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Editor-in-Chief of *World Journal of Gastrointestinal Endoscopy*, Sang Chul Lee, MD, PhD, Chief Doctor, Full Professor, Surgeon, Surgical Oncologist, Division of Colorectal Surgery, Department of General Surgery, Catholic University of Korea, Daejeon St. Mary's Hospital, Daejeon 34943, South Korea. zambo9@catholic.ac.kr

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REVIEW

Recent advances in endoscopic management of gastric neoplasms

Hira Imad Cheema, Benjamin Tharian, Sumant Inamdar, Mauricio Garcia-Saenz-de-Sicilia, Cem Cengiz

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Hira Imad Cheema, Department of Internal Medicine, Baptist Health Medical Center, Little Rock, AR 72205, United States

Benjamin Tharian, Department of Interventional Endoscopy/Gastroenterology, Bayfront Health, Digestive Health Institute, St. Petersberg, FL 33701, United States

Sumant Inamdar, Mauricio Garcia-Saenz-de-Sicilia, Cem Cengiz, Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Arkansas for Medical Sciences, Little Rock, AR 72205, United States

Cem Cengiz, Division of Gastroenterology and Hepatology, Department of Internal Medicine, John L. McClellan Memorial Veterans Hospital, Little Rock, AR 72205, United States

Cem Cengiz, Division of Gastroenterology and Hepatology, Department of Internal Medicine, TOBB University of Economics and Technology, Ankara 06510, Turkey

Corresponding author: Cem Cengiz, MD, Chief Physician, Division of Gastroenterology and Hepatology, Department of Internal Medicine, John L. McClellan Memorial Veterans Hospital, 4300 W 7th Street, Little Rock, AR 72205, United States. cemcengizmd@yahoo.com

Abstract

The development and clinical application of new diagnostic endoscopic technologies such as endoscopic ultrasonography with biopsy, magnification endoscopy, and narrow-band imaging, more recently supplemented by artificial intelligence, have enabled wider recognition and detection of various gastric neoplasms including early gastric cancer (EGC) and subepithelial tumors, such as gastrointestinal stromal tumors and neuroendocrine tumors. Over the last decade, the evolution of novel advanced therapeutic endoscopic techniques, such as endoscopic mucosal resection, endoscopic submucosal dissection, endoscopic full-thickness resection, and submucosal tunneling endoscopic resection, along with the advent of a broad array of endoscopic accessories, has provided a promising and yet less invasive strategy for treating gastric neoplasms with the advantage of a reduced need for gastric surgery. Thus, the management algorithms of various gastric tumors in a defined subset of the patient population at low risk of lymph node metastasis and amenable to endoscopic resection, may require revision considering upcoming data given the high success rate of *en bloc* resection by experienced endoscopists. Moreover, endoscopic surveillance protocols for precancerous gastric lesions will continue to be refined by systematic reviews and meta-analyses of further research. However, the lack of familiarity with subtle endoscopic changes associated with EGC, as well as longer procedural time, evolving resection techniques and tools, a steep learning curve of such high-risk procedures, and lack of coding are issues that do not appeal to many gastroenterologists in the field. This review summarizes recent advances in the endoscopic management of gastric neoplasms, with special emphasis on diagnostic and therapeutic methods and their future prospects.

Key Words: Gastric tumors; Endoscopic ultrasound; Endoscopic mucosal resection; Endoscopic submucosal dissection; Endoscopic surveillance; Gastric neoplasm

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Core Tip: Minimally invasive and advanced endoscopic procedures have reduced the need for extensive and invasive surgical procedures for early gastric cancer and subepithelial tumors. These novel techniques have decreased side effects, duration of hospitalization, and sedation requirements. The possibilities evolve constantly from improved diagnosis to better therapeutic techniques. This review discusses current endoscopic techniques for the diagnosis and treatment of gastric neoplasms, with special focus on guidelines and newly developed tools and methods.

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INTRODUCTION

Since the advent of gastroscopy in 1868, the evolution of endoscopy has dramatically changed the natural history of several gastrointestinal pathologies. Since the initial challenge of fitting a light source with the scope of adding artificial intelligence (AI)-guided probes, the evolution has been exponential. Wolff and Shinya[1] performed the daunting task of removing colonic polyps endoscopically. In the era of laparotomy and colotomy for polyp removal, 303 polyps were removed endoscopically with minor bleeding in four patients[1]. In 2004, Kalloo *et al*[2] reported a "novel" endoscopic peroral transgastric approach for the peritoneal cavity. During this trial, the peritoneal cavity was accessed by a needle-like puncture of the gastric wall, the peritoneal cavity was examined, and a liver biopsy was performed. Gastric wall defects were closed using clips. This successful endeavor in 50 pigs led to what is now known as natural orifice transluminal endoscopic surgery[2].

Since the introduction of endoscopic ultrasonography (EUS) in 1980, its clinical role has continuously expanded from a diagnostic imaging approach for various gastric neoplasms to EUS-guided fine-needle aspiration (FNA) or fine-needle biopsy (FNB) to facilitate a cytological or histological diagnosis with locoregional staging of malignant gastric tumors. Treating gastric cancer by radical gastrectomy and lymph node dissection has several side effects, including internal hernias and dumping syndrome. With the development of endoscopic mucosal resection (EMR) in Japan over the past 20 years, the need for radical surgery has declined. Endoscopic submucosal dissection (ESD), which is organ-preserving and avoids surgical risks such as bleeding, leakage, and postoperative stenosis, is now a standard practice for early gastric cancer (EGC) resection. These minimally invasive techniques have provided advanced endoscopy a unique status. Our review aims to discuss these latest endoscopic diagnostic and therapeutic measures for managing epithelial and subepithelial gastric neoplasia.

DIAGNOSIS OF MAIN GASTRIC NEOPLASMS

Gastric epithelial tumors

Adenoma: Adenomas account for 10% of all gastric polyps in most Western countries[3]. Malignant transformation, which is common in flat adenomas, is also directly related to adenoma size. Lesions larger than 2 cm have a 40%-50% chance of malignant transformation, whereas smaller lesions (< 2 cm) have a 2% risk of malignant transformation[4]. Moreover, the irregular surface and microvascular pattern under magnification endoscopy (ME) with NBI (ME-NBI) and the color change from pale to red under white-light endoscopy (WLE) suggest the transition of adenoma to early adenocarcinoma.

Adenocarcinoma: Gastric cancer remains the second most common cancer worldwide, accounting for 60% of all cases in East Asian countries, such as China, Japan, and Korea[5]. It is the third leading cause of cancer-related deaths worldwide. According to the World Health Organization (WHO) database, gastric cancer is uncommon in North America[6]. The probabilities of acquiring and dying of gastric cancer were 1.5% and 1%, respectively. Several case-control studies from South Korea and Japan showed that the odds ratio for death from gastric cancer among subjects who underwent gastric endoscopic examinations was significantly decreased compared to those who did not undergo such screening, revealing that endoscopic screening reduces gastric cancer mortality rates[7,8]. The overall case fatality rate for gastric cancer is 81.6% among countries with limited focus on screening and, hence, typically late diagnoses of gastric cancer. In countries such as Japan, where EGC is being diagnosed promptly, the case fatality rate is 58.3%[9]. This striking difference forms the basis of this review article, which makes early cancer detection and treatment using advanced and sophisticated endoscopic procedures non-negotiable.

Adenocarcinoma is the most common histological type of gastric cancer. An estimated 95% of all gastric malignancies are adenocarcinoma[10]. Adenocarcinoma can be divided by anatomic location into non-cardia (distal) gastric adenocarcinoma and gastric cardia (proximal) adenocarcinoma. The incidence of non-cardia gastric adenocarcinoma has declined worldwide because of better eradication regimens for *Helicobacter pylori* (*H. pylori*), reduced smoking rates, and positive lifestyle changes. In contrast, the incidence of gastric cardia cancer has increased in the Western world and is primarily related to gastroesophageal reflux disease owing to increasing obesity rates[11].

Early detection is the gold standard for the management of all types of cancers, including EGC. The 2014 edition of the Japanese Guidelines for Gastric Cancer Screening recommended routine endoscopy screening every 2 years for individuals 50 years and older[12]. The Japan Gastroenterological Endoscopy Society (JGES) 2020 guidelines recommend a 1-3-year interval surveillance endoscopy for patients with clinical and endoscopic risk factors for gastric cancer[13]. The European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group, European Society of Pathology, and the Sociedade Portuguesa de Endoscopia Digestiva in a joint commission reached the consensus that WLE alone is insufficient for the diagnosis of precancerous gastric lesions. They recommended the use of magnification chromoendoscopy, NBI, or ME-NBI for the surveillance and diagnosis of these lesions[14].

It is essential to determine the depth of invasion of EGC as mucosal (cT1a) or submucosal (cT1b) to enable rational decisions regarding therapeutic strategies. Conventional WLE is the most common modality used to determine invasion depth. Indicators of cancer invasion deeper than 500 μm from the submucosa (pT1b2) on WLE include hypertrophy or fusion of concentrated folds, tumor size at least 30 mm, marked redness, irregular surface, marginal elevation, submucosal tumor-like raised margins, and non-extension sign[15-20]. The positive predictive value for diagnosing cT1b2 cancer using these indicators is reported to be 63%-89%[20,21]. EGC can be successfully managed using advanced endoscopic procedures such as EMR and ESD.

Oxyntic gland adenoma and gastric adenocarcinoma of the fundic gland type: First reported in 2007, gastric adenocarcinoma of the fundic gland type (GAFG) is an extremely rare variant of gastric adenocarcinoma composed of columnar cells with differentiation to chief and/or parietal cells[22,23]. It is more common in elderly people aged ≥ 60 years. Considering the benign biological behavior of this tumor, Singhi *et al*[24] proposed the term oxyntic gland adenoma/polyp, as it is usually confined to the mucosa with minimal infiltration of the submucosa and no reported lymphovascular invasion or metastasis. In the latest version of the classification of gastric neoplasms issued by the WHO, a neoplasm confined to the mucosa is called an oxyntic gland adenoma, while a neoplasm with submucosal invasion is classified as GAFG[25].

Oxyntic gland adenomas and GAFG are located in the upper third of the stomach (*i.e.*, fundus, cardia, and upper third of the body) and originate from a deeper area of the gastric mucosa[22-24]. Therefore, they may mimic fundic gland polyps or gastric neuroendocrine tumors (NETs) on endoscopy. The four most common endoscopic features of oxyntic gland adenoma/GAFG are a submucosal tumor shape, whitish color, dilated vessels with branch architecture, and background mucosa without atrophic changes[26]. However, immunohistochemical staining is essential for the differential diagnosis. A recent multicenter study from Japan has suggested that endoscopic resection using EMR or ESD is a suitable initial treatment strategy for oxyntic gland adenoma and GAFG without reported recurrence[27].

Gastric subepithelial tumors

Gastric subepithelial tumors (SETs) usually arise from the submucosa or muscularis propria (MP) and exhibit distinct EUS features (Table 1). EUS can be used to identify subepithelial lesions based on the originating layer, characteristic echo patterns, and echo levels. EUS with FNB can facilitate histological evaluation, especially for smaller lesions.

Gastrointestinal stromal tumor: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the GI tract. A recent systematic review of the global epidemiology of GISTs reported an incidence of 10-15 per million per year, with the highest incidence reported in China, Taiwan, and Norway[28]. GISTs appear as hypoechoic tumors of the fourth layer (MP), usually round on EUS (Figure 1A)[29]. EUS with FNB has a high yield of approximately 86% for the diagnosis of GISTs

Table 1 Endoscopic ultrasonography features of subepithelial tumors

Subepithelial tumor	Endoscopic ultrasound layer	Histological layer	Echogenicity	Shape	Other features
Gastrointestinal stromal tumor	4th	Muscularis propria	Hypo	Irregular or round	Heterogenous, marginal halo, cystic spaces, lymphadenopathy
Leiomyoma	2nd or 4th	Deep mucosa or muscularis propria	Hypo	Round	Homogenous, fine margins
Neuroendocrine tumor (carcinoid)	2nd	Deep mucosa	Hypo or iso	Round, sessile or polypoid	Erythematous depression or ulceration, smooth margin
Lipoma	3rd	Submucosa	Hyper	Round	Homogenous
Schwannoma	4th	Muscularis propria	Hypo	Round	Heterogenous, exophytic
Granular cell tumor	2nd	Deep mucosa	Hypo	Round	Homogenous, fine margins
Inflammatory fibroid polyp	2nd	Deep mucosa	Hypo	Irregular	Heterogenous, diffuse margins
Ectopic pancreas	2nd, 3rd or 4th	Depending on layer	Mixed	Irregular	Ductal structure, anechoic microcysts

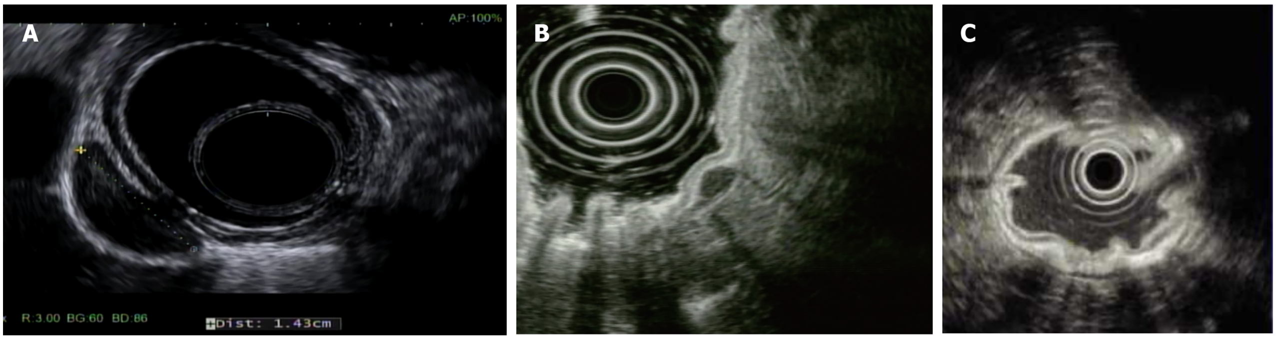

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Figure 1 Endoscopic ultrasound imaging. A: Gastric gastrointestinal stromal tumor. Hypoechoic mass with smooth margins originating from the muscularis propria; B: Gastric carcinoid. Small, round hypoechoic mass in the submucosa; C: T1 gastric cancer. The tumor invades the submucosa.

[30]. Although these are mostly benign tumors, tumor size and mitotic count are prognostic factors for malignancy potential. The National Comprehensive Cancer Network (NCCN) recommends the surgical resection of all GISTs ≥ 2 cm and symptomatic GISTS ≤ 2 cm[31]. In recent years, studies have shown that many SETs, including GISTs originating from the submucosa and even the MP, can be resected endoscopically using techniques such as ESD, submucosal tunneling endoscopic resection (STER), endoscopic full-thickness resection (EFTR), and endoscopic submucosal excavation (ESE) with admissible complication rates[32-36].

NETs: NETs account for 0.5% of all malignancies, with over half found in the GI tract (62%-70%)[37]. Carcinoid tumors, the most common type of NET, are primarily observed in the stomach and rectum. Its overall worldwide incidence has been increasing, likely due to improved diagnostic modalities and extensive use of acid-suppressive medications, leading to secondary hypergastrinemia, enterochromaffin-like cell hyperplasia, and ultimately neoplasia. They appear as small, round, sessile, or polypoid lesions on endoscopy. They also have dilated vessels, central depressions, or ulcerations. It is more common in women after their fifth decade of life. EUS shows hypo-or isoechoic lesions, originating from the third layer (submucosa) (Figure 1B). The NCCN recommends surveillance for tumors ≤ 20 mm in size and surgical resection for larger lesions[31]. The American Society for Gastrointestinal Endoscopy (ASGE) recommends endoscopic resection of types 1, 2, and 3 gastric carcinoids ≤ 1 cm and surgical removal of type 3 gastric carcinoids ≥ 1 cm and all type 4 carcinoids, regardless of size, given the high risk of lymph node invasion and metastasis. Although the optimal surveillance interval is not currently clear, some experts recommend endoscopic surveillance every 1-2 years post-resection[38].

Leiomyoma: Leiomyomas are usually benign tumors that arise from the muscularis mucosa or MP. EUS can be used to identify and distinguish them from other more sinister growths[29], particularly GISTs.

Schwannoma: The stomach is the most common location for gastrointestinal schwannomas. Schwannomas account for 0.2% of all gastric tumors[39]. They can be identified using computed tomography and contrast-enhanced harmonic EUS (CEH-EUS). These usually appear as exophytic, moderately homogenous, or heterogeneous enhancements on EUS[29].

Gastric lymphoma: Although the stomach is the most frequent site of gastrointestinal lymphoma, gastric lymphoma is a rare malignancy, accounting for only 3% of all gastric cancer cases. Gastric lymphoma may be primarily confined to the stomach and regional lymph nodes or secondary, as part of a systemic disease. More than 95% of gastric lymphomas are non-Hodgkin's lymphomas, mostly the B-cell type. Marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) is the most common form in Western populations, followed by diffuse large B-cell lymphomas. MALT lymphoma is usually a low-grade lymphoma that is strongly associated with *H. pylori* infection.

On endoscopy, gastric lymphomas present in a localized or diffuse pattern with a variety of appearances, ranging from ulcers (single or multiple), nodules, polypoid, exophytic masses, or submucosal tumors to diffuse or localized thickening of gastric folds or irregular cobblestone-type mucosa with or without ulcerations, most commonly involving the distal half of the stomach. Of note, standard superficial biopsies may not be diagnostic, therefore, deeper biopsies obtained by the endoscopic snare technique, mucosal resection, or jumbo forceps are often needed for a pathologic diagnosis due to frequent submucosal involvement. EUS is a part of the work-up for local tumor staging in which depth and regional lymph node infiltration are investigated using FNA, as needed. The accuracy of EUS for T-staging of gastric lymphoma was 59% in a prospective multicenter study[40]. Because the disease is frequently multifocal within the stomach, treated patients require endoscopic follow-up to identify local recurrences.

Precancerous conditions

Intestinal metaplasia and dysplasia: Correa *et al*[41] described the gastric cancer cascade as a series of changes from non-atrophic gastritis (AG) to AG, intestinal metaplasia (IM), dysplasia, and eventually adenocarcinoma. IM is a precancerous lesion of the stomach associated with *H. pylori* infection. If left unidentified or untreated, IM may transform into low-grade dysplasia, high-grade dysplasia (irreversible), and eventually carcinoma.

More recently, image-enhanced endoscopy and ME-NBI have shown higher diagnostic sensitivity than conventional WLE for the surveillance of IM[42,43]. The morphological appearance of dysplasia could be polyploid or flat, with a reddish or discolored mucosa. Japanese data suggests an overall 5-year cumulative gastric cancer incidence of 1.9%-10% in AG and 5.3%-9.8% in IM[44]. The risk of progression of low-grade dysplasia and high-grade dysplasia to gastric cancer in different populations is reportedly 2.8%-11.5% and 10%-68.8%, respectively; therefore, guidelines recommend endoscopic resection of a defined lesion with any degree of biopsy-proven dysplasia, especially considering a meta-analysis showing the upstaging of gastric low-grade dysplasia in 25% of lesions, with 7% being upstaged to malignant following endoscopic resection[45-49].

Consensus is lacking on the interval and methodology of surveillance for IM among societies, primarily due to the variation in gastric cancer prevalence with background genotypic and phenotypic differences among various geographical regions. In a significant study from the Netherlands, IM was integrated with the previously proposed histologic scoring system, Operative Link on Gastritis Assessment, to stage IM by replacing AG to create a more consistent and accurate staging system to estimate gastric cancer risk - Operative Link on Gastric Intestinal Metaplasia (OLGIM), because histological evaluation of atrophy is subject to poor inter-or intra-observer agreement[50]. The high-risk lesions showing significant IM in the antrum and corpus corresponding to stage III-IV have an odds ratio of 2.41 and 3.99 for gastric cancer. Accordingly, the ESGE recommends endoscopic surveillance with protocol biopsies taken from at least two topographic sites (lesser and greater curvature of the antrum and corpus) and labeled in two separate vials every 3 years for patients with IM and gastric adenocarcinoma at the gastric antrum and corpus (OLGIM stage III-IV)[14].

Patients with advanced AG and a family history of gastric cancer may benefit from more intensive follow-up (*e.g.,* every 1 - 2 years after diagnosis). The ESGE has also set out a weak recommendation of 3-5 years of endoscopic follow-up for autoimmune gastritis, which is a chronic progressive inflammatory condition leading to corpus-predominant AG, due to the lack of large cohort data. The JGES 2020 guidelines linked atrophy, IM, enlarged folds, and xanthomas to a risk of gastric cancer[13]. They recommend that nonspecific IM be diagnosed using image-enhanced endoscopy, particularly NBI, or confocal laser endomicroscopy (CLE).

On the other hand, the Japanese and Korean guidelines do not routinely recommend risk stratification using biopsy-proven gastric adenocarcinoma or IM because of its policy of screening endoscopy at 2-year intervals for all individuals aged ≥ 40 years because of the high prevalence of *H. pylori* infection and gastric cancer. However, they generally recommend 1-3-year intervals for endoscopic surveillance of IM, with preferably shorter intervals for the detection of endoscopically resectable EGC. In the United States, a country with a low incidence of gastric cancer, the ASGE and American Gastroenterological Association (AGA), recommend a surveillance strategy for high-risk patients that considers the risk factors (*i.e.*, complete *vs* incomplete IM, extensive *vs* limited IM, family history, immigration from endemic areas, ethnic minority race, and longstanding history of *H. pylori*)[51,52]. For high-risk patients with an incidental diagnosis of IM, a repeat endoscopy may be warranted within 1 year to determine the anatomic extent (gastric mapping), histologic subtype of IM, and possible high-risk stigmata such as nodularity. Overall, further population-based studies are needed to establish clear guidelines on this vague topic.

ADVANCES IN ENDOSCOPIC MANAGEMENT

Diagnostics

EUS: EUS is the most reliable non-surgical method for evaluating primary gastric tumor depth and invasion as part of loco-regional tumor staging. The ASGE recommends the use of EUS for locally staging gastric cancer[53]. The NCCN and European Society for Medical Oncology recommend pretreatment in all cases of non-metastatic gastric cancers[31,54]. CEH-EUS and elastography have improved the diagnostic performance of EUS. It can define SET size, layer of origin, margins, and echogenicity. Sakamoto *et al*[55] utilized CEH-EUS to evaluate GIST vascularity. It identified vascular irregularities and diagnosed GISTs with a sensitivity of 100%, specificity of 63%, and accuracy of 83%. Kim *et al*[56] utilized elastography with EUS to identify SETs. In this study, EUS elastography differentiated GISTs from leiomyomas with a sensitivity and specificity of 100% and 94.1%, respectively. EUS showed a 79% tumor staging accuracy in a case series of 126 patients with gastric cancer. For nodal staging, EUS has a sensitivity of 82.8% and specificity of 74.2%[57]. Dittler and Siewert[58] evaluated 254 patients with gastric adenocarcinoma using preoperative EUS. EUS was correct in determining the tumor (T) and nodal (N) stages in 83% and 66% of cases, respectively, compared with postoperative histopathological staging. Moreover, the actual complete resection rate (R0)(78%) was approximately equal to the preoperative rate predicted by EUS (81%).

Accurate assessments of gastric cancer depth and complete resection are directly related to patient prognosis and disease management. EUS helps evaluate otherwise operable diseases. This makes it a unique tool that increases physician confidence when planning a treatment course. However, the data are insufficient to recommend its routine use as part of the endoscopic work-up for EGC. Several reports have indicated the usefulness of EUS for determining EGC invasion depth, although other observational studies have not confirmed this[16,21,59-61]. Therefore, conventional WLE should be used to determine EGC invasion depth and EUS should be used as an auxiliary method for lesions diagnosed as cT1b on conventional endoscopy (Figure 1C)[16,18]. In addition, EUS is generally indicated for a suspicious lesion without a diagnosis by conventional biopsy.

Dye-based image-enhanced chromoendoscopy: The use of dye highlights differences in mucosal elevation, changes in surface structure and color, and lesion borders (demarcation line). WLE combined with indigo carmine chromoendoscopy has been widely used to determine the borders between cancerous and non-cancerous mucosa and the invasion extent of EGC. Identifying the horizontal lesion border before endoscopic resection increases the complete resection rate and reduces the local recurrence risk. Chromoendoscopy using indigo carmine more accurately estimated lesion borders in EGC than WLE (75.9% *vs* 50.0%), while chromoendoscopy using indigo carmine and acetic acid estimated lesion borders with a 90.7% accuracy[62]. A Korean study also reported that chromoendoscopy using indigo carmine and acetic acid more accurately estimated lesion borders in EGC than WLE (84.1% *vs* 66.9%)[63]. Sakai *et al*[64] examined 53 EGC lesions and gastric adenomas and compared the diagnostic performances of different endoscopic modalities. WLE had a performance rate of 17.0%, chromoendoscopy combined with indigo carmine dye was 52.8%, acetic acid was 41.5%, and indigo carmine dye added to acetic acid was 94.3%. They also showed that routine endoscopy missed 20 lesions of EGC. In a recent study of 104 patients, the diagnostic accuracies of WLE, indigo carmine, and acetic acid-indigo carmine mixture were 50%, 75.9%, and 90.7%, respectively[62]. However, indigo carmine chromoendoscopy reportedly fails to accurately diagnose the horizontal extent of invasion in approximately 20% of cases, even when modern high-resolution endoscopy is used to determine the circumferential borders of EGC[65-68]. Of note, Kang *et al*[69] showed that margin biopsy prior to ESD with onsite frozen histopathological examination of EGCs with obscure margins, despite chromoendoscopy using acetic acid and indigo carmine, enables significantly better prediction of lateral extent; therefore, frozen section biopsy can be used to perform more accurate ESD in these patients.

NBI and ME: NBI is a useful technique, particularly for evaluating vascularized lesions. NBI enhances blood vessels using green and blue light to aid in the identification of mucosal patterns and lesion margins that are otherwise difficult to detect using standard endoscopy. Dysplasia and EGC can present as subtle mucosal changes that can be missed on routine endoscopy. A recent multicenter randomized control trial showed that NBI improved mucosal surface contrast and increased the detection rate of EGC and dysplastic lesions[70]. Magnification of the fine mucosal patterns of the gastric pits aids the preliminary evaluation of suspected lesion. These findings were used in conjunction with the histological results to achieve a diagnosis.

ME can highlight patterns, such as coarse and irregular mucosa, in elevated-type cancers or a finer pattern in depressed-type cancers. It can also show changes to the vascular microstructure. A multicenter randomized controlled trial to distinguish between depressed gastric cancer and non-cancerous lesions measuring ≤ 1 cm reported that the accuracy rate of diagnosis, sensitivity, and specificity of ME-NBI for small depressed gastric lesions were 90.4%, 60.0%, and 94.3%, respectively, with the diagnostic accuracy and specificity rates being significantly better than those of WLE[71]. A recent meta-analysis also showed that the rate of presumptive diagnosis of small gastric cancers was significantly higher when ME was used than when conventional endoscopy was used. In this study, the sensitivity and specificity of ME as a diagnostic method were 96% and 95.5%, respectively[72]. In a prospective study, 165 patients with depressed-type EGCs were evaluated. These lesions were examined without magnification, magnification, or ME-NBI. The results showed that ME-NBI can predict the histological features of EGC[73]. Moreover, several studies have compared the accuracy of border prediction between ME-NBI and chromoendoscopy using indigo carmine, reporting the superiority of the former technique in estimating the horizontal borders of lesions more accurately than the latter[65-68]. Overall, both chromoendoscopy and image-enhanced endoscopy are recommended to determine the extent of resection before endoscopic resection of EGC. ME-NBI is reportedly useful for differentiating elevated lesions of gastric cancer from adenomas[74,75]. Other narrow-band light methods include blue laser imaging (BLI), linked color imaging (LCI), and i-scan optical enhancement. The BLI system involves two types of lasers with wavelengths of 410 and 450 nm as the light source and fluorescent light, respectively, which is useful for examining mucosal surface patterns. LCI is a color enhancement technology that provides slight color differences in mucosal color, which are easy to recognize with sufficient brightness compared to BLI. Randomized controlled trials for the detection of EGC using BLI and LCI are also underway. However, several studies have shown that magnifying BLI endoscopy is useful for the qualitative diagnosis of EGC similar to magnifying NBI endoscopy[76,77].

CLE: CLE is a combination of endoscopy and electron microscopy for immediate tissue and vessel analysis during ongoing endoscopy. CLE has been studied in several upper and lower GI tract diseases, including Barrett's esophagus, gastric cancers, celiac disease, and colorectal adenoma and carcinoma [78]. This enables the endoscopist to obtain real-time *in vivo* magnification of the tissue in question and leads to targeted sampling. Two approved versions are currently available. One was incorporated into the distal tip of a high-resolution endoscope, while the other was a standalone probe introduced *via* the instrument channel during endoscopy. The probe was placed in contact with the mucosa, and the tissue in question was magnified 1000-fold[79]. Visual analysis of microarchitecture and subsurface imaging is a powerful diagnostic tool. Several studies demonstrated that CLE successfully distinguished between normal and regenerative or neoplastic tissues[80,81]. CLE has a sensitivity of 98% for the diagnosis of GIM[82]. Its sensitivity of diagnosing gastric dysplasia is 89%, while that for EGC is 91%[83,84]. In a recent study by Jeon *et al*[85], the accuracy of CLE diagnosis was compared with that of ESD biopsy and histopathology. The results showed a higher diagnostic accuracy of CLE *vs* traditional biopsy for EGC. This may help reduce the need for unnecessary interventions and invasive procedures.

AI: Gastric cancer diagnosis is largely dependent on the clinical expertise of endoscopists, radiologists, and pathologists. The miss rate of gastric cancer by EGD can be as high as 25.8%, depending on the experience of endoscopists[86-88]. The use of AI eliminates 'human errors' and can help identify lesions that can be missed by the human eye. AI has been used for the diagnosis, screening, and surveillance of gastric cancer. AI utilizes computer algorithms known as machine learning and deep learning on convolutional neural network (CNN) and computer-aided diagnosis, which range from automatically identifying endoscopic images of gastric cancers to analyzing pathological images with remarkable accuracy. This self-learning computer-cognition is now being used to identify precancerous conditions, such as AG[89], and detect EGC[90,91], and working cooperatively with ME-NBI[92,93]. AI-assisted CNN computer-aided diagnostic systems help endoscopists detect and confirm WLE and chromoendoscopic characteristics of gastric cancer, reduce diagnostic error rates, and choose optimal treatment. Moreover, a recent study from Japan showed that AI has reached even higher sensitivity than experts with similar specificity detecting EGC[94]. Several studies have highlighted the role of AI in recognizing the depth of invasion of EGC using CNN-based models[95-97]. Notably, Ling *et al*[96] showed that their CNN-based AI model outperformed endoscopists in assessing the depth of invasion. Zhu *et al*[98] developed an algorithm to differentiate between submucosal lesions < 500 μm (Sm^1) and > 500 μm (Sm^2) . AI has a sensitivity of 76% and specificity of 96% in identifying lesions that can otherwise be missed on visual inspection. AI also assists pathologists with whole-slide imaging[99], identification of tumor-infiltrating lymphocytes[100], and computer-assisted identification of gastric tumors[101]. Overall, AI works like a peripheral brain that increases the diagnostic accuracy of EGC and is valuable even to the most experienced endoscopist and pathologist.

Resection

EMR: Rosenberg first reported using EMR for rectal and sigmoid polyp resections[102]. It has become an effective method for removing precancerous and cancerous lesions from the GI tract. EGC (1-2 cm in size) without risk of lymph node metastases can be successfully managed using EMR[103]. Different techniques are used for EMR. Injection-assisted EMR and lift-assisted polypectomy were first introduced in 1955 for rigid sigmoidoscopy. Normal saline (NS) solution was injected into the submucosal space to create a cushion, and the lesion was resected using a snare.

Multiple submucosal injection solutions are available on the market that provide long-lasting cushion *vs* NS. Hyaluronic acid (0.13%-0.4%) is most commonly used in the East, such as Japan and South Korea, and has the longest duration, making it more advantageous, especially for ESD, despite its high expense. Hydroxypropyl methyl cellulose (0.3%-0.8%), succinylated gelatin, glycerol, and hydroxyethyl starch (6% in NS) are other less expensive options with a shorter duration. In addition, the United States Food and Drug Administration approved pre-filled, pre-dyed, ready-to-use syringe Eleview (Cosmo Pharmaceuticals, NV, United States) and newly released EndoClot SIS (EndoClot Plus Inc., CA, United States) which is a starch-based powder of absorbable modified polymer distributed by Olympus are commercially available in the United States, offering a long cushion duration but at high cost. Another commonly used pre-filled syringe, Orise gel (Boston Scientific, MA, United States), has recently been recalled from the market due to higher incidence of adverse events of foreign body granulomatous reactions.

Cap-assisted EMR also begins with a submucosal injection. A specialized endoscope with a prefixed cap at the tip is positioned over the lesion, and the lifted mucosa is suctioned into the cap, after which it is resected using standard snare excision and electrocautery. Ligation-assisted EMR can be performed with or without a submucosal injection. The target lesion is suctioned into a banding cap, and a band is deployed at the base of the lesion to create a pseudopolyp. This pseudopolyp is then resected with an electrocautery snare.

Another useful technique, especially for patients undergoing repeat gastric EMR or who underwent previous partial resections, biopsies, or recurrent EGC, is underwater EMR[104]. Conventional EMR is difficult to perform for such lesions because severe submucosal fibrosis prevents mucosal lifting during submucosal injection. In this technique, the GI lumen is suctioned, and air is removed; it is then filled with water or NS to immerse the target lesion. This raises the target lesion, including the mucosa and submucosa, from deeper layers without requiring a submucosal injection[105]. There are several benefits of this method, such as facilitating the capture of flat lesions and eliminating the possible risk of seeding neoplastic cells into deeper layers and the peritoneum.

The intraprocedural bleeding rate during gastric EMR ranges from 0% to 11.5%, and it can be managed using standard endoscopic hemostasis techniques[106,107]. Delayed bleeding after gastric EMR occurs in approximately 5% of cases, with intraprocedural bleeding being the best predictor of delayed bleeding[108]. According to a systematic review, the risk of perforation due to gastric EMR was 1%[109]. The main disadvantage of EMR techniques is lesion size, which precludes *en bloc* resection. *En bloc* resection by EMR is limited to lesions less than 20 mm, and piecemeal EMR performed for larger lesions carries a higher risk of local recurrence and problems in the accurate evaluation of tumor depth by pathologists. Therefore, a thorough evaluation of lesions for submucosal invasion is of paramount importance in addition to the use of ESD *vs* EMR if invasion is identified.

ESD: ESD was developed for *en bloc* resection of EGC with lesions greater than 20 mm in size. First described in 1988 by Hirao *et al*[110] for the resection of EGC, ESD gained popularity in Japan in the 1990s due to the high prevalence of gastric cancer and avoidance of gastrectomy due to its complications and decreased postoperative quality of life. In a multicenter retrospective study by Oda *et al*[111] that evaluated the results of EMR and ESD for EGC, ESD was superior to EMR in terms of major outcomes. For 714 lesions, the *en bloc* resection rate was significantly higher with ESD than with EMR (92.7% *vs* 56%). Similarly, the complete resection rate was significantly higher with ESD (73.6%) *vs* EMR (61.1%). The 3-year residual/recurrence-free rate was also significantly higher in the ESD group (97.6%) than the EMR group (92.5%). However, the incidence of perforation was significantly more common than that with EMR (3.6% *vs* 1.2%). In addition, the longer procedure time associated with gastric ESD *vs* EMR makes the latter more attractive for patients with significant comorbid conditions.

The most recent (2nd edition) guidelines of the JGES, in collaboration with the Japanese Gastric Cancer Association for ESD for EGC, defined absolute indications for endoscopic therapy for lesions that are considered to have less than 1% risk of lymph node metastasis and long-term outcomes similar to those of surgical gastrectomy[13]. Accordingly, the absolute indications include lesions that are: (1) cT1a (clinically intramucosal) differentiated-type carcinomas with a long diameter greater than 2 cm and no ulcer; (2) cT1a differentiated-type carcinomas with a long diameter measuring 3 cm or less and an ulcer; and (3) cT1a undifferentiated-type carcinomas with a long diameter of 2 cm or less.

Previously recommended expanded indications have been integrated into absolute indications for ESD in recent guidelines based on the results of multicenter prospective studies. Thus, only lesions that can be considered as expanded indications for ESD are those differentiated-type absolute indication lesions that locally recur as intramucosal cancer after initial ESD/EMR, as they were either not resected *en bloc* or had a positive horizontal margin. They recommended surveillance endoscopy 6 mo after complete resection of EGC by ESD[112]. The AGA 2021 guidelines also advise a repeat exam during the first year. If unremarkable, repeat endoscopy can be performed on an annual basis[113]. The indications for ESD have expanded in later years for the treatment of gastric SETs, which were conventionally resected surgically. A growing body of evidence suggests that ESD is a feasible, effective, and relatively safe method with the potential to preserve the stomach with a less invasive nature, and reduced cost compared to surgical resection for gastric SETs[114-118].

The growth pattern of SET is an important predictor of complete resection and risk of perforation. Intramural and subserosa (extraluminal) SETs are more likely to be incompletely resected. In contrast, the complete resection rates of tumors originating from the submucosal layer were significantly higher than those of tumors originating from the MP[33]. Some studies suggested that a tumor size ≥ 2 cm and tumor location in the upper third of the stomach as predictors of incomplete resection[115,118]. However, a large Chinese study reported a high *en bloc* complete resection rate of ESD (92.4%) with no recurrence during follow-up for gastric SETs originating in the MP with diameters of up to 5 cm[119]. Major complications include perforation, which is more often seen with tumors of the MP, and bleeding, which can be managed endoscopically in most cases[33,119].

The success rate of endoscopic treatment is considerably affected by gastric SET location and is technically more challenging with significantly higher perforation risk in the retroflexion position for those located at the fundus and high gastric body[120,121]. Of note, intramural-type schwannomas, which are the most common gastric schwannomas, have been reported to be difficult to resect from the MP because they are not encapsulated, in contrast to soft tissue schwannomas; therefore, perforation occurs more frequently[120]. ESD has evolved significantly with the development of new tools and techniques and has become a more common practice now in the West. The most commonly used endoscopic knives for gastric ESD are listed in Table 2.

Modified ESD techniques such as ESE and, more recently, the pocket creation method (PCM) and the tunneling technique, which will be detailed below, using the principles of third space or intramural endoscopy have been applied to improve outcomes of ESD for endoscopic resection of SETs. The major difference between ESD and ESE procedures is the endoscopic resection depth. As deep excavation is necessary during ESE, the use of an insulated-tip knife, such as an IT knife2 or TT knife, is usually recommended during excavation to avoid or reduce thermal injury. Several studies have demonstrated the efficacy of ESE for gastric GISTs, with a favorable complete resection rate and low recurrence rate, but at the expense of a higher perforation rate of up to 50%[119,120]. The PCM technique utilizes a minimal incision instead of a traditional circumferential mucosal incision. This further improves outcomes, reduces the risk of submucosal fibrosis, and decreases perforation rates[122].

Tumors located in the lesser curvature, posterior or anterior wall of the gastric body, or cardia are technically challenging to approach and resect. A multibanding, two-channel scope with two independent bending segments has been developed, which enables safer and faster ESD for EGC localized to difficult sites[123]. The distal flexible segment can bend in any of the four major directions, and the proximal flexible segment can bend in two directions, providing a closer approach to the lesion with a favorable angle to facilitate endoscopic dissection.

Two reports recently demonstrated that underwater ESD (U-ESD) is a promising novel gastric ESD method. Yoshii *et al*[124] reported using the first gastric U-ESD procedure to facilitate *en bloc* resection of a challenging EGC located on the greater curvature of the gastric body. Another comparative study on EGC and gastric adenoma showed that U-ESD had shorter procedural times (27.5 *vs* 41 min, $P < 0.001$) than and similar *en bloc* resection rates (97.9% *vs* 95.8%, $P > 0.99$) to standard ESD[125]. However, U-ESD was used with the PCM and compared to standard ESD; therefore, it is unclear whether the benefits could be attributed to the underwater technique, PCM, or their combined use. The advantages of U-ESD are twofold. First, during standard ESD, the borderline between air and water obstructs the visual field, while during U-ESD, enhanced visualization of the submucosal space can be achieved by the obliteration of any gas/fluid interface within the distal attachment and maintaining a clear view of the lumen with transparent NS solution. Second, U-ESD leverages the "buoyancy effect". In standard ESD, the patient's position is changed to facilitate lifting of the mucosal flap using gravity, which may be difficult for the lesions located on the greater curvature of the gastric body. In contrast, with the U-ESD technique, creation of the mucosal flap is assisted by buoyancy (Figure 2). Further comparative studies are required to confirm the advantages of U-ESD over standard ESD techniques.

Bleeding is a common complication associated with ESD. The risk of immediate and delayed bleeding associated with gastric ESD is reportedly 22% and 4.5%-5.5%, respectively[109,126,127]. Intraprocedural bleeding interferes with precise endoscopic resection by obstructing the operating field, which can lead to longer procedure times or increased perforation frequencies. Different types of lasers have been used for surgery owing to their precise excision capability and reduced risk of bleeding. In recent years, to mitigate the risk of bleeding and perforation, the feasibility of laser systems such as CO_2 laser[128,129], Nd:YAG laser[130], thulium laser[131], and diode laser[132,133] has been evaluated for upper and lower gastrointestinal ESD in several animal and human studies. Cho *et al*[131] reported a very high technical success rate, with a 100% *en bloc* resection rate and 90% complete resection rate for EGC in a human study using a thulium laser. Moreover, there were no cases of active intraprocedural or delayed bleeding or perforation with minimal or no thermal injury to the MP with adjustment of power and wavelength and use of a submucosal injection to limit ablation to the superficial layers. However,

Table 2 Common endoscopic knives used for gastric endoscopic submucosal dissection

Endo knife type	Name (manufacturer)	Advantages	Disadvantages
Insulated tip knife	IT knife (Olympus, Tokyo, Japan)	Less risk of muscle layer injury and perforation due to ceramic insulated tip, more suitable for submucosal dissection. Can be used for hemostasis	Cannot be used for marking, precutting or injection. More difficult to maneuver. Pull-cut limits direction of incision. Cutting performance tends to deteriorate in cases with severe fibrosis such as ulcer scars. Lateral cutting is difficult as the ceramic tip at the distal end catches in the mucosa. Laying the knife down too much increases the risk of perforation
	IT knife 2 (Olympus, Tokyo, Japan)	Improved incision and cutting performance in lateral cutting and fibrotic tissue with three blades attached to the back of the insulated ceramic tip. Faster incision and cutting, shorter operating time compared to IT knife. Safer than dual knife for beginners	Needle knife for marking, precutting and injection. Difficult to manipulate in cardia and greater curvature of upper body. Sharper than IT knife which may increase the risk of perforation if firm pressure or too much downward angle is used. Needs more gentle manipulation than IT knife
Needle knife	Dual knife (Olympus, Tokyo, Japan)	Easy to maneuver. Can be used for all steps of ESD: Marking, injection, incision, dissection and hemostasis. Offers more precise fine incision with better cutting performance on fibrotic tissue and ulcer scar	Higher risk of perforation when dissecting close to the muscularis propria, especially since the tip of the electrode is exposed (not insulated)
Scissor knife	SB knife (Sumitomo Bakelite, Tokyo, Japan)	External insulation, curved blades to protect muscle layer with reduced risk of perforation for gastric lesions. Superior safety profile. Rotatable to adjust cutting line. Useful to cut the fibrotic tissue. Sufficient coagulation before incision to minimize bleeding. Suitable for trainees	Cannot control severe bleeding. Discontinuous cutting
	Clutch cutter (Fujifilm, Japan)	Scissor-type knife similar to SB knife. More secure incision. Serrated cutting edge enables more efficient bleeding control than SB knife. Better self-completion rates and shorter procedure times for gastric ESD by nonexperts than IT2, probably due to hemostatic efficacy	Thicker than SB knife, cannot make a sharp mucosal incision as SB knife
Waterjet knife	Hybrid knife (Erbe, Germany)	Waterjet knife with needleless injection. Multi-function probe, can be used for all steps of ESD. Shorter procedure time compared to non-waterjet knives. Lower risk of bleeding by water cushion. Three types with different functionalities	Requires ERBEJET® 2 hydro surgery system. More costly
RFA knife	Speedboat (Creo Medical, United Kingdom)	Multi-function probe, integrated injection needle, able to complete the entire procedure with a single instrument. Only bipolar RFA knife in the market, no grounding needed. RF cutting with lower voltage and minimal bleeding. Microwave coagulation with possibly lower rates of post polypectomy syndrome. Potentially faster procedure	Requires therapeutic scope with at least 3.7 mm accessory channel

ESD: Endoscopic submucosal dissection.

further human studies are required to optimize the settings and compare laser ESD with conventional electrosurgical knives.

STER: Third space endoscopy is a unique concept that involves the mucosal flap valve principle with creation of a tunnel in the submucosal layer. Deeper layers of the GI tract are accessed by a proximally placed mucosal incision. Desired interventions such as myotomy and tumor resection can then be performed, followed by endoscopic closure of the mucosal incision using clips or sutures[134]. This methodology was first described for the treatment of achalasia cardia using peroral endoscopic myotomy 12 years ago. It has since rapidly evolved, and several new procedures such as STER, gastric and Zenker peroral endoscopic myotomy, and recanalization for complete esophageal obstruction are now being performed.

SETs with malignant potential such as GISTs and NETs can be endoscopically removed using STER. First, a 2-cm longitudinal mucosal incision is made 3-5 cm from the proximal margin of the lesion after submucosal injection and lifting, and a submucosal tunnel is created between the mucosal and MP layers by repetitive lifting and dissection to allow the endoscope to advance inside the tunnel. Then, meticulous dissection is performed with an endoknife until the tumor is completely exposed and resected. Finally, the mucosal incision is closed using endoclips (Figure 3). This is a safer technique than standard ESD with a very low risk for full-thickness perforation as the overlying mucosa of the SET is untouched, and the defects in the muscle and mucosa are at different locations[34,135]. However, STER has its limitations, with technical difficulties encountered at certain anatomic positions, such as the gastric fundus or lesser curvature. For malignant or premalignant lesions, complete resection margins

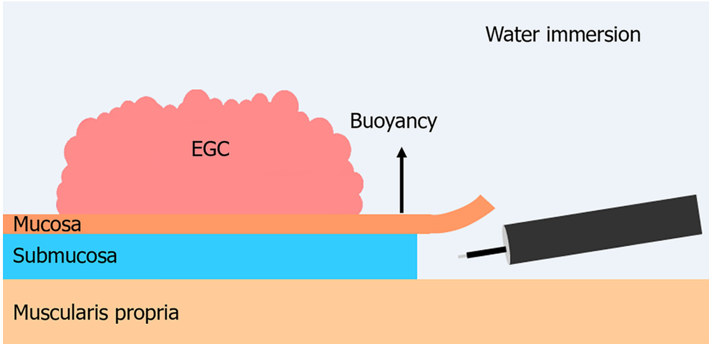

Figure 2 Underwater endoscopic submucosal dissection technique. EGC: Early gastric cancer.

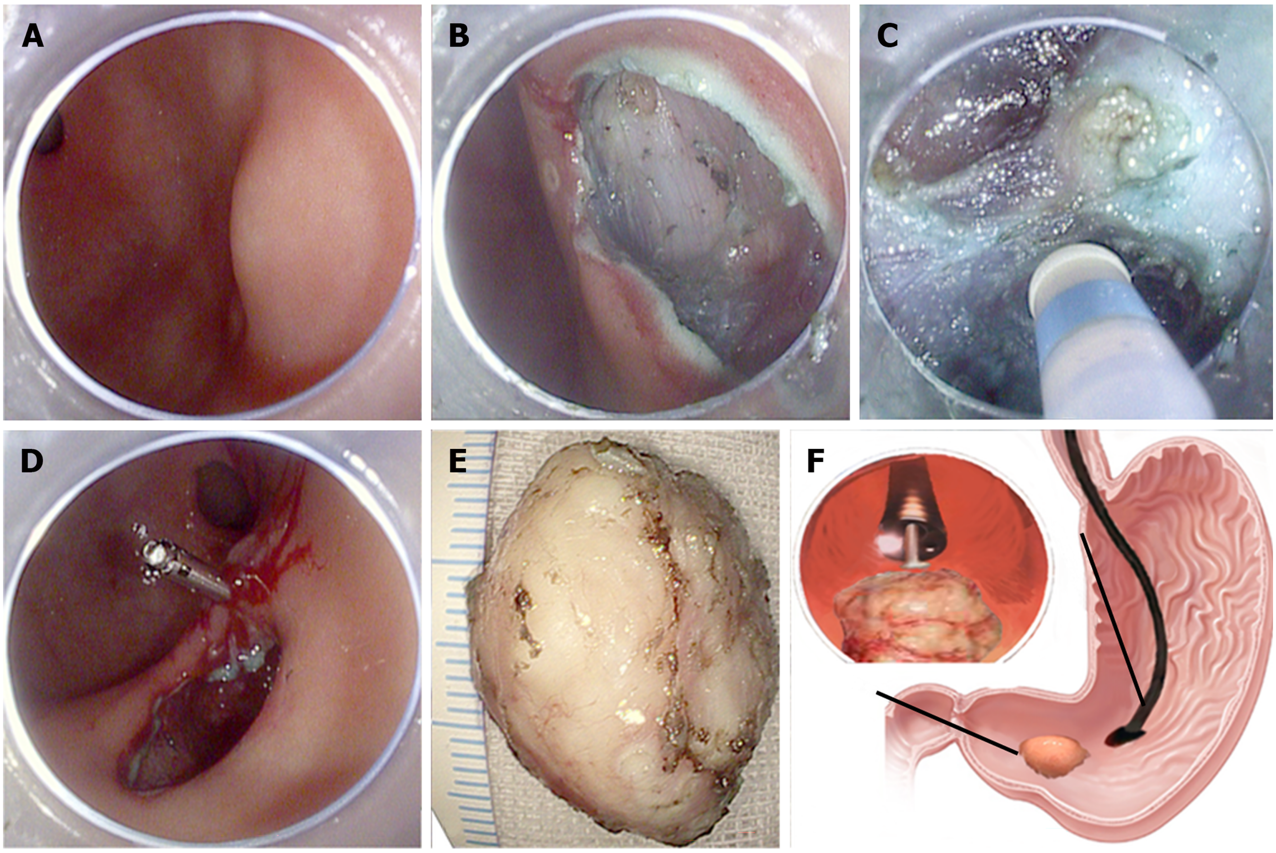

Figure 3 Submucosal tunneling endoscopic resection of a gastric subepithelial tumor located in the antrum. A: A gastric subepithelial tumor located in the antrum; B: A longitudinal mucosal incision was made about 3 cm from targeted tumor after submucosal injection; C: The tumor was gradually exposed by endoscopic dissection in the submucosal tunnel; D: After tumor resection and retrieval, the submucosal tunnel was closed by metal clips; E: The resected submucosal tumor; F: Schematic picture of the procedure; upper left picture showing the endoscope approaching the tumor in the tunnel for dissection. A-F: Citation: Lu J, Jiao T, Li Y, Liu Y, Wang Y, Wang Y, Zheng M, Lu X. Heading toward the right direction-solution package for endoscopic submucosal tunneling resection in the stomach. PLoS One 2015; 10: e0119870. Copyright© The Authors 2014. Published by PLOS. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited (available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0119870).

can also be challenging for STER. EFTR is used to address this issue.

EFTR: Although EMR and ESD are established procedures for endoscopic resection of larger lesions, both have limitations that make EFTR a viable alternative. EFTR can be classified as “exposed” or “nonexposed” indictive of an intentional perforation in the GI tract lumen to the peritoneal cavity. Exposed EFTR in the stomach can be performed using a tunneled or non-tunneled approach, with subsequent closure of the defect. The defects or perforations can be closed using over-the-scope clips (OTSC) or an endoscopic suturing device (Apollo suturing device). Nonexposed EFTR relies on pre-resection apposition of the serosa to prevent full-thickness perforation[136]. An important aid to EFTR is the full-thickness resection device (FTRD), which combines resection and closure using a full-thickness OTSC in a single device. In this procedure, the lesion is grasped and pulled into a transparent hood, followed by the application of a clip to its base and resection above the clip using the inbuilt snare (Figure 4). Although FTRD is indicated for the resection of lesions ≤ 25 mm in the stomach and duodenum, the resection size for SETs is limited by the 12.1-mm inner cap diameter. Moreover, insertion of the Ovesco FTRD requires a scope with a larger accessory channel (at least 3.7 mm) and assistance with a stiff guidewire to pass an enclosed insertion balloon to dilate the esophagus and pylorus to compensate for the FTRD cap diameter. The positive outcomes of EFTR for gastric lesions include high technical success, complete resection rates, low recurrence, and adverse events[137]. EFTR has been especially useful in the management of gastric SETs, including GISTs, NETs, leiomyomas, adenomas, and EGCs with submucosal invasion. EFTR allows definite histological diagnosis, including risk stratification, in cases of GIST or NET, as opposed to conventional biopsy. Complete resection is possible in most cases and may obviate the need for further surveillance endoscopies in selected patients[138,139].

Lee *et al*[140] recently reported a new method called mechanical spray lumpectomy as a modified technique for EFTR to remove gastric SETs originating from the MP layer. In this method, mucosectomy is first performed using a standard snare, followed by repeated injections in the subserosal layer. The lesion is then mechanically pushed to separate the MP from the serosa using an endoscopic cap. Finally, the SET with the MP is completely dissected using the spray coagulation mode, and the defect is closed by clipping. The study showed a 100% *en bloc* resection rate and only one small perforation among 13 cases, which was successfully closed using hemostatic clips with no serious intra- or post-operative complications. Although this was a small study, its results are promising regarding its feasibility and safety[140]. Comparative studies are required to reveal which EFTR method might work better for individual cases, considering different variables, including lesion size and location.

Ablation

Argon plasma coagulation (APC) is an established measure of tissue coagulation. APC is effective at treating EGC in patients who cannot undergo EMR or surgery. In a retrospective pilot study, Kitamura *et al*[141] showed that intestinal-type intramucosal carcinoma was successfully eradicated after one or two APC sessions. The more resistant types were locally controlled by follow-up APC sessions.

Palliation

Gastric outlet obstruction is a debilitating sequela of gastric, duodenal, and pancreatobiliary malignancies. Gastrojejunostomy is usually the traditional treatment; however, it is an extensive surgical procedure with high morbidity rates. EUS-guided gastrojejunostomy with placement of a lumen-apposing metal stent is now an accepted alternative to invasive surgery[142]. Endoscopically-placed self-expandable metallic stents are an excellent alternative. A meta-analysis analyzed the outcomes of 307 procedures from nine studies. Endoscopic stenting was associated with higher clinical success (P = 0.007), a shorter time from the procedure to starting oral intake (P < 0.001), lower morbidity (P = 0.02), a lower incidence of delayed gastric emptying (P = 0.002), and a shorter hospital stay (P < 0.001) than surgical gastroenterostomy[143].

CONCLUSION

Gastrointestinal endo-surgery is the future of advanced and minimally invasive flexible endoscopic procedures. Like any other cancer, the most important prognostic factors for SETs and EGC are timely detection and early treatment. Sophisticated endoscopic procedures are assisting gastroenterologists to detect early changes in the gastrointestinal tract and identify malicious lesions on time. Endoscopic ultrasound, AI, chromoendoscopy, and image-enhanced endoscopy improve diagnostic precision. More refined guidelines for the endoscopic surveillance of premalignant gastric lesions are required. Minimally invasive procedures help remove gastric neoplasms at an early stage. Interventions such as EMR and ESD are becoming a standard practice universally with the addition of new tools and accessories to the armamentarium alongside novel methods. Comparative studies are required to determine the optimal method and tool for the endoscopic treatment of a variety of gastric neoplasms. There is still scope to incorporate palliative measures for the benefit of gastric cancer patients, as they are being used for other GI malignancies.

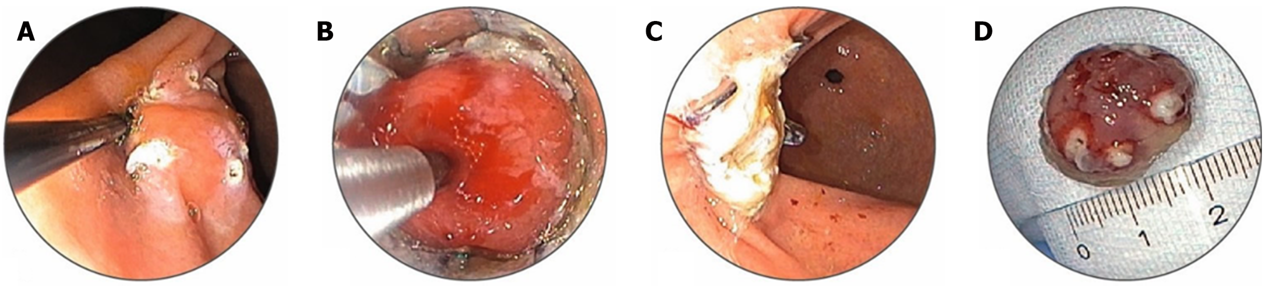

Figure 4 Endoscopic full-thickness resection of a gastrointestinal stromal tumor in the stomach with full-thickness resection device. A: Marking of the lesion with full-thickness resection device marking probe; B: Pulling and fixing the lesion in the cap with anchor to ensure the entire lesion is in the cap. Of note, no suction is used at this step. Clip is deployed before resection; C: Resection site with deployed clip; D: Retrieved lesion, a 2 cm gastrointestinal stromal tumor. A-D: Citation: Ovesco Endoscopy United States Inc (Supplementary material).

FOOTNOTES

Author contributions: All authors contributed equally to the following: (1) Substantial contributions to conception and design of the study, and acquisition, analysis, and interpretation of the data; (2) Drafting the article and making critical revisions related to important intellectual content of the manuscript; and (3) Final approval of the version of the article to be published.

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Country/Territory of origin: United States

ORCID number: Hira Imad Cheema 0000-0001-8925-1559; Sumant Inamdar 0000-0002-1002-2823; Mauricio Garcia-Saenz-de-Sicilia 0000-0003-0886-5175; Cem Cengiz 0000-0003-3233-8041.

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REVIEW

Unlocking quality in endoscopic mucosal resection

Eoin Keating, Jan Leyden, Donal B O'Connor, Conor Lahiff

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Eoin Keating, Jan Leyden, Conor Lahiff, Department of Gastroenterology, Mater Misericordiae University Hospital, Dublin 7, Ireland

Eoin Keating, Jan Leyden, Conor Lahiff, School of Medicine, University College Dublin, Dublin 4, Ireland

Donal B O'Connor, Department of Surgery, Tallaght University Hospital, Dublin 24, Ireland

Donal B O'Connor, School of Medicine, Trinity College Dublin, Dublin 2, Ireland

Corresponding author: Eoin Keating, MBChB, MRCPI, Doctor, Department of Gastroenterology, Mater Misericordiae University Hospital, Eccles Street, Dublin 7, Ireland. eoinkeating@mater.ie

Abstract

A review of the development of the key performance metrics of endoscopic mucosal resection (EMR), learning from the experience of the establishment of widespread colonoscopy quality measurements. Potential future performance markers for both colonoscopy and EMR are also evaluated to ensure continued high quality performance is maintained with a focus service framework and predictors of patient outcome.

Key Words: Endoscopic mucosal resection; Colonoscopy; Quality in endoscopy; Advanced therapeutic endoscopy; Large non pedunculated colorectal polyps; Key performance indicators

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Core Tip: Colonoscopy quality and key performance indicators (KPIs) are a mainstay of endoscopy practice. Adherence to colonoscopy KPIs is important for trainees and consultant endoscopists and is closely linked to patient outcomes. High quality colonoscopy often yields complex polyps, the management of which is now primarily endoscopic. Endoscopic resection of complex polyps thus requires similar scrutiny to diagnostic colonoscopy, to ensure consistent standards are applied. In this review, we discuss existing colonoscopy quality indicators, evaluate some potential new markers and the evidence base for KPIs in the management of complex polyps.

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INTRODUCTION

Colonoscopy has proven benefit in screening for colorectal cancer and pre-malignant polyps, as well as utility in symptomatic populations for the detection and management of significant non-malignant pathologies[1,2]. Providing access to high-quality colonoscopy is an ongoing challenge for health services internationally. Ensuring that colonoscopy is performed to an acceptable standard requires an open framework of assessment of service and endoscopist performance as well as feedback mechanisms and training supports to improve quality.

International guidelines recommend a range of key performance indicators (KPIs) for colonoscopy which are evidence based and aim to quality assure and standardise the delivery of colonoscopy to patients. Technological advances as well as adoption of KPI standards have resulted in consistent improvements in colonoscopy quality over time[3,4].

While quality assurance in colonoscopy has become part of routine clinical care and service development, equivalent quality assurance standards in therapeutic procedures have yet to be achieved. These procedures carry significantly increased risk of complications compared to diagnostic endoscopy.

The specialised field of Endoscopic Mucosal Resection (EMR) has developed to allow safe management of complex or large non-pedunculated colorectal polyps (LNPCPs), which traditionally required surgery. Originally pioneered by Japanese endoscopists in the 1990s to facilitate resection of early gastric cancers[5], EMR was subsequently demonstrated to be effective in all areas of the gastrointestinal tract. An initial review on the efficacy of EMR in all areas of the gastrointestinal tract was conducted by the American Society for Gastrointestinal Endoscopy (ASGE) in 2008, followed by a second technical analysis in 2015[6,7]. The British Society of Gastroenterology (BSG) also produced an initial guideline in 2015 to assess colonic EMR performance in Western populations and was the first to establish recommended key performance indicators to assess EMR practitioners[8]. This was followed by European Society of Gastrointestinal Endoscopy (ESGE) recommendations in 2017, which included a framework for referral practices, equipment and peri-procedural management, in addition to strategies to improve performance, minimise complications and reduce the risk of recurrence for LNPCPs[9].

Quality assurance for EMR remains a challenge in day-to-day practice and the organisation of services in most settings has yet to allow for a robust framework to develop in a similar manner to diagnostic colonoscopy. In this article we will review the evidence for established and aspirational colonoscopy KPIs as well as discussing quality assurance metrics for endoscopic resection of LNPCPs, and training considerations.

CURRENT QUALITY INDICATORS IN COLONOSCOPY

Caecal intubation rate

Successful colonoscopic evaluation for colorectal pathology must adequately survey all anatomical areas of the colon. As the anatomical endpoint of the colon, intubation of the caecum confirms that the colonoscope has successfully traversed the remainder the colon. Caecal intubation has been demonstrated to significantly affect the detection of proximal colorectal cancers[10,11].

Current guidelines recommend a minimum caecal intubation rate (CIR) of greater than 90% for all intended full colonoscopies with an aspirational target of greater than 95%[12-14]. Caecal intubation is confirmed with the identification of the anatomical landmarks of the appendiceal orifice, tri-radiate fold and ileo-caecal valve. Photographic or video recording of these landmarks should be completed to document caecal intubation. Higher quality caecal landmark photographs, associated with higher quality endoscopy, have also been shown to have a higher polyp detection rate[15,16].

Adenoma detection rate

The adenoma detection rate (ADR) is defined as the proportion of patients where at least one adenoma is found among all patients examined by an endoscopist[14]. Higher ADR has an inverse relationship with interval colorectal cancer development[4,17]. ADR has thus been proposed as an important quality indicator for mucosal inspection[18].

While previous BSG guidelines had suggested a minimum ADR of 15% with an aspirational goal of 20%, the most recent 2021 American Gastroenterological Association (AGA) guidelines have suggested a target minimum ADR of 30% with an aspirational target of 35%[12,13]. Similar ESGE guidelines have offered a minimum ADR target of 25%[14]. ADR amongst endoscopists is known to vary significantly with reported overall adenoma miss rates of 17% to 26%[19-22]. Corley *et al*[17] demonstrated that achieving a 1% improvement in ADR correlates with a 3% decrease in the risk of post colonoscopy colorectal cancer. Therefore, strategies to even marginally improve ADR, particularly amongst endoscopists with lower ADRs, can potentially yield the greatest benefit for patients.

Adenoma rates are recognised to vary depending on patient demographics such as age and indication for colonoscopy[23]. Increasing age is consistently associated with increased adenoma occurrence, across all ethnicities, demonstrated in studies of black, Caucasian, Middle Eastern and Asian populations[23-26]. However adjustment to target ADRs is not generally required, but may be factored in to post-hoc reviews of endoscopist performance should this KPI fall short on an individual basis[27].

A concern has been raised at the potential for endoscopist manipulation of the binary mechanic of ADR through a "one and done" approach[28]. However, the prevalence of such behaviour was found to be infrequent and did not require a change to measuring ADR as a quality assurance indicator[29]. Suggested alternative quality metrics such as adenoma per colonoscopy (APC), have been considered to improve reliability[30-33] and are reported in parallel with ADR routinely in endoscopic trials.

Bowel preparation

To confidently assess the bowel mucosa, adequate bowel cleansing is required. Polyethylene Glycol is the bowel cleansing regimen most commonly prescribed, formulated into a high (> 3 L) or low (< 3 L) volumes depending on patient factors such as fluid balance restrictions. Suboptimal bowel preparation is associated with lower ADRs and increased hospital costs[34,35]. Published rates of inadequate bowel preparation for colonoscopy approach 25%[36]. The causes of poor bowel preparation are multifactorial and include age, educational level and sex, in addition to hospital inpatient colonoscopies[37]. Adequate bowel preparation, defined as the ability of an endoscopist to detect adenomas > 5 mm in size[38], requires patient understanding of and adherence to strict dietary and medication regimens for up to 24 hours prior to a colonoscopy. Timing of procedures to align with bowel preparation is another factor with same-day administration encouraged and colonoscopies ideally scheduled not more than 5 hours after commencement of the final sachet of preparation.

Strategies to improve dietary compliance, encourage patient education and medication tolerance have been trialled, leading to ESGE guidelines on recommended practice[37,39]. A recommended target of over 90% 'adequate' or 'excellent' bowel preparation has been proposed to be measured as a unit KPI[4,14].

Withdrawal time

Colonic mucosal inspection is primarily completed during colonoscope withdrawal post caecal intubation. The time allocated from caecal examination to removal of colonoscope from the rectum is recorded as the colonoscopy withdrawal time (CWT). CWT > 6 min is associated with a significant increase in ADR[19,40,41]. Conversely a CWT of < 6 min is linked to increased risk of interval colorectal cancer[42].

For expert endoscopists, defined as over 3000 procedures[19], the increase in ADR plateaus at a CWR of > 10 min[43]. For trainee endoscopists however, a CWT of greater than 10 min may be beneficial[44]. Thus, the recommendation is for a minimum CWT of 6 minutes and an aspirational target of 10 min[12-14].

Artificial intelligence (AI) is likely to play a role here in the near future. The introduction of a CWT speedometer, warning endoscopists of rapid withdrawal, inserted into the overlay of the endoscopic image, was successful in significantly improving the ADR versus standard colonoscopy in a recent Chinese study (24.54% *vs* 14.76%)[45].

Sedation

The majority of colonoscopies are completed using pharmacological sedatives. Standard practice targets conscious sedation achieved *via* a combination of benzodiazepine (most commonly midazolam or diazepam) and opioid (most commonly fentanyl or pethidine) administration. Acceptable sedation targets require factoring in the patient age, in addition to co-morbidities. The BSG has a recommended sedation of ≤ 2 mg of midazolam (or equivalent) and ≤ 50 micrograms of fentanyl (or equivalent) in patients over the age of 70. In patients under 70, the recommended sedative dose is ≤ 5 mg of midazolam and ≤ 100 mcg of fentanyl[12]. The ASGE guidelines also recommend the use of a combination of opioid and benzodiazepine but do not specify a recommended dose[46].

These targets for sedation were included in the Performance Indicator of Colonic Intubation (PICI) study as a collective indicator of endoscopist performance[47]. This devised a binary outcome based on caecal intubation, patient comfort and sedation administered. Valori *et al*[48] showed that a PICI positive colonoscopy was significantly associated with a higher polyp detection rate (PDR). However, the real world practice of sedation for colonoscopy has significant geographical variation and PICI outcomes may therefore be difficult to standardise internationally.

Rectal examination and rectal retroflexion

Digital rectal examination, or justification for omission is recommended in 100% of procedures by the BSG guidelines[12]. This prepares the anal canal for the entry of the colonoscope and may provide tactile information to the endoscopist of potential strictures or pathology which may impede colonoscope insertion.

Rectal retroflexion was demonstrated to be useful in the detection of low rectal pathology in the 1980s [49]. Consequently, it has been taught to all endoscopists and a target retroflexion rate of 90% has been proposed as a KPI[12]. However, the diagnostic yield of retroflexion has been demonstrated to be minimal[50,51]. Retroflexion can rarely cause perforation[52] and this needs to be considered in the context of patient factors.

Procedural volume

An acceptable minimum volume of procedures to achieve colonoscopy proficiency has been suggested at 200 procedures[12,53]. However studies on competency curves have identified a range from 233 to 500 procedures to achieve reliable CIR of > 90%[54-57]. This suggests that the currently accepted volume is slightly below the mean number of procedures required for colonoscopy training.

Similarly, the volume of procedures required to maintain competence has been recommended at 100 procedure per year but evidence suggests a higher target of 200 procedures per year is beneficial[58]. Quality indicators including CIR and ADR are shown to be significantly associated with annual colonoscopy volume and would advocate for a higher competency maintenance target of 250 procedures[59].

Comfort scores

Recording of accurate comfort scores is essential to maintaining a patient centred service. Patients with positive experiences during colonoscopy are more likely to return and re-engage with services[60]. The accurate estimation of comfort scores is challenging due to the subjective nature of discomfort[61,62]. Multiple endoscopic comfort-scoring systems are available. These include subjective reporting of discomfort (*e.g.,* Modified Gloucester Comfort Scale) and objective scales (*e.g.,* St Pauls Endoscopy Comfort Scale)[63,64]. Current BSG guidelines recommend frequent auditing of comfort scores in endoscopy and targeting < 10% moderate or severe discomfort in patients[12].

Comfort scores are recorded on the endoscopy reporting system and evidence suggests comfort scores are best provided by the endoscopy nurse. Inter-operator agreement on comfort scores is recognised to be inconsistent, particularly during periods of increased patient discomfort[65]. Nurse recorded comfort levels are strongly correlated with patient reported comfort scores[66].

Overall, endoscopists with lower average comfort scores have associated higher rates of CIR and lower sedation scores. Similarly, higher annual procedural volume are associated with lower comfort scores[66].

EMERGING QUALITY INDICATORS AND INTERVENTIONS IN COLONOSCOPY

Right colon retroflexion

Colonoscopy has been considered to be more effective at preventing left sided colorectal cancers than right sided cancers[67]. The higher rate of post colonoscopy colorectal cancers occurring in the right colon is thought to relate to missed adenomas at the index colonoscopy[68-70]. This has led to evaluation of strategies considered to enhance right colon visualisation.

Prolonged examination of the right colon may occur in anterograde view or in retroflexion. Both methods are demonstrated to increase the ADR[71,72]. Research into the use of RCR in increasing ADR significantly over multiple anterograde views has had mixed results[73-76]. Case studies have demonstrated that RCR can also be associated with colonic perforation[77]. In the absence of significant benefit over 2nd anterograde colonic intubation, RCR has not yet been recommended as a standard approach. Second look antegrade examination is favoured by many, with potential benefit using image-enhancement to support the second withdrawal[78].

MEDICATION ADJUNCTS

Anti-spasmodics

Anti-spasmodic agents such as hyoscine-n-butylbromide or glucagon are used by some endoscopists as smooth muscle relaxants to reduce mucosal folds and enhance colonic surface area exposure. Regular or intermittent usage of hyoscine during endoscopy as an has been reported by 86% of endoscopists in the United Kingdom[79].

Initial studies suggested that hyoscine use trends towards elevated ADR[80]. As such, it was included in the quality improvement in colonoscopy study bundle which showed a benefit when used with other adjuncts in colonoscopy[81,82]. Meta-analysis of the use of hyoscine in isolation however, has not been demonstrated to significantly affect the ADR[83-85]. Hyoscine is recognised to be associated with cardiac dysrhythmias and haemodynamic instability in patients with pre-existing cardiac conditions such as heart failure and its use in these patients is cautioned against.

Simethicone

Simethicone is an emulsifying agent often used to clear bubbles in the gastrointestinal tract[86]. It can be incorporated into the pre-procedural bowel preparation to improve endoscopic visibility[87]. Pre-procedural simethicone administration has shown mixed results on improving ADR[88-90].

Intra-procedural use of simethicone can result in suboptimal decontamination and[91]. Endoscope manufacturers have recommended against the use of intra-procedural simethicone[92]. Position statements from international endoscopic guidelines have cautioned against the intraprocedural use of simethicone whilst advocating for pre-procedural use[93,94].

Dynamic colonoscopy

Patient positional changes during colonoscopy, described as dynamic colonoscopy, refer to rotating the patient, from the left lateral position to a supine, right lateral or prone position intra-procedure. This is facilitated by the endoscopy nurse to ensure a safe positional change occurs. This is a cost neutral, safe and very quick technique, consistently associated with improved CIR, ADR and mucosal views[95-98]. Barriers to positional changes during colonoscopy include patients with arthropathy, spinal injuries or external adjuncts such as percutaneous drains.

Dynamic colonoscopy is recognised to be an effective and achievable adjunct to colonoscopy. At present, it does not feature in endoscopist KPIs, likely due to inability to record and verify accurately.

Image definition and electronic chromoendoscopy

The image quality of modern colonoscopes has increased dramatically in recent years to incorporate the second generation high definition instruments available today. Magnification is now widely available and further enhances their diagnostic capability. Improved image quality from high definition colonoscopes has been proven to increase ADR[99-101] and also provides in advantages in other areas, including surveillance for Inflammatory Bowel Disease[102]. Virtual chromoendoscopy, such as the use of Narrow Band Imaging (NBI), facilitated by high definition colonoscopes has been shown in meta-analysis to improve ADR[78]. Similar to NBI, blue laser imaging and i-scan have been shown to improve ADR when compared to white light imaging[103-105].

DEVICE ASSISTED COLONOSCOPY

Cap assisted colonoscopy

Meta-analysis of CAC versus standard colonoscopy (SC) has demonstrated increased PDR and reduced procedural time[106,107]. CAC has been consistently to achieve higher ADR yields *vs* SC[108-110], although studies comparing CAC with cheaper adjuncts such as position changes or NBI are lacking. As in many areas of endoscopic research, further head-to-head trials of distal attachment devices would be welcome[111].

Endocuff assisted colonoscopy

While first generation Endocuff can be considered to have equivocal benefit in terms of ADR, with most advantages over SC relating to diminutive polyps, the second generation endocuff vision has shown benefit within screening populations. The well-conducted ADENOMA trial showed a significant improvement in ADR and MAP, without improved detection per unit withdrawal time, suggesting a value in supporting more efficient colonoscopy[112]. Cuff devices have also been shown to be superior to cap-assisted colonoscopy for ADR and lower adenoma miss rates and have particular utility in colon cancer screening[113,114].

MACHINE LEARNING/COMPUTER ASSISTED DIAGNOSTICS

Computer aided detection and computer aided diagnosis

Initial single centre trials of CADe have demonstrated positive results with reported increase in ADR with the addition of CADe[115]. However, the increased ADR was primarily due to the detection of non-advanced diminutive and hyperplastic polyps. Recent multi-centre studies indicated a significant improvement in APC and a non-significant trend towards greater ADR with the addition of CADe *vs* standard colonoscopy[116]. A potential adverse effect of CADe adoption will be the workload associated with diminutive and hyperplastic polyp assessment and removal[117], which can be offset by adoption of a resect and discard strategy, which has proven utility in the hands of specialist endoscopists using AI (CADx) support[118,119].

The ESGE comprehensively assessed both the potential benefits and concerns relating to AI In GI endoscopy and machine learning. Risk of external interference (hacking), endoscopist deskilling, over-reliance on AI and the impact of biased datasets are all raised as concerns regarding AI adoption[120] and mitigation strategies will need to be incorporated as this field develops.

CURRENT QUALITY INDICATORS IN ENDOSCOPIC MUCOSAL RESECTION

Recurrence/residual polyp evident at 12 months

EMR has been demonstrated to be a safe and effective alternative to surgery in the management of LNPCPs. However, early adenoma recurrence post EMR is recognised to occur in 15%-30% of patients [121,122] and necessitates a strict surveillance programme for early identification and resection of residual adenoma.

Recurrence rates are also shown to be dependent on the index resection method. En-bloc resections have a significant lower rate of adenoma recurrence compared to piecemeal[121]. Other factors with regard to recurrence rates include increased adenoma size[123], intra-procedural bleeding (IPB) at time of resection[123] and endoscopist experience[124]. Recurrence rates according to colonic location have demonstrated mixed results, with some studies indicating elevated recurrence rates in proximal locations[125,126], possibly reflecting increased resection difficulty in the right colon. Conversely, Lim *et al*[127] indicated significantly higher recurrence rates in the distal colon and rectum.

Endoscopic thermal strategies such as snare-tip soft coagulation (STSC) have consistently demonstrated efficacy in reducing adenoma recurrence after piecemeal EMR (5.2% *vs* 21%)[128] and (12% *vs* 30%)[129]. Safety data from these analyses did not demonstrate any additional adverse risks.

Recurrence analysis may need to consider the mode of initial resection, with different recurrence rates likely for conventional EMR when compared with other modalities such as underwater EMR[130] and cold piecemeal EMR[131], which is primarily employed for resection of sessile serrated lesions.

Acknowledging the high rates of adenoma recurrence post EMR emphasises the requirement for a reliable surveillance programme. Meta-analysis indicates that 90% of recurrence is detectable by site check colonoscopy 6 months post EMR procedure[121]. Prospective studies, similarly examining surveillance intervals have confirmed the optimal timing of initial surveillance to be 6 months post resection[132]. Recurrence detected at initial surveillance colonoscopy is most commonly unifocal and diminutive[123]. The vast majority of early detected recurrence is suitable for endoscopic management [123,133].

Consolidating the information above, the 2015 BSG guidelines agreed a KPI threshold for recurrence of < 10% at 12 months post EMR with an aspirational target of < 5%[8]. This acknowledges the occurrence of early recurrence which can be managed endoscopically, while also accounting for cases of "late recurrence", not detected at the initial post-EMR surveillance colonoscopy.

Perforation rate

Standard colonoscopy and polypectomy confers an accepted perforation risk of 0.07%-0.19%[134,135]. Although rare, colonic perforation carries a considerable morbidity and mortality burden[136]. Perforation during EMR remains rare, but is higher than standard colonoscopy, and must be addressed specifically during the informed patient consent process. Perforation rates during EMR range from 0.3%-1.3%[7,137,138].

Recognition and early intervention in the management of colonic perforation is essential to optimise patient outcomes[135]. Swan *et al*[139] described routine close inspection of the mucosal defect to examine for deep muscle injury. The benefit of immediate recognition of a potential MP injury affords the opportunity to apply endoscopic therapies such as clip placement to close defects with a view to minimising further complications[140,141].

Consequently, the BSG workgroup adopted a minimum standard of < 2% perforation rate with an aspirational standard of < 0.5%[8].

Post procedural bleeding

The reported incidence of PPB ranges from 2.6%-9.7%[142] but is limited by a lack of consensus definition for PPB. 65% of PPB is apparent within 24 hours of EMR, increasing to 88% at 48 hours[143]. Post procedural bleeding was defined by the BSG working group as rectal bleeding occurring up to 30 days post EMR and could be further subcategorised as minor/intermediate/major or fatal according to the severity. PPB is accepted to be the most common serious complication of EMR procedures and is differentiated from IPB which can be managed endoscopically at the time of EMR.

Risk factors to predict clinically significant PPB were examined by Metz *et al*[143] in 2011, demonstrating that proximal (right) colonic location compared to distal colon (11.3% *vs* 3.5%) and antiplatelet therapy were significantly associated with increased risk of PPB.

Electrocautery at the time of EMR, has also been shown to affect the rates and timing of PPB. Higher rates of IPB is associated with the use of pure cutting current as demonstrated by Kim *et al*[144]. Conversely, a pure coagulation current, with lower risk of intra-procedural bleeding, confers additional risk of delayed-bleeding and potentially also perforation due to transmitted deep thermal injury[145]. The ESGE recommends the use of a blended coagulation/cutting diathermy current for EMR[9].

Heterogeneity amongst study outcomes on the benefit of prophylactic clipping (through the scope clips, TTSC) in preventing PPB led to a meta-analysis which indicated no significant benefit to additional clip placement on PPB rates[146]. Citing the low rate of PPB in the control group of this meta-analysis (2.7%), Albeniz *et al*[142] conducted a RCT of prophylactic clipping in high risk lesions and demonstrated a non-significant trend towards less PPB. Further investigation by Pohl *et al* confirmed that prophylactic clipping was beneficial for proximal, large lesions, especially in patients on antiplatelet or anticoagulant medications[147]. The ongoing use of prophylactic clips to prevent TTSC should be patient-specific with recent studies favouring efficacy in clipping to reduce risk of PPB in the right colon [148]. Cost-analysis in this area will by driven by the relative costs of TTSCs and hospital admission costs in different countries, with high levels of variability evident[149].

The ESGE guidelines do not recommend prophylactic clipping as standard post EMR management [9]. However, their guidelines do recognise the need for prophylactic clipping in a subset of high risk patients. A clinical predictive score, "clinically significant bleeding" (CSPEB) was developed by Bahin *et al*[150], finding lesions > 30 mm in size, proximal location and additional co-morbidities warranted consideration for prophylactic clipping.

With regard to PPB as a performance indicator, the BSG guidelines have set a minimum PPB rate of < 5% to be analysed at both an endoscopist and unit level[8].

Time from diagnosis to referral for definitive therapy and definitive therapy itself

Recognising the high risk of potential malignant transformation of LNPCPs, a 28 day cut-off for referral for consideration for EMR has been proposed by the BSG guidelines[8]. This 28 day standard was proposed but no minimum proportional standard has been published or disseminated. There is limited published data indicating compliance with this KPI, making interpretation of its impact challenging. A recommended 56 day period was allocated from referral to definitive endoscopic therapy with no minimum standard suggested as yet.

Audit data on real world clinical practice achievement of these EMR guidelines is necessary to establish the feasibility of the 28 and 56 day rule, respectively.

Procedural volume - Minimum annual EMR volume

As discussed above, procedural volume and clinical exposure are recognised contributory factors in colonoscopy performance. Bowel cancer screening programmes require an annual minimum volume of 150 procedures to ensure competency standards are maintained[151,152] although based on evidence discussed above, this may be a conservative Figure 1. Reviewing available literature, an initial training volume of 50 EMRs to establish proficiency with a minimum annual volume of 30 procedures to maintain competency are suggested[153].

ADDITIONAL AND FUTURE QUALITY INDICATORS IN ENDOSCOPIC MUCOSAL RESECTION

Lesion complexity

Traditionally polyp complexity has been inferred by size, conventionally > 20 mm. Recognising polyp complexity as multifactorial, Gupta *et al*[154] developed the Size-Morphology-Site-Access (SMSA) score. This score assigns each component a difficulty rating, forming a composite polyp score (SMSA Score), reflecting overall complexity and was evaluated by ESGE. Increased SMSA score accurately predicts recurrence, adverse events and incomplete resection[155]. We suggest that the SMSA score should be reported by all endoscopists when they encounter complex polyps, as they can be useful in planning resection approach, time slots for lists as well as predicting outcome.

Snare tip soft coagulation

STSC is a safe and effective procedural method in reducing recurrence post piecemeal EMR[128] and has been revalidated by a recent 2022 meta-analysis[156]. Due to the strong evidence in favour of STSC use, the majority of endoscopists now employ this method to minimise recurrence. Consequently, the recording of a unit STSC rate as a KPI should be considered.

Unit compliance with recommended site check surveillance intervals

A reliable surveillance programme is an essential component of an EMR service. Optimal surveillance intervals are established and discussed above but the proportion of patients who successfully complete timely surveillance can vary. Measuring the proportion of patients achieving site checks at appropriate intervals would underline adherence to surveillance programmes and support management of EMR recurrences. Based off the meta-analysis findings of Belderbos *et al*[121] that 90% of recurrence is detectable at 6 months, we suggest an interval of less than 180 days from date of resection for first site

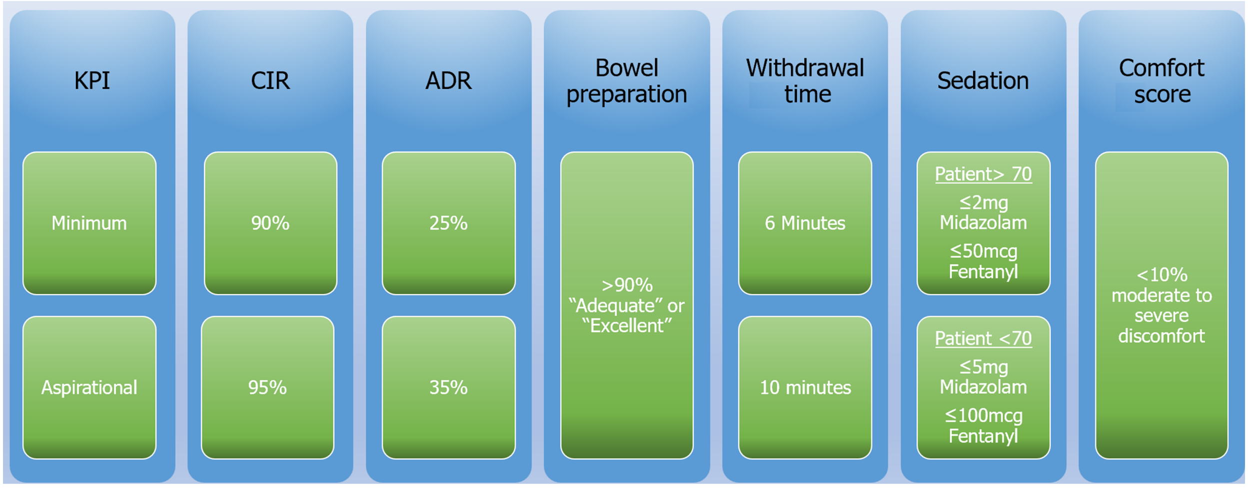

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Figure 1 Algorithm for quality indicators in colonoscopy. KPI: Key performance indicators; CIR: Caecal intubation rate; ADR: Adenoma detection rate.

check (SC1) and 18 months from index for SC2, provided SC1 is clear. We further suggest that recurrences should be managed appropriately and in this scenario the next SC interval should again be < 180 days.

Surgical referral rates and incomplete resection

EMR has less morbidity, lower complication rates and is associated with shorter hospital stays compared to surgical resection[157] for benign polyps. However, recognising that EMR may not be possible in a proportion of referred patients, measurement of surgical referral rates were recommended by the BSG guidelines in 2015[8]. This is another area which may benefit from accurate SMSA assessment at index referral. Similarly, the rate of incomplete resection and subsequent surgical referral are a necessary performance indicator of EMR quality. This metric needs to incorporate the complexity of EMRs undertaken and should be subject to regular audit.

CONCLUSION

The focus on gastrointestinal endoscopy quality assurance and improvement has led to the development of standardised colonoscopy key performance indicators such as caecal intubation rate and adenoma detection rates[158]. The rapid endorsement of KPIs by international endoscopy societies [159] led to the widespread adoption of these benchmarks. New candidates for colonoscopy KPIs have since emerged and the arrival of artificial intelligence to general colonoscopy practice is likely to influence the field over the coming years.

Today, colonoscopy KPIs are valuable to ensure adequate endoscopist performance, identify underperforming practitioners and to target training interventions. Colonoscopy KPI monitoring and awareness is now instituted from the beginning of endoscopy training and regular audits are completed to ensure unit performance is adequate.

However, the adoption and widespread acceptance of endoscopic performance metrics has not permeated equally through all fields of endoscopy. Guidelines examining performance in gastroscopy have been detailed but adherence to these KPIs is suboptimal[160,161]. Specifically with regard to advanced endoscopic procedures, although publications recommending minimum standard practices have been available since 2015 for EMR, there is yet to be a similar consensus push towards outcome monitoring.

One of the challenges to KPI implementation for EMR is the limitation of endoscopy reporting systems. Continuous monitoring of complex data and surveillance metrics requires significant resource and it is not yet clear how we might achieve this. The collation and review of complication and, recurrence rates as well as referral timelines requires significant time, adding to endoscopist workload.

Quality assurance in endoscopy will always require practitioner performance measurement through KPIs. Both patients and the endoscopy community have benefited from the introduction and participation in colonoscopy KPIs. Replicating these enhanced standards of performance measurement in therapeutic endoscopy is therefore a logical next step in the evolution of endoscopy.

FOOTNOTES

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Country/Territory of origin: Ireland

ORCID number: Eoin Keating 0000-0002-1466-8752.

Corresponding Author's Membership in Professional Societies: Irish Society of Gastroenterology.

S-Editor: Ma YJ
L-Editor: A
P-Editor: Cai YX

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MINIREVIEWS

Improving polyp detection at colonoscopy: Non-technological techniques

Ragul Rajivan, Sreedhari Thayalasekaran

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Ragul Rajivan, Buckingham Medical School, Milton Keynes MK18 1EG, United Kingdom

Sreedhari Thayalasekaran, Department of Gastroenterology, University Hospitals of Leicester, Leicester LE1 5WW, United Kingdom

Corresponding author: Sreedhari Thayalasekaran, MBBS, MRCP, PhD, Doctor, Department of Gastroenterology, University Hospitals of Leicester, Leicester Royal Infirmary, Infirmary Square, Leicester LE1 5WW, United Kingdom. sreedhari.thayalasek@uhl-tr.nhs.uk

Abstract

Colonoscopy and polypectomy remain the gold standard investigation for the detection and prevention of colorectal cancer. Halting the progression of colonic adenoma through adequate detection of pre-cancerous lesions interrupts the progression to carcinoma. The adenoma detection rate is a key performance indicator. Increasing adenoma detection rates are associated with reducing rates of interval colorectal cancer. Endoscopists with high baseline adenoma detection rate have a meticulous technique during colonoscopy withdrawal that improves their adenoma detection. This minireview article summarizes the evidence on the following simple operator techniques and their effects on the adenoma detection rate; minimum withdrawal times, dynamic patient position change and proximal colon retroflexion.

Key Words: Colonoscopy; Minimum withdrawal times; Dynamic position change; Proximal colon retroflexion

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Core Tip: Excellent endoscopists use effective mucosal exposure techniques to increase their adenoma detection rate. This minireview summarizes some of the non-technological techniques that have shown the potential to improve the adenoma detection rate.

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INTRODUCTION

Colorectal cancer is the 3rd most common cancer globally[1] occurring in 8% and 12% of all new cancer cases in the USA and UK, respectively[2]. Most colorectal cancers develop *via* the adenoma-carcinoma sequence[3,4]. Sessile serrated lesions are also recognised precursor lesions to colorectal cancer *via* the CpG island-methylated pathway[5]. The polyp and adenoma detection rate is defined as the number of colonoscopies where at least one polyp and adenoma are detected respectively[6].

Colonoscopy remains the gold standard investigation for the detection and prevention of colorectal cancer[6]. The strength of colonoscopy lies in its ability to not only detect colorectal cancer but also prevent it through the early removal of polyps *via* polypectomy, halting the progression of adenoma to colorectal cancer[7]. Despite, colonoscopy being the best investigative tool, colonic neoplasia is still missed at colonoscopy[8,9]. The reported miss rates of colorectal cancer and adenoma are 5% and up to 20% respectively[8-10]. The beneficial effects of colonoscopy are less obvious in the prevention of right-sided colonic cancers[11].

The adenoma detection rate (ADR) has been identified as a key performance indicator in colonoscopy [6]. The ADR is inversely proportional to the risk of interval colorectal cancer. In a large cohort study, endoscopists with an ADR ≥ 20% were found to have the lowest rates of interval colorectal cancer[12]. Another pivotal study found a 3% reduction rate for interval colorectal cancers, with every 1% increase in the endoscopist's ADR[13].

There has been significant research focusing on the identification of factors that could potentially improve the adenoma detection rate. Initial studies focused on evaluating simple operator techniques. More recently, research has been published with conflicting evidence evaluating both digital and dye-based chromoendoscopy, water-assisted colonoscopy, distal attachment devices, wide-angle colonoscopy, and artificial intelligence in the role of polyp detection.

This minireview gives an outline of the simple operator techniques (minimum withdrawal time, position change and proximal colon retroflexion) to improve polyp detection.

WITHDRAWAL TIMES

Withdrawal time is the time taken to inspect the colonic mucosa from the caecum to the anal canal after caecal intubation has been achieved[14]. The first study to show an association between a minimum withdrawal time and high-quality colonoscopy was a small study by Rex *et al*[15]. In this study 2 endoscopists (one with a greater adenoma miss rate than the other) had 10 consecutive colonoscopy withdrawals videotaped and evaluated by a group of 4 expert endoscopists who were blinded to which endoscopist had performed each procedure. Along with a minimum withdrawal time, each video was evaluated for adequacy of examination of proximal flexures and folds, washing, suctioning and luminal distension. The experts scored the colonoscopist with the lower miss rate much higher in each of the domains, $P < 0.001$[15]. The recommendation from the Multi-Society Task Force on Colorectal Cancer that a withdrawal time for colonoscopy should average 6-10 min (without the inclusion of time taken for polypectomy and biopsy) followed[16], but was based on limited scientific information[15].

In a landmark prospective study of 12 Gastroenterologists performing 7882 colonoscopies in a community-based setting by Barclay *et al*[17] over 15 mo, the adenoma detection rate in endoscopists with mean withdrawal times of < 6 min was compared to the adenoma detection rate in endoscopists with mean withdrawal times of > 6 min. Gastroenterologists with a mean withdrawal time of 6 min or more detected a greater number of adenomas (28.3%) compared to endoscopists with a mean withdrawal time of 6 min or less (11.8%), $P < 0.001$. This trend was also reflected in the greater detection of advanced neoplasia in 6.4% where withdrawal time ≥ 6 min *vs* 2.6% where withdrawal times were ≤ 6 min, $P = 0.005$. The definition of advanced adenoma in this study included; ≥ 10 mm in size, villous component, high-grade dysplasia, or cancer. Most of the advanced lesions were ≥ 10 mm in size. 2 small polyps with high-grade dysplasia and invasive cancer were 5 mm and 7 mm in size respectively[17].

In another study, the same group compared the detection of colonic neoplasia amongst 12 endoscopists following the implementation of a quality improvement intervention. The intervention incorporated techniques such as adequate air insufflation, washing the colonic mucosa, torque manoeuvres to flatten colonic folds, and repeated examination of colonic segments, within a minimum withdrawal time of 8 min. Following the intervention, endoscopists with mean withdrawal times of ≥ 8 min had greater rates of neoplasia detection (37.8% *vs* 23.3%, $P < 0.0001$) and also advanced neoplasia detection (6.6% *vs* 4.5%, $P = 0.13$)[18]. Advanced adenomas occur less frequently, and it is often difficult to make statistically significant conclusions from sub-group analysis. Larger studies are required to obtain adequate power, which is often not feasible. A limitation of this study was the comparison of a historical control group with the post-intervention group.

This study showed that the incorporation of a minimum withdrawal time into a quality intervention improves neoplasia detection. Evidence from this study is not enough to support minimum withdrawal times in isolation, without considering the implementation of other withdrawal techniques[18].

In a large study of 23910 colonoscopies, adherence to a departmental-wide policy of a 7-min minimum withdrawal time for negative colonoscopies (no polyps removed) showed no statistically significant improvement in the polyp detection rate. A limitation of this study is that the withdrawal times were only available as < 7 min or ≥ 7 min, which limited the ability to establish if there was a trend. Strengths of this study included the large size with the incorporation of 42 endoscopists with wide levels of experience, reflecting more widespread endoscopic practice[19]. Good withdrawal technique involves careful inspection behind folds and flexures, adequately distending the colonic lumen, washing the colonic mucosa, and suctioning excess fluid or faecal debris[19]. Endoscopists who perform high-quality colonoscopies are likely to take more time performing these manoeuvres than those that don't. Longer withdrawal times are more likely to be a correlation between good colonoscopy technique, than causation. The study from Sawhney *et al*[19] shows that simply implementing a mandatory departmental-wide policy of minimum withdrawal time, without incorporation of other high-quality colonoscopy manoeuvres, was not sufficient to increase neoplasia detection[19]. By contrast, the study by Barclay *et al*[18], showed that with a quality intervention program focusing on improving colonoscopy manoeuvres, coupled with a minimum withdrawal time, a significant improvement in neoplasia detection was noted.

More of the studies performed so far have focused on evaluating the effects of a minimum withdrawal time on experienced endoscopists[17,18,20]. Gromski *et al*[21] performed a study evaluating the performance of four 1st year Gastroenterology trainees at a teaching centre who had to adhere to a 6-min minimum withdrawal time. Trainees that had withdrawal times > 10 min had an ADR of 32.3% compared to trainees with withdrawal times < 10 min who had an ADR of 9.5%, P < 0.001[21]. This study was limited in its ability to draw firm conclusions as it was a single-centre study, involving the analysis of only 4 trainees performing 1210 colonoscopies in total[21].

In the largest observational study to date, 31,088 screening colonoscopies in the National Health Service bowel cancer screening program performed by 147 colonoscopists in the United Kingdom were evaluated[20]. This study found that with a withdrawal time of < 7 min, the ADR was 42.5% compared to an ADR of 47.1% with a withdrawal time of ≥ 11 min, P < 0.001. The main increase was noted in sub-centimetre or proximally located adenomas. No statistically significant difference was noted in the detection of advanced adenoma with longer withdrawal times. The entire study cohort had a positive faecal occult blood test[20]. The optimal withdrawal time suggested was 10 min[20], rather than 6-8 min as previously reported[17,18,22]. Beyond 10 min, there were minimal gains in the ADR[20]. The current minimum standard in bowel cancer screening programmes is 6 min, which is sufficient to detect advanced adenoma. The study by Lee *et al*[20] suggests that increasing it to between 6-10 min might increase the detection of small and proximal adenomas. The miss rate of proximal neoplasia is well recognised[10]. Proximal colorectal neoplasia is more difficult to detect; it can be flatter and quicker to progress to colorectal cancer[23]. A strength of the study by Lee *et al*[20] is that it did look at the prevalence of adenoma detected according to lesion location in the colon. The ability to make conclusions outside of a positive faecal occult blood cohort as in this study is a limitation[20].

In a prospective multi-centre Norwegian study by Moritz *et al*[24], no statistically significant difference was found in the detection of polyps between endoscopists with a withdrawal time of < 6 min compared to those with withdrawal times ≥ 6 min[24]. The overall withdrawal time, which includes time for polypectomy and biopsy, was separated from the visual withdrawal time, where therapy was not included. This methodological approach was a strength of their study design. In other studies[22,25] withdrawal times for negative colonoscopies were used for the analysis[24].

In a single centre randomized controlled trial (RCT) with 1160 patients, Coghlan *et al*[26] compared colonoscopy with specified withdrawal times in different colonic segments (right colon, transverse colon, and left colon) to a minimum free colonoscopy withdrawal time of at least 6 min[26]. A strength of this study was the cessation of recording times when polypectomy was performed, with re-starting when re-examination of the colon continued. The overall ADR was 41% supporting other studies that withdrawal times of at least 6 min are associated with increased neoplasia detection. No significant statistical differences in ADR were seen when comparing the fixed withdrawal limb to the conventional free withdrawal limb; 42.1% *vs* 39.8%, P = 0.43 respectively. This RCT was the first study to evaluate timed colonic segment withdrawal to conventional minimum withdrawal. It is, however, a single-centre study, so limited conclusions can be drawn in terms of widespread applicability[26].

An observational study by Gellad *et al*[27] was the first study to evaluate the association of withdrawal time to missed adenomas at subsequent colonic examination[27]. In this multi-centre study, 1441 of 3121 patients in total had no polyps at baseline colonoscopy. 304/1441 subjects returned for follow-up colonoscopy within 5.5 years. 16.2% (49 people) of the study participants with no polyps seen initially had interval neoplasia, including 7 advanced adenomas and 1 invasive cancer. No association between the withdrawal time and risk of interval neoplasia was seen. A mean baseline withdrawal time of > 12 min was observed. The study findings did show a statistically significant association between the mean withdrawal time and adenoma detection rate at baseline, P = 0.03[27]. However, after a threshold between 5.2 and 8.6 min, no additional benefit was conferred to the detection of neoplasia[27]. Other studies have shown that increased withdrawal time led primarily to the detection of less clinically significant small and diminutive polyps[20,22].

Results from a population-based registry study showed a statistically significant increase in the polyp and adenoma detection rate when the withdrawal time was > 9 min. The PDR of 53.1% and ADR of 33.6% were found to be highest at 9 min. Endoscopists with median withdrawal times of < 6 min, were significantly worse than endoscopists with median withdrawal times of > 9 min; PDR was 10.5% less, and ADR was 9.8% less respectively. Serrated polyp detection rates were 4.5% higher amongst endoscopists with median withdrawal times of 9 min compared to those with median withdrawal times of 6 min. Roughly 10% of the data was missing, which could cause a degree of attrition bias[28].

A recent large multi-centre RCT of 1027 patients randomized to a 9-min or 6-min withdrawal showed a statistically significantly higher ADR in the 9-min limb compared to the 6-min limb, respectively this was 36.6% *vs* 27.1%, P = 0.001. Similar improvements were noted in the sub-group analysis for the right colon; 9-min (21.4%) and 6-min (11.9%), P < 0.001. Small and diminutive adenoma detection also increased in the 9-min limb compared to the 6-min limb. Significant improvements in the ADR in less experienced endoscopists were noted when compared to experienced ones, P = 0.03[29].

The idea that the greater time spent evaluating the colonic mucosa would naturally increase polyp detection is a rationale one. However, simply spending more time without performing actions such as repeated examinations of colonic segments and adequate luminal distension might not make a significant improvement in polyp detection. It is difficult to evaluate minimum withdrawal time in isolation, as it is likely to be an indication of a superior operator technique, than a causal factor[30].

In general, most colonic polyps are benign and unlikely to transform into cancer[31]. Large polyps harbour the greatest risk of progression to colorectal cancer. Larger polyps are also more visible and harder to miss[32]. Two studies have shown that the association between minimum withdrawal times and polyp detection is less for larger polyps[22,25]. An obvious conclusion to make from these findings is that larger polyps are readily visible and unlikely to be missed in comparison to smaller polyps in the same amount of time. The infrequent occurrence of larger polyps means that much larger studies are needed to show statistical significance when a subgroup analysis is performed in the small cohort of larger polyps ≥ 20 mm[22,25].

Small and diminutive polyps are less likely to progress to cancer but also easier to miss during colonoscopy[31]. The studies by Lee *et al*[20] and Zhao *et al*[29] showed that increasing withdrawal times to between 6-10mins increased the detection of small and proximally located adenomas. The translation of this concerning the clinical advantage is unclear.

Sessile serrated lesions have a subtle appearance and are more difficult to detect. Their prevalence varies between 7%-10%[33]. A registry-based study reported that the detection of sessile serrated lesions was higher with longer withdrawal times > 11 min compared to ≤ 6 min[5]. Most of the large studies evaluating minimum withdrawal times did not address sessile serrated lesion detection[17,18,20]. Two studies did report that the detection rates of sessile serrated lesions improved with increasing withdrawal times[5,28].

The 2 Largest studies, both observational in size showed conflicting evidence with one showing a positive effect of increased withdrawal time on the ADR[20] and the other showing no benefit[19]. A recent meta-analysis showed an improvement in the ADR with a 9-min colonoscopy withdrawal compared to withdrawal times between 6-9 min[34]. Overall, the evidence supporting the use of longer withdrawal times and increasing polyp/adenoma detection rates is conflicting[17-20,24].

Simply implementing minimum withdrawal times without the adoption of other mucosal inspection techniques is not likely to be as effective. This finding was highlighted in the study by Sawhney *et al*[19] where a mandatory minimum withdrawal time was adopted without any benefit. In comparison, the study by Barclay *et al*[18] incorporated a minimum withdrawal time alongside a quality improvement intervention that included other operator techniques and reported a significant benefit (Table 1 and Table 2).

POSITION CHANGES ON WITHDRAWAL

An essential component of the colonoscopy technique is adequate luminal distension on withdrawal to provide enhanced endoscopic fields of view[35]. Position change during colonoscopy results in the elevation of gas to the highest position with fluid moving away from the area of interest, facilitating improved distension of the lumen[36]. Although prolonged insufflation may improve colonic distension, it does not move the fluid away and may not automatically improve the ADR as position changes, which provides a different field of view[37].

The use of changing the patient's position during the withdrawal phase of colonoscopy has shown mixed results[38-40]. Adoption of the technique of position change during the withdrawal phase of colonoscopy is often done at the discretion of the endoscopist and not routinely performed. Endoscopists may be unaware or not convinced of the benefit, given the conflicting evidence to position change during colonic withdrawal. It may simply be technically easier and faster to perform the colonic withdrawal in one position than incorporate position change in colonic segments, especially in heavily sedated patients[38].

Table 1 Summary of studies evaluating colonic withdrawal times

Ref.	Year	Design	*n*	Outcome
Barclay *et al*[17]	2006	Prospective	7882	WT > 6 min associated with increased ADR
Barclay *et al*[18]	2008	Prospective	2053	WT ≥ 8 min associated with increased ADR
Sawhney *et al*[19]	2008	Prospective	23,910	Minimum 7 min WT not associated with increased PDR
Gellad *et al*[27]	2010	Prospective	304	WT ≥ 12 min not associated with risk of interval neoplasia
Gromski *et al*[21]	2012	Prospective	1210	WT ≥ 10 min associated with increased ADR
Moritz *et al*[24]	2012	Prospective	4429	WT ≥ 6 min not associated with increased ADR
Lee *et al*[20]	2013	Prospective	31088	WT up to 10 min associated with increased ADR
Butterly *et al*[28]	2014	Prospective	7996	WT ≥ 9 min associated with increased ADR
Zhao *et al*[29]	2022	RCT	1027	Increased ADR associated with WT of 9 min *vs* WT of 6 min

WT: Withdrawal times; RCT: Randomized controlled trial; ADR: Adenoma detection rate; PDR: Polyp detection rate.

Table 2 Results of studies evaluating colonic withdrawal times

Ref.	Intervention limb, %	Control limb, %	*P* value
Barclay *et al*[17]	28.3%	11.8%	< 0.001
Barclay *et al*[18]	34.7%	23.5%	> 0.0001
Sawhney *et al*[19]	NA	NA	NA
Gellad *et al*[27]	NA	NA	NA
Gromski *et al*[21]	32.3%	9.5%	< 0.001
Moritz *et al*[24]	NA	NA	NA
Lee *et al*[20]	47.1%	42.5%	< 0.001
Butterly *et al*[28]	ADR: IRR = 1.50		0.001
Zhao *et al*[29]	36.6%	27.1%	0.001

ADR: Adenoma detection rate; IRR: Incidence rate ratio; NA: Not available.

Dynamic position change is often adopted in the following fashion; Left lateral position for the cecum, ascending colon, and hepatic flexure; Supine position for the transverse colon; Right lateral position for the splenic flexure, descending colon, and sigmoid colon[36,37].

In a tandem-design RCT of 130 patients, dynamic position change compared to the left lateral position alone was evaluated[37]. The colonic examination was performed segmentally: (1) Caecum, ascending colon, and hepatic flexure; (2) transverse colon (TC); and (3) splenic flexure and descending colon (DC). Each segment was examined for 2 min in both the left lateral position and position changes. Polypectomy was performed only after examination in both comparison arms. The definition of position changes used in the study are outlined; accordingly: (1) Caecum, ascending colon, and hepatic flexure = left lateral position; (2) transverse colon = supine position; and (3) splenic flexure and descending colon = right lateral position. The ADR improved by 11% in the cohort where position change other than left lateral (TC, splenic flexure and DC) was adopted when compared to left lateral position change alone, $P = 0.01$[37]. This was more noticeable in the transverse colon where a supine position was adopted; left lateral position limb 15% *vs* position change limb 24%, $P = 0.02$. Similarly, there was an 18% increase in the PDR in position changes that were not in the left lateral *vs* left lateral position only, $P < 0.001$. The median size of polyps that were detected in the position change limb was 3 mm (range 1-10 mm). A strength of this study is the RCT design. However, as it is a single-centre, single-endoscopist study, there are limitations in the widespread applicability of the findings[37].

In a tandem design 102 patient RCT, colonoscopic withdrawal in the left lateral position compared to dynamic position change was evaluated[41]. In concordance with the findings of East[37], this RCT also showed positive findings with dynamic position change on colonoscopic withdrawal. This single-centre study was performed in a Turkish hospital and adopted the following examination pattern; right colon (left lateral twice), transverse colon (left lateral and supine), and left colon (left lateral, right lateral and supine). The PDR in the left lateral position compared to the dynamic position limb was 30.3% and 43.1% respectively, $P < 0.001$. The ADR in the left lateral position was 23.5% and 33.3% in the dynamic position limb, $P = 0.002$ respectively. The increase in the ADR was more noticeable in the transverse and left colon[41].

In a multi-centre RCT (parallel design) study, 1072 patients were randomized to either the left lateral position or the dynamic position change on withdrawal. Dynamic position change was followed accordingly: (1) Caecum, ascending colon, and hepatic flexure = left lateral position; (2) transverse colon = supine position; and (3) splenic flexure and descending colon = right lateral position. A higher ADR was found in the dynamic position change limb; 42.4% *vs* 33.0% in the left lateral position, $P = 0.002$. An increase in the number of adenomas per patient was evident in the intervention limb 0.9 *vs* 0.67, $P = 0.01$. Furthermore, in the transverse colon, the increase in adenoma in the intervention limb was 0.22 *vs* 0.13, $P = 0.016$ and in the left colon 0.37 *vs* 0.27, $P = 0.045$ respectively. The mean size of the adenomas in both limbs was 5mm. This study showed that endoscopists with a lower baseline ADR (< 35%) had a significant increase in their ADR when position change was adopted compared to endoscopists with a higher baseline ADR (> 35%). The detection of sessile serrated adenoma was also greater in the position change limb 2.3% *vs* left lateral position 0.8%, but this did not reach statistical significance. No statistically significant improvement in the detection of advanced adenoma was shown in the intervention limb. This RCT is the largest study conducted so far, with the additional merit of being a multi-centre trial[36].

The tandem design (130 patient) RCT by Ball *et al*[42], had a different methodology in their evaluation of position change to previous studies[36,37]. Each colonic segment was evaluated twice; right colon (left lateral and supine), transverse colon (supine twice), and left colon (supine and right lateral position). In this single-centre study in a large teaching hospital, a statistically significant increase in the polyp detection rate in the right colon when withdrawal was performed in the left lateral position rather than supine was noted; 26.2% *vs* 17.7% respectively, $P = 0.01$[42]. In contrast to other studies[37,41], the study by Ball *et al*[42], found no significant difference in PDR in the left colon when comparing the right lateral and supine position adoption[42].

In a parallel design RCT of 776 patients, randomization to the endoscopist's usual adopted position change or dynamic position change failed to show any improvement in the PDR and ADR. Deviation from prescribed position changes in the dynamic limb was allowed if the endoscopist deemed it clinically necessary[40]. This study was unique, in that the control limb contrary to other studies[37,41] was not limited to performing withdrawal solely in the left lateral position. It is noteworthy that because of this, roughly half of the patients in the usual practice limb underwent right colon examination in the left lateral position and transverse colon examination in the supine position. This would reduce any possible advantage of the position change.

The study by Ou *et al*[40] was the only RCT to show no benefit in ADR with prescribed position changes. A significant feature of the methodology of this study was the adoption of the endoscopist's usual position change as the control limb. As a result, almost half the patients underwent a right colonic examination in the left lateral position and a transverse colon examination in the supine position. The potential advantages of position change would be reduced due to the lack of a single, standard position serving as a control limb[40].

The studies by East *et al*[37], Köksal *et al*[41] and Lee *et al*[36] found a more noticeable increase in the ADR in the dynamic position limb in the transverse colon, splenic flexure and descending colon. These 3 studies adopted a very similar definition of dynamic position change in their methodology. Heterogeneity in the study design makes it difficult to compare all RCTs as the other 2 studies by Ball *et al*[42] and Ou *et al*[40] adopted a different position as their control limb. Other than the study by Lee *et al*[36] which was a multi-centre one, the remaining studies[37,40-42] were all single-centre studies in academic units. The widespread applicability of these studies to routine community practice is therefore limited. A strength of the mentioned studies is all were randomized controlled trials[36,37,40-42].

A recent meta-analysis showed that dynamic position change during colonic withdrawal increased ADR. The recommendations from the meta-analysis for position change adoption were; left lateral position for the right colon, supine for the transverse colon and right lateral position for the left colon [43] (Table 3 and Table 4).

PROXIMAL COLON RETROFLEXION

Retroflexion is thought to improve the detection of polyps in blind spots (behind the proximal aspect of folds). Proximal colon retroflexion involves the following manoeuvres: Maximum up deflection, maximum left wheel deflection and left torque. Colonoscopy is less beneficial in the detection of right-sided colonic neoplasia[11]. The theory that polyps located on the proximal sides of folds or flexures are missed because they are not within the endoscopic field of view is plausible[44]. Retroflexion has been speculated to assist the visualization of the posterior aspect of haustral folds and is more commonly performed in the rectum[45]. Theoretically, proximal colon retroflexion as a technique may expose polyps located on the proximal haustra.

Table 3 Summary of studies evaluating dynamic position change

Ref.	*n*	Design	Control limb	Dynamic position change limb
East *et al*[37]	130	RCT	Left lateral	RC = left lateral, TC = supine, LC = right
Koksal *et al*[41]	102	RCT	Left lateral	RC = left lateral, TC = supine, LC = right lateral + supine
Lee *et al*[36]	1072	RCT	Left lateral	RC = left lateral, TC = supine, LC = right lateral
Ball *et al*[42]	130	RCT	Supine	RC = left lateral, TC = supine, LC = right lateral
Ou *et al*[40]	776	RCT	Usual position	RC = left lateral, TC = supine, LC = right lateral

RCT: Randomized controlled trial; RC: Right colon; TC: Transverse colon; LC: Left colon.

Table 4 Results of studies evaluating dynamic position change

Ref.	Year	Outcome	Control limb position	Dynamic position change limb	*P* value
East *et al*[37]	2011	Increased ADR	23% ADR	34% ADR	0.01
Koksal *et al*[41]	2013	Increased ADR	23.5% ADR	33.3% ADR	0.002
Lee *et al*[36]	2016	Increased ADR	33.3% ADR	42.4% ADR	0.002
Ball *et al*[42]	2015	Increased PDR in RC only	17.7% ADR	26.2% ADR	0.01
Ou *et al*[40]	2014	No effect on ADR	37.9% ADR	40.7% ADR	0.44

ADR: Adenoma detection rate; PDR: Polyp detection rate; RC: Right colon.

In a randomized controlled trial, one of two 2nd year Gastroenterology fellows performed colonic withdrawal and polypectomy from the caecum to the splenic flexure. The attending physician re-intubated the caecum and was randomized to perform colonic withdrawal to the splenic flexure in either a forward or retroflexed view. This study failed to show a statistically significant benefit in the adenoma miss rates between the standard forward view and retroflexed view in the 2nd examination, with a lower adenoma miss rate in the standard forward view (33.3%) compared to the retroflexed view (23.7%), P = 0.31[44]. Withdrawal in retroflexion can be technically challenging; the colonoscope may fall back more in the retroflexed view, increasing the likelihood of missed adenoma. Furthermore, the colonoscope shaft may conceal a small part of the mucosa, which could be another explanation for the negative findings. The first withdrawal was performed by trainees in forward view, whereas the second withdrawal was performed by the attending physician. This is a small single-centre study so has significant limitations in its ability to draw conclusions in widespread clinical practice[44].

In a large observational study (1000 patients), Hewett *et al*[46] performed an initial withdrawal to the hepatic flexure in the standard forward view (SFV), with a repeat 2nd examination in the retroflexed view (RV). This was a single-centre study (without randomisation) and performed by only 2 endoscopists limiting its generalisability. Furthermore, the 2 endoscopists that were evaluated were also experts with considerable experience. An adenoma miss rate (AMR) of 9.8% in the 2nd examination in the retroflexed view was found[46], which is comparable to the AMR of studies with a 2nd examination in the standard view[47,48].

In a large observational study, (1351 consecutive patients) a comparison between ADR in the forward view *vs* ADR in the retroflexed view from the caecum to the hepatic flexure was performed. The study found that in the forward view, the ADR was 24.6% compared to the retroflexed view with an ADR of 26.4%, $P < 0.001$. The increase in ADR was small but did reach statistical significance. The limitations of this study are the lack of randomisation. As a double-take procedure was performed, the mere fact that a 2nd look examination was performed could account for the increased ADR, rather than because it was performed in retroflexion. The strengths of this study are that it was multi-centre (5 hospitals). In this study, the detection of polyps in the forward view was the only single predictor for the detection of additional polyps in the retroflexed view (odds ratio 4.13; 95%CI: 2.43-7.09; $P < 0.001$)[45]. This might add weight to the theory that if polyps are detected in the right colon on forward view, then a 2nd examination should be performed in retroflexion. The strengths of this study are the multi-centre design, representing both tertiary and private centres. However, the lack of randomization is a significant limitation[45].

In a randomized controlled study (parallel blind design), 850 patients were randomized to a 2nd right colon examination in either the forward view or retroflexed view. No statistically significant difference in the ADR was observed between the SFV and RV in the 2nd examination. Retroflexion may not be exposing all aspects of the colonic mucosa. The lack of difference between SFV and RV might also be explained by the lack of an endoscopist's ability to detect sessile serrated lesions (SSL), which are flatter, more difficult to detect and occur more commonly in the right colon. Interestingly this study did show a 20% adenoma miss rate in the right colon on the 2nd examination. Furthermore, the shape of colonic folds and colonic distension vary between each examination, so more polyps are exposed on 2nd view. This study was performed in 2 academic units, so although multi-centred only involved 2 centres. This does pose some limitations in the applicability of this in the widespread community. However, as 10 endoscopists with varying levels of experience participated, this did lessen any effect[49].

A large (1020 patient) observational study by Lee *et al*[50] where 3 colonic withdrawal examinations were performed; the first 2 in forward view and the 3rd in retroflexed view, demonstrated a statistically significant increase in the ADR in retroflexion than the ADR with the combined forward view examinations; forward view (25.5% ADR) *vs* total examination (27.5% ADR), $P < 0.001$. A transparent cap was used for each of the examinations. Polyps detected at each examination were then resected. In contrast to other studies[46,49], retroflexion was only successful in 82.4% of cases here. Lee *et al*[50] found that proximal colon retroflexion improved the ADR, despite 2 forward-view examinations beforehand. Caution should be used in the interpretation of this study as it has the confounding factor of the transparent cap in the colonic examination. The cap probably flattened the folds on subsequent examinations, with alteration in the shape of the haustra and the degree of luminal distension. Most of the adenomas identified in the retroflexed view were < 5 mm in size. The clinical significance of diminutive polyps is still undetermined and not likely to be very relevant[50].

A recent multi-centre RCT of 692 patients with a positive FIT test[51] randomized patients to a repeat right colon examination in standard forward view or retroflexed view. The repeat examination increased the ADR by 11%, with no statistically significant difference between SFV and RV; 12% and 9% respectively, $P = 0.21$. The detection of sessile serrated lesions in the right colon at the second examination was 11.1%, with no significant difference between SFV and RV. The success of retroflexion was only 83%. This study backs existing evidence that a repeat examination improves the ADR, whichever, view (SFV or RV) is adopted[46,47]. The strengths of this study are that it is a parallel blinded RCT across 3 Spanish centres. However, a limitation, in this case, is the lack of blinding of the endoscopists which could potentially incorporate more operator bias[51].

In an RCT of 205 patients randomly assigned to SFV or RV on 2nd examination of the whole colon, not just the right colon. The initial withdrawal was always in SFV. An increased adenoma detection rate was noted in the 2nd examination, despite whether there was randomization to either the SFV or the RV. A reasonable assumption to make is that the increased detection is related to the factor of a 2nd examination itself, rather than the examination technique. Most adenoma detection on the 2nd examination regardless of the limb of randomization was in the transverse and left-sided colon[52]. This is a relatively small study, limiting the opportunities for firm conclusions to be drawn[52].

A smaller (655-patient) observational study by Michopoulos *et al*[53] had a similar study design to Lee *et al*[50]. In this observational study, 2 withdrawal examinations were performed in the forward view and a 3rd in the retroflexed view. The transparent cap was not used in this study. A statistically significant improvement in the ADR in the retroflexed view was noted, in comparison to the forward view 22.75% *vs* 14.2%, $P < 0.01$. The improvement was more noticeable with diminutive adenomas and in the proximal 1/3 of the ascending colon[53]. This recent study showed the largest benefit of retroflexion. Polypectomy was performed after completion of the inspection, not immediately after detection. Most additional polyps noted in this study were diminutive and close to the hepatic flexure [53].

In a single-centre prospective observational study in a tertiary hospital, 463 patients were evaluated. When retroflexion was performed, additional adenoma was identified in 6.7% of patients, showing some benefit. In this study, the degree of right colon retroflexion was recorded as follows; grade 1; 1-2 haustra exposed and grade 3; ≥ 5 haustra exposed. A strength of this study was the evaluation of the degree of adequate mucosal exposure on retroflexion as most of the additional polyps (73.5%) were detected when a grade 3 right colon retroflexion (RCR) was recorded. This sub-group analysis was not reported in many of the other studies[54].

Studies have shown that retroflexion is relatively easy to perform with success rates ranging between 82.4%-96%[46,49-51,53,54]. Most studies have found no complications with proximal colon retroflexion [44,45,49,53]. One observational study found that 3% of patients had a minor bleed, 0.8% a mucosal tear and no cases of perforation with proximal colon retroflexion[55].

The evidence for proximal colon retroflexion is conflicting with some studies showing a benefit[45,50, 53] and others showing none[44,49]. A previous meta-analysis supported the idea that a 2nd standard forward view was equally successful in improving the ADR as a 2nd examination in the retroflexed view [56]. A more recent meta-analysis found that the additional detection of adenoma was lower in the retroflexed view in 4 RCTs than with SFV colonoscopy. This meta-analysis also found that in 6 observational studies, the ADR was marginally higher in combined examinations with a retroflexed view than in both single-pass and double-pass forward view examinations[57].

The evidence supports the role of a 2nd inspection of the right colon[56], especially when polyps are found in the 1st withdrawal[45]. A repeat colonic evaluation in a standard forward view is easier to perform than a retroflexed view. One should consider a repeat right colon examination, especially if right colonic polyps are noted on the initial withdrawal. Further information is needed before recommendations can be made to support the role of a repeat right colon examination in the retroflexed view (Table 5 and Table 6).

CONCLUSION

The performance of colonoscopy is highly variable amongst endoscopists. Evidence has shown that increasing the ADR can reduce the risk of interval colorectal cancer[12,13]. A considerable amount of research has focused on the skills and technologies that could potentially improve the ADR[30]. Skilled endoscopists use several withdrawal techniques to increase their adenoma detection rate. One single technique in isolation is unlikely to make a significant impact. For this minireview, we focused on evaluating the literature on the following aspects of operator technique; minimum withdrawal times, dynamic position change on withdrawal and proximal colon retroflexion. The evidence supporting each technique is conflicting.

Most of the available literature on the role of simple operator techniques in adenoma detection during colonoscopy are from retrospective and prospective studies. This poses a limitation on the conclusions that can be drawn from the findings, as the lack of randomization in these study designs introduces inherent bias. There are only a few large, multi-centred RCTs addressing this area.

The study designs discussed in this minireview have some limitations that apply across all forms of endoscopic trials. In most instances, it is not possible to blind the endoscopist to the intervention limb. The endoscopist is instructed to follow a particular technique or use a device and will instantly know what is being evaluated. This can introduce a degree of investigator bias. Most endoscopic trials are performed by enthusiastic endoscopists in academic hospitals. The translation of this evidence into widespread clinical practice can therefore be challenging. Single-centre studies pose a similar limitation.

Studies are often not adequately powered to detect differences between sub-groups. The adoption of various endoscopic techniques and technologies may be more effective in different endoscopists and different patient cohorts. One technique may be more beneficial to 'low adenoma detector' endoscopists in comparison to those with a high baseline ADR. The non-technological techniques outlined in this minireview may help endoscopists with a lack of experience to improve their ADR.

Similarly, techniques may have more of a role in the detection of diminutive polyps than larger polyps. The infrequent occurrence of larger polyps ≥ 1 cm poses a challenge in obtaining statistically significant data that show a difference in the intervention limb, as a very large trial will need to be performed. The practicality of arranging large multi-centre-controlled trials is often not possible in real-world research settings.

Studies showed a trend towards greater detection of small and diminutive adenomas in comparison to larger polyps ≥ 1cm across all the 3 operator techniques outlined[20,29,36,42,46,50]. Although the clinical significance of small polyps remains unclear[31], as data shows that ADR reduces the interval risk of colorectal cancer[12,13], even if this is more pronounced in small polyps, cancer prevention is likely to be improved.

SSLs are increasingly recognized as important precursor lesions to colorectal cancer. The evidence supporting the role of colonoscopy withdrawal techniques in this sub-group is limited. Data supporting the role of minimum withdrawal times[5,28], dynamic position change[36] and proximal colon retroflexion[51] show a positive trend towards increasing detection of SSLs. Further studies adequately powered to perform sub-group analysis for small polyps and sessile serrated lesions are required.

Studies have shown that interventions that focus on improving endoscopist technique have improved endoscopists' performance[58-62]. The initial QIC (Quality Improvement in Colonoscopy) study evaluated the outcomes of endoscopists following a training intervention that included withdrawal times of ≥ 6 min, supine position in the transverse colon, use of hyoscine butylbromide and rectal retroflexion. The study participants were evaluated 3 mo before and 9 mo after the implementation. 17508 colonoscopies were evaluated in total[58]. A 2.1% absolute increase in the ADR (P = 0.002) was noted after the training. The improvement was more noticeable amongst the lower-performing endoscopists. A limitation of this study is that bundle compliance was determined by the uptake of hyoscine butylbromide alone and might not reflect the uptake of all the other parameters. A strength of this study is that 12 community hospitals participated, which is more representative of widespread clinical practice. The follow-up study found that the training from the initial QIC study still maintained the ADR 3 years after, with a statistically significant improvement maintained amongst the poorer-performing endoscopists[59].

In the Endoscopic Quality Improvement Program (EQUIP) study[61] the baseline ADR of 15 endoscopists were calculated before 8/15 were randomized to a training intervention and 7/15 were not. An ADR of 47% was noted in the group that was randomized to the training intervention, in comparison to an ADR of 35% in those that did not receive training, P = 0.0013. The educational interventions consisted of the following: Withdrawal time, careful inspection behind folds, and adequate cleansing of the colonic mucosa. Video recordings were utilized as training. An NBI learning module was also used to teach differentiation between neoplastic and non-neoplastic polyps with the

Table 5 Summary of studies evaluating proximal colon retroflexion

Ref.	Year	*n*	Design
Harrison *et al*[44]	2004	100	RCT
Hewett *et al*[46]	2011	1000	Prospective
Chandran *et al*[45]	2015	1351	Prospective
Kushnir *et al*[49]	2015	850	RCT
Lee *et al*[50]	2017	1020	Prospective
Núñez Rodríguez *et al*[51]	2020	692	RCT
Rath *et al*[52]	2020	205	RCT
Michopoulos *et al*[53]	2021	655	Prospective

RCT: Randomized controlled trial.

Table 6 Results of studies evaluating proximal colon retroflexion

Ref.	Outcome	RV	SFV	*P* value
Harrison *et al*[44]	No difference in AMR in SFV *vs* RV	23.7%	33.3%	0.31
Hewett *et al*[46]	AMR in RV comparable to 2nd examination in SFV	NA	NA	NA
Chandran *et al*[45]	Increased ADR in RV *vs* SFV	26.40%	24.60%	< 0.001
Kushnir *et al*[49]	No difference in ADR in SFV *vs* RV	47%	46%	0.75
Lee *et al*[50]	Increased ADR in RV *vs* SFV	27.50%	25.50%	< 0.001
Núñez Rodríguez *et al*[51]	No difference in ADR in SFV *vs* RV	9%	12%	0.28
Rath *et al*[52]	No difference in ADR in SFV *vs* RV	42%	44.3%	0.88
Michopoulos *et al*[53]	Increased ADR in RV *vs* SFV	22.75%	14.20%	< 0.01

AMR: Adenoma miss rate; ADR: Adenoma detection rate; SFV: Standard forward view; RV: Retroflexed view; NA: Not available.

use of still images. The limitation of this study is that it was performed in a tertiary academic unit, so the results are not generalizable to routine widespread clinical practice. In this study, only 8 endoscopists received the training interventions. This is a relatively small number and more endoscopists need to be evaluated for the results to be more applicable[61]. The follow-up study 5 mo after the initial study showed that the ADR improvements were maintained in the EQUIP-trained group at 46%[62].

A plethora of evidence evaluating the use of technologies such as distal attachment devices, chromoendoscopy, and wide-angle colonoscopes has been published, with conflicting results[2,30,63]. Evidence shows that endoscopists with a low baseline ADR gain more from the use of distal attachment devices[2,64,65]. The use of these devices, is, however, seldom performed outside of academic institutions. The purpose of continuing to evaluate technologies that are not widely used by most Gastroenterologists should be questioned.

Meticulous technique by a skilled operator could be the most important factor. Instead of researching endoscopy technologies that are rarely used outside of a trial setting, perhaps the focus should be on evaluating quality intervention programs that focus on improving endoscopists ‘performance with simple operator skills.

Gathering the resources required to remove high-performing endoscopists from their day-to-day work to train lesser-performing endoscopists would pose significant challenges. Another option would be to encourage ‘low adenoma detector’ endoscopists to undergo a colonoscopy training course. A recent study did show a sustained improvement in the ADR amongst screening centre leaders who undertook a ‘Train the Colonoscopy Leaders ‘course with improvement in the performance of the overall centre, sustained over 1.5 years[60]. Further work is required in this area.

FOOTNOTES

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Country/Territory of origin: United Kingdom

ORCID number: Ragul Rajivan 0000-0002-3605-3978; Sreedhari Thayalasekaran 0000-0002-6290-2144.

Corresponding Author's Membership in Professional Societies: British Society of Gastroenterology, No. BSG61606.

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MINIREVIEWS

Rectal neuroendocrine tumours and the role of emerging endoscopic techniques

Eoin Keating, Gayle Bennett, Michelle A Murray, Sinead Ryan, John Aird, Donal B O'Connor, Dermot O'Toole, Conor Lahiff

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Eoin Keating, Gayle Bennett, Conor Lahiff, Department of Gastroenterology, Mater Misericordiae University Hospital, Dublin 7, Ireland

Eoin Keating, Gayle Bennett, Michelle A Murray, John Aird, Conor Lahiff, School of Medicine, University College Dublin, Dublin 4, Ireland

Michelle A Murray, National Lung Transplant Unit, Mater Misericordiae University Hospital, Dublin 7, Ireland

Sinead Ryan, John Aird, Department of Pathology, Mater Misericordiae University Hospital, Dublin 7, Ireland

Donal B O'Connor, Department of Surgery, Tallaght University Hospital, Dublin 24, Ireland

Donal B O'Connor, Dermot O'Toole, School of Medicine, Trinity College Dublin, Dublin 2, Ireland

Dermot O'Toole, Department of Clinical Medicine and Gastroenterology, St. James Hospital, Dublin 8, Ireland

Corresponding author: Eoin Keating, MBChB, MRCP, Doctor, Department of Gastroenterology, Mater Misericordiae University Hospital, Eccles Street, Dublin 7, Ireland. eoinkeating@mater.ie

Abstract

Rectal neuroendocrine tumours represent a rare colorectal tumour with a 10 fold increased prevalence due to incidental detection in the era of colorectal screening. Patient outcomes with early diagnosis are excellent. However endoscopic recognition of this lesion is variable and misdiagnosis can result in suboptimal endoscopic resection with subsequent uncertainty in relation to optimal long-term management. Endoscopic techniques have shown particular utility in managing this under-recognized neuroendocrine tumour.

Key Words: Rectal neuroendocrine tumour; Carcinoid; Endoscopic mucosal resection; Endoscopic submucosal dissection; Knife-assisted snare resection

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Core Tip: Rectal neuroendocrine tumours (r-NETs) are increasingly detected during colorectal screening. Endoscopists may not accurately distinguish r-NETs from other polyps and inadvertent resection attempts result in significant post resection challenges. r-NETs have an unpredictable metastasis pattern, requiring appropriate pre-resection assessment. Accurate endoscopic assessment and resection provides an effective option in the management of r-NETs.

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INTRODUCTION

Neuroendocrine tumours (NETs), previously described as carcinoid tumours, describes a classification of neoplastic cells originating from a neuroendocrine cell lineage. NETs can occur in multiple organ systems throughout the body and have a specific classification criteria according to the World Health Organization (WHO)[1]. These criteria include a grading of tumours based on mitotic counts and Ki-67 proliferation index (G1/G2/G3). The gastroenteropancreatic tract is the most common site for NETs (GEP-NETs), accounting for 73.7% of all NETs[2]. Overall, colonic NETs remain a rare occurrence compared to colorectal adenocarcinoma incidence rates, accounting for only 1.5% of all colorectal cancers[3].

Rectal neuroendocrine tumours (r-NETs) are one of the most frequent sites of GEP-NETs, representing 27% of GEP-NETs and 18% of all NETs[4]. The incidence of r-NETs is estimated to have risen 10 fold over the past 4 decades, attributed to increased incidental detection during colorectal cancer screening[5]. Weinstock *et al*[6] demonstrated that the majority of r-NETs are asymptomatic, with only a minority reporting symptoms such as altered bowel habit (12.8%), rectal bleeding (6.4%) or unexplained weight loss (2.1%). The carcinoid syndrome of flushing or diarrhoea is rarely associated with r-NETs[7].

The primary prognostic factor for r-NETs is driven by the disease stage at diagnosis. Five year survival for localised disease is excellent with rates of 94%-100%[8]. Regional and metastatic spread are uncommon as 75%-85% of r-NETs are localised at time of diagnosis[9]. According to the WHO grading criterion, r-NETs are predominantly G1 or G2 due to low proliferative activity.

The risk factors for nodal involvement or metastatic disease include lymphovascular invasion, muscularis propria involvement and tumour size/grade[8-10]. Pre-resection staging with endoscopic ultrasound (EUS) or magnetic resonance imaging (MRI) is necessary to adequately assess for regional or metastatic disease. Multiple approaches to achieve R0 resection may be utilised, primarily depending on lesion size, such as endoscopic mucosal resection (EMR, band or ligation approach), endoscopic submucosal dissection (ESD), combination approaches [*e.g.*, knife-assisted snare resection (KAR)] or surgical approaches such as transanal resection (*e.g.*, Transanal endoscopic microsurgery) or radical resections.

The classical described endoscopic appearance of r-NETs is of a small, typically < 20 mm, solitary nodule with a yellow coloration, embedded in the rectal submucosa. However, the correct endoscopic diagnosis of r-NET is not always achieved by the endoscopist, demonstrated by Fine *et al*[11], to be as low as 18%. As prognosis in r-NETs is dependent on the appropriate resection method, lack of recognition may result in a compromised initial resection, affecting patient prognosis.

PLANNED RECTAL NEUROENDOCRINE TUMOUR MANAGEMENT

Endoscopic diagnosis and inspection of r-NETs

The standard description of an r-NET at endoscopy is of a solitary nodular structure, appearing to be embedded in the normal rectal mucosa, and most often associated with a yellow coloration. r-NETs can be endoscopically differentiated from rectal adenomas by the presence of overlying normal rectal mucosa. The majority of r-NETs are < 20 mm in size[6] and increasing tumour size is also associated with increased risk of metastasis, especially once size exceeds 20 mm[12]. Lesion size is thus a primary consideration in planning excision strategies.

However, metastatic disease has been confirmed in small r-NETs of < 10 mm diameter[13], indicating that tumour size cannot be used in isolation. Therefore close inspection of the surface mucosa at endoscopy is required as the presence of overlying ulceration, depression or erosions is also associated with tumour metastasis[14].

Pre-intervention management

If r-NET is suspected at time of endoscopy, the European Neuroendocrine Tumour Society (ENETS) guidelines, published in 2012 and revised in 2016, recommends completing a pre-intervention workup with a rectal EUS to establish tumour size, tumour depth (including involvement of muscularis propria) and evidence of lymphovascular involvement[5,9,15]. EUS accuracy of tumour depth is high, with rates of 91-100% correlation with post-resection findings reported[16,17]. Accurate, pre-intervention EUS is therefore essential in determining r-NET stage and selection of optimal resection strategy.

r-NETs of > 10 mm in size are also recommended to undergo MRI pelvis examination to assess for muscularis propria invasion and lymphovascular involvement. If muscularis propria involvement or nodal positivity is confirmed, a surgical approach with anterior resection and total mesenteric excision is recommended[9].

Beyond a lesion size of 20 mm, the risk of r-NET metastasis is significant and evaluation with CT thorax, abdomen and pelvis, in addition to MRI pelvis is required, prior to surgical management[8,9].

Endoscopic resection approaches

As outlined above, resection approach for r-NETs depends on accurate assessment of size, grade (if biopsies completed) and locoregional involvement. Complete excision of r-NETs < 10 mm is considered the gold standard and can be safely achieved using advanced endoscopic techniques[5,8].

Strategies to excise r-NETs of 10-19 mm in size have not reached consensus acceptance and there are no comparative studies of endoscopic resection *vs* surgical outcomes for this size cohort[9,15,18]. The requirement for a general anaesthetic for surgical approaches such as transanal endoscopic microsurgery may favour advanced endoscopic techniques in a selection of patients. A metastatic risk of 10%-15% is quoted for this category[10]. Therefore, a case-by-case strategy may be required for r-NETs 10-19 mm in size, based on patient characteristics (*e.g.*, comorbidities), in addition to the EUS and/or MRI findings predicting potential locoregional spread or metastatic disease.

The ENETS 2012 guideline stipulates that the only guaranteed curative option is complete resection in a localised lesion[9]. Pathological interpretation of r-NET margin clearance is therefore of primary importance to determine risk of locoregional spread. En-bloc resections are preferential to piecemeal resection to aid pathological assessment. The goal of achieving en-bloc pathology specimens influences the choice of advanced endoscopic technique employed to resect the r-NET (Table 1).

EMR

EMR is widely used in the safe and successful resection of large non-pedunculated colorectal polyps (LNPCPs) by Western endoscopists[19]. Conventional EMR (C-EMR) en-bloc resection rates in Western centres, across all polyp sizes, approach 35%[20]. En-bloc resections have significantly lower rates of recurrence over piecemeal EMR[21]. In relation to r-NETs therefore, caution must be exercised in lesion assessment, to ensure that an en-bloc resection is feasible.

C-EMR

The ENETS guidelines endorse the use of C-EMR for r-NET lesions < 10 mm in size, once muscularis propria involvement has been out ruled with rectal EUS[15]. However, Nakamura *et al*[22] demonstrated that C-EMR had complete resection rates of 36.4% and curative resection rates of only 27.3%.

Modified EMR

In the same Nakamura study, modified EMR (M-EMR) strategies such as band ligation EMR or cap assisted EMR achieved significantly higher complete resection and curative resection rates, 88.0% and 69.4% respectively. Additionally, M-EMR achieved a 100% en-bloc resection rate. While this study was limited by a small number of EMRs (n = 11), its results are consistent with other studies regarding EMR resection of r-NETs outcomes and support the use of M-EMR over C-EMR for resection of r-NETs < 10 mm.

With regard to cap-assisted EMR (EMR-C), it is superior to EMR in complete histologic resection rates (94.1% *vs* 76.8%) without significant additional perforation or bleeding risks[23]. Similarly for band ligation EMR, complete resection rates outperform C-EMR, 93.3% *vs* 65.5% respectively, again without additional procedural times or complication rates[24].

M-EMR is restricted in its use to lesions < 10 mm in size, due to the specifications of the band or cap diameter of the equipment. M-EMR outcomes, for r-NETs < 10 mm in diameter, approach the resection results of ESD[5], and may be more accessible to Western endoscopists who lack suitable ESD exposure. A recent Japanese study demonstrated superior M-EMR complete resection rates and lower recurrence rates *vs* ESD, but this did not reach significance[25]. Yang *et al*[23] have also demonstrated that EMR-C histologic resection rates approach those of ESD (94.1% *vs* 93.8%) , but again, this did not reach significance.

Table 1 Endoscopic techniques for rectal neuroendocrine tumour resection

Technique	Size limitation	En bloc resection rate (%)	R0 resection rate (%)	Procedural time (min)	Availability
C-EMR	< 10 mm	36.4-80	27.3-76.8	3.3 ± 0.8	Widely available
M-EMR	< 10 mm	89.3-100	88.0-93.5	5.7 ± 1.2	Available
EMR-C	< 10 mm	87.0-100	69.4-94.1	4.2 ± 2.0	Available
ESD	< 20 mm	98.2-100	90.38-93.8	8.1 ± 9.4/19.8 ± 11.3	Limited to experienced centres
KAR	< 10 mm	Limited to case series	Limited to case series	Limited to case series	Available

C-EMR: Conventional endoscopic mucosal resection; M-EMR: Modified endoscopic mucosal resection; EMR-C: Cap-assisted endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; KAR: Knife-assisted snare resection.

The ENETS 2016 guidelines, factoring the improved en-bloc resection rates, recommend M-EMR, and specifically band ligation EMR, for r-NET resections of lesions < 10 mm[15].

ESD

ESD uses an endoscopically deployed thermal-knife to dissect the submucosal plane, facilitating en-bloc resection and aiding pathological interpretation. ESD was pioneered in Japan for the resection of gastric neoplasia and consequently, there are significant differences in the R0 outcomes and exposure to ESD practice between Asian and non-Asian countries[26].

ESD affords excellent r-NET en-bloc resection rates ranging from 98.2% to 100% and high R0 resection rates (90.38%-90.9%) for lesions < 20 mm[27,28]. Due to these superior outcomes, systematic reviews have recommended ESD over EMR for the resection of r-NETs < 10 mm and for ESD consideration in lesions < 20 mm[27,29].

Analysing the utility of ESD, there are several limitations to consider. Colonic ESD for LNPCPs is associated with higher complication rates including perforation and post-polypectomy bleeding (PPB) when compared to EMR[30]. Specifically considering r-NETs, there is a non-significant trend towards perforation and PPB but this is limited by small sample sizes[31]. Increased endoscopist experience is associated with a reduction in ESD complication rates[27]. Another consistent limitation of ESD is the increased procedural time required *vs* EMR[29,31].

Chen *et al*[27] also highlighted the coagulation or burn effect on normal tissues at time of ESD and potential effects on R0 pathologic interpretation. To counter this phenomenon, Yoshii *et al*[32] demonstrated an “underwater” ESD approach which afforded a heat sink effect, successfully limiting burn artefact.

Hybrid technique-KAR

ESD requires extensive training and procedural exposure to perform safely and effectively with a significant learning curve[33]. As demonstrated above, ESD outcomes differ between Asian and non-Asian endoscopists. Attempting to accelerate the learning curve of ESD for Western endoscopists has led to the development of a hybrid technique, combining familiar EMR practices with elements of ESD.

KAR described by Bhattacharya *et al* in the resection of LNPCPs incorporates standard submucosal injection, followed by circumferential submucosal dissection[34]. Once a circumferential margin has been established, a snare is deployed to facilitate en-bloc resection. The study achieved a 53% en- bloc resection rate in polyps < 50 mm in size and demonstrated a recurrence rate of 4.3% for en-bloc specimens. The KAR technique was subsequently shown to be effective in the management of scarred polyps with previous EMR[35].

Lisotti *et al*[36] applied the KAR technique for two < 5 mm r-NETs in a case series, successfully achieving en-bloc resections and negative resection margins. The following case report from our institution further illustrates the utility of KAR in this context.

We present the case of a 33-year-old male with a background history of cystic fibrosis, referred for consideration for lung transplantation. During a pre-transplantation screening colonoscopy at a local hospital a 6mm submucosal lesion was identified 3 cm above the anorectal junction (Figure 1A). Re-evaluation at our institution included EUS, which confirmed a hypoechoic, homogenous, well circum-scribed lesion, arising from the submucosa and consistent with a r-NET (Figure 1B). Submucosal injection (gelofusion and methylene blue) was followed by hybrid KAR to successfully achieve en-bloc resection (Figure 1C and D). Histopathological examination confirmed a grade 1, well-differentiated neuroendocrine tumour, with no evidence of lymphovascular involvement and negative margins (Figure 1F). After multidisciplinary discussion, and corresponding to 2012 ENETs guidelines on sub-centimetre r-NETs, surveillance was not considered necessary for this 6mm lesion and the patient has

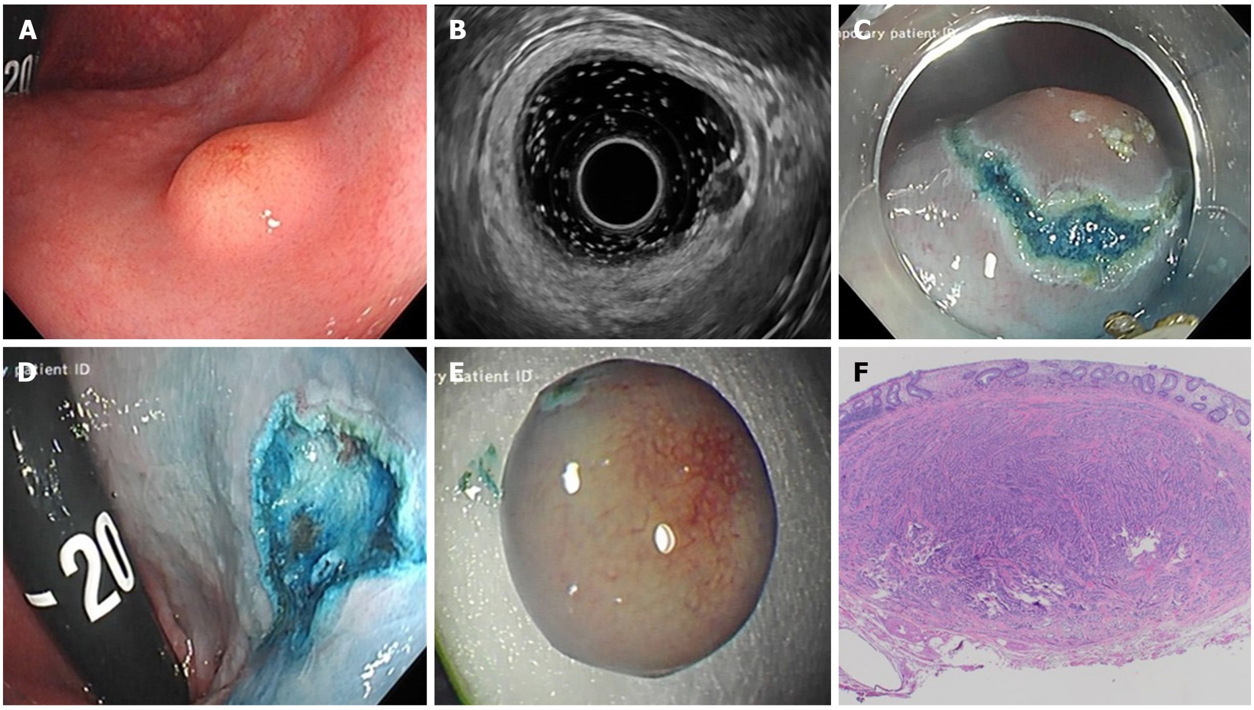

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Figure 1 Case of a 33-year-old male with a background history of cystic fibrosis, referred for consideration for lung transplantation. A: Endoscopic image of 6mm rectal neuroendocrine tumour (r-NRT) in retroflexion, 3 cm from anal verge; B: Endoscopic ultrasound images of the same 6 mm hypoechoic homogenous lesion, seen at 10 MHz frequency, consistent with a NET; C: Endoscopic image of hybrid Knife assisted snare resection approach; post circumferential submucosal incision; D: Endoscopic image of post en-bloc knife-assisted snare resection site in retroflexion; E: Excised en-bloc r-NET specimen; F: Neuroendocrine tumour composed of neuroendocrine cells arranged in anastomosing trabeculae with overlying rectal mucosa. The tumour is well circumscribed and has been excised (haematoxylin and eosin stain, 20× magnification).

been listed for transplantation.

Surveillance post resection

ENETS guidelines for surveillance post r-NET resection are determined by size, in addition to mitotic grade[9]. Follow-up modalities recommended include colonoscopy, rectal EUS and cross sectional imaging. G1 or G2 r-NETS, < 10 mm in size, with no evidence of lymphovascular invasion or muscularis propria involvement are not recommended for follow-up at present. All r-NETs 10-20 mm require annual endoscopic follow up. r-NETs > 20 mm require intensive follow-up due to the risk of metastasis.

The surveillance guidelines have generated debate, particularly for r-NETs of <10mm in diameter. The reported metastatic risk of these small r-NETs has varied from 0% to 10%[16,37,38]. Holinga *et al* [38], proposed an intensive EUS surveillance programme at 3 mo post resection, in addition to 6 moly EUS for the 3 years post resection.

MANAGEMENT OF INCIDENTAL OR UNRECOGNISED R-NETS

Prevalence

Fine *et al*[11] confirmed that the real time endoscopic recognition of r-NETs is low at only 18%. Of 284 unsuspected r-NETs in the French study, 190 (67%) underwent attempted resection, primarily by standard polypectomy (n = 148/190, 78%)[11]. The successful R0 resection rate for patients who underwent polypectomy at initial colonoscopy was only 17%. As the prognosis of r-NETs depends on the successful complete excision of the lesion, salvage therapies such as EMR, ESD or trans-anal endoscopic microsurgery were required.

Surveillance

The retrospective diagnosis of r-NET poses a challenge in determining appropriate surveillance. Polypectomy or piecemeal EMR are often associated with R1 pathology as well as difficulty assessing for lymphovascular invasion, a key factor in surveillance algorithms. Therefore, appropriate surveillance for these cases is yet to be determined and results in local variation in practice. Such difficulties can largely be avoided by accurate index endoscopic assessment.

CONCLUSION

Rectal neuroendocrine tumours represent a rare colorectal tumour, with increasing prevalence due to incidental diagnosis during standard colorectal screening. Accurate endoscopic recognition rates of r-NETs are disappointing and the area requires increased focus in endoscopy training to improve specificity. Endoscopist education on the differentiation of rectal adenomas from r-NETs is a priority in this regard. Management strategies for diagnosed r-NETS are well established. Advanced endoscopic resection techniques have resulted in improved outcomes and can be an effective alternative for surgical resection for intermediate (10-19 mm) r-NETs but further studies are required. Newer techniques such as KAR may be valuable but require further study. International surveillance guidelines are clear but adherence to guidelines is variable and need to be more consistently applied.

FOOTNOTES

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Country/Territory of origin: Ireland

ORCID number: Eoin Keating 0000-0002-1466-8752.

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ORIGINAL ARTICLE

Case Control Study

Effect of modified ShengYangYiwei decoction on painless gastroscopy and gastrointestinal and immune function in gastric cancer patients

Sui-Cai Mi, Ling-Yan Wu, Zheng-Jin Xu, Li-Yan Zheng, Jian-Wen Luo

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Sui-Cai Mi, Jian-Wen Luo, Department of Oncology, Xiamen Hospital of Traditional Chinese Medicine, Xiamen 361000, Fujian Province, China

Ling-Yan Wu, Zheng-Jin Xu, Department of Nephropathy, Xiamen Hospital of Traditional Chinese Medicine, Xiamen 361000, Fujian Province, China

Li-Yan Zheng, Department of Anesthesiology, Xiamen Hospital of Traditional Chinese Medicine, Xiamen 361000, Fujian Province, China

Corresponding author: Ling-Yan Wu, MMed, Deputy Director, Department of Nephropathy, Xiamen Hospital of Traditional Chinese Medicine, No. 1739 Xianyue Road, Huli District, Xiamen 361000, Fujian Province, China. 418569189@qq.com

Abstract

BACKGROUND

Painless gastroenteroscopy is a widely developed diagnostic and treatment technology in clinical practice. It is of great significance in the clinical diagnosis, treatment, follow-up review and other aspects of gastric cancer patients. The application of anesthesia techniques during manipulation can be effective in reducing patient fear and discomfort. In clinical work, the adverse drug reactions of anesthesia regimens and the risk of serious adverse drug reactions are increased with the increase in propofol application dose application dose; the application of opioid drugs often causes gastrointestinal reactions, such as nausea, vomiting and delayed gastrointestinal function recovery, after examination. These adverse effects can seriously affect the quality of life of patients.

AIM

To observe the effect of modified ShengYangYiwei decoction on gastrointestinal function, related complications and immune function in patients with gastric cancer during and after painless gastroscopy.

METHODS

A total of 106 patients with gastric cancer, who were selected from January 2022 to September 2022 in Xiamen Traditional Chinese Medicine Hospital for painless gastroscopy, were randomly divided into a treatment group (n = 56) and a control group (n = 50). Before the examination, all patients fasted for 8 h, provided their health education, and confirmed if there were contraindications to anesthesia and gastroscopy. During the examination, the patients were placed in the left decubitus position, the patients were given oxygen through a nasal catheter (6 L/min), the welling needle was opened for the venous channel, and a multifunction detector was connected for monitoring electrocardiogram, oxygen saturation, blood pressure, *etc.* Naporphl and propofol propofol protocols were used for routine anesthesia. Before anesthesia administration, the patients underwent several deep breathing exercises, received intravenous nalbuphine [0.nalbuphine (0.025 mg/kg)], followed by intravenous propofol [1.propofol (1.5 mg/kg)] until the palpebral reflex disappeared, and after no response, gastroscopy was performed. If palpebral reflex disappeared, and after no response, gastroscopy was performed. If any patient developed movement, frowning, or hemodynamic changes during the operation (heart rate changes during the operation (heart rate increased to > 20 beats/min, systolic blood pressure increased to > 20% of the base value), additional propofol [0.propofol (0.5 mg/kg)] was added until the patient was sedated again. The patients in the treatment group began to take the preventive intervention of Modified ShengYangYiwei decoction one week before the examination, while the patients in the control group received routine gastrointestinal endoscopy. The patients in the two groups were examined by conventional painless gastroscopy, and the characteristics of the painless gastroscopies of the patients in the two groups were recorded and compared. These characteristics included the total dosage of propofol during the examination, the incidence of complications during the operation, the time of patients' awakening, the time of independent activities, and the gastrointestinal function of the patients after examination, such as the incidence of reactions such as malignant vomiting, abdominal distension and abdominal pain, as well as the differences in the levels of various immunological indicators and inflammatory factors before anesthesia induction (T0), after conscious extubation (T1) and 24 h after surgery (T2).

RESULTS

There was no difference in the patients' general information, American Society of Anesthesiologist classification or operation time between the two groups before treatment. In terms of painless gastroscopy, the total dosage of propofol in the treatment group was lower than that in the control group ($P < 0.05$), and the time of awakening and autonomous activity was significantly faster than that in the control group ($P < 0.05$). During the examination, the incidence of hypoxemia, hypotension and hiccups in the treatment group was significantly lower than that in the control group ($P < 0.01$). In terms of gastrointestinal function, the incidences of nausea, vomiting, abdominal distension and abdominal pain in the treatment group after examination were significantly lower than those in the control group ($P < 0.01$). In terms of immune function, in both groups, the number of CD4+ and CD8+ cells decreased significantly ($P < 0.05$), and the number of natural killer cells increased significantly ($P < 0.05$) at T1 and T2, compared with T0. The number of CD4+ and CD8+ cells in the treatment group at the T1 and T2 time points was higher than that in the control group ($P < 0.05$), while the number of natural killer cells was lower than that in the control group ($P < 0.05$). In terms of inflammatory factors, compared with T0, the levels of interleukin (IL) -6 and tumor necrosis factor-alpha in patients in the two groups at T1 and T2 increased significantly and then decreased ($P < 0.05$). The level of IL-6 at T1 and T2 in the treatment group was lower than that in the control group ($P < 0.05$).

CONCLUSION

The preoperative use of modified ShengYangYiwei decoction can optimize the anesthesia program during painless gastroscopy, improve the gastrointestinal function of patients after the operation, reduce the occurrence of examination-related complications.

Key Words: Modified ShengYangYiwei decoction; Gastric cancer patients; Painless gastroscope; Gastrointestinal function

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Core Tip: The preoperative use of modified ShengYangYiwei decoction can optimize the anesthesia program during painless gastroscopy, significantly reduce the total dose of propofol during the examination without affecting the quality of the examination, thereby shortening the time of awakening and independent activity, and reducing the occurrence of hypoxemia, hypotension and hiccup during the examination; It improves the gastrointestinal function of patients after operation, reduces the incidence of nausea, vomiting, abdominal distension, abdominal pain and other complications of patients, reduces the inhibition of opioids on the immune system of the body, reduces the inflammatory reaction of patients, is beneficial to the development of painless gastroscopy for gastric cancer patients in clinical practice, reduces the occurrence of examination related complications, and improves the compliance and tolerance of treatment.

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INTRODUCTION

Painless gastroenteroscopy is a widely developed diagnostic and treatment technology in clinical practice. It is of great significance in the clinical diagnosis, treatment, follow-up review and other aspects of gastric cancer patients. It can also be used to evaluate patients with reflux esophagitis, esophageal cancer, gastroduodenal ulcer, *etc*[1,2]. The application of anesthesia techniques during manipulation can be effective in reducing patient fear and discomfort[3]. Propofol combined with opioids are common clinical drugs for painless endoscopic sedation and anesthetics[4]. On the one hand, in clinical work, the adverse drug reactions and the risk of anesthesia regimens are increased with the increase in propofol application dose; on the other hand, the application of opioid drugs often causes gastrointestinal reactions, such as nausea, vomiting and delayed gastrointestinal function recovery, after examination. These adverse effects can seriously affect the quality of life of patients.

Modified ShengYangYiwei decoction is related to Li Dongyuan's theory, which has the effect of replenishing Qi and rising Yang, clearing heat and detoxification, and removing dampness and turbidity. It has achieved fine effect in the field of digestive endoscopy[5]. Therefore, this study observed the treatment interventions of gastric cancer patients and observed the impact on patients' gastrointestinal function, related complications and immune function during and after painless gastroscopy.

MATERIALS AND METHODS

Clinical data

This study was approved by the Medical Ethics Committee of the Xiamen Hospital of Traditional Chinese Medicine (2022-K028-01), and informed consent was signed by all patients.

The inclusion criteria were as follows: (1) Aged 18–65 years, with a body mass index index of 28 kg/m^2; (2) American Society of Anesthesiologist grade of I-II; and (3) no contraindications for gastroscopy.

The exclusion criteria were as follows: (1) Major cardiovascular and cerebrovascular diseases and failure to cooperate with the examination; (2) gravida; (3) propofol, opioid allergy or intolerance; and (4) psychotropic drugs use or abnormal coagulation function before surgery.

General Information: A total of 106 gastric cancer patients from January 2022 to September 2022 who were selected for painless gastroscopy in Xiamen Hospital of Traditional Chinese Medicine, were divided into a treatment group (n = 56) and a control group (n = 50) by the random number table method. The purpose of painless gastroscopy for the two groups of patients is to conduct health screening and timely diagnosis. The general data between the two groups were not significantly different (P > 0.05) and were comparable Table 1.

Treatment methods

Before the examination, all patients fasted for 8 h, provided their health education, and confirmed if there were contraindications to anesthesia and gastroscopy. During the examination, the patients were

Table 1 Comparison of the general data between the two patient groups

Group	Sex		ASA classify		Median age (age)
	Man	Woman	I level	II level	
Treatment group (*n* = 56)	32	24	44	12	36 (20-66)
Control group (*n* = 50)	26	24	42	8	41 (19-61)
χ^2/t value	0.564		0.218		0.461
P value	> 0.05		> 0.05		> 0.05

ASA: American Society of Anesthesiologist.

placed in the left decubitus position, the patients were given oxygen through a nasal catheter (6 L/min), the welling needle was opened for the venous channel, and a multifunction detector was connected for monitoring electrocardiogram, oxygen saturation, blood pressure, *etc.*

For the control group, the protocols followed the Expert Consensus on Sedation and Anesthesia in the Diagnosis and Treatment of Digestive Endoscopy in China[6]. Naporphl and propofol protocols were used for routine anesthesia. Before anesthesia administration, the patients underwent several deep breathing exercises, received intravenous nalbuphine (0.025 mg/kg), followed by intravenous propofol (1.5 mg/kg) until the palpebral reflex disappeared, and after no response, gastroscopy was performed. If any patient developed movement, frowning, or hemodynamic changes during the operation (heart rate increased to > 20 beats/min, systolic blood pressure increased to > 20% of the base value), additional propofol (0.5 mg/kg) was added until the patient was sedated again.

The patients in the treatment group began oral Modified ShengYangYiwei decoction one week before gastroscopy, with one dose a day, compared with the control group. The Modified ShengYangYiwei decoction specific composition is "30 g of ginseng, 9 g of atractylodes macrocephala, 9 g of poria, 60 g of astragalus, 15 g of white peony, 30 g of pinellia ternata, 6 g of rhizoma coptidis, 9 g of rhizoma alismatis, 12 g of dried tangerine peel, 10 g of magnolia officinalis, 9 g of rhizoma Notopterygii, 9 g of angelica pubescens, 9 g of fangfeng, 9 g of bupleurum chinense, 5 g of ginger, 6 g of jujube (denuded), 6 g of cohosh, 9 g of kudzu, 9 g of pueraria lobata, 15 g of Shijian Chuan, 12 g of divine koji, and 6 g of raw licorice". Boil and concentrate the drug with 500 mL water to 200 mL, twice in total. Then divide into two portions and take orally after breakfast and dinner.

Observation indicators: The painless gastroscopy data was recorded: (1) In the two groups, and these data included the operation time (from the beginning to the end of the examination), awakening time (From the end of the examination to the time when the patient can correctly answer questions such as his name and birthday), autonomous walking time (from the end of the examination to when the patient can go to bed and walk steadily), the total dose of propofol during the examination; (2) the incidence of complications (hypoxemia, hypotension, hiccup, *etc.*) during anesthesia; (3) gastrointestinal reactions (nausea, vomiting, abdominal distension, abdominal pain, *etc.*) occurred after examination; and (4) T-cell subsets and inflammatory levels at different times. T-cell subpopulation was detected by flow cytometry, and the level of inflammatory factors was detected by biochemical immunoassay.

Statistical methods

SPSS 22.0 software was used for data analysis. The measurement data are expressed as (mean ± SD), after verifying the normal distribution of indicators in each group and *t* tests were utilized. The counting data are expressed as [*n* (%)] using χ^2 analysis. The *F* test for analysis of variance was used for comparisons among multiple groups, and the difference was considered statistically significant if $P < 0.05$.

RESULTS

Comparison of gastroscopy between the two groups

The operation time of gastroscopy was 4-6 min, without any obvious difference ($P > 0.05$); the awakening time of the treatment group were significantly faster than the control group ($P < 0.05$); the Self-ambulation time of the treatment group were significantly faster than the control group ($P < 0.05$) and for the treatment, the total dose of propofol was was significantly lower than the control group ($P < 0.01$), shown in Table 2.

Comparison of complication occurrence during the examination between the two groups

In the two groups, hypoxemia, hypotension and hiccups were common during painless gastroscopy,

Table 2 Comparison of gastroscopy in the two groups

Group	Operation time (min)	Wakeup time (min)	Self-ambulation time (min)	Total dose of propofol (mg)
Treatment group (*n* = 56)	4.43 ± 2.41	3.36 ± 0.27	6.02 ± 0.26	115.36 ± 8.17
Control group (*n* = 50)	4.35 ± 2.33	6.71 ± 0.34	7.68 ± 0.61	146.21 ± 10.17
t value	0.497	4.215	3.234	3.213
P value	> 0.05	< 0.01	< 0.05	< 0.01

and the incidences of these complications were lower than that in the control group. There were significant differences ($P < 0.05$), as shown in Table 3.

Comparison of gastrointestinal function after completing the examination in the two groups

After the end of the examination, as shown in Table 4, the incidence of abdominal distension, nausea, abdominal pain, and vomiting in the treatment group was significantly lower than that in the control group ($P < 0.05$).

Immune cell numerical values at different times

At T0, there was no significant difference in the CD4+, CD8+, and natural killer (NK) cell numbers between the two groups ($P > 0.05$). After examination, the CD4+ and CD8+ cells and NK cells at T1 and T2 were significantly decreased ($P < 0.05$). Comparing the two groups, the CD4+ and CD8+ cells at T1 and T2 were higher than that in the control group ($P < 0.05$); and NK cells at T1 and T2 were lower than that in the control group ($P < 0.05$) Table 5.

Comparison of inflammatory factors at different times

At the T0 time point, the interleukin (IL) -6 and tumor necrosis factor-alpha (TNF-α) levels were comparable ($P > 0.05$); after the examination operation, IL-6 and TNF-α at T1 and T2 were significantly higher than before the examination ($P < 0.05$). With further comparisons between the two groups, IL-6 and TNF-α at T1 and T2 were significantly lower than the control group ($P < 0.05$), as shown in Table 6.

DISCUSSION

Painless gastroscopy is gradually becoming a widely accepted examination means in the clinical diagnosis and treatment of gastric cancer, premalignant diseases, tissue mucosal lesions and other diseases[7,8]. The use of propofol in combination with naborphine painless treatment has become a safer anesthesia regimen commonly used in clinical practice[9-11]. However, patients with gastric cancer have a poor physique and are often more prone to anesthesia-related adverse reactions and gastrointestinal-related complications during examination[12]. At present, combining other methods to further reduce the impact of examination on gastrointestinal function in gastric cancer patients has become an area of exploration in current research.

We have summarized the experience in clinical practice for a long time and formed a special treatment agreement of "Modified Shengyang Yiwei Decoction". In this prescription, the whole recipe can replenish the middle and disperse the hair and recover the hair so that the positive qi can be sufficient, and the yang qi can be generated. It can improve the local inflammatory response of the gastric mucosa, regulate the imbalance between cell proliferation and apoptosis, repair the local blood circulation of the gastric mucosa, and improve the pathological state of the gastric mucosa[13]. Xu *et al*[14] found that Shengyangyi gastric soup could inhibit the expression of nuclear factor-kappaB (NF-κB), B cell lymphoma-2 (Bcl-2), c-myc, and Cyclin-D1 in the gastric mucosa tissue of precancerous lesions of gastric cancer (PLGC) rats and regulate gastric mucosal cell apoptosis, thus improving the gastrointestinal function of patients. Zeng *et al*[15] found that it inhibited the conduction of the NF-κB/ signal transducer and activator of transcription 3 signaling pathway, with significant upregulation of target gene p21 expression, downregulation of Bcl-2 and c-myc, and reduced expression of the inflammatory factors mediated by it. Zhao *et al*[16] found that the application of Shengyangyi gastric soup, and the scattered knot method can promote the wound healing of hyperplastic gastric polyps after gastroscopy and may reduce the degree of their precancerous lesions by reducing the expression of Bcl-2, which has positive significance for the prevention and treatment of hyperplastic polyps and their precancerous lesions. Wu *et al*[17] also found that the intervention treatment of Shengyang Yiwei decoction on PLGC rats can upregulate the expression of p16 and wild-type p53 protein, promote local microvascular proliferation, and improve the structure of patients' gastrointestinal mucosa, and they confirmed that Shengyang Yiwei decoction can effectively block the disease progression of precancerous lesions of gastric cancer. This shows that Modified Shengyang Yiwei Decoction can improve the repair

Table 3 Comparison of complications between the two groups during anaesthesia, *n* (%)

Group	Hypoxemia	Hypotension	Hiccup	*F* value	*P* value
Treatment group (*n* = 56)	6 (10.71)	22 (10.54)	3 (5.36)	17.19	< 0.05
Control group (*n* = 50)	10 (20)	15 (30.00)	6 (12.00)		

Table 4 Comparison of gastrointestinal reactions between the two groups after examination, *n* (%)

Group	Nausea	Vomiting	Abdominal distension	Abdominal pain	*F* value	*P* value
Treatment group (*n* = 56)	10 (17.86)	4 (7.14)	8 (14.29)	4 (7.14)	11.78	< 0.05
Control group (*n* = 50)	13 (26.00)	8 (16.00	13 (26.00)	6 (12.00)		

Table 5 Comparison of immune cell values in T0, T1 and T2 between the two groups (%), mean ± SD

Group	CD4+			CD8+			NK cell		
	T0	T1	T2	T0	T1	T2	T0	T1	T2
Treatment group (*n* = 56)	40.65 ± 6.73	37.16 ± 5.78[a,b]	33.75 ± 5.36[a,c]	25.91 ± 6.25	22.35 ± 5.49[a,b]	21.03 ± 4.35[a,c]	14.54 ± 1.34	16.61 ± 1.80[a,b]	20.74 ± 1.77[a,c]
Control group (*n* = 50)	41.56 ± 7.19	35.19 ± 6.31[a]	29.09 ± 5.63[a]	26.15 ± 5.58	21.11 ± 4.74[a]	18.49 ± 4.56[a]	14.40 ± 1.34	21.79 ± 1.45[a]	26.81 ± 1.39[a]

[a]*P* < 0.05 *vs* T0.
[b]*P* < 0.05 *vs* controls with T1.
[c]*P* < 0.05 *vs* controls with T2. NK: Natural killer.

Table 6 Comparison of inflammatory indicators in T0, T1 and T2 between the two groups, mean ± SD

Group	IL-6 (pg/mL)			TNF-α (ng/L)		
	T0	T1	T2	T0	T1	T2
Treatment group (*n* = 56)	50.18 ± 9.05	109.58 ± 14.95[a,b]	70.81 ± 9.50[a,c]	9.63 ± 2.17	12.53 ± 2.27[a,b]	10.48 ± 3.48[a,c]
Control group (*n* = 50)	49.06 ± 9.41	128.64 ± 18.61[a]	89.61 ± 9.41[a]	9.70 ± 1.99	16.28 ± 3.74[a]	14.62 ± 3.57[a]

[a]*P* < 0.05 *versus* T0.
[b]*P* < 0.05 compared to controls with T1.
[c]*P* < 0.05 compared to controls with T2. TNF-α: Tumor necrosis factor-alpha.

and reproduction of gastric mucosal cells, regulate cell apoptosis, and even inhibit the malignant proliferation of gastric parietal cells. According to the literature, Modified Shengyang Yiwei decoction can increase cerebral blood flow, accelerate the passage of propofol through the blood brain barrier, and thus reduce the induced dose of propofol[18,19]. In this study, the operation time of the two groups of patients undergoing gastroscopy lasted approximately 4 minutes. However, in the treatment group, the total dose of propofol used by patients is less, and after examination, the recovery time and independent walking time of patients were significantly shorter than those in the control group. It may be relatde to that the treatment with ShengYangYiwei Decoction reduced the dose of propofol or increased in β-endorphin secretion[20], which deserves further study.

On the other hand, during painless gastroscopy, especially in the application of large propofol doses, the risk of inducing respiratory suppression and blood pressure fluctuations is high, and these are the most common cardiopulmonary complication of painless gastroscopy[21]. In our study, the incidence of hypoxemia and hypotension in the Modified ShengYangYiwei decoction treatment group was significantly lower than that in the control group, and this medication is likely associated with reducing the dose of propofol. Thus, the incidence of respiratory depression and hypotension was reduced. Moreover, the most common complication after painless gastroscopy is the gastrointestinal reaction, and patients often have nausea, vomiting, abdominal distension and abdominal pain within several hours or even a few days after the examination[22,23]. Our study suggested that hiccups, nausea, vomiting, abdominal distension, and abdominal pain occurred. The rate was significantly lower in the treatment group than that in the control group (P < 0.05). After further querying the literature, treatment with Modified ShengYangYiwei Decoction can reduce the activity and reduce sympathetic nerve stimulation. The decrease in the vagus nerve stimulation then relieves gastrointestinal spasms to relieve nausea and vomiting and reduce the occurrence of abdominal distension and abdominal pain[24,25]. The degree of pain of the patients after gastroscopy was slight, and the satisfaction of the surgeons and patients with painless gastroscopy was relatively high in both groups, which also suggested that the patients and the surgeons both recognized the anesthesia method of this examination, which was worthy of promotion and research.

Moreover, the inhibition of cell-mediated immunity (mainly NK cells and T lymphocytes) and excessive proinflammatory responses are key features of perioperative cytokine cascade activation[26,27]. The results of the present study show that, in contrast to the T0, T1, and T2 time stages, C. NK cells increased significantly in both groups, which was associated with the postoperative inflammatory nature. The number of CD4+ and CD8+ cells decreased significantly in both groups, illustrating that surgery and anesthesia induced a stress response in the patient's body, producing significant immunosuppression. However, the values of CD4+ and CD8+ cells in the treatment group at T1 and T2 were higher than that in the control group, which indicates that the cellular immunity was less suppressed in the treatment group, and this is beneficial in reducing the postoperative complications in the patients. The IL-6 and TNF-α expression levels were further analyzed in both groups. IL-6 and TNF-α are released into the body with proinflammatory cytokines and can inhibit the effects of NK cells, CD4+ Th1-type cells and CD8+ T cells, which are associated with cancer cell proliferation and survival. This trial showed that the expression levels of IL-6 and TNF-α at T1 and T2 were significantly lower than those in the control group, preventing the excessive inflammatory response in the body, and the potential antitumor effect is also worth further study.

CONCLUSION

In summary, the preoperative use of modified ShengYangYiwei decoction can optimize the anesthesia program during painless gastroscopy and can significantly reduce the total dose of propofol during the inspection process without affecting the quality of inspection operation, thus shortening the time of awakening and independent activity and reducing the occurrence of hypoxemia, hypotension and hiccups during the inspection process. It improves the gastrointestinal function of patients after operation, reduces the incidence of nausea, vomiting, abdominal distension, abdominal pain and other complications of patients, reduces the inhibition of opioids on the immune system of the body, reduces the inflammatory reaction of patients, is beneficial to the development of painless gastroscopy for gastric cancer patients in clinical practice, reduces the occurrence of examination-related complications, and improves the compliance and tolerance of treatment. It is safe and feasible.

ARTICLE HIGHLIGHTS

Research background

Gastroscopy is of great significance in the clinical diagnosis, treatment, follow-up review and other aspects of gastric cancer patients, it can also be used to evaluate patients with reflux esophagitis, esophageal cancer, gastroduodenal ulcer, *etc. I*n clinical practice, painless gastroscopy is a widely accepted examination means. The use of propofol in combination with naborphine painless treatment has become a safer anesthesia regimen commonly used in clinical practice. However, patients with gastric cancer have a poor physique and are often more prone to anesthesia-related adverse reactions and gastrointestinal-related complications during examination. At present, combining other methods to further reduce the impact of examination on gastrointestinal function in gastric cancer patients has become an area of exploration in current research.

Research motivation

In order to explore a new intervention plan to optimize the anesthesia drug plan for painless gastroscopy and reduce the anesthesia related complications and postoperative discomfort of patients during the examination.

Research objectives

Modified ShengYangYiwei decoction is related to Li Dongyuan's theory, which has the effect of replenishing Qi and rising Yang, clearing heat and detoxification, and removing dampness and turbidity. It has gradually achieved fine effects in the field of digestive endoscopy. Therefore, this study observed the treatment interventions of gastric cancer patients and observed the impact on patients' gastrointestinal function, related complications and immune function during and after painless gastroscopy.

Research methods

A total of 106 gastric cancer patients from January 2022 to September 2022 who were selected for painless gastroscopy in Xiamen Hospital of Traditional Chinese Medicine, were divided into a treatment group (n = 56) and a control group (n = 50) by the random number table method. Before the examination, all patients fasted for 8 h, provided their health education, and confirmed if there were contraindications to anesthesia and gastroscopy. During the examination, for the control group, the protocols followed the Expert Consensus on Sedation and Anesthesia in the Diagnosis and Treatment of Digestive Endoscopy in China. The patients in the treatment group began oral Modified Sheng-YangYiwei decoction one week before gastroscopy, with one dose a day, compared with the control group.

Research results

There was no difference in the patients' general information, American Society of Anesthesiologist classification or operation time between the two groups. In terms of painless gastroscopy, the total dosage of propofol in the treatment group was lower than that in the control group (P < 0.05), and the time of awakening and autonomous activity was faster than that in the control group (P < 0.05). During the examination, the incidence of hypoxemia, hypotension and hiccups in the treatment group was lower than that in the control group (P < 0.01). After examination, the incidences of nausea, vomiting, abdominal distension and abdominal pain were lower than those in the control group (P < 0.01). In terms of immune function, in both groups, the number of CD4+ and CD8+ cells decreased significantly (P < 0.05), and the number of natural killer (NK) cells increased (P < 0.05) at T1 and T2, compared with T0. The number of CD4+ and CD8+ cells in the treatment group at the T1 and T2 time points was higher, while the number of NK cells was lower than that in the control group (P < 0.05). In terms of inflammatory factors, the level of IL-6 at T1 and T2 in the treatment group was lower than that in the control group (P < 0.05).

Research conclusions

The preoperative use of Modified ShengYangYiwei decoction can optimize the anesthesia program during painless gastroscopy, improve the gastrointestinal function of patients after the operation, reduce the occurrence of examination-related complications.

Research perspectives

At present, combining other methods to further reduce the impact of examination on gastrointestinal function in gastric cancer patients has become an area of exploration in current research. The preoperative use of Modified ShengYangYiwei decoction can improve the gastrointestinal function of patients after the operation. This trial showed that the expression levels of IL-6 and TNF-α at T1 and T2 were significantly lower than those in the control group, preventing the excessive inflammatory response in the body, and the potential antitumor effect is also worth further study.

FOOTNOTES

Author contributions: Mi SC, Wu LY, and Zheng LY performed the research; Mi SC, and the research; Mi SC designed the research study; Luo JW and Xu ZJ contributed collection and assembly of data; Zheng LY and Wu LY analysed the data; Zheng LY and Wu LY analysed the data; Mi SC and Wu LY wrote the pape.

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Country/Territory of origin: China

ORCID number: Sui-Cai Mi 0000-0002-1378-9915; Ling-Yan Wu 0000-0002-9453-0605.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Expanding endoscopic boundaries: Endoscopic resection of large appendiceal orifice polyps with endoscopic mucosal resection and endoscopic submucosal dissection

Ankur P Patel, Mai A Khalaf, Margarita Riojas-Barrett, Tara Keihanian, Mohamed O Othman

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Ankur P Patel, Department of Internal Medicine, Baylor College of Medicine, Houston, TX 77030, United States

Mai A Khalaf, Department of Tropical Medicine, Tanta University, Tanta 31527, Egypt

Margarita Riojas-Barrett, Tara Keihanian, Mohamed O Othman, Department of Gastroenterology, Baylor College of Medicine, Houston, TX 77030, United States

Corresponding author: Mohamed O Othman, MD, Chief Physician, Professor, Department of Gastroenterology, Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030, United States. mohamed.othman@bcm.edu

Abstract

BACKGROUND

Large appendiceal orifice polyps are traditionally treated surgically. Recently, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have been utilized as alternative resection techniques.

AIM

To evaluate the efficacy and safety of endoscopic resection techniques for the management of large appendiceal orifice polyps.

METHODS

This was a retrospective observational study conducted to assess the feasibility and safety of EMR and ESD for large appendiceal orifice polyps. This project was approved by the Baylor College of Medicine Institutional Review Board. Patients who underwent endoscopic resection of appendiceal orifice polyps ≥ 1 cm from 2015 to 2022 at a tertiary referral endoscopy center in the United States were enrolled. The main outcomes of this study included *en bloc* resection, R0 resection, post resection adverse events, and polyp recurrence.

RESULTS

A total of 19 patients were identified. Most patients were female (53%) and Caucasian (95%). The mean age was 63.3 ± 10.8 years, and the average body mass index was 28.8 ± 6.4. The mean polyp size was 25.5 ± 14.2 mm. 74% of polyps were localized to the appendix (at or inside the appendiceal orifice) and the remaining extended into the cecum. 68% of polyps occupied ≥ 50% of the appendiceal orifice circumference. The mean procedure duration was 61.6 ± 37.9 minutes. Polyps were resected *via* endoscopic mucosal resection, endoscopic submucosal dissection, and hybrid procedures in 5, 6, and 8 patients, respectively. Final pathology was remarkable for tubular adenoma (n = 10) [one with high grade dysplasia], sessile serrated adenoma (n = 7), and tubulovillous adenoma (n = 2) [two with high grade dysplasia]. En bloc resection was achieved in 84% with an 88% R0 resection rate. Despite the large polyp sizes and challenging procedures, 89% (n = 17) of patients were discharged on the same day as their procedure. Two patients were admitted for post-procedure observation for conservative pain management. Eight patients underwent repeat colonoscopy without evidence of residual or recurrent adenomatous polyps.

CONCLUSION

Our study highlights how endoscopic mucosal resection, endoscopic submucosal dissection, and hybrid procedures are all appropriate techniques with minimal adverse effects, further validating the utility of endoscopic procedures in the management of large appendiceal polyps.

Key Words: Appendiceal orifice polyps; Endoscopic mucosal resection; Endoscopic submucosal dissection; Polyp resection; Adenomatous polyps; *En bloc* resection

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Core Tip: In this study, we evaluated endoscopic mucosal resection, endoscopic submucosal dissection, and hybrid procedures for the resection of large appendiceal polyps. Compared to previously published studies, we noticed a higher *en bloc* resection rate and R0 resection rate in our study, despite a larger polyp size. Our data supported these procedures as safe and efficacious for the management of large polyps in a challenging location such as the appendiceal orifice, with minimal to no adverse events.

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INTRODUCTION

Appendiceal orifice polyps are usually found during autopsy or surgery, with an estimated prevalence of 0.08%[1]. According to the Size, Morphology, Site, Access scoring system that has been proposed to determine the complexity of polypectomy, appendiceal polyps are often classified as "high risk polyps" [2]. Traditionally, despite being visualized by colonoscopy, many of these polyps are referred for surgical resection[3].

Although removal of minute appendiceal orifice polyps is feasible, larger lesions are harder to remove and require advanced endoscopic resection techniques. More recently, many expert endoscopists have considered endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), or full thickness resection (FTR) for the removal of complex appendiceal orifice polyps. Multiple studies have highlighted the predominance of EMR over ESD for the management of appendiceal polyps[4,5]. The anatomic configuration of the appendix makes it difficult to perform ESD for appendiceal polyps. Challenges include limited room for scope maneuverability, higher risk of perforation, limited available devices for appropriate closure post-ESD due to polyp location, and higher risk of appendicitis after complete resection. Because of these challenges and limited expertise in colonic resection with ESD in the Western population, ESD has not been the preferred method of resection for large appendiceal polyps.

With evolving advances in the field of endoscopic resection, removing complex appendiceal polyps has become the preferred approach. However, there is still limited published data examining advanced resection techniques for appendiceal polyps. Data on outcomes of endoscopic resection of large appendiceal orifice polyps is especially lacking in the Western population. Thus, the aim of this study is to evaluate the efficacy and safety of EMR and ESD for the management of appendiceal orifice polyps at a tertiary referral center in the United States.

MATERIALS AND METHODS

Study design

This was a retrospective observational study conducted to assess the feasibility and safety of EMR and ESD for large appendiceal orifice polyps. This project was approved by the Baylor College of Medicine Institutional Review Board.

Study population

Patients who underwent endoscopic resection of appendiceal orifice polyps ≥ 1 cm by EMR or ESD from 2015 to 2022 at Baylor St. Luke's Medical Center were qualified for initial enrollment. Inclusion criteria included adult patients (ages 18 years and older) and polyp size ≥ 1 cm. Exclusion criteria included pediatric patients (less than 18 years of age), patients with polyps < 1 cm, and patients with a history of a prior appendiceal orifice polypectomy.

The decision to define large appendiceal polyps as ≥ 1 cm was based on the following. Multiple prior studies that evaluated endoscopic resection had average appendiceal polyp sizes around 1 cm[4-6]. Additionally, two other studies had average polyp sizes around 1.5 cm[7,8]. Furthermore, one of these prior studies showed that the odds of polyp recurrence can potentially increase by 3.2 times in polyps ≥ 1 cm with conventional polyp removal techniques[4], so we wanted to specifically evaluate outcomes in this population.

Technique

All procedures were performed by one advanced endoscopist experienced in endoscopic resection techniques. All procedures were performed using Pentax EC38-i10L adult colonoscopes (Pentax America, Montvale, NJ, United States). The technique of performing EMR or ESD has been described elsewhere[9]. In brief, EMR was performed using an assisted lifting technique with saline mixed with methylene blue. ESD was performed using a dual knife (Olympus America, Center Valley, PA, United States) or Orise Knife (Boston Scientific, Marlborough, MA, United States). The decision to perform EMR or ESD was based on the endoscopist's discretion, depending on lesion size and time allotted to perform the procedure. In certain occasions, hybrid EMR/ESD technique was used to expedite the procedure or to facilitate resection when ESD was not feasible. The hybrid EMR/ESD technique involves a circumferential incision of the lesion margins by dual knife, followed by snare resection of the lesion in one or multiple pieces. Post-EMR and ESD defects were routinely closed using Instinct or Instinct plus clip (Cook Medical, Winston Salem, NC, United States). Stabilization devices such as Dilumen (Lumendi, Westport, CT, United States) or Pathfinder (Neptune Medical, Burlingame, CA, United States) were selectively used in some procedures where significant looping or scope instability hindered the performance of endoscopic resection. Patients were scheduled for a follow up colonoscopy in 6 mo to 1 year.

EMR was considered for the resection of pedunculated or sessile appendiceal polyps that were smaller than 1.5 cm, did not extend into the appendiceal orifice, and were easily liftable after injecting solution. ESD and hybrid EMR/ESD were considered for polyps that extended into the appendiceal orifice, flat polyps, polyps with underlying scar and previous manipulation, or polyps that did not adequately lift after injecting solution. The overall goal was to achieve *en bloc* resection.

Study variables and outcomes

Outcome data included *en bloc* resection, R0 resection rate, hospitalizations, post-procedure adverse events, and polyp recurrence on follow up colonoscopy. Demographic variables [age, sex, race, body mass index (BMI)] and clinical history were collected retrospectively by chart review. Endoscopic appearance of polyps, including size, appearance, location (including degree of lateral spreading), Paris Classification, and lesion fibrosis were collected as well. Endoscopic procedure variables included procedure duration (including clip-closure time), technique, type of ESD knife, use of traction and stabilization methods, number of clips used for closure, need for hemostasis, adverse events, and recurrence rates.

En bloc resection was defined as resection of the entire polyp in one piece. R0 (complete) resection was defined as *en bloc* resection with negative horizontal and vertical margins. Curative resection was defined as histological complete resection with no risk of lymph node metastasis by histological examination of the resected specimen, according to the Japanese Society for Cancer of the Colon and Rectum guideline criteria[10]. Patients with piecemeal or R1 resection were considered to not have achieved curative resection.

Procedure time was defined as the time from introduction of the colonoscope into the rectum until withdrawal of the colonoscope. Postoperative bleeding was defined as immediate and long-term bleeding (defined as up to 2 wk after the procedure) from the polypectomy site that resulted in rectal bleeding or melena. Perforation was defined as transmural injury of the bowel wall resulting in free air in the abdomen. Appendicitis was defined as inflammation of the appendix at any time period after polypectomy.

Statistical analyses

Descriptive statistics were performed using means and standard deviations (SD) for continuous variables, and frequency and percentages for categorical variables. Analysis of variance was used to evaluate continuous variables, where appropriate. A P value of less than 0.05 was considered statistically significant. All analyses were performed using built-in Microsoft Excel 2019 software packages. The statistical review of the study was performed by a biomedical statistician.

RESULTS

Patient demographics

A total of 19 patients with appendiceal polyps were identified (Table 1). Most patients were female (53%) and Caucasian (95%). The mean age was 63.3 ± 10.8 (SD) years, and the average BMI was 28.8 ± 6.4. Patients were categorized as having an American Society of Anesthesiology score of II and III in 43% (n = 10) and 47% (n = 9) of cases, respectively.

Polyp appearance

The mean appendiceal polyp size was 25.5 ± 14.2 mm (min: 10 mm - max: 60 mm) (Table 2). 74% of polyps were localized to the appendix (at or inside the appendiceal orifice) and the remaining extended into the cecum. 68% of polyps occupied ≥ 50% of the appendiceal orifice circumference. Two polyps (11%) covered the entire appendiceal orifice, while five polyps (26%) covered 75%-80% of the appendiceal orifice. Figure 1 demonstrates ESD of a 30mm polyp. Twelve polyps were classified as Is under the Paris classification (protruding and pedunculated). Final pathology was remarkable for tubular adenoma (n = 10) (one with high grade dysplasia), sessile serrated adenoma (n = 7), and tubulovillous adenoma (n = 2) (two with high grade dysplasia). Two polyps that were removed by hybrid EMR/ESD were noted to have submucosal fibrosis.

Procedure details

Polyps were removed *via* hybrid EMR/ESD, ESD and EMR techniques in 8, 6 and 5 patients, respectively. The mean procedure duration was 61.6 ± 37.9 min. Ten procedures (53%) required a stabilization device over the colonoscope (Dilumen or Pathfinder). This occurred mainly in ESD or hybrid EMR/ESD procedures (n = 9). In order to facilitate dissection, traction was performed in two procedures with a Dilumen double balloon platform and one procedure with a rubber-band clip. A 1.5 mm DualKnife was used in 4 patients who underwent ESD and 7 patients who underwent hybrid EMR/ESD. The remaining polyps were removed using a 2 mm Orise ProKnife. Post-polypectomy defects were closed in all cases, except in one patient with a 20 mm polyp that was removed *via* EMR. An average of 3.9 ± 1.6 clips were used for defect closure.

Outcomes

The overall *en bloc* resection rate was 84%. The *en bloc* resection rate was 100% for the EMR and ESD groups, and 63% for the hybrid EMR/ESD group. The overall R0 resection rate for *en bloc* resected polyps was 88%. R0 resection rates for the EMR group, ESD group, and hybrid EMR/ESD group were 80%, 100% and 80%, respectively. The overall curative resection rate was 74%. Curative resection rates were 80% for the EMR group, 100% for the ESD group, and 50% for the hybrid EMR/ESD group.

Adverse events

No major adverse events, such as bleeding or perforation, were observed. Despite the large polyp sizes and challenging procedures, 89% (n = 17) of patients were discharged on the same day as their procedure. Two patients were admitted post-procedure for conservative pain control, for one and four days, respectively. One patient developed delayed appendicitis and required appendectomy four months after hybrid EMR/ESD polyp resection.

Follow up

Eight patients (57%) had a repeat colonoscopy, with 2 from the ESD group and 6 from the hybrid EMR/ESD group. The average length of follow up was 365 ± 281 d. There was no evidence of polyp recurrence in any of the patients with available follow up colonoscopy.

Between group analysis

There was no statistically significant difference in tumor size amongst the EMR, ESD, and hybrid EMR/ESD groups (P value = 0.99). Although the average time for ESD and hybrid procedures were slightly higher in comparison to EMR, no statistically significant difference was observed (P value = 0.48). The average procedure time (P value = 0.76) and polyp size (P value = 0.94) were not significantly different if stabilization with overtube was used. The *en bloc* resection rate (P value = 0.09), R0 resection rate (P value = 0.56), and curative resection rate (P value = 0.11) did not significantly differ between the three

Table 1 Baseline patient characteristics, *n* (%)

	Total patients (*n* = 19)
Age, yr (mean ± SD)	63.3 ± 10.8
BMI, kg/m^2 (mean ± SD)	28.9 ± 6.4
Sex	
Male	9 (47)
Female	10 (53)
Race	
Caucasian	18 (95)
African American	1 (5)
Comorbidities	
Family history of colon cancer	0 (0)
Smoking history	9 (47)
Alcohol use	12 (63)
COPD	2 (11)
CAD	2 (11)
ESRD	0 (0)
Prior appendectomy	2 (11)

n: Number; SD: Standard deviation; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CAD: Coronary artery disease; ESRD: End-stage renal disease.

groups (Table 2).

DISCUSSION

In this single center study, we observed an 84% *en bloc* resection rate and 88% R0 rate for *en bloc* resection of large appendiceal orifice polyps. When compared against each other, EMR, ESD, and hybrid EMR/ESD procedures all revealed similar efficacy without significant differences in procedure time, R0 resection rate, *en bloc* resection rate, or adverse effects.

There has been an increasing interest in natural orifice transluminal endoscopic surgery (NOTES) for removal of complex polyps, due to advances in third space endoscopy. It is associated with less post-procedural morbidity and adverse events, is cost effective, and leads to a decreased length of hospital stay[11-19].

There are a limited number of published literatures addressing the efficacy of advanced endoscopic resection for appendiceal polyps. Furthermore, many of the existing studies involve smaller appendiceal polyps when compared to our study. In a retrospective study by Hassab *et al*[4], 28 patients with appendiceal polyps underwent removal with EMR or ESD technique, with a median polyp size of 10 mm. Song *et al*[5] in their study of 131 patients (median polyp size 10mm), utilized piecemeal EMR as the most common method of resection (57.3%), followed by EMR (23.3%) and ESD (3.8%). In this study, *en bloc* resection was only achieved in 68.7% with a reported 90% R0 resection rate. Underwater EMR yielded *en bloc* resection in only 59% of 27 patients with appendiceal polyps (average polyp size 15 mm), in another study by Binmoeller *et al*[8]. In comparison to the published literature, our study observed higher *en bloc* and R0 resection rates, despite a larger average polyp size. There are two studies focusing on the role of ESD in the management of appendiceal polyps. In one Japanese study of 76 polyps (median size 35.5 mm) in the cecum adjacent to the appendix (only 29 located at the orifice), *en bloc* resection and R0 resection were achieved in 94.7% and 92.1% of the patients, respectively[20]. In another Japanese study of 27 appendiceal orifice polyps (mean size 31.8 mm), *en bloc* resection and R0 resection were achieved in 77.8% and 70.4% of patients, respectively[21].

In order to improve *en bloc* resection of challenging appendiceal polyps, there are two published studies demonstrating the utility of FTR. In a single center study of seven patients with appendiceal polyps that underwent polypectomy *via* FTR (polyp size min: 5 mm - max: 20 mm), en bloc resection and R0 resection rates were 100% and 85.7%, respectively[7]. In another multicenter study of 66 polyps (mean polyp size 14.5 ± 6.2 mm), *en bloc* resection was achieved in 80% with a reported R0 resection rate

Table 2 Endoscopic results of appendiceal polyp resection by procedure type, *n* (%)

	Total	EMR	ESD	Hybrid EMR/ESD	*P* value
Total patients (*n*)	19	5	6	8	
Polyp Appearance (mean ± SD)					
Size (mm)	25.5 ± 14.2	26.0 ± 13.4	25.0 ± 18.4	25.6 ± 13.2	0.99
Localized to appendix (at or inside the appendiceal orifice)	14 (74)	3 (60)	6 (100)	5 (63)	
50% or more involvement of the appendiceal orifice	13 (68)	3 (60)	5 (83)	5 (63)	
Granular, lateral-spreading	5 (26)	0 (0)	2 (33)	3 (30)	
Flat, lateral-spreading	1 (5)	0 (0)	0 (0)	1 (13)	
Not lateral-spreading	13 (68)	5 (100)	4 (67)	4 (50)	
Paris classification: Is	12 (63)	3 (60)	2 (33)	7 (88)	
Lesion fibrosis	2 (11)	0 (0)	0 (0)	2 (25)	
Procedure (mean ± SD)					
Duration of Procedure (min)	61.6 ± 37.9	43.8 ± 31.5	71.0 ± 54.4	65.8 ± 26.1	0.48
Procedures needing clips	18 (95)	4 (80)	6 (100)	8 (100)	
Number of clips used	3.9 ± 1.6	2.8 ± 0.5	3.5 ± 2.2	5.0 ± 1.2	0.02
Additional resection of non-appendiceal polyps	4 (21)	2 (40)	0 (0)	2 (25)	
ESD knife used (DualKnife/Orise ProKnife)	N/A	N/A	4/2 (67/33)	7/1 (88/12)	
Traction method used	3 (21)	0 (0)	1 (16.7)	2 (25)	
Stabilization (Dilumen or Pathfinder)	10 (53)	1 (20)	4 (67)	5 (63)	
Hemostasis needed (with Cograsper)	3 (16)	0 (0)	2 (33)	1 (13)	
Outcome (mean ± SD)					
Admission for post-procedure observation	2 (11)	0 (0)	1 (17)	1 (13)	
Duration of Admission (d)	2.5 ± 2.1	0 ± 0	4.0 ± 0	1.0 ± 0	
Post-Procedure Pain	1 (5)	0 (0)	1 (17)	0 (0)	
Adenoma on pathology report	19 (100)	5 (100)	6 (100)	8 (100)	
Submucosal/Perineural/Lymphovascular Invasion	0 (0)	0 (0)	0 (0)	0 (0)	
R0 rate for *en bloc* resection	14 (88)[a]	4 (80)	6 (100)	4 (80)[a]	0.56
Curative resection rate	14 (74)	4 (80)	6 (100)	4 (50)	0.11
En Bloc resection rate	16 (84)	5 (100)	6 (100)	5 (63)	0.09
Repeat colonoscopy done	8 (57)[b]	0 (0)	2 (67)[b]	6 (75)	

[a]Three patients from the hybrid EMR/ESD group were not included as they underwent piecemeal resection.

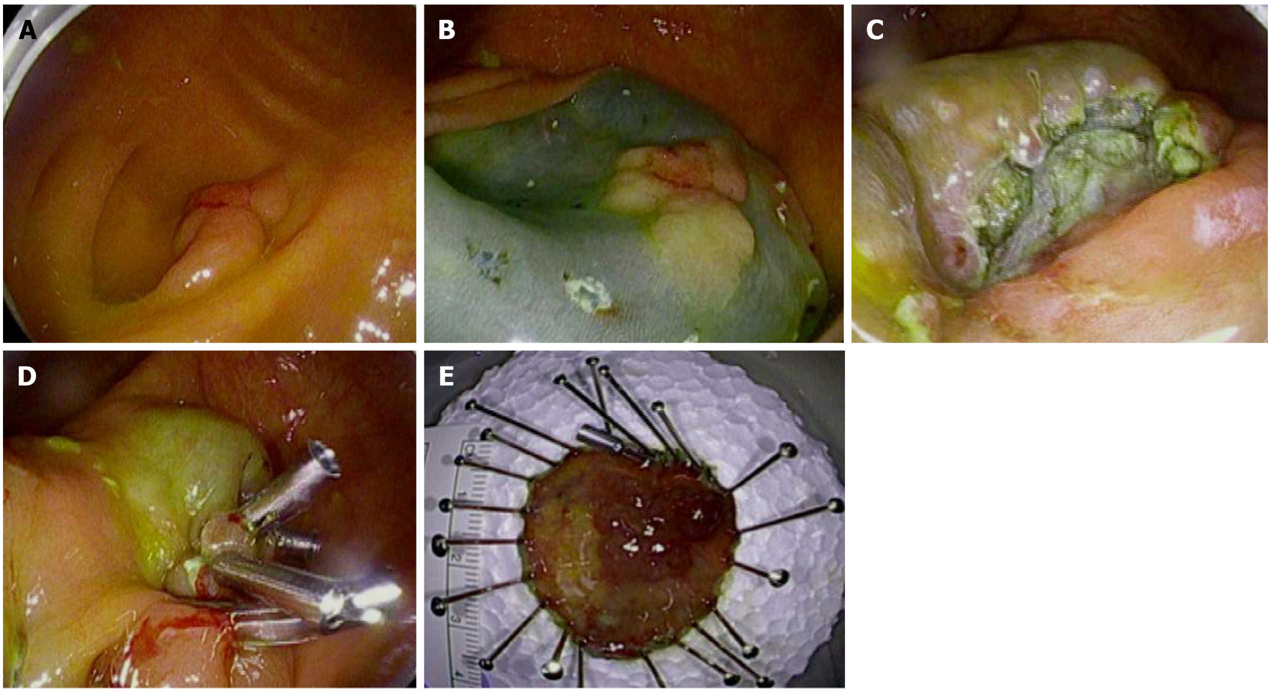
[b]In the EMR group, one patient died from unrelated causes prior to consideration of a repeat colonoscopy and one patient refused a follow up colonoscopy. In the ESD group, three patients were not due for follow up endoscopy.

EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; n: Number; SD: Standard deviation; Is: Protruding and pedunculated; R0: Microscopically margin-negative.

of 93%[6].

En bloc resection of appendiceal polyps can vary from 59% to 100%, depending on the polyp size and resection method as discussed earlier. In our cohort, 74% of polyps were resected *via* ESD or hybrid EMR/ESD, despite our larger average polyp size (median 20 mm, min: 10 mm - max: 60 mm). Comparatively, we observed a higher *en bloc* resection rate (84%) and R0 rate for *en bloc* resection (88%). Furthermore, our procedure times compared similarly to the aforementioned studies.

As ESD technique yields *en bloc* resection, it has been associated with lower recurrence rates in comparison to conventional EMR techniques[22]. The recurrence rate after appendiceal polyp resection has been varied in the literature, depending on the removal method. The reported incidence of recurrence ranges from 10% with underwater EMR to 15.6% when conventional polyp removal



DOI: 10.4253/wjge.v15.i5.386 **Copyright** ©The Author(s) 2023.

Figure 1 Step-by-step demonstration of a polyp removal *via* endoscopic submucosal dissection. A: A 30 mm polyp occupying 50% of the appendiceal orifice circumference is visualized; B: The polyp borders are marked using the tip of the dual knife. Adequate lifting of the submucosa is achieved after the injection of Hespan Solution; C: The resection bed is seen after the dissection of the polyp from the underlying deeper layers; D: The defect is completely closed with 4 hemostatic clips; E: The result is an *en bloc* resection of the polyp.

techniques have been applied[4,5,8]. The odds of polyp recurrence can potentially increase by 3.2 times in polyps ≥ 10 mm with conventional polyp removal techniques[4]. In our study, due to a higher proportion of *en bloc* polyp removal *via* ESD and hybrid EMR/ESD, we observed no polyp recurrence in our eight patients with available follow up colonoscopy.

Adverse events such as bleeding or perforation after appendiceal polypectomy have been reported in up to 14.5% of patients that underwent EMR or ESD[5,20]. Although appendiceal polyp sizes ≥ 20 mm have been described as a risk factor for developing adverse events[5], no major adverse events such as bleeding or perforation were observed in our study, despite our larger average polyp size. This may have been a result of operator experience, as all procedures were performed by a single operative with enhanced experience in performing third space endoscopy.

One of the unique adverse events after endoscopic resection of appendiceal and peri-appendiceal polyps is appendicitis, as a result of post-polypectomy edema and cautery effect adjacent to the appendiceal orifice. Appendicitis has been reported in up to 17% of cases in the literature, although the majority of cases occurred < 10 d after endoscopy and all cases occurred < 1 mo after endoscopy[6,23,24]. Only one patient in our cohort developed appendicitis requiring laparoscopic appendectomy, although the event occurred four months after hybrid EMR/ESD, suggesting that her appendicitis was not related to her polypectomy. In our study, clipping was attempted in all cases, except for one case where a polyp with Paris classification Ip was not invading the appendiceal orifice. This patient did not develop appendicitis or require appendectomy. Nevertheless, clipping should still be attempted to prevent postoperative appendicitis. In our study, despite larger polyps and challenging polyp locations, same day discharge was achieved in 89.5% of patients.

Advanced polypectomy of appendiceal polyps with ESD or hybrid EMR/ESD seems to be a safe and effective method for the management of large polyps at a challenging location such as the appendiceal orifice, with minimal to no adverse events. However, resection of appendiceal polyps *via* advanced endoscopic techniques requires a certain expertise due to the difficult location and anatomical configuration of the appendix. One of the main challenges encountered during polyp resection within the right side of the colon, and in particular at the appendiceal orifice, is maintaining scope stability. Ismail *et al*[9] have previously described the utility of the DiLumen platform for scope stability and expedited resection in challenging polyp locations. In our cohort, scope stabilization with the Dilumen platform or Pathfinder overtube was utilized in half of the cases (52.6%) to assist with stability and facilitate dissection, especially in ESD or hybrid EMR/ESD. Utilization of these devices provided adequate visualization of the dissection plane and made ESD resection easier, without any significant difference in procedure time (P value = 0.76). Another technique to consider when removing appendiceal polyps would be applying traction in order to relocate the polyp in various orientations, to assist with dissection and the plane of view[25,26]. In our study, traction with Dilumen and rubber-band traction resulted in expedited dissection as well as polyp resection in a safe manner.

After evaluating our study and prior evidence, we suggest that EMR is safe for pedunculated appendiceal polyps not extending into the orifice, smaller than 15 mm, and easily liftable after injecting solution. For polyps that extend into appendiceal orifice, flat polyps, polyps with underlying scar and previous manipulation, and polyps not adequately lifting, ESD and hybrid EMR/ESD should be chosen. The overall goal should be to achieve *en bloc* resection.

For evaluation of polyps that may require surgical intervention, the Japanese Gastroenterological Endoscopy Society guidelines for ESD and EMR can be utilized[27]. Criteria for surgery may include polyps that meet deep invasion guidelines or have increased concern for malignancy. We suggest that appendiceal orifice polyps that are larger than 2 cm should be evaluated on a case to case basis in a multi-disciplinary team for consideration of surgical or endoscopic resection. This decision may vary by institution, depending on the availability of expertise in complex endoscopic resection. Furthermore, patient comorbidities must be considered when pursuing surgical intervention.

Narrow band imaging (NBI), white light endoscopy, and chromoendoscopy are also strategies that can be considered to aid in the detection of high-risk polyps that may harbor advanced neoplasia and require surgical resection rather than endoscopic intervention[28]. Based on the NBI International Colorectal Endoscopic Classification (NICE) criteria, type 2 Lesions can be addressed with endoscopic resection, while type 3 Lesions should be referred for surgical resection[29].

There are many strengths to our study, including an in-depth evaluation of innovative endoscopic procedures for the resection of large appendiceal polyps ≥ 1 cm. Furthermore, we assessed EMR, ESD, and hybrid procedures, identifying the efficacy and safety of these procedures in the management of large appendiceal orifice polyps. This study has certain limitations as well. This is a single center retrospective study with a non-randomized controlled trial design and a limited number of patients, which may limit its generalizability to a larger population. All procedures were performed by a single operative with enhanced experience in performing third space endoscopy. Furthermore, follow up colonoscopy information is missing in some patients that were due for repeat colonoscopy, due to the retrospective nature of the study and lack of patient follow up despite multiple attempts. Although no major adverse events were noted in our study and the removal of complex appendiceal polyps appears to be safe, larger prospective trials are needed to efficiently demonstrate the utility and safety of advanced endoscopic polyp resection techniques in the challenging appendiceal orifice location, in the hands of experienced and naïve endoscopists.

CONCLUSION

In conclusion, although appendiceal polyps are frequently referred for surgical resection, endoscopic techniques including EMR and ESD are efficacious and safe methods for large polyp removal. The results of our study are comparative to the previous published studies, with higher *en bloc* resection and R0 resection rates in our study despite a larger average polyp size.

ARTICLE HIGHLIGHTS

Research background

Appendiceal orifice polyps are often referred for surgical resection. More recently, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have been considered by expert advanced endoscopists for the removal of complex appendiceal polyps.

Research motivation

However, there is still limited published data investigating EMR and ESD for appendiceal polyps in the Western population.

Research objectives

The main objective of this study is to evaluate the safety and efficacy of EMR and ESD for the management of complex appendiceal orifice polyps.

Research methods

This was a retrospective observation study involving adult patients who underwent endoscopic resection of appendiceal orifice polyps ≥ 1 cm by EMR, ESD, or hybrid EMR/ESD from 2015 to 2022 at Baylor St. Luke's Medical Center. All procedures were performed by one advanced endoscopist experienced in endoscopic resection. Data collection included demographic information, polyp characteristics, procedure details, and procedure outcomes. The main outcomes of interest were *en bloc* resection rate, R0 resection rate, and adverse events.

Research results

A total of 19 patients were identified, with a mean polyp size of 25.5 ± 14.2 mm. The overall *en bloc* resection rate was 84%, with an R0 resection rate of 88% and no significant difference in between EMR, ESD, and hybrid EMR/ESD. 89% of patients were discharged on the same day as their procedure, with only two patients admitted conservatively post-procedure for pain management. Despite our larger overall polyp size, we observed high *en bloc* and R0 resection rates for EMR, ESD, and hybrid EMR/ESD procedures without any significant adverse effects.

Research conclusions

In conclusion, EMR and ESD are efficacious and safe techniques for large appendiceal orifice polyp removal.

Research perspectives

Future large, prospective trials can be conducted to demonstrate the safety and utility of EMR and ESD for the resection of complex appendiceal polyps. These studies can also incorporate both experienced and naïve endoscopists across multiple centers in the United States.

FOOTNOTES

Author contributions: Patel AP collected the data, analyzed and interpreted the data, drafted the manuscript, and performed statistical analysis; Khalaf MA and Riojas-Barrett M collected the data; Keihanian T collected the data, analyzed and interpreted the data, performed statistical analysis, and revised the manuscript; Othman MO created the study design, revised the manuscript, and supervised the study; all authors have read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Baylor College of Medicine Institutional Review Board (Approval Number: H-50836).

Informed consent statement: A waiver of consent was obtained from the Baylor College of Medicine Institutional Review Board.

Conflict-of-interest statement: Tara Keihanian has received fees for serving as a consultant for Lumendi and Neptune Medical. Mohamed O Othman has received fees for serving as a consultant for Olympus America, Abbvie, Boston Scientific Corporation, Lumendi, Apollo, Conmed, and Medtronic. Mohamed O Othman has received research funding from Olympus America, Abbvie, Boston Scientific Corporation, and US Biotest.

Data sharing statement: The dataset is available from the corresponding author at mohamed.othman@bcm.edu. Consent was not obtained but the presented data are anonymized and the risk of identification is low.

STROBE statement: The authors have read the STROBE Statement - checklist of items, and the manuscript was prepared and revised accordingly.

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Country/Territory of origin: United States

ORCID number: Ankur P Patel 0000-0001-7670-5590; Mohamed O Othman 0000-0002-5888-4334.

Corresponding Author's Membership in Professional Societies: American Association for the Study of Liver Diseases, No. 263777; American Association for the Study of Liver Diseases, No. 66811.

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ORIGINAL ARTICLE

Retrospective Study

Effect of music on colonoscopy performance: A propensity score-matched analysis

Eun Jeong Choi, Sam Ryong Jee, Sang Heon Lee, Jun Sik Yoon, Seung Jung Yu, Jong Hyun Lee, Han Byul Lee, Sang Wook Yi, Myeong Pyo Kim, Byung Cheol Chung, Hong Sub Lee

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Eun Jeong Choi, Sam Ryong Jee, Sang Heon Lee, Jun Sik Yoon, Seung Jung Yu, Jong Hyun Lee, Myeong Pyo Kim, Byung Cheol Chung, Hong Sub Lee, Department of Internal Medicine, Inje University College of Medicine, Busan Paik Hospital, Busan 47392, South Korea

Han Byul Lee, Department of Public Health, Ajou University Graduate School of Public Health, Suwon 16499, South Korea

Sang Wook Yi, Department of Preventive Medicine and Public Health, Catholic Kwandong University College of Medicine, Gangneung 25601, South Korea

Corresponding author: Hong Sub Lee, MD, PhD, Professor, Department of Internal Medicine, Inje University College of Medicine, Busan Paik Hospital, 75 Bokji-ro, Busanjin-gu, Busan 47392, South Korea. hslee@paik.ac.kr

Abstract

BACKGROUND

Music has been used to reduce stress and improve task performance during medical therapy.

AIM

To assess the effects of music on colonoscopy performance outcomes.

METHODS

We retrospectively reviewed patients who underwent colonoscopy performed by four endoscopists with popular music. Colonoscopy performance outcomes, such as insertion time, adenoma detection rate (ADR), and polyp detection rate (PDR), were compared between the music and non-music groups. To reduce selection bias, propensity score matching was used.

RESULTS

After one-to-one propensity score matching, 169 colonoscopies were selected from each group. No significant differences in insertion time (4.97 *vs* 5.17 min, P = 0.795) and ADR (39.1% *vs* 46.2%, P = 0.226) were found between the two groups. Subgroup analysis showed that the insertion time (3.6 *vs* 3.8 min, P = 0.852) and ADR (51.1% *vs* 44.7%, P = 0.488) did not significantly differ between the two groups in experts. However, in trainees, PDR (46.9% *vs* 66.7%, P = 0.016) and ADR (25.9% *vs* 47.6%, P = 0.006) were significantly lower in the music than in the non-music group.

CONCLUSION

The current study found that listening to music during colonoscopy did not affect procedure performance. Moreover, it suggested that music may distract trainees from appropriately detecting adenomas and polyps.

Key Words: Music; Colonoscopy; Performance; Adenoma; Colonic polyps; Cecal insertion time

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Core Tip: Music has shown the positive effect on the surgical team in the operating room, no data has been available regarding the effects of music on endoscopist performance. The study aimed to assess the effects of music on colonoscopy performance outcomes. The patients who underwent colonoscopy while listening to music were retrospectively reviewed for colonoscopy performance outcomes, such as insertion time, adenoma and polyp detection rates. Accordingly, our findings showed that listening to music during colonoscopy had no effect on procedure performance. Moreover, our results suggested that listening to music during colonoscopy may distract trainees from appropriately detecting adenomas and polyps.

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INTRODUCTION

Music has been used in medical treatment to reduce pain and anxiety[1]. Music, which is commonly played in operating rooms during surgical procedures, has a positive effect on the surgical team[2] considering that not only the patient but also the surgeon may feel tense and stressed. Surgeons' stress can negatively affect their skills[3], which can have adverse consequences for the patients. However, there are few means for relieving the surgeon's tension in a constrained operating room. Given its positive effect on the surgical team through a significant decrease in autonomic reactivity, music has been considered one of the few options for relieving the surgeon's tension[4]. Moreover, music performance increases surgical accuracy and shortens the operative time[5,6].

Colonoscopy has been widely performed for the screening of colorectal cancer[7] and evaluation of lower gastrointestinal diseases. However, this procedure causes anxiety and pain in patients due to abdominal clamping or bloating[8]. To reduce the pain of patients and prevent the movement of patients from interfering with the procedure, endoscopists administer a sedative. However, sedatives may increase the risk of cardiovascular disease in elderly people[9]. Several studies have proven that music has a significant effect on reducing anxiety and pain in patients undergoing colonoscopy and the dosage of sedatives required for colonoscopy[10,11]. However, no data has been available regarding the effects of music on endoscopist performance. Therefore, the current study aimed to assess the effects of music on colonoscopy performance outcomes.

MATERIALS AND METHODS

Patients

Subjects who underwent colonoscopy at the Gastroenterology Department of Busan Paik Hospital, Korea between June 2019 and March 2021 were enrolled. Since June 2020, all endoscopy procedures had been performed while listening to music. A total of 402 patients underwent colonoscopy during the said period. The identified patients were then divided into two groups: The non-music group, who underwent endoscopy without listening to music from June 2019 to May 2020, and the music group, who underwent endoscopy while listening to music from June 2020 to March 2021.

Clinical data, including the American Society of Anesthesiologists (ASA) score, colonoscopy indications, and pathological findings, were obtained by reviewing past medical records. The ASA score was evaluated to assess patient risk prior to colonoscopy. Patients underwent colonoscopy for several indications, including abdominal pain, hematochezia, melena, diarrhea, constipation, and screening purposes in asymptomatic individuals.

Endoscopists

Four endoscopists, consisting of two experts and two trainees, participated in the study. Both experts were board-certified and experienced endoscopists, each of whom had performed more than 5000 colonoscopies, whereas both trainees had < 1 year of experience. Their preferred pop music was played through the blue-tooth speakers in the endoscopic room at a volume of between 50 and 60 dB. A colonoscope (CF-H260AL or CF-HQ290L; Olympus, Tokyo, Japan) was used to perform the colonoscopy from June 2019 to March 2021.

Bowel preparation

Bowel preparation was performed using the bowel cleansing product consisting of 2 L of a solution containing polyethylene glycol. The quality of bowel preparation was scored according to the Boston Bowel Preparation Scale (BBPS) and characterized as adequate (BBPS score ≥ 6 and/or all segment scores ≥ 2) or fair (total score of 3-5).

Colonoscopy performance outcomes

Primary endpoints were cecal insertion time, polyp detection rate (PDR), and adenoma detection rate (ADR). The PDR was defined as the number of colonoscopies in which at least one polyp was detected divided by the total number of colonoscopies performed. The ADR was defined as the number of colonoscopies in which at least one adenoma was detected divided by the total number of colonoscopies.

Statistical analysis

Descriptive data were reported as median and interquartile range. Differences in categorical variables were analyzed using χ^2 test. Continuous variables were analyzed using Mann-Whitney *U* test. Analyses were performed using R Statistical Software 4.1.0 (The R Foundation for Statistical Computing, Vienna, Austria), *P* values of < 0.05 indicating statistical significance. To reduce selection bias, one-to-one propensity score matching was performed using the R package "Matchlt". One-to-one matching was conducted with age, sex, body mass index (BMI), ASA score, BBPS, surgical history, and indication for colonoscopy as covariates using greedy matching with caliper of 0.2. Univariable and multivariable logistic regression analyses were performed to assess independent prognostic factors. The covariates for matching estimation included age, sex, BMI, ASA score, BBPS, previous abdominal surgery, and indication for colonoscopy. Covariate selection for multivariate analysis was based on a *P* value of < 0.2 in univariable analysis, with a logistic regression model.

Ethical statements

This retrospective study was approved by the Institutional Review Board of Busan Paik Hospital and was conducted in accordance with the ethical guidelines stated in the Declaration of Helsinki (IRB number: 2020-01-192). Requirement for informed consent was waived by the Institutional Review Board given that the researchers only retrospectively accessed a de-identified database for analysis purposes.

RESULTS

Patient characteristics

From June 2019 to March 2021, 402 colonoscopies were performed by four endoscopists. A total of 202 colonoscopies were performed while listening to pop music preferred by the endoscopists, whereas 200 were performed without music. The baseline characteristics of the patients are shown in Table 1. Before the propensity score matching, there were significant differences between surgical history and colonoscopy indications. After one-to-one propensity score matching, 169 colonoscopies were selected for each group. The most common indication for colonoscopy was screening of colon cancer, with both groups having the same amount of patient at 51.5% (*P* = 1.000) after propensity score matching. Cecal intubation rate was 100% in both groups.

Outcomes of colonoscopy performance

The insertion time (4.97 *vs* 5.17 min, *P* = 0.795) and withdrawal time (10.57 *vs* 11.87 min, *P* = 0.142) did not significantly differ between both groups. In addition, no significant differences in ADR (39.1% *vs* 46.2%, *P* = 0.226) were observed between the two groups, although PDR tended to higher in the non-music group than in music group (56.8% *vs* 66.9%, *P* = 0.073) (Table 2).

Subgroup analysis according to colonoscopy proficiency

Subgroup analysis was performed to evaluate differences according to colonoscopy proficiency (Table 3). Among experts, the insertion time (3.57 *vs* 3.83 min, *P* = 0.852), withdrawal time (10.30 *vs* 10.90

Table 1 Baseline characteristics of patients who did and did not listen to music before and after propensity score matching

	Before propensity score matching					After propensity score matching				
	Total (*n* = 402)	Music (*n* = 200)	No music (*n* = 202)	*P* value	d	Total (*n* = 338)	Music (*n* = 169)	No music (*n* = 169)	*P* value	d
Age, yr	63.0 (54.0-70.0)	63.0 (54.5-69.0)	64.0 (54.0-70.0)	0.642	0.08	64.0 (55.0-70.0)	63.0 (53.0-69.0)	64.0 (56.0-70.0)	0.353	0.13
Female sex	190 (47.3%)	96 (48.0%)	94 (46.5%)	0.846	0.03	157 (46.4%)	83 (49.1%)	74 (43.8%)	0.383	0.11
BMI, kg/m^2	23.7 (21.9-26.0)	23.7 (21.9-26.2)	23.7 (21.8-25.9)	0.992	0.00	23.7 (22.0-25.9)	24.0 (22.1-26.2)	23.6 (21.8-25.8)	0.383	0.09
ASA score				0.746	0.01				0.546	0.12
1	171 (42.5%)	86 (43.0%)	85 (42.1%)			152 (45.0%)	79 (46.7%)	73 (43.2%)		
2	204 (50.7%)	100 (50.0%)	104 (51.5%)			167 (49.4%)	83 (49.1%)	84 (49.7%)		
3	26 (6.5%)	14 (7.0%)	12 (5.9%)			18 (5.3%)	7 (4.1%)	11 (6.5%)		
4	1 (0.2%)	0 (0.0%)	1 (0.5%)			1 (0.3%)	0 (0.0%)	1 (0.6%)		
BBPS				0.768	0.04				0.684	0.06
3-5	87 (21.6%)	45 (22.5%)	42 (20.8%)			68 (20.1%)	32 (18.9%)	36 (21.3%)		
6-9	315 (78.4%)	155 (77.5%)	160 (79.2%)			270 (79.9%)	137 (81.1%)	133 (78.7%)		
Surgical history				0.041	0.07				0.060	0.02
None	259 (64.4%)	121 (60.5%)	138 (68.3%)			206 (60.9%)	98 (58.0%)	108 (63.9%)		
Colon	99 (24.6%)	60 (30.0%)	39 (19.3%)			94 (27.8%)	56 (33.1%)	38 (22.5%)		
Other abdominal organ	44 (10.9%)	19 (9.5%)	25 (12.4%)			38 (11.2%)	15 (8.9%)	23 (13.6%)		
Indication for colonoscopy				0.002	0.32				1.000	0.00
Screening	207 (51.5%)	89 (44.5%)	118 (58.4%)			174 (51.5%)	87 (51.5%)	87 (51.5%)		
Post operation surveillance	128 (31.8%)	66 (33.0%)	62 (30.7%)			120 (35.5%)	60 (35.5%)	60 (35.5%)		
Patients with symptoms	67 (16.7%)	45 (22.5%)	22 (10.9%)			44 (13.0%)	22 (13.0%)	22 (13.0%)		

Data are expressed as *n* (%), median (interquartile range). *P* values were calculated using Kruskal-Wallis test and χ^2 test. d: Standardized mean differences of propensity-matched population; BMI: Body mass index; ASA score: American Society of Anesthesiologists score; BBPS: Boston Bowel Preparation Scale.

min, *P* = 0.560), PDR (65.9% *vs* 67.1%, *P* > 0.999) and ADR (51.1% *vs* 44.7%, *P* = 0.488) did not significantly differ between the two groups. Among trainees, the cecal insertion time (6.30 *vs* 6.27 min, *P* = 0.831) and the withdrawal time (10.82 *vs* 13.68 min, *P* = 0.123) did not significantly different between music *vs* non-music groups. However, among trainee, the PDR was significantly lower in the music group than in the non-music group (46.9% *vs* 66.7%, *P* = 0.016). A significant difference in the ADR was

Table 2 Outcomes of colonoscopy performance with and without music

	Total (n = 338)	Music (n = 169)	No music (n = 169)	P value
Polyp detection rate	209 (61.8%)	96 (56.8%)	113 (66.9%)	0.073
Adenoma detection rate	144 (42.6%)	66 (39.1%)	78 (46.2%)	0.226
Insertion time (min)	5.09 (3.32-7.33)	4.97 (3.28-7.03)	5.17 (3.43-7.78)	0.795
Withdrawal time (min)	11.1 (8.48-17.25)	10.57 (8.40-16.35)	11.87 (8.63-17.5)	0.142

Data are expressed as n (%), median (interquartile range), P values were calculated using Kruskal-Wallis test and χ^2 test.

Table 3 Outcomes of colonoscopy performance according to expert and trainee subgroups

	Polyp detection rate	Adenoma detection rate	Insertion time (min)	Withdrawal time (min)
Expert				
Total (n = 173)	115 (66.5%)	83 (48.0%)	3.75 (2.57-5.68)	10.68 (8.22-15.22)
Music (n = 88)	58 (65.9%)	45 (51.1%)	3.57 (2.59-5.80)	10.30 (7.95-15.27)
No music (n = 85)	57 (67.1%)	38 (44.7%)	3.83 (2.42-5.65)	10.90 (8.48-14.10)
P value	> 0.999	0.488	0.852	0.560
Trainee				
Total (n = 165)	94 (57.0%)	61 (37.0%)	6.30 (4.58-8.82)	12.07 (8.92-19.0)
Music (n = 81)	38 (46.9%)	21 (25.9%)	6.30 (4.50-8.70)	10.82 (8.78-17.43)
No music (n = 84)	56 (66.7%)	40 (47.6%)	6.27 (4.78-9.11)	13.68 (9.31-20.33)
P value	0.016	0.006	0.831	0.123

Data are expressed as n (%), median (interquartile range), P-values were calculated using Kruskal-Wallis test and χ^2 test.

also noted, with the rate in the music group being significantly lower than that the in non-music group (25.9% *vs* 47.6%, P = 0.006).

Prognostic factors for adenoma detection and insertion time

Adenoma detection and fast insertion time (< median insertion time of 310 s) were regressed on potential predictors using logistic regression analysis. Among all patients (n = 402), univariable and multivariable analyses found that music was not associated with ADR and fast insertion time (Table 4, Figure 1). Expert endoscopists detected more adenoma, although not statistically significant [odds ratio (OR) = 1.42, P = 0.085)], while younger age (OR = 1.04, P < 0.001), women (OR = 0.55, P = 0.004), and surgical history of colon (OR = 0.62, P = 0.048) showed a significant association with lower ADR in univariable and multivariable regression analyses. Expert endoscopist (OR = 4.69, P < 0.001), higher BMI (OR = 1.07, P = 0.023), adequate BBPS (OR = 2.09, P = 0.003), and previous surgical history of colon (OR = 1.05, P = 0.090) were associated with fast insertion time in univariable analyses, and the results of multivariable analyses were the same except for BBPS.

DISCUSSION

Music has been known to provide a positive effect on surgical performance[12]. On study showed that surgeons who listened to music had reduced operative time and better surgical quality[5]. As with surgeons, music might influence and consequently improve endoscopist's performance, which can lead to reduced insertion time and increased ADR. In support of this finding, a study by Ardalan *et al*[13] showed that PDR and ADR increased when listening to Star Wars music. However, the current study showed that music did not significantly affect colonoscopy performance. Although endoscopist and patient factors may have played a role in these different results, the type of music may also be a factor. Indeed, one study showed that listening to Mozart music improve task performance during laparoscopic surgery simulations[6]. Furthermore, a study on the effect of different music genres on surgical performance showed better performance when listening to classical music or hip-hop music compared to exposure to mixed radio music or rock[14]. While the endoscopist's preferred Korean pop music,

Table 4 Prognostic factors for colonoscopy performance (*n* = 402)

	No.	Univariable analysis[1]		Multivariable analysis[1]		Univariable analysis[2]		Multivariable analysis[2]	
		OR (95%CI)	*P* value	aOR (95%CI)	*P* value	OR (95%CI)	*P* value	aOR (95%CI)	*P* value
Music									
No	202	Reference				Reference			
Yes	200	0.86 (0.58-1.28)	0.470			1.24 (0.84-1.84)	0.273		
Endoscopist									
Trainee	207	Reference		Reference		Reference		Reference	
Expert	195	1.42 (0.95-2.11)	0.085	1.35 (0.89-2.06)	0.163	4.69 (3.10-7.19)	< 0.001	4.48 (2.87-7.11)	< 0.001
Age, yr		1.04 (1.02-1.06)	< 0.001	1.05 (1.03-1.07)	< 0.001	0.99 (0.98-1.01)	0.298		
Sex									
Male	212	Reference		Reference		Reference			
Female	190	0.55 (0.37-0.82)	0.004	0.51 (0.34-0.78)	0.002	0.98 (0.66-1.45)	0.916		
BMI, kg/m^2		1.04 (0.98-1.10)	0.193	1.05 (0.99-1.12)	0.123	1.07 (1.01-1.14)	0.023	1.09 (1.02-1.16)	0.010
BBPS									
Fair	87	Reference				Reference		Reference	
Adequate	315	0.78 (0.48-1.26)	0.303			2.09 (1.29-3.45)	0.003	1.17 (0.67-2.04)	0.583
Surgical history									
None	259	Reference		Reference		Reference		Reference	
Colon	99	0.62 (0.38-0.99)	0.048	0.49 (0.29-0.81)	0.006	1.50 (0.94-2.42)	0.090	1.71 (1.02-2.88)	0.042
Other	44	0.74 (0.38-1.41)	0.369	0.76 (0.37-1.50)	0.427	0.25 (0.11-0.52)	< 0.001	0.35 (0.15-0.77)	0.012
Indication									
Screening	207	Reference				Reference			
Post operation surveillance	128	0.76 (0.48-1.19)	0.232			1.09 (0.70-1.69)	0.708		
Patient with symptoms	67	0.88 (0.50-1.53)	0.653			0.76 (0.43-1.31)	0.323		

[1]Adenoma detection.

[2]Fast insertion (< median insertion time of 310 s).

P value for independent variables from logistic regression analysis; No.: Number of patients; OR: Odds ratio; aOR: Adjusted odds ratio; CI: Confidence interval; BMI: Body mass index; BBPS: Boston Bowel Preparation Scale.

which contains mostly lyrics, classical, or Star Wars music has no lyrics. Although a preference for music with lyrics can bring psychological stability, it can actually be a hindrance in terms of improving concentration[15]. Moreover, the volume of the music can influence the efficacy of task performance. Music played too loudly can interfere with communication among operating room staff and act as noise [16], thereby increasing the risk of surgical site infection[17]. As such, we kept the music at 60 dB to facilitate communication.

Trainees who listened to music had low PDR and ADR. This result was in contrast to that found in the expert group where no significant findings were noted. A previous study found similar results to those presented herein after examining the effects of music on novice surgeons[18,19]. They explained that music could have distracted surgeons as they performed new or complex tasks. These results can also be applied to endoscopy trainees. Endoscopy trainees are unfamiliar with endoscopic manipulation and require frequent assessment of the patient's condition, which inevitably consumes their attention, with music possibly making this situation worse.

The quality of colonoscopy is best determined by the ADR. Variables that can influence the ADR include age, sex, bowel preparation, and endoscopist experience[20]. The current study showed that age, sex, and surgical history were independent prognostic factors for adenoma detection. The ADR and age were positively correlated, with men having higher ADRs than women[21]. A history of abdominal or pelvic surgery makes colonoscopy difficult[22]. In particular, colon surgery affects insertion time, and prolonged insertion time reduces ADR[23,24]. A significant difference in the baseline characteristic of surgical history for colonoscopy was observed between the two groups. However, propensity score

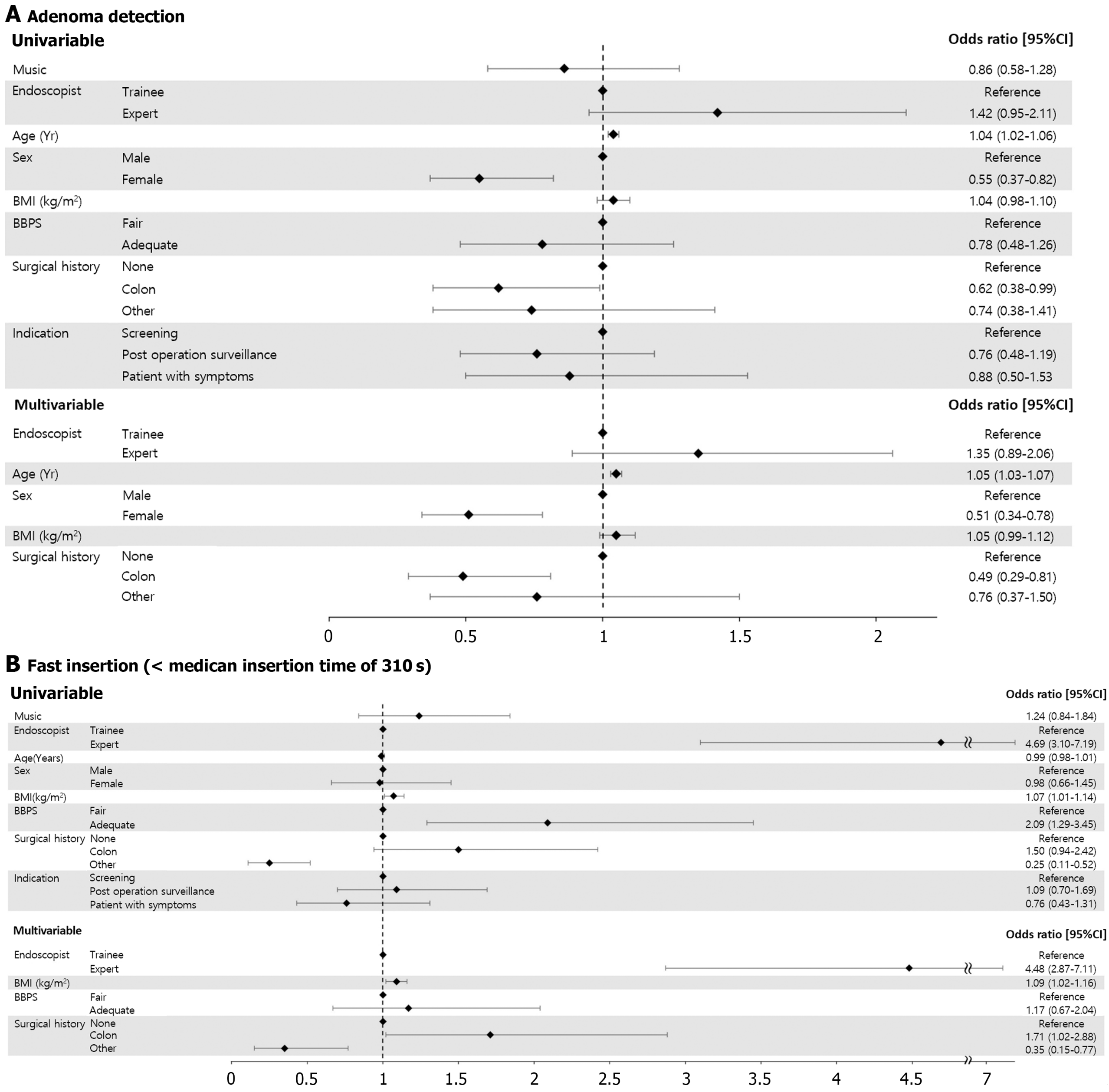

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Figure 1 Forest plot for the prognostic factor of colonoscopy performance. A: Adenoma detection; B: Fast insertion. BMI: Body mass index; BBPS: Boston Bowel Preparation Scale; 95%CI: 95% confidence interval.

matching was performed to minimize the differences in factors that may affect colonoscopy performance.

The role of music in medicine has been growing and expanding. Evidence has shown that music may reduce congestive heart failure by reducing plasma cytokine and catecholamine levels, thereby enhancing parasympathetic activity[25]. Moreover, it influences brain activation and can be helpful in neurorehabilitation[26]. As such, we sought to determine how these positive effects of music might affect colonoscopy performance. Safe, high-quality colonoscopy is important for colorectal cancer screening and diagnosis, as well as treatment of colorectal diseases. High-quality colonoscopy by endoscopists can reduce the incidence of intermittent cancer[27]. However, colonoscopy is a relatively invasive procedure that can cause complications and pain in patients and requires high concentration by endoscopy specialists[28]. Although studies have confirmed the positive effects of music in patients undergoing colonoscopy, no data have been available regarding its effects on the operator. Through this study, we confirmed that music did not have a significant effect on the performance of colonoscopy. Nonetheless, we expect that more studies will be conducted on this matter based on our findings.

The current study has some limitations worth noting. First, given the retrospective nature of our study, selection bias may have occurred. To reduce this bias, we created two groups by matching patients according to indications, age, and sex after they had started listening to music during colonoscopy at the hospital. A randomized study on the effect of music on colonoscopy is needed in the future. Second, the segmentation of abdominal surgery history was insufficient. Although gastric and pelvic surgery may have different effects on colonoscopy performance, we did not divide our patients according to surgery type. Given that pelvic surgery is mostly conducted among women, sex differences should be analyzed; however, the insufficient number of patients prevented us from doing so. Third, the genre of music was limited. While the most preferred and familiar Korean pop music was selected, diversifying the music is necessary considering that the presence of lyrics and music genre may affect colonoscopy performance.

CONCLUSION

In conclusion, listening to music during colonoscopy did not affect procedure performances. Moreover, our findings suggested that listening to music during colonoscopy can distract trainee's ability to detect adenomas and polyps.

ARTICLE HIGHLIGHTS

Research background

Music has been used to improve task performance and relieving the surgeon's tension in operating rooms. There are no studies related to the effects of music on the performance of endoscopists.

Research motivation

The role of music in medicine has been growing. Listening to music during colonoscopy affect performance of endoscopists.

Research objectives

The study aimed to assess the effects of music on colonoscopy performance outcomes.

Research methods

We retrospectively reviewed patients who underwent colonoscopy performed by endoscopists with popular music. Colonoscopy performance outcomes, such as cecal insertion time, adenoma detection rate (ADR), were compared between the music and non-music groups. The study was performed by propensity score matching to reduce selection bias.

Research results

After one-to-one propensity score matching, 169 colonoscopies were selected for each group. The cecal insertion time and ADR did not significantly differ between both groups. In trainees, ADR (25.9% *vs* 47.6%, P = 0.006) were significantly lower in the music than in the non-music group.

Research conclusions

The current study found that listening to music during colonoscopy did not affect procedure performance. Moreover, it suggested that music may distract trainees from appropriately detecting adenomas.

Research perspectives

A randomized study on the effect of music on colonoscopy is needed in the future.

FOOTNOTES

Author contributions: Lee HS contributed to study design, acquisition and critically reviewed the manuscript; Choi EJ contributed to the data interpretation, and drafting the manuscript; Lee HS, Yoon JS, Yu SJ and Lee JH performed the endoscopy; Yi SW contributed to statistical analysis; Lee HS, Choi EJ, and Lee HB edited the manuscript; Kim MP and Chung BC collected data; Jee SR and Lee SH provided clinical advice and supervised the report; and all authors have read and approve the final manuscript.

Institutional review board statement: This retrospective study was approved by the Institutional Review Board of Busan Paik Hospital and was conducted in accordance with the ethical guidelines stated in the Declaration of Helsinki (IRB number: 2020-01-192).

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Country/Territory of origin: South Korea

ORCID number: Eun Jeong Choi 0000-0003-0897-8815; Sam Ryong Jee 0000-0002-7928-1153; Sang Heon Lee 0000-0001-8210-0889; Jun Sik Yoon 0000-0003-4328-3955; Seung Jung Yu 0000-0003-3725-3901; Jong Hyun Lee 0000-0002-4979-5946; Han Byul Lee 0000-0002-5945-3237; Sang Wook Yi 0000-0002-6656-6205; Myeong Pyo Kim 0000-0002-1764-4502; Byung Cheol Chung 0000-0002-0403-8490; Hong Sub Lee 0000-0002-2962-0209.

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ORIGINAL ARTICLE

Observational Study

Diagnostic role of fractional exhaled nitric oxide in pediatric eosinophilic esophagitis, relationship with gastric and duodenal eosinophils

Panamdeep Kaur, Rachel Chevalier, Craig Friesen, Jamie Ryan, Ashley Sherman, Stephanie Page

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Panamdeep Kaur, Department of Pediatric Gastroenterology, Connecticut Children's Medical Center, University of Connecticut School of Medicine, Hartford, Connecticut, CT 06106, United States

Rachel Chevalier, Craig Friesen, Jamie Ryan, Department of Pediatric Gastroenterology, Children's Mercy Kansas City, University of Missouri-Kansas City School of Medicine, Kansas City, Missouri, MO 64108, United States

Rachel Chevalier, Craig Friesen, Department of Pediatrics, University of Kansas School of Medicine, Kansas City, Kansas, KS 66160, United States

Ashley Sherman, Department of Biostatistics, Children's Mercy Kansas City, Kansas City, Missouri, MO 64108, United States

Stephanie Page, Department of Pediatric Gastroenterology, Midwest Pediatric Specialists, Overland Park, Kansas, KS 66215, United States

Corresponding author: Panamdeep Kaur, MD, Assistant Professor, Department of Pediatric Gastroenterology, Connecticut Children's Medical Center, University of Connecticut School of Medicine, 282 Washington Street, Hartford, Connecticut, CT 06106, United States. dr.panam.chd@gmail.com

Abstract

BACKGROUND

Eosinophilic esophagitis (EoE) is an eosinophilic-predominant inflammation of the esophagus diagnosed by upper endoscopy and biopsies. A non-invasive and cost-effective alternative for management of EoE is being researched. Previous studies assessing utility of fractional exhaled nitric oxide (FeNO) in EoE were low powered. None investigated the contribution of eosinophilic inflammation of the stomach and duodenum to FeNO.

AIM

To assess the utility of FeNO as a non-invasive biomarker of esophageal eosinophilic inflammation for monitoring disease activity.

METHODS

Patients aged 6-21 years undergoing scheduled upper endoscopy with biopsy for suspected EoE were recruited in our observational study. Patients on steroids and with persistent asthma requiring daily controller medication were excluded. FeNO measurements were obtained in duplicate using a chemiluminescence nitric oxide analyzer (NIOX MINO, Aerocrine, Inc.; Stockholm, Sweden) prior to endoscopy. Based on the esophageal peak eosinophil count (PEC)/high power field on biopsy, patients were classified as EoE (PEC ≥ 15) or control (PEC ≤ 14). Mean FeNO levels were correlated with presence or absence of EoE, eosinophil counts on esophageal biopsy, and abnormal downstream eosinophilia in the stomach (PEC ≥ 10) and duodenum (PEC ≥ 20). Wilcoxon rank-sum test, Spearman correlation, and logistic regression were used for analysis. *P* value < 0.05 was considered significant.

RESULTS

We recruited a total of 134 patients, of which 45 were diagnosed with EoE by histopathology. The median interquartile range FeNO level was 17 parts *per* billion (11-37, range: 7-81) in the EoE group and 12 parts *per* billion (8-19, range: 5-71) in the control group. After adjusting for atopic diseases, EoE patients had significantly higher FeNO levels as compared to patients without EoE (*Z* = 3.33, *P* < 0.001). A weak yet statistically significant positive association was found between the number of esophageal eosinophils and FeNO levels (*r* = 0.30, *P* < 0.005). On subgroup analysis within the EoE cohort, higher FeNO levels were noted in patients with abnormal gastric (*n* = 23, 18 *vs* 15) and duodenal eosinophilia (*n* = 28, 21 *vs* 14); however, the difference was not statistically significant.

CONCLUSION

After ruling out atopy as possible confounder, we found significantly higher FeNO levels in the EoE cohort than in the control group.

Key Words: Nitric oxide; Fractional exhaled nitric oxide; Eosinophilic esophagitis; Esophagus; Pediatric; Gastroenterology

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Core Tip: Multiple endoscopies are required as a part of diagnosis and surveillance in pediatric eosinophilic esophagitis (EoE). We assessed fractional exhaled nitric oxide (FeNO)'s role as a non-invasive marker to aid in management of EoE. FeNO may have a role in a subset of pediatric EoE patients to indicate response to therapy. This could potentially be used as an adjunct in pediatric EoE.

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INTRODUCTION

Eosinophilic esophagitis (EoE) is an immune-mediated chronic inflammatory disease of the esophagus histologically characterized by an eosinophil-predominant inflammation of the esophageal mucosa[1]. Active inflammation leads to dysphagia, odynophagia and, in younger patients, vomiting, abdominal pain, and poor growth[1]. Chronic inflammation results in fibrosis, causing strictures and dysmotility. Stricturing requires repeated, invasive dilations to maintain adequate swallowing[2]

In vitro and *in vivo* studies have demonstrated the role of IL-4, 5, and 13 in promoting eosinophilic inflammation, loss of barrier function, and tissue remodeling in the esophagus[3]. A subset of EoE is responsive to proton-pump inhibitors; the remaining cases are managed with either topical glucocorticoids or dietary food group eliminations[4]. The gold standard for diagnosis is endoscopic biopsy where the degree of eosinophil infiltration in the esophageal mucosa is quantified as the number of eosinophils *per* high power field (HPF). Any patient with ≥ 15 eosinophils/HPF meets criteria for diagnosis of EoE[5].

EoE and asthma are both considered atopic conditions and frequently occur concurrently in patients [6]. The diagnosis of asthma is largely based upon the observation of symptoms of airway hyper-responsiveness and their response to bronchodilators. The degree of airflow obstruction is demonstrated using spirometry along with subjective assessment standardized questionnaires to assess limitation and severity of asthma symptoms. The presence of eosinophils in the bronchi is an integral part of the inflammatory process and is responsible for the production of exhaled nitric oxide from the pulmonary epithelium[7]. The advent of exhaled nitric oxide testing as a Food and Drug Administration (FDA)-approved device has brought forth a new tool capable of capturing the degree of pulmonary inflammation in exhaled breath[8,9]. Clinical studies have validated the concept of FeNO as a surrogate marker of eosinophilic airway inflammation[10].

The abundance of eosinophils in the esophageal mucosa in EoE prompts evaluation of their contribution to exhaled nitric oxide in individuals with EoE. Previous studies assessing correlation of fractional exhaled nitric oxide (FeNO) with degree of esophageal eosinophilic inflammation were low powered but noted a trend for association. If it could serve as a robust marker of disease activity in EoE, FeNO could potentially replace the need to perform periodic, invasive, and cumbersome endoscopies.

MATERIALS AND METHODS

Study design and study participants

We performed a cross -sectional study that enrolled patients aged 6-19 years seen in the Gastroenterology Clinic at Children's Mercy Kansas City between July 2011 and July 2016. Patients 6 years and older were most likely to be able to use the chemiluminescence nitric oxide analyzer (NIOX MINO, Aerocrine, Inc.; Stockholm, Sweden) machine as instructed. All patients with upper gastrointestinal complaints (dysphagia, food impactions, vomiting, upper abdominal pain, or reflux) who were scheduled to undergo esophagogastroduodenoscopy (EGD) with biopsies were eligible. Patients taking swallowed, inhaled, or systemic corticosteroids within a month prior to enrollment in the study were excluded to decrease the confounding factors that would affect the FeNO scores. Given the high prevalence of concurrent atopic disorders with EoE, only patients with persistent asthma requiring use of daily controller medications including corticosteroids or leukotriene modifiers were excluded from the study. Other exclusions included history of tobacco use, history of celiac disease, inflammatory bowel disease, diabetes, or other multi-system inflammatory diseases. Patients were excluded if they had ingested caffeine or nitrate-containing food 3 hours prior to the procedure as this could potentially modify FeNO scores. Data was collected retroactively by chart review to include the clinical characteristics of patients including symptoms, endoscopic, and histology findings.

FeNO

Each patient provided 2 exhaled nitric oxide samples, measured in parts *per* billion (ppb), using a chemiluminescence analyzer (NIOX MINO, Aerocrine, Inc.; Stockholm, Sweden) prior to endoscopy. The NIOX MINO unit was stationed in the endoscopy suite. A member of the study group trained on the use of the NIOX MINO unit based on FDA-approved technique and specifications instructed subjects to breathe deeply then blow into the NIOX MINO's plastic mouthpiece for approximately 10-15 s. This procedure was then repeated in order to meet the 2005 American Thoracic Society guidelines [11]. Mean value of two FeNO readings was used for purpose of analysis.

Atopy

Atopy was assessed *via* a 11-point questionnaire (Tables 1 and 2) developed collaboratively between the Pediatric Gastroenterology and Pediatric Allergy divisions. The questionnaire consisted of elementary reading level questions designed to screen and identify patients with symptoms suggestive of or a known diagnosis of atopic disease (*e.g.*, allergic rhinitis, eczema, asthma) that may falsely elevate the FeNO score. Patients were considered to be atopic if they answered positively to 1 or more questions. The presence of atopy was also controlled for and analyzed in a multivariate logistic regression model to discern its effects on FeNO in EoE patients.

Esophageal eosinophils

All subjects underwent standard-of-care EGD with two biopsies in the mid and distal esophagus, two in stomach antrum, and duodenum. A trained pathologist performed eosinophil counts on hematoxylin and eosin-stained mucosa. EoE was defined as ≥ 15 eosinophils/HPF at either of the esophageal locations. Patients with eosinophils ≥ 15/HPF were included in the EoE group; patients with esophageal eosinophils ≤ 14/HPF were in the control group.

Downstream eosinophils

Eosinophils in the stomach (antrum) and/or duodenum were considered "downstream." The eosinophils in stomach and duodenum were verified by 2 gastroenterologists in the EoE patient cohort. To determine eosinophil density, hematoxylin and eosin-stained sections were initially scanned at a low magnification (10 x objective magnification) to determine areas of maximal density. Then, using 40 x objective magnification, the eosinophils were counted in 5 consecutive non-overlapping HPF.

Table 1 Atopy screening questionnaire

Atopy screening questionnaire
(1) Has the patient ever been allergy tested?
Yes
No
(2) Has the patient ever been on allergy shots?
Yes
No
(3) In past 12 mo, has the patient had the following symptoms lasting for > 4 wk at a time? (Check all that apply)
Itching of eyes or nose
Sneezing
Stuffiness of nose
Seasonal or year-round runny nose
Eye itching/tearing/redness
(4) What seasons are the above symptoms most noticeable? (Check all that apply) Spring
Summer
Fall
Winter
Year-round
(5) Has the patient ever had one of the following? (Check all that apply)
Doctor diagnosed "allergic rhinitis"
Doctor diagnosed "allergic conjunctivitis"
(6) In past 12 mo, has the patient had any of the following skin symptoms lasting > 4 wk at a time? (Check all that apply)
Itchy skin
Red skin
Bumpy skin
Rash on the face, or at the elbow, or knee joints, behind the ear, tops of feet, wrists
Rash that you have put steroid cream on (hydrocortisone, triamcinolone)
(7) Has the patient ever had doctor diagnosed "eczema"?
Yes
No
(8) Has the patient ever had doctor diagnosed "reactive airways disease," "asthma," or "chronic bronchitis?"
Yes
No
(9) In the past 12 mo, has the patient ever required the use of an inhaler or nebulizer?
Yes
No
(10) In the past 12 mo, has the patient had any of the following respiratory symptoms that have lasted > 2 wk at a time? (Check all that apply)
Wheeze
Shortness of breath
Difficulty breathing
Sputum production
Chest pain/tightness

Cough
Nighttime wakening from cough
Exercise that required the use of an inhaler to help breathe
(11) Has the patient taken any of the following medications in the past year? (Check all that apply)

Table 2 Has the patient taken any of the following medications in the past year

Drug	Yes	No	Maybe
Claritin (loratadine)			
Zyrtec (cetirizine)			
Allegra (fexofenadine)			
Sudafed (pseudoephedrine)			
Singulair (montelukast)			
Rynatan (chlorpheniramine)			
Pro-Air, Ventolin (albuterol)			
Flovent (fluticasone)			
Pulmicort (budesonide)			
Advair (fluticasone/salmeterol)			
Orapred (prednisone)			
Xolair (omalizumab)			
Flonase (fluticasone)			
Nasonex (mometasone)			
Nasacort (triamcinolone)			
Rhinocort (budesonide)			
Veramyst (fluticasone)			
Omnaris (ciclesonide)			
Astelin (azelastine)			
Astepro (azelastine)			
Patanase (olopatadine)			
NasalCrom (cromolyn)			

Eosinophils were counted separately for the stomach and duodenum. The 5 counts were averaged to determine final eosinophil cell count for each location. Cutoff values for normal eosinophils (≤ 10 eos/HPF in the stomach and ≤ 20 eos/HPF in the duodenum) were derived from a control group of 10 patients previously identified[12]. This control group consisted of patients with a chief complaint of constipation who had an EGD as part of their clinical evaluation and whose pathology showed no diagnostic abnormality. The EoE patient cohort was then divided into 2 groups – with and without abnormal downstream eosinophils.

Ethical considerations and patient safety

The study was approved by the Children's Mercy Institutional Review Board. Prior to enrollment, an informed consent was obtained from the subjects and the caregivers, and assent was obtained from minors when appropriate.

Statistical analysis

All analysis was performed using SPSS (version 24) and SAS (version 9.4). The statistical methods of this study were reviewed by a statistician from Children's Mercy Kansas City. Patients were classified into EoE and control (non-EoE) groups. Median FeNO levels with interquartile range (IQR) are reported for both groups. Peak eosinophil count (PEC) was the absolute number from mid and distal esophagus. Wilcoxon rank-sum test was used to determine if there were any differences in FeNO levels between

EoE and non-EoE subjects. Similarly, differences in FeNO were ascertained in reference to downstream eosinophilia. Receiver operator curves (ROC) were used to further assess the best cutoff for FeNO in terms of predicting eosinophilic esophageal inflammation. A Spearman's rank-order correlation was run to analyze the relationship between FeNO and PEC. A logistic regression model was used to ascertain the effects of atopy on FeNO scores. P value < 0.05 was considered statistically significant.

RESULTS

The demographics of the study population are described using mean and standard deviation and summarized in Table 3. The patients ranged from age 6 to 19 years (mean age was 13.3 years ± 3.2, 55% females, 84% Caucasians). Overall, 124 patients were recruited with 134 discrete encounters between July 2012 and July 2016. Eight patients had repeat encounters for upper endoscopies. Ten patients were excluded for being on corticosteroids at the time of EGD or for other comorbidities not noted in the pre-assessment. Four withdrew from the study (Figure 1). Of the 134 encounters, 45 were diagnosed with EoE by histopathology. The clinical characteristics of the study subjects including symptoms, visual esophageal endoscopy findings and esophageal pathology are summarized in Table 4. The peak eosinophils in mid and distal esophagus ranged from 0 to 120 eos/HPF. The eosinophils ranged from 0 to 29 eos/HPF in the stomach and from 15 to 50 eos/HPF in the duodenum for the EoE cohort.

FeNO and EoE

The EoE group had higher FeNO levels with a median of 17 ppb (IQR: 11-37, range: 7-81) as compared to the control group, which had a median of 12 ppb (IQR: 8-19, range: 5-71), P = 0.001 (Figure 2). On multivariate analysis adjusting for presence of atopy, similar relation between FeNO and EoE was noted with P value of 0.003 (Supplementary Table 1). To predict the best cutoff for FeNO in terms of predicting EoE, ROC analysis was done (Figure 3), which indicated the area under the curve (AUC) as 0.677. With FeNO cutoff of ≥ 14 ppb, sensitivity is 60% and specificity is 57.3%, with positive predictive value (PPV) of 41.5 and negative predictive value (NPV) of 73.9%. If FeNO cutoff is increased to ≥ 30, sensitivity decreases to 35.6%, and specificity significantly increases to 92.1%, with PPV of 69.6% and NPV of 73.9%.

FeNO and esophageal eosinophilia

A Spearman's rank-order correlation to ascertain the relationship between FeNO and esophageal eosinophilia demonstrated weakly positive, but statistically significant, correlation, r_s = 0.30, P < 0.005 (Figure 4).

FeNO and downstream eosinophils

We further analyzed the EoE cohort to determine differences between FeNO levels in patients with and without elevated downstream eosinophilia. Out of 45 EoE patients, 23 patients had elevated gastric eosinophils and 28 patients had elevated duodenal eosinophils. Higher FeNO levels were noted in patients with elevated gastric [n = 23, median 18 (IQR: 12-34) *vs* 15 (IQR: 11-42)] and duodenal eosinophilia [n = 28, median 21 (IQR 12-43) *vs* 14 (IQR 11-17)]; however, the difference was not statistically significant.

DISCUSSION

Upper gastrointestinal endoscopy with mucosal biopsy remains the histological gold standard in diagnosis and management of EoE[13-15]. Endoscopic evaluation is needed at every step of management in EoE patients as it is currently the only way to assess response. Apart from being an invasive modality, repeat endoscopy carries its own risks along with rare anesthesia complications. Additionally, the cumulative cost of the procedures over the years is a financial burden for families. Multiple studies in the literature have evaluated different biomarkers as an objective measure to monitor esophageal inflammation associated with EoE, but none have been conclusive[16]. Measurement of nitric oxide in exhaled breath FeNO is a clinically useful non-invasive test in measuring airway inflammation in pulmonary inflammatory disorders like asthma and other atopic disorders, as FeNO has been noted to correlate with pulmonary eosinophils. Exhaled nitric oxide (NO) is understood to be a marker of T-helper cell type 2-mediated immune response, which is seen in chronic airway or allergic inflammation [17-19].

Based on a similar concept, a few previous studies have looked at FeNO as a non-invasive alternative to assess any correlation with esophageal inflammation in EoE patients[20]. A prospective multicenter study looked at change in FeNO levels in response to corticosteroid treatment in 11 non-asthmatic patients with EoE[21]. Although the difference between pre- and post-treatment FeNO levels were noted to be statistically significant, they did not predict a clinical or histological response. Another study measured exhaled nitric oxide in 55 pediatric patients with chronic upper gastrointestinal symptoms,

Table 3 Patient demographics, *n* (%)

	Total, *n* = 124	EoE, *n* = 37	No EoE, *n* = 87
Age (mean ± SD), yr	13.3 ± 3.2	13.5 ± 3.3	13.2 ± 3.2
Gender			
Female	67 (55.4)	12 (32.4)	55 (65.5)
Male	54 (44.6)	25 (67.6)	29 (34.5)
Race			
American Indian or Alaska Native	2 (1.6)	0 (0)	2 (2.3)
African American	5 (4.0)	4 (10.8)	1 (1.2)
White	104 (83.9)	31 (83.8)	73 (83.9)
Hispanic, Latin or Spanish origin	4 (3.2)	0 (0)	4 (4.6)
From multiple races	2 (1.6)	1 (2.7)	1 (1.2)
Not specified	7 (5.6)	1 (2.7)	6 (6.9)

EoE: Eosinophilic esophagitis.

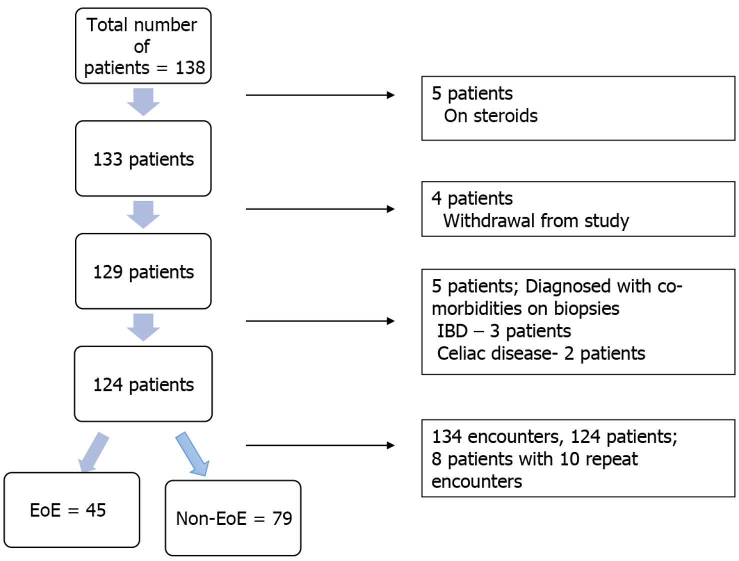

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Figure 1 Flow diagram of patient selection. IBD: Inflammatory bowel disease; EoE: Eosinophilic esophagitis.

out of which 18 were diagnosed with EoE, half of which had elevated FeNO[22]. The authors concluded that a normal FeNO level (15 ppb) may be used to rule out EoE with high specificity (> 87%), and NPV (78%); however, they did not correlate well enough to use for diagnostic purposes. Similarly, a more recent prospective study in adults demonstrated a weak relationship between FeNO and esophageal eosinophilia, deeming limited clinical utility of FeNO in EoE except for patients with high FeNO levels (> 40 ppb)[23].

Our study examined the relationship between FeNO levels and histological diagnosis of EoE, esophageal eosinophilia, and any contributory effect of downstream eosinophils in pediatric patients. The EoE cohort in our study was noted to have a higher FeNO level as compared to the patients who histologically did not have EoE. Since patients with EoE have a high incidence of atopic diseases, a subgroup analysis was performed to control for atopy, which still produced similar correlation results between FeNO and presence of EoE. These findings have not been noted in the previous studies and may attribute to an adequately powered study. Similar to a study by Johnson *et al*[23], our study also noted high FeNO levels (> 30 ppb) to be more specific in ROC analysis and may have a clinical role in predicting active esophageal inflammation.

American Thoracic Society (ATS) clinical practice guidelines for asthma suggest to use cut-off points as opposed to reference values to interpret FeNO in a clinically useful way due to multiple confounding

Table 4 Clinical patient characteristics, *n* (%)

	EoE (*n* = 45)	Non-EoE (*n* = 89)
Symptoms		
Dysphagia	14 (31.1)	21 (23.5)
Feeling of impaction	9 (20.0)	1 (1.1)
Food impaction	3 (6.67)	1 (1.1)
Choking	1 (2.2)	3 (3.4)
Throat tightness	1 (2.2)	0 (0)
Throat clearing	3 (6.67)	1 (1.1)
Abdominal pain	14 (31.1)	55 (61.8)
Vomiting	6 (13.3)	14 (15.7)
Chest pain	2 (4.4)	4 (4.5)
Heartburn	4 (8.9)	8 (8.9)
Poor appetite	0 (0)	2 (2.3)
Endoscopy		
Edema	2 (4.44)	1 (1.1)
Rings	2 (4.4)	0 (0)
Exudates	2 (4.4)	0 (0)
Furrowing	26 (57.8)	4 (4.5)
Nodularity	4 (8.9)	1 (1.1)
Histology		
Basal zone hyperplasia	43 (95.5)	23 (25.8)
Intercellular edema	40 (88.9)	24 (26.9)
Micro abscesses	4 (8.9)	0 (0)
Lamina propria fibrosis	5 (11.1)	0 (0)

EoE: Eosinophilic esophagitis.

factors and overlap between normal populations and those with asthma. Cut-off point of < 20 ppb was considered low in children and indicated less likelihood of eosinophilic inflammation and responsiveness to corticosteroids[11]. In a study that looked at FeNO measurements in healthy children of 4 to 17 years of age concluded their FeNO values to be below 15-25 ppb depending on age and atopy[24]. A value > 35 ppb was considered elevated and provided higher specificity for eosinophilic inflammation [11]. Our data suggests that given the specificity of high FeNO levels (> 30 ppb) in prediction of histological diagnosis of EoE, a similar FeNO cutoff could be established for surveillance in EoE patients, particularly those with high initial FeNO levels. Following an individual patient's FENO levels over time could allow for monitoring of esophageal inflammation in this subgroup of EoE with high FeNO scores. The ATS guidelines further suggest that a reduction of at least 20% in FeNO for values > 50 ppb (or > 10 ppb for values lower than 50 ppb) be used as the cutoff point to indicate a significant response to anti-inflammatory therapy[11]. New ATS guidelines suggest that FeNO should be combined with other clinical markers to assess disease control[25]. Potentially, a similar reduction value in FeNO scores can be established for EoE patients that can be integrated with other clinical characteristics to demonstrate response to therapy.

This is the first study to evaluate any elevations in FeNO levels that could be contributed by the eosinophils in the stomach and duodenum (downstream eosinophils). FeNO levels were noted to be elevated in patients with high gastric and duodenal eosinophilia, which had a trend towards significance. Previous studies in patients with inflammatory bowel disease have shown elevations in NO levels from intestinal inflammation[26,27]. Since intestinal inflammation downstream may affect the FeNO levels, monitoring esophageal inflammation by FeNO might not be reliable in patients with systemic inflammatory disease. Further studies are needed to assess if perhaps a higher FeNO cut off can be utilized for EoE surveillance in patients with high downstream eosinophils.

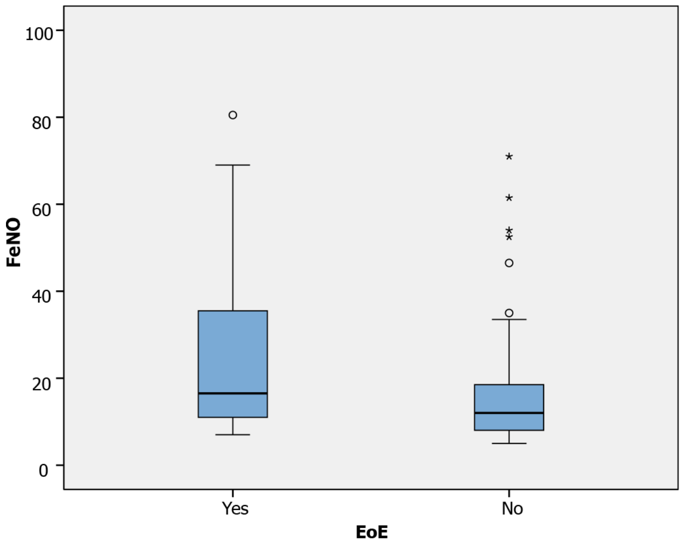

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Figure 2 Wilcoxon rank-sum test to assess fractional exhaled nitric oxide levels in eosinophilic esophagitis group compared to control. FeNO: Fractional exhaled nitric oxide; EoE: Eosinophilic esophagitis.

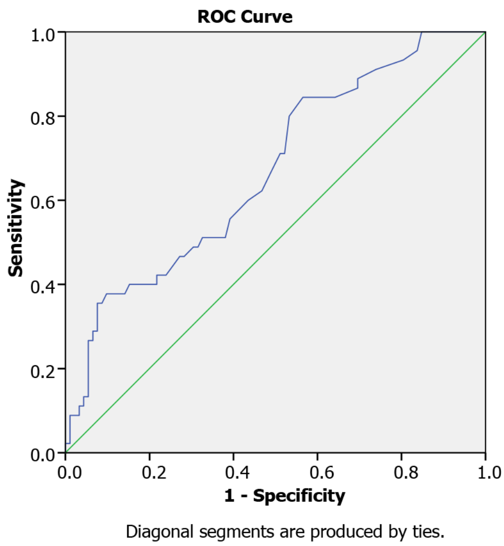

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Figure 3 Receiver operating characteristics analysis to predict fractional exhaled nitric oxide cut off. ROC: Receiver operating characteristics; FeNO: Fractional exhaled nitric oxide; EoE: Eosinophilic esophagitis.

This study is novel as it includes a large pediatric cohort, which allows us more power to assess patients with high FeNO levels. Overall, a greater percentage of our cohort had high FeNO levels than in previously published studies, indicating there might be a difference in FeNO product of pediatric EoE patients as compared to adults. Additionally, our study is the first to evaluate downstream eosinophils as a potential confounder of FeNO levels.

This study is limited by being conducted at a single institution. To reduce confounding factors, the study did not include patients with asthma which limits assessment of the group of patients that have both EoE and asthma. Due to the study design, EoE patients being treated and in remission could not be assessed for more accurate FeNO correlation. More patients with high (> 50 ppb) FeNO levels would have improved the ability to assess this subgroup. Future studies would benefit from larger sample sizes, particularly patients with higher eosinophil counts and, including patients with existing diagnosis of EoE being treated and in remission to predict more precisely whether a higher FeNO cutoff can be used to predict changes in esophageal inflammation.

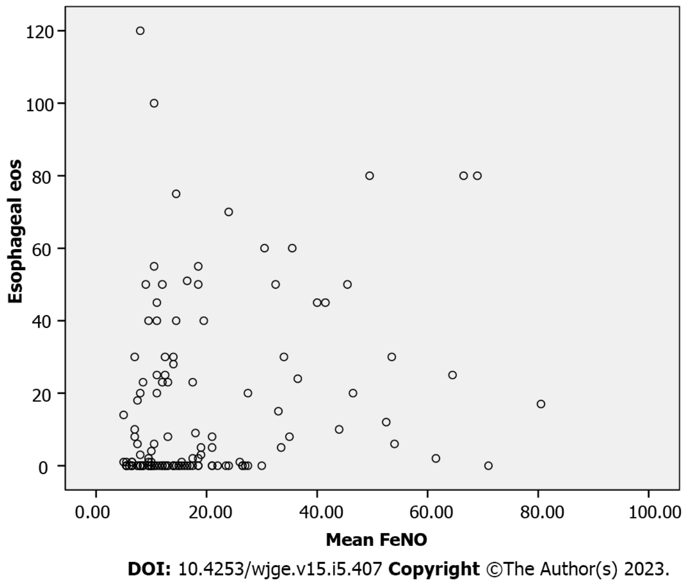

Figure 4 Spearman correlation analysis between fractional exhaled nitric oxide and esophageal eosinophils. FeNO: Fractional exhaled nitric oxide; eos: Eosinophils.

CONCLUSION

In conclusion, EoE cohort was noted to have higher FeNO levels compared to control. FeNO levels of more than 30ppb were found to be more specific for eosinophilic esophageal inflammation. FeNO may have a clinical role in assessing treatment response in a subset of EoE patients.

ARTICLE HIGHLIGHTS

Research background

Eosinophilic esophagitis (EoE) is characterized by eosinophilic inflammation of esophageal mucosa and symptoms of esophageal dysfunction. To avoid the burden of multiple endoscopies and associated risks of procedures, search for a surrogate marker for esophageal inflammation has been ongoing and inconclusive till date. Previous low powered studies assessing Fractional exhaled nitric oxide (FeNO)'s utility in EoE were noted to have a trend for association. No previous studies investigated the effect of eosinophilia in stomach and duodenum on FeNO.

Research motivation

To identify a non-invasive marker of disease activity in EoE that could be a low-risk, low-cost alternative to endoscopic evaluation. FeNO measurements have been successfully utilized in management of eosinophilic airway inflammatory disorders such as asthma. Our study assessed FeNO as a potential biomarker to monitor esophageal eosinophilic inflammation in EoE.

Research objectives

Main objective of our study is to evaluate utility of FeNO in management of Pediatric EoE. Our study also analyzed if gastric and duodenal eosinophils (downstream eosinophilia) have any effect on FeNO scores.

Research methods

Pediatric patients with upper gastrointestinal symptoms and suspected EoE were enrolled in this cross-sectional study. Chemiluminescence nitric oxide analyzer (NIOX MINO, Aerocrine, Inc.; Stockholm, Sweden) machine was used to obtain FeNO measurements prior to endoscopy. Clinical characteristics data for all EoE and non-EoE patients was collected. Correlation of FeNO levels with esophageal eosinophils, EoE and abnormal downstream eosinophilia in the stomach and duodenum was analyzed. A comprehensive atopy questionnaire was utilized for presence of atopy, which was controlled for in a separate logistic regression analysis to assess its effect on FeNO in EoE patients.

Research results

Higher FeNO levels were found in patients with EoE compared to the non-EoE cohort, after adjusting for atopy. FeNO levels more than 30 ppb were noted to be more specific for active esophageal inflammation. Elevated FeNO levels were also noted in patients with high gastric and duodenal eosinophils, with a trend towards significance.

Research conclusions

Given the specificity of high FeNO levels (> 30 ppb) in prediction of histological diagnosis of EoE, a FeNO cutoff could be established for surveillance in EoE patients, particularly those with high initial FeNO levels. Cautious interpretation or perhaps a higher FeNO cut off may be needed in patients with high downstream eosinophils. FeNO may have a clinical role in management of EoE to suggest response to therapy in a subset of pediatric EoE patients. Future studies are needed to evaluate this further.

Research perspectives

Future studies should focus on including EoE patients from the time of diagnosis, and in remission while following an individual patient's FeNO levels over time to allow monitoring of esophageal inflammation. This could provide a precise assessment for utilization of a FeNO cutoff in prediction of esophageal eosinophilic inflammation.

FOOTNOTES

Author contributions: Kaur P modified the study design, collected, analyzed and interpreted the data, wrote and revised the manuscript; Chevalier R modified the study design, collected, analyzed and interpreted the data, wrote and revised the manuscript; Friesen C modified the study design, analyzed and interpreted the data, edited and revised the manuscript; Ryan J interpreted the data and edited the manuscript; Sherman A interpreted data, performed statistical analysis of the data and revised analysis and manuscript; Page S designed and performed the research study, interpreted the data and edited the manuscript; All authors have approved the manuscript.

Institutional review board statement: The study was reviewed and approved by the Children's Mercy Institutional Review Board (Approval No. 11120665).

Informed consent statement: Informed consent was obtained from patients/caregivers prior to enrollment into the study.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

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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Country/Territory of origin: United States

ORCID number: Panamdeep Kaur 0000-0002-9016-8119.

Corresponding Author's Membership in Professional Societies: American College of Gastroenterology.

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