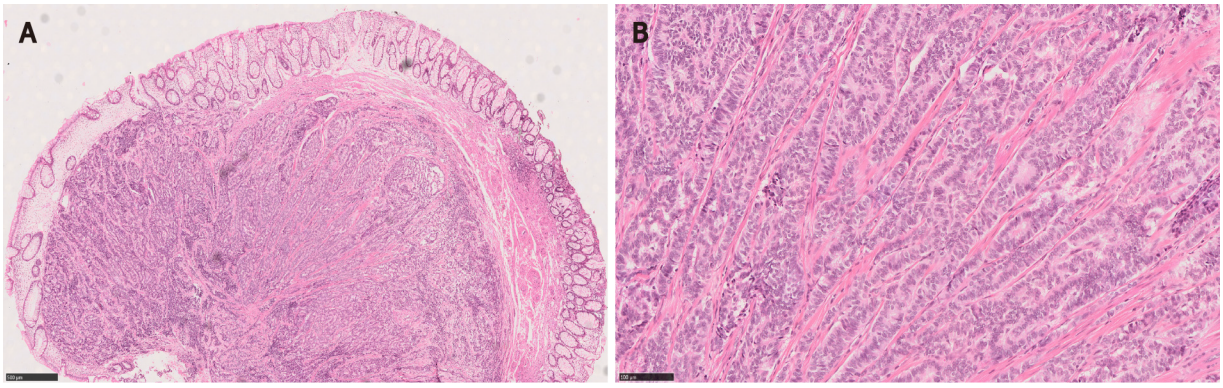

Figure 6 Rectal neuroendocrine tumor forming a nodule/polyp. A: The epicenter of the tumor is in the submucosa and the tumor extends to the deep margin (Hematoxylin and eosin, 40 ×); B: High magnification view shows typical trabecular growth pattern (Hematoxylin and eosin, 200 ×).

(Figure 7). The tumor nests stain positively for neuroendocrine markers and mucin [14]. Despite its mixed phenotype, GCA is officially recognized as a subtype of adenocarcinoma in the current WHO given its aggressive biologic behavior that is akin to adenocarcinoma[14,48]. GCA may co-exist with adjacent cecal adenoma[49]. Therefore, it is possible that cecal adenoma with underlying GCA may be interpreted as CIAM. Indeed, based on the provided illustrations, some authors raised a possibility that one of Lin *et al*[5]'s CIAM cases with lymph node metastasis may represent GCA with overlying adenoma[3,50]. GCA is an aggressive tumor and often presents with metastatic disease[51-53]. Further surgical management and chemotherapy are commonly required[53].

CIAM *VS* COLLISION TUMOR *VS* MINEN

Composite tumor, such as CIAM, is considered pathogenetically distinct from collision tumor. MiNEN is a broader category than CIAM.

Collision tumor

Lewin[54] first proposed to separate composite tumor and collision tumor when neoplastic endocrine cells and nonendocrine epithelial cells are admixed. In a composite tumor, glandular and neuroendocrine components are intermingled, and both components may share common origin. Whereas in a collision tumor, the two elements "collide" but are pathogenetically independent of each other. One of the two elements may represent a metastasis from another primary site[14,54].

Recently, Schizas *et al*[55] carried out a literature review on collision tumors of the digestive system. In this review, the authors defined collision tumors as those consisting of two or more independent neoplasms without intermingling (thus

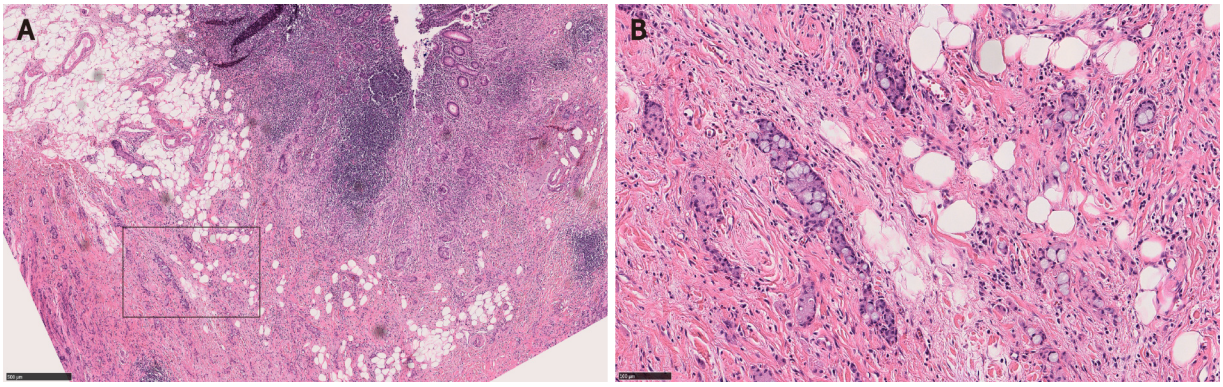

Figure 7 Appendiceal goblet cell adenocarcinoma. A: The tumor nests infiltrate and undermine the appendiceal mucosa (Hematoxylin and eosin, 50 ×); B: Bland cytology may mimic well-differentiated neuroendocrine tumor such as seen in the microcarcinoid component of composite intestinal adenoma-microcarcinoid (Hematoxylin and eosin, 200 ×).

without transition zone). In colon, adenocarcinoma was the main component of collision tumors, found in 78.6% of the cases, followed by carcinoid, seen in 35.7%[55]. Collision tumors are often high grade with early metastasis and a shorter survival[56-58].

Traditionally, collision tumors have been believed to represent "double primaries" though a few studies challenged this concept[56,58,59]. For example, Minaya-Bravo *et al*[58] reported a case of colonic collision tumor consisting of adenocarcinoma and large cell neuroendocrine carcinoma without identifiable transition zone. Three years later, the tumor metastasized to the retroperitoneum. Interestingly, both components metastasized, suggesting that both components of this collision tumor may have originated from the same clone[58]. Similarly, Pecorella *et al*[56] reported a cecal collision tumor consisting of adenocarcinoma and high grade well-differentiated neuroendocrine tumor (reported Ki67 proliferation index was 36%). There was focal positivity for CEA in the neuroendocrine tumor component without clear transition zone between the two components. The authors concluded that some mixed tumors cannot be precisely classified.

MiNEN

MiNEN is a recently introduced umbrella terminology referring to a neoplasm demonstrating a mixture of neuroendocrine and non-neuroendocrine components[4,12,14]. The terms "low grade" MiNEN and MANET have been proposed to describe mixed tumors with adenomatous components and well-differentiated neuroendocrine tumors (to include WHO grades 1 to 3)[4,12]. However, neither low grade MiNEN nor MANET has been officially recognized as a subtype of MiNEN in the current WHO [14]. In fact, in the gastrointestinal tract and hepatopancreatobiliary organs, WHO limits the use of the MiNEN term only to the mixed tumors with malignant non-neuroendocrine components[14] (Figure 8).

Even if low grade MiNEN (MANET) were to be recognized by WHO, there are differences between CIAM and low grade MiNEN. In MiNEN, each component should represent at least 30% of the total volume of the neoplasm. Therefore, some CIAMs with minor MC components would not meet the 30% cutoff criterion for low grade MiNEN. As many studies on CIAM did not specify the amount of MC components relative to the tumor volume, it is difficult to assess how many of the reported CIAM cases had MC components that occupied over 30% of the total tumor volume[2,5,7]. In our study, all 6 CIAM cases had minor MC components constituting much less than 30% of the tumor volume[1]. In addition, most of the MC components in CIAM are low grade with a negligible ki67 proliferation index, whereas low grade MiNEN can have grade 2 and 3 levels of proliferation in the neuroendocrine components[4]. Typical MiNEN with malignant non-neuroendocrine component mixed with neuroendocrine carcinoma is an aggressive neoplasm with a median overall survival of 13.2 mo. The ki67 proliferation index of the neuroendocrine component may drive the prognosis of these tumors[60].

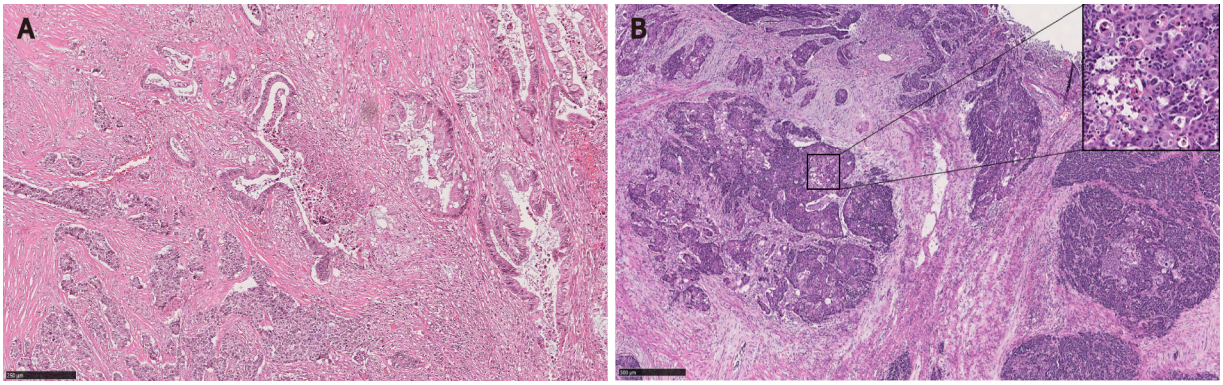

Figure 8 Mixed neuroendocrine-non-neuroendocrine neoplasm. A: Mixed colonic adenocarcinoma (upper right) and large cell neuroendocrine carcinoma (lower left); B: Mixed colonic squamous cell carcinoma and large cell neuroendocrine carcinoma (Inset: high magnification view shows squamous differentiation). Hematoxylin and eosin, 100 ×.

PROGNOSIS

CIAM is an indolent disease with a favorable outcome. One study found that after mean follow-up of 6 (range 0.5 to 27) years, none of the patients had recurrence of CIAM or metastasis after endoscopic or surgical treatment[4,15]. In our study, after mean follow-up of 53 mo, all patients were free of CIAM. In addition, all the lymph nodes retrieved during the surgical resection were devoid of adenocarcinoma or neuroendocrine tumor. Our two patients with MC components extending into the submucosa were followed for 14 and 15 mo, respectively. There was no evidence of recurrence or metastasis of neuroendocrine tumor at the end of the follow-up[1]. In La Rosa *et al*[4]'s study, one CIAM case had MC in the submucosa. The patient was followed for 12 years without evidence of disease[4]. No tumor-related death has been reported in the literature.

The size of MC component appears to have no bearing on the outcome[3]. This is likely due to the fact that the MC component tends to be small, and is usually confined in the mucosa. Likewise, the lesional cells constituting MC are bland with low proliferative activity.

TREATMENT

Given its indolent course, complete removal of both adenoma and MC by polypectomy is considered curative[4]. Additional radical surgeries should be reserved for cases with adverse histologic features such as deep submucosal extension or increased proliferative activity of the MC component[3].

CONCLUSION

CIAM is a rare intestinal lesion consisting of a conventional adenoma and a well differentiated MC component at its base. CIAM is considered to represent a true composite tumor wherein both adenoma and MC appear to share a common origin and develop *via* the Wnt/β-catenin pathway. MC in CIAM poses diagnostic challenges with its morphologic resemblance to other benign and malignant lesions. CIAM is an indolent lesion with a favorable outcome. Complete removal of both adenoma and MC by polypectomy is considered curative. Raising awareness of this rare entity will lead to correct diagnosis and appropriate management.

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MINIREVIEWS

Endoscopic ultrasound-guided biliary drainage-current status and future perspectives

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Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) with stenting is the treatment modality of choice for patients with benign and malignant bile duct obstruction. ERCP could fail in cases of duodenal obstruction, duodenal diverticulum, ampullary neoplastic infiltration or surgically altered anatomy. In these cases percutaneous biliary drainage (PTBD) is traditionally used as a rescue procedure but is related to high morbidity and mortality and lower quality of life. Endoscopic ultrasound-guided biliary drainage (EUS-BD) is a relatively new interventional procedure that arose due to the development of curvilinear echoendoscope and the various endoscopic devices. A large amount of data is already collected that proves its efficacy, safety and ability to replace PTBD in cases of ERCP failure. It is also possible that EUS-BD could be chosen as a first-line treatment option in some clinical scenarios in the near future. Several EUS-BD techniques are developed EUS-guided transmural stenting, antegrade stenting and rendezvous technique and can be personalized depending on the individual anatomy. EUS-BD is normally performed in the same session from the same endoscopist in case of ERCP failure. The lack of training, absence of enough dedicated devices and lack of standardization still makes EUS-BD a difficult and not very popular procedure, which is related to life-threatening adverse events. Developing training models, dedicated devices and guidelines hopefully will make EUS-BD easier, safer and well accepted in the future. This paper focuses on the technical aspects of the different EUS-BD procedures, available literature data, advantages, negative aspects and the future perspectives of these modalities.

Key Words: Endoscopic ultrasound-guided biliary drainage; Malignant bile duct obstruction; Endoscopic ultrasound-guided hepaticogastrostomy; Endoscopic ultrasound-

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guided rendezvous technique; Endoscopic ultrasound-guided choledochoduodenostomy; Endoscopic ultrasound-guided antegrade stenting; Endoscopic retrograde cholangiopancreatography

Core Tip: Endoscopic retrograde cholangiopancreatography is the current standard of care for bile duct obstruction but is not always possible. The traditional rescue modality is percutaneous transhepatic biliary drainage which has many disadvantages. Endosonography-guided biliary drainage is a new promising interventional technique, showing many advantages over percutaneous biliary drainage and is able to fully replace it when the expertise is available. Developing new devices, training models and guidelines is expected to make this procedure easier, safe and widely accepted in the near future.

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a first-line treatment option for patients with biliary obstruction. The success rate is between 90% and 97% and the adverse event rate is less than 10%[1,2]. Some clinical situations: surgically altered anatomy, inaccessible papilla, unsuccessful cannulation require alternative approaches. Percutaneous transhepatic biliary drainage (PTC-D) is a widely accepted alternative after failed ERCP. Despite a high technical success rate (over 95%), the reported mortality remains high. The possible adverse events (AE) are bleeding, infection, drain dislodgement, tract seeding, bile leak, external fistula with a cumulative rate of 30%[2,3]. Contraindications for PTC-D performance are ascites, liver metastasis and obesity. PTB-D is related to the quality of life deterioration[4]. The palliative derivation surgery is related to high morbidity and mortality (35%-50% and 10%-15%)[5] and remains the last choice option for selected cases.

With the implementation of curvilinear-array echoendoscope, various interventional procedures have been made possible, including endoscopic ultrasound-guided biliary drainage (EUS-BD). The first successful EUS-BD was described by Giovannini *et al*[6] in 2001, which indicates the beginning of a new era for mini-invasive biliary drainage.

Currently, three EUS-based techniques are available- EUS-guided rendezvous technique (RV), EUS-guided antegrade stenting (AS), EUS-guided transmural stenting, EUS-guided hepaticogastrostomy (HGS), EUS-guided choledochoduodenostomy (CDS), and EUS-guided hepaticoduodenostomy. These procedures offer same-session internal drainage in cases of ERCP failure. EUS-BD includes complex and risky procedures which are performed in highly specialized centers by a very skilled endoscopist. The widely accepted indications include ERCP failure, duodenal obstruction due to tumor infiltration, duodenal diverticulum, bile duct tortuosity and previous duodenal stent placement or presence of altered anatomy.

EUS-BD TECHNIQUES

EUS-HGS

The technique was first introduced in 2003. In current times, this is a single-step procedure and consists of a transhepatic puncture of the biliary system and the creation of a stable fistula between the gastrointestinal lumen and the bile ducts.

This approach is preferred when the papilla cannot be reached endoscopically (duodenal obstruction or surgically altered anatomy). The most common indications for HGS are palliative therapy of hilar obstruction or distal obstruction when the papilla is not accessible. In rare cases, HGS is used for the creation of a temporary tract to the biliary tree in order to manage benign stricture or lithiasis. Sufficient intrahepatic bile duct dilation is needed for the HGS performance. The major contraindications are tumor infiltration of the gastric wall at the site of puncture, massive ascites, and coagulopathy[7].

This technique is not standardized. The tip of the echoendoscope is positioned in the stomach body at the lesser curvature. The dilated left hepatic duct can be seen (Segment III). Segment II is not a preferred approach to avoid transesophageal puncture and risk of mediastinitis. The puncture is performed using 19G needle and after bile aspiration contrast medium is injected (Figure 1). The procedure is performed under combined endosonographic and fluoroscopic guidance. A hydrophilic guidewire (0.025-inch or 0.035-inch) is inserted through the needle and manipulated in the bile ducts (Figure 2). Large caliber needles reduce the risk of shearing off the guidewire coating. A special needle was developed-19G EchoTip Access Needle (Cook Ireland Ltd., Limerick, Ireland) to avoid shearing off the guidewire coating and leaving a part in the liver. The needle is smooth with a sharp stylet, used to puncture the gastric wall and the liver. After removing the stylet, the guidewire manipulation is more easily compared with the standard FNA needle and reduces the risk of wire stripping. The most important step is the creation of a stable fistula and the proper technique is the prerequisite to avoid major complications like bile peritonitis, bleeding and perforation. The needle is exchanged over the guidewire with a 6 French cystotome and electrocautery-enhanced tract dilation is performed. Biliary dilation catheters or balloons could also be used (Figure 3). The procedure is finished by placing a stent (Figure 4). Especially dedicated HGS stents [Giobor stent TAEWOONG, proximal covered (NC) stent, HANARO] are commonly used for this technique. These are specially designed partially covered metallic stents with a proximal uncovered part to prevent blockage of segmental bile duct branches and a distal covered part to reduce the risk of bile leakage. Fully covered stents can be used in benign obstruction, but are related to increased risk of focal cholangitis, liver abscess, and migration. Plastic stents are not a reasonable option due to unacceptable high risk of bile peritonitis. An alternative to Giobor stents is the so-called "stent in stent technique" with transgastric placement of two metallic stents- a first one uncovered 8 or 10 cm to prevent bile duct blockage and a second 6 cm fully covered to secure the transmural tract[8,9].

EUS-AS

The procedure was first described by Nguyen-Tang *et al*[10] in 2010 and offers a possibility of physiological bile flow in cases of an inaccessible papilla or failed bile duct cannulation during ERCP. The authors report about 5 cases with malignant bile duct obstruction and endoscopically inaccessible biliary orifice. At the time of failed ERCP they performed transhepatic or transbulbar bile duct puncture and self-expandable metal stent (SEMS) deployment in an antegrade fashion without any AE and concluded that EUS-AS is an efficient technique for palliation of bile duct obstruction when standard ERCP has failed[10].

The initial steps of the intervention are the same as HGS-bile duct puncture, guidewire manipulation and tract dilatation. The procedure consists of transgastric left intrahepatic bile duct puncture with 19-gauge needle under EUS visualization. Color Doppler imaging is used to exclude intervening blood vessels and to prevent intra-and postprocedural bleeding. After bile aspiration contrast medium is injected to obtain cholangiogram. The guidewire is inserted through the needle and manipulated and advanced through the stricture and transpapillary in the duodenum or through a biliary anastomosis in the small intestine. After needle tract dilatation using ERCP catheter and mechanical dilators, a stent is placed at the stricture site and most commonly through the papilla of Vater in an antegrade fashion (Figure 5).

There is an increased risk of bile leakage at the puncture site and in cases of stent dysfunction reintervention could be extremely difficult or impossible. For that reason, some authors combine antegrade stenting with HGS. Placing a transenteric metallic stent simultaneously with the antegrade SEMS placement at the stricture site reduces the risk of leakage and bile peritonitis and makes reinterventions through the transhepatic tract possible[11].

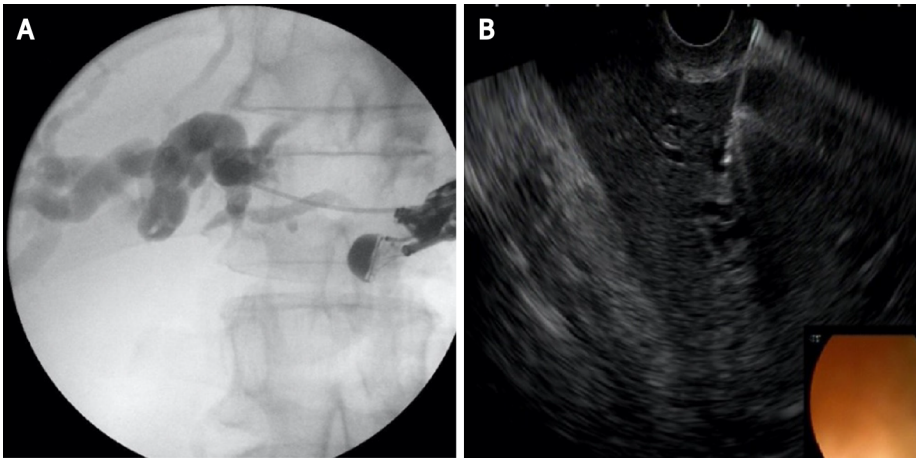

Figure 1 Left hepatic duct puncture and contrast injection. A: Cholangiogram; B: endoscopic ultrasound image.

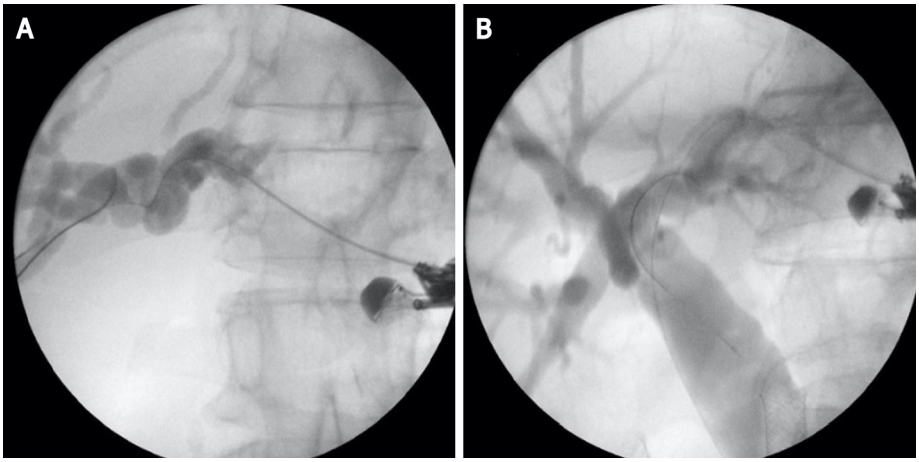

Figure 2 Hydrophilic guidewire insertion. A: In left hepatic duct; B: To the distal common bile duct.

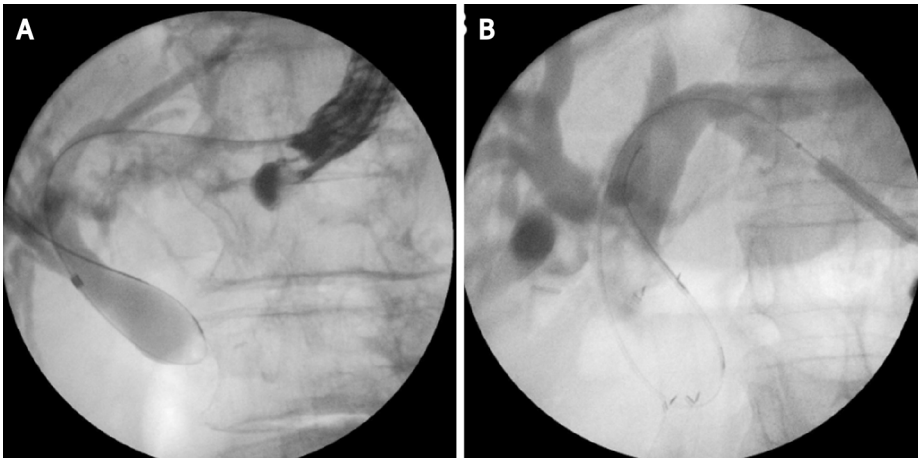

Figure 3 Tract dilatation. A: Biliary dilation catheter; B: 4 mm balloon dilatator.

EUS-CDS

The procedure is usually performed in cases of malignant distal bile duct obstruction when standard cannulation has failed or when endoscopic access to the papilla is not possible. The technique was first described by Giovannini *et al*[6] in 2001.

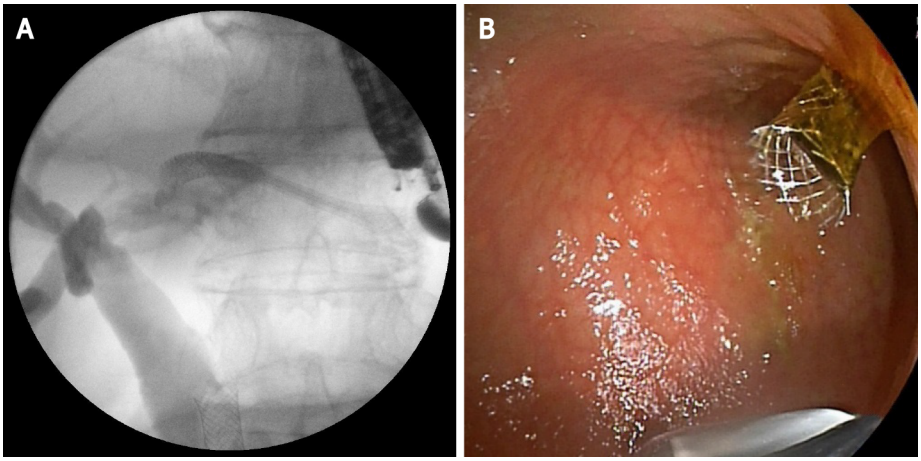

Figure 4 Stent placement-self-expandable metal stent. A: Cholangiogram; B: Endoscopic image.

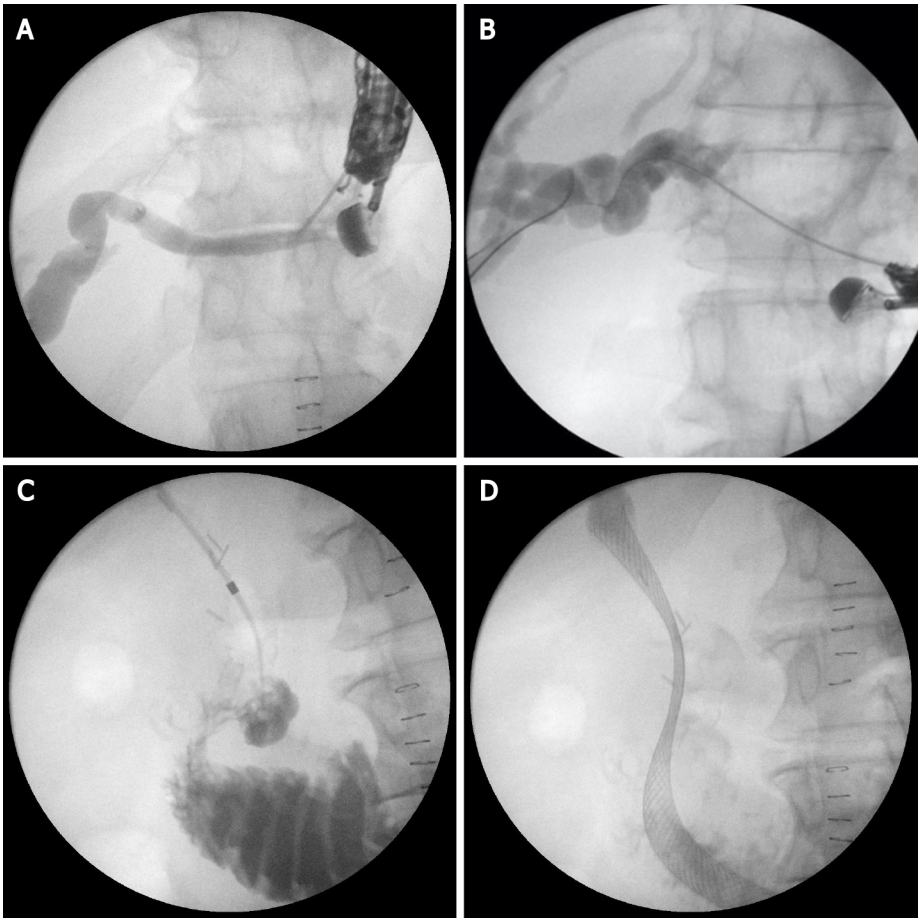

Figure 5 Endoscopic ultrasound-guided antegrade stenting. A: Left hepatic duct puncture with 19G needle; B: Guide-wire insertion; C: Tract dilatation and advancing the biliary catheter tip transpapillary in the duodenum; D: Self-expandable metal stent placement.

The tip of the echoendoscope is positioned in the duodenal bulb (or in the antrum) where the common bile duct (CBD) is very close to the duodenal or gastric wall. Before puncture, fluoroscopy is used to align the direction of the needle tip towards the liver hilum. The CBD is punctured with a 19-gauge needle. After the bile aspiration guidewire is inserted and manipulated in the direction of the intrahepatic bile ducts, the needle is exchanged over the wire with a 6 French cystotome, biliary catheter or a small (4 mm) dilation balloon to dilate the tract. Most commonly a fully covered SEMS is placed (Figure 6). Using plastic stent or a recently developed lumen-apposing metal stent (LAMS) is also possible[9,12].

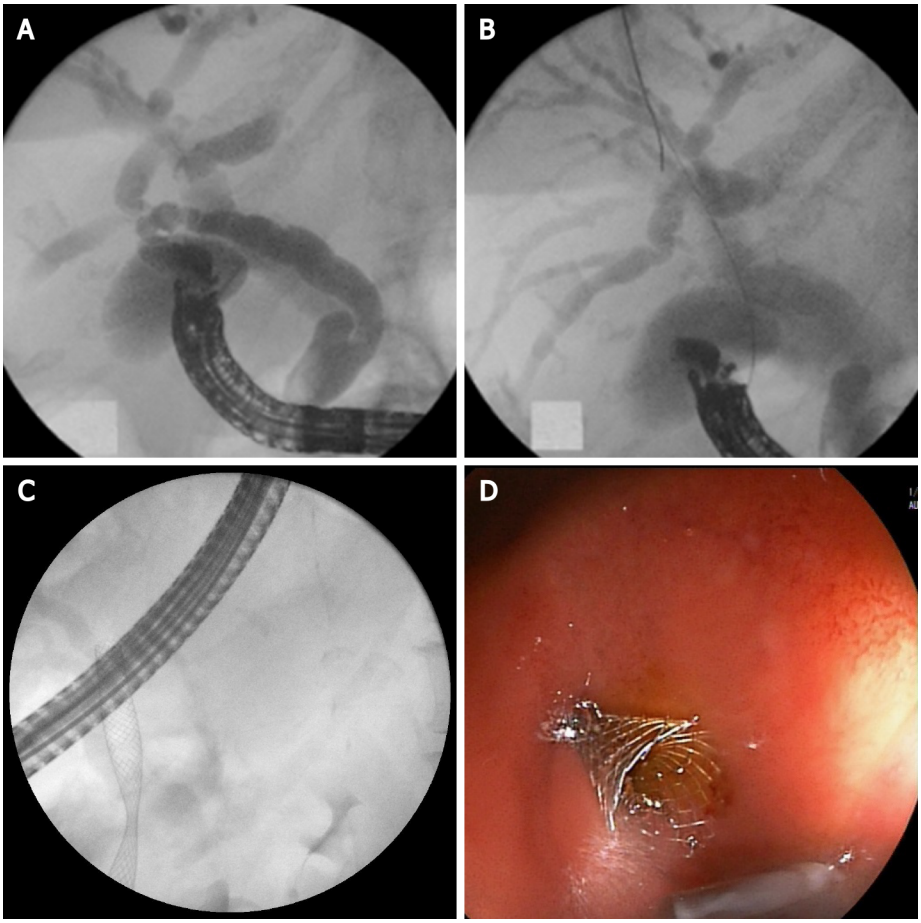

Figure 6 Endoscopic ultrasound-guided choledochoduodenostomy. A: Puncture of the common bile duct with 19G needle and contrast injection; B: Hydrophilic guidewire inserted through the needle into bile ducts; C: Fluoroscopic image of self-expandable metal stent (SEMS); D: Endoscopic image of SEMS.

EUS-RV

EUS-RV was first reported in 2004. The technique is considered when the papilla of Vater is endoscopically accessible but selective bile duct cannulation with ERCP has failed[13].

The procedure consists of intra- or extrahepatic bile duct puncture under EUS guidance with a 19-gauge needle. Contrast is injected through the needle and after obtaining a cholangiogram, a guidewire is inserted and manipulated to negotiate the stricture and to pass across the papilla in the duodenum in an antegrade manner. To maintain a stable position, several loops of the guidewire in the duodenum should be made. Then, the linear echoendoscope is exchanged by duodenoscope. Retrograde cannulation is performed alongside the guidewire or over the guidewire by grasping it with a rath tooth forceps or a snare and pulling it in the duodenoscope working channel. The procedure seems to be the safest of all EUS-guided bile duct approaches. The most common reasons for failure is the inability to manipulate the guidewire across the stricture and the papilla or to reach the bile duct orifice endoscopically (Figure 7). The need for the exchange of two endoscopes and the fact that the procedure is not feasible in cases of altered anatomy are limiting factors for this intervention[12,14].

EFFICACY AND SAFETY OF EUS-BD

A large amount of data that has been collected demonstrates the fast improvement in the technical and clinical success of EUS-BD[15-18]. A recently published systematic review, including 42 studies with 1192 patients, reports about a 94.7% technical success and 91.7% clinical success with a 23.3% adverse even rate. These data indicate that EUS-BD is an acceptable alternative in cases when ERCP has failed or is not possible. The morbidity is high but most of the reported AE are mild, self-limited and respond to conservative therapy. The most commonly reported AE are bleeding (4%),

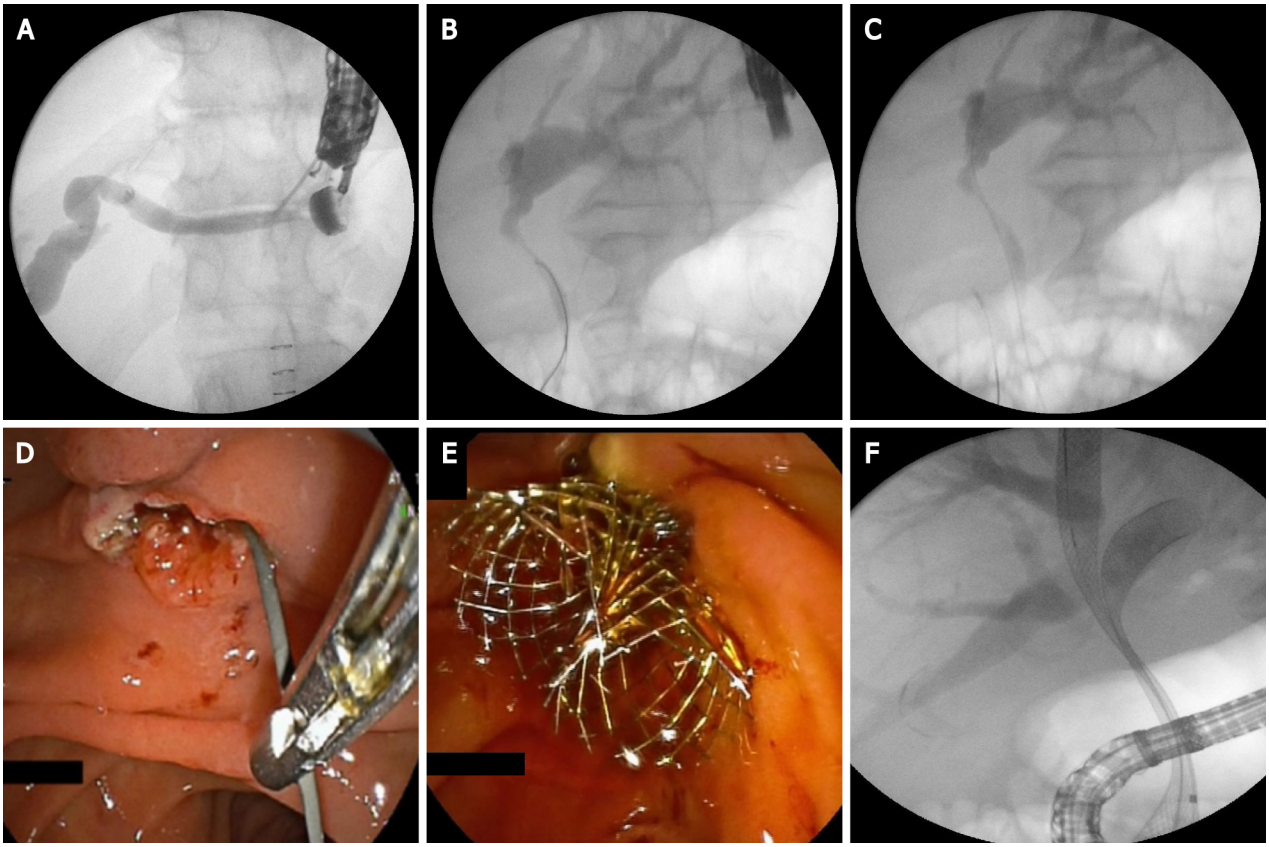

Figure 7 Endoscopic ultrasound-guided rendezvous technique. A: Puncture the left hepatic duct with 19G needle; B: Guide-wire insertion in bile ducts; C: Guide-wire insertion transpapillary in the duodenum; D: Grasping the guide-wire with a rath tooth forceps; E: Endoscopic image of two self-expandable metal stent (SEMS); F: Fluoroscopic image of two SEMS.

bile leakage (4%), pneumoperitoneum (3%), stent migration (2.7%), cholangitis (2.4%), peritonitis (1.3%), abdominal pain (1.5%)[19].

The important point here is that these results are reported from high-volume centers and the procedures were performed by highly experienced endoscopists. "Real-world" data could be much worse and the AE rate-unacceptably high. A national survey in Spain, including 106 patients who have EUS-BD performed, reports 67.2% technical success and a 63.2% clinical success. Improving the safety and reducing the complexity of EUS- BD are the main issues regarding this procedure[20].

ALGORITHM FOR EUS-BD

Algorithms for the EUS-BD approach, based on the nature of obstruction and anatomy of the patient were developed. The patients with a dilated intrahepatic bile duct on cross-sectional imaging should be approached intrahepatically and antegrade stenting should be attempted. When antegrade stenting fails or is not possible, HGS is a suitable option. When the intrahepatic approach fails, conversion to an extrahepatic approach is advisable. In cases without intrahepatic bile duct dilatation, the extrahepatic approach is the method of choice. After transbulbar or transantral puncture of CBD, rendezvous technique is advised. In case of failure, CDS should be performed[21].

According to the published data, there is no significant difference between the EUS-BD techniques in terms of technical, clinical success and AE. Khashab *et al*[22] compared the outcomes of HGS and CDS in a multicenter comparative trial. The technical and clinical success was similar in both groups[22].

CAN EUS-BD REPLACE ERCP AS A PRIMARY TREATMENT MODALITY?

EUS-BD is still used mostly when ERCP is not successful or not feasible. A

retrospective multicenter analysis comparing ERCP with EUS-BD, however, indicated that both techniques have similar efficacy[23]. The growing expertise and the advances in specially dedicated equipment have led to better clinical results with success rates over 90% and comparable AE rates[24,25].

Many clinical situations (altered anatomy, periampullary tumors, presence of duodenal stent covering the ampulla) suggest difficult biliary cannulation. Extended procedural time and numerous cannulation attempts are related to increased AE, consisting mainly in post-ERCP pancreatitis. On the other hand, tumor ingrowth/overgrowth is the major reason indicating the need for re-intervention. Both disadvantages could be overcome by resorting to a EUS-BD procedure[26,27].

Several prospective randomized trials and meta-analyses, published over the last 2 years, have compared the two techniques as a first-choice option for biliary drainage (Table 1).

In a single-center randomized trial Bang *et al*[28] compared EUS-CDS (n = 33) and ERCP (n = 34) as primary treatment for malignant distal biliary obstruction. There was no significant difference in the rates of technical success (90.9% *vs* 94.1%), clinical success and rate of reinterventions. AE rate was reported in 21.2% in the first and 14.7% in the second group (P = 0.49). The authors highlight the potency of EUS to ensure diagnostics (FNA, FNB), and palliative therapy (biliary drainage, celiac plexus neurolysis) in a single endoscopic session. Additionally in this study, the CDS performance did not affect the surgical technique in the operable cases[28].

In another prospective randomized controlled study Park *et al*[29] compared the EUS-BD and ERCP as a primary treatment modality for malignant extrahepatic bile duct obstruction. The authors (n = 30) suggest that EUS-BD has equivalent efficacy to ERCP. No severe AE were observed in both groups. In the ERCP group, four cases were reported with tumor ingrowth, and in the EUS group, two cases were reported with food impaction and another two with stent migration. In cases of stent migration in the EUS-BD group reintervention was not needed because the iatrogenic choledocho-duodenal fistula, created during the procedure provided sufficient bile drainage[29].

In a multicenter randomized trial including 125 patients, Paik *et al*[30] aim to compare EUS-BD (either CDS or HGS) with ERCP-BD for palliative drainage of distal malignant stenosis. The study confirms the similar efficacy and safety of the two techniques. EUS-BD was found to have lower AEs, including post-procedural pancreatitis, also lower re-intervention rate[30].

A meta-analysis (10 studies and 756 patients) from 2019[24] comparing EUS-BD with ERCP as a primary treatment modality of malignant distal bile duct obstruction reports equivalent clinical and technical success in both groups (over 90%), with similar rates of AE (15.5% for EUS-BD and 18.6% for ERCP). The EUS drainage demonstrated longer stent patency and lower rates of reinterventions, but without statistical significance. The most common AE in the EUS-BD group was bile peritonitis, while in the ERCP group, pancreatitis[24].

Another systematic review and meta-analysis by Jin *et al*[26] published in the same year announce similar results in terms of technical and clinical success, AE, reinterventions, procedure duration, stent patency and overall survival for both techniques. EUS-BD was associated with lower rates of stent dysfunction and tumor in/overgrowth[26].

A meta-analysis comparing EUS-BD with ERCP-drainage for primary management of malignant biliary obstruction regardless of stricture site from 2020 by Kakked *et al*[31] demonstrated identical technical and clinical success and AE rates. Patients after ERCP required significantly more re-interventions[31].

A meta-analysis, published in 2019[32] and involving 222 patients, reports comparable procedure time, technical and clinical success and complication rate. In conclusion, the authors report a significantly lower rate of stent dysfunction in the EUS-BD group and distinguish EUS as a reasonable option of the first choice for patients with malignant obstruction[32].

A final meta-analysis, published by Lou *et al*[33] includes 428 patients, (EUS-BD n = 215, ERCP n = 213). No significant difference was reported concerning procedure duration, technical and clinical success. EUS-BD, however, was associated with a lower rate of re-intervention and fewer procedure-related AE regarding pancreatitis and cholangitis[33].

In summary, given the comparable results in terms of AE and treatment outcomes, EUS is likely to become a feasible alternative to ERCP for primary biliary decompression.

Table 1 Summary of outcomes in recently published data on endoscopic ultrasound-guided biliary drainage-endoscopic retrograde cholangiopancreatography comparative analysis

Ref.	Type of evidence	Patients, *n* (%)	Technical success, EUS-BD–ERCP, *n* (%)	Clinical success, EUS-BD-ERCP, *n* (%)	AE, EUS-BD-ERCP, *n* (%)
Dhir *et al*[23], 2015	Multicenter retrospective analysis	208	94.23-93.26 (98/104-97/104)	N/A	8.65-8.65 (N/A)
Kawakubo *et al*[27], 2016	Retrospective study	82	N/A	96.2-98.2 (25/26-55/56)	26.9-35.7 (7/26-20/56)
Park *et al*[29], 2018	Prospective randomized controlled study	30	92.9-100.0 (13/14-14/14)	92.9-100.0 (13/14-14/14)	0.0-0.0 (0/14-0/14)
Paik *et al*[30], 2018	Multicenter randomized trial	125	93.8-90.2 (60/64-55/61)	84.4-85.2 (54/64-52/61)	10.9-39.3 (7/64-24/61)
Bang *et al*[28], 2018	Prospective randomized trial	125	90.9-94.1 (30/33-32/34)	97.0-100.0(32/33-34 /34)	21.2-14.7 (7/33-5/34)
Logiudice *et al*[34], 2019	Meta-analysis	222	91.96-91.81 (N/A)	84.81-85.53 (N/A)	N/A (4/79–25/76)

ERCP: Endoscopic retrograde cholangiopancreatography; EUS-BD: Endoscopic ultrasound-guided biliary drainage-endoscopic.

EUS-BD *VS* PTBD

Over the last decade, enough data have been collected to allow comparative analyses between EUS-BD and percutaneous biliary drainage (PTBD). Several advantages of EUS-BD over PTBD have been proved over time: It could provide drainage of intra- and extrahepatic ducts, according to the obstruction level; it is less invasive and eliminates the need for an external catheter. The latter spare the possibility for catheter-related complications like bleeding, infection, dislocation and bile leak.

The first meta-analysis comparing EUS-BD and PTBD in terms of efficacy and safety is published by Sharaiha *et al*[34] in 2017. Nine studies with 483 patients were included. No difference in technical success and length of hospital stay was found, but EUS-BD was found to have better clinical success, fewer post-procedure AE, lower rate of re-interventions and was more cost-effective[35].

In conclusion, published data suggest that EUS-BD is better compared with PTBD, reducing the risk of AE, hospital stay, the need for re-interventions and offers a better quality of life for the patients[36]. In cases of ERCP failure, whenever an experienced endoscopy team is available EUS-BD should be performed instead of PTBD.

FUTURE OUTLOOK

At the moment, EUS-BD is primarily used as a rescue procedure following a failed ERCP. According to the published data, EUS-BD demonstrates some clinical advantages over ERCP but further randomized studies will determine the real place of EUS as therapy in cases of malignant biliary obstruction. We suggest a simple scheme summarizing the current role of EUS in endoscopic biliary drainage therapy (Figure 8).

There are many questions in consideration before the adoption of EUS as a standard first-line therapeutic option. Despite the promising results, published in the literature, these procedures remain difficult and are not routine outside a few expert centers. The reasons are lack of training, lack of procedure standardization, and few available dedicated devices. Although the similar rate of AE for both procedures, according to some authors, EUS complications are more severe and difficult to be managed. Most of the published data comes from experienced endoscopists in high volume expert centers and it remains unclear if these results can be achieved in smaller centers[36]. On the other hand, EUS-BD is rarely indicated and expertise acquisition is difficult.

The low case volume limits the training opportunities and the existing training models are not able to simulate all the difficulties encountered when performing these procedures. Developing training models is a key step to understand, learn and perform more safely EUS-BD. Dhir *et al*[37] created and evaluated a hybrid model consisting of pig esophagus and stomach and synthetic duodenum and biliary system and concluded that it replicates real situations encountered during EUS-RV and EUS-BD and training and mentoring using this model improves the chances of success

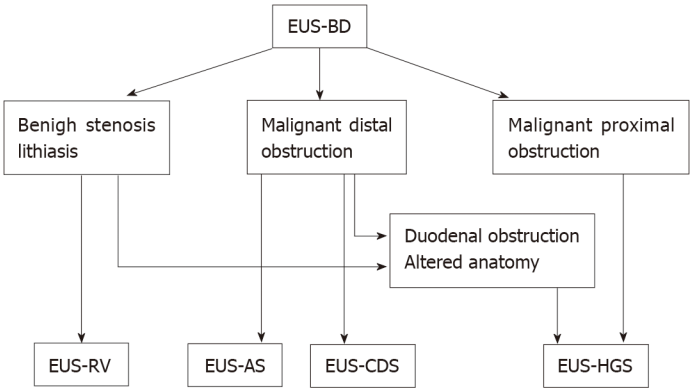

Figure 8 Current place of endoscopic ultrasound-guided biliary drainage in endoscopic biliary drainage therapy. EUS-BD: Endoscopic ultrasound-guided biliary drainage; EUS-RV: EUS-guided rendezvous technique; EUS-AS: EUS-guided antegrade stenting; EUS-CDS: EUS-guided choledochoduodenostomy/choledochoantrostomy; EUS-HGS: EUS-guided hepaticogastrostomy.

performing these procedures[37].

Taking into consideration the above-mentioned limitations, important steps were made to improve safety, reduce complexity, and standardize these procedures. The creation of the dedicated devices, training models, and guidelines presume a promising future of EUS-BD.

The development of dedicated devices is an important step toward making EUS-BD easier, reducing procedure time, and improving safety. The introduction of cautery-enhanced LAMS and their implementation for EUS-CDS is a step forward to make the procedure less complex and to reduce the number of AE. Significant progress has been made by the development of dedicated stents for EUS-HGS (Giobor-TaeWoong; Proximally covered SEMS-Hanarostent). This has led to a substantial reduction of severe AE like cholangitis, stent migration and bile peritonitis. Cautery-enhanced HGS- stents and "one step delivery" stents without the need for tract dilation are on the way and hopefully will make EUS-HGS a more popular, easy and safe intervention. There is a real perspective of full replacement of PTBD and surgery in malignant bile duct disease and ERCP failure cases. Gaining experience and widely spread expertise for the technique could lead to further expansion of indications and new treatment opportunities.

In an attempt to standardize EUS-BD the Asian EUS group published the first guideline on the optimal management in interventional EUS procedures. Fifteen statements address the indications, technical aspects, pre-and post-procedural management, management of complications, competency and training of EUS-BD[38].

CONCLUSION

EUS-BD is a new, promising mini-invasive biliary drainage modality, offering many advantages over traditional interventional methods and surgery. The accepted indications are ERCP failure, duodenal obstruction or biliary diseases in patients with surgically altered anatomy. EUS-BD includes several techniques which could be adapted to the unique patient anatomy and condition such as EUS-guided rendezvous technique, antegrade stenting or transmural drainage. A large amount of data suggests that EUS-BD should be preferred over PTBD if required expertise is available.

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MINIREVIEWS

When should we perform colonoscopy to increase the adenoma detection rate?

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Abstract

The rate of adenoma detection is the most reliable quality indicator of colonoscopy. Studies have reported that colonoscopy performed in morning has a higher adenoma detection rate (ADR) than that performed in the afternoon. These studies have explained that several physician-related factors such as undergoing an emergency procedure the night before colonoscopy, accumulated workload, and increased fatigue level in the afternoon might have led to such finding. However, several opposing articles have indicated that the time of day and ADR is not quite related. Complex confounding factors can impact study results. Colonoscopy withdrawal time and bowel preparation quality are key factors. However, queue list numbers, participation of academic fellows, nurses' assistance, and the number of colonoscopies allocated *per* hour are also notable factors. Recently, an attempt has been made to homogenize the ADR in the morning and afternoon through artificial intelligence-assisted colonoscopy. This review article introduces the history of this long-debated topic, discusses points to consider in real-world practice, and suggests new ideas for planning future research. By understanding this issue, the rate of adenoma detection during colonoscopy is expected to be improved further.

Key Words: Colonoscopy; Colorectal cancer; Time of endoscopy; Afternoon colonoscopy; Adenoma detection rate

Core Tip: Adenoma detection rate is the most reliable indicator of colonoscopy quality. Studies suggest that colonoscopy performed in the morning is associated with a higher detection rate of adenoma than the procedure performed in the afternoon. However, it is important to endeavor not only to improve patients' bowel preparation quality in the

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afternoon, but also to create an environment conducive to adenoma detection by physicians during afternoon sessions.

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INTRODUCTION

According to the statistics from the World Health Organization (WHO)[1], colorectal cancer is the third most common cancer around the world, with approximately 1.93 million newly diagnosed cases in the year 2020. It is the second most commonly diagnosed cancer in women and the third most common cancer in men, accounting for 9.4% (2nd) of the total number of cancer deaths. In the United States, the mortality due to colorectal cancer has substantially declined over the past few decades mainly due to a decrease in the incidence of colorectal cancer thanks to a sensitive detection[2] and the removal of adenomas by colonoscopy[3].

Since more than 95% of colon cancers originate from colorectal adenomas, the rate of adenoma detection [adenoma detection rate (ADR)] during colonoscopy is concerned as the most reliable benchmark quality assessment indicator for determining adequate screening efficacy[3,4]. Some studies have reported that patients examined by endoscopists with ADR of less than 20% have over ten times greater risk of interval colorectal cancer[5,6].

Factors associated with ADRs include nonmodifiable factors (such as age, gender, race, body mass index, and comorbidities) and modifiable factors such as scope withdrawal time (WT) and bowel preparation[7-9]. However, most of these factors are either technical or patient-related factors. On the other hand, studies regarding endoscopist-related factors are scarce. Since the first report by Sanaka *et al*[10] showing that there might be a difference in ADR between morning and afternoon colonoscopies in 2006, several studies have shown that physician's fatigue in the afternoon is related to ADR. However, conflicting results have also been reported. Therefore, we are still uncertain whether colonoscopies performed in the morning show better ADR than those performed in the afternoon.

This review article will introduce the history of this long-debated topic with the latest study results and discuss points to consider when planning future research.

THE BEGINNING OF THE DEBATE

Previous studies have shown that fatigue of medical professionals, including anesthesiologists[11], surgeons[12] and resident trainees[13] has a negative impact on patient safety outcomes. This phenomenon is not only observed for medical personnel, but also observed for non-medical employees such as pilots[14] and truck drivers[15].

In the early 2000s, several retrospective studies have reported that fatigue caused by doctors' sleep deprivation can affect laparoscopic performance[13], and that patients who are hospitalized at weekend have higher mortality than weekday patients in some disease entities[16]. These were the first reports showing that a patient's treatment outcome could vary by the day of the week. In 2004, a study suggested that a decrease in the detection rate of polyps of more than 9 mm was due to the practice pattern with a rapid increase in the number of screening colonoscopy after July based on the National Endoscopic Database[17]. As a result, it has been hypothesized that if the number of colonoscopy procedures by the time increases, the polyp detection rate (PDR) may be inversely affected. This result has been thought to be related to the fatigue of endoscopists.

The first article suggesting that an endoscopist's fatigue during the day might affect colonoscopic cecal intubation rate (CIT) was published in 2006[10]. The authors investigated colonoscopic incompletion rates through a retrospective chart review of total 2087 colonoscopies (1084 in the morning and 999 in the afternoon). As a result, a significantly higher failure rate in the afternoon (6.5% *vs* 4.1%) was found. Even after

correcting for poor bowel cleansing quality in the afternoon, the afternoon failure rate was still significantly higher (5.0% *vs* 3.2%). The authors explained that the time of day could possibly be an independent predictor of the completion rate of colonoscopy. Considering such result, the time factor could also lead to a decrease in the afternoon WT, which was expected to reduce ADR consequently. In a retrospective study[18] of 3619 colonoscopies, ADR was found to be significantly higher in morning colonoscopies than in afternoon colonoscopies (29.3% *vs* 25.3%). In addition, there was a trend toward declining ADR for each subsequent hour of the day.

A prospective study of Veteran's administration teaching hospital[19] has shown comparable results. Data were analyzed both as a dichotomous time period ("early-morning case" *vs* "later case") and as a continuous variable (start time). In univariate analysis, early-morning cases yielded 27% more polyps *per* patient than later cases. Numbers of hyperplastic and adenomatous polyps decreased hour-by-hour as the day progressed. These early studies were pioneer studies for many subsequent community-based studies (Table 1 and Figure 1).

TIME OF DAY MAY NOT AFFECT ADR

However, several articles have indicated that the time of the day and ADR are not quite actually related. According to retrospective studies of single center hospitals that used a 3-h colonoscopy shift schedule[20] or an assigned time of 45 min *per* colonoscopy[21], PDR was the highest during the mid-day (shift 2)[20], showing no decrease in PDR as the day progressed[21]. In these studies, patients with poor bowel preparation were relatively less included using exclusion criteria and split-dose preparation methods. In addition, these studies could not reflect various amounts of workload among endoscopists for each institution.

In a retrospective study[22] based on a tertiary medical center where only attending physicians (excluding fellows) participated, PDR showed a decreasing trend for both half and all-day shifts (OR: 0.67, 95%CI: 0.44-1.00). However, due to related small numbers of confirmed adenomas, it could not demonstrate a significant difference in ADR. This result implicates that even in tertiary medical centers where endoscopists suffer high workload, the time of day alone may not have a strong influence on ADR as previously reported.

ENDOSCOPIST FATIGUE AND ADR

Despite these negative results, studies focusing on physician's fatigue and ADR were steadily published in 2014 and 2015. One study has compared ADR between a control group and cases of on-call duty or emergency procedure the night before screening colonoscopy[23]. Interestingly, overnight on-call duty was irrelevant to ADR. However, undergoing an emergency procedure the night before colonoscopy resulted in a significant decrease (24%) in ADR compared to the control group, indicating the influence of sleep deprivation on procedural outcomes. In a prospective, multi-center study[24] on screening colonoscopies when endoscopist fatigue was measured using a Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire with a cutoff score of 25, ADR was found to be lower for fatigued endoscopists than for the non-fatigued group. FACIT-F was 3.6 time higher for the ADR in a multivariate regression analysis.

LATEST RESEARCH

A prospective observational study[25] performed in 2016 analyzed the influence of endoscopist-related characteristics on quality indicators for colonoscopy. In that study, factors associated with ADR were found to be age and life-long number of colonoscopies. Only exclusive dedication to endoscopy practice was found to be independently related to adenoma detection of proximal colon. Besides, none of other endoscopist characteristics, including the number of hours/week or annual volume of colonoscopies, was associated with a higher ADR. This was also supported by a following large community-based study[26] including more than 76000 colonoscopies with the aim to objectively reflect procedure related fatigue, considering both the number of colonoscopy procedures and the complexity of the procedure using

Table 1 Study characteristics (including evaluated adenoma detection rate result)

Ref.	Country	Study design	Investigated blocks	Physician (Fellow inclusion: O, X)	Bowel preparation	No. of a.m./p.m. procedure	ADR (%)
Sanaka *et al*[18], 2009	United States	Retrospective	Full day	Certified endoscopist (O)	Single PEG 4 L or oral fleet	1748/1871	AM (29.3); PM (25.3)
Chan *et al*[19], 2009	United States	Prospective	Full day	Certified endoscopist (O)	Single PEG 4 L or oral fleet	432/15	AM (49.2); PM (45.1)
Freedman *et al* [21], 2011	United States	Retrospective	Full day	Certified endoscopist (X)	Split dose PEG 4 L	756/730	AM (41); PM (44)
Long *et al*[22], 2011	United States	Retrospective	Full day	Certified endoscopist (X)	Single PEG 4 L	2219/1202	24.9
Lurix *et al*[23], 2012	United States	Retrospective	Half day. Full day	Certified endoscopist (O)	Single or Split PEG 4 L	2148/937	AM (30); PM (33)
Paeck *et al*[39], 2013	South Korea	Retrospective	Half day. Full day	Certified endoscopist (O)	Single PEG 4 L	420/881	AM (42.3); PM (34.7)
Subramanian *et al* [40], 2015	United Kingdom	Retrospective	Half day. Full day	Certified endoscopist (O)	Single PEG. Sodium picosulphate	1091/994 (evening:489)	27.6
Singh *et al*[41], 2016	United States	Retrospective	Full day	Certified endoscopist (O)	Split dose PEG 4 L	1574/731	AM (23.1); PM (18.3)
Teng *et al*[42], 2016	Singapore	Prospective	Full day	Certified endoscopist (X)	Single PEG (morning); Split-dose PEG (afternoon)	270/263	AM (29); PM (21)
Lei *et al*[27], 2020	China	Retrospective	Full day	Certified endoscopist (O)	Split-dose PEG	261/223	AM (36); PM (35)

Detection of adenoma was assisted by computer-aided detection (CADe). ADR: Adenoma detection rate.

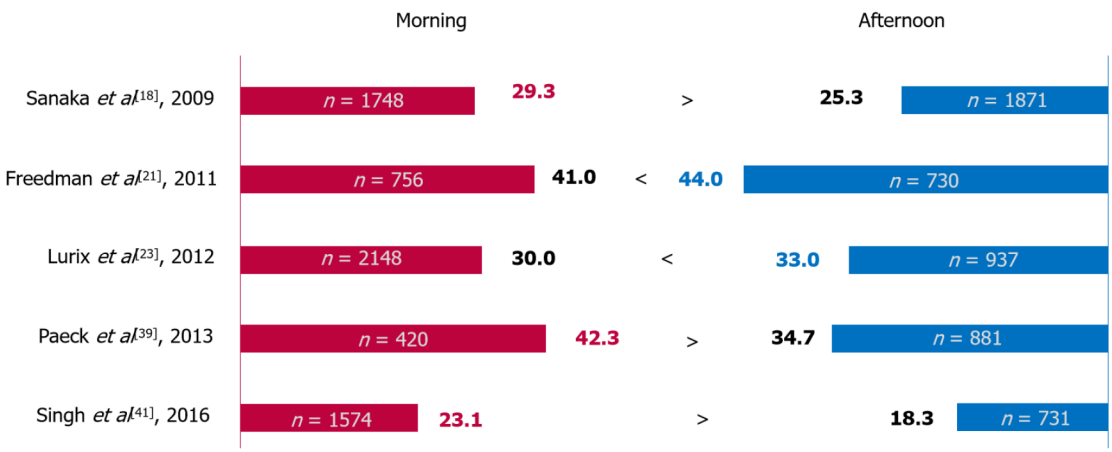

Figure 1 Comparison of morning and afternoon adenoma detection rates of studies with more than 1000 patients.

consensus weights and relative value units. As a result, there was no association between ADR and endoscopist fatigue. Increasing levels of fatigue did not impact ADR, even after adjusting for confounding factors at patient-level and provider-level in multivariable regression analyses.

Meanwhile, the latest study has determined whether there is a difference in ADR between morning and afternoon colonoscopies assisted by artificial intelligence[27]. It was a prospective, single-center study with 484 colonoscopies through computer-aided detection (CAD) for polyps. There seemed to be no significant difference in ADR between morning and afternoon colonoscopies. Indeed, deep learning algorithm with real-time computer-aided polyp detection was proven to produce a significant increase in the detection of smaller adenomas compared to conventional colonoscopy (RR: 1.69; 95%CI: 1.48-1.84), according to a recent systemic review and meta-analysis[28]. It is expected that AI technology will be an effective tool minimizing the influence of 'endoscopist-related' factors in ADR.

Since 2006, numerous works have been done on whether colonoscopies performed in the afternoon are below the standard quality. It is not as easy as expected to conclude because various confounding variables such as patient, physician, assistant nurse, and the type of hospital are all factors that can affect the detection of adenomas during colonoscopy.

COMPLEX CONFOUNDERS

Increasing colonoscopy WT is thought to be able to improve ADR. A minimum WT of over 6 min during a normal colonoscopy is widely recommended[29]. A prospective observational study has been performed to determine how endoscopist fatigue can affect performance quality according to continuous and embedded volumes of colonoscopies[30]. It was found that WT and ADR remained stable while median CIT was lengthened as the repetitive procedure progressed. According to a prospective study (BECOP-3) that analyzed endoscopist factors related to ADR, WT within 6 to 11 min was not related to a reduced ADR[31]. However, ADR showed a significant reduction regardless of sufficient WT when a physician performed an emergency overnight procedure the day before the index colonoscopy[32]. If a physician sacrifices the WT to make up for a longer insertion time, less adenomas is expected to be found.

Along with WT, another substantial factor for ADR is bowel preparation quality. As it is crucial for adenoma detection, afternoon colonoscopies are known to be associated with both inadequate bowel preparation and lower ADR. There is no difference in the detection of adenomas by the time of day in studies when bowel preparation quality in the afternoon is maintained relatively well using a split-dose method[21] or statistically corrected for bowel cleanliness[33]. Another study has stated that bowel preparation is an inevitable confounder in assessing the quality of colonoscopy[34]. Therefore, various ways need to be investigated to improve the preparation quality of afternoon colonoscopies.

Other possible confounding factors include hospital system-related issues such as the participation proportion of academic fellows in endoscopy[34], queue list numbers that differ quite a lot for each endoscopic clinic[35], overnight duty systems for endoscopists or nurses[32], and the number of colonoscopies allocated every hour[20] (Table 2). If an endoscopist is in state of sleep deprivation or if an awaited patient comes in right after a previous laborious colonoscopy, it would be reasonable to question the procedural quality. However, if a highly skilled physician who performs more than 200 colonoscopies a year and if WT can be secured to be over 6 min, ADR can remain stable throughout the day[31]. Factors that might interfere with concentration on endoscopic procedures such as attending educational conferences, replying to frequent consultations, and educating medical students should be emphasized[25, 36]. "Social influencing" using notice or posters, personal auditing reports, and physical or electronic reminders are emerging as part of efforts to prevent deterioration of polyp and ADRs due to fatigue in the afternoon in busy academic teaching institutions[37] .

Finally, how many hours of the day the endoscopist devotes to colonoscopies is another issue that should be pointed out. Some physicians may only work in the morning or afternoon (half-day block), while others may perform colonoscopies the entire day (full-day block). This can significantly affect study results. However, it has been poorly controlled across studies. For example, only half-day blocks were included in some studies, whereas full-day and half-day blocks of work were all taken into account in other studies. It seems inappropriate to compare these studies on the same line[33].

WHERE DO WE STAND? AND WHAT'S NEXT?

Meta-analyses on whether a morning colonoscopy is superior to an afternoon colonoscopy have shown cautious but consistent results. According to a study that analyzed a total of 16 eligible publications (14 retrospective studies and two prospective studies), ADRs for morning and afternoon colonoscopies were similar. However, the PDR of the afternoon was significantly less than that of the morning. Since it is generally considered that PDR does not significantly affect the quality of colonoscopy, there should be no change in the quality of colonoscopies throughout the day. Interestingly, the authors also concluded that fellow participation did not impact ADR difference between morning and afternoon colonoscopies. Barakat *et al*[38]

Table 2 Factors related with higher adenoma detection rate

Category	Factors
Patient-related	Good Bowel preparation
	Age (Older age), gender (male)
	Obesity (Higher body mass index)
Endoscopist-related	Withdrawal time (> 6 min)
	Assist from nurses/additional observer
	Queue list numbers (Small)
	Overnight duty (Less or none)
	Number of colonoscopies allocated *per* hour (Less)
	Half-day or Full-day schedule (Half-day)
	Attending CMEs, conferences, frequent consultations (Less)
Device-related	Higher definition processors, endoscopes

analyzed the effect of the time of day on ADR through multiple subgroup analyses in 2020, showing that the net effect of the time of day did not impact ADR in general. In addition, there was no difference in ADR between morning and afternoon not only for physicians with a half-day block schedule, but also for endoscopists who continuously performed full-day colonoscopies by the same operator.

These meta-analyses have strengths, including a large number of studies with a large sample size with a diverse international population. However, due to relatively high heterogeneity existed in data used for the analysis (allotted time for a colonoscopy, WT, indications for colonoscopy), homogenization of the study design is required. In addition, it must be acknowledged that the unevenness of data among included studies in terms of different fellow participation and bowel preparation quality might affect the interpretation of results. Besides, as these meta-analyses did not estimate operator fatigue, results reflecting a physician's various stamina levels and the complexity of previous procedures might come out differently.

Every colonoscopy is performed under different circumstances. There would be the first procedure of the day, some might be performed after a number of arduous duties. Performing 'full-day' colonoscopies may not necessarily lead to a less careful procedure. The physician who performs colonoscopy until the afternoon may receive additional financial compensation accordingly, which will increase the operator's motivation. Therefore, it is presumable that 'financial compensation policy' of each institution should be also considered as one of the various factors affecting ADR in the afternoon. On the other hand, from experience, the procedural result is not good from time to time when the following colonoscopy is forced to be started immediately after a difficult therapeutic endoscopy due to long waiting patients. We hope that future well-designed studies will be able to evaluate effects of previous endoscopies on ADR. Besides, it will be interesting to see if ADR in the morning and afternoon can be differently affected by the experience of endoscopists (novice/experienced), weekday or weekend, and gender of patients through subgroup analysis.

NO EFFECT OF TIME OF THE DAY ON ADR

Several studies indicated the lack of correlation between the time of the day and the ADR. Single-center retrospective studies at hospitals based on 3-h colonoscopy shift schedule or an assigned time of 45 min *per* colonoscopy revealed that PDR was the highest during the mid-day (shift 2), without decreasing as the day progressed. In these studies, relatively few patients with poor bowel preparation were included based on exclusion criteria and split-dose preparation methods. In addition, these studies failed to reflect various levels of workload among endoscopists at each institution.In a retrospective study based on a tertiary medical center involving only attending physicians (excluding fellows) as the participants, the PDR showed a decreasing trend in both half and full-day shifts (OR: 0.67, 95%CI: 0.44-1.00). However, due to the small number of confirmed adenomas, the study failed to demonstrate a

significant difference in ADR, suggesting that even in tertiary medical centers with endoscopists ensuring increased workload, the time of day alone may not have a strong influence on ADR as previously reported.

CONCLUSION

In conclusion, data up to date did not demonstrate a significant difference in the quality of colonoscopies by the time of the day in either a full day setting or in a half-day block setting. Despite negative results, we believe it is still too early to conclude on this issue. Future systematic randomized clinical trials that can control for confounding factors mentioned above and analyze an endoscopist's fatigue level more objectively might change conclusions on this subject. For now, considering that the PDR (or maybe ADR) in the afternoon may get deteriorated in the full-day block schedule, it is important to make efforts not only to improve patients' bowel preparation quality in the afternoon, but also to create an environment that a physician can focus solely on detecting adenomas during afternoon colonoscopy sessions.

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MINIREVIEWS

Primary prophylaxis of variceal bleeding in patients with cirrhosis: A comparison of different strategies

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Abstract

Patients with cirrhosis and esophageal varices bleed at a yearly rate of 5%-15%, and, when variceal hemorrhage develops, mortality reaches 20%. Patients are deemed at high risk of bleeding when they present with medium or large-sized varices, when they have red signs on varices of any size and when they are classified as Child-Pugh C and have varices of any size. In order to avoid variceal bleeding and death, individuals with cirrhosis at high risk of bleeding must undergo primary prophylaxis, for which currently recommended strategies are the use of traditional non-selective beta-blockers (NSBBs) (*i.e.*, propranolol or nadolol), carvedilol (a NSBB with additional alpha-adrenergic blocking effect) or endoscopic variceal ligation (EVL). The superiority of one of these alternatives over the others is controversial. While EVL might be superior to pharmacological therapy regarding the prevention of the first bleeding episode, either traditional NSBBs or carvedilol seem to play a more prominent role in mortality reduction, probably due to their capacity of preventing other complications of cirrhosis through the decrease in portal hypertension. A sequential strategy, in which patients unresponsive to pharmacological therapy would be submitted to endoscopic treatment, or the combination of pharmacological and endoscopic strategies might be beneficial and deserve further investigation.

Key Words: Cirrhosis; Esophageal varices; Primary prophylaxis; Non-selective beta-

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Core Tip: Variceal hemorrhage still is an important cause of death among patients with cirrhosis, and primary prophylaxis against variceal bleeding is of the utmost importance. Traditional non-selective beta-blockers, carvedilol or endoscopic variceal ligation are currently recommended for primary prophylaxis, and the superiority of one alternative over the others is controversial. This review will provide a comparison of the strengths and weaknesses of the different strategies for primary prophylaxis against variceal bleeding, so that practitioners make an informed decision when choosing among them.

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INTRODUCTION

In patients with compensated cirrhosis, esophageal varices develop in an annual rate of 7%-8%, characterizing state 2 in the natural history of the disease. Once they develop, they will bleed in 5%-15% of patients *per* year, marking their transition to decompensated cirrhosis (state 3 in the natural history of cirrhosis). When patients bleed, the mortality rate reaches 20%[1,2].

In order to avoid bleeding and death, individuals with cirrhosis should be screened for esophageal varices, and primary prophylaxis against their rupture is recommended to patients at higher risks[3-6]. The Baveno VI consensus recommends that patients with cirrhosis and medium-large varices should be submitted to prophylaxis with either traditional non-selective beta-blockers (NSBBs) (*i.e.*, propranolol or nadolol), carvedilol (a beta-blocker with an alpha-adrenergic blocking effect) or endoscopic variceal ligation (EVL). Patients with small varices should also be submitted to prophylaxis with NSBBs as long as they are classified as Child-Pugh C or have varices with red signs[3]. The most important medical associations in the field of hepatology support these recommendations[4,5]. Nevertheless, there are divergences in medical literature regarding the superiority of one prophylactic alternative over the others[7-9].

This article aims at reviewing the main strategies for primary prophylaxis against variceal hemorrhage, as well as comparing their strengths and weaknesses (Table 1). Knowing the characteristics of each prophylactic strategy will enable physicians to make better decisions when choosing among them in the management of particular patients.

TRADITIONAL NSBBs

NSBBs are considered the main pharmacological intervention in the treatment of portal hypertension since Lebrec *et al*[10] demonstrated that propranolol administration effectively reduced the hepatic venous pressure gradient (HVPG) in patients recovering from an acute episode of gastrointestinal bleeding due to ruptured esophageal varices. This reduction was associated with a significant decrease in portal blood flow, which is usually increased in patients with cirrhosis due to significant splanchnic arterial vasodilation. Later studies confirmed that NSBBs-induced portal blood flow reduction is caused by the activity of these drugs on beta-1 cardiac receptors, determining a negative chronotropic response and a reduced cardiac output, and, most importantly, by their effects on beta-2 receptors of the splanchnic vascular bed, resulting in splanchnic vasoconstriction[11,12].

Table 1 Strengths and weaknesses of the different strategies for primary prophylaxis of variceal bleeding in cirrhosis

	NSBBs	Carvedilol	EVL
Prevention of mortality	+	+?	+?
Prevention of bleeding	+	+	++
Prevention of other complications of cirrhosis	+	+	-
Reduction in HVPG	+	++	-
Adverse effects	--	--	-
Serious adverse effects	-	-	--

The plus sign (+) indicates strength. The minus sign (-) indicates weakness. The question mark (?) indicates uncertainty. NSBBs: Traditional non-selective beta-blockers; EVL: Endoscopic variceal ligation; HVPG: Hepatic venous pressure gradient.

When NSBBs are used in primary prophylaxis of variceal bleeding, the hemodynamic goal is to achieve an HVPG reduction ≥ 20% of the baseline levels or a decrease in absolute levels to under 12 mmHg. Below those thresholds, patients would be protected from variceal bleeding[13]. Even a reduction ≥ 10% is likely to be clinically relevant for primary prophylaxis[3]. Nevertheless, only 33%-50% of patients undergoing NSBB prophylaxis achieve the proposed hemodynamic goals[8].

Different randomized controlled trials (RCTs) have evaluated the role of NSBBs in primary prophylaxis against variceal bleeding. A meta-analysis evaluating 6 of these studies and including 811 patients with cirrhosis and medium or large varices demonstrated that primary prophylaxis with NSBBs was more effective than placebo, with 2-year bleeding rates of 30% in the control group and 14% in the NSBB group[14].

In clinical practice, the most commonly used NSBBs are propranolol and nadolol, and treatment with these drugs should begin with low doses that are gradually increased to the maximum tolerated dose or to a heart rate target around 55-60 beats *per* minute. Propranolol can be started at 20-40 mg twice a day, and maximal daily dose should be 320 mg/d in individuals without ascites or 160 mg/d in those with ascites[4] (80 mg/d for patients with severe or refractory ascites according to the European Association for the Study of the Liver[5]). Nadolol can be started at 20-40 mg once a day, and maximal daily dose should be 160 mg/d in patients without ascites or 80 mg/d in those with ascites[4].

Some concern has been shown regarding the use of NSBBs by patients with end-stage cirrhosis. According to the window hypothesis, the therapeutic window for the use of NSBBs would close at end-stage cirrhosis, particularly with the development of refractory ascites, because these drugs would not only be less effective in that stage, but also might lead to a higher risk of hepatorenal syndrome and mortality due to a negative impact on the cardiac compensatory reserve[15]. This hypothesis was based on an observational study of 151 individuals with cirrhosis and refractory ascites, in which those using propranolol had a shorter survival[16]. Later on, other observational studies associated the use of NSBBs to a higher risk of hepatorenal syndrome and a lower transplant-free survival among patients with spontaneous bacterial peritonitis[17] and to a higher risk of acute kidney injury among those with severe alcoholic hepatitis[18]. Nevertheless, the methodological limitations of these observational studies should be noticed, and a meta-analysis of 11 studies (3145 patients) failed to demonstrate evidence of a negative impact of NSBBs on the mortality of individuals with ascites (including a subgroup analysis focused on patients with refractory ascites)[19].

Therefore, considering existing evidences, the current recommendations are that NSBBs should be reduced or discontinued (or should not be initiated) in patients with systolic blood pressure < 90 mmHg, with acute kidney injury or with serum sodium < 130 mEq/L[3-5]. In the settings of acute decompensation of cirrhosis with spontaneous bacterial peritonitis, sepsis or bleeding, NSBBs should be discontinued. If NSBBs cannot be reinitiated after 3-6 d, EVL should be considered[5].

As previously mentioned, international guidelines recommend the use of either NSBBs or EVL as first-line options with similar effectiveness for primary prophylaxis of variceal bleeding[3]. Yet, some issues should be considered when choosing between these options in clinical practice. Firstly, NSBBs work by reducing portal hypertension through a decrease in splanchnic blood flow. Theoretically, this could benefit patients in relation to the prevention of other complications of portal hypertension, such as

ascites, hepatic encephalopathy or infections[20]. Indeed, a recent RCT on the role of NSBBs in patients with clinically significant portal hypertension (individuals who did not have an indication for primary prophylaxis against variceal bleeding) has demonstrated that those receiving propranolol or carvedilol had a lower risk of developing the primary endpoint (cirrhosis decompensation or death, hazard ratio of 0.51, P = 0.041). Interestingly, the benefit was predominantly related to the lower incidence of ascites among individuals receiving the intervention (hazard ratio of 0.42, P = 0.03)[21]. Of course, this is not an expected effect of EVL, which works mechanically on the obliteration of varices.

Another important aspect that might influence the choice of the method of prophylaxis is the occurrence of adverse events. Usually, studies suggest that there are more side effects with NSBBs (around 15% of patients require dose reduction due to fatigue or hypotension), although they are more severe with EVL (pain, esophageal ulcers, strictures, and bleeding). In addition, NSBBs are cheap and easy to manage, while EVL requires more complex resources and permanent endoscopic surveillance to monitor the recurrence of varices[4].

Finally, although strong evidence is lacking in medical literature, prophylaxis against the rupture of small varices is recommended for individuals classified as Child-Pugh C or for those who have red wale marks on the surface of the varices[22]. These red signs reflect increased tension on the vessel wall and imminent risk of rupture. Currently, the recommendation for these patients is that primary prophylaxis should be performed with NSBBs, since the use of EVL for these varices can be technically complex[3-5].

CARVEDILOL

Carvedilol is a NSBB with an additional activity on alpha-1 cardiac receptors. Therefore, aside from reducing cardiac output (beta-1 blocking effect) and from leading to splanchnic vasoconstriction (beta-2 blocking effect), it promotes sinusoidal vasodilation (alpha-1 blocking effect). For this reason, most authors believe that carvedilol promotes greater reductions in HVPG than NSBBs, leading to better hemodynamic response rates during primary prophylaxis against variceal bleeding [23]. However, the superiority of carvedilol over NSBBs regarding portal hypertension improvement is still not consensual[24].

Four RCTs evaluated the role of carvedilol in the primary prophylaxis against variceal bleeding. Two of them demonstrated that this drug was superior to EVL in preventing first variceal bleeding[25,26]. On the other hand, the other 2 RCTs failed to identify a benefit of carvedilol when compared to EVL[27] or to either EVL or propranolol[28]. The largest RCT on this issue is currently in progress and will hopefully put an end to this controversy[29].

While that trial is not published, another recent study contributed with data on the comparison between NSBBs and carvedilol. The study evaluated patients with a past history of ascites who were undergoing both primary or secondary prophylaxis against variceal bleeding with propranolol. Subjects were randomized either to switch to carvedilol or to remain under propranolol. When compared to individuals remaining on propranolol, patients switching to carvedilol had significant decreases in plasma renin activity, plasma aldosterone and serum noradrenaline, as well as significant increases in systemic vascular resistance and glomerular filtration rate. Moreover, patients on carvedilol had fewer decompensating events at 2 years than their counterparts (10.3% *vs* 37.5%, P = 0.002), as well as lower liver-related mortality (64.1% *vs* 86%, P = 0.01). It must be highlighted, though, that an intention-to-treat approach was not used in this study[30].

In clinical practice, carvedilol should be started at a dose of 6.25 mg/d and increased to 12.5 mg/d after three days, as long as systolic blood pressure does not fall below 90 mmHg[4]. The adverse effects profile of carvedilol does not seem to be different from that of NSBBs, but doses should not be increased over 12.5 mg/d, except in patients with persistent systemic arterial hypertension[4,23]. Heart rate should not be used as a target while titrating the dose of carvedilol. Non-invasive methods of verifying the response to carvedilol have been studied as an alternative to HVPG. In a recent prospective cohort study, the difference between baseline and post-treatment spleen stiffness measured by acoustic radiation force impulse elastography was able to predict hemodynamic response to carvedilol during primary prophylaxis with areas under the receiver operating characteristic curve over 0.8. This might become a useful tool for verifying response to carvedilol after further validation[31].

EVL

EVL was first described in 1986[32]. Ten years later, the first RCT on the efficacy of EVL for primary prophylaxis against variceal bleeding was published. In that trial, in which 62 individuals with cirrhosis and 6 with non-cirrhotic portal hypertension were included, EVL was associated with a significantly lower incidence of first variceal bleeding when compared to no treatment (8.5% *vs* 39.4%, $P < 0.01$). There was also a trend towards lower bleeding-related mortality favoring EVL (2.9% *vs* 15.2%, $P = 0.08$) [33]. In the following years, EVL also was compared with NSBBs, with evidence suggesting that the endoscopic treatment was associated with a significant lower probability of variceal bleeding, which did not translate into lower mortality[34].

EVL has replaced injection sclerotherapy as the endoscopic therapy of choice not only for the prevention of the first variceal hemorrhage, but also for the treatment of acute variceal bleeding and for secondary prophylaxis. This was due to lower rates of mortality[35], recurrent hemorrhage and adverse events[35,36] with EVL when compared to sclerotherapy. Because of mounting evidence showing an increase in mortality in subjects submitted to sclerotherapy for the prevention of variceal hemorrhage[35-38], most experts and international associations no longer recommend sclerotherapy for primary prophylaxis[3-5,39]. Moreover, there does not seem to be a role for combined EVL and sclerotherapy in order to improve variceal eradication[40]. EVL has also been compared to tissue adhesive injection for primary prophylaxis with varying results, but there is no evidence-based recommendation advocating the latter over the former, not even in Child-Pugh C patients[32]. Thus, up to this moment, EVL should be considered the best endoscopic therapy to prevent the first bleeding from medium to large esophageal varices and it is considered as a first line option for primary prophylaxis, along with NSBBs and carvedilol[3-5,39].

According to the American Association for the Study of Liver Diseases (AASLD), EVL should be performed every 2-8 wk until esophageal varices eradication is achieved. Then, first follow-up esophagogastroduodenoscopy (EGD) would be repeated in 3-6 mo and every 6-12 mo thereafter. If esophageal varices reappear during follow-up, EVL should be reinitiated[4]. We believe, however, that a shorter interval of time between each EVL session (2-4 wk) could be advisable in order to avoid bleeding from occurring while varices are not eradicated, and that first follow-up EGD should be ideally performed at 3 mo[39].

Small esophageal varices and gastroesophageal varices type 1 (GOV1) are less likely to bleed unless in the presence of red signs or advanced Child-Pugh C cirrhosis. In this scenario, EVL is not considered to be the best option[3-5,39] since it may not be technically feasible and might be more prone to induce complications[32]. Moreover, despite anecdotal reports, EVL is not considered the procedure of choice for gastric or ectopic varices, because those vessels tend to have large diameters and to lay deep in the submucosa, making them not amenable to fully entrapment under suction to perform banding. Tissue adhesive injection is instead the procedure of choice for gastric or ectopic varices[32].

OTHER STRATEGIES FOR PRIMARY PROPHYLAXIS AGAINST VARICEAL BLEEDING

As previously mentioned, NSBBs, carvedilol or EVL are first line options for primary prophylaxis against esophageal varices hemorrhage. These options are recommended in monotherapy, and the choice should take into account the status of cirrhosis (compensated or decompensated), individual preferences, local resources and expertise, contraindications, potential complications of each strategy and their costs[3-5]. Nevertheless, combining therapies in order to achieve a greater reduction in the risk of the first episode of bleeding has been examined in the literature. An RCT comparing the combination of propranolol and EVL *vs* EVL alone for primary prophylaxis failed to demonstrate differences in the incidence of bleeding or death between groups. On the other hand, combination therapy was associated with a higher number of side effects[41]. Another RCT compared primary prophylaxis with carvedilol, EVL or the combination of both in 270 individuals with cirrhosis classified as Child-Pugh B or C. In that study, the probability of the first bleeding was lower with combination therapy when compared to either carvedilol or EVL alone (8.9%, 37.8% and 22.2% respectively)[42].

Considering that pharmacological therapy has beneficial effects on other complications of portal hypertension aside from preventing variceal bleeding, the combination of pharmacological agents has also been studied in order to promote greater reductions in portal pressure. The combination of NSBBs and nitrates, for instance, has resulted in conflicting evidences. In a long-term study, 146 patients assigned to receive nadolol monotherapy or nadolol along with isosorbide mononitrate were followed up for a median of 55 mo. Cumulative risk of bleeding was 29% and 12% respectively, and authors concluded that nadolol plus isosorbide mononitrate was significantly more effective than nadolol alone in the long-term use[43]. In contrast, another RCT could not demonstrate the benefits of combination therapy. A total of 349 subjects were randomized to receive either propranolol plus placebo or propranolol plus isosorbide mononitrate, and no significant differences in 1- and 2-year actuarial probabilities of variceal bleeding were observed between the groups (monotherapy 8.3% and 10.6% respectively; combination therapy 5% and 12.5% respectively)[44].

It was also hypothesized that adding statins to carvedilol could improve its effects on portal hypertension. The rationale for this lies on the fact that statins could decrease intrahepatic vascular resistance due to a reduction in stellate cells contractility, an increase in the levels of nitric oxide and thrombomodulin and a reduction in the levels of endothelin-1. Nevertheless, in the only RCT on the addition of simvastatin to carvedilol for primary prophylaxis against variceal bleeding, there was no significant benefit of the combined prophylaxis regarding either hemodynamic or clinical outcomes[45].

Other strategies for primary prophylaxis against variceal bleeding have been studied, particularly focused on specific clinical settings. Gastric varices, for instance, are less common in patients with cirrhosis and seem to bleed less frequently, but bleeding episodes are usually more severe and difficult to control when compared to those originating in esophageal varices. No single method has yet been established and there are no robust recommendations for the prophylaxis against the first bleeding from gastric varices. Despite the lack of strong evidences, GOV1 should be approached as esophageal varices. Aside from NSBBs, which are the suggested prophylaxis for gastroesophageal varices type 2 (GOV2) and isolated gastric varices type 1 (IGV1), endoscopic variceal obliteration with cyanoacrylate and balloon occluded retrograde transvenous obliteration (BRTO) have been evaluated[3-5].

Data from a single RCT suggested that endoscopic variceal obliteration with cyanoacrylate might be more effective than NSBBs in preventing the first bleeding episode from GOV2 or IGV1, despite increasing portal pressure during the follow-up. However, the risk of thromboembolic events and increasing the size of esophageal varices represents a serious concern[46]. More data are required for stablishing recommendations in this regard[3].

BRTO is a radiological technique for obliteration of gastric varices both for prophylaxis and for treatment of bleeding. It is a much more popular modality in Asian countries than in Western ones. It requires the patency of a large gastro-renal shunt, which is accessed to delivery sclerosant or obliterative agents and coils. Preliminary data suggest that it is safe and effective for the prevention of bleeding in the subset of patients with high-risk gastric varices in connection with large shunts [47]. Transjugular intrahepatic portosystemic shunt (TIPS) is another radiological technique, which is more widely used than BRTO in the treatment of portal hypertension. However, studies specifically evaluating the efficacy of TIPS in the setting of primary prophylaxis are lacking, and there is a concern regarding the increased risk of hepatic encephalopathy induced by this technique. Currently, neither BRTO nor TIPS are recommended by AASLD for primary prophylaxis against variceal bleeding[4].

COMPARATIVE ANALYSIS

Several meta-analyses have compared NSBBs, carvedilol and EVL[7-9,48,49]. Li *et al* [48] performed a meta-analysis of 12 RCTs on this issue. Authors only included RCTs that were peer-reviewed and fully-published, and there was no evidence of significant differences between pharmacological therapy and EVL regarding the prevention of gastrointestinal bleeding, all-cause mortality or bleeding-related deaths.

In the following year, the Cochrane group published a meta-analysis, including 19 RCTs, which compared NSBBs, including propranolol (17 trials), nadolol (1 trial) and carvedilol (1 trial), to EVL. In the main analysis, the authors found a lower rate of bleeding favoring EVL, with no effect on mortality. Nevertheless, in subgroup

analyses excluding trials of lower quality, the benefit of EVL could not be confirmed [7].

In the former meta-analyses, NSBBs and carvedilol were considered together as beta-blockers. This is why another systematic review by the Cochrane group aimed at comparing NSBBs and carvedilol for both primary or secondary prophylaxis against variceal bleeding. Eleven RCTs were included in the systematic review, and 10 in the meta-analysis. Carvedilol led to a significantly greater decrease in HVPG when compared to NSBBs, but there was no evidence of a significant benefit of carvedilol regarding the achievement of a satisfactory hemodynamic response. Moreover, there was no evidence of significant difference between NSBBs and carvedilol regarding mortality, upper gastrointestinal bleeding and serious adverse events[8].

More recently, one further meta-analysis compared carvedilol to EVL. Seven RCTs met the inclusion criteria, 4 of which were focused on primary prophylaxis, while the other 3 assessed secondary prophylaxis. Considering studies on primary prophylaxis, there was no evidence of difference between carvedilol and EVL regarding the incidence of the first bleeding episode, bleeding-related mortality or all-cause mortality. The risk of side effects, though, was significantly higher with carvedilol [risk ratio (RR): 4.18, 95% confidence interval (CI): 2.19-7.95]. On the other hand, EVL seemed to be associated with more severe complications than carvedilol[49].

The most relevant and comprehensive comparative study on this matter, however, is a network meta-analysis, which included 32 RCTs and evaluated NSBBs, carvedilol, isosorbide mononitrate, EVL and their combinations in the primary prophylaxis of variceal bleeding among individuals with cirrhosis. Regarding mortality (the primary outcome), NSBBs in monotherapy [odds ratio (OR): 0.70, 95%CI: 0.49-1.00] or in combination with EVL (OR: 0.49, 95%CI: 0.23-1.02) or with isosorbide mononitrate (OR: 0.44, 95%CI: 0.21-0.93) were significantly better than placebo or no intervention, but none of the evaluated therapies was significantly superior to another active treatment. Concerning the prevention of first variceal bleeding, EVL was significantly superior to NSBBs (OR: 0.51, 95%CI: 0.34-0.76), any active treatment was significantly better than isosorbide mononitrate alone, and any active treatment was significantly superior to placebo, except for isosorbide mononitrate alone or in combination with NSBBs[9].

It is important to highlight that the benefits of NSBBs regarding mortality might probably result not only from the prevention of variceal bleeding, but also from the prevention of other life-threatening complications of cirrhosis and maybe particularly those related to ascites[21]. Such advantages are especially noticed in those subjects achieving hemodynamic response to NSBBs[50]. Since EVL does not act on the pathophysiology of portal hypertension, but directly on its consequence (esophageal varices), it is not reasonable to expect that it could prevent other complications of cirrhosis. In this context, the combination of NSBBs and EVL might be a quite interesting alternative, since it would add the systemic effects of these drugs to the local effects of the endoscopic therapy. Nevertheless, it must be stressed that there is no recommendation for this association at the moment.

Evidences are still scarce regarding the best approach for patients with intolerance or no hemodynamic response to NSBBs. Carvedilol seems to be more potent and better tolerated than other NSBBs and might be considered as an alternative for individuals both intolerant or unresponsive to these drugs. In these circumstances or in patients also intolerant or unresponsive to carvedilol, EVL could be a good option[51]. In this context, Reiberger *et al*[52] proposed an interesting strategy, using NSBBs, carvedilol or EVL sequentially according to the hemodynamic response to the previous treatment. The authors evaluated a cohort of 104 individuals with cirrhosis who were initially treated with propranolol. Ten patients were intolerant to propranolol, while 37 achieved a satisfactory hemodynamic response. The 57 patients who were propranolol non-responders and 10 individuals who were intolerant to the drug received carvedilol, to which 38 were hemodynamic responders. Finally, the 29 patients unresponsive to either propranolol or carvedilol were submitted to EVL. In this study, carvedilol was superior to propranolol in decreasing HVPG (-19% *vs* -12% respectively, $P < 0.001$). Moreover, there was no additional benefit when the dose of carvedilol was increased over 12.5 mg/d. First variceal bleeding occurred in 11% of patients under propranolol, in 8% of those receiving carvedilol and in 24% of the individuals submitted to EVL ($P = 0.0429$). Transplant-free survival was higher with propranolol or carvedilol than with EVL ($P = 0.0455$). Hemodynamic responders to either of these drugs also developed less ascites than individuals requiring EVL ($P = 0.031$). Despite worse outcomes among patients undergoing EVL, it must be highlighted that only individuals unresponsive to propranolol and carvedilol were treated with EVL, so that it is likely that this was a more severely ill population[52].

CONCLUSION

Primary prophylaxis against variceal bleeding is of the utmost importance for patients with cirrhosis and high-risk varices. Currently recommended strategies include NSBBs, carvedilol or EVL. While EVL might be superior to pharmacological therapy regarding the prevention of the first bleeding episode, pharmacological therapy seems to prevent different complications of liver disease and probably play a more prominent role concerning mortality reduction. The sequential use of these alternatives or their combination should be further studied so that patients might benefit from the best aspects of each strategy.

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MINIREVIEWS

Large polyps: Pearls for the referring and receiving endoscopist

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Abstract

Polyps are precursors to colorectal cancer, the third most common cancer in the United States. Large polyps, *i.e.*,, those with a size ≥ 20 mm, are more likely to harbor cancer. Colonic polyps can be removed through various techniques, with the goal to completely resect and prevent colorectal cancer; however, the management of large polyps can be relatively complex and challenging. Such polyps are generally more difficult to remove en bloc with conventional methods, and depending on level of expertise, may consequently be resected piecemeal, leading to an increased rate of incomplete removal and thus polyp recurrence. To effectively manage large polyps, endoscopists should be able to: (1) Evaluate the polyp for characteristics which predict high difficulty of resection or incomplete removal; (2) Determine the optimal resection technique (*e.g.*, snare polypectomy, endoscopic mucosal resection, endoscopic submucosal dissection, *etc.*); and (3) Recognize when to refer to colleagues with greater expertise. This review covers important considerations in this regard for referring and receiving endoscopists and methods to best manage large colonic polyps.

Key Words: Adenoma; Endoscopic mucosal resection; Endoscopic tattoo; Colorectal cancer; Polypectomy

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Core Tip: Large polyps, often defined as ≥ 20 mm in size, are generally more challenging to resect than smaller polyps with regard to both difficulty of complete removal and risk of adverse events. To effectively manage large polyps, endoscopists should be able to evaluate them for characteristics which may increase the difficulty of endoscopic resection, determine the optimal resection technique, and recognize when to refer to colleagues for more advanced approaches. Herein, we review important considerations and methods to best manage large colonic polyps.

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INTRODUCTION

Colonic polyps have a risk of developing into colorectal cancer (CRC), the third most common cause of cancer-related deaths in the United States[1]. Prior studies have demonstrated that the removal of adenomatous polyps during a colonoscopy is associated with a significant reduction in CRC-related death[2,3]. However, achieving complete resection of a polyp can be challenging, especially with larger polyps. Previous studies have reported that 70%-90% of CRCs are preventable with routine screening colonoscopy and polypectomy[3]; however, 7%-9% are reported to occur despite being up-to-date with colonoscopy[4]. This subset of CRCs is thought to be likely due to either missed polyps or incompletely removed polyps.

The risk of incomplete polyp removal has been reported to increase with increasing polyp size[5]. "Large polyps" are generally defined as being ≥ 20 mm in size (though other cut offs may also be used) and carry a greater likelihood of underlying advanced dysplasia and carcinoma[6]. Indeed, the term "advanced adenoma"[7] has been introduced to stress the clinical and histopathological significance of polyps ≥ 10 mm in size. With advances in polyp removal techniques, management of large polyps has shifted away from surgery and towards endoscopic resection, using novel methods like endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR). In this review, we expound key considerations and techniques to best manage large colonic polyps from the perspective of both the referring and the receiving endoscopist.

INITIAL EVALUATION OF A COLONIC POLYP

Inspection goals and components

When a polyp is detected, a decision must be made whether endoscopic resection is possible[8,9], and if so, what the best method of resection may be (Figure 1). Certain features, including large size, can pose a technical challenge for complete resection and may indicate a need for advanced endoscopic techniques, as discussed in forthcoming sections, or surgical resection[10]. In addition to polyp size, features including morphology, location, and associated local features are all important determinants in gauging endoscopic resectability[10]. For instance, pedunculated polyps tend to be, on average, easier to grasp (along the peduncle or "stalk") and resect as opposed to sessile polyps[11,12]. Polyp location also influences resectability, as right-sided lesions tend to be more difficult to resect due to the presence of colonic folds which can impede visualization and maneuverability, increasing the risk of incomplete removal, among other factors[13]. Surface characteristics, discussed in the next section, can also predict submucosal invasion, which may prevent safe resection. Invasive cancers are associated with polyps that fail to lift with submucosal injection, a non-granular surface, depressed subtype, firmness, and redness[14-16]. However, non-lifting does not always predict invasion, as a failure to lift can also be seen in previously biopsied or partially resected polyps with associated tissue fibrosis. Finally, associated local

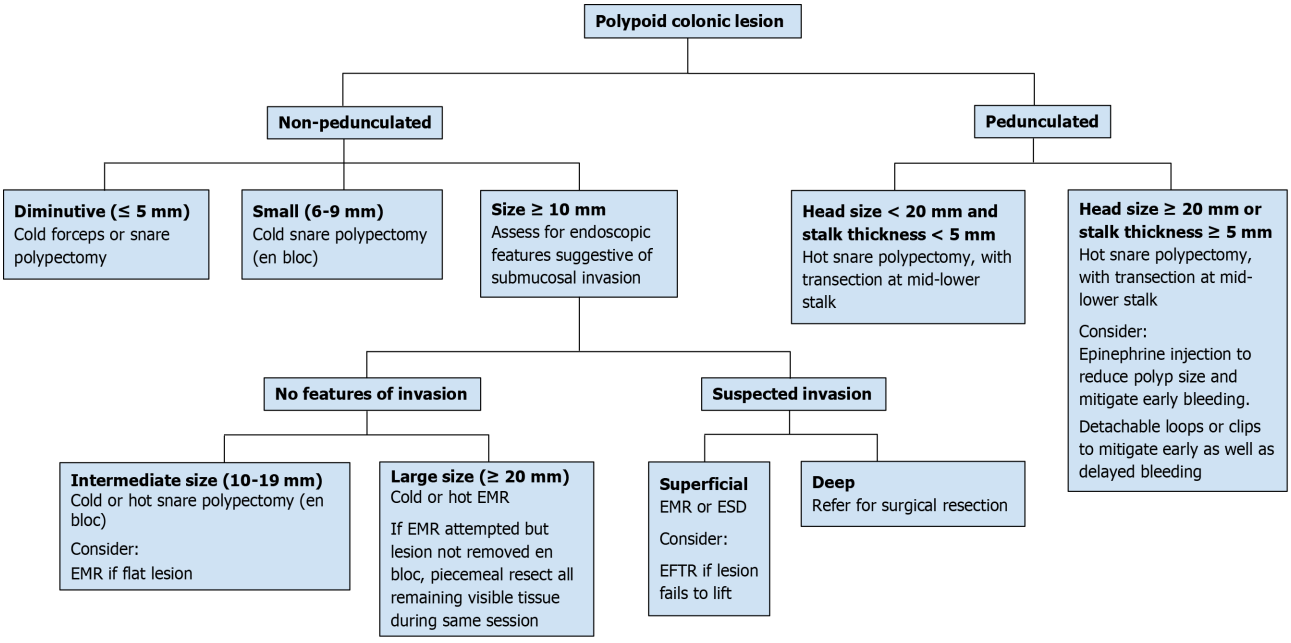

Figure 1 Polyp management algorithm based on morphology, size, and suspicion of submucosal invasion.

features can impact endoscopic resection; for instance, severe refractory colitis can impede large polyp resection and potentially result in the need for a colectomy[17]. Endoscopic ultrasound (EUS) can be used to evaluate rectal polyps (in particular T stage) and determine feasibility of endoscopic resection when the endoscopic appearance is concerning for possible deep invasion[18,19]. When EUS is not available or feasible (*e.g.,* polyps proximal to the rectosigmoid), cross-sectional imaging such as magnetic resonance or computed tomography can be considered.

Size, morphology, site, access (SMSA) is a scoring system used to predict the difficulty encountered during polyp resection[20]. The scoring is as follows: size (1-9 points), morphology (1-3 points), site (1-2 points), and access (1-3 points). Based on the total score, polyps are classified as Level 1 (4-5), Level 2 (6-9), Level 3 (10-12), or Level 4 (> 12). This system provides an objective assessment of the complexity of a polyp with higher scores suggesting increased complexity. Endoscopists should be aware of complex (and usually large) polyps scored under this system and consider the level of expertise needed to deal with these difficult polyps, referring the patient in necessary cases. Endoscopically unresectable polyps are generally referred to surgery, and are often managed with segmental colectomy, though studies have reported success using hybrid laparoendoscopic approaches *i.e.,,* combined endoscopic laparoscopic surgery (CELS), to avoid colon resection[21,22].

Polyp classifications systems

In addition to the features mentioned thus far, critically important here is determining whether a polyp is benign or premalignant, and within the latter, the degree of dysplasia that may be harbored within. There are several validated systems that can help to characterize and classify polyps in this regard, including the Paris classification [23], the narrow-band imaging international colorectal endoscopic (NICE) classification[24], and the Kudo pit pattern classification[25]. The Paris classification classifies polyps as pedunculated (1p), sessile (1s), flat (IIa, IIb, IIc), or ulcerated (III) [24]. It also classifies surface morphology as granular or non-granular for non-pedunculated polyps (1s and II). However, recent studies have questioned the validity of the Paris classification because of interobserver variability, recommending the system not be used for routine practice[26,27]. The NICE classification classifies polyps as hyperplastic or sessile serrated polyps (SSP) (type 1), conventional adenomas (type 2), or deep submucosal invasive cancer (type 3) based on color, associated vessels, and surface patterns[24]. The Kudo classification classifies polyps based on mucosal surface analysis. Also called the pit-pattern system, it requires magnification during colonoscopy to evaluate the pit pattern of polyps. This classification system classifies pit patterns as round (Type I), papillary/stellar (Type II), tubular or small round (Type III-S), large tubular or round (Type III-L), gyrus/branch-like (Type IV), non-structured/amorphous (Type V-I), and decrease of amorphous pits (Type V-N). Type I

and II polyps are considered benign while types III-V are considered to show neoplastic and malignant changes[28]. Despite the existence of the above classification systems, it is important to note that there is significant variability and agreement as to what the optimal method of classifying polyps should be.

Artificial intelligence and polyp detection

The emergence of artificial intelligence (AI) applications has direct implications in colonoscopy practices. The use of computer-aided detection (CADe) software has been demonstrated to decrease the polyp miss rate[29], especially for non-polypoid lesions in the right colon. AI has also been used to characterize polyps, also known as colonoscopy practice-polyp characterization (CADx). This can improve the accuracy of polyp diagnosis and reduce unnecessary resection of non-dysplastic polyps[29]. Although data on the outcomes of AI for polyp detection are evolving rapidly, the few completed studies have demonstrated a significant increase in the detection of adenomas and polyps[30,31]. However, the detection of more polyps does not necessarily improve outcomes; one study found that non-advanced adenomas were detected to a greater extent using AI-colonoscopies while identification of advanced adenomas was not substantially improved[32]. More research is needed to determine the value of AI systems in polyp detection and characterization.

CONSIDERATIONS FOR THE REFERRING ENDOSCOPIST

Provider experience

Studies have shown that incomplete polyp removal in daily clinical practice, especially in the case of large polyps, can contribute to future interval cancers[33]. Consequently, appropriate technique and complete resection of large colonic polyps is essential in preventing CRC (Figure 1). Incomplete removal renders future endoscopic resection more challenging; therefore, an endoscopist should aim for complete resection on the first attempt. For polyps ≥ 20 mm in size, the United States Multi-Society Task Force (USMSTF) recommends that an endoscopist be experienced in advanced polyp resection techniques to ensure complete resection[9]. Although polyps that are endoscopically resectable are occasionally sent for surgery, studies show that only about 5-10% of patients subsequently require surgery if they undergo endoscopic resection first[34]. Knowing your expertise and comfort level is particularly important on a variety of levels in the case of polyps that may be challenging to resect; for instance, it is relevant to ensuring the best outcome for the patient, peace of mind for the performing provider, and to avoid potential medical professional liability. Referring to a more experienced provider for a complete resection is thus generally recommended over attempting to complete a polypectomy but failing to achieve complete resection, especially if thermal energy is applied in the process and/or when the *a priori* probability of incomplete removal seems high. In addition, biopsies of the polyp should be performed with caution so as to avoid scarring and complicating future endoscopic resection. If a biopsy is needed, the biopsy should be performed cold and avoid flat areas of the lesion[35].

Tattoo placement

If a polyp is deemed unresectable by a provider, it is often advised to tattoo so it can be easily recognized by the receiving provider. Currently, India Ink, a compound known commercially as "Spot Ex," is most commonly used for endoscopic tattooing [36]. With respect to tattoo location and number of tattoos, best practice depends in large part on whether the polyp is planned for referral to a surgeon or to an advanced endoscopist, as shown in Figure 2[37,38]. Generally speaking, a tattoo should be placed a) immediately distal to the polyp and circumferentially in multiple quadrants to facilitate intraoperative visualization when planning to refer for surgical resection or b) in one quadrant 3-5 cm distal to the polyp, with care to not inject into or under the polyp, when planning to refer for advanced endoscopic resection. Tattoo placement may not be necessary if the polyp is in the cecum or distal rectum, as these locations are typically easily identifiable on future examinations, but this may vary based on individual (*e.g.*, anatomical) and institutional (*e.g.*, surgeon or advanced endoscopist preference) factors[9]. Irrespective of such factors, photodocumentation and clear description regarding tattoo placement are critical[39,40].

With respect to tattoo injection technique, a few options exist. The "bleb" method is one which is considered reliable for the placement of tattoos[41], wherein, 0.5 to 1.0 mL of saline is placed into the submucosa, followed by a needle inserted into the saline

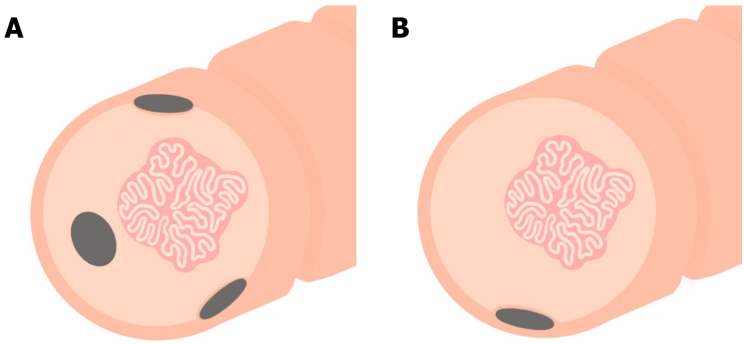

Figure 2 Guidelines for placing an endoscopic tattoo prior to resection. As an overarching principle, the location of the tattoo relative to a polyp should be guided by anatomical factors and institutional practices in addition to being well-described and photodocumented in the procedure report. A: When tattooing with the intent of referral for surgical resection, the tattoo should generally be placed immediately distal to the polyp and circumferentially in multiple quadrants to facilitate intraoperative visualization; B: When tattooing with the intent of referral for advanced endoscopic resection, tattoo should not be injected into or under the polyp, and care should be taken to not inject an excess volume of ink, as this may spread submucosally toward the polyp and subsequently complicate resection; a single tattoo, 3-5 cm distal to the polyp (or one haustral fold distal), is generally appropriate.

bleb to inject the tattoo agent. The bleb method ensures that the tattoo only enters the submucosal space and not into extracolonic tissue. A second method involves directly injecting the tattoo into the submucosa and lifting the needle toward the center of the lumen, although this technique requires greater expertise[36]. Of note, analogous to polypectomy snares, different length and caliber injection needles are available, the appropriate choice of which may, depending on polyp location and other considerations, best facilitate tattoo placement[42-44]; for instance, a shorter, smaller caliber needle may be opted for when tattooing a right colonic polyp in a coagulopathic patient (as opposed to a standard/larger length and caliber needle for a rectal polyp).

Adverse events with tattoo placement

Adverse events (AEs) associated with endoscopic tattooing, albeit rare, have been reported. For example, tattooing can cause submucosal fibrosis (Figure 3) and consequent muscle injury during future endoscopic resection if the tattoo ink spreads underneath the polyp, *e.g.*, if injection is performed too close to or into the polyp or if an excess volume of ink is injected (which can later dissipate laterally to involve the submucosa below the polyp)[40]. Thus, when a polyp is planned for referral for endoscopic resection, the closer the tattoo is to the polyp, the less tattoo volume should be used. Reports of inflammatory responses, localized necrosis from an inflammatory pseudotumor, and rectus muscle abscess have also been described[45-47]. These potential AEs should be taken into account when placing an endoscopic tattoo and accordingly established techniques should be followed.

THE PERFORMING ENDOSCOPIST: RESECTION TECHNIQUES AND CONSIDERATIONS

The endoscopic resection technique that is used largely depends on the morphology of the polyp, in particular its size and whether it is pedunculated or not, as discussed below[9].

Pedunculated polyps

Large polyps can be pedunculated or non-pedunculated. For pedunculated polyps ≥ 10 mm in size, hot snare polypectomy (HSP), in which electrocoagulation is used for resection, is suggested[9]. For larger pedunculated polyps, epinephrine injection into the head or stalk can also be considered to reduce the polyp size and make resection easier[48]. Other strategies include using a detachable loop or placing clips at the polyp stalk before resection. Cold snare polypectomy (CSP) may also be used for resection and has been reported to have a lower rate of post-polypectomy bleeding [49]; however, the rate of complete resection may be higher with HSP compared with CSP when resecting large pedunculated polyps[50].

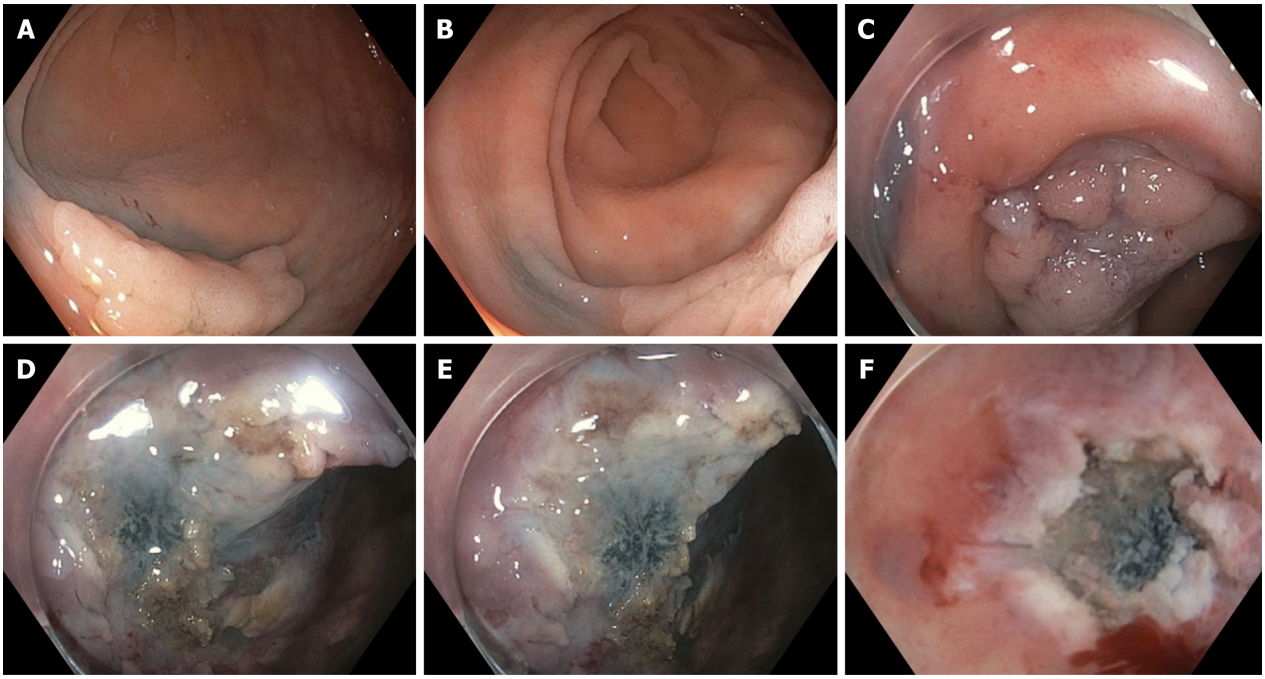

Figure 3 Endoscopic mucosal resection complicated by prior endoscopic tattooing. A and B: Presence of previously placed tattoo ink proximal and lateral to a large (25 mm) sessile polyp, suggestive of injection being made too close to (or under) the polyp and/or an excess volume of ink injected; C: Suboptimal lifting after 10 cc of saline and 13 cc of submucosal injectable composition as a result of submucosal fibrosis from the prior tattoo, complicating en bloc endoscopic mucosal resection; D, E and F: Tattoo ink and associated tissue fibrosis can be seen infiltrating the submucosa directly under the polyp.

Non-pedunculated polyps

Endoscopic mucosal resection: The majority of non-pedunculated (*i.e.*, sessile) polyps can be removed by endoscopic mucosal resection (EMR). In this technique, fluid is injected submucosally to lift the polyp and facilitate resection. Many variations of this technique have been developed, such as hot snare EMR, cold snare EMR, and underwater EMR.

In the hot snare EMR (HS-EMR) technique, the underlying submucosa is first injected with a contrast dye, such as methylene blue, to achieve lifting of the polyp, which allows optimal placement of a snare to grab the polyp away from the mucosa, followed by resection with application of electrocautery. Polyps < 20 mm in size can be removed entirely (en bloc resection), while larger polyps can be removed in segments (piecemeal resection). Because HS-EMR utilizes electrocautery, it can minimize intraprocedural bleeding of cut tissue due to its coagulation effect and also destroy the polyp margins, thus leading to a lower recurrence rate[9]. However, the use of electrocautery is also associated with a higher risk of post-procedural bleeding and perforation, compared to the cold snare technique[51].

Cold snare EMR (CS-EMR) allows for large polyp resection without use of electrocautery. In this variation of EMR, the submucosa may be injected to raise the polyp, similar to HS-EMR, after which the snare is then opened slightly larger than the area of the polyp (resecting some normal tissue margin) to remove it en bloc or piecemeal. As previously mentioned, this technique is associated with lower rates of post-procedural bleeding and perforation compared to HS-EMR. Studies of CS-EMR have shown low rates of polyp recurrence and AEs with excellent resection rates[52-54]. Although HS-EMR is currently the standard of care in endoscopic resections, CS-EMR represents an equally effective and safe resection method for large polyps.

Given that complete en bloc resection rates decrease in polyps ≥ 10 mm using traditional EMR techniques (which in turn increases the rate of recurrence), underwater EMR (UEMR) has been proposed as an alternative effective strategy to resect large polyps[18,19]. This method avoids the use of submucosal injection by aspirating gas and instilling water into the colonic lumen, which raises the mucosal pathology (polyp) away from the underlying submucosa, allowing safer and complete resection of the polyp. Especially useful in the case of large polyps, UEMR has shown significantly increased rates of R0 resections for polyps 10-20 mm in size without increasing the rate of AEs[55]. This variant of EMR represents a viable alternative to traditional resection techniques for large polyps that are difficult to remove

completely.

Endoscopic submucosal dissection: Endoscopic submucosal dissection (ESD) allows for the complete removal of polyps too large for EMR (≥ 20 mm in size) and/or that are strongly suspicious for cancer. ESD is also utilized in cases with suspected submucosal invasion, local early carcinoma, or laterally spreading polyps/tumors[56]. Studies have demonstrated that ESD may have better outcomes for larger polyps, as EMR often requires piecemeal removal which has an increased rate of recurrence (about 20%)[57].

In the ESD technique, the area underneath the polyp is first injected to lift the polyp, followed by creation of an incision into the mucosa using an ESD knife. The submucosal edges are trimmed to allow access to the submucosal plane where the dissection is performed (Figure 4), resulting in an en bloc resection of large polyps/tumors. While ESD has excellent rates of en bloc resection, it has higher rates of AEs compared to EMR, including perforation, bleeding, and hospitalization related to the procedure[58]. Low-voltage coagulation ("soft" ESD) can be performed after resecting the polyp to reduce the risk of post-resection bleeding[59].

Endoscopic full-thickness resection: Endoscopic full-thickness resection (EFTR) is a novel approach which enables all layers of the colon wall to be removed[60,61]. This technique is often used for polyps < 30 mm in size which either fail to lift after submucosal injection or that are difficult to resect with conventional EMR techniques. Multiple studies have shown the efficacy and safety of EFTR[59], in both animal models and human patients, with excellent resection rates for non-lifting adenomas and low rates of AEs (about 14%)[62]. The technique uses a full-thickness resection device (FTRD®), which has been shown to enable complete resection of polyps beneath the mucosa[63]. At this time, EFTR is not widely practiced as few endoscopists are trained in this technique.

Post-resection elements

Endoscopic clipping: Bleeding, the most common AE after EMR, is more likely to occur in patients undergoing resection of large polyps, polyps ≥ 10 mm with a thick stalk, right-sided polyps, and in patients on anticoagulation/antiplatelet agents or with comorbid conditions that increase the risk of bleeding[64,65]. Clipping can be used to effectively stop or prevent bleeding through mechanical pressure. In one study, endoscopic clipping significantly reduced the risk of bleeding after resection of large polyps (≥ 20 mm), with 7.6% of subjects without clipping having bleeding compared to 4.3% with clipping[66]. In addition, clip placement is often utilized to close post-polypectomy mucosal defects[67].

Surveillance: After complete resection of large polyps, close surveillance is recommended to detect disease recurrence and/or metachronous colorectal polyps. Surveillance is important for early detection of asymptomatic and resectable recurrences, which increases patients' chances for curative therapy[68]. The USMSTF recommends that colonoscopy should be performed within 1 year after resection to look for metachronous polyps. If this examination is normal, a subsequent examination should be performed after 3 years, and then 5 years (if the second examination is also normal). However, shorter examination intervals may also be used if additional polyps are found[68]. Shorter examinations are also favored in the case of piecemeal resection of a large polyp because of the significantly increased risk of residual polyp tissue and recurrence. Thus, a period of 2-6 mo is typically the recommended interval for surveillance colonoscopy in such cases[69].

CONCLUSION

As endoscopic resection techniques have evolved, there has been a shift in the management of large colonic polyps from being referred for colon surgery to endoscopic resection. Effective resection of these large polyps can be complex, but success has been documented using methods like EMR and ESD. Endoscopists should be comfortable at recognizing large colonic polyps through classification systems such as the NICE or Paris classification, and these polyps should be resected by endoscopists experienced with advanced resection techniques. Standardized practices coupled with clear communication can help ensure optimal outcomes.

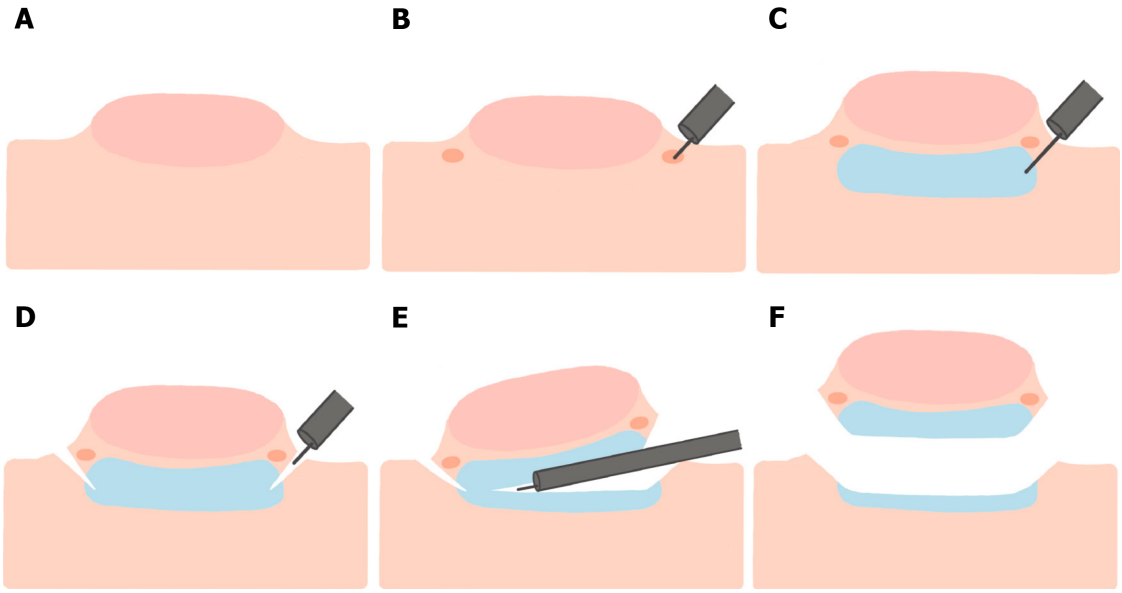

Figure 4 Key steps in performing endoscopic submucosal dissection. A: A large polyp is encountered and deemed to be endoscopically resectable; B: Markings are made around the polyp to delineate the borders; C: The polyp is raised with a submucosal injection solution; D: Incision is made into the submucosa using an endoscopic submucosal dissection (ESD) knife; E: The ESD knife is subsequently used to dissect the polyp in conjunction with serial additional injections; F: The polyp is removed en bloc.

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ORIGINAL ARTICLE

Retrospective Study

Role of endoscopic ultrasound guided fine needle aspiration/biopsy in the evaluation of intra-abdominal lymphadenopathy due to tuberculosis

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Author contributions: Priya SK helped in subject recruitment and data entry of the study; Rao B H and Nair P were involved with data analysis, interpretation and drafted the manuscript; George A and Sathyapalan DT gave initial insight related to the pathology and management of TB; Koshy AK and Venu RP revised the article critically for important intellectual content.

Institutional review board statement: This study was approved by the Amrita Institute of Medical Sciences Research Review Board (Kochi, Kerala, India).

Informed consent statement: All study participants or their legal guardian provided informed written consent for personal and medical data collection prior to study enrolment.

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Abstract

BACKGROUND

Intra-abdominal lymphadenopathy due to tuberculosis (TB) poses a diagnostic challenge due to difficulty in tissue acquisition. Although endoscopic ultrasound guided fine needle aspiration/biopsy (EUS-FNA/B) has shown promise in the evaluation of mediastinal lymph nodes, its role in the evaluation of intra-abdominal lymphadenopathy is not clear.

AIM

To assess the role of EUS-FNA/B in the evaluation of intra-abdominal lymphadenopathy due to TB.

METHODS

This was a retrospective study where patients with intra-abdominal lymphadenopathy who underwent evaluation with EUS-FNA/B were included. TB was diagnosed if the patient had any one of the following: (1) Positive acid fast bacilli (AFB) stain/TB GeneXpert/TB-polymerase chain reaction/AFB culture of tissue sample; and (2) Positive Mantoux test and response to anti-tubercular therapy. EUS-FNA reports, clinical reports and imaging characteristics of patients were recorded for a detailed analysis of patients with TB.

RESULTS

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A total of 149 patients underwent an EUS-FNA/B from lymph nodes (mean age 51 ± 17 years, M:F = 1.2). Benign inflammatory reactive changes were seen in 45 patients (30.2%), while 54 patients (36.2%) showed granulomatous inflammation with/without caseation. Among these, 51 patients (94.4%) were confirmed to have TB as *per* pre-defined criteria. Patients with TB were more likely to have hypoechoic and matted nodes [40 patients (67.7%)]. EUS-FNA/B was found to have a sensitivity and specificity of 86% and 93% respectively, with a diagnostic accuracy of 88% in the evaluation of intra-abdominal lymphadenopathy due to TB.

CONCLUSION
EUS-FNA/B has a high diagnostic yield with a good sensitivity and specificity in the evaluation of intra-abdominal lymphadenopathy due to TB. However, the validity of these findings in populations with low prevalence of TB needs further evaluation.

Key Words: Endoscopic ultrasound; Lymph nodes; Tuberculosis; Mesenteric; Intra-abdominal

Core Tip: Intra-abdominal lymphadenopathy due to tuberculosis (TB) poses a significant diagnostic challenge primarily due to difficulty in tissue acquisition. Endoscopic ultrasound guided fine needle aspiration/biopsy (EUS-FNA/B) has shown promise in the evaluation of TB presenting with mediastinal lymph nodes; however, its role in intra-abdominal lymphadenopathy due to TB remains unclear. In this study, a large cohort of patients who underwent EUS-FNA/B were studied. EUS-FNA/B was found to have a sensitivity and specificity of 86% and 93%, respectively, with a high diagnostic accuracy of 88% in the evaluation of intra-abdominal lymphadenitis due to TB. This study provides valuable data on the pivotal role of EUS-FNA/B in the evaluation of this difficult sub-group of patients. However, the validity of these findings in populations with low prevalence of TB needs further evaluation.

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INTRODUCTION

Intra-abdominal lymphadenopathy due to tuberculosis (TB) is a common clinical entity in regions endemic for the disease. The presence of concomitant lung parenchymal findings can aid in the diagnosis of these patients[1]. However, isolated mesenteric lymphadenopathy usually poses a significant diagnostic challenge[1-3]. Multiple factors including clinical scenario, number, size and imaging characteristics have been described that can help in the differential diagnosis of patients with intra-abdominal lymphadenopathy[4]. Moreover, a positive Mantoux test and/or adenopathy with peripheral rim enhancement with a low density center is supportive for TB at best with fungal infections, atypical mycobacteria and sarcoidosis also presenting with a similar clinical picture[5,6]. The causes of mesenteric lymphadenopathy other than TB include sarcoidosis, lymphoma, metastatic deposits from other malignancies and other rare infectious causes[7].

Tissue acquisition is usually essential for establishing the diagnosis in patients with intra-abdominal lymphadenopathy. Earlier, tissue acquisition was accomplished by computed tomography guided/laparoscopy assisted biopsy. Currently, these modalities have largely been replaced by endoscopic ultrasound guided fine needle aspiration/ biopsy (EUS-FNA/B) over the last decade owing to superior reliability and safety profile and is now the modality of choice in the evaluation of intra-

abdominal and mediastinal lymphadenopathy. EUS has been reported to be capable of imaging and enabling tissue sampling from nodes as small as 5 mm[8]. It has also been proven to be safe for tissue acquisition from lymph nodes with a reported complication rate of less than 0.5%[9].

EUS-FNA/B has been shown to be invaluable in the diagnosis of malignancy (primary/metastatic) during evaluation of intra-abdominal lymphadenopathy. There is also a growing body of evidence that highlights the role of EUS-FNA/B in the manage-ment of mediastinal lymphadenopathy[4-6,10]. However, there is no clarity on the efficacy of EUS-FNA in the evaluation of intra-abdominal lymphadenopathy due to TB. In this study, we analyzed the patients who underwent EUS-FNA for intra-abdominal lymphadenopathy, at a high-volume tertiary care center and assessed the diagnostic yield of EUS-FNA for TB in these patients.

MATERIALS AND METHODS

This was a single center retrospective study conducted in a large tertiary care hospital where patients with intra-abdominal lymphadenopathy referred for EUS-FNA/B between January 1, 2015 and December 31, 2019 were included. Institutional ethics committee clearance for data acquisition and analysis were obtained. All relevant data such as patient demographics (age, gender, comorbidities), procedure details (type of needle, number of passes, size of nodes, echogenicity) and post-procedure complications were noted. On retrospective analysis, TB was diagnosed if the patient had any one of the following: (1) Positive acid fast bacilli (AFB) staining of the tissue sample/positive TB GeneXpert of the tissue sample/positive TB-polymerase chain reaction (PCR) of the tissue sample; (2) Granulomas with caseation; (3) Positive AFB culture; and (4) Positive Mantoux test and an adequate response to anti-tubercular therapy (ATT). EUS-FNA reports, demographics and imaging characteristics of patients with TB were studied in detail to determine the diagnostic yield of the procedure.

EUS procedure

All EUS-FNA procedures were performed by an experienced endosonographer. Institutional protocol was followed wherein procedures were performed under moderate or deep sedation which was provided by a dedicated anaesthetist. All patients received prophylactic antibiotics prior to the procedure as *per* protocol. Initial diagnostic endosonographic evaluation was carried out using a linear array echoendoscope (Olympus GFUCT180, Tokyo, Japan) and upon identification of the lymph nodes, relevant imaging characteristics were noted. Only EUS-FNA/B results of abdominal lymph nodes were analyzed in the study. All procedures were performed with Rapid On-Site Evaluation (ROSE) by a dedicated cytopathologist. Depending upon the site of the nodes, gastric or duodenal approaches were considered. A 22 gauge needle was used for all procedures. A FNA needle (22G Cook EchoTip®, 22G Olympus EZ-shot 3) was used in most cases; while a fine needle biopsy needle (22G Boston Scientific Acquire™) was used in only 10 patients. The needle was passed *via* the instrument channel and the node was targeted under sonographic guidance. The sharp tip of the needle punctured the node after unlocking the needle apparatus and multiple passes were made into the target node. Suctioning was reserved for cases where the initial few passes were inadequate as assessed by the on-site cytopathologist. The needle was passed multiple times into the node typically for 20-30 s each pass while continuously adjusting the position of the needle in a "fanning" pattern to maximize tissue volume. The needle was then removed from the endoscope, and the tissue was prepared for pathological examination.

Pathological examination

All the FNA material was placed onto glass slides and smears were made. Smears for ROSE were fixed in 80% isopropyl alcohol which was then rapidly stained with 1% Toluidine blue. The on-site cytopathologist evaluated the adequacy of tissue in each pass and also gave a preliminary opinion on pathological changes on the slide. The number of passes were determined on the basis of this information until a maximum of 5 passes were made. When staining was complete, all EUS-FNA specimens were evaluated for cytological diagnosis and cellular preservation by a pathologist. These slides were subsequently stained with Papanicolaou stain in the cytology laboratory for further evaluation. Visible core tissue was placed in formalin-alcohol mixture (formalin and 80% isopropyl alcohol in 1:1 ratio) and subsequently paraffin embedded to produce cell blocks. Sections from the cell blocks were stained with hematoxylin

and eosin. The slides were meticulously observed to arrive at a final diagnosis.

On pathological examination, reactive nodes will exhibit a polymorphous lymphoid population including mature lymphocytes, germinal center cells and tingible body macrophages. Granulomatous inflammation was diagnosed when there were collections of epithelioid histiocytes forming an epithelioid cell granuloma with or without necrosis(Figure 1). In such cases, further sampling was performed with microbiological tests such as AFB staining, GeneXpert and TB culture. Diagnosis of lymphoma was applicable when the lymphoid cells were monomorphic populations of atypical lymphoid cells. Secondary malignant deposits in the node were identified when tumor cells were admixed with a reactive lymphoid population.

Diagnosis and follow-up

Patients with features of lymphoma or metastatic malignancy were treated with an appropriate chemotherapy regimen as *per* hospital protocol by the oncologist. Patients with TB as defined above, received ATT for 6 mo. Patients with sarcoidosis were treated with steroids. All patients were followed up 15 d after the procedure to discuss biopsy findings and treatment plan. All patients were followed up clinically every month for symptomatic improvement or drug side effects.

Statistical analysis

Statistical analysis was carried out using IBM SPSS software version 20.0. The pathology reports were correlated with clinical diagnosis in order to determine the diagnostic validity of EUS-FNA in the evaluation of intra-abdominal lymph nodes resulting from TB. A descriptive analysis of all patients with TB was carried out. Comparisons of means for continuous variables were carried out using the independent 2-sample *t* test and Mann Whitney U tests for parametric and non-parametric variables, respectively. Categorical variables were analyzed using Chi square test/Fisher's Exact test. A $P < 0.05$ was considered statistically significant.

RESULTS

EUS-FNA/B in the evaluation of intra-abdominal lymphadenopathy

A total of 149 patients underwent EUS-FNA/B of lymph nodes. The mean age of these patients was 51 ± 17 years with a male to female ratio of 1.2. The most common clinical presentation was fever of unknown origin [78 patients (52.3%)], whereas, 48 patients (32.2%) underwent EUS-FNA of lymph nodes for staging of malignancy and the remaining 23 patients (15.5%) were incidentally detected to have abdominal lymphadenopathy. A total of 91 patients (61.1%) had only abdominal lymphadenopathy and the remaining 58 patients (38.9%) had both mediastinal as well as abdominal lymphadenopathy. Most of the patients (n = 139) underwent EUS-FNA using a 22G aspiration needle (22G Cook EchoTip®, 22G Olympus EZ-shot 3), while only 10 patients (6.7%) underwent the procedure using a 22G biopsy needle (22G Boston Scientific Acquire™). No differences in patient characteristics and procedures results were observed between the two needle types. All patients had adequate cellularity to make a diagnosis, from the samples taken from abdominal lymph nodes, as assessed by the on-site cytopathologist, in this study. The cytology results showed only reactive changes in 45 patients (30.2%), while 54 patients (36.2%) showed granulomatous inflammation with or without caseation. Malignant cells were seen in a total of 50 patients (33.6%), of which, features suggestive of lymphoma were seen in 11 patients (22%) and metastatic deposits were seen in 39 patients (78%) (Table 1). Among the 54 patients with granulomatous inflammation on EUS-FNA cytology, 51 patients (94.4%) were confirmed to have TB on the basis of confirmatory tests or response to ATT on follow-up; and 3 patients (5.55%) had elevated angiotensin I-converting enzyme levels along with systemic symptoms of sarcoidosis which was managed accordingly. On follow-up of patients with reactive changes on EUS-FNA cytology (n = 45), 30 patients (66.67%) showed non-specific inflammation which was managed conservatively, 8 patients (17.78%) had TB and were treated accordingly, 1 patient (2.22%) was diagnosed with sarcoidosis, while 3 patients (6.66%) showed malignant cells as *per* the surgical histopathology report; 3 patients (6.66%) were lost to follow-up.

EUS-FNA/B in the evaluation of intra-abdominal lymphadenopathy due to TB

A total of 59 patients were diagnosed with TB during follow-up and were treated with

Table 1 Baseline characteristics of patients who underwent endoscopic ultrasound fine needle aspiration/biopsy for abdominal lymphadenopathy

Baseline characteristics	Overall (*n* = 149)
Age (mean ± SD) in yr	51 ± 17
Gender, *n* (%)	
Male	84 (56.38)
Female	65 (43.62)
Clinical presentation, *n* (%)	
Fever of unknown origin	78 (52.3)
Staging of malignancy	48 (32.2)
Incidental	23 (15.5)
Cytology, *n* (%)	
Granulomatous inflammation	54 (36.2)
Reactive changes	45 (30.2)
Malignant cells	50 (33.6)
Final clinical diagnosis, *n* (%)	
Tuberculosis	59 (39.59)
Primary lymphoid malignancy (lymphoma)	11 (7.38)
Secondary malignant deposits	39 (26.17)
Sarcoidosis	3 (2.01)
Benign inflammatory lymphadenopathy	37 (24.8)

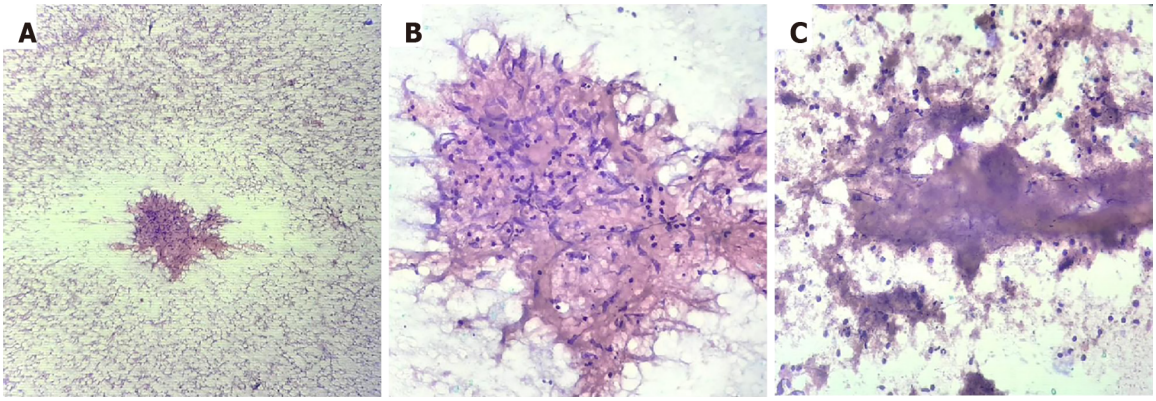

Figure 1 Histopathology findings on the fine needle aspiration sample of a patient with tuberculosis. A: An epithelioid cell granuloma with scattered lymphocytes and red blood cells in the background (100 ×); B: Collection of epithelioid histiocytes forming a granuloma (400 ×); C: Necrotic material and inflammatory cells (400 ×).

standard anti-tubercular drugs. The baseline characteristics of these patients are shown in Table 2. Isolated abdominal lymphadenopathy was seen in 31 patients (52.5%), while 28 patients (47.4%) had both mediastinal and abdominal lymphadenopathy. All the patients presented with fever of unknown origin and a majority of them also had systemic symptoms such as weight loss and night sweats [40 patients (67.7%)].

Patients with TB were more likely to have hypoechoic nodes [37 patients (62.7%)], while 22 patients (37.3%) had heteroechoic nodes on endosonographic examination (Figure 2). A majority of these patients also had matted nodes forming a conglomerate lymphnodal mass [40 patients (67.7%)]. All patients underwent EUS-FNA using an aspiration needle except for 2 patients (3.4%) in whom a biopsy needle was used. TB GeneXpert of the biopsy sample was performed in a total of 34 patients (57.6%), of which only 14 patients (41.1%) had a positive result and the remaining 20 patients

Table 2 Characteristics of patients diagnosed with tuberculosis (*n* = 59)

Baseline characteristics	Overall (*n* = 59)
Age (mean ± SD) in yr	45 ± 18
Gender, *n* (%)	
Male	31 (52.5)
Female	28 (47.4)
Echogenicity, *n* (%)	
Hypoechoic node	37 (62.7)
Heteroechoic node	22 (37.3)
Matting of lymph nodes, *n* (%)	
Yes	40 (67.7)
No	19 (32.2)
Cytology, *n* (%)	
Granulomatous inflammation with or without caseation	51 (86.4)
Reactive changes only	8 (13.5)
TB GeneXpert, *n* (%), *n* = 34	
Positive	14 (41.1)
Negative	20 (58.9)
TB culture, *n* (%), *n* = 38	
Growth	12 (31.6)
No growth	26 (68.4)
Fine needle aspiration (22 Gauge needle) (%)	
Sensitivity	86
Specificity	93
Accuracy	88

TB: Tuberculosis.

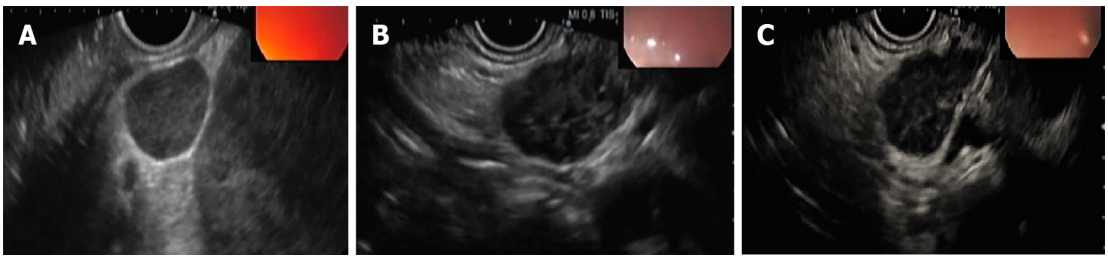

Figure 2 Endoscopic ultrasound. A: Hypoechoic node due to tuberculosis (TB) as seen on endoscopic ultrasound (EUS); B: Heteroechoic node due to TB as seen on EUS; C: Typical findings of TB lymphadenitis on EUS and fine needle aspiration cytology.

(58.9%) had a false negative result. Samples from a total of 38 patients were sent for TB culture. Of these, only 12 samples (31.6%) grew *Mycobacterium tuberculosis*, while the remaining 26 samples (68.4%) did not show any growth of organisms.

Among the patients with confirmed TB, EUS-FNA/B showed granulomatous inflammation with or without caseation in 51 patients (86.4%), while the remaining patients showed non-specific reactive changes [8 patients (13.5%)]. EUS-FNA/B was found to have a sensitivity and specificity of 86% and 93%, respectively, with a diagnostic accuracy of 88% in the evaluation of mesenteric lymphadenitis due to TB.

DISCUSSION

Extrapulmonary TB accounts for 15%-20% of all cases of TB[11,12]. TB presenting with isolated lymphadenopathy is common in endemic areas and poses a significant diagnostic challenge[13]. In the absence of characteristic symptoms or pathognomic radiographic features, isolation of the bacilli and/or identification of caseous granulomas from biopsy samples remains the gold standard. Therefore, accurate and reliable tissue acquisition from these nodes remains the cornerstone in the diagnostic evaluation of these patients. However, intra-abdominal lymphadenopathy poses unique challenges and this is where EUS-FNA/B can potentially prove invaluable in establishing a correct diagnosis. Historically, FNA cytology in conjunction with the presence of AFB, caseating necrosis and granulomas can usually provide the diagnosis in most patients. However, the sensitivity of these findings are less than ideal[14-16]. In one study, 272 patients with a proven diagnosis of tubercular lymphadenopathy had AFB positivity only in 30% of direct and concentrated smears. Moreover, TB cultures were positive only in 49% with only a marginal improvement when combined with cytologic necrosis (63%)[14]. In another study which included 390 patients with tubercular lymphadenopathy, only 24% were positive for AFB on the smear and cultures yielded a positive result in 35%[17]. These findings highlight the poor sensitivity of tests that rely on identification of the bacilli in FNA samples.

EUS-FNA/B has seen tremendous progress in the last decade with improved image resolution, increased experience with therapeutic interventions and unique biopsy needles that can increase the quantum of tissue obtained and thereby potentially address existing pitfalls of FNA cytology in establishing a diagnosis of TB. EUS-FNA has also already been evaluated for mediastinal lymphadenopathy with an overall accuracy of 93%, sensitivity of 71% and specificity of 100% for the diagnosis of TB in the Indian population[7]. However, the role of EUS-FNA/B in the evaluation of intra-abdominal lymphadenopathy due to TB remains an area that merits further evaluation. The results of the present study provide valuable evidence of the validity of EUS-FNA/B in the evaluation of TB presenting with intra-abdominal lymphadenopathy. Granulomas were seen in a total of 54 samples (36.2%) and the finding of granulomatous inflammation in the biopsy specimens correlated well with the diagnosis of TB in this study, with only 3 patients diagnosed with sarcoidosis. Only a minority of patients [8 patients (13.5%)] with TB (based on follow-up data and response to treatment) did not show granulomas on the FNA/B sample. Overall, EUS-FNA/B was found to be a safe and reliable modality in the evaluation of intra-abdominal lymphadenopathy due to TB with a diagnostic accuracy of 88% and a reasonable sensitivity and specificity for TB. Based on the findings of this study, an approach for the evaluation of intra-abdominal lymphadenopathy is proposed in Figure 3.

In general, the quantum of tissue samples obtained from lymph nodes after EUS-FNA have been found to be sufficient in most indications[4]. Ancillary techniques such as applying suction and slow withdrawal have been evaluated in the setting of pancreatic lesions. However, the utility of these techniques in the setting of lymph nodes needs further clarity. In our experience, we have found no added benefit with these ancillary techniques. A thorough endosonographic evaluation prior to FNA with emphasis on choosing an ideal node that is adequately enlarged and with sharp borders, with/without matting is essential to ensure a high yield. Particular attention should be paid to the morphology of the lymph node wherein hypoechoic areas which might indicate necrosis should be avoided. Sampling of peripheral tissue within the node has yielded better tissue samples in our experience. However, this requires further validation in larger studies.

There are a few limitations in the present study. This study was performed in an area endemic for TB. Therefore, the pre-test probability of TB would be high and as such, the findings of this study would be applicable only in similar demographic groups. In addition, a definitive diagnosis of TB requires a positive culture/GeneXpert and/or PCR for tubercular bacilli. A proportion of our study population could not undergo these tests due to financial considerations and poor patient compliance. Empirical ATT is a practice followed in most regions endemic for TB, but carries with it a high risk of treatment failure and can even pose a risk for the emergence of resistant organisms. Tissue acquisition in these cases can provide valuable information and dictate therapy. Moreover, a high pre-test probability of TB, a positive Mantoux test and granulomas on the FNA sample has been shown to be a reasonable approach to start a patient on ATT[18]. Moreover, all the patients who were treated with ATT using this approach showed good response to treatment on follow-up.

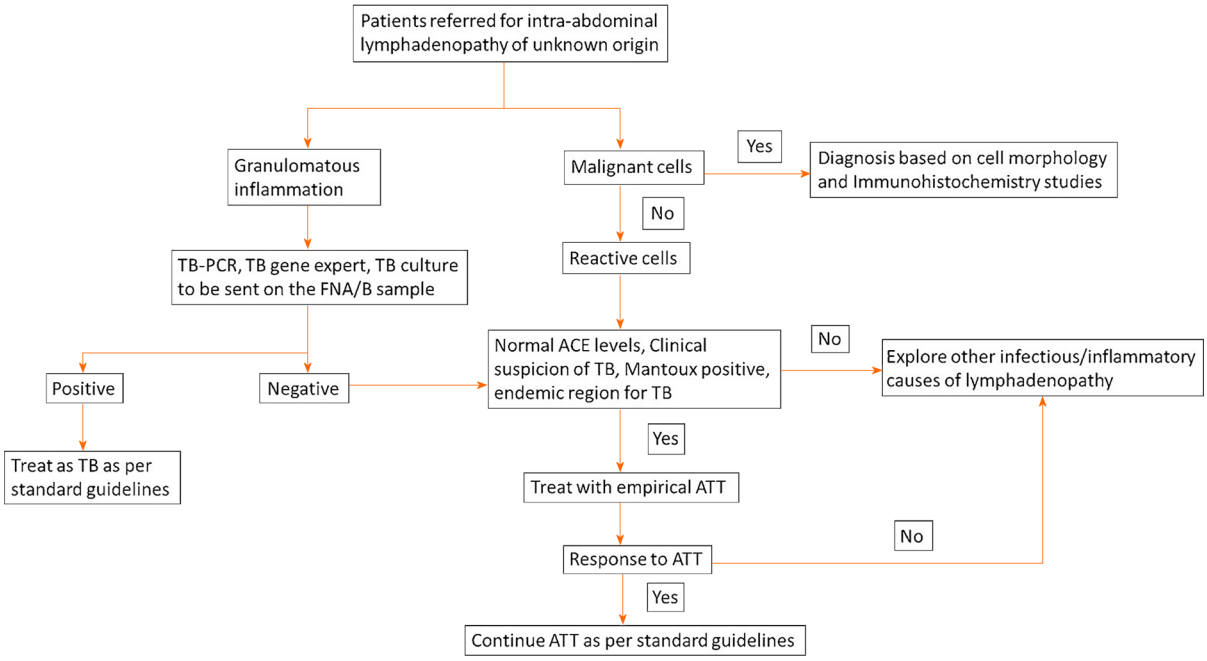

Figure 3 Proposed approach to intra-abdominal lymphadenopathy in a region endemic for tuberculosis. TB: Tuberculosis; PCR: Polymerase chain reaction; ATT: Anti-tubercular therapy; FNA/B: Fine needle aspiration/biopsy; ACE: Angiotensin I-converting enzyme.

CONCLUSION

In conclusion, EUS-FNA/B has a high diagnostic yield with a good sensitivity and specificity in the evaluation of intra-abdominal lymphadenopathy in patients with a clinical suspicion of TB. The procedure is safe, performed with moderate sedation and can potentially prevent further invasive testing in this subgroup of patients. However, the utility of this procedure in populations with a low prevalence of TB needs more clarity. In addition, a protocol-based approach with additional tests such as TB culture, AFB stain, TB-PCR or GeneXpert in specific subgroups of patients at risk for TB needs to be developed and evaluated in future studies.

ARTICLE HIGHLIGHTS

Research background

Intra-abdominal lymphadenopathy due to tuberculosis (TB) poses a diagnostic challenge due to difficulty in tissue acquisition.

Research motivation

Endoscopic ultrasound guided fine needle aspiration/biopsy (EUS-FNA/B) has shown excellent results in patients with mediastinal lymphadenopathy. However, its role in the evaluation of abdominal lymphadenopathy due to TB needs further clarity.

Research objectives

The utility of EUS-FNA/B in the evaluation of intra-abdominal lymphadenopathy was assessed by evaluating the diagnostic yield in patients with confirmed TB.

Research methods

This was a single center retrospective study conducted in a large tertiary care hospital where patients with intra-abdominal lymphadenopathy referred for EUS-FNA/B were studied. The diagnosis of TB was confirmed and EUS-FNA/B results including cytology, pathological diagnosis, ancillary test findings (TB culture, GeneXpert) and demographics in these patients were carefully analyzed.

Research results

This study showed that EUS-FNA/B has a high diagnostic yield with good sensitivity

(86%), specificity (93%) and diagnostic accuracy (88%) in the evaluation of intra-abdominal lymphadenopathy in patients with a clinical suspicion of TB. Morphological findings on EUS evaluation of intra-abdominal lymphadenopathy include hypoechoic/heteroechoic nodes, with sharp borders, with/without matting.

Research conclusions

EUS-FNA/B is a viable, reliable and safe procedure, which can be performed with moderate sedation and can potentially prevent further invasive testing in this subgroup of patients.

Research perspectives

This study provides vital information that can guide the approach and management of patients with intra-abdominal lymphadenopathy. A management algorithm that highlights key points during the management of these patients is provided. However, the utility of this procedure in populations with a low prevalence of TB needs more clarity. In addition, a protocol-based approach with additional tests such as TB culture, acid fast bacilli stain, TB-polymerase chain reaction or GeneXpert in specific subgroups of patients at risk for TB needs to be developed and evaluated in future studies.

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ORIGINAL ARTICLE

Observational Study

Efficacy and tolerability of high and low-volume bowel preparation compared: A real-life single-blinded large-population study

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Abstract

BACKGROUND

Low-volume preparations for colonoscopy have shown similar efficacy compared to high-volume ones in randomized controlled trials (RCT). However, most RCTs do not provide data about clinical outcomes including lesions detection rate. Moreover, real-life comparisons are lacking.

Institutional review board statement: The study was approved by the local Ethics Committee of San Raffaele Hospital (Approval No. 90/INT/2014).

Informed consent statement: A specific written informed consent was taken from all the study participants.

Conflict-of-interest statement: The authors declare that there is no conflict of interest.

Data sharing statement: Dataset of this study is available from the corresponding author at luca.pastorelli@unimi.it, upon reasonable request. Informed consent for data sharing was not obtained but the presented data are anonymized and risk of identification is low.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

AIM

To compare efficacy (both in terms of adequate bowel preparation and detection of colorectal lesions) and tolerability of a high-volume (HV: 4 L polyethylene glycol, PEG) and a low-volume (LV: 2 L PEG plus bisacodyl) bowel preparation in a real-life setting.

METHODS

Consecutive outpatients referred for colonoscopy were prospectively enrolled between 1 December 2014 and 31 December 2016. Patients could choose either LV or HV preparation, with a day-before schedule for morning colonoscopies and a split-dose for afternoon procedures. Adequate bowel preparation according to Boston Bowel Preparation Scale (BBPS), clinical outcomes including polyp detection rate (PDR), adenoma detection rate (ADR), advanced adenoma detection rate (AADR), sessile/serrated lesion detection rate (SDR) and cancer detection rate and self-reported tolerability of HV and LV were blindly assessed.

RESULTS

Total 2040 patients were enrolled and 1815 (mean age 60.6 years, 50.2% men) finally included. LV was chosen by 52% of patients (50.8% of men, 54.9% of women). Split-dose schedule was more common with HV (44.7% *vs* 38.2%, P = 0.005). High-definition scopes were used in 33.4% of patients, without difference in the two groups (P = 0.605). HV and LV preparations showed similar adequate bowel preparation rates (89.2% *vs* 86.6%, P = 0.098), also considering the two different schedules (HV split-dose 93.8% *vs* LV split-dose 93.6%, P = 1; HV day-before 85.5% *vs* LV day-before 82.3%, P = 0.182). Mean global BBPS score was higher for HV preparations (7.1 ± 1.7 *vs* 6.8 ± 1.6, P < 0.001). After adjustment for sex, age and indications for colonoscopy, HV preparation resulted higher in PDR [Odds ratio (OR) 1.32, 95%CI: 1.07-1.63, P = 0.011] and ADR (OR 1.29, 95%CI 1.02–1.63, P = 0.038) and comparable to LV in AADR (OR 1.51, 95%CI 0.97-2.35, P = 0.069), SDR and cancer detection rate. The use of standard-definition colonoscopes was associated to lower PDR (adjusted OR 1.59, 95%CI: 1.22-2.08, P < 0.001), ADR (adjusted OR 1.71, 95%CI: 1.26–2.30, P < 0.001) and AADR (adjusted OR 1.97, 95%CI: 1.09-3.56, P = 0.025) in patients receiving LV preparation. Mean Visual Analogue Scale tolerability scored equally (7, P = 0.627) but a ≥ 75% dose intake was more frequent with LV (94.6% *vs* 92.1%, P = 0.003).

CONCLUSION

In a real-life setting, PEG-based low-volume preparation with bisacodyl showed similar efficacy and tolerability compared to standard HV preparation. However, with higher PDR and ADR, HV should still be considered as the reference standard for clinical trials and the preferred option in screening colonoscopy, especially when colonoscopy is performed with standard resolution imaging.

Key Words: Bowel preparation volume; Polyethylene glycol; Bisacodyl; Colonoscopy; Colonic adenomas; Tolerability

Core Tip: Quality of bowel preparation is one of the main factors influencing outcomes of colonoscopy. This prospective real-life study compared bowel cleansing (according to the Boston Bowel Preparation Scale), clinically relevant colonoscopy outcomes (lesions detection rate) and tolerability of a standard high-volume bowel preparation and a low-volume preparation (2 L polyethylene glycol + bisacodyl). Even if the two study groups did not show differences in terms of adequate bowel preparation, the use of the high-volume preparation was associated with higher polyp and adenoma detection rates. There were no differences in terms of advanced adenomas, sessile/serrated lesions and cancer detections. Performance of low-volume preparation seems influenced by image resolution of colonoscopes, with fewer lesions detected compared to high-volume when using standard-definition colonoscopes. The two preparations were comparable in terms of patients' self-reported tolerability, but

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complete adherence to preparation was more common with the low-volume product.

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INTRODUCTION

The clinical performance of colonoscopy is markedly influenced by the quality of bowel preparation. In fact, inadequate bowel preparation has proved to have a detrimental effect on different clinically significant outcomes, such as complete colonoscopy rate[1-3], polyp (PDR) and adenoma detection rates (ADR)[4-6]. Moreover, inadequate preparation may require to repeat the procedure, with the subsequent increase in waiting times, risks and costs[7,8]. Large volumes (4 L) of polyethylene glycol (PEG) have been classically prescribed to achieve adequate cathartic effect. Over the past years, several low-volume preparations have been developed to increase the patients' acceptability, compliance and willingness to repeat the procedure. Randomized controlled trials (RCTs) and some meta-analysis have shown that low-volume preparations have similar efficacy in terms of adequate bowel preparation rate compared to high-volume preparations[9-15], however two meta-analysis[16,17] reported a superiority of high-volume PEG over low-volume PEG. Moreover, the direct comparison of clinical outcomes such as ADR is available only in a minority of trials[11,12], and real-life data suggest higher detection rates with high-volume preparations[18].

Therefore, we have performed a real-life study to (1) compare efficacy of HV and LV preparations by means of adequate bowel preparation rate and detection of colonic lesions; and (2) to compare self-reported tolerability of different regimens.

MATERIALS AND METHODS

Study design and subjects

We prospectively enrolled the consecutive patients referred for colonoscopy to the Digestive Endoscopy Outpatient Service of IRCCS Policlinico San Donato between 1 December 2014 and 31 December 2016. The patients enrolled in the regional colorectal cancer screening program were not included as in our Center they are all advised to use high-volume PEG-based preparation. If a patient underwent multiple colonoscopies during the study period, only the first procedure was taken into account for the study.

The exclusion criteria were: inability to give informed consent, use of cleansing products different from the recommended ones, incomplete patient forms as to the type of preparation used, incomplete colonoscopy because of a pathological stricture.

At the time of booking the examination, all the patients received written detailed instructions about the diet regimen (no fruit, legumes, or vegetables for 3 d before the procedure; light breakfast and lunch the day before colonoscopy, followed by clear liquids only) and about bowel preparation. Instructions contained an introductory paragraph underlying the importance to adhere to the prescriptions provided in order to increase the chance to achieve good diagnostic and therapeutic results and to reduce adverse events of colonoscopy. Patients were free to choose either a high-volume (HV) or a low-volume (LV) preparation. The HV preparation (SELG ESSE; Promefarm, Italy) was a PEG 4000 solution plus simethicone and electrolytes that had to be diluted in 4L still water, while the LV preparation was a combination of a PEG 4000 solution plus simethicone and electrolytes (Lovol-Esse; Alfasigma, Italy) diluted in 2 L still water and the stimulant laxative bisacodyl (Lovoldyl; Alfasigma, Italy). In the written instructions handed to the patients, the two preparations were stated as equally effective and tolerated and complete free choice was left to patients' preferences. The

preparations were listed with the HV preparation first.

For the procedures planned before 12:00 pm, the patients were instructed to take the entire quantity of the PEG solution the evening before colonoscopy, starting from 7 pm; in case of LV preparation, 4 tablets (20 mg) of bisacodyl were also taken at 3:00 pm. For afternoon procedures a split-dose regimen was prescribed: half the dose of PEG was taken in the afternoon before and half the dose at 7:00 a.m. in the morning on the day of the colonoscopy; in case of LV preparation 20 mg bisacodyl was taken at sleep time.

The study was approved by the local Ethics Committee of San Raffaele Hospital and a specific written informed consent was taken from all the study participants. The study was conducted in accordance with the Declaration of Helsinki 1975 and subsequent amendments.

Colonoscopy

All the procedures were performed under mild-to-moderate sedation (midazolam ± pethidine i.v.) by 5 experienced endoscopists (> 1000 colonoscopies overall, > 300/year), well-trained in the use of bowel preparation rating scales and blinded to the content of the patient form and to the preparation taken. The indication for colonoscopy was collected by the endoscopist matching medical prescription and pre-colonoscopy interview, following the standard clinical protocol. The endoscopes used were either standard-definition (SD) or high-definition (HD) scopes by Pentax (Tokyo, Japan).

Data collection

On the morning of colonoscopy, the patients were asked to fill a specific questionnaire covering the kind of bowel preparation used (HV or LV), amount of PEG solution taken (the 75% threshold was chosen to define the PEG intake as "full"), time of the exam, demographics, morphometrics, social circumstances (living alone, instruction level) and clinical data. The questionnaire included a specific section about personal bowel habits (Bristol stool chart, frequency of bowel movements per week). Constipation was defined as Bristol stool chart type 1-2 and less than 3 bowel movements/week, and/or chronic constipation as indication for colonoscopy. The form also contained a section about general satisfaction about the used preparation [evaluated by visual analogue scale (VAS) score, from 0 = 'absolutely unsatisfied' to 10 = 'perfectly satisfied'] and symptoms (nausea, vomit, bloating, abdominal pain) experienced during the preparation.

The quality of bowel preparation was assessed using the Boston bowel preparation scale (BBPS)[19]. Bowel preparation was defined adequate if a global score ≥ 6 with segmental scores ≥ 2 in all colonic segments was achieved. For any patients with previous bowel resection, the preparation was considerate adequate if all the segmental sub-scores were ≥ 2.

The number, size and final histology of lesions resected or biopsied during the procedures were collected. PDR, ADR, advanced adenoma (adenomas ≥ 1 cm or with villous component or harboring high-grade dysplasia) detection rate (AADR), sessile/serrated lesion detection rate (SDR, excluding hyperplastic polyps) and cancer detection rate were calculated.

Statistical analysis

Considering an expected adequate preparation rate of 87.1% with LV preparation and of 92.5% with HV preparation from a previous study[20], power of 90% with an alpha error of 0.05, we estimated that 1384 patients would be sufficient. A possible drop-out rate of 30% was considered for the study, therefore the final required sample size was 1977 patients.

The descriptive statistics were expressed as counts and percentages for categorical variables and mean ± SD or median (interquartile ranges, IQR) for continuous variables, as appropriate. Normality assumption was to be tested in continuous variables by visual inspection of the qq-plot.

The association between bowel preparation and baseline variables was investigated with the χ^2 test for categorical variables; the continuous variables were compared by analysis of variance ANOVA or by the non-parametric Kruskal–Wallis test for non-normally distributed data.

Univariate and multi-variate logistic regression was used to identify if adequate bowel preparation and volume of bowel preparation were independently associated with clinical outcomes (PDR, ADR, AADR, SDR and cancer). Multivariate analysis was performed considering age (as a continuous variable), sex and indications for

colonoscopy [positive fecal blood test (FBT), surveillance, symptoms or inflammatory bowel disease (IBD)]. Separate analysis was also performed considering the type of colonoscopes used (HD or SD imaging). Odds ratios (ORs) with their corresponding 95%CIs were calculated, and *P* values were considered statistically significant if they were less than 0.05.

Statistical analysis was carried out by computer software SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Total 2040 patients were enrolled and 1815 patients (mean age 60.6 years, 50.2% male) were finally included according to exclusion criteria (study flowchart in Supplementary Figure 1). 944 patients (52%) chose a LV preparation, while 871 patients (48%) preferred a HV preparation. 750 patients (41.3%) had their colonoscopy scheduled in the afternoon and thereafter used a split-dose regimen; the use of a split-dose regimen was more common in the HV group (44.7% *vs* 38.2%, *P* = 0.0055).

Indications for colonoscopy were symptoms (altered bowel movements, anemia or bleeding, abdominal pain) in 60.6%, post-polypectomy or post-colorectal cancer surveillance in 24.0%, positive FBT in 8.3% and follow-up of known IBD in 7.1% of the cases. Positive FBT was more common in the HV group and known IBD in the LV group. The patients in the HV preparation group were more frequently male, had higher body mass index and more frequently had a cardiac disease and a low-level education. There were no statistically significant differences in terms of age and other possible risk factors for poor bowel preparation (previous abdominal/pelvic surgery, constipation, living-alone status or non-adherence to low-fiber dieting before colonoscopy). HD colonoscopes were used in 606 patients (33.4%), without difference in the two groups (*P* = 0.605) (Table 1).

Overall, adequate preparation was observed in 1595/1815 (87.9%) patients. Complete colonoscopy was possible in 1793 patients (98.8%). At least one polypoid lesion was found in 520/1815 colonoscopies (PDR 28.7%). Histology revealed at least one adenoma in 381/1815 colonoscopies (ADR 20.1%) and at least one sessile/serrated lesion in 28/1815 colonoscopies (SDR 1.5%). Non adenomatous/non serrated lesions were mostly hyperplastic (*n* = 81) or inflammatory (*n* = 23) polyps, with less common histology encountered in 7 cases.

Adequate bowel preparation was associated with a higher complete colonoscopy rate (99.7% *vs* 92.5%, OR 24.05, 95%CI: 7.82–73.92, *P* < 0.001), higher PDR (29.8% *vs* 20.1%, OR 1.69, 95%CI: 1.20–2.40, *P* = 0.003) and ADR (21.8% *vs* 15.5%, OR 1.52, 95%CI: 1.04–2.23, *P* = 0.033), while no significant differences were found in AADR, cancer detection and SDR (Table 2).

PDR, ADR, AADR and cancer rates were higher in the positive FBT group, followed by the surveillance, symptoms and IBD groups (Supplementary Table 1). The use of HD instruments was related to significantly higher ADR (*P* = 0.040) compared to standard definition instruments, without significant difference in other clinical outcomes (Supplementary Table 2).

Efficacy of bowel preparation

The adequacy of preparation was independent of the use of HV or LV preparations (89.2% *vs* 86.6%, *P* = 0.098). The split-dose schedule was superior to day-before for either HV (93.8% *vs* 85.5%, *P* < 0.001) or LV preparation (93.6% *vs* 82.3%, *P* < 0.001). Also considering the two different schedules, there was no difference among HV and LV preparation (HV split-dose 93.8% *vs* LV split-dose 93.6%, *P* = 1; HV day-before 85.5% *vs* LV day-before 82.3%, *P* = 0.182) (Figure 1). The efficacy of HV and LV preparations was similar in all the colonic segments (Supplementary Figure 2), irrespective of the use of the day-before or a split-dose schedule (Supplementary Figure 3).

The mean global BBPS scores were higher with HV preparations compared to LV (overall: 7.1 ± 1.7 *vs* 6.8 ± 1.6, *P* < 0.001; day-before schedule: 6.9 ± 1.7 *vs* 6.6 ± 1.7, *P* = 0.003; split-dose schedule: 7.5 ± 1.6 *vs* 7.2 ± 1.5, *P* = 0.019).

Clinical endpoints

As compared to LV preparation, HV preparation was associated with higher PDR (32.5% *vs* 25.1%, OR 1.43, 95%CI: 1.17–1.76, *P* < 0.001), higher ADR (24.1% *vs* 18.1%, OR 1.44, 95%CI: 1.14-1.80, *P* = 0.002) and higher AADR (6.4% *vs* 3.7%, OR 1.79, 95%CI: 1.16–2.75, *P* = 0.009) without differences in cancer detection and SDR. After adjustment for age, sex and indication for colonoscopy, the difference remained statistically

Table 1 Demographic and clinical features of the study population, *n* (%)

Characteristics	High volume (*n* = 871)	Low volume (*n* = 944)	*P* value[1]
Age	61.2 ± 14.3	60.1 ± 14.6	0.092
Male sex	463 (53.2)	448 (47.5)	0.015[3]
Split-dose	389 (44.7)	361 (38.2)	0.006[3]
High-definition colonoscope	296 (33.9)	310 (32.8)	0.605
Indication			
Symptoms	538 (61.8)	563 (59.6)	
Surveillance			< 0.001[3]
Post polypectomy	134 (15.4)	154 (16.3)	
Post colonic resection for CRC	73 (8.4)	73 (7.7)	
Positive FBT	94 (10.8)	57 (6.1)	
IBD	32 (3.6)	97 (10.3)	
BMI, mean ± SD[2]	25.5 ± 4.3	25.0 ± 4.0	0.015[3]
Previous abdominal surgery	98 (11.3)	96 (10.2)	0.456
Constipation	66 (7.6)	86 (9.1)	0.239
Comorbidities			
Heart disease	90 (10.3)	65 (6.9)	0.009[3]
Diabetes	72 (8.3)	65 (6.9)	0.266
Stroke/dementia	19 (2.2)	25 (2.6)	0.518
Severe CKD	21 (2.4)	15 (1.6)	0.209
Cirrhosis	12 (1.4)	13 (1.4)	0.999
GERD	192 (22.0)	219 (23.2)	0.557
Waiting time > 1 mo	485 (55.7)	570 (60.4)	0.090[3]
Non-adherence to low fiber diet	91 (10.5)	112 (11.9)	0.329
Lives alone[2]	123 (14.8)	149 (16.3)	0.395
Low instruction[2]	157 (19.6)	122 (14.1)	0.002[3]

[1]*P* value degrees of freedom = 1, except for age (1814), indication (4) and body mass index (BMI) (1726).
[2]BMI available for 1727 patients; information about living alone available for 1747 patients; instruction level available for 1662 patients.
[3]Significant different.
CRC: Colorectal cancer; FBT: Fecal blood test; IBD: Inflammatory bowel disease; BMI: Body mass index; CKD: Chronic kidney disease; GERD: Gastroesophageal reflux disease.

significant for PDR (adjusted OR 1.320, 95%CI: 1.07-1.63, P = 0.011) and for ADR (adjusted OR 1.29, 95%CI: 1.02-1.63, P = 0.038) but not for AADR (adjusted OR 1.51, 95%CI: 0.97–2.35, P = 0.069) (Table 3).

HV and LV preparations were associated to comparable PDR, ADR, AADR, SDR and cancer detection when colonoscopy was performed under HD endoscopic imaging (Table 4). On the contrary, the use of HV preparation was linked to significantly higher PDR, ADR and AADR compared to LV preparation in patients receiving colonoscopy with SD imaging, after adjustment for age, sex and indications for colonoscopy (Table 5).

The use of the split-dose schedule was not linked with significantly better clinical outcomes as compared to day-before for either HV or LV preparations (Table 6).

Tolerability

Overall, HV and LV preparations were equally well tolerated (median VAS score 7, interquartile range 5-9 for both preparations). Total 860 patients (47.4%) reported gastrointestinal symptoms during preparation: nausea (26.5%) and bloating (19.9%) were the most frequently self-reported symptoms. The occurrence of nausea, vomiting

Table 2 Clinical outcomes according to quality of preparation, *n* (%)

Outcome	Adequate preparation (*n* = 1595)	Inadequate preparation (*n* = 220)	OR (95%CI)	*P* value[1]
Complete examination	1590 (99.7)	203 (92.3)	26.63 (9.72-72.96)	< 0.001[2]
PDR	476 (29.8)	44 (20.1)	1.69 (1.20-2.40)	0.003[2]
ADR	347 (21.8)	34 (15.5)	1.52 (1.04-2.23)	0.033[2]
AADR	82 (5.1)	9(4.1)	1.27 (0.63-2.57)	0.505
Cancer	27 (1.7)	7 (3.2)	0.52 (0.23-1.22)	0.133
SDR	26 (1.6)	2 (0.9)	1.81 (0.43-7.66)	0.423

[1]*P* value degrees of freedom = 1.
[2]Significant different.
OR: Odds ratio; PDR: Polyp detection rate; ADR: Adenoma detection rate; AADR: Advanced adenoma detection rate; SDR: Sessile lesion detection rate.

Table 3 Clinical outcomes according to volume of bowel preparation, *n* (%)

Outcome	High volume (*n* = 871)	Low volume (*n* = 944)	OR (95%CI)	*P* value[1]	Adjusted[2] OR (95%CI)	*P* value[2]
PDR	283 (32.5)	237 (25.1)	1.43 (1.17–1.76)	< 0.001[3]	1.32 (1.07–1.63)	0.011[3]
ADR	210 (24.1)	171 (18.1)	1.44 (1.14–1.80)	0.002[3]	1.29 (1.02–1.63)	0.038[3]
AADR	56 (6.4)	35 (3.7)	1.79 (1.16–2.75)	0.009[3]	1.51 (0.97–2.35)	0.069
Cancer	19 (2.2)	15 (1.6)	1.38 (0.70–2.74)	0.354		
SDR	16 (1.8)	12 (1.3)	1.45 (0.68–3.09)	0.331		

[1]*P* value degrees of freedom = 1.
[2]Adjustment for age (as a continuous variable), sex and indications for colonoscopy; *P* value degrees of freedom = 7.
[3]Significant different.
OR: Odds ratio; PDR: Polyp detection rate; ADR: Adenoma detection rate; AADR: Advanced adenoma detection rate; SDR: Sessile lesion detection rate.

Table 4 Clinical outcomes according to volume of bowel preparation, high-definition colonoscopes, *n* (%)

Outcome	High volume (*n* = 296)	Low volume (*n* = 310)	OR (95% CI)	*P* value[1]
PDR	97 (32.7)	93 (30.0)	1.13 (0.81–1.60)	0.462
ADR	70 (23.6)	74 (23.9)	0.99 (0.68–1.44)	0.948
AADR	21 (7.1)	17 (5.5)	1.31 (0.68–2.54)	0.415
Cancer	5 (1.7)	5 (1.6)	1.05 (0.30–3.66)	0.941
SDR	4 (1.4)	4 (1.3)	1.05 (0.26–4.23)	0.947

[1]*P* value degrees of freedom = 1.
OR: Odds ratio; PDR: Polyp detection rate; ADR: Adenoma detection rate; AADR: Advanced adenoma detection rate; SDR: Sessile lesion detection rate.

and abdominal pain was more frequent among the patients in the LV group (Table 7). Self-reported incomplete (*i.e.*, ≤ 75%) intake of the PEG solution was more common in the HV group (7.9% *vs* 5.4%, *P* = 0.003). For the HV preparation the split-dose regimen was related to better tolerability (higher VAS score) as compared to day-before, even if with no differences in terms of reported symptoms. For the LV preparation, the split-dose regimen was related to lower incidence of symptoms (in particular nausea and bloating) (Table 8).

DISCUSSION

The standard high-volume PEG-based preparation is safe and effective, but even in

Table 5 Clinical outcomes according to volume of bowel preparation, standard-definition colonoscopes, *n* (%)

Outcome	High volume (*n* = 575)	Low volume (*n* = 634)	OR (95%CI)	*P* value[1]	Adjusted[2] OR (95%CI)	*P* value[2]
PDR	186 (32.3)	144 (22.7)	1.63 (1.26–2.10)	< 0.001[3]	1.59 (1.22–2.08)	< 0.001[3]
ADR	140 (24.3)	97 (15.3)	1.78 (1.34–2.38)	< 0.001[3]	1.71 (1.26–2.30)	< 0.001[3]
AADR	35 (6.1)	18 (2.8)	2.23 (1.24–3.96)	0.007[3]	1.97 (1.09–3.56)	0.025[3]
Cancer	14 (2.4)	10 (1.6)	1.56 (0.69–3.53)	0.289		
SDR	12 (2.1)	8 (1.3)	1.67 (0.68–4.11)	0.266		

[1]*P* value degrees of freedom = 1.
[2]Adjustment for age (as a continuous variable), sex and indications for colonoscopy; *P* value degrees of freedom = 7.
[3]Significant different.
OR: Odds ratio; PDR: Polyp detection rate; ADR: Adenoma detection rate; AADR: Advanced adenoma detection rate; SDR: Sessile lesion detection rate.

Table 6 Clinical outcomes of high and low-volume preparations according to different schedules, *n* (%)

Outcome	High volume day before (*n* = 482)	High volume split-dose (*n* = 389)	*P* value[1]	Low volume day before (*n* = 583)	Low volume split-dose (*n* = 361)	*P* value[1]
PDR	149 (30.9)	134 (34.4)	0.277	145 (24.9)	92 (25.5)	0.833
ADR	108 (22.4)	102 (26.2)	0.191	103 (17.7)	68 (18.8)	0.650
AADR	30 (6.2)	26 (6.7)	0.783	20 (3.4)	15 (4.2)	0.567
Cancer	11 (2.3)	8 (2.1)	0.827	6 (1.0)	9 (2.5)	0.088
SDR	5 (1.0)	11 (2.8)	0.050	8 (1.4)	4 (1.1)	1.000

[1]*P* value degrees of freedom = 1.
PDR: Polyp detection rate; ADR: Adenoma detection rate; AADR: Advanced adenoma detection rate; SDR: Sessile lesion detection rate.

Table 7 Self-reported tolerability of bowel preparations according to volume, *n* (%)

	Total (*n* = 1815)	High volume (*n* = 871)	Low volume (*n* = 944)	*P* value[1]
Global tolerance, VAS score[2], median (interquartile range)	7 (5-9)	7 (5-9)	7 (5-9)	0.627
Incomplete preparation (< 75% of PEG assumed)	116 (6.6)	67 (7.9)	49 (5.4)	0.032[3]
Any symptom during preparation	860 (47.4)	369 (42.4)	491 (52)	< 0.001[3]
Bloating	363 (20)	183 (21)	180 (19.1)	0.301
Nausea	480 (26.5)	187 (21.5)	293 (31)	< 0.001[3]
Vomiting	174 (9.6)	55 (6.3)	119 (12.6)	< 0.001[3]
Abdominal pain	281 (15.5)	104 (11.9)	177 (18.8)	< 0.001[3]

[1]*P* value degrees of freedom = 1.
[2]Visual analogue scale: 0 absolutely non-tolerated, 10 perfectly tolerated. Data available for 1772 patients.
[3]Significant different.
VAS: Visual analogue scale; PEG: Polyethylene glycol.

clinical studies a significant proportion of patients is unable to take all the prescribed dose[21] with detrimental effect on its efficacy. RCTs and some meta-analyses have shown a comparable efficacy of different low-volume preparations compared to high-volume PEG[9,10,13-15,22], and the use of these preparations is now recommended in both the European[23] and North American[24] guidelines. However, robust comparisons in RCTs between HV and LV preparations in terms of clinically relevant outcomes (such as ADR) are missing, in particular for the two most recently introduced LV preparations: 2 L PEG plus citrate and 1L PEG plus ascorbate. The former has been compared to HV preparation in a RCT[14] in terms of adequate bowel

Table 8 Tolerability of high and low-volume preparations according to different schedules, *n* (%)

	High volume one-day (*n* = 482)	High volume split dose (*n* = 389)	*P* value[1]	Low volume one-day (*n* = 583)	Low volume split dose (*n* = 361)	*P* value[1]
Global tolerance, VAS score[2], median (interquartile range)	7 (5-8)	7 (5-9)	0.006[3]	7 (5-9)	7 (5-9)	0.033
Incomplete preparation	37 (7.9)	30 (7.9)	0.994	31 (5.5)	18 (5.2)	0.840
Any symptom during preparation	211 (43.8)	158 (40.6)	0.384	324 (55.6)	167 (46.3)	0.005[3]
Bloating	103 (21.4)	80 (20.6)	0.772	126 (21.6)	54 (14.9)	0.011[3]
Nausea	112 (23.2)	75 (19.3)	0.158	196 (33.6)	97 (26.9)	0.029[3]
Vomiting	33 (6.9)	22 (5.7)	0.473	73 (12.5)	46 (12.7)	0.921
Abdominal pain	54 (11.2)	50 (12.9)	0.455	105 (18.0)	72 (19.9)	0.459

[1]*P* value degrees of freedom = 1.
[2]Visual Analogue Scale: 0 absolutely non-tolerated, 10 perfectly tolerated. Data available for 1772 patients.
[3]Significant different.
VAS: Visual analogue scale.

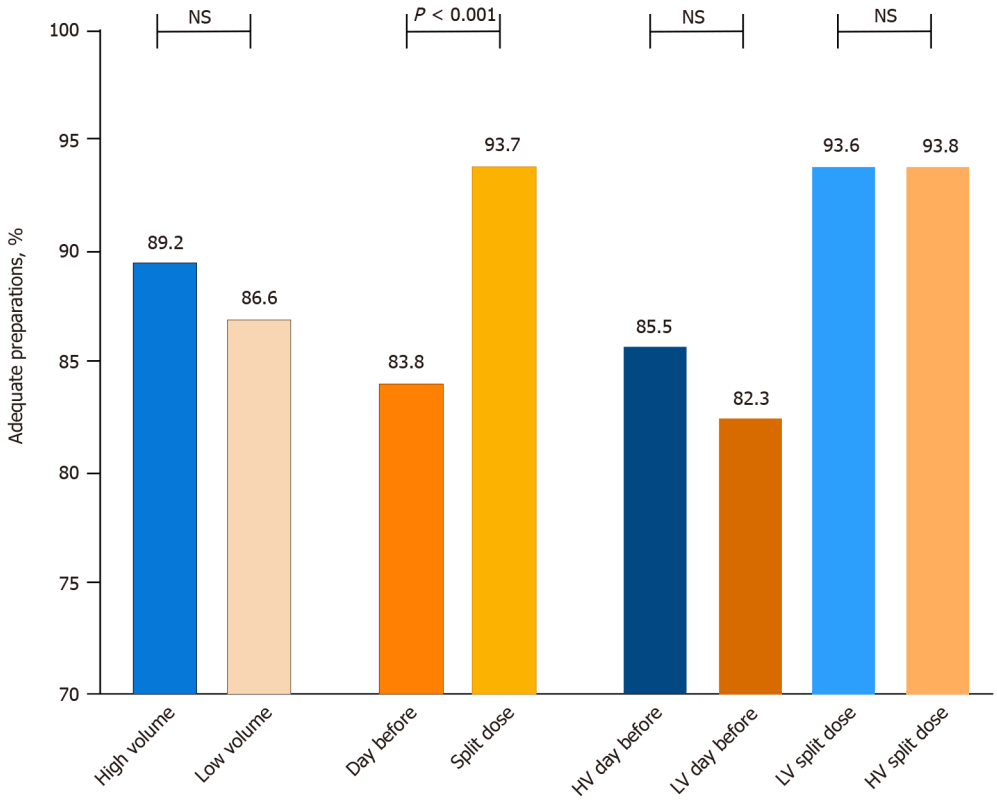

Figure 1 Frequency of adequate preparations (Boston Bowel Preparation Scale ≥ 2 in all bowel segments) according to volume and schedules of preparations. NS: Not significant; HV: High volume; LV: Low volume.

preparation rate and tolerability but not in terms of lesions detection rates, while the latter has been compared in RCTs[25-27] only to other low-volume preparations. Moreover, real-life data are scarce and conflicting: a recent real-life direct comparison of 1 L PEG plus ascorbate and HV preparation[28] has showed higher cleansing success and tolerability in the LV group, but did not analyze lesions detection. Lesions detection rates were not reported also in a recently presented abstract comparing HV and 2 L PEG plus ascorbate and sodium sulfate[29]. In addition, a recent prospective observational study has shown better cleansing results and higher ADR and AADR with 4 L PEG compared to lower volume preparations[18].

In our real-life setting, we confirmed that the low-volume PEG plus bisacodyl preparation is equally effective than HV in all the colonic segments (while some studies have shown worse performances of low-volume preparations in the right colon [30]) and irrespective of the intake schedule, with split-dose regimens largely superior to day-before ones. In particular, it is to note that the split LV preparation was as effective as the split HV preparation, confirming the results achieved in a recent meta-analysis[22], in opposition to previous ones[16,17].

Overall, 87.9% of our patients achieved adequate preparation. This result is in line or superior to the results reported in the literature[31,32], even if slightly inferior to the 90% target proposed by the European Society of Gastrointestinal Endoscopy in 2019 [33]. We confirmed the importance of bowel preparation in terms of relevant outcomes such as complete colonoscopy rate, PDR and ADR, while we did not find differences in terms of AADR, SDR and cancer detection. Advanced adenomas and cancers are usually bigger lesions, easier to find even in a not well-prepared colon[6], while the SDR result can be explained by their low prevalence in our population.

Quite surprisingly, only a slight majority of patients (52%) preferred the LV preparation over the standard HV. This may be partially explained by the order in which the two preparations were listed in the instructions handed to the patients (HV preparation listed first). Even if stated equally effective in the instructions given, it is also possible that the patients perceived more effective a high-volume preparation and leaned towards that choice, especially for "strong" indications such as positive FBT. In fact, we have observed a different distribution of indications for colonoscopy in the two study groups. While FBT-positive patients chose more frequently the HV preparation, the large majority (75.2%) of IBD patients chose LV preparation. Women also used more frequently the LV preparation, while we did not find any age-related difference. Interestingly, 52% of patients with colonoscopy planned in the afternoon chose the HV preparation. This may suggest that the possibility to reduce the volume of PEG was not felt so compelling once given the possibility to split its assumption.

Quite surprisingly, despite similar efficacy in terms of bowel cleansing, the use of the HV preparation was related to higher PDR, ADR and AADR compared to the LV preparation. To remove confounding factors due to the absence of randomization, we adjusted the OR considering three main characteristics related to the prevalence of colorectal lesions such as age, sex and indication. Even after this adjustment, the HV preparation showed better results, with a statistically significant difference for PDR (adjusted OR 1.32, $P = 0.011$) and ADR (adjusted OR 1.29, $P = 0.038$). This result is unlikely to be explained by the more frequent use of split-dose in the HV group, considering that we did not find differences in lesions detection among split and day-before schedules. The type of colonoscopes used seems to have a relevant role in our study. HD colonoscopes, that have shown better diagnostic performances compared to SD ones[34], were used in a similar proportion of patients in the two groups. However, while we did not observe a difference in performance in the two preparations with HD instruments, performance of LV preparation was significantly inferior to HV in terms of lower PDR, ADR and AADR when SD imaging colonoscopy was adopted. This is likely to be linked to the lower mean BBPS score observed in patients using LV preparation. We hypothesize that the persistence of some fluids in the bowel lumen may reduce visibility of lesions, especially when SD scopes are used. Our results suggest that the use of SD definition colonoscopes in patients prepared with LV preparation should be avoided because of an increased risk of missed lesions.

About tolerability, LV preparations[10,14] and in particular 2 L PEG plus bisacodyl [9] were found to be better tolerated as compared to high-volume PEG in previous RCTs. On the contrary, we have observed more self-reported gastrointestinal symptoms such as nausea, vomiting and abdominal pain in the LV group. This result can be explained by the real-life observational design of our study, rather than reflecting an intrinsic lower tolerability of the LV preparation. Nonetheless, these GI symptoms affected neither the patients' adherence nor tolerability. In fact, the LV preparation was judged as tolerable as the HV preparation according to the VAS scale, and it was more frequently taken completely. The use of a split-dose regimen increased the reported tolerability of both the HV (higher VAS score) and the LV (less frequent symptoms) preparations, as previously shown in RCTs and meta-analyses[17, 35].

We recognize that our study has several limitations. The most important limitation is the adoption of day-before schedule for morning procedures; day-before preparations are not recommended by guidelines because of its inferior efficacy when compared to split-dose, as confirmed by our results. Due to the extension of the metropolitan area served by our center, however, we decided to maintain the possibility to choose a day-before regimen. In fact, living far from the endoscopic

centers has been demonstrated to be a significant limitation for adherence to split dose regimen, especially for early morning scheduled colonoscopy[36]. Secondly, the opportunity to leave the choice of the preparation to the patient may be debatable. However, both the preparations used in this study are equally recommended by international guidelines[23,24] and clinical criteria to prefer a specific preparation over another in a specific patient are lacking. Thirdly, as compared to RCTs, the real-life "patients-determined" allocation among different study groups could result in an unbalanced distribution of risk factors. Even if most of the baseline characteristics were comparable in the two study groups, the higher number of male and FBT-positive patients in the HV group could lead to overestimation of performances of HV preparation. However, we performed multivariate analysis considering these factors to provide reliable adjusted odds ratio for lesions detection rates in the two study groups. Fourthly, in our study HD scopes were used only in approximately one-third of cases. We recognize that the use of HD colonoscopes is preferable over SD because of better mucosal visualization. However, SD colonoscopes are still widely used in many centers worldwide. For this reason, we think that our real-life observation that LV preparations could be less effective combined with SD scopes may be of particular interest. Lastly, the single-center observational design implies the risk of sub-optimal reproducibility. However, the large sample size and the prospective nature of this study support our results. On the other hand, additional strengths of our study consist in the blindness of the endoscopists to the type of preparation taken, the use of a well-validated bowel preparation scale and the available histology for all the resected lesions.

CONCLUSION

To resume, this large prospective single-blinded real-life study reveals that adequate bowel cleansing can be equally achieved by means of either HV or LV preparation, showing better result with split dosage. However, in the real-life setting the HV preparation is associated with higher PDR and ADR as compared to the LV preparation, due to reduced performances of LV preparation when SD colonoscopes are used. Our results suggest that the HV preparation should still be proposed as one of the preferred options in screening colonoscopy, and that the use of LV preparations should be avoided in average-to-high risk patients if HD scopes are not available. Looking forward to large multi-center real-life studies, we believe that 4L PEG should be still considered the reference standard for new RCTs assessing both the bowel cleansing and the ADR in screening colonoscopy.

ARTICLE HIGHLIGHTS

Research background

Colonoscopy is a key procedure for the diagnosis of several colorectal pathologies and for prevention of colorectal cancer. The diagnostic yield of colonoscopy is strongly influenced by quality of bowel preparation. In the last years, several low-volume (LV) preparations have been introduced with the aim to improve patients' adherence and compliance.

Research motivation

LV preparations have demonstrated similar cleansing effects compared to standard, high-volume (HV) preparation in randomized controlled trials. However, few real-life studies have compared these two types of preparation in terms of clinically relevant outcomes such as lesions detection.

Research objectives

Primary aim of our study was to compare the real-life efficacy of a standard HV preparation (4 L polyethylene glycol) and of a LV preparation (2 L polyethylene glycol with bisacodyl), either in terms of adequate bowel preparation rate (defined as Boston Bowel Preparation Scale score ≥ 2 in all bowel segments) or in terms of lesions detection. Secondary aim was to compare patients' self-reported adherence and tolerability.

Research methods

A prospective study was conducted from 1 December 2014 to 31 December 2016, enrolling all the consecutive outpatients referred for colonoscopy in a single endoscopy center in Italy. Patients were free to choose one of the two proposed preparations (HV or LV). A questionnaire was administered to the patients to collect comorbidities, type of preparation chosen, adherence to preparation and tolerability. Indications for colonoscopy, type of scope used (high-definition, HD, or standard-definition, SD), Boston Bowel Preparation Scale (BBPS) score for each colonic segment, histology of all the lesions resected or biopsied were collected.

Research results

LV was chosen by 52% of patients (50.8% of men, 54.9% of women). HD scopes were used in 33.4% of patients, without difference in the two groups (P = 0.605). There was no difference between HV and LV preparations in terms of adequate bowel preparation, even if mean global BBPS score was higher for HV preparation when compared to LV. Compared to LV, HV preparation resulted higher in polyp detection rate (PDR) but not in advanced adenoma detection rate (AADR) and cancer detection rate. Considering the type of colonoscope used, we observed lower PDR, adenoma detection rate (ADR) and AADR with LV preparation with SD colonoscopes, without differences between the two preparations with HD instruments.

Research conclusions

Despite similar adequate bowel preparation rate among the two preparations compared, we observed higher PDR, ADR and AADR with HV preparation compared to LV. The difference is mainly observed when SD endoscopes are used. The two preparations were stated as equally tolerated by the patients, but self-reported adherence was higher with LV.

Research perspectives

In the last years we have observed an increasing trend towards the use of LV preparations to increase patients' satisfaction. However, primary aim of bowel preparation is to minimize the risk of missing colorectal lesions. Further studies, either randomized controlled trials or real-life studies, are warranted to compare efficacy in lesions detection of new LV products to standard HV preparation.

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SYSTEMATIC REVIEWS

Application of robotic technologies in lower gastrointestinal tract endoscopy: A systematic review

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Abstract

BACKGROUND

Conventional optical colonoscopy is considered the gold standard investigation for colorectal tract pathology including colorectal malignancy, polyps and inflammatory bowel disease. Inherent limitations exist with current generation endoscopic technologies, including, but not limited to, patient discomfort, endoscopist fatigue, narrow field of view and missed pathology behind colonic folds. Rapid developments in medical robotics have led to the emergence of a variety of next-generation robotically-augmented technologies that could overcome these limitations.

AIM

To provide a comprehensive summary of recent developments in the application of robotics in lower gastrointestinal tract endoscopy.

METHODS

A systematic review of the literature was performed from January 1, 2000 to the January 7, 2021 using EMBASE, MEDLINE and Cochrane databases. Studies reporting data on the use of robotic technology in *ex vivo* or *in vivo* animal and human experiments were included. In vitro studies (studies using synthetic colon models), studies evaluating non-robotic technology, robotic technology aimed at the upper gastrointestinal tract or paediatric endoscopy were excluded. System ergonomics, safety, visualisation, and diagnostic/therapeutic capabilities were assessed.

RESULTS

Initial literature searching identified 814 potentially eligible studies, from which 37 were deemed suitable for inclusion. Included studies were classified according to the actuation modality of the robotic device(s) as electromechanical (EM) (n = 13), pneumatic (n = 11), hydraulic (n = 1), magnetic (n = 10) and hybrid (n = 2) mechanisms. Five devices have been approved by the Food and Drug Administration, however most of the technologies reviewed remain in the early phases of

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testing and development. Level 1 evidence is lacking at present, but early reports suggest that these technologies may be associated with improved pain and safety. The reviewed devices appear to be ergonomically capable and efficient though to date no reports have convincingly shown diagnostic or therapeutic superiority over conventional colonoscopy.

CONCLUSION
Significant progress in robotic colonoscopy has been made over the last couple of decades. Improvements in design together with the integration of semi-autonomous and autonomous systems over the next decade will potentially result in robotic colonoscopy becoming more commonplace.

Key Words: Robotics; Colonoscopy; Endoscopy; Automation; Actuation; Propulsion

Core Tip: Robotic technologies have the potential to transform lower gastrointestinal tract endoscopy into a quicker, safer, more reliable and less painful procedure. In the long term, benefits for patients, endoscopists and the wider healthcare industry are foreseeable, though these have yet to be convincingly demonstrated in human trials. Most studies to date have employed *ex vivo* modelling and high quality level 1 evidence is currently lacking in this field. Robotic technologies are evolving with such rapidity at the moment, that future robo-endoscopic systems are likely to look and behave very differently to conventional master-slave systems currently in use. Exciting developments in 3D printing, soft robotics, autonomous functionality and augmented reality are likely to converge to lead to the development of truly next generation robotic endoscopy devices.

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INTRODUCTION

Conventional optical colonoscopy represents the gold standard investigation for lower gastrointestinal (LGI) tract pathology including colorectal cancer (CRC), polyps and inflammatory bowel disease[1]. Current generation colonoscopes consist of a semi-rigid flexible scope containing fibre optic bundles with a camera at the distal end allowing visualisation of the colonic lumen. The scope tip can be manoeuvred in two directions *via* twin-wheels located on the control shaft of the scope, where buttons controlling air insufflation, suction and irrigation mechanisms are also located. Passage of instruments through a working channel running along the body of the scope also allows the endoscopist to perform diagnostic and therapeutic interventions. Typically, a standard scope will have a diameter of 11-13 mm with a length of approximately 160 cm[2,3]. Though this model has undergone subtle refinements in recent years, the basics of the technology remain largely unchanged. While being a familiar, well developed and effective tool for LGI tract diagnosis and therapy, current technologies in optical colonoscopy remain imperfect and are subject to a number of inherent limitations. These include the limited field of view, challenges identifying and treating mucosal lesions proximal to haustral folds, procedure-related pain, and risk of perforation. Pain during colonoscopy is multifactorial in origin, most often resulting from gas distension, looping of the scope and stretching of the mesocolon[4]. Loop formation and mucosal scope trauma have the potential to cause significant iatrogenic injury to the bowel, especially in areas affected by disease[4,5] In addition, colonoscopy is associated with a long learning curve [typically > 200 procedures are required before 90% caecal intubation rates (CIR) are achieved[6,7]] and poor user ergonomics, which have been shown to result in musculoskeletal injury for the endoscopist[8].

Patient discomfort during LGI endoscopy is primarily responsible for 94.6% of colonoscopies being performed under intravenous sedation in Great Britain, and 96% in the United States[9]. However sedation does not improve CIR, increases discharge times and is costly[10]. Therefore, the development of better tolerated methods for endoscopic assessment of the large bowel with reduced sedation requirements is an urgent priority. The most serious complications associated with colonoscopy are perforation and bleeding, which occur with a frequency of 3-8 *per* 10000 and 1.6 *per* 1000 colonoscopies, respectively[1]. Though these are infrequent endpoints, addressing current physical limitations with the optical colonoscope may help to further diminish their likelihood[11]. Future technologies for colorectal tract assessment would ultimately benefit from being safer and better tolerated whilst simultaneously maximising on outputs in terms of key performance indicators such as achieving CIR ≥ 95% and adenoma detection rates (ADR) of ≥ 20%[1]. Recent advances in medical robotics offer the potential to overcome the disadvantages of conventional colonoscopy, and engineers have been seeking to develop robotic prototypes capable of endoluminal exploration and visualisation since the early 1990s[12]. In particular, the concept of 'front-wheel' actuation, in contrast to the 'rear wheel' pushing mechanism used in conventional colonoscopy has generated considerable interest, as this may possibly reduce procedural pain, the need for sedation and the incidence of iatrogenic colonic injury[13]. Robotic systems may offer a wider field of view and implementation of higher degrees of motional freedom may enhance manoeuvrability and luminal views, leading to improved ADR. The introduction of semi-automated and even fully automated robotic endoscopic platforms has the potential to flatten the learning curve and minimise endoscopist fatigue[14].

The successful application of robotic devices in coronary artery bypass procedures or valvular surgery, and in advanced bronchoscopy, highlight the potential utility of this advanced technology in circumstances where the operator is performing fine tasks within a restricted working environment[15,16]. The same should apply in endoscopy, though comparatively LGI endoscopy has been slow to embrace robotic technologies potentially because of perceived cost barriers, and a lack of understanding of how the technology can improve on the existing formula. Herein we provide a comprehensive narrative review of the state-of-the-art of robotics in lower GI endoscopy.

MATERIALS AND METHODS

Search strategy

Systemic review principles were adhered to in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines[17] An electronic literature search was undertaken using EMBASE, MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) databases (from January 1, 2000 to January 7, 2021). The following MeSH terms were used: "robot", "robotic", "robot assist", "colonoscopy", "flexible sigmoidoscopy", "proctoscopy". Original work reviewing the use of robotic technology in lower GI endoscopy (colonoscopy, flexible sigmoidoscopy or proctoscopy) utilising *ex vivo* or *in vivo* studies in animal and human colons were included. There was no limitation on language and type of bowel pathology studied (polyp, CRC, inflammatory bowel disease *etc*.). Studies evaluating non-robotic technology, robotic technology aimed at the upper gastrointestinal tract, robotic-assisted endoscopy for minimally invasive surgery, robot assisting devices for conventional colonoscopy (such as the The EndoDrive® (ECE Medical Products, Erlangen, Germany) or the Endoscopic Operation Robot)[18] and paedia-tric endoscopy were excluded.

Data extraction

Two authors (HKSIS and EA) independently performed literature searches and determined eligibility of studies. Once consensus was reached on studies meeting predefined inclusion criteria, the following data were extracted from included studies: First author's name, country in which the study was performed, month and year of publication, study design, components of the robotic endoscopic platform, size/length of the endoscopic capsule or flexible scope, illumination method, visualization method, actuation method, data transmission method, aim of robot intention (visualization, diagnosis, treatment, other), degree of robot navigational assistance, type of colon model and results were collected.

RESULTS

A total of 814 records were identified through initial literature searching. Duplicates and obviously irrelevant abstracts were excluded at title and abstract level, leaving 62 articles, which were reviewed fully. Twenty-five articles were further excluded because they were: Review articles (n = 13); studies evaluating robotic devices using *in vitro* synthetic colon/other (n = 4); assessing robot assistance devices coupled to a standard colonoscope (n = 2); evaluating swallowable wireless capsules without active actuation mechanisms (n = 4); evaluating surgical rather than endoscopic platforms (n = 2). A total of 37 studies were included in the final qualitative analysis (Figure 1). For ease of interpretation of this review, studies have been classified according to mode of actuation, that is the principle active method of robotic motion for each technology. Modes of actuation were defined as EM (n = 13), pneumatic (n = 11), hydraulic (n = 1), magnetic (n = 10) and hybrid (n = 2).

EM actuation

EM actuation is where electrical energy is used to bring about mechanical motion. This is usually brought about by a tether (containing wires) attached to the robotic device and to an external power source. Wireless devices without a tether will require an internal battery to provide power which takes up space. The tether will provide additional weight and friction as it slides along the mucosa which the robot will need to overcome. Either way considerable power is usually required[19,20]. A summary of studies investigating this mode of actuation is provided in Table 1.

Two EM actuation robotic endoscopic systems were developed and received Food and Drug Administration (FDA) approval, though these are now no longer commercially available[19]. The Invendoscope SC40 (Invendo Medical, Kissing, Germany) is a motorised colonoscope, controlled by a joystick and actuated by an inverted sleeve mechanism and a driving unit with 8 wheels. It is 18 mm in diameter and has a visualisation module and a 3.2 mm working channel (Figure 2). Two trials on humans have been carried out to evaluate this platform. The first, in 34 healthy volunteers showed a CIR of 82%, with 92% of patients 'pain free' and no acute complications were reported [21]. The purported strength of this system was the combination of a highly flexible endoscope shaft with the proprietary 'inverted sleeve' technology, which the developers believed could permit potentially 'painless' colonoscopy, as no direct forces are applied against the intestinal walls while the device passes through narrow intestinal convolutions. Invendo medical Gmbh was acquired by Ambu A/S with plans to release a single use robotic colonoscope in 2021[19,22]. Another study in 61 asymptomatic individuals with an average risk of CRC willing to undergo CRC screening found a CIR of 98.4%, with a median caecal intubation time (CIT) of 15 min. Only 4.9% of patients required sedation[23]. The Neoguide Endoscopy System (Neoguide Endoscopy System Inc., Los Gatos, CA United States) has a scope diameter of 14-20 mm and consists of 16 actuator segments under EM control to bring about movement. It also contains a tip position sensor, an external position sensor and a 3.2 mm working channel. A trial on 10 individuals undergoing CRC screening or routine diagnostic colonoscopy showed a CIR of 100% with a median CIT of 20.5 min. Adenomas were successfully removed with snare or forceps and there was no evidence of complications at 30 d follow up[24]. With this platform, the position and angle of the scope's tip are encoded into a computer algorithm. As the scope moves forwards, the algorithm directs each successive actuator segment to assume the same shape/position that the tip had for that given insertion depth. The insertion tube thus changes its shape at different insertion depths in a "follow-the-leader" manner, which should minimise discomfort. Neoguide Endoscopy System Inc. was acquired by Intuitive Surgical Inc. and the technology translated to robotic lung biopsy[19]. Several other non-certified EM actuation devices have been developed and below these have been categorised further based on their distinct physical properties which bring about motion.

Legs: A 12-legged capsule was developed by Valdastri *et al*[25], comprising two motors, a bidirectional communication platform and a human machine interface (HMI) capable of semi-autonomous intrinsic EM actuation (Figure 2). The capsule measures 12.8 mm in diameter and 33.5 mm in length. The device was designed to strike a versatile balance between size and ability to traverse the bowel. The device was tested in a porcine gut model and was able to traverse the complete length of the colon (140 cm) at an average speed of 5 cm/min[25]. Though a little slower in terms of pace, this device highlights the potential for miniaturisation of devices in robotic endoscopy.

Table 1 Summary of the included studies reviewing robotic lower gastrointestinal endoscopy devices with electromechanical actuation

Ref.	Design and actuation components of evaluated robotic system(s)	Endoscope and/or capsule dimensions	Mode(s) of actuation	Mode(s) of illumination and luminal visualisation	Capabilities evaluated	Degree of robot navigational assistance	Study methodology	Main findings
Rösch *et al* [21], 2008 (Germany)	InvendoscopeTM SC40 (Invendo Medical, Kissing, Germany): Colonoscope with an inverted sleave mechanism, propulsion connector, endoscope driving unit, hand-held control unit, 3.2 mm working channel	18 mm diameter, 170-200 cm length.	Electromechanical	Three white LEDs, CMOS vision chip with a field of view of 114 degrees	Visualisation	Direct Robot control	*In vivo*: *n* = 34 Human, heathy volunteers	CIR of 82%. Pain free procedure in 92% of cases. Mean pain score 1.96/6. 0% required sedation. No complications
Groth *et al* [23], 2011 (Germany)	InvendoscopeTM SC40 (Invendo Medical, Kissing, Germany): Colonoscope with an inverted sleave mechanism, propulsion connector, endoscope driving unit, hand-held control unit, 3.2 mm working channel	18 mm diameter, 170-200 cm length	Electromechanical	Three white LEDs, CMOS vision chip with a field of view of 114 degrees	Visualisation, Diagnosis, Treatment	Direct Robot control	*In vivo*: *n* = 61 Human, Asymptomatic individuals at average risk of CRC willing to undergo CRC screening	CIR of 98.4%. Sedation required in 4.9%. Median CIT of 15 min. Mean pain/discomfort score: 2.6. 32 of 36 polyps successfully removed with snare or forceps. 1 flat polyp required referral for conventional colonoscopy and 3 polyps seen on introduction could not be found on withdrawal
Eickhoff *et al* [24], 2007	The NeoGuide Endoscopy System (NeoGuide Endoscopy System Inc., Los Gatos, CA United States): Scope with 16 actuator segments, steering dials to control the tip and Tip position sensor. External position sensor, support arm, 3.2 mm working channel, video processor and control unit. Computed 3D mapping of the colon	173 cm in length, 14-20 mm in diameter	Electromechanical	Conventional CCD camera	Visualisation, safety and ease of use	Semi-autonomous	*In vivo*: *n* = 10 Humans requiring screening or diagnosis	CIR is 100%. Median CIT is 20.5 min. Adenomas successfully removed with snare or forceps. No acute colonic trauma (bleeding, perforation, submucosal petechiae). No complications at 30 d follow up. Detection and correction of looping is 100%. Physician satisfaction is 100%
Valdastri *et al*[25], 2009 (Italy)	Legged capsule consisting of two leg sets (six legs each with hooked round tips), 2 motors, bidirectional communication platform, HMI in LabVIEW	11 mm diameter by 25 mm long	Electromechanical	No camera in this prototype	Locomotion and safety	Semi-autonomous	*Ex vivo*- Porcine colon between two fixtures and 140 cm porcine colon placed in an abdominal phantom	Porcine colon between two fixtures: The 12-legged capsule distended the colon in a uniform manner. Maximum pulling force of the capsule on the colon wall: 0.2 N. Porcine colon in abdominal phantom: Capsule was able to traverse the complete length of the colon, Average speed was 5 cm/min
Lee *et al*[26], 2019 (Korea)	Legged robotic colonoscope, reel controller with external motor, Bowden cable and control system. The robot has 6 legs covered with silicone	Robot: 16 mm diameter (33 mm with legs deployed) by 49 mm in length. Bowden cable: 5 mm diameter by 1 m length	Electromechanical	Not described	Locomotion and safety	Autonomous	*Ex vivo*: Excised porcine colon	Locomotion velocities: Straight path: 9.5 mm/s. Incline at 30 degrees: 7.1 mm/s. Incline at 60 degrees: 5.1 mm/s. No mucosal damage or perforations
Trovato *et al* [27], 2010 (Japan)	Robotic colonic endoscope consisting of a front body with a clockwise helical fin, DC motor and rear body with an anti-clockwise helical fin; Reinforcement	170 mm in length, 30 mm in diameter	Electromechanical	Not described. No Visualisation module in this prototype	Locomotion and safety	Semi-autonomous	*Ex vivo*: < 1 m Swine colon (6 specimens) attached to the inside of a cylindrical plastic	*Ex vivo*: Best travelled distance around 70 cm. Average velocity with Fixed input (15 trials): 21.47 mm/min. Average velocity with SARSA (18 trials): 40.71 mm/min (P = 0.02).

	learning algorithm (Q-learning and State-Action-Reward-State-Action)						tube. *In vivo*: Swine colon–10 trials, 5 min each	Average velocity with Q-learning (21 trials): 36.05 mm/min (P = 0.039). Robot with learned algorithms are more likely to pass through bends/tight passages. *In vivo*: Speed 11 mm/min. Best travelled distance is 55 mm. No acute mucosal damage
Kim *et al* [28], 2010 (Korea)	Paddling-based capsule endoscope: Capsule with camera module, DC motor and 6 paddles. Tether consisting of 4 cables extend from the capsule to the external controller	Capsule: 15 mm in diameter and 43 mm in length. Tether: 2 m	Electromechanical	A camera module with 125 degree field of view and which transmits images at 10 frames *per* second	Locomotion and safety	Semiautonomous	*Ex vivo*: Porcine colon set up in 2 positions (sloped 27.5 degrees, straight length 35 cm or sloped 37.5 degrees, straight length 62 cm). *In vivo*: 1 pig–8 trials	*Ex vivo*: Velocity in sloped 27.5 degrees, straight length 35 cm colonic segment: 36.8 cm/min. Velocity in sloped 37.5 degrees, straight length 62 cm colonic segment: 37.5 cm/min. *In vivo*: Mean velocity: 17 cm/min over 40 cm length. Complications: Pinpoint erythema on colonic mucosa seen
Wang *et al* [29], 2006 (China)	Worm like robotic endoscope system consisting of a microrobot, controller and personal computer. The microrobot consists of a head cabin with the visualisation module and 3 mobile cells connected to the controller by an electric cable. Each mobile cell contains a linear electromagnetic driver	9.5 mm in diameter, 120 mm in length	Electromechanical	CCD camera and lights	Locomotion	Semi-autonomous	*Ex vivo*: Porcine colon	Robot travels the colon length (112 cm) in 7.3 min. Robot able to move forward, backward or remain static based on controller commands
Wang *et al* [30], 2007 (China)	Worm like robotic endoscope system consisting of a microrobot, controller and personal computer. The microrobot consists of a head cabin with the visualisation module and 3 mobile cells connected to the controller by an electric cable. Each mobile cell contains a linear electromagnetic driver. Additional deflection mechanism after the head cabin controls the camera's pose	10 mm in diameter, 110 mm in length	Electromechanical	CCD camera and lights	Locomotion	Semi-autonomous	*Ex vivo*: Porcine colon	Robot travels the colon length (112 cm) in 7.3 min
Wang *et al* [31], 2017 (China)	Worm like robotic endoscope consisting of a head cabin and three independent segments; each segment is composed of a linear locomotor with micromotor, turbine-worm and wire wrapping-sliding mechanism. The robot is entirely covered by an external soft bellow	13 mm diameter, 105 mm in length	Electromechanical	Not described	Locomotion and safety	Semi-autonomous	*In vivo*: Porcine colon	Greater speed in straight rather than curved paths. Speed ranges from 1.62-2.2 mm/s. Robot travels the entire colon in 119 s. Distance is not specified. No breakage or damage to the colonic mucosa
Naderi *et al* [32], 2013 (Iran)	Robot with a camera, 2 clampers, 5 discs and 15 springs allowing bending and steerability, 3 motors; Driving kit, HMI in MATLAB and Joystick	19 mm in diameter, 180 mm in length.	Electromechanical	Camera	Locomotion and safety	Semi-autonomous	*Ex vivo*: Sheep colon, 2 positions: Straight or with an 84 degree bend	Velocity: Straight path: 18.4 cm/min. Curved path: 10.5 cm/min. No significant trauma
Lee *et al*[26], 2019 (Korea)	3 elastic PTFE caterpillars with worm gear, steering module, camera module, flexible shaft with steering knobs and wires, external motor and controller	130 mm in length, 55 mm maximum diameter	Electromechanical	LED lamps and camera	Locomotion and visualisation	Direct robot operation	*Ex vivo*: 1 m excised porcine colon placed in an abdominal phantom. *In vivo*: 1 mini pig	*Ex vivo*: Velocity of the robotic colonoscope: 3.0 mm/s; CIR is 50%; CIT is 8.55 min. *In vivo* : Failed caecal intubation with difficulty travelling through fluid and faecal material
Formosa *et*	Endoculus- treaded (4) robotic capsule	2 m tether	Electromechanical	CMOS camera with	Locomotion,	Direct robot	*Ex vivo*: 40 cm excised	*Ex vivo*: Able to move in forward/reverse

al[34], 2020 (United States)	endoscope consisting of an inertial measurement unit, two motors, air/water channels, a tool port, flexible tether connected to a control board and laptop with controller		adjustable LEDs	visualisation and channel function	operation	porcine colon. *In vivo*: 1 pig	directions at 40 mm/s and whether the colon was collapsed or inflated. Also able to pass tight haustra and make turns. *In vivo*: Camera, insufflation, irrigation and biopsy tools functioned as expected

LEDs: Light emitting diodes; CMOS: Complementary metal-oxide-semiconductor; CIR: Caecal intubation rate; CIT: Caecal intubation time; CCD: Charged coupled device; HMI: Human machine interface.

A legged colonoscope consisting of six legs covered in silicone and a Bowden cable connecting the device to an external motor and control system was tested in excised porcine colon of varying paths to determine locomotive efficacy and safety. It was able to travel at decreasing velocities of 9.5 mm/s, 7.1 mm/s and 5.1 mm/s on straight, 30 degree curved and 60 degree curved paths, respectively. No mucosal damage or perforations were observed during testing[26]. The diameter of the device is 16 mm without the legs deployed and 33 mm when they are.

Fins: A novel capsular device, 170 mm in length and 30 mm in diameter, consisting of a front body with a clockwise helical fin and rear body with an anti-clockwise helical fin was developed by a team in Japan. The bodies are connected by a DC motor and the device is computationally reinforced with learning algorithms to improve effectiveness of motion through iterative learning. It was tested in *ex vivo* and *in vivo* porcine colon models and *ex vivo* trials demonstrated improved movement performance with learned algorithms. *In vivo* trials showed an average speed of 11 mm/min with no acute mucosal damage[27].

Paddles: A tethered capsule endoscope containing a camera module, DC motor and 6 paddles measuring 15 mm in diameter was evaluated in *ex vivo* porcine colon as well as in an *in vivo* porcine model (Figure 2). At a slope of 27.5 degrees (length: 32 cm) and 37.5 degrees (straight length: 62 cm), impressive forward motion speeds of 36.8 cm/min and 37.5 cm/min were achieved. The mean velocity reached in the *in vivo* model over a distance of 40 cm was 17 cm/min. A degree of minor paddle-trauma was noted on the mucosa which may present a safety concern[28].

Worm-like: Wang *et al*[29,30] created two similar earth-worm like robotic endoscopes. The initial system consisted of a microrobot, controller and user interface. The microrobot in turn consists of a head cabin with the visualisation module and 3 mobile cells connected to the controller by an electric cable. Each mobile cell contains a linear electromagnetic driver[29,30]. The microrobot was able to travel along the porcine colon length (112 cm) in 7.3 min[29,30]. The worm-like device is pictured in Figure 2.

Later, a similar microrobot was created by the same team with two notable design adjustments: Each segment with this updated prototype is composed of a linear locomotor with its own micromotor, turbine-worm and wire wrapping-sliding mechanism, and the microrobot is entirely covered by an external soft 'bellow'. The soft bellow acts to increase the friction gradient between the robot and the colonic

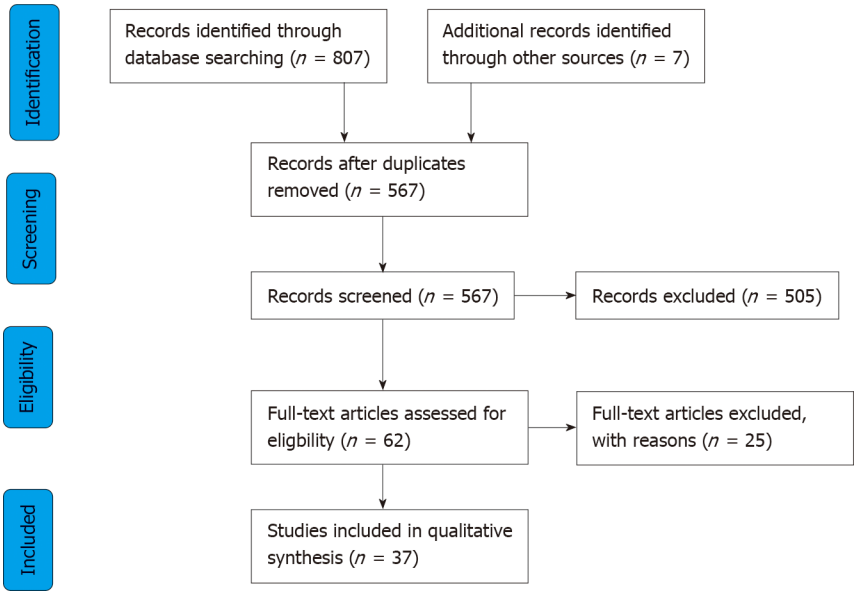

Figure 1 PRISMA flow diagram.

mucosa which should improve locomotion ability. This device was tested in *in vivo* porcine experiments and demonstrated average speeds of up to 2.2 mm/s, with no mucosal damage reported[31].

A robot with a camera, two clampers, three motors, 5 discs and 15 springs was created to allow worm-like flexible movement. It could be driven using a joystick and is 19 mm in diameter and 180 mm long. Motion ability and safety were tested in sheep colon in a straight or curved (84 degree bend) path. The device travelled at 18.4 cm/min and 10.5 cm/min in straight and curved colonic segments, respectively. No mucosal trauma was seen[32]. Overall worm-like devices appear safe with a variable speed.

Caterpillars: A robot with 3 elastic caterpillars, designed to expand the colonic lumen while causing little trauma was able to travel at 3 mm/s and achieve caecal intubation 50% of the time at 8.55 min in porcine colon placed within a human abdominal phantom[33]. Unfortunately, in an *in vivo* experiment, the robot failed to achieve caecal intubation as it had difficulty travelling through fluid and faeces[33].

Treads: A treaded (4 treads) robotic capsule with two motors, connected *via* a flexible tether to a control printed circuit board and laptop (Figure 2) was tested in excised porcine colon and was able to move in forward and reverse directions at 40 mm/s even with the bowel wall collapsed[34]. The treads allow traction between the device and the colonic mucosa to allow effective locomotion. It was also able to pass tight haustra and make turns due to the presence of the second motor and resulting increased degrees of locomotion freedom. The device also had a visualisation module and channels for air, water and tools. Camera, insufflation, irrigation and biopsy tools all functioned effectively during *in vivo* porcine testing[34].

Electropneumatic actuation

Electropneumatic (EP) actuation involves the use of pressurised gas to bring about motion. The Aer-o-scope (GI View Ltd, Ramat Gan, Israel), Endotics [ERA Endoscopy S.r.l., Peccioli (Pisa), Italy] and Sightline Colonosight systems (Stryker GI, Dallas, Tex, Haifa, Israel) are all examples of FDA approved EP robotic systems with a visualisation module and channels for insufflation, suction and irrigation.

The Aer-o-scope system works by generating a gas (carbon dioxide) pressure gradient between a rectal balloon inflated in the anus and a balloon located at the tip of the scope. Safety mechanisms ensure that the pressure in the colon does not exceed 54 m bar. The scope is only 5.5 mm in diameter (Figure 3). *In vivo* studies on healthy human volunteers (n = 12) or those requiring CRC screening (n = 56) have reported CIR ranging from 83%-98%, average CIT of 23 min and no acute complications other than mild mucosal petechiae in some instances[35,36]. Four of twelve patients required sedation[35]. In those undergoing CRC screening, the polyp detection rate was 87.5% and mucosal visualisation was rated as 'excellent' by participating endoscopists[30].

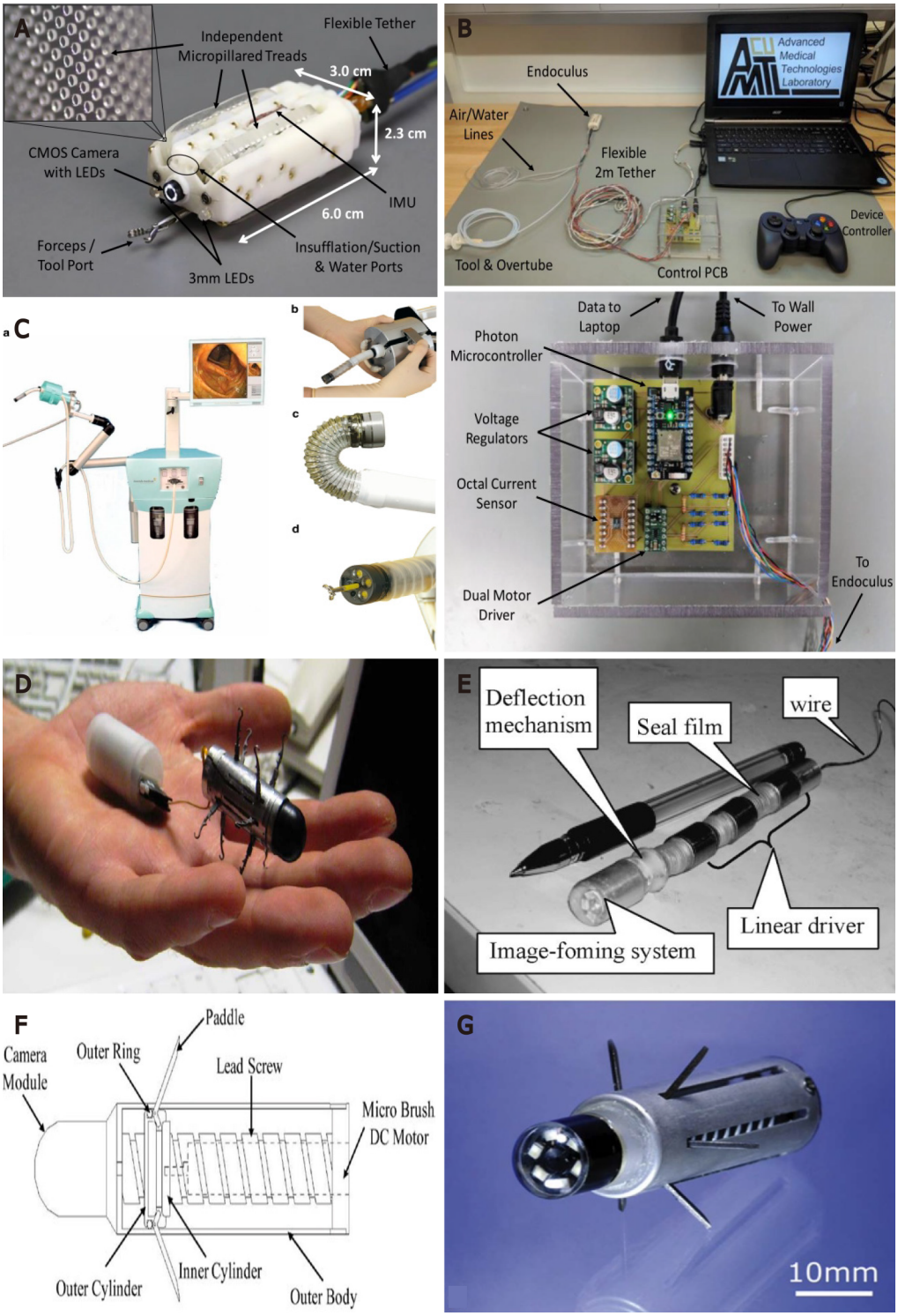

Figure 2 Examples of electromechanical robotic devices. A: The treaded "Endonculus" tethered robot in isolation; B: The treaded "Endonculus" robot with its full operational set up and printed circuit board.Citation for A and B: Formosa GA, Prendergast JM, Edmundowicz SA, Rentschler ME. Novel Optimization-Based Design and Surgical Evaluation of a Treaded Robotic Capsule Colonoscope 2020; 36: 545-552. Copyright© The Authors 2020. Published by IEEE. C: The Invendoscope System with the tip in the driving motor, in full flexion and with a biopsy forceps in the working channel. Citation: Groth S, Rex DK, Rösch T, Hoepffner N. High cecal intubation rates with a new computer-assisted colonoscope: a feasibility study. *Am J Gastroenterol* 2011; 106: 1075-1080. Copyright© The Authors 2011. Published by American College of Gastroenterology. D: The six legged capsule device by Valdastri *et al*[25]. Citation: Valdastri P, Webster RJ, Quaglia C, Quirini M, Menciassi A Dario P. A New Mechanism for Mesoscale Legged Locomotion in Compliant Tubular Environments. *IEEE Transactions on Robotics* 2009; 25: 1047-1057. Copyright© The Authors 2009. Published by IEEE. E: A worm-like endoscope prototype. Citation: Wang K, Yan G. Micro robot prototype for colonoscopy and *in vitro* experiments. *J Med Eng Technol* 2007; 31: 24-28. Copyright© The Authors 2007. Published by Taylor & Francis Ltd. F: Cross-sectional paddled capsular device; G: Complete paddled capsular device. Citation for F and G: Kim HM, Yang S, Kim J, Park S, Cho JH, Park JY, Kim TS, Yoon ES, Song SY, Bang S. Active locomotion of a paddling-based capsule endoscope in an *in vitro* and *in vivo* experiment (with videos). *Gastrointest Endosc* 2010; 72: 381-387. Copyright© The Authors 2010. Published by Elsevier.

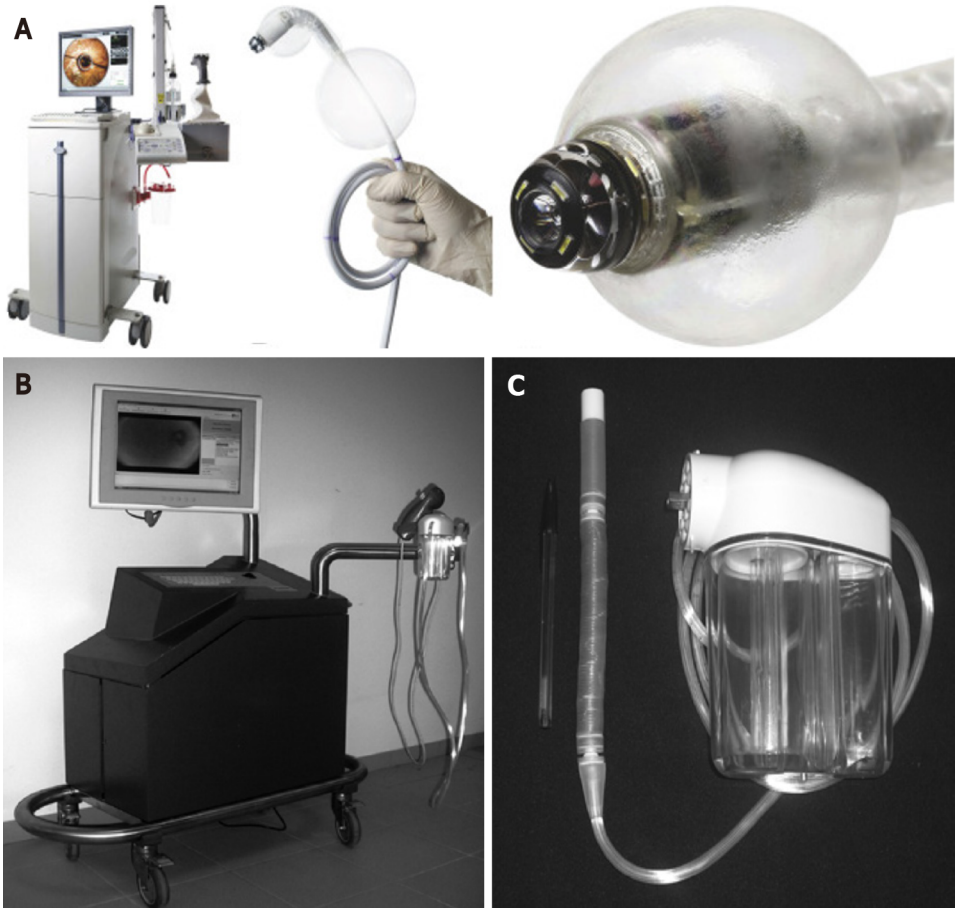

Figure 3 Examples of pneumatic robotic devices. A: The Aer-O-scope system. Citation: Gluck N, Melhem A, Halpern Z, Mergener K, Santo E. A novel self-propelled disposable colonoscope is effective for colonoscopy in humans (with video). *Gastrointest Endosc* 2016; 83: 998-1004.e1. Copyright© The Authors 2016. Published by ELSEVIER open access. B: and C: The Endotics System. Citation: Cosentino F, Tumino E, Passoni GR, Morandi E, Capria A. Functional evaluation of the endotics system, a new disposable self-propelled robotic colonoscope: *in vitro* tests and clinical trial. *Int J Artif Organs* 2009; 32: 517-527. Copyright© The Authors 2009. Published by SAGE Publications, Ltd.

The Aer-o-scope provides a 360 panoramic vision system in addition to a complementary metal-oxide-semiconductor (CMOS) camera which allows improved visualisation. In an *In vivo* study with 12 anaesthetised pigs with surgically simulated colonic 'polyps' the Aer-o-scope visualised 94.9% of polyps compared to 86.8% achieved with standard optical colonoscopy ($P = 0.002$)[37].

The Endotics system consists of a flexible probe with a head, body and tail, EP connector and a workstation (Figure 3). Two clampers located at the proximal and distal ends of the probe aid movement. *Ex vivo* testing using porcine colon has suggested that the stress exerted on the colonic wall using this device is 90% less than in standard colonoscopy[38]. This should in theory translate into a reduced need for analgesia and sedation. In fact, two human trials showed that Endotics was less painful on a scale of 1 to 10 (0.9 *vs* 6.9)[38] and did not require any sedation (0% *vs* 19.7%, $P < 0.001$)[39] compared to conventional colonoscopy[38,39]. This device can achieve CIR as high as 92.7% within 29 min[40]. Diagnostically, in individuals with a family history of CRC and/or polyps, the Endotics System showed a sensitivity, specificity, positive predictive value and negative predictive value of 93.3%, 100%, 100% and 97.7%, respectively[39]. The Endotics system has also demonstrated a short learning curve: Two blocks of consecutive patients underwent LGI endoscopy using the Endotics platform with improvements in CIR (85.2% *vs* 100%), intubation time (55 min *vs* 22 min, $P = 0.0007$) and withdrawal time (21 min *vs* 16 min)[40]. Importantly, in an evaluation of 102 patients previously having undergone failed colonoscopy, 95 patients (93.2%) underwent successful caecal intubation with the Endotics system[41].

The Sightline ColonoSight system consists of a reusable scope covered by a disposable sleeve and connected to an air pressure engine[42]. Shike and colleagues evaluated the performance of this system in 178 human study participants and reported a CIR of 90% with a mean CIT of 11.2 min. Scope advancement with this device is facilitated by self-propulsion of the instrument affected by an air-pressure-

powered engine and LED illumination eliminates the need for fiber optics and an external light source.

Other non-certified EM actuation robotic devices include the "EndoCrawler" which consists of longitudinal and circumferential rubber bellow pneumatic actuators joined in four segments with a bending tube to allow steering between the first two segments [43]. When pressurised air enters the bellow, it extends longitudinally. It has a central hollow cavity for insufflation, irrigation, suction and instrument channels as well as charged coupled device cables to pass through. It has undergone *ex vivo* testing in human cadaveric colon which demonstrated clear visualisation capabilities and an average speed of 200 mm/min. *In vivo* assessment using a live porcine model also demonstrated some encouraging findings, though difficulties were encountered when attempting to negotiate sharp bends. These issues notwithstanding, this early prototype again demonstrates the potential for self-propulsive, remotely controlled robotic devices for endoluminal assessment[43].

In 2017, a simple colonoscopy robot consisting of the robot (tip with camera, latex tubing and anal fixture) with an external pneumatic circuit was developed. Locomotion feasibility and safety was tested in porcine colon. The device was able to traverse the entire length of the colon in 71.4% of trials, able to traverse the entire length of colon with additional bends in 90.9% of trials, had an average speed of 28 mm/s with an average CIT of 54.2 s. The maximum propulsive force was 6 N *i.e.*, an acceptable pressure on the colonic mucosa however balloon rupture led to damage including tearing of the porcine colon[44].

A further pneumatic device consisting of three segments, each containing two soft pneumatic balloons and two rigid connectors was developed and tested in excised pig colon. The balloons are twisted in the proximal and distal gripper segments but linear in the middle propulsion segment. A camera and channels for air flow and instruments are built in. The unactuated device is 22 mm in diameter. The robot travelled at 1 mm/s and was able to clearly visualise the colonic mucosa[45].

A summary of all studies evaluating robotic EM actuation systems for LGI endoscopy is provided in Table 2.

Hydraulic actuation

Hydraulic actuation uses a pressurised fluid medium such as water to progress through the colon. A meta-analysis of randomised controlled trials has previously shown that water immersion colonoscopy does significantly decrease pain scores and sedation rates without affecting the diagnostic quality or completeness of colonoscopy when compared with air intubation[46].

The "Hydraulic Colonoscope" system consists of a colonic vehicle (CV) connected to external pumps and valves *via* a tether. The CV contains a magnetic tracker and is surrounded by a balloon which may be inflated or deflated to create an appropriate seal with the colonic wall. The pump system is used to pump water into the colon behind the CV. An anal port prevents water from escaping the colon. Motion ability was trialled in porcine colon and compared to conventional colonoscopy. The device was able to reach the caecum in all attempts. There was no difference in the CIT or caecal pressure between the device and colonoscopy. However, significant differences were found in the maximum force exerted on the colon (0.63 N *vs* 2.2 N, $P = 0.004$), maximum anal pressure (1.53 kPa *vs* 4.53 kPa, $P = 1 \times 10^{-7}$) and mean anal pressure (0.05 kPa *vs* 1.5 kPa, $P = 0.0003$) between the device and conventional colonoscopy, respectively[47] (Table 2).

Magnetic actuation

Magnetic actuation is brought about externally through magnetic fields created either by an external permanent magnet (EPM) or electromagnetic coils[48]. Control of this field is crucial for locomotion as controlling the field allows movement of the device in a particular direction and orientation. The main advantage of external magnetic actuation is that it allows a 'front-wheel' motion without the need for large internal actuating motors. When an EPM is used, small internal permanent magnets (IPMs) incorporated into the luminal robot are required to generate the magnetic field. A power supply is generally not required. The resulting device is therefore less bulky and more likely to reduce pain and the need for sedation. Additionally, there is more scope to incorporate other subsystems. The EPMs can be moved manually and the magnetic field controlled directly by the user to cause luminal device movement. However, movement is non-linear and therefore complex. Other disadvantages include the ongoing need for insufflation and the continuous contact between the device and the colonic mucosa due to the continuous attraction between the EPM and IPM[48]. The magnetic fields generated may also interfere with nearby equipment as

Table 2 Summary of the included studies reviewing robotic lower gastrointestinal endoscopy devices with pneumatic or hydraulic actuation

Ref.	Design and actuation components of evaluated robotic system(s)	Endoscope and/or capsule dimensions	Mode(s) of actuation	Mode(s) of illumination and luminal visualisation	Capabilities evaluated	Degree of robot navigational assistance	Study methodology	Main findings
Vucelic *et al*[35], 2006 (Israel)	Aer-O-scope (GI View Ltd, Ramat Gan, Israel): Workstation and Disposable unit consisting of a rectal introducer, supply cable, scanning balloon, scope and rectal balloon. The supply cable connects the disposable unit to the workstation with its joystick and is able to transmit air, water and suction	5.5 mm diameter, 2.5 m length	Pneumatic	White LED, 360 panoramic vision system with CMOS camera with a field of view of 57 degrees	Visualisation and safety	Semi-autonomous	*In vivo*: n = 12 Human, healthy volunteers	CIR is 83%. Median CIT is 14 min with an average procedure duration of 23 min. Analgesia required in 2 patients. 4 patients had submucosal petechial lesions. No complications at 30 d follow up
Gluck *et al*[36], 2016 (Israel)	Aer-O-scope (GI View Ltd, Ramat Gan, Israel): Workstation and Disposable unit consisting of a rectal introducer, supply cable, scanning balloon, scope and rectal balloon. The supply cable connects the disposable unit to the workstation with its joystick and is able to transmit air, water and suction	5.5 mm diameter, 2.5 m length	Pneumatic	White LED, 360 panoramic vision system with CMOS camera with a field of view of 57 degrees	Visualisation and safety	Semi-autonomous	*In vivo*: n = 56 Human, CRC screening	CIR is 98.2%. Mean withdrawal time is 14 min. Polyp detection rate of 87.5%. 0 patients had submucosal damage. No complications at 48 h follow up. Rated as excellent visualisation by endoscopists
Gluck *et al*[37], 2015 (Israel)	Aer-O-scope (GI View Ltd, Ramat Gan, Israel): Workstation and Disposable unit consisting of a rectal introducer, supply cable, scanning balloon, scope and rectal balloon. The supply cable connects the disposable unit to the workstation with its joystick and is able to transmit air, water and suction	5.5 mm diameter, 2.5 m length	Pneumatic	White LED, 360 panoramic vision system with CMOS camera with a field of view of 57 degrees	Visualisation and detection	Semi-autonomous	*In vivo*: n = 12 pigs with surgically simulated colonic 'polyps'	A total of 36 Aer-O-scope and 24 colonoscopy procedures were performed. The Aer-o-scope visualised 94.9% of polyps compared to 86.8% with colonoscopy. This was significant (P = 0.002). Miss rates for polyps was 5.1% with Aer-O-scope and 13.2% (P = 0.002) with conventional colonoscopy. This significant difference is true for > 6 mm polyps
Cosentino *et al*[38], 2009 (Italy)	Endotics System [ERA Endoscopy S.r.l., Peccioli (Pisa), Italy]: Workstation with console and disposable flexible probe. The probe has 2 clampers to aid locomotion and a head (contains the camera, LEDs and channels for suction, irrigation and insufflation) a body and a tail	23-37 cm in length, 17 mm in diameter	Pneumatic	LED light source and CMOS camera with a field of view of 110 degrees	Visualisation and Safety	Semi-autonomous	*Ex vivo*: n = 1 porcine colon fixed to a human adult abdominal phantom. *In vivo*: n = 40 Humans, with a family Hx of CRC, known previous polyps and FOB positive requiring investigation	*Ex vivo*: The stress pattern was 90% less than with colonoscopy. *In vivo*: CIR was 27% for the endotics system compared to 82% with colonoscopy. The mean CIT was 57 min. The endotics system was described as less painful (0.9 *vs* 6.9). The endotics system has a higher diagnostic accuracy as it detected 2 polyps and 2 angiodysplastic lesions not identified with colonoscopy
Tumino *et al*[39], 2010 (Italy)	Endotics System (ERA Endoscopy S.r.l., Peccioli (Pisa), Italy): Workstation with console and disposable flexible probe. The probe has 2 clampers to aid locomotion and a head (contains the camera, LEDs and channels for suction, irrigation and insufflation) a body and a tail	25-43 cm in length, 17 mm in diameter	Pneumatic	LED light source and CMOS camera with a field of view of 110 degrees	Visualisation, sensitivity and specificity	Semi-autonomous	*In vivo*: n = 71 Humans, with a family Hx of CRC or polyps	Endotics system versus colonoscopy: CIR: 81.6% *vs* 94.3%. The average time for procedure completion: 45 min *vs* 23 min (P < 0.001). Patients requiring sedation: 0% *vs* 19.7% (P < 0.001). Endotics system for detecting polyps: Sensitivity: 93.3%; Specificity: 100%; Positive predictive value:

								100%; Negative predictive value: 97.7%
Trecca *et al*[40], 2020 (Italy)	Endotics System [ERA Endoscopy S.r.l., Peccioli (Pisa), Italy]: Second generation system- Workstation with console and disposable flexible probe. The probe has 2 clampers to aid locomotion and a head (contains the camera, LEDs, chromoendoscopy and channels for suction, irrigation and insufflation) a body and a tail	23-37 cm in length, 17 mm in diameter	Pneumatic	LED light source, chromoendoscopy and CMOS camera with a field of view of 140 degrees	Learning curve, visualisation and diagnostic accuracy, safety	Semi-autonomous	*In vivo*: n = 55 Humans, requiring diagnosis, CRC screening or surveillance. Training progress was evaluated by comparing two consecutive blocks of patients i.e. group A (first 27) and group B (last 28)	CIR is 92.7%. Median CIT is 29 min. Median withdrawal time is 18 min. Polyp detection rate: 40%; Adenoma detection rate: 26.7%; Advanced neoplasm: 0%; Complication: 1.8%-bleeding with polypectomy; Successful polypectomy and hot biopsy coagulation for bleeding. Mean VAS pain/discomfort: 1.8. Learning curve assessment, Group A *vs* Group B: CIR: 85.2% *vs* 100%. Median CIT: 55 min *vs* 22 min (P = 0.0007). Median withdrawal time: 21 min *vs* 16 min
Tumino *et al*[41], 2017 (Italy)	Endotics System (ERA Endoscopy S.r.l., Peccioli (Pisa), Italy): Workstation with console and disposable flexible probe. The probe has 2 clampers to aid locomotion and a head (contains the camera, LEDs and channels for suction, irrigation and insufflation) a body and a tail	25-43 cm in length, 17 mm in diameter	Pneumatic	LED light source and CMOS camera with a field of view of 110 degrees	Visualisation and performance	Semi-autonomous	*In vivo*: n = 102 Humans, previously failed caecal intubation on colonoscopy	CIR was 93.1% and therefore had a 95% performance. Mean CIT was 51 min
Shike *et al*[42], 2008 (Italy/Israel/United States)	Sightline ColonoSight (Stryker GI, Dallas, Tex, Haifa, Israel): A reusable scope with LEDs and camera at the tip and steering dials proximally. Tips is covered by a disposable sleeve with 3 working channels for suction, irrigation, insufflation and instruments. Electropneumatic unit, control unit and video monitor	Not described	Pneumatic	LED light source and camera	Visualisation, diagnosis and treatment	Semi-autonomous	*In vivo*: 2 pigs–To assess safety in terms of bacterial transmission to the reusable scope with a disposable sleeve covering. *In vivo*: 178 Humans, healthy volunteers and various clinical indications for colonoscopy	*In vivo*, Pigs: E.coli and E. Fergusonii from scope handle, shaft and tip before the procedure: Nil growth. E.coli and E. Fergusonii from scope handle, shaft and tip after the procedure: Nil growth. E.coli and E. Fergusonii from sheath covering after the procedure: Heavy growth. *In vivo*, Humans: CIR is 90%. Mean CIT is 11.2 min. Diagnoses of diverticulosis, polyps, colitis, haemorrhoids, normal or other was given. Successful polypectomy, biopsy and argon plasma coagulation. No complications at 2 wk follow up
Ng *et al*[43], 2000 (Singapore)	EndoCrawler: Longitudinal and circumferential rubber bellow actuators joined in four segments with a bending tube to allow steering between the first two segments and vision module; Central hollow cavity for instruments, insufflation, irrigation and suction channels and CCD cables. These exit the proximal end as a flexible cable similar to a colonoscope; LabWindows user interface and joystick	28 mm in diameter, 420 mm length	Pneumatic	CCD camera and light source	Locomotion and visualisation	Direct robot operation	*Ex vivo*- Cadaveric colon. *In vivo*-Pig	*Ex vivo*: Clear visualisation of colonic wall. Speed: 200 mm/min however required external pushing and couldn't progress beyond bends unless the head was deflected away from the colonic wall. *In vivo*: 'Red out' images throughout most of the robot's journey. Average speed: 150 mm/min with external pushing. Unable to progress beyond an acute bend
Dehghani *et al*[44], 2017 (United States)	Pneumatically driven colonoscopy robot consisting of the robot (tip with camera, latex tubing, tethered camera and anal fixture) and external pneumatic circuit and electric circuit with laptop	Not described	Pneumatic	Camera	Locomotion feasibility and safety	Semi-autonomous	*Ex vivo*: 1.5 m porcine colon in human phantom. Tests repeated 5-14 times depending on analysis performed	Able to traverse the entire length 71.4% (10/14 trials). Able to traverse the entire length with additional bends 90.9% (10/11 trials). Robot speed of 28 mm/s (5 trials). Average CIT is 54.2 s. (5 trials). Maximum propulsive force is 6 N (44 mmHg) which is less than the safe intraluminal pressure of 80

								mmHg. Balloon rupture led to damage including tearing of the porcine colon
Chen *et al*[45], 2019 (China)	Soft endoscopic device which consists of two gripper segments and one propulsion segment. Each segment contains two soft pneumatic balloons and two rigid connectors. The balloons are twisted in the gripper segments but linear in the propulsion segment. The connectors contain inner channels for air flow and instruments; Lab view interface. Air compressor with regulators, pressure sensors, valves and air pipes connected to the endoscopic device and a power source	The unactuated device is 95 mm in length and 22 mm in diameter.	Pneumatic	CCD camera	Locomotion and visualisation capability	Semi-autonomous	*Ex vivo*: Pig colon-one end fixed to a pipe, the other free. Colon placed in a horizontal position	Velocity to traverse the colon: 1 mm/s. Clear visualisation of the colonic mucosa
Coleman *et al*[47], 2016 (United Kingdom)	Hydraulic colonoscope system: A CV connected to extra-corporeal pumps and valves *via* a tether. The CV contains a magnetic tracker and is surrounded by a balloon which is flexible and may be inflated or deflated. The pump system is used to pump water into the colon behind the CV; Anal port and control system on HMI	CV dimensions not described. Tether: 1.8 m long, 6 mm in diameter	Hydraulic	No camera in this prototype however a dummy with a diameter if 11 mm and length of 25 mm is incorporated to simulate its presence	Comparison of CV locomotion under manual control or automatic control to colonoscopy	Direct or semi-autonomous	*Ex vivo*: Two 120 cm porcine colon placed in human abdominal phantom–6 trials *per* manual control, automatic control and colonoscopy	100% CV reached the caecum. CV *vs* colonoscopy: CIT: 3.95 *vs* 4.91 min (P = 0.43). Maximum force to the colon: 0.63 *vs* 2.2 N (P = 0.004). Maximum anal pressure: 1.53 *vs* 4.53 kPa ($P = 1 \times 10^{-7}$). Mean anal pressure: 0.65 *vs* 1.5 kPa (P = 0.0003). No difference in maximum or mean caecal pressure. Manual CV versus Auto CV: CIT: 2.11 *vs* 5.79 min (P = 0.02). Mean anal pressure: 1.86 *vs* 1.31 kPa (P = 0.03). No difference maximal anal pressure and maximum or mean caecal pressure

LEDs: Light emitting diodes; CMOS: Complementary metal-oxide-semiconductor; CIR: Caecal intubation rate; CIT: Caecal intubation time; CCD: Charged coupled device; HMI: Human machine interface; CV: Colonic vehicle.

they are permanent and cannot be turned on or off[3]. Electromagnetic coils can improve control over the magnetic field however they do require a power supply[19]. We have further classified these devices into whether or not they are wireless or tethered.

Wireless capsules

A swallowable wireless capsule with the aim of therapeutic control of bleeding was developed[49]. It consists of a surgical clip, 4 IPMs and a bidirectional communication platform and is able to actively locomote *via* a magnetic link generated by its interaction with an EPM. The EPM is mounted on a passive hydraulic arm that is moved manually by the user. A HMI under direction by the controller controls clip deployment. When tested 10 times in *ex vivo* porcine colon, the clip release occurred 100% of the time and was instantaneous. Moving the capsule was effective and fast although it took 2-3 min to align it appropriately against the mucosa to be clipped. *In vivo* in a pig, 'good' movement and positioning of the device with the EPM was observed. The clip was released successfully onto the desired target and it remained *in situ*. The amount of tissue grasped was also satisfactory. This capsule was 12.8 mm in

diameter and 33.5 mm in length[49].

Another wireless capsule with a set of IPMs, inertial and vision sensors and vision module, with an EPM mounted on a robotic arm was created[50]. The robotic arm was moved intelligently *via* closed loop steering and the HMI (Figure 4). Visualisation, motion feasibility and learning curve were tested in insufflated or collapsed porcine colon (500 mm) placed in a human abdominal phantom. In the collapsed colon, the device was only able to travel very short distances whereas there was a 100% success rate in traversing the whole length when the colon was insufflated with air. The average time required was 10 min. Novice medical doctors were able to drive the EPM in an effective way within 40 trials[50]. Using a robotic arm to steer the EPM was shown to provide better manoeuvrability and lesion detection rates compared to manual steering of the EPM[51].

Carpi and colleagues used the readily available PillCam capsule created by Given Imaging Ltd, Israel to visualise the small bowel and covered it in a magnetic shell to create a simple wireless capsule capable of magnetic actuation. The magnetic link was created between the shell and two EPMs controlled by a magnetic navigation system (Niobe, Stereotaxis, Inc, United States). This navigation system is already clinically in use in the field of robotic cardiology. A remote computer workstation and mouse was used to navigate the capsule. *In vivo* testing in a pig showed simply that such a capsule is capable of travelling through the colon without causing damage[52].

The magnetic controlled capsule endoscopy (MCCE) system (Chongqing Jinshan Science & Technology Group Co, Ltd) consists of an ingestible colon capsule with IPM and battery, an external magnetic manipulator with EPM, and an image transmission system. The capsule measures 27.9 mm in length and 13.0 mm in diameter. It was tested in 52 volunteers for CRC screening. The average time to reach the caecum was 3.63 h. Manoeuvrability of the capsule was good (94.3%) or moderate (5.77%). It was capable of providing good-quality pictures and identified 6 positive findings (polyps, diverticulum) which were confirmed by colonoscopy. All volunteers were able to swallow the capsule and excreted the capsule within 2 d. Complications included 7 mild adverse events (abdominal discomfort, nausea, and vomiting) lasting 24 h only [53].

Tethered capsules

Using the technology from[51] the "Magnetic Air Capsule", a device consisting of a capsule like frontal unit and a compliant multi-lumen tether was created[13]. The incorporation of the multi-lumen tether allows for intervention in addition to basic colonoscopy functions. The frontal unit contains a vision module, an IPM, a magnetic field sensor, and two channels, one for lens cleaning and the other for insufflation/suction/irrigation or instrument passage. The capsule is 11 mm in diameter, 26 mm in length and the tether is 2 m in length. 12 trials in 850 mm porcine colon placed in a human abdominal phantom with attached coloured beads (5 mm) mimicking polyps showed an 85% detection rate. 100% of which were successfully removed with a polypectomy snare. The mean completion time (inspection of the colon as well as removal of the 'polyps') was 11.3 min. Six trials in anaesthetised pigs showed device ability to navigate around bends and folds, retroflexion capability and successful operation of the working channels without a loss of magnetic link. In addition, there was no mucosal damage[13]. Using a similar prototype (Figure 5), visualisation and diagnostic ability was assessed 22 times in 850 mm of porcine colon and compared to that of colonoscopy. CIR for both was 100%. Compared to colonoscopy, pin detection rate was lower (80.9% with *vs* 85.8%) and procedure completion time (visualisation and diagnosis) was significantly longer [556 s *vs* 194 s ($P = 0.0001$)]. There was no difference in intuitiveness score[54].

Further advancement led to the "Magnetic flexible endoscope" (MFE). This tethered robot has a standard visualisation module and working channels for instruments, irrigation and insufflation. Additionally, it has a unique retroflexion control algorithm to improve this repetitive but technically challenging skill. Autonomous retroflexion ability was examined 30 times in an anaesthetised pig. Successful retroflexion manoeuvres with a mean time of 11.3 s were performed 100% of the time. No acute tissue trauma or perforation was seen[55]. A comparison of different degrees of locomotion autonomy was performed recently using the MFE in two pigs[14]. Completion times for Direct robot operation *vs* teleoperation *vs* semi-autonomous operation *vs* colonoscopy showed similar results over distances of 45 cm (9 min 4 s *vs* 2 min 20 s *vs* 3 mins 9 s *vs* 1 min 39 s) and 85 cm (unable to reach marker *vs* 8 min 6 s *vs* 9 min 39 s *vs* 3 min 29 s). Intelligent and semi-autonomous control had NASA Task Load Index[56] mean ratings lower/less demanding than colonoscopy or direct robot operation[14].

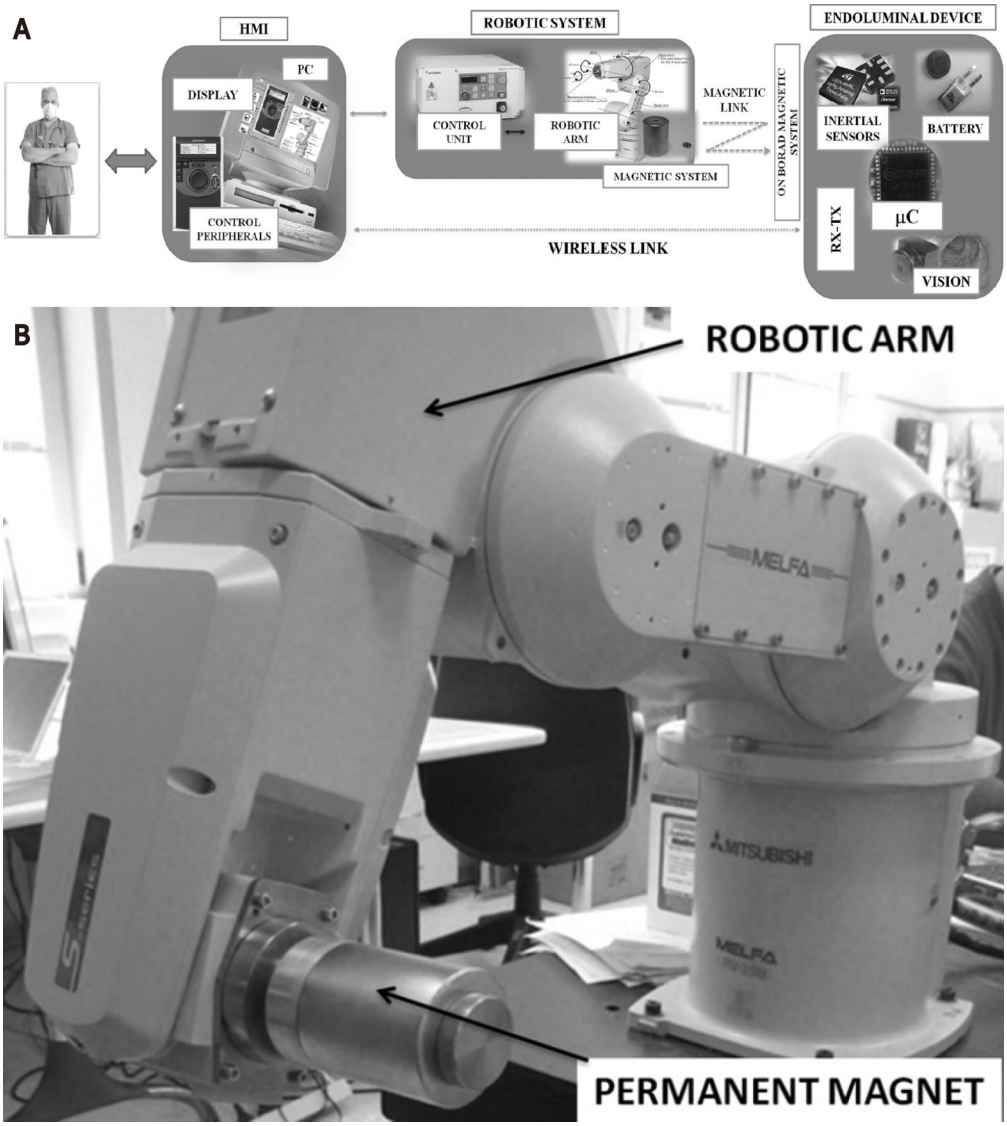

Figure 4 An example of a magnetic device device by Ciuti *et al*[50]. A: The system architecture of the wireless magnetic robot; B: The Robotic arm with external permanent magnet. Citation for A and B: Ciuti G, Valdastri P, Menciassi A, Dario P. Robotic magnetic steering and locomotion of capsule endoscope for diagnosis and surgical endoluminal procedures. Robotica. *Cambridge University Press* 2010; 28: 199-207. Copyright© The Authors 2010. Published by Cambridge University Press.

An Endoo capsule with a permanent magnet, visualisation module, tether with 4 working channels for suction, insufflation, irrigation and instruments was developed in Italy within a European H2020 project[57]. The system consists of an external robot with EPM, a localisation system and medical workstation with a joystick. The workstation and joystick allow the user to control all functions of the Endoo capsule (Figure 5). In addition, the vision system contains 4 green/blue UV-LEDs. Compared to colonoscopy CIR was 67% *vs* 100% at 9.5 min *vs* 3.5 min respectively. Interaction forces between the Endoo capsule and colonic wall as well as polyp detection rates was lower than colonoscopy [1.17 N *vs* 4.12 N; 87% *vs* 91% (P = 0.16)]. The magnetic link was lost an average of 1.28 times *per* complete procedure, but it was restored in 100% of cases[57]. All studies are summarised in Table 3.

Hybrid actuation

Hybrid actuation involves the combination of different propulsive mechanisms to achieve motion. A wireless endocapsule consisting of a 3 legged mechanism, DC motor, battery and small IPMs was created and tested by Simi and colleagues (Figure 6)[58]. Magnetic and EM mechanisms are combined here: The IPMs interact with an EPM to primarily move and orient the capsule while the legged mechanism is used to extract the capsule out of collapsed areas of the colon when it might otherwise get trapped. Motion feasibility was examined 10 times on 20 cm porcine colon and in 4 anaesthetised pigs. In the *ex vivo* trials, the average time taken to travel 20 cm and

Table 3 Summary of the included studies reviewing robotic lower gastrointestinal endoscopy devices with magnetic or hybrid actuation

Ref.	Design and actuation components of evaluated robotic system(s)	Endoscope and/or capsule dimensions	Mode(s) of actuation	Mode(s) of illumination and luminal visualisation	Capabilities evaluated	Degree of robot navigational assistance	Study methodology	Main findings
Valdastri *et al* [49], 2008 (Italy)	Swallowable wireless capsule with surgical clip, electromagnetic motor, 4 IPMs and a bidirectional communication platform. The EPM on a passive hydraulic arm is controlled manually by the user. A HMI controls clip deployment	Diameter of 12.8 mm and a length of 33.5 mm	Magnetic	No camera in this prototype however 300 mm^3 space was left for future integration. Throughout the experiments the capsule was monitored with a flexible endoscope	Therapeutic clip application for bleeding	Direct robot operation	*Ex vivo*- Porcine colon placed in a model of the abdomen–10 trials. *In vivo*-1 pig	*Ex vivo*: Clip release: 100%; Clip release occurred instantly, and moving of the capsule was effective and fast. It took 2-3 min to position the capsule against the mucosa to be clipped. *In vivo*: Good locomotion and positioning with the EPM. The clip was released successfully onto the desired target. The clip remained in situ. The amount of tissue grasped was satisfactory
Ciuti *et al*[50], 2010 (Italy)	Magnetic wireless capsule with inertial and vision sensors and a set of IPM; External robotic arm with EPM and human machine interface. The working distance is 150 mm. The HMI is used to control the robotic arm and receives input from the capsule	Capsule: 40 mm in length, 18 mm in diameter	Magnetic	CMOS camera and 4 white LEDs	Visualisation, locomotion and learning curve	Intelligent teleoperation	*Ex vivo*: 500 mm porcine colon in human phantom model–40 trials (some insufflated and collapsed colons)	Insufflated colon: 100% of success rate in traversing the entire colon. Short learning curve (descriptive analysis) to drive the robotic arm. The average time required to traverse the colon was approximately 10 min. Collapsed colon: Capsule was able to travel only really short distances and manual assistance was required
Ciuti *et al*[51], 2009 (Italy)	Wired capsule with 3 IPMs and vision module; EPM either controlled manually or robotically *via* a robotic arm controlled by a HMI and controller. The working distance is 150 mm	14 mm in diameter and 38 mm in length	Magnetic	CMOS camera with illumination system	Robotic versus manual steering	Direct or Intelligent teleoperation	*Ex vivo*: 480 mm porcine colon in human phantom model–10 trials each for robot and manual arm steering. *In vivo*: 2 Pigs–5 trials each for robot and manual arm steering	*Ex vivo*: Robot versus manual steering: The mean completion time: 423 s *vs* 201 s ($P < 0.01$). The mean percentage of '4 mm white spherical targets' reached: 87% versus 37% ($P < 0.01$). *In vivo*: Manual steering was usually faster, whereas manoeuvrability was better with robotic movement of the EPM (Descriptive analysis)
Carpi *et al*[52], 2011 (Italy/United States)	PillCam (Given Imaging Ltd, Israel) capsule covered in a magnetic shell; Two EPMs, a magnetic navigation system (Niobe, Stereotaxis, Inc, United States), a remote computer work-station and mouse. Fluoroscopic images were continuously acquired by means of a digital scanner to provide visual feedback regarding capsule manoeuvres	13 mm in diameter and length	Magnetic	Not described	Steering and localisation capability	Intelligent teleoperation	*In vivo*: Pig (Number of pigs and trials not described)	The capsule was freely moved within the colon. No complications
Gu *et al*[53], 2017 (China)	The MCCE system (Chongqing Jinshan Science & Technology Group Co, Ltd): Ingestible colon capsule with IPM and battery, an external magnetic manipulator with an EPM, and an image transmission system	Capsule measures 27.9 mm in length by 13.0 mm in diameter	Magnetic	Not described	Manoeuvrability, visualisation, diagnosis and safety	Direct robot operation	*In vivo*: $n = 52$ Human, CRC screening volunteers. Capsule movement was	Average CIT: 3.63 h. Maneuverability of the capsule was good (94.3%) or moderate (5.77%). MCCE provided good-quality pictures and identified 6 positive findings (polyps, diverticulum) which

							visualised *via* colonoscopy 5 h after ingestion	were confirmed by colonoscopy. 78% reached the rectosigmoid colon in 25 min. All 57 volunteers were able to swallow the capsule and excreted the capsule within 2 d. Complications: 7 mild adverse events (abdominal discomfort, nausea, and vomiting) lasting 24 h. No complications at one week follow up
Valdastri *et al* [13], 2012 (Italy)	MAC consists of capsule-like frontal unit and a compliant multi-lumen tether. The frontal unit contains a vision module, an IPM, a magnetic field sensor, and two channels, one for lens cleaning and the other for insufflation/suction/irrigation or instrument passage. The IPM is controlled by an EPM mounted on a robotic platform. A control device allows the user to directly control the position of the EPM. The working distance is 150 mm. The tether connects to an external control box	Capsule: 11 mm diameter, 26 mm in length. Tether: 5.4 mm diameter, 2 m length	Magnetic	CCD camera with 120 degree field of view and 4 white LEDs	Diagnostic and treatment ability, safety, usability	Intelligent teleoperation	*Ex vivo*: 850 mm porcine colon in human phantom model–12 trials. *In vivo*: 2 Pigs–3 trials each	*Ex vivo*: Mean percentage of 5 mm coloured beads (polyps) detected was 85%. 100% successful removal (polypectomy loop) of identified beads. Mean completion time (inspection and bead removal) was 678 s. Mean bead removal time was 18 s. Good manoeuvrability, low friction from the tether on the colon wall and reliable feedback from the vision module. *In vivo*: No mucosal damage or perforation. Able to navigate around bends and folds, retroflexion of the camera and successful operation of the tools (loop, forceps, retrieval basket, grasper) without loss of magnetic link
Arezzo *et al* [54], 2013 (Italy)	Robotic arm with EPM controlled by HMI and controller; Wired capsule with 3 IPMs, camera, LEDs and magnetic sensor. The working distance is 150mm. The wired sheath allows transmission from the vision module and electric energy	Capsule: 13.5 mm in diameter and 29.5 mm in length. Wired sheath: 2 mm in diameter	Magnetic	CCD camera with 120 degree view and 6 white LEDs	Visualisation and diagnostic ability compared to colonoscopy	Intelligent teleoperation	*Ex vivo*: 850 mm porcine colon in human phantom model–22 trials each for capsule and colonoscope	Robot *vs* colonoscopy: CIR: 100% for both. Pin detection rate: 80.9% *vs* 85.8%. Procedure completion time (visualisation and diagnosis): 556 s *vs* 194 s (P = 0.0001). No difference in intuitiveness score
Slawinski *et al* [55], 2018 (United States/United Kingdom)	MFE with IPM, camera, illumination module, working channel for instruments, channel for irrigation and insufflation, EPM on robotic arm and HMI. Additional sensing, retroflexion and software control systems	Tip: 20.6 mm in diameter and 18.1 mm in length. Body: 6.5 mm in diameter	Magnetic	Camera and illumination module	Retroflexion ability	Intelligent teleoperation with task autonomy	*In vivo*: 1 Pig–30 trials	100% successful retroflexion manoeuvres with a mean time of 11.3 s. No acute tissue trauma or perforation
Martin *et al* [14], 2020 (United Kingdom)	MFE with an IPM, camera, an insufflation channel, irrigation channel, working channel for instruments and localisation circuit; A robotic arm with EPM; Robot operating system and joystick	Capsule: 20.6 mm in diameter and 18.1 mm in length. Tether: 6.5 mm in diameter	Magnetic	Camera and LED	Comparison of different degrees of autonomy for locomotion and novice usability	Direct robot or intelligent teleoperation or semi-autonomous	*In vivo*: 2 Pigs–3 trials for each MFE control and colonoscopy in the first pig and 4 trials for each in the second pig	First porcine model–colon distance of 45 cm: Task completion times for direct robot operation, teleoperation, semi-autonomous operation and conventional colonoscopy were 9 min 4 s, 2 min 20 s and 3 min 9 s and 1 min 39 s, respectively. Second porcine model-colon distance of 85 cm: Task completion times for, teleoperation, semi-autonomous operation and conventional colonoscopy were 8 min 6 s, 9 min 39 s and 3 min 29 s, respectively. It was not possible to reach the marker with direct robotic operation. Intelligent and semi-autonomous had

								NASA task force mean Index ratings lower/less demanding than colonoscopy or direct robot operation
Verra *et al*[57], 2020 (Italy)	Endoo system: An Endoo capsule with a IPM, soft tether connection with 4 working channels for suction, insufflation, irrigation and instruments; An external robot with EPM, force-torque sensor and movable platform, localisation system and medical workstation with a joystick complete the system. The robot with EPM is controlled *via* the workstation but can also be steered manually. The localisation system provides information on the capsule position and orientation	Tether: 160 cm long	Magnetic	Two CMOS cameras with 170 degree field of view, 4 white LEDs and 4 green/blue UV-LEDs	Visualisation, locomotion, diagnosis and safety	Semi-autonomous	*Ex vivo*: 100-120 mm porcine colon in human phantom model	*Ex vivo* Endoo alone: 100% success rate in operating channel (use of polypectomy snares, biopsy forceps and needles). 100% success rate for target approach tests (using these instruments to target a polyp). *Ex vivo* Endoo (21 trials) *vs* colonoscopy (13 trials): Completion rate: 67% *vs* 100%. Interaction forces: 1.17 N *vs* 4.12 N. Polyp detection rate: 87% *vs* 91% ($P = 0.16$). Mean CIT: 9.5 min *vs* 3.5 min. The magnetic link was lost an average of 1.28 times *per* complete procedure, but it was restored in 100% of cases
Simi *et al*[58], 2010 (Italy)	Wireless endocapsule with legged mechanism (3 legs), DC motor, battery, small IPMs which interacts with an EPM. LabVIEW HMI is present and is also compatible with voice commands	14 mm in diameter, 44 mm in length.	Hybrid-Electromechanical and Magnetic	No camera in this prototype however 450 mm^3 space was left for future integration. Throughout the experiments the capsule was monitored with a gastroscope	Locomotion and lumen dilatation	Semiautonomous	*Ex vivo*: 20 cm porcine colon–10 trials. *In vivo*: 4 pigs–10 trials. Capsule was placed 40 cm from the anus and expected to travel towards the anus	*Ex vivo*: Ability to travel 20 cm in 10 min: 70%. Average time to traverse 20 cm and number of leg activations: 4 min and 5 mechanism activations. Average speed: 5 cm/min. *In vivo*: Ability to travel 40 cm in 20 min: 60%. Average time to traverse 40 cm and number of leg activations: 5 min and 5 activations. Average speed: 8 cm/min
Nouda *et al* [59], 2018 (Japan)	Self-propelling capsule endoscope (SPCE) consisting of a silicon resin fin with micro-magnet connected to the PillCam SB2 capsule; External magnetic field generating controller (Minimermaid System), human interface with joystick	45 mm in length and 11 mm in diameter	Hybrid-Mechanical and Magnetic	Camera with 156 degree field of view	Locomotion and safety	Semi-autonomous	*In vivo*: 1 Human	The SPCE could swim smoothly in forward and backward directions but had difficulty bypassing bends. No acute complications

IPM: Internal permanent magnet; EPM: External permanent magnet; HMI: Human machine interface; LEDs: Light emitting diodes; CMOS: Complementary metal-oxide-semiconductor; CIT: Caecal intubation time; CIR: Caecal intubation rate; CCD: Charged coupled device; MCCE: Magnetic controlled capsule endoscopy; MFE: Magnetic flexible endoscope.

number of times the legs were activated was 4 min with 5 activations. The average speed was 5 cm/min. In the *in vivo* trials, the average time taken to travel 40 cm and number of times the legs were activated was 5 min with 5 activations. The average speed was 8 cm/min. The colon was not insufflated with air[58]. In Japan, a self-propelling capsule was created by attaching a silicon resin fin with micro-magnet to the commercially available Pillcam SB2 capsule (Covidien, Dublin, Ireland). In the presence of a magnetic field and water, the fin vibrates and propels the capsule. When placed in the rectum and descending colon of a human subject, it was shown to be able to swim forwards and backwards without causing damage to the mucosa however it had difficulty by-passing the bend of the sigmoid colon[59] (Table 3).

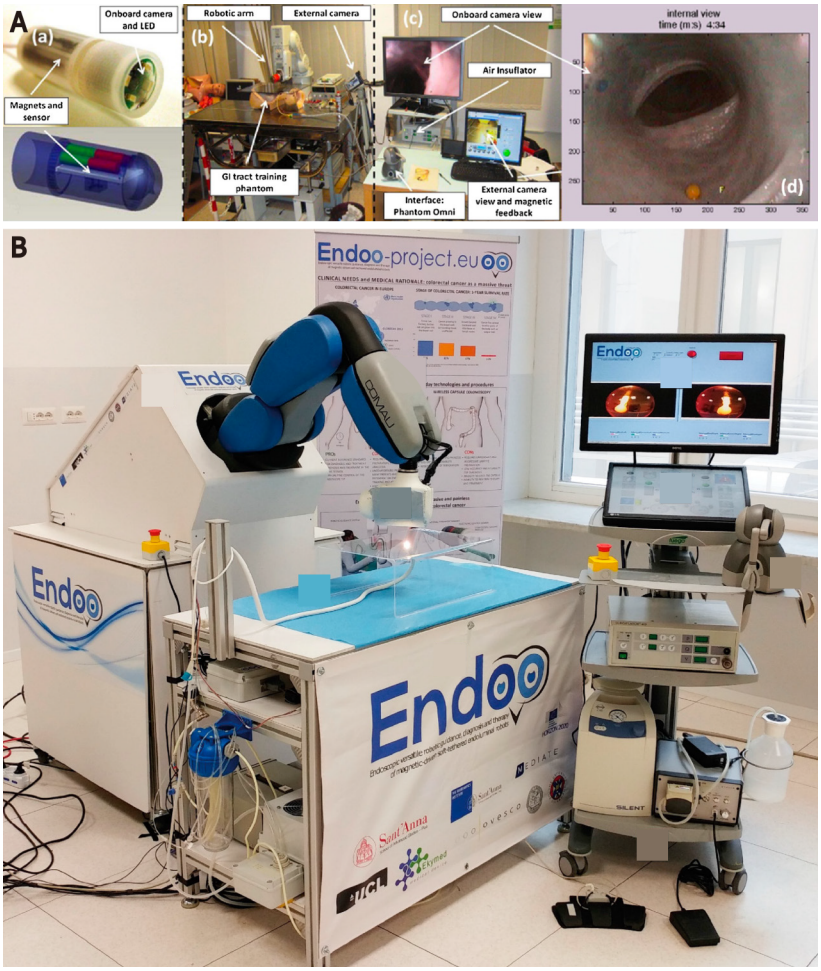

Figure 5 Examples of tethered magnetic robotic devices. A: Shows the overall tethered device and system with an image of the internal view provided by the device camera in Arezzo *et al*. Citation: Arezzo A, Menciassi A, Valdastri P, Ciuti G, Lucarini G, Salerno M, Di Natali C, Verra M, Dario P, Morino M. Experimental assessment of a novel robotically-driven endoscopic capsule compared to traditional colonoscopy. *Dig Liver Dis* 2013; 45: 657-662. Copyright© The Authors 2013. Published by Elsevier. B: Shows the Endoo system with a clear image of the capsule in the lower left corner. Citation: Verra M, Firrincieli A, Chiurazzi M, Mariani A, Lo Secco G, Forcignanò E, Koulaouzidis A, Menciassi A, Dario P, Ciuti G, Arezzo A. Robotic-Assisted Colonoscopy Platform with a Magnetically-Actuated Soft-Tethered Capsule. *Cancers (Basel)* 2020; 12: 2485. Copyright© The Authors 2020. Published by Open access.

DISCUSSION

Medical robotics is realising its potential in a variety of healthcare disciplines, and the last couple of decades have seen increasing demand for robotic platforms designed specifically for endoscopy. In terms of LGI tract 'robo-endoscopy', significant strides have been made over this period, with five devices receiving FDA approval. These devices represent a heterogeneous group in terms of actuation modality (EM or pneumatic), and many studies have been performed using *ex vivo* models. These models, while able to demonstrate proof of concept, cannot effectively capture data on *in vivo* motion ability, pain perception or device safety. Nevertheless, the human data that is available suggests that the evaluated robo-endoscopic systems are able to locomote effectively (*i.e.*, achieve CIR > 90%[23,24,36,40-42]), to locomote safely (*i.e.*, be associated with mild if any mucosal disruption or complications[21,24,35,36,40,42])and to achieve endoscopic tasks with minimal associated pain[21,23,35,39]. Reducing discomfort associated with LGI endoscopy represents a key directive in robotic endoscopy and in two trials, human participants gave the Invendoscope an average pain score of 1.96/6 and 2.6/6, which translated into 0% and 4.9% requiring sedation, respectively[21,23]. When compared to colonoscopy, pain scores and sedation rates were also significantly lower with the Endotics system[38,39]. Early data suggest that the Endotics system may even have superior diagnostic capabilities compared with conventional colonoscopy as indicated by its ability to detect lesions missed on colonoscopy[38]. These reports are certainly encouraging, though overall it is important to appreciate that most devices presented in this review remain in the relatively early phases of translational application, and few have met the goal of

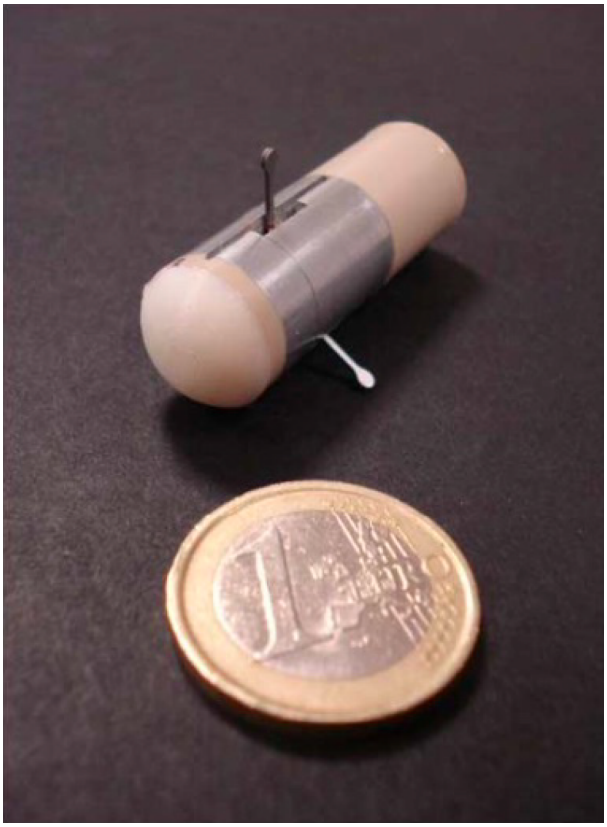

Figure 6 Hybrid robotic device by Simi *et al*[58]. Citation: Simi M, Valdastri P, Quaglia C, Menciassi A, Dario P. Design, Fabrication, and Testing of a Capsule With Hybrid Locomotion for Gastrointestinal Tract Exploration. *IEEE/ASME Trans Mechatron* 2010; 15: 170-180. Copyright© The Authors 2010. Published by IEEE.

clinical deployment outside of academic institutions. An inherent limitation lies in the fact that most systems provide primarily diagnostic functionality, with large scale trials evaluating therapeutic robotic LGI endoscopy currently lacking.

Improved reproducibility, enhanced procedural efficiency and a shorter learning curve have all been suggested as possible areas where robotic endoscopy could make a positive impact. In addition, they may offer a more comfortable system for the user, which may have potential to minimise fatigue and injury and ultimately this may equate to more years of professional service. More intuitive control and visualisation systems have the potential to shorten learning curves. For example, one trial evaluating a robotic endoscopic system suggested that only an average of 30 procedures was required for the user to achieve CIR, CIT and scope withdrawal time comparable to standard colonoscopy performed by an 'expert'[40].

From a broader perspective, it is important to acknowledge that this review has focused entirely on the specific application(s) of robotic systems in LGI endoscopy. However, robotic advances in this area are not made in isolation from advances in other luminal organs such as the upper GI tract or in natural orifice transluminal endoscopic surgery. Thus, it is likely that advances in one field will complement another.

One can anticipate that in the future, as the technology becomes more sophisticated, it should be possible to exploit the 'computational interface' that robotic endoscopy provides further, with the potential for integration of AI based algorithms and novel augmented reality systems for 'smart' therapeutics. It is doubtful whether these next-generation technologies will work to their full capabilities if operating within anything other than a robotic system. It is an exciting time in medical robotics with recent reports confirming the potential for the development of 'soft' robotic systems with in-built autonomic functionality[60]. Such systems are likely to represent the long-term direction of luminal robotics. In the near- to mid-term, the goal will be to continue to stimulate strong collaborative links between GI physicians and medical engineers in order to continue to refine design and functionality.

CONCLUSION

Robotic technologies have the potential to transform LGI endoscopy into a quicker, safer, more reliable and less painful procedure. In the long term, benefits for patients, endoscopists and the wider healthcare industry are foreseeable, though these have yet to be convincingly demonstrated in human trials. Most studies to date have employed *ex vivo* modelling and high quality level 1 evidence is currently lacking in this field. Robotic technologies are evolving with such rapidity at the moment, that future robo-endoscopic systems are likely to look and behave very differently to conventional master-slave systems currently in use. Exciting developments in 3D printing, soft robotics, autonomous functionality and augmented reality are likely to converge over the coming decade to lead to the development of truly next generation robotic endoscopy devices.

ARTICLE HIGHLIGHTS

Research background

Inherent limitations exist with conventional colonoscopy which may be overcome by a variety of next-generation robotically-augmented technologies.

Research motivation

Robotic technologies have the potential to transform lower gastrointestinal (LGI) tract endoscopy with long term, benefits for patients, endoscopists and the wider healthcare industry. High quality evidence is currently lacking in this field.

Research objectives

This review provides a comprehensive summary of recent developments in the application of robotics in LGI tract endoscopy.

Research methods

A systematic review of the literature was performed. Studies reporting on the use of robotic endoscopic technology in *ex vivo* colon models or *in vivo* animal and human experiments were included.

Research results

Of 37 studies were included of varying actuation modality. Five devices have been approved by the Food and Drug Administration, however the majority remain in the early phases of testing and development. Level 1 evidence is lacking at present, but early reports suggest that these technologies may be associated with improved pain and safety.

Research conclusions

Significant progress in robotic colonoscopy has been made over the last couple of decades. The reviewed devices appear to be ergonomically capable and efficient though to date no reports have convincingly shown diagnostic or therapeutic superiority over conventional colonoscopy.

Research perspectives

Future improvements in design together with the integration of semi-autonomous and autonomous systems over the next decade will potentially result in robotic colonoscopy becoming more commonplace.

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