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Contents

Monthly Volume 13 Number 9 September 16, 2021

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Study

Observational Study

CASE REPORT

LETTER TO THE EDITOR

World Journal of Gastrointestinal Endoscopy

Monthly Volume 13 Number 9 September 16, 2021

Contents

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MINIREVIEWS

Endoscopic management of colorectal polyps: From benign to malignant polyps

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Abstract

Colorectal cancer (CRC) is the third most common cancer worldwide and the second leading cause of cancer related death in the world. The early detection and removal of CRC precursor lesions has been shown to reduce the incidence of CRC and cancer-related mortality. Endoscopic resection has become the first-line treatment for the removal of most precursor benign colorectal lesions and selected malignant polyps. Detailed lesion assessment is the first critical step in the evaluation and management of colorectal polyps. Polyp size, location and both macro- and micro- features provide important information regarding histological grade and endoscopic resectability. Benign polyps and even malignant polyps with superficial submucosal invasion and favorable histological features can be adequately removed endoscopically. When compared to surgery, endoscopic resection is associated with lower morbidity, mortality, and higher patient quality of life. Conversely, malignant polyps with deep submucosal invasion and/or high risk for lymph node metastasis will require surgery. From a practical standpoint, the most appropriate strategy for each patient will need to be individualized, based not only on polyp- and patient-related characteristics, but also on local resources and expertise availability. In this review, we provide a broad overview and present a potential decision tree algorithm for the evaluation and management of colorectal polyps that can be widely adopted into clinical practice.

Key Words: Colorectal cancer; Colon polyps; Malignant polyps; Endoscopic resection; Endoscopic mucosal resection; Endoscopic submucosal dissection

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Core Tip: Endoscopic resection is a proven strategy for the management of benign and selected malignant colorectal polyps. When compared to surgery, endoscopic resection is less costly and associated with improved clinical outcomes and patient satisfaction. Detailed lesion assessment, including endoscopic imaging and histopathology, play a critical role in directing subsequent treatment strategies. Ultimately, the most appropriate intervention will depend on various factors, including patient and lesion characteristics, as well as local resources and expertise availability. Establishing the multidisciplinary collaboration between referring physicians, endoscopists, surgeons and pathologists is the basis for ensuring best practices for the management of colorectal polyps.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide and the second leading cause of cancer death in the world[1]. A well-recognized characteristic of CRC carcinogenesis is that most cancers arise from precursor benign polyps[2]. The increasingly widespread adoption of colonoscopy has reduced CRC incidence and mortality *via* the early detection and removal of these precursor lesions and even early cancers[3,4]. In this review, we provide a broad overview and decision algorithm on the endoscopic evaluation and management of colorectal polyps.

DEFINITIONS

Colorectal polyps are growths or protuberances into the lumen above the adjacent colonic mucosa. The two major histologic types of neoplastic polyps that serve as direct precursors to most CRCs are conventional adenomas and serrated polyps[5].

Adenomas

Adenomas are commonly regarded as the prototypical precursor of CRC, given that nearly 85%-90% of sporadic CRCs derive from adenomas[6]. These lesions are identified histologically by epithelial clusters of dysplastic glands; and are divided into tubular, tubulovillous, or villous types according to the World Health Organization (WHO) classification system[7]. The adenoma-carcinoma sequence is characterized by chromosomal instability and a stepwise progression of gradual genetic and epigenetic mutations that culminate in the transformation of these precancerous lesions to CRC [8-10].

Serrated polyps

Serrated polyps encompass three main types:

Hyperplastic polyps (HPs): are the most common type of serrated polyp. They are usually small (less than 5 mm), predominantly located in the rectosigmoid colon, and are not associated with a risk for malignant transformation[6].

Sessile serrated lesions (SSLs): The term SSL is often used interchangeably with sessile serrated adenomas (SSAs). These lesions are traditionally larger than HPs, predominantly in the right colon, and according to the WHO criteria, distinguished from HPs based on the presence of crypt distortion on histology[7].

Traditional serrated adenomas (TSAs): TSAs are more commonly located in the distal colon and may have an erythematous "pine cone" gross appearance on endoscopy[11, 12]. Histologically, TSAs feature prominent cytoplasmic eosinophilia, elongated nuclei and ectopic crypts[7].

Unlike HPs, both SSL/SSAs and TSAs have malignant potential and account for approximately 15%-30% of all sporadic CRCs[6,11]. The inactivation of tumor suppressor genes *via* hypermethylation plays a critical role in the progression of serrated polyps to cancer, which is the basis of the CpG island methylator phenotype pathway[11-13]. From a histological standpoint, it is important to note that unlike conventional adenomas, not all SSL/SSAs have dysplasia. As opposed to SSL/SSAs without dysplasia, serrated polyps with dysplasia have advanced molecular changes; although there is some controversy in what constitutes these dysplasia patterns[14]. Irrespectively, SSL/SSAs with dysplasia should be distinguished from those without dysplasia given their significantly higher risk for progression to CRC[15].

CRC and the malignant polyp

CRC is defined as the invasion of neoplastic cells beyond the muscularis mucosa. As opposed to other organs in the gastrointestinal tract, the colonic mucosa is devoid of lymphatics. Therefore, neoplastic lesions confined to the muscularis mucosa have a negligible risk for lymph node metastasis (LNM) and, according to the National Comprehensive Cancer Network, do not meet the clinically accepted definition for CRC[16]. These lesions are defined as benign (non-malignant) polyps.

The term malignant polyp is used to describe a colorectal lesion in which neoplastic cells have invaded into, but not beyond the submucosa[17]. Hence, a malignant polyp represents early CRC and is categorized as pT1 according to the American Joint Committee on Cancer tumor-node metastasis classification system[18]. It has been estimated that at least 0.2% to 8.3% of colorectal polyps are malignant polyps[19-22].

ENDOSCOPIC ASSESSMENT OF COLORECTAL POLYPS

Detailed lesion assessment is the first critical step in the evaluation and management of colorectal polyps. Every polyp should be evaluated according to its size, location, and carefully inspected for macro- and micro- features. These details may provide important information regarding its histological grade and direct subsequent management decisions.

Polyp gross morphology

Paris classification: The Paris classification is a consensus system widely used to describe colorectal polyp morphology[23]. Although studies have shown only moderate agreement among experts using the Paris classification, it serves as a validated standardized nomenclature that helps categorize colorectal polyps and stratify according to the risk of CRC. Broadly speaking, lesions are categorized as polypoid (type 0-I) or non-polypoid (type 0-II) (Figure 1). The polypoid type can be either pedunculated (type 0-Ip) or sessile (type 0-Is). Nonpolypoid type 0-II can be further subdivided into those that are superficially elevated (0-IIa), flat (0-IIb), or depressed (0-IIc). Excavated lesions are designated type 0-III. The risk of CRC [*i.e.* submucosal invasion (SMI)] has been shown to be directly proportional to polyp size and the presence of depression: with the risk being as high as 40% in smaller lesions (6-10 mm) to nearly all lesions measuring more than 20 mm[24-26].

Lateral spreading tumors: Superficial non-polypoid colorectal lesions measuring more than 10 mm in diameter extending laterally rather than vertically are commonly referred as laterally spreading tumors (LSTs). The incidence of LSTs on routine colonoscopy is approximately 9%[25], and these can be broadly subdivided into the granular (LST-G) or non-granular (LST-NG) types (Figure 2). Similar to the Paris classification, LST morphology provides prognostic information regarding the risk for SMI. LST-G with a homogenous nodular pattern have a low risk of local invasion (< 2%) compared to LST-G with mixed-size nodules, in which the risk can be as high as 30% for those measuring more than 30 mm in size[27]. As opposed to the nodularity in LST-Gs, LST-NGs are characterized by a smooth surface and can be either flat or pseudo-depressed. In all, LST-NG with pseudo-depression carries the highest risk of SMI among LSTs (31.6%; 95%CI: 19.8%-43.4%)[28]. In addition to morphology, location is another important factor, with LST-G mixed type or LST-NG lesions in the rectosigmoid colon carrying the highest risk for malignancy[29].

Polyp surface pattern

In addition to its gross morphology, the surface vascular and pit pattern of a polyp can provide information about the risk of SMI and thereby assist with management

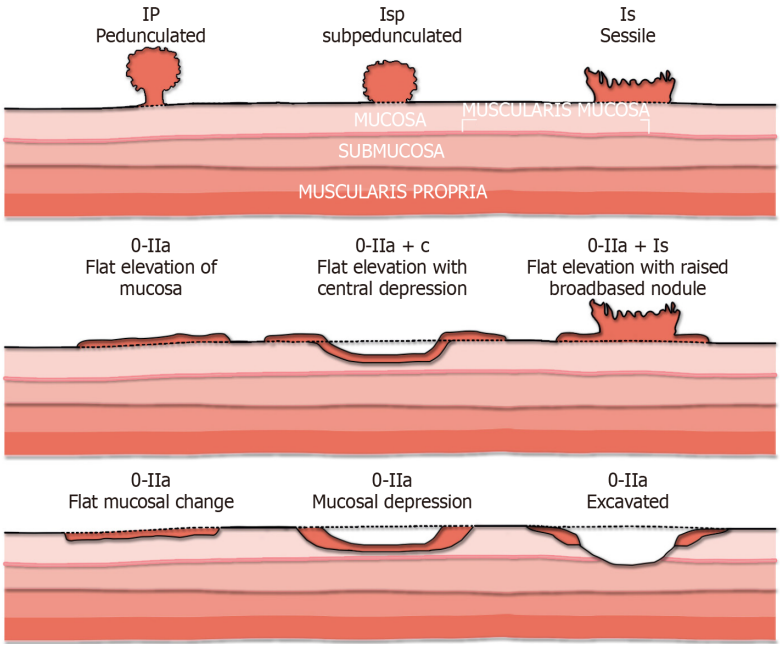

Figure 1 The Paris endoscopic classification of colorectal polyps. Adapted from[23].

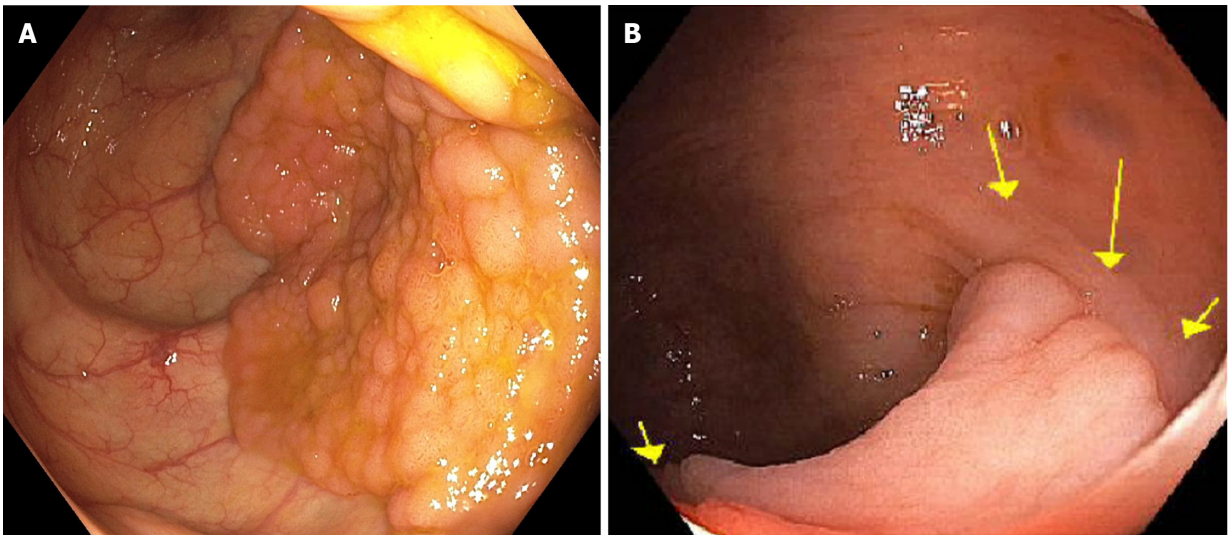

Figure 2 Lateral spreading tumor. A: Lateral spreading tumor with granular surface; B: Lateral spreading tumor non-granular type highlighted by arrows.

decisions. Multiple classification systems have been developed for polyp characterization and are outside the scope of this review. As part of this overview, we briefly discuss the Narrow Band Imaging International Colorectal Endoscopic (NICE) classification system and Kudo pit pattern nomenclature, which are possibly the most commonly utilized classification systems in the West.

NICE classification system: Narrow-band imaging (NBI) is a form of digital chromoendoscopy that enables detailed assessment of the capillary mucosal pattern of polyps by filtering white light into specific wavelengths to enhance the superficial microvascular structures. Using NBI, the NICE classification system provides a validated criterion for the optical diagnosis of colorectal polyps[30,31]. In this classification scheme, polyps can be divided into three categories (type 1, 2 or 3) based on their appearance (Table 1). NICE type 1 and 2 polyps are benign and can be resected endoscopically. Conversely, type 3 Lesions, characterized by disrupted/missing vessel pattern and amorphous or absent surface pattern on NBI, are highly suggestive of deep SMI, and thereby not amenable to endoscopic resection.

Table 1 Narrow-Band Imaging International Colorectal Endoscopic classification system

	Color	Vessels	Pits	Association
Type 1	Same or lighter than background	No or lacy vessels	Dark or white spots of uniform size	Hyperplastic or serrated polyps
Type 2	Browner than background	Brown vessels	Oval or tubular white pits	Adenomatous polyps
Type 3	Dark brown	Disrupted or missing vessels	Amorphous or absent pits	Deep submucosal invasion

This system uses color, vessel and surface pattern on Narrow-band imaging to predict the most likely polyp histology

Japan NBI Expert Team classification system: The Japan NBI Expert Team (JNET) introduced an NBI magnifying endoscopic classification system for colorectal polyps in 2014[32]. The JNET system is mainly used in Asian countries and less frequently in the Western Hemisphere. By focusing on vessel and surface pattern, the JNET system classifies colorectal polyps into four types (Types 1, 2A, 2B, and 3); each type representing the histological feature of the polyps (Table 2). Similar to NICE, irregular /amorphous vessel and surface patterns on the JNET classification system are indicative of a higher likelihood of submucosal invasive cancer.

Kudo pit pattern: Kudo and colleagues first highlighted the feasibility of examining and classifying pit patterns to distinguish type of polyps by using magnifying endoscopy[33]. This scheme broadly categorizes pit patterns into 7 types based on the pit appearance and structure (Figure 3). Most colorectal polyps (Kudo pit pattern types I through IV) fall within the spectrum of benign polyps that can be managed endoscopically. On the other hand, lesions with Kudo pit pattern V (amorphous, non-structured pit pattern) are often indicative of deep SMI, CRC and therefore the need for surgery[26,34].

HISTOLOGICAL ASSESSMENT OF COLORECTAL POLYPS

Accurate histopathological assessment is critical in determining adequacy of endoscopic resection. In this section, we briefly discuss some of the specific histopathological criteria associated with risk of recurrence and LNM in the context of malignant polyps.

Depth of invasion

Haggitt classification of pedunculated polyps: Haggitt *et al*[35] developed a classification system to describe the level of invasion in pedunculated polyps. This system categorizes polyps into five classes: level 0 to 4 (Figure 4). Level 0 corresponds to neoplastic cells limited to the mucosa without breaching the muscularis mucosa, thereby not meeting the clinical definition of CRC. Level 1 corresponds to those pedunculated polyps in which cancer cells have invaded the submucosa of the polyp head. Level 2 and 3 indicate cancer cells invading into the submucosa of the neck (junction between head and stalk) and any region of the stalk, respectively. Lastly, level 4 denotes invasion of cancer cells into the submucosa of the colorectal wall below the stalk of the polyp, but not into the muscularis propria.

Kudo and Kikuchi classification of sessile polyps: Both Kudo *et al*[36] and Kikuchi *et al*[37] introduced the concept of classifying sessile polyps into three levels based on the degree of SMI: Sm^1–invasion into the upper third of the submucosa; Sm^2–invasion into the middle third; and Sm^3–invasion into the lower third (Figure 5). The main challenge of implementing this classification system in routine clinical practice is the need for a significant portion of the submucosa within the resected specimen to define the deepest border of the submucosa. Hence, for practical purposes, this scheme has been largely modified to measure the depth of SMI from the muscularis mucosa. A SMI depth of 1000 μm is used to differentiate those lesions with superficial (< 1000 μm) *vs* deep (≥ 1000 μm) invasion. Deep SMI has been shown to be highly associated with risk for lymph node spread (10%-18%), independent of other histological features[38-40].

Tumor differentation, lymphosvacular invasion and tumor budding

In addition to depth of invasion, several histological features have been identified as

Table 2 Japan Narrow-band imaging Expert Team classification system

	Type 1	Type 2A	Type 2B	Type 3
Vessel pattern	Invisible	Regular caliber and distribution (meshed/spiral)	Variable caliber, irregular distribution	Loose vessel areas, interruption of thick vessels
Surface pattern	Uniform dark or white spots similar to surrounding mucosa	Regular (tubular/branched/papillary)	Irregular or obscure	Amorphous areas
Most likelyhistology	Hyperplastic or sessile serrated polyps	Low grade dysplasia	High grade dysplasia/shallow submucosal invasive cancer	Deep submucosal invasive cancer

This system uses vessel and surface pattern evaluation under magnified endoscopy with narrow-band imaging to predict the most likely polyp histopathology.

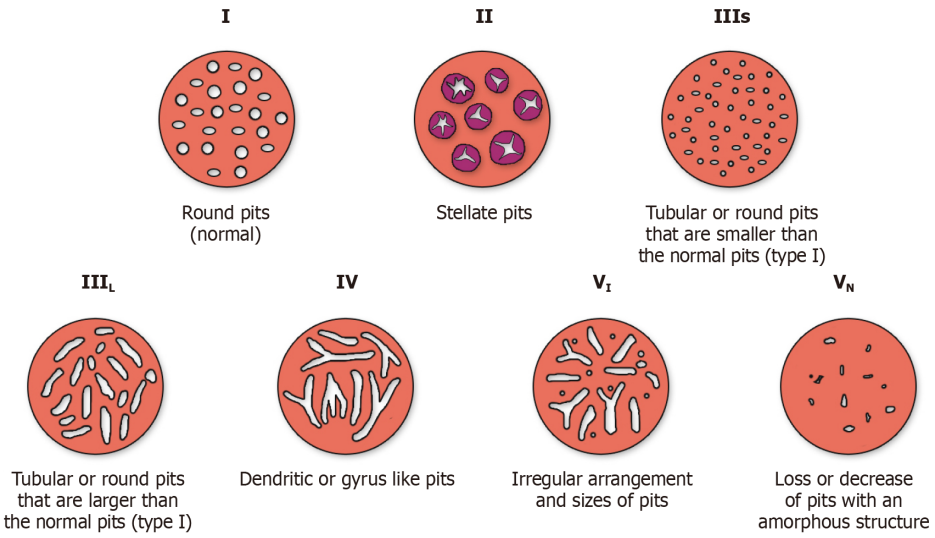

Figure 3 Kudo classification of pit pattern (Adapted from Kudo *et al*[33]).

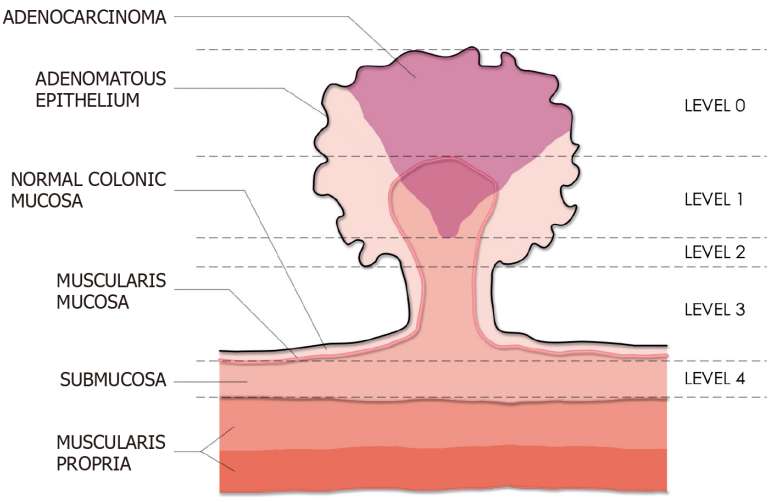

Figure 4 Haggitt classification system of pedunculated polyps (Adapted from Haggitt *et al*[35]). This system categorizes polyps into five levels (level 0 to 4) based on the degree of invasion. In this illustration, an adenocarcinoma confined to the head of the polyp would be classified as Level 1.

predictors for LNM.

Tumor differentiation: Three tumor grades have been used to described CRC based on the degree of glandular differentiation: grade 1 (well-differentiated), grade 2 (moderately differentiated), and grade 3 (poorly differentiated). When compared to

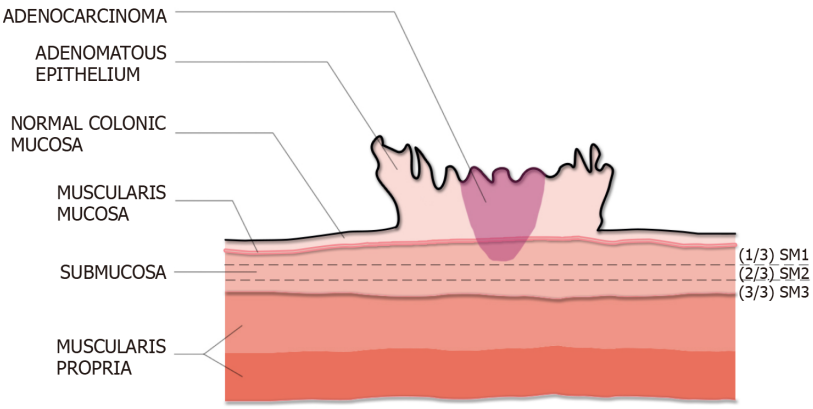

Figure 5 Kudo and Kikuchi classification (adapted from Kikuchi *et al*[37]). Depth of submucosal invasion is divided into Sm^1 (invasion into the upper third of the submucosa), Sm^2 (invasion into the middle third), Sm^3 (invasion into the lower third). In this illustration, the adenocarcinoma is a superficial lesion with Sm1 invasion.

grade 1 or 2, poorly differentiated adenocarcinomas have been shown to be associated with a significantly higher incidence of lymphatic spread [odds ratio (OR): 5.60; 95%CI: 2.90-10.82; $P < 0.00001$] and cancer-related mortality[39].

Lymphovascular invasion: Lymphovascular invasion (LVI) is recognized as a poor prognostic indicator and predictor of patient outcome. The presence of LVI in malignant polyps has been associated with an increased risk of regional LNM (OR: 4.81; 95%CI: 3.14-7.37; $P < 0.0001$)[39].

Tumor budding: Tumor budding is defined as a single or cluster of up to 5 tumor cells at the advancing front of the tumor[5,40]. This phenomenon has been recognized as a potential indicator of aggressive tumor biology with substantial evidence identifying it as a significant risk factor for LNM (OR: 7.74; 95%CI: 4.47-13.39, $P < 0.001$)[39].

Clinical ambiguity of the terms "intramucosal carcinoma" and "carcinoma in-situ"

Endoscopic resection should be the first-line preferred approach for the management of non-malignant polyps. Multiple studies have shown that endoscopic resection is more cost-effective, associated with less adverse events and higher patient quality of life when compared to surgery[41-45]. Nonetheless, despite the data favoring endoscopic resection, surgery remains a common practice and increasing trend in the United States over the past two decades[46]. In a recent study on referral patterns for the management of colorectal polyps, we demonstrated that polyps with a baseline histopathology diagnosis of "intramucosal adenocarcinoma" or "carcinoma in-situ" were associated with a significant higher likelihood of being scheduled for surgery as compared to endoscopic resection (OR: 5.72; 95%CI: 1.16-28.19, $P = 0.03$)[7]. The terms intramucosal adenocarcinoma, intraepithelial carcinoma, carcinoma in-situ or high-grade dysplasia are commonly used interchangeably by pathologists to define lesions in which neoplasia has invaded into the lamina propria but without extension through the muscularis mucosa. In all, these lesions can be adequately treated endoscopically given the absence of lymphatics within the colon mucosa and the aforementioned negligible risk for LNM. However, the inclusion of the word "carcinoma" on the diagnosis can be easily misinterpreted by providers as equivalent to CRC, which in turn can lead to inappropriate management decisions[7,17]. More recently, the terminology for these precursor lesions has been somewhat standardized in the recent 2019 WHO classification of tumors of the digestive system (5th edition)[7,47]. Indeed, the term "dysplasia" is preferred for these precursor lesions in the colon, with the two-tiered system (low- *vs* high-grade) considered the standard grading system. Conversely, the use of "carcinoma in-situ" and "intramucosal adenocarcinoma" is strongly discouraged so as to reduce the clinical ambiguity associated with these terms [5,7,47].

This standardization of pathological diagnostic reporting unifies these diagnoses under the term high-grade dysplasia, potentially reducing the likelihood of misinterpreting these non-malignant polyps as CRC, and thereby the surgical referrals for otherwise endoscopically resectable lesions.

MANAGEMENT OF COLORECTAL POLYPS: A PROPOSED ALGORITHM

The optimal management of colorectal polyps can be complex and dependent on various factors, including patient and lesion characteristics, as well as local resources and expertise availability. In this section, we propose a potential strategy for the evaluation and management of colorectal polyps that can be adapted in clinical practice. The decision tree is depicted in Figure 6.

Polyps with signs of deep submucosal invasion

Lesions should be carefully evaluated endoscopically for "overt" signs of deep SMI including NICE type 3, Kudo class V, surface ulceration without prior manipulation (*i.e.* biopsies or resection attempts), or stiffness of the lesion and colon wall[17]. According to the recent recommendations by the United States Multi-Society Task Force (USMSTF) on CRC, non-pedunculated lesions with features of deep SMI should be biopsied (in the area with surface feature disruption), tattooed near the base of the polyp and on the opposite lumen wall, and referred to surgery[48]. These recommendations by the USMSTF stem from data showing that both NICE type 3 and Kudo type V patterns are highly specific predictors of deep SMI, which are associated with LNM and need for surgery[49,50]. However, it should be highlighted that these outcomes on real-time optical diagnosis are derived from endoscopists highly trained in advanced imaging and may not reflect performance in routine clinical practice. In fact, optical diagnosis alone is notoriously endoscopist-dependent and its performance outside of specialized academic centers has been disappointing[51].

Hence, reliance on optical diagnosis alone, as proposed by the USMSTF, may have some potential drawbacks. For one, misclassification of endoscopically resectable polyps as having deep SMI can lead to premature surgical referral and a slew of potentially unnecessary diagnostic staging tests (*i.e.* EUS, CT, MRI, PET-scan, *etc*), directly impacting the patient's mental health and resource utilization[52]. Secondly, tattooing a lesion at or near its base is associated with significant submucosal fibrosis, which in turn can render subsequent endoscopic resection attempts significantly more difficult if not impossible[53-55]. Therefore, if a tattoo is deemed necessary, we recommend strictly tattooing 3 cm distal to the polyp, with appropriate photo documentation of its location with respect to the lesion[56]. Based on the aforementioned issues, we suggest that surgical referral be initiated only for those lesions with biopsy-proven invasive adenocarcinoma (Figure 6). When biopsies are performed, they should be directed to the area exhibiting features of deep SMI. This targeted biopsy strategy increases the yield for histological diagnosis and minimizes the risk of inducing submucosal fibrosis for those lesions that may be amenable for endoscopic intervention. For lesions with the following indeterminate characteristics, we recommend considering referral to a high-volume center with expertise in both endoscopic imaging and resection of complex polyps: Lesions with endoscopic appearance suggestive of deep SMI yet negative for invasive cancer on biopsies[55,57]; Lesions with equivocal endoscopic appearance for deep SMI; Lesions with equivocal biopsy results (*i.e.* histopathology showing "at least" high-grade dysplasia yet deeper invasion cannot be excluded based on the limited sample).

While we recognize that this biopsy-driven algorithm is not without its limitations, including false negative histopathology for invasive disease due to sampling error, it may potentially curtail the current trend of surgical referrals for endoscopically resectable colorectal polyps. Of note, the exception to this approach includes pedunculated polyps with either biopsy-proven and/or signs of deep SMI limited to the head of the polyp (Haggitt level 0-2). In these cases, even when invasive CRC is present, *en-bloc* resection at the level of the stalk is associated with favorable prognosis and is often curative[48,58]. Most of these pedunculated polyps can be adequately transected at the stalk with endoscopic polypectomy. In select cases, maneuvering a snare around the large head of a pedunculated polyp with a long, wide stalk can be technically challenging and endoscopic submucosal dissection (ESD) has been reported as an alternate approach to ensure *en-bloc* resection[59,60].

Polyps with probable superficial submucosal invasion

In the absence of endoscopic features of overt deep SMI, the next step is to evaluate for morphological features associated with an increased risk for superficial SMI, as this may influence the endoscopic resection strategy. Predictors associated with a relative high risk of superficial SMI include the following; polyps with depressed morphology (Paris IIc), LST-NG with depression or bulky sessile appearance (Paris Is component), and LST-G with dominant nodules[26]. While neither lesion size nor location by itself

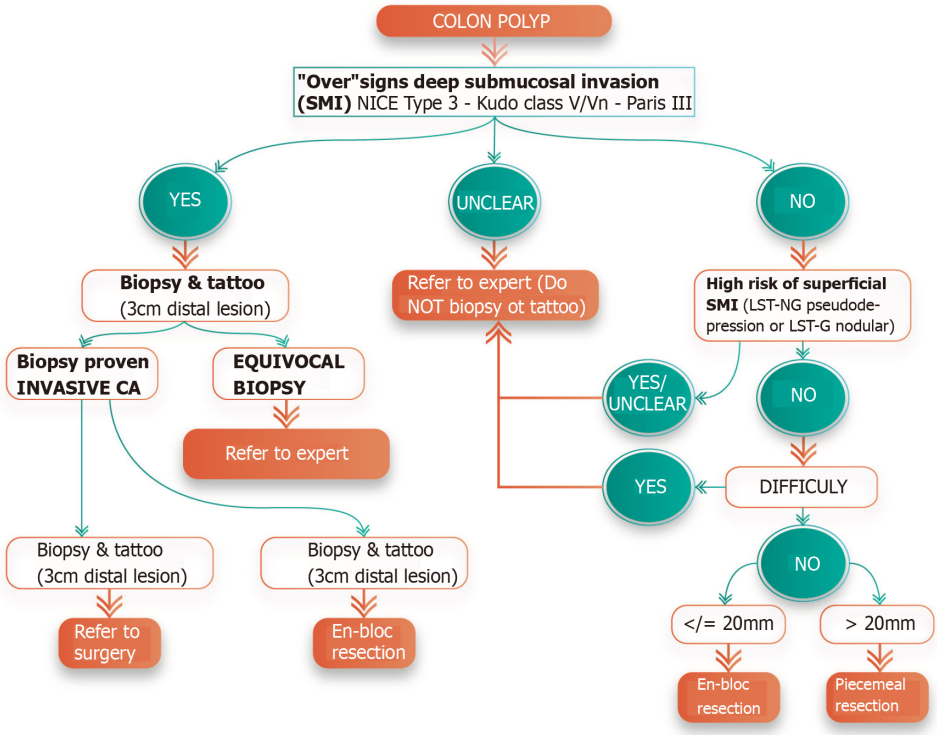

Figure 6 Decision tree algorithm for the evaluation and management of colorectal polyps.

can reliably predict superficial SMI, multiple studies have shown that the risk increases with lesions ≥ 20 mm and LSTs located in the right colon, rectosigmoid, and rectum[26,48].

As outlined by the recent recommendations by the USMSTF on CRC, lesions with suspected superficial SMI should ideally be approached with *en-bloc* endoscopic resection[48]. *En-bloc* removal of these lesions is necessary for accurate histological assessment, as piecemeal resection results in fragmented tissue specimens that compromise specimen orientation and interpretability of the resection margins. Inasmuch, the National Comprehensive Cancer Network practice guidelines specify that patients with otherwise endoscopically curable malignant polyps (*i.e.* those with superficial SMI and favorable histopathological features) who undergo piecemeal endoscopic resection will inevitably still require surgery due to the high risk of understaging the lesion because of compromised pathological interpretation[61]. Hence, the approach to a lesion with suspected superficial SMI is largely dependent on polyp size.

Lesions ≤ 20 mm in size: *En-bloc* resection may be achievable with endoscopic mucosal resection (EMR) for lesions ≤ 20 mm. Although a recent systematic review and meta-analysis suggested that underwater EMR may be associated with superior *en-bloc* resection rate when compared to conventional EMR (OR: 1.49; 95%CI: 1.02-2.16; P = 0.04), high-quality comparative studies are scarce. Therefore, the most appropriate strategy remains to be determined[62]. When performing EMR for these lesions, it is important to ensure that the snare encloses an additional margin of normal tissue around the polyp. By including a wider margin, risk of inadvertent incomplete *en-bloc* resection is decreased, which would otherwise require piecemeal removal.

Lesions > 20 mm in size: These polyps usually require ESD to achieve *en-bloc* resection. Attempt to *en-bloc* resect polyps > 20 mm with EMR is associated with a higher risk of potential complications and failure. A recent meta-analysis showed that the pooled proportion of successful *en-bloc* resection for polyps > 20 mm with either conventional or underwater EMR was unacceptably low (49.7%-58.7%)[62]. Hence, the European Society of Gastrointestinal Endoscopy, the Japan Gastroenterological Endoscopy Society and a recent American Gastroenterological Association clinical practice update recommend ESD as the preferred strategy for the resection of select colorectal lesions with suspected superficial SMI[63-65]. When compared to EMR, ESD is associated with a higher *en-bloc* and curative resection rate, and lower risk of recurrence[66]. However, ESD is a technically more complex procedure, associated

with a steep learning curve and higher rate of serious adverse events[66,67]. Due to these and other factors, the adoption of colonic ESD in the Western Hemisphere has been slower; albeit recent studies from North America have shown comparable outcomes to those reported in Asia. In a recent North American multicenter study, rectal ESD (n = 171) was associated with an *en-bloc* and complete (R0) resection rate of 82.5% and 74.9%, respectively[54]. Importantly, this study demonstrated that ESD was curative for 82% of these rectal malignant polyps[54]. It is worth noting that compared to surgery in the proximal colon, rectal operations for malignant polyps have an exceedingly high morbidity (40%-45%)[68,69]. Based on the above, referral for ESD to a center with expertise should be the preferred approach for the management of rectal lesions with suspected superficial SMI.

ESD in the proximal colon is more challenging than in the rectum, given issues with bowel peristalsis, scope positioning, and the relatively thinner colon wall[70]. As such, we recommend referring these lesions to a dedicated center with appropriate endoscopic and surgical expertise for multi-disciplinary discussion regarding the most optimal approach on a case-by-case basis.

Polyps without signs of submucosal invasion

All colorectal polyps without signs of superficial or deep SMI are benign and have no risk for LNM. Endoscopic resection should be the preferred management strategy over surgery, given the well-established advantages as previously mentioned in this review.

EMR remains the treatment of choice for the removal of benign colorectal polyps [71]. For lesions ≤ 20 mm in size, *en-bloc* resection should be attempted as this is associated with a lower risk of recurrence and need for re-intervention when compared to piecemeal removal[66,70]. Piecemeal EMR will invariably be necessary for the removal of larger non-pedunculated polyps, which increases the risk of recurrence, reportedly as high as 40%[70]. Recent strategies, including endoscopic ablation of the resection margins appear to decrease recurrence rate following piecemeal EMR[72], albeit future studies are needed to corroborate its efficacy in routine clinical practice.

Irrespective of the EMR approach, complete endoscopic resection (no visible residual tissue) should be the procedural benchmark. Partial resection or endoscopic ablation of residual visible tissue is associated with a prohibitively high risk for recurrence and even more concerning, significantly jeopardizes the ability to endoscopically remove the lesion on subsequent attempts. Notably, colorectal EMR can be technically challenging for complex polyps. Thereby, the USMSTF recommends that lesions ≥ 20 mm should be removed by endoscopists with experience in advanced polypectomy[48].

Approach to the "difficult" polyp

Several features have been commonly used to define a "difficult polyp", including variables such as size (usually ≥ 40 mm) and challenging location (*i.e.* involving the ileocecal valve, appendiceal orifice, dentate line, behind folds)[73]. More broadly, a "difficult polyp" should be defined as any lesion that the endoscopist feels he/she may not be able to completely resect endoscopically with high confidence; therefore, needing to be referred to a center with the appropriate expertise. When referring these lesions, we recommend against routine biopsy. Pretreatment biopsies do not necessarily change the management strategy in the absence of signs of SMI and can induce submucosal fibrosis, leading to prolonged procedure times and higher incomplete resection rates during succeeding endoscopic resection[74,75]. Furthermore, tattooing is not necessary if the lesion is in the cecum or rectum. If the lesion cannot be easily identified on colonoscopy, tattoo for lesion localization should be placed approximately 3 cm distal to the polyp and documented in the endoscopy report.

CONCLUSION

Endoscopic resection is a proven strategy for the management of benign and select malignant colorectal polyps. When compared to surgery, endoscopic resection is less costly and associated with improved clinical outcomes and patient satisfaction. Detailed lesion assessment, including endoscopic imaging and histopathology, play a critical role in directing subsequent treatment strategies. Ultimately, the most

appropriate intervention will depend on various factors, including patient and lesion characteristics, as well as local resources and expertise availability. Establishing the multidisciplinary collaboration between referring physicians, endoscopists, surgeons and pathologists is the basis for ensuring best practices for the management of colorectal polyps.

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ORIGINAL ARTICLE

Retrospective Study

Outcomes of inpatient cholecystectomy among adults with cystic fibrosis in the United States

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Author contributions: Ramsey ML designed and performed the research and wrote the paper; Sobotka LA, Krishna SG designed the research and supervised the report; Hinton A performed the statistical analysis and supervised the report; Kirkby SE, Li SS, Meara MP, Conwell DL supervised the report; Stanich PP designed and performed the research and supervised the report; all authors approved the final version of the article.

Institutional review board statement: As the NIS is a publicly available database of de-identified patients, The Ohio State University Institutional Review Board deemed studies utilizing this resource as exempt.

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Abstract

BACKGROUND

Symptomatic biliary and gallbladder disorders are common in adults with cystic fibrosis (CF) and the prevalence may rise with increasing CF transmembrane conductance regulator modulator use. Cholecystectomy may be considered, but the outcomes of cholecystectomy are not well described among modern patients with CF.

AIM

To determine the risk profile of inpatient cholecystectomy in patients with CF.

METHODS

The Nationwide Inpatient Sample was queried from 2002 until 2014 to investigate outcomes of cholecystectomy among hospitalized adults with CF compared to controls without CF. A propensity weighted sample was selected that closely matched patient demographics, patient's individual comorbidities, and hospital

meet criteria for human subject research. Therefore, there is no risk to any individual subject so informed consent is not necessary and was not obtained.

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characteristics. The propensity weighted sample was used to compare outcomes among patients who underwent laparoscopic cholecystectomy. Hospital outcomes of open and laparoscopic cholecystectomy were compared among adults with CF.

RESULTS

A total of 1239 inpatient cholecystectomies were performed in patients with CF, of which 78.6% were performed laparoscopically. Mortality was < 0.81%, similar to those without CF (P = 0.719). In the propensity weighted analysis of laparoscopic cholecystectomy, there was no difference in mortality, or pulmonary or surgical complications between patients with CF and controls. After adjusting for significant covariates among patients with CF, open cholecystectomy was independently associated with a 4.8 d longer length of stay (P = 0.018) and an $18449 increase in hospital costs (P = 0.005) compared to laparoscopic cholecystectomy.

CONCLUSION

Patients with CF have a very low mortality after cholecystectomy that is similar to the general population. Among patients with CF, laparoscopic approach reduces resource utilization and minimizes post-operative complications.

Key Words: Laparoscopic cholecystectomy; Nationwide Inpatient Sample; Cystic fibrosis; Mortality; Length of stay; Symptomatic biliary disorders

Core Tip: Cholecystectomy has been considered to be a high-risk intervention in adults with cystic fibrosis (CF). Our study used a sample of adults with closely matched baseline characteristics to compare hospital outcomes among patients with and without CF. There was no difference in mortality or pulmonary or surgical complications between adults with and without CF. Patients with CF who underwent an open cholecystectomy had a longer length of stay than those who underwent a laparoscopic cholecystectomy. This study suggests that cholecystectomy is safe in selected adults with CF and that a laparoscopic approach should be preferred.

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INTRODUCTION

Cystic fibrosis (CF) is a multisystem disease resulting from defects in the CF transmembrane conductance regulator (CFTR) apparatus. The highest incidence of CF is seen in people of northern European descent, where CF occurs in one out of 3000 live births and approximately one in 25 people carry a pathogenic allele[1]. When initially described in the 1930s, median survival was only a few months but advances in pulmonary treatments have since increased the median predicted survival beyond 40 years[2,3]. While the natural history and treatment of pulmonary and pancreatic diseases in CF have been well characterized, other affected organs, such as the biliary tree and gallbladder, have less epidemiologic and clinical data to guide care. Management of these other organ systems which affect quality of life will become increasingly important as median survival improves.

Biliary disorders are thought to be common in CF due to the high expression of the CFTR gene in the gallbladder and biliary tree[4]. The mechanism of gallstone formation in CF is incompletely understood, but is likely the result of biliary stasis due to gallbladder dysmotility and prolonged transit through the bile ducts[4,5]. Cholelithiasis is reported in 20%-30% of patients with CF, and symptomatic biliary colic is experienced by 4% to 40% of subjects in retrospective studies[6-8]. One case

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series suggested that the incidence of cholelithiasis increases with age, from 0.1% in those less than 5 years of age, to nearly 10% in those aged 30-40[8]. Additionally, the use of CF transmembrane conductance regulator (CFTR) modulators may increase the risk of biliary colic[9]. The population of patients with CF are aging and CFTR modulators are increasingly used, which are leading to a greater number of patients at risk for biliary and gallbladder disorders.

In patients without CF, symptomatic biliary disorders are managed surgically by cholecystectomy. However, few CF patients undergo cholecystectomy, due at least in part to concerns for perioperative complications[3,10]. The few published case series of cholecystectomy show an aggregate mortality rate of 4% (3/71) among patients with CF, which is considerably higher than the 0.15% mortality reported in the general population[6,8,10-15]. However, the CF surgical case series were completed over 25 years ago, and surgical technique and patient characteristics have changed dramatically since then. We hypothesized that the outcomes of cholecystectomy in a modern cohort of subjects with CF will be no different than the general population, especially when controlling for comorbidities. We aimed to evaluate the safety of cholecystectomy in subjects with CF compared to non-CF controls using a large national database.

MATERIALS AND METHODS

Data source

A retrospective analysis was performed using the Nationwide Inpatient Sample (NIS) (2002 to 2014), available through the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality. The NIS represents more than 35 million individual hospitalizations annually across the United States and is one of the largest publicly available databases. This database can be used to evaluate patient and hospital characteristics as well as resource utilization such as costs, mortality, and length of stay[16]. As the NIS is a publicly available database of de-identified patients, The Ohio State University Institutional Review Board deemed studies utilizing this resource as exempt.

Study sample

Subjects were required to have a procedure code for cholecystectomy, defined as open, laparoscopic, or laparoscopic converted to open (Supplementary Table 1). Subjects were excluded if they were under the age of 18, pregnant, had cirrhosis, or underwent a partial cholecystectomy. Patients who underwent laparoscopic converted to open approach were categorized as open cholecystectomy. The cohorts were then defined by the presence or absence of CF diagnosis codes.

Outcomes of interest

The primary outcome of interest was mortality following cholecystectomy. As secondary outcomes, we evaluated length of stay, cost of hospitalization, and the rates of post-operative complications based on a validated set of diagnosis and procedure codes (Supplementary Table 1)[17,18]. Additionally, we analyzed the indications for cholecystectomy among patients with CF using previously defined diagnosis codes (Supplementary Table 1)[19-21]. Patients with choledocholithiasis and gallstone pancreatitis were included in the category of gallstone disease without cholecystitis (Supplementary Table 1). All outcomes were compared between patients with and without CF using survey weighting and propensity weighting and between patients with CF who received open or laparoscopic cholecystectomy using univariate and multivariate analyses. A study flowchart of patient inclusion and analyses is presented in Figure 1.

Definition of variables

Other variables evaluated include age, gender, race, income, type of insurance, hospital size, type of hospital, and hospital region. The presence of comorbid conditions were evaluated using the Elixhauser comorbidity index, which has been used widely since it was developed in 2005[22].

Statistical analysis

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, United States) on weighted data and accounted for the complex survey designs of the NIS.

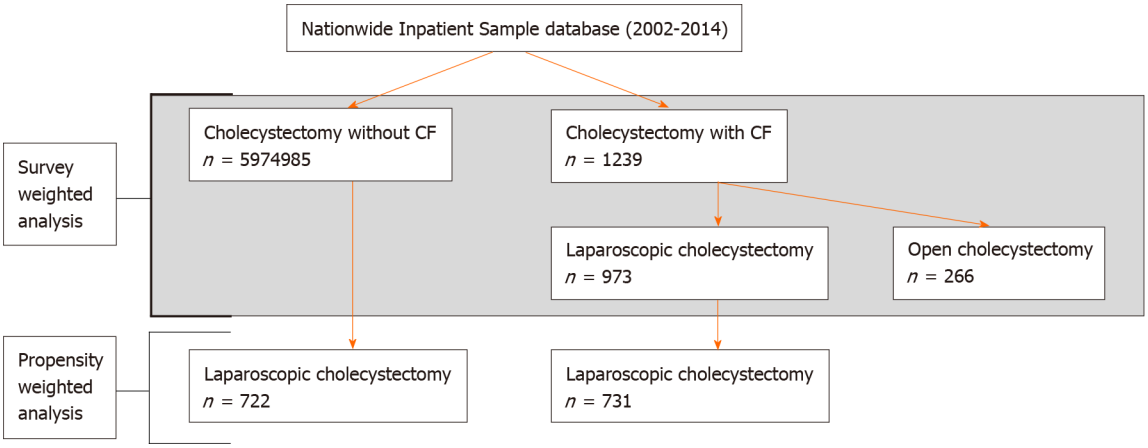

Figure 1 Study flowchart demonstrating survey weighted and propensity weighted analyses. CF: Cystic fibrosis.

Differences between patient characteristics, hospital characteristics, and outcomes were compared between patients with and without CF through the use of chi-square tests for categorical variables and *t*-tests for continuous variables. Similar comparisons were made between the populations of patients with CF who underwent open or laparoscopic cholecystectomy. Multivariate linear regression models were created for length of stay and hospital costs using a stepwise selection process. Where less than 10 observations are recorded, the exact number is censored to protect subject privacy, per NIS regulations. Missing data is listed in Supplementary Table 2.

Propensity weighted analysis

Among patients who underwent a laparoscopic cholecystectomy, propensity scores were calculated using a multivariable logistic regression model for CF containing all patient and hospital characteristics and indications for cholecystectomy as well as all individual Elixhauser comorbidities. The logistic regression model was weighted and accounted for all aspects of the complex survey design.

After deriving propensity scores (e) for each subject, propensity score weights were defined as 1 for subjects with CF and as $e/(1-e)$ for subjects without CF. These propensity score weights were then multiplied by the original survey weights defined by HCUP to arrive at the new weights which were used in place of the original HCUP weights in the following propensity weighted analysis, as previously described[23]. After propensity weighting was applied, all variables were well balanced between the two groups. The propensity weights were then used to evaluate differences in outcomes between patients with and without CF.

RESULTS

Demographics

From 2002 to 2014, a total of 5976224 adults underwent inpatient cholecystectomy, of which 1239 (0.021%) had CF (Table 1, Figure 1). Subjects with CF were younger and were more likely to be white, have private insurance, be treated at an urban teaching hospital, and have comorbid chronic respiratory failure (Table 1). A laparoscopic approach was used more often in CF subjects than in controls (78.6% *vs* 70.2%, P = 0.003) (Table 1). The indications for surgery between these groups were different: subjects with CF were less likely to undergo cholecystectomy for acute cholecystitis (48.1% *vs* 60.4%, P < 0.001), but more likely to have gallstone disease without cholecystitis (26.6% *vs* 18.0%, P < 0.001) or biliary dyskinesia (5.0% *vs* 1.2%, P < 0.001) (Table 1). Mortality was not significantly different between those with CF and those without (≤ 0.81% *vs* 0.99%, P = 0.719) (Supplementary Table 3). Length of stay and total hospitalization costs were higher for CF patients than controls (10.1 d *vs* 5.4 d, P < 0.001; $27561 *vs* $14059, P < 0.001) (Supplementary Table 3).

Propensity weighted analysis

After propensity weighting was applied to patients who underwent laparoscopic cholecystectomy, the variables were well balanced between groups

Table 1 Comparison of characteristics between subjects with and without cystic fibrosis who underwent cholecystectomy from 2002 to 2014

	Without cystic fibrosis (*n* = 5974985)		With cystic fibrosis (*n* = 1239)		
	n	**%**	***n***	**%**	***P* value**
Patient and hospital characteristics					
Age (mean ± SE)	53.81	0.05	31.28	0.80	< 0.001
Gender					0.342
Male	2113648	35.45	475	38.35	
Female	3848224	64.55	764	61.65	
Race					< 0.001
White	3377462	68.16	917	90.92	
Black	486644	9.82	15	1.51	
Hispanic	784975	15.84	38	3.81	
Other	306042	6.18	38	3.75	
Income quartile					0.669
First	1443591	26.81	270	23.36	
Second	1423075	26.43	322	27.83	
Third	1342530	24.94	313	27.06	
Fourth	1174730	21.82	251	21.76	
Primary payer					< 0.001
Medicare	2013023	33.76	255	20.62	
Medicaid	689680	11.57	215	17.34	
Private insurance	2550634	42.77	646	52.16	
Other	710118	11.91	122	9.88	
Elixhauser co-morbidity score					0.095
< 3	4425355	74.06	974	78.62	
≥ 3	1549630	25.94	265	21.38	
Chronic respiratory failure	16136	0.27	24	1.96	< 0.001
Hospital bed size					0.044
Small	744565	12.50	89	7.27	
Medium	1569622	26.36	306	24.87	
Large	3639976	61.13	835	67.86	
Hospital location/teaching status					< 0.001
Rural	786013	13.20	57	4.67	
Urban non-teaching	2724014	45.75	252	20.52	
Urban teaching	2444135	41.05	920	74.82	
Hospital region					0.184
Northeast	1048152	17.54	210	16.93	
Midwest	1248121	20.89	335	27.00	
South	2369451	39.66	467	37.65	
West	1309262	21.91	228	18.42	
Cholecystectomy approach					0.003

Laparoscopic	4192051	70.16	973	78.55	
Open	1782934	29.84	266	21.45	
Indication for cholecystectomy[1]					< 0.001
Acute cholecystitis	3606140	60.35	597	48.14	
Chronic cholecystitis	317489	5.31	98	7.90	
Gallstone disease without cholecystitis	1077090	18.03	329	26.58	
Biliary dyskinesia	71204	1.19	62	5.03	
Other	903063	15.11	153	12.35	

[1]Hierarchy model.

(Supplementary Table 4). Hospital mortality was low among both groups, with less than 10 events observed (Table 2). Subjects with CF experienced a mean length of stay (LOS) of 9.4 d, compared to 5.2 d in those without CF ($P < 0.001$) (Table 2). Similarly, total hospital costs were greater for subjects with CF ($25891 *vs* $14103, $P = 0.003$) (Table 2). There was no difference between CF and controls in post-operative surgical complications (4.5% *vs* 2.3%, $P = 0.094$) or pulmonary complications (6.6% *vs* 4.1%, $P = 0.109$) (Table 2).

Impact of surgical route on outcomes in CF

Of the 1239 patients with CF who underwent cholecystectomy, 973 (78.6%) had a laparoscopic approach. Compared to an open approach, patients with a laparoscopic cholecystectomy were more likely to be female, but other demographics were similar (Table 3). There was no significant difference in mortality (≤ 1.0% *vs* ≤ 3.8%, $P = 0.286$) but the LOS was longer and total hospital costs were greater in the open cholecystectomy group (14.5 d *vs* 8.9 d, $P = 0.009$; $43024 *vs* $23288, $P = 0.005$) (Supplementary Table 4). After adjusting for significant covariates, open route at surgery was associated with longer LOS (4.82 d, 95%CI: 0.82 d, 8.83 d, $P = 0.018$) and increased hospital costs ($18449, 95%CI: $5582, $31316, $P = 0.005$) (Table 4 and Supplementary Table 5). There were insufficient observations of mortality and post-operative complications to fit a multivariate model for these outcomes.

DISCUSSION

More patients with CF are reaching adulthood due to advances in CF care and CFTR modulators are increasingly used. With this, clinicians are likely to see an increasing prevalence of biliary disorders for which cholecystectomy will be considered as a definitive treatment. Therefore, it is important to clarify the safety of cholecystectomy. In this study, we used a nationally-representative database to evaluate the post-operative outcomes among adult patients with CF who undergo cholecystectomy. Importantly, we found that cholecystectomy had very low in-hospital mortality that was not significantly different from the general population. The surgical indications and approach were different between patients with and without CF. Open cholecystectomy was independently associated with longer LOS and greater hospital costs compared to laparoscopic approach. Finally, there is increased healthcare utilization among patients with CF compared to a propensity weighted cohort following laparoscopic cholecystectomy.

Our data shows a low mortality rate in a large and nationally representative cohort of CF patients, comparable to previous case series of cholecystectomy among CF patients. Aggregate data from case series show no deaths out of 12 patients who underwent laparoscopic surgery and 3/59 (5.1%) who underwent open cholecystectomy (although many of these surgeries were performed over 25 years ago)[6,8,10-12,15]. The previous case series also reported long lengths of stay after open cholecystectomy, up to 22 d in one series, partially due to prolonged pre- and post-operative intravenous antibiotics and frequent respiratory care[12]. Compared to these older studies, the current mean length of stay for laparoscopic cholecystectomy (8.9 d, standard error 0.71 d) is shorter. Similarly, CF patients experience longer LOS after sinus surgery compared to non-CF patients[24]. In one study using the American College of Surgeons' National Surgical Quality Improvement Program-Pediatric

Table 2 Univariate analysis of outcomes between propensity weighted cohort of patients with and without cystic fibrosis who underwent laparoscopic cholecystectomy in the Nationwide Inpatient Sample 2002-2014

	Without cystic fibrosis (*n* = 722)		With cystic fibrosis (*n* = 731)		
	n	**%**	***n***	**%**	***P* value**
Mortality[1]	≤ 10	≤ 1.39	≤ 10	≤ 1.37	0.662
Length of stay (mean ± SE)	5.18	0.33	9.36	0.89	< 0.001
Cost ($) (mean ± SE)	14103	842	25891	3859	0.003
Pulmonary complications	29	4.05	49	6.64	0.109
Surgical complications	16	2.27	33	4.48	0.094

[1]Where $n \leq 10$, the exact value is censored to protect patient privacy, per Nationwide Inpatient Sample regulation.

database, the authors suggested that the longer LOS was not due to complications but rather due to extended monitoring and intravenous antibiotics[24]. Our study shows this also appears to be true for cholecystectomy: Patients with CF have longer LOS than controls despite similar rates of post-operative complications.

Post-operative pulmonary decompensation and infection has been reported in previous case series, with an overall incidence of 7.0% (5/71) that is similar to our study[6,8,10-13,15]. To mitigate this risk, chest physiotherapy and antibiotics were used pre- and post-operatively. One group targeted pre-operative pulmonary function tests at the "highest level attained in the past 2 years, or until a prolonged period of therapy reaches a plateau of improvement" for elective surgery[10]. Increased pulmonary complications after open cholecystectomy may be attributed to derangements in respiratory mechanics due to the surgical incision near the diaphragm and increased post-operative pain[25]. Accordingly, laparoscopic cholecystectomy is recommended over open cholecystectomy for subjects with chronic pulmonary comorbidities to minimize risks of post-operative complications[25,26]. These data suggest that optimal outcomes are attained by elective laparoscopic intervention, and further study may be required to determine the best approach for pre- and post-operative pulmonary optimization among patients with CF.

While the incidence of post-cholecystectomy pulmonary complications has been described, the risk of surgical complications including soft tissue infections, perforation during surgery and need for recurrent surgery in CF compared to the general population has not been previously reported. We demonstrate an increased risk of surgical complications in patients with CF compared to the general population in the survey weighted cohort, and an increased risk with open compared to laparoscopic cholecystectomy among patients with CF. In the propensity weighted analysis, we found no significant difference in the rate of surgical complications. Patients with CF have an increased risk of infections with drug resistant bacteria, which may place this population at higher risk of infection after surgical intervention as these organisms may not be treated by routine pre-operative antibiotics[27].

Our study has several limitations inherent to the use of a large database, such as the potential for coding errors. Additionally, we cannot account for characteristics that are not included in the NIS which may influence outcomes, such as medication use, nutritional status, and baseline pulmonary function, nor can we evaluate survival beyond the inpatient period. Lastly, there may be selection bias, as only patients with acceptable surgical risk would have undergone cholecystectomy. Due to these limitations, "causality" cannot be inferred from large database analyses. However, in the absence of a prospectively collected surgical registry among patients with CF, the NIS remains an excellent data source due to its large number of observations and sophisticated sampling design. The NIS included 1239 inpatient cholecystectomies among patients with CF which greatly outnumbers the 71 cases reported in the literature to date. Additionally the NIS represents national demographics so the reported outcomes are likely to be generalizable to similar CF patients encountered in clinical practice. Finally, the volume of cholecystectomy in the control population allowed for a propensity weighted analysis to approximate a randomized trial, which could not be reasonably accomplished outside of a large database.

Table 3 Comparison of characteristics between subjects with cystic fibrosis who underwent open compared to laparoscopic cholecystectomy from 2002 to 2014

	Laparoscopic CCY (*n* = 973)		Open CCY (*n* = 266)		
	n	**%**	***n***	**%**	***P* value**
Patient and hospital characteristics					
Age (mean ± SE)	30.78	0.86	33.11	1.95	0.272
Gender					0.005
Male	330	33.92	145	54.60	
Female	643	66.08	121	45.40	
Race					0.911
White	718	90.92	199	90.93	
Black	≤ 10	≤ 1.03	≤ 10	≤ 3.76	
Hispanic	29	3.65	≤ 10	≤ 3.76	
Other	33	4.13	≤ 10	≤ 3.76	
Income quartile					0.110
First	210	23.22	60	23.86	
Second	221	24.47	100	39.95	
Third	264	29.20	48	19.34	
Fourth	209	23.11	42	16.85	
Primary payer					0.265
Medicare	221	22.73	34	12.86	
Medicaid	177	18.23	37	14.07	
Private insurance	482	49.56	164	61.69	
Other	92	9.47	30	11.38	
Elixhauser co-morbidity score					0.311
< 3	778	79.93	196	73.81	
≥ 3	195	20.07	70	26.19	
Chronic respiratory failure	24	2.50	0	0.00	-
Hospital bed size					0.244
Small	71	7.29	19	7.21	
Medium	219	22.58	87	33.34	
Large	679	70.13	155	59.45	
Hospital location/teaching status					0.476
Rural	53	5.45	≤ 10	≤ 3.76	
Urban non-teaching	193	19.94	59	22.67	
Urban teaching	723	74.61	197	75.56	
Hospital region					0.812
Northeast	167	17.15	43	16.12	
Midwest	258	26.53	76	28.73	
South	378	38.85	88	33.27	
West	170	17.47	58	21.88	
Indication for cholecystectomy[1]					
Acute cholecystitis	527	54.17	69	26.07	

Chronic cholecystitis	84	8.61	14	5.28
Gallstone disease without cholecystitis	285	29.25	45	16.82
Biliary dyskinesia[2]	58	5.95	≤ 10	≤ 3.76
Other	20	2.02	133	50.18

[1]Hierarchy model.
[2]Where $n \leq 10$, the exact value is censored to protect patient privacy, per Nationwide Inpatient Sample regulation. CCY: Cholecystectomy.

Table 4 Multivariate comparison of post-operative outcomes between subjects with cystic fibrosis who underwent open compared to laparoscopic cholecystectomy from 2002 to 2014

	Length of stay			Hospitalization cost		
	Days	95%CI	*P* value	$	95%CI	*P* value
Open cholecystectomy	4.82	(0.82, 8.83)	0.018	18449	(5582, 31316)	0.005
Elixhauser co-morbidity score ≥ 3	8.35	(4.28, 12.43)	< 0.001	28344	(10548, 46141)	0.002
Hospital location/teaching status			< 0.001			< 0.001
Rural	-5.88	(-11.53, -0.24)		-13801	(-22490, -5111)	
Urban non-teaching	-3.69	(-5.71, -1.68)		-13709	(-20684, -6734)	
Urban teaching	Ref.			Ref.		

Adjusted for significant covariates.

CONCLUSION

Cholecystectomy among adult patients with CF did not carry an increased risk of in-hospital mortality compared to controls. Length of stay and hospital costs are higher in patients with CF and there is a higher risk of post-operative surgical complications and a tendency to develop more pulmonary complications, although this risk of complications is no longer seen when demographic and health variables are taken into account. A laparoscopic approach is safer and reduces healthcare utilization compared to an open approach in adults with CF. These results should inform the discussion between clinicians and patients with CF when cholecystectomy is considered.

ARTICLE HIGHLIGHTS

Research background

Symptomatic biliary disorders are common in cystic fibrosis (CF) and may become more common now that patients with CF are living longer. Biliary disorders are often managed with cholecystectomy but this surgery carries high risk of morbidity and mortality among adults with CF. However, the reported rate of complications is based on older studies, and may not represent modern surgical outcomes.

Research motivation

Currently, there is insufficient data examining the safety of cholecystectomy among adults with CF using modern surgical techniques.

Research objectives

To investigate the outcomes of inpatient cholecystectomy among adults with and without CF.

Research methods

The Nationwide Inpatient Sample was used to collect data on inpatient cholecystectomies between 2002 and 2014. Subjects without CF were matched 1:1 to subjects with CF, accounting for over 20 variables including age, sex, and comorbidities.

Research results

Among patients with CF, 1239 cholecystectomies were performed during the study period. Open cholecystectomy was independently associated with an $18449 increase in hospital costs (P = 0.005) and a 4.8 d longer length of stay (P = 0.018) compared to laparoscopic cholecystectomy. The mortality rate among patients with CF was < 0.81%, which was similar to the mortality rate among patients without CF (P = 0.719). Similarly, there was no significant difference in mortality or post-operative surgical complications (4.5% *vs* 2.3%, P = 0.094) or pulmonary complications (6.6% *vs* 4.1%, P = 0.109) after laparoscopic cholecystectomy between patients with and without CF in the propensity weighted analysis.

Research conclusions

With modern anesthesia and surgical techniques, cholecystectomy is equally safe for patients with and without CF.

Research perspectives

Cholecystectomy may be increasingly considered for the management of biliary symptoms among adults with CF. Future research will need to clarify if there are unique indications for cholecystectomy among patients with CF.

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ORIGINAL ARTICLE

Retrospective Study

Endoscopic balloon dilation for management of stricturing Crohn's disease in children

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Author contributions: McSorley B and Quiros JA collaborated in initial study design and performed all the data acquisition, data analysis, drafting of the manuscript and approval of the final submission; Cina RA, Jump C and Palmadottir J supported initial study conception, data interpretation and approval of final submission.

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Informed consent statement: The need for informed consent was waived by the Institutional Review Board at the Medical University of South Carolina due to the study being a retrospective chart review and causing no more than minimal risk to the patients.

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Abstract

BACKGROUND

Crohn's disease (CD) has a multitude of complications including intestinal strictures from fibrostenotic disease. Fibrostenotic disease has been reported in 10%-17% of children at presentation and leads to surgery in 20%-50% of cases within ten years of diagnosis. When symptoms develop from these strictures, the treatment in children has primarily been surgical resection. Endoscopic balloon dilation (EBD) has been shown to be a safe and efficacious alternative to surgery in adults, but evidence is poor in the literature regarding its safety and efficacy in children.

AIM

To evaluate the outcomes of children with fibrostenosing CD who underwent EBD *vs* surgery as a treatment.

METHODS

In a single-center retrospective study, we looked at pediatric patients (ages 0-18) who carry the diagnosis of CD, who were diagnosed after opening a dedicated Inflammatory Bowel Disease clinic on July 1, 2012 through May 1, 2019. We used

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diagnostic codes through our electronic medical record to identify patients with CD with a stricturing phenotype. The type of intervention for patients' strictures was then identified through procedural and surgical billing codes. We evaluated their demographics, clinical variables, whether they underwent EBD *vs* surgery or both, and their clinical outcomes.

RESULTS

Of the 139 patients with CD, 25 (18%) developed strictures. The initial intervention for a stricture was surgical resection in 12 patients (48%) and EBD in 13 patients (52%). However, 4 (33%) patients whom initially had surgical resection required follow up EBD, and thus 17 total patients (68%) underwent EBD at some point in their treatment process. For those 8 patients who underwent successful surgical resection alone, 4 of these patients (50%) had a fistula present near the stricture site and 4 (50%) had strictures greater than 5 cm in length. All patients who underwent EBD had no procedural complications, such as a perforation. Twenty-two (88%) of the treated strictures were successfully managed by EBD and did not require any further surgical intervention during our follow up period.

CONCLUSION

EBD is safe and efficacious as an alternative to surgery for palliative management of strictures in selected pediatric patients with CD.

Key Words: Crohn's disease; Intestinal strictures; Endoscopic dilation; Pediatrics; Endoscopic balloon dilation

Core Tip: Endoscopic balloon dilation (EBD) has been shown to be a safe and efficacious alternative to surgery in adults, but evidence is poor in the literature regarding its safety and efficacy in children. In our retrospective cohort, 22 of the 25 (88%) treated strictures were successfully managed by EBD and did not require any further surgical intervention during our follow up period. All patients who underwent EBD had no procedural complications, such as a perforation, showing that EBD is safe and efficacious as an alternative to surgery for palliative management of strictures in selected pediatric patients with Crohn's disease.

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INTRODUCTION

In pediatric Crohn's disease (CD), intestinal strictures are a major cause of morbidity and one of leading causes for surgery with cumulative incidence of 20%-50% after 10 years of diagnosis[1]. It is estimated that strictures, defined by a luminal narrowing and thickening of the intestinal wall that results in obstructive clinical symptoms, are present in approximately 10%-17% of children at the time of diagnosis[2]. Strictures can appear at any point in the gastrointestinal tract, but most commonly appear in the ileocecal region and can cause symptoms, such as abdominal pain, bloating, emesis, decreased energy, and growth failure[3]. Surgery has been a mainstay treatment for intestinal strictures in pediatric CD with resection for longer strictures (> 5 cm in length) or strictureplasty for simple, shorter strictures[4]. Strictureplasty is a surgical procedure that repairs a stricture by widening the narrowed area with intestinal conservation[5,6]. Post-operative complications from surgical resection include fistulas, leaks, short bowel syndrome, and recurrence of the stricture at the anastomosis site[7]. One study shows that clinical recurrence of strictures occurs in 55% of patients in the first two years after initial surgery, which leads to the need for

subsequent surgical interventions[6]. Overall, 75% of CD patients undergo surgery for disease related complications at least once in the course of their disease[8].

Given the high likelihood of surgery in a CD patient, attempts should be made to find alternatives to surgery in these patients. One such alternative is endoscopic balloon dilation (EBD), through which an endoscopist traverses the stricture with a balloon device that is then inflated in an effort to increase the diameter of the intestinal lumen. EBD has been demonstrated to be a safe and efficacious alternative to surgery in adults with CD, but there was a paucity of evidence regarding use in children until our initial publication in 2008[3,7]. Evolution of our knowledge regarding outcomes from fibrostenosing CD and anti-inflammatory effects of biologic therapy suggested stenosing disease evolves independently, which is propelled by local myofibroblast activity, soluble chemokines, and growth factors[9]. The accumulation of this understanding led to the eventual guidelines published by the European Crohn's and Colitis Organization in 2016[10]. The aim of our study is to evaluate the longitudinal outcomes of children with CD who underwent EBD *vs* surgical resection as a treatment of their strictures in order to show that EBD is efficacious as an alternative to surgery for management of simple strictures in pediatric fibrostenosing CD.

MATERIALS AND METHODS

Study design

In a single-center retrospective study, we looked at pediatric patients (ages 0-18) who carry the diagnosis of CD who were diagnosed after opening a dedicated Inflammatory Bowel Disease clinic on July 1, 2012 through May 1, 2019. We used diagnostic codes through our electronic medical record to identify patients with CD with a stricturing phenotype. The type of intervention for patients' strictures was then identified through procedural and surgical billing codes. Patient demographics, disease characteristics and longitudinal clinical outcomes were obtained through review of the electronic medical record. Demographic data included: age at diagnosis of CD, age at time of procedure, body mass index (BMI) at time of procedure, and race. Disease characteristics included: modality of CD diagnosis, time (years) from diagnosis of CD until the development of symptomatic strictures, the Paris classification of disease, and medication at the time of the procedure. Symptomatic strictures were defined as new onset or worsening of baseline abdominal pain, postprandial bloating, and/or emesis. Information obtained about the intestinal stricture and procedure(s) included the location, length, number of strictures, the presence of penetrating disease near the stricture site, the type of stricture intervention (EBD, surgery, or both), and if any medication was injected into the stricture at the time of EBD. Strictures were classified as simple, which were defined as single and < 5 cm, or complex, which were defined by multiple, > 5 cm or associated with a fistula.

EBD

All patients with complex strictures underwent surgical resection of their stricture sites rather than strictureplasty. All EBDs were done by a single provider, using the same technique (JAQ). First, a 0.25 mm soft tip guidewire was passed through the stricture. In the case of medication injected at the stricture site, 2 mg/kg up to 80 mg of triamcinolone was diluted in 5 mL of saline and was then injected into all four quadrants of the stricture area prior to dilation. A single patient received an injection of an infliximab biosimilar (0.5 mg/kg) diluted in 25 mL of saline at the stricture site before dilation. After the injection of the stricture, a through the scope controlled radial release (CRR) colonic balloon dilator was placed over the guidewire and serial dilations were done until the desired diameter was achieved to allow endoscope passage for inspection of the proximal bowel (Figure 1).

RESULTS

Stricturing CD

Of the 139 active patients diagnosed with CD in the study period, 25 (18%) developed intestinal strictures; 13 patients (52%) were male and 22 patients (88%) were Caucasian (Table 1). BMI was recorded in the 25 patients and nine (36%) were in the overweight BMI category (BMI > 85th and < 95th percentiles). Six of those patients had complex strictures and went directly to surgical resection. The mean age at diagnosis of CD was

Table 1 Patient demographics and clinical variables

	Surgery only, *n* = 8	EBD only, *n* = 11	Surgery and EBD, *n* = 6
Sex, *n* (%)			
Male	4 (50)	6 (55)	3 (50)
Female	4 (50)	5 (45)	3 (50)
Age at diagnosis, *n* (%)			
0-10	1 (12)	1 (9)	1 (17)
11-18	7 (88)	10 (91)	5 (83)
Race, *n* (%)			
Caucasian	7 (88)	11 (100)	4 (67)
African-American	1 (12)	0	2 (33)
BMI, *n* (%)			
Underweight	2 (25)	2 (18)	0 (0)
Normal	0	7 (64)	5 (83)
Overweight	6 (75)	2 (18)	1 (17)
On biologic, *n* (%)	6 (75)	10 (91)	5 (83)
On steroids, *n* (%)	0	2 (18)	1 (17)
Location of stricture, *n* (%)			
Terminal ileum	6 (75)	2 (18)	4 (66)
Ileocecal valve	2 (25)	5 (46)	1 (17)
Colon	0	1 (9)	0
Duodenum	0	1 (9)	0
Rectum/anus	0	2 (18)	1 (17)
Average years of disease until development of stricture	2.1	1.9	1
Stricturing disease only, *n* (%)	4 (50)	8 (73)	2 (33)
Stricturing and penetrating disease, *n* (%)	4 (50)	3 (27)	4 (67)

EBD: Endoscopic balloon dilation; BMI: Body mass index.

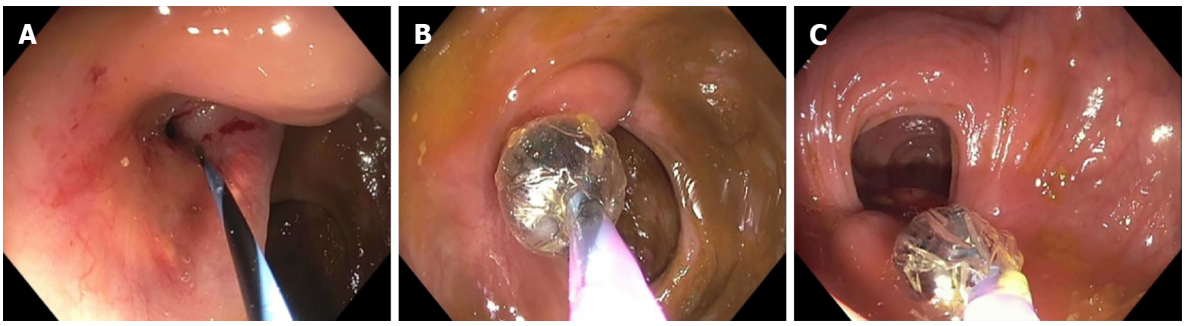

Figure 1 Endoscopic appearance. A: Endoscopic appearance of a Crohn's disease fibrostenotic lesion in the ileocecal valve; B: Wire-guided 18 mm balloon dilation catheter (CRE PRO, Boston Scientific, Marlborough, MA, United States); C: Appearance after dilation.

13 years. In 23 of the 25 patients, diagnosis was made *via* upper and lower endoscopy with biopsies confirming CD, and the other two patients had stricturing and penetrating disease at the time of diagnosis, and CD was confirmed on histologic review of the surgically-resected specimen. Using the Paris Classification, CD location was classified as: ileocolonic (*n* = 20, 80%), distal 1/3 of the ileum with limited cecal disease (*n* = 3, 12%), colonic (*n* = 1, 4%), or upper disease proximal to the ligament of

Treitz and ileocolonic (n = 1, 4%). CD behavior was classified as: stricturing (n = 11, 44%), stricturing and penetrating (n = 9, 36%), stricturing and perianal disease (n = 3, 12%), or stricturing, penetrating and perianal disease (n = 2, 8%). The mean time of development of symptomatic strictures from time of diagnosis was 1.5 years. Twenty (80%) of these strictures were located in the terminal ileum, 3 (12%) in the rectum, 1 (4%) in the duodenum, and 1 (4%) in the ascending colon (Figure 1).

At the time of intervention, most patients (n = 21, 84%) were on biologic therapy; 11 patients were on infliximab or an infliximab biosimilar, 9 patients were on adalimumab, and one patient was on vedolizumab. Of the four patients not receiving biologic therapy, three patients were managed with azathioprine and one was managed with mesalamine alone. Three patients (12%) were on low-dose corticosteroids in addition to biologic therapy.

EBD outcomes

The initial intervention for a stricture was surgical resection in 12 patients (48%) and EBD in 13 patients (52%). However, 4 (33%) patients whom initially had surgical resection required follow-up EBD, and thus 17 total patients (68%) underwent EBD at some point in their treatment process. The frequency of EBD procedures performed on an individual patient was: one EBD (n = 7, 41%), 2-3 EBD (n = 8, 47%), 4 or more EBD (n = 2, 12%) (Figure 2). All patients that underwent EBD had strictures with a length less than or equal to 5 cm in length and inflammation was controlled with medications prior to EBD. Fifteen patients received a triamcinolone injection into the stricture site and one patient received an infliximab biosimilar injection at the stricture site. There were no post-EBD perforations, bleeding requiring intervention, or infections. Of the 8 patients who underwent successful surgical resection alone, 4 patients (50%) had a fistula present near the stricture site and 4 (50%) had strictures greater than 5 cm in length. Overall, 88% (15/17) with stricturing disease treated endoscopically did not require any further surgical interventions.

DISCUSSION

The natural history of CD in children suggests that most children present with inflammatory disease but a proportion will develop more complicated stricturing or penetrating disease[11]. Given the high overall rate of surgery in CD, the rate of recurrence of strictures post-surgery, and the risk of complications post-surgery, there exists the need for alternative interventions[6,7,12]. EBD offers a minimally invasive, therapeutic approach that can reduce or obviate the need for surgical intervention[13]. It has been shown to be efficacious in adult stricturing CD with overall reported technical success rate of 89.1% to 94.9% and associated clinical efficacy of 80.8%-82.3% [14,15]. Complications are also minimal in EBD compared to surgery with a complication rate averaging around 2% overall[16]. Here, we aim to demonstrate similar efficacy and safety in our pediatric CD cohort.

In our single-center cohort, 88% (15/17) of patients with stricturing CD treated *via* EBD did not require any further surgical interventions. This is a higher success rate than the adult literature where a meta-analysis of 33 studies showed that surgical intervention was avoided in 57% of adult patients who had undergone EBD[14]. In our cohort, there was a need for repeat EBD in 6/17 (35%) patients whom had initial EBD and a need for EBD after surgical resection in 4/12 (33%) patients. The adult literature cites that need for repeat EBD as 73.5% in a meta-analysis and 47% in another study, and the need for EBD after surgical resection at 62%[14,17]. It is difficult to compare our rates of success and need for repeat dilations to adult studies given the small number of patients in our study and a different range in follow up time. In our study, follow up ranged from 6 mo to 2 years compared to the two years used in adult literature[14,17].

In our population, there were no complications of perforation, bleeding, or infection for any patient who underwent EBD. Although this is reassuring, our study is again limited by the small number of patients making it difficult to compare to the rate of complications in the literature which is around 2%[8]. In addition, patients who were deemed high risk by the adult literature, those with longer strictures (≥ 5 cm) and the presence of a nearby abscess or fistula, were not candidates for EBD and underwent primary surgical resection instead[14,17,18]. Our data does support previous literature about the safety of EBD in patients with uncomplicated, fibrostenotic, non-inflammatory and short segment strictures (< 5 cm in length) (Figure 3)[18].

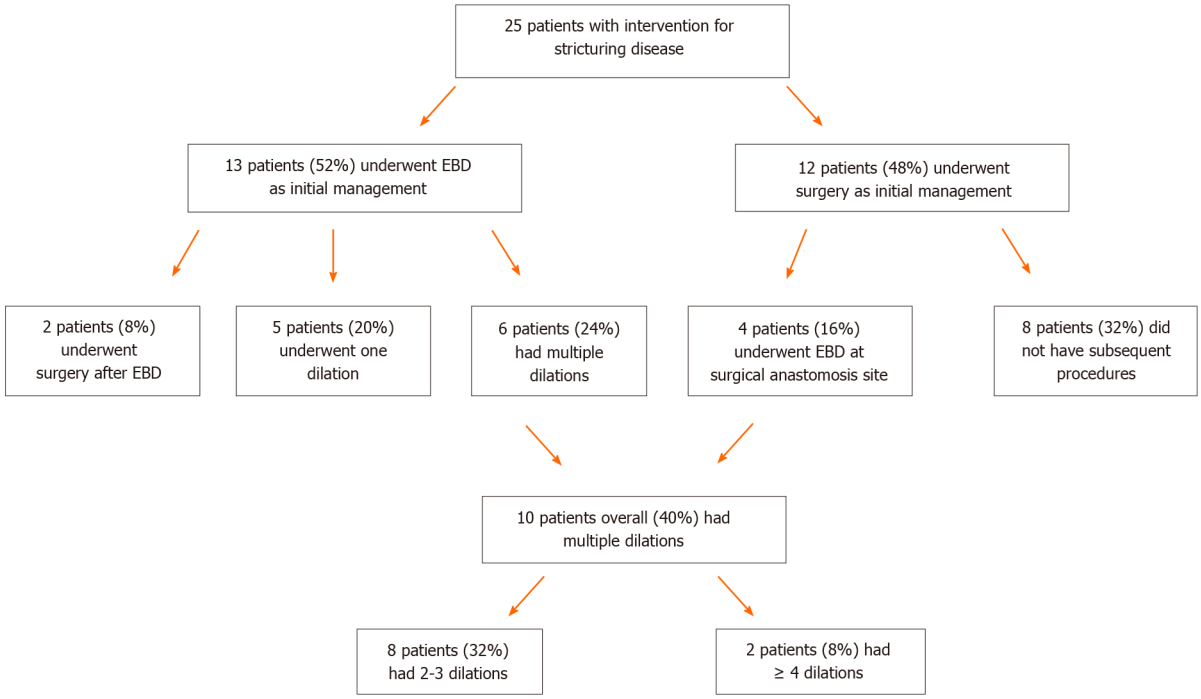

Figure 2 Management of patients with stricturing Crohn's disease *via* surgery or endoscopic balloon dilation. EBD: Endoscopic balloon dilation.

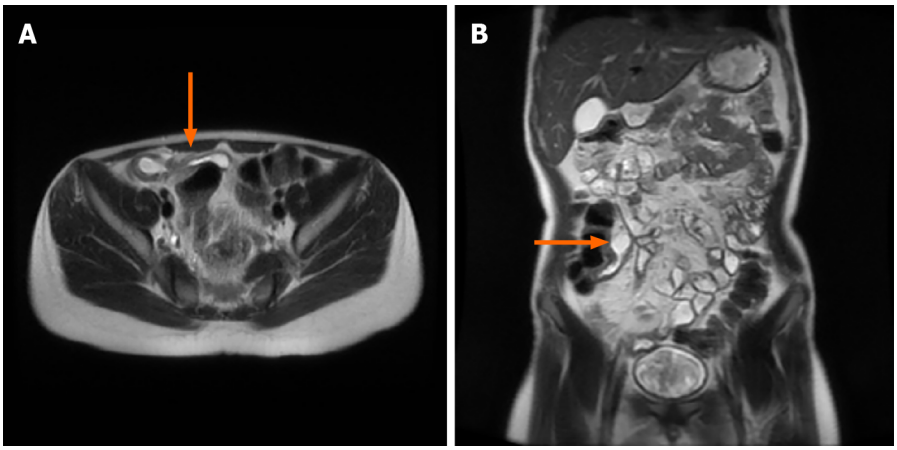

Figure 3 Magnetic resonance imaging of fibrostenosing Crohn's disease. A: Cross sectional magnetic resonance imaging showing the lesion in the distal ileum; B: Coronal cut on magnetic resonance imaging of fibrostenosing Crohn's disease with proximal dilation.

The majority of our patients (15/17) also received intralesional steroid injection into the stricture site. This has been documented as effective by showing the reduction in the need for further endoscopic dilations and surgical interventions in a double-blinded controlled trial in pediatric patients[5]. One patient in our study received an injection of an infliximab biosimilar at the stricture site prior to dilation. This patient had a high-grade duodenal stricture at presentation of her disease which did not allow for tolerance of enteral nutrition. Due to severity of her clinical condition, surgical risk and after internal discussion and family approval, the suitability of this approach was felt to be acceptable. One study in the adult literature showed that injection of 40 mg of infliximab into strictures in six patients was successful[19]. All six patients at the final follow-up at six months described relief of obstructive symptoms and no patients were referred to surgery during the follow-up period[19]. Our patient did require two dilations with infliximab biosimilar injection, and she eventually had resolution of her symptoms and was able to advance to a regular diet. Although there are some smaller studies describing success of injection of biologics into strictures, this has not been proven to be fully efficacious due to the small number of patients that have received a

biologic injection into their stricture site. In contrast, a multicenter study from the United States did not show that intra-lesional steroids or biologics lower the risk of further interventions or surgery[20].

In addition, our data suggests that there seems to be an interesting correlation with higher BMI and worsening disease. Six patients (66%) in the overweight BMI category (BMI > 85th and < 95th percentiles) were those patients with complex strictures that went directly to surgical resection. This correlates with a study that was published in the journal of Biomolecules in 2019 which showed that increased visceral adipose tissue, "creeping fat," can worsen intestinal inflammation through increased altered adipocyte function and through deregulated leptin and adiponectin production[21]. Another recent prospective study from Australia suggested that visceral adipose tissue to subcutaneous adipose tissue ratio was positively associated with risk of stricturing disease behavior and elevated fecal calprotectin in patients with ileocolonic disease; however, these findings are controversial and ongoing research is required to better classify this correlation[22].

Though EBD is shown to be safe and efficacious based on our initial data and the data in the literature, it does have limitations. Surgical resection is still recommended as initial management in longer strictures or for complicated strictures due to an increased risk for perforation[18]. Before EBD is performed, it is recommended to characterize the number, nature and length of the stricture using magnetic resonance enterography or small intestine contrast ultrasonography[18]. Furthermore, EBD requires a skilled endoscopist who is comfortable performing these procedures, and this may not be available at all pediatric centers.

There has been a small amount of published data on EBD in pediatric fibrostenosing CD since our first publication in 2008. Our initial experience suggested that EBD was safe and efficacious in children with short and uncomplicated strictures secondary to fibrostenosing CD which we proceeded to implement in our active day to day care of pediatric CD with these results. Our study is limited by a modest follow-up interval and relatively small number of patients. Further research is most definitely needed in order to find the ideal role for EBD in the management of fibrostenosing CD in children and to further assess the long-term efficacy of the procedure when comparing to surgical intervention in children. We also need to determine if biologic injection at the site of a stricture is a superior option in prevention of stricture recurrence at the dilation site and need to develop ideal tools and techniques to reproducibly manage patients with CD-related intestinal strictures.

CONCLUSION

EBD is safe and efficacious as an alternative to surgery for palliative management of strictures in selected pediatric patients with CD with a high response rate and low complication rate directly related to the procedure.

ARTICLE HIGHLIGHTS

Research background

Currently up to 75% of patients with Crohn's disease (CD) are expected to need surgery due to disease related complications. Intestinal fibrostenosing disease is a common complication and biologic therapy has not limited its appearance even with much improved clinical response rates. Due to a high risk for surgery, attempts to find alternatives to surgery need to be made. Endoscopic balloon dilation with adequate technique promises to have an important role in his area.

Research motivation

Endoscopic balloon dilation has already been shown to be efficacious in adults but no large case series involving pediatric patients exists currently in literature.

Research objectives

We aimed to evaluate the short and long term outcomes of CD who developed fibrostenosing disease and underwent endoscopic balloon dilation as primary or secondary therapy.

Research methods

This is a single-center case series in which all subjects who were diagnosed with diagnosed between 2012 and 2019 were included in the study, and those that developed fibrostenosing disease were identified. Their records were then reviewed for types of interventions performed and outcomes. Patients were classified into primary surgical or endoscopy-treated subjects and those that subsequently required surgery or endoscopy were thus classified. Demographic data included: age at diagnosis of CD, age at time of procedure, body mass index (BMI) at time of procedure, and race. Disease characteristics included: modality of CD diagnosis, time (years) from diagnosis of CD until the development of symptomatic strictures, the Paris classification of disease, and medication at the time of the procedure.

Research results

We identified 139 subjects diagnosed with CD in this study period. Of these patients, 25 (17%) were noted to have a fibrostenotic lesion anywhere in the small and large bowel. 13 (52%) underwent primary endoscopic therapy *vs* 12 (48%) who underwent surgical management. Of the patients who went to surgery, 4 (16%) had to have further endoscopic treatment after surgery, compared to just 2 (8%) of those who had endoscopy as primary therapy. Of note, 5 (20%) required just one endoscopic therapy session for resolution of their stricture.

Research conclusions

Endoscopic balloon dilation is a safe and effective treatment in children with CD-related fibrostenosing disease. Adequate patient selection is key to ensure a high success rate. Pediatric patients undergoing surgery for fibrostenosing disease should be cautioned that a 1 in 5 risk of requiring further endoscopic therapy is a distinct possibility.

Research perspectives

Our data suggested an interesting correlation between higher BMI and risk of stricturing disease. Pediatric patients with BMI > 85% and < 95% had a higher risk of complex strictures requiring surgery. This brings into new light publications associating an increase in visceral adipose tissue with intestinal inflammation through dysregulated leptin and adiponectin production.

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ORIGINAL ARTICLE

Retrospective Study

Gastrointestinal hemorrhage in the setting of gastrointestinal cancer: Anatomical prevalence, predictors, and interventions

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Abstract

BACKGROUND

Gastrointestinal hemorrhage (GIH) is a common complication with gastrointestinal cancers (GIC). There is no comprehensive research that examines GIH in different types of GIC.

AIM

To study the prevalence, predictors, and interventions of GIH based on the anatomical location of GIC.

METHODS

This is a retrospective analysis of the 2016-2018 National Inpatient Sample database, the largest inpatient care database in the United States. All adult inpatients (≥ 18-year-old) were included. ICD-10-CM codes were used to identify patients with GIH and GIC. Prevalence of GIH was obtained based on the anatomical location of GIC. Predictors of GIH in the GIC population were studied using multivariate analysis. Interventions including endoscopy were compared to the non-intervention group to determine the differences in inpatient mortality.

RESULTS

Out of a total of 18173885 inpatients, 321622 (1.77%) cases had a diagnosis of GIC. Within GIC patients, 30507 (9.5%) inpatients had GIH, which was significantly ($P < 0.001$) more than the prevalence of GIH in patients without GIC (3.4%). The highest to lowest GIH rates are listed in the following order: Stomach cancer (15.7%), liver cancer (13.0%), small bowel cancer (12.7%), esophageal cancer

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(9.1%), colorectal cancer (9.1%), pancreatic cancer (7.2%), bile duct cancer (6.0%), and gallbladder cancer (5.1%). Within gastric cancer, the GIH rate ranged from 14.8% in cardia cancer to 25.5% in fundus cancer. Within small bowel cancers, duodenal cancers had a higher GIH rate (15.6%) than jejunal (11.1%) and ileal cancers (5.7%). Within esophageal cancers, lower third cancers had higher GIH (10.7%) than the middle third (8.0%) or upper third cancers (6.2%). When studying the predictors of GIH in GIC, socioeconomic factors such as minority race and less favorable insurances (Medicaid and self-pay) were associated with significantly higher GIH on multivariate analysis ($P < 0.01$). Chemotherapy and immunotherapy were also identified to have a lower risk for GIH [odds ratios (OR) = 0.74 (0.72-0.77), $P < 0.001$]. Out of 30507 GIC inpatients who also had GIH, 16267 (53.3%) underwent an endoscopic procedure, *i.e.*, upper endoscopy or colonoscopy. Inpatient mortality was significantly lower in patients who underwent endoscopy compared to no endoscopy [5.5% *vs* 14.9%, OR = 0.42 (0.38-0.46), $P < 0.001$].

CONCLUSION

The prevalence of GIH in patients with GIC varies significantly based on the tumor's anatomical location. Endoscopy, which appears to be associated with a substantial reduction in inpatient mortality, should be offered to GIC patients with GIH. Nevertheless, the decision on intervention in the GIC population should be tailored to individual patient's goals of care, the benefit on overall care, and long-term survival.

Key Words: Gastrointestinal hemorrhage; Gastrointestinal cancer; Anatomy; Risk factors; Gastrointestinal endoscopy

Core Tip: This is a retrospective analysis of the National Inpatient Sample database aiming to study the prevalence, predictors, and interventions of gastrointestinal hemorrhage (GIH) in the setting of gastrointestinal cancer (GIC). The prevalence of GIH varies based on the anatomical location of cancer, ranging between 15.7% in gastric cancer and 5.1% in gallbladder cancer. Many risk factors, including socioeconomic factors such as insurance and race, can affect the rates of GIH. Endoscopy is significantly associated with lower inpatient mortality in bleeding patients with GIC.

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INTRODUCTION

Gastrointestinal hemorrhage (GIH) is a common complication in patients with gastrointestinal cancers (GIC). In terms of incidence and mortality, GICs are among the highest globally[1]; and thus remain an ongoing challenge as to management and treatment. GIH often serves as the initial symptom for GIC, locally invasive, and metastatic disease[2]. It can also carry a high mortality rate, as in the case of upper GIH [3]. An earlier study documented that bleeding gastrointestinal (GI) tumors accounted for roughly 12 percent of cases involving GIH[4]. Another analysis of studies purported that neoplasia constituted between 3%-11% of lower GIH[5]. On the other hand, in 5% of patients with upper GI bleeds, biopsy-proven tumors were the source of bleeding[6]. While existing literature studied the prevalence of GIC in GIH, and some assess GIH as a clinical symptom of a specific type of tumor[2,4,7,8], there are no inclusive studies that assess GIH in different types of GIC. Therefore, a more comprehensive and large sample size analysis is warranted to study GIH in all types of GIC.

Bleeding in GIC patients could be the result of many causes and risk factors. One study revealed that bleeding from the tumor site is the predominant source of upper GI bleeds in patients with cancer[9]. Another study found GIH common after chemoradiotherapy in patients with locally advanced pancreatic cancer[10]. Some existing literature examines the risk factors behind GIH in specific tumors, such as gastrointestinal stromal tumors[11]. In one study, risk factors implicated in GIH included initial tumor stage, smoking, and carbohydrate antigen 19-9 Levels at the time of pancreatic cancer diagnosis[8]. This current retrospective analysis assesses predictors of GIH in the setting of GIC. Another study found that GIH rate can vary based on pancreatic cancer location; however, the study was limited by the small sample size[8]. Therefore, further analysis on the prevalence of GIH regarding the anatomical location of neoplasm would assist in future clinical management of GIH in these patients.

Most importantly, investigating different interventions for GIH in the setting of GIC would provide vital information in developing treatment plans for these patients and preventing mortality. For example, literature reviews endoscopic hemostasis of GIH in both cancer and non-cancer settings, but data remains limited in specifically the setting of tumor bleeding[2,6,12,13]. Endoscopic therapy is often recommended for non-cancer related GIH, as it may decrease overall morbidity and the need for invasive surgery [14,15]. However, while hemostasis is often successfully achieved by endoscopic therapy for bleeding GIC, rebleeding rates, unfortunately, remain common[6,13].

This study's goals involve estimating the prevalence of GIH in patients with GIC based on the anatomical location of tumors, evaluating the predictors of GIH in GIC, and the outcomes of different procedure modalities used in bleeding GIC patients.

MATERIALS AND METHODS

Study setting

This study is a retrospective analysis of the 2016 to 2018 National (Nationwide) Inpatient Sample (NIS) database, the largest national inpatient database. NIS is drawn from 48 states and includes more than 97% of the United States population. The NIS does not contain any patient identifier; therefore, it does not require review by the institutional review board.

Inclusion/exclusion criteria

All adult inpatients (≥ 18-year-old) were included.

Outcomes

(1) Estimate GIH prevalence in patients with GIC based on the anatomical location of cancer; (2) Study the predictors of GIH in patients with GIC; and (3) Study the mortality outcome of various procedural modalities used in GIH patients with GIC: (a) Endoscopy; (b) Surgery; (c) Trans-arterial embolization; and (d) Radiation therapy.

Exposure

(1) In all adult inpatients, the prevalence of GIH was compared between patients with and without GIC; (2) In inpatients with GIC, the prevalence of GIH was determined according to the anatomic location of GIC; (3) In inpatients with GIC, demographics, socioeconomic factors, comorbidities, and other disease-related factors were compared based on GIH status; and (4) In inpatients with GIC and GIH, mortality outcome was compared between patients who underwent or did not undergo interventions such as endoscopy, surgery, embolization, and radiation therapy.

Definitions

All diagnoses and procedures were reported based on ICD-10-CM and PCS coding listed in Table 1. GIH was defined as the presence of upper or lower GIH or the presence of hematemesis, melena, hematochezia, or unspecified source of GIH.

Statistical analysis

Continuous variables were presented as mean and standard deviation. Categorical variables were presented as frequencies and percentages (%). Student *t*-test was used for the comparison of continuous variables, and Pearson's χ^2 test was used for categorical variables. *P* values were adjusted according to the Bonferroni method when pairwise comparisons were used. In a few instances, analysis was not performed

Table 1 ICD-10-CM and PCS codes for diagnoses and procedures

Diagnosis	ICD-10-CM
GI hemorrhage	Upper: I85.x1; (K25-K28).0,2,4,6; K29.x1; K318.11 K31.82
	Lower: K50.x11; K51.x11; K55.21; K57.x1; K57.x3
	Total = upper + lower + K62.5; K92.0-2
GI cancer	
Esophageal cancer	C15; C49.A1; D00.1
Upper third	C15.3
Middle third	C15.4
Lower third	C15.5
Other/unspecified	C15.8-9; C49.A1; D00.1
Gastric cancer	C16; C49.A2; D00.2
Cardia	C16.0
Fundus	C16.1
Body	C16.2
Pyloric antrum	C16.3
Pylorus	C16.4
GIST	C49.A2
Other/unspecified	C16.5-9; D00.2
Small bowel cancer	C17; C49.A3; D01.49
Duodenum	C17.0
Jejunum	C17.1
Ileum	C17.2
GIST	C49.A3
Other/unspecified	C17.3-9; D01.49
Liver cancer	C22; D01.5
Hepatocellular carcinoma	C22.0
Other primary liver	C22.2-8; D01.5
Biliary cancer	C22.1; C24
Intrahepatic	C22.1
Extrahepatic	C24.0
Ampulla of Vater	C24.1
Other/unspecified	C24.8-9
Gallbladder cancer	C23
Pancreatic cancer	C25
Head	C25.0
Body	C25.1
Tail	C25.2
Duct	C25.3
Endocrine	C25.4
Other/unspecified	C25.7-9
Colorectal cancer	C18; C19; C20; C26.0; C49.A4-5; D01.0-4
Cecum	C18.0

Appendix	C18.1
Ascending colon	C18.2
Hepatic flexure	C18.3
Transverse colon	C18.4
Splenic flexure	C18.5
Descending colon	C18.6
Sigmoid	C18.7
Rectosigmoid junction	C19
Rectum	C20
Other/unspecified	C188.9-9; C26.0; C49.A4-5; D01.0-4
Acute kidney injury	N17; N19; N99.0; O90.4
Chronic kidney disease	D63.1; (E08-E13).22; I12.0,9; I13.10,11,20; N18; R88.0; Z49
Congestive heart failure	I50; I97.13x; O29.12x; Z95.812; I09.81; I11.0; I13.0,2
Cirrhosis and liver failure	K70.4; K70.3; K72; K91.82; K71.7; K74; K76.(6,7); K65.2; I85
Radiation gastroenteritis/proctitis	K52.0; K62.7
Metastasis	C77; C78; C79; C80.0
Chemotherapy and immunotherapy	Z92.21; Z51.11-12; T45.1X; K12.31; D61.81; D64.81
Severe malnutrition and cachexia	E40-43; R64
Obesity	E66.01; E66.09; E66.(1,2,8,9); Z68.3-4
Palliative care	Z521.5
Aspirin/antiplatelets	Z79.82; Z79.02
Anticoagulants	Z79.01
Intestinal infection	A00-09; A18.32; A21.3; A22.2; B37.82; B25.8-9
Hypovolemic shock	R57.1
Procedures	ICD-10-PCS
Upper endoscopy	06L34CZ; 0D5(1-9)8ZZ; 0DB(1-9)8ZX; 0DB(1-9)8ZZ; 0DBA8ZX; 0DJ08ZZ; 0DQ(6,7,9)8ZZ; 3E0G8TZ
Colonoscopy	06LY4CC; 0D5(E-Q)8ZZ; 0DB(B-Q)8ZZ; 0DB(B-Q)8ZX; 0DJD8ZZ
Surgery	0D(1,5,B,J,T); 0F(5,B,T); OW(J,3) excluding endoscopic approach
Trans-arterial embolization	04(L,V)(1,2,3,5,6,7,9,B)3DZ
Radiation therapy	D(D,F,W)0(0-7)(0-6)Z(0,Z)

GI: Gastrointestinal; GIST: Gastrointestinal stromal tumor.

due to lack of enough sample size (≤ 10 patients in a table cell), and the affected cells were left unfilled in the table.

Binary multiple logistic regression was performed for the following outcomes: (1) GIH (to assess the predictors of GIH in patients with GIC); and (2) Inpatient mortality (to assess the association between mortality and interventions such as endoscopy, surgery, embolization, and radiation therapy).

Multivariate analysis was used in the backward stepwise regression to select statistically significant variables. The binary logistic regression results were represented with adjusted OR and 95% confidence interval. Statistical significance was set at the 5% level. Statistical analysis was performed using IBM SPSS, version 27 (IBM Inc., Armonk, NY, United States).

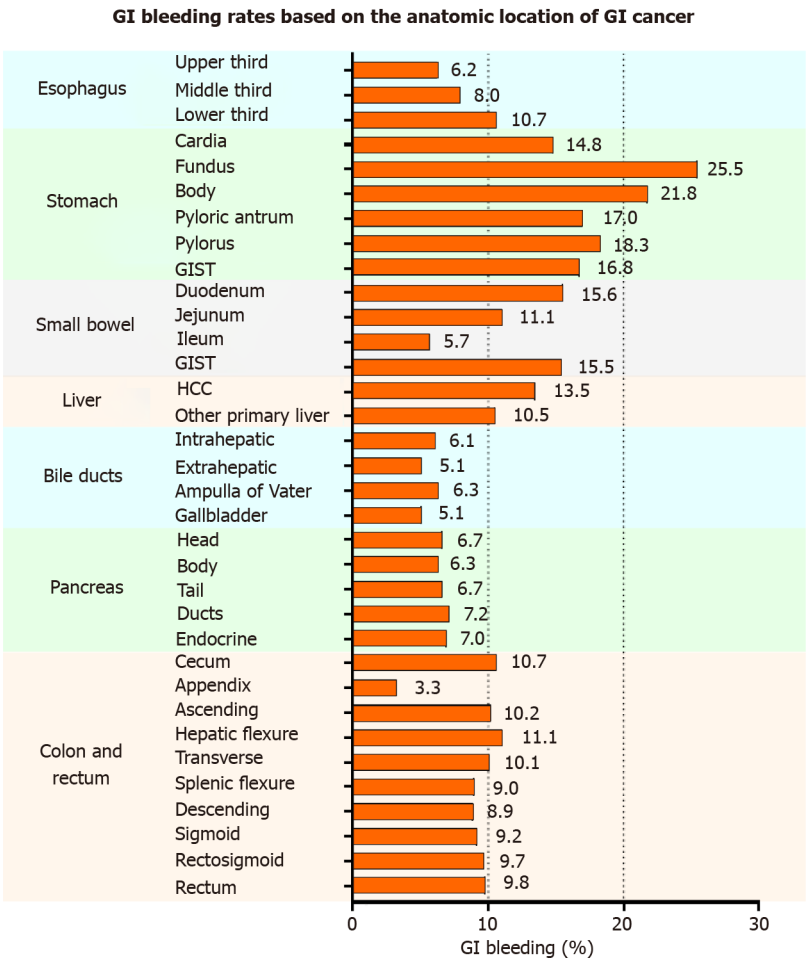

Figure 1 The proportion of gastrointestinal bleeding in inpatients according to the anatomical location of gastrointestinal cancer. GI: Gastrointestinal; GIST: Gastrointestinal stromal tumor; HCC: Hepatocellular carcinoma.

RESULTS

Prevalence of GIH in the setting of GIC

The prevalence of GIH in adult inpatients was compared based on GIC (Table 2). Out of a total of 18173885 inpatients, 321622 (1.77%) cases had a diagnosis of GIC. Within patients with GIC, 30507 (9.5%) inpatients had GIH, which was significantly (P < 0.001) more than the prevalence of GIH in patients without GIC (3.4%).

Prevalence of GIH based on the anatomical location of GIC

The highest to lowest GIH rates are listed in the following order: stomach cancer (15.7%), liver cancer (13.0%), small bowel cancer (12.7%), esophageal cancer (9.1%), colorectal cancer (9.1%), pancreatic cancer (7.2%), bile duct cancer (6.0%), and gallbladder cancer (5.1%). The prevalence of GIH was dissected more in detail by the anatomical location of GIC, as displayed in Figure 1. In esophageal cancer, GIH appears to become more prevalent in lower esophageal lesions (GIH in upper third esophageal cancer: 6.2% < middle third: 8.0% < lower third: 10.7%). Patients with stomach cancer have the highest GIH rates compared to other locations. The highest GIH rate occurs in patients with cancer of the stomach fundus (25.5%), and the lowest rate occurs in the cancer of the stomach cardia (14.8%). In the small bowel, cancer of the duodenum had the highest rate of GIH (15.6%), followed by jejunum (11.1%) and ileum (5.7%). Hepatocellular carcinoma was associated with a GIH rate of 13.5%, whereas biliary and gallbladder cancers had a GIH rate approximately 5%-6%, slightly differing by location. Patients with pancreatic cancers had GIH of approximately 6%-7%, slightly differing by location. Patients with cancers of the colon and rectum had comparable GIH rates (approximately 9%-11%) except for appendiceal cancer with a low bleeding rate (3.3%). The highest GIH rate in colorectal cancer patients belonged to hepatic flexure tumors (11.1%), and the lowest GIH (after appendiceal cancer) was for descending colon cancer (8.9%). Detailed data showing the patient counts

Table 2 Comparison of gastrointestinal hemorrhage between inpatients who have and do not have gastrointestinal cancer

		GI cancer				Total	
		No		Yes			
		Count	Within GI cancer (%)	Count	Within GI cancer (%)	Count	Within total (%)
GI bleeding	No	17242568	96.6	291115	90.5	17533683	96.5
	Yes	609695	3.4	30507	9.5	640202	3.5
	Total	17852263	100	321622	100	18173885	100

$P < 0.001$. GI: Gastrointestinal.

determining the percentages mentioned above are available in Table 3. No statistical comparison was performed between different anatomical locations due to the numerous possibilities for comparisons and combinations; however, assessing the clinical significance of percentages and their differences is still valuable in making comparisons.

Predictors of GIH in patients with GIC

In this section, the predictors of GIH were studied in the population of patients with GIC. Table 4 shows a comparison of various demographic, socioeconomic, and other disease-related factors based on GIH status. Patients with GIH were slightly older compared to patients without GIH (68.2 ± 13.2 *vs* 66.2 ± 12.8 years old, $P < 0.001$). Patients with GIH were less likely to be females (37.8% *vs* 43.3%, $P < 0.001$). While minority races, including Black, Hispanic, Asian, and Native American, were more prevalent in patients with GIH, White race was less common in GIH patients (63.0% *vs* 68.3%, $P < 0.001$). Socioeconomic factors also were associated with varying GIH rates. Patients with GIH were more likely to be Medicare (60.3% *vs* 55.5%, $P < 0.001$), Medicaid, or self-pay patients, and they were less likely to have private insurance (21.3% *vs* 28.1%, $P < 0.001$). Likewise, GIH patients had a lower median household income compared to patients without GIH. Comorbidities such as acute kidney injury, chronic kidney disease, heart failure, cirrhosis, and liver failure were more common in patients with GIH. For cancer-related variables, patients with GIH had less metastatic disease (39.7% *vs* 43.1%, $P < 0.001$), were less treated with chemotherapy or immunotherapy (14.1% *vs* 19.6%, $P < 0.001$), and had more radiation gastroenteritis or proctitis (0.6% *vs* 0.3%, $P < 0.001$). GIH patients were also less obese and were more diagnosed with severe malnutrition and cachexia compared to non-GIH patients.

Table 5 shows the multivariate analysis results, which validates the results of the bivariate analysis discussed above. In summary, predictors (in favor) of GIH were age, minority races (Black, Hispanic, Asian, Native American compared to White race), Insurance (Medicaid and Self-pay compared to Medicare), acute kidney injury, chronic kidney disease, heart failure, cirrhosis, and liver failure, radiation gastroenteritis or proctitis, severe malnutrition and cachexia, use of aspirin, antithrombotic and anticoagulants. Predictors against having GIH were female gender, private insurance (compared to Medicare), higher median household income, presence of metastatic disease, patient on chemotherapy or immunotherapy, and obesity. The factor with the highest OR for GIH was radiation gastroenteritis and proctitis [OR = 2.39 (2.02-2.81)]. The factor with the lowest OR for GIH was chemotherapy or immunotherapy [OR = 0.74 (0.72-0.77)].

Interventions for GIH

Interventions that have been proposed and utilized in GIH patients with GIC were studied. Inpatient mortality was the outcome of interest. The four studied interventions were endoscopy, surgery, trans-arterial embolization, and radiation therapy. Multivariate analysis, using stepwise binary logistic regression, accounted for the following factors: Age, female, race, income, acute kidney injury, chronic kidney disease, heart failure, cirrhosis and liver failure, intestinal infection, metastasis, chemotherapy and immunotherapy, radiation gastroenteritis, palliative care, hypovolemic shock, endoscopy, surgery, embolization, and radiation therapy.

Endoscopy

Out of 30507 inpatients with GIC who also had GIH, 16267 (53.3%) underwent an

Table 3 Tabulated representation of data of Figure 1 which shows to the prevalence of gastrointestinal hemorrhage according to the anatomic location of gastrointestinal cancer

Anatomic location of cancer		GI hemorrhage			
		No		Yes	
	n	Count	Row (%)	Count	Row (%)
Esophagus	23674	21508	90.90	2166	9.10
Upper third	773	725	93.80	48	6.20
Middle third	1467	1349	92.00	118	8.00
Lower third	6540	5843	89.30	697	10.70
Other/unspecified	15161	13842	91.30	1319	8.70
Stomach	27409	23103	84.30	4306	15.70
Cardia	6829	5815	85.20	1014	14.80
Fundus	471	351	74.50	120	25.50
Body	1284	1004	78.20	280	21.80
Pyloric antrum	1881	1561	83.00	320	17.00
Pylorus	398	325	81.70	73	18.30
GIST	2477	2060	83.20	417	16.80
Other/unspecified	14410	12256	85.10	2154	14.90
Small bowel	6469	5646	87.30	823	12.70
Duodenum	3270	2760	84.40	510	15.60
Jejunum	513	456	88.90	57	11.10
Ileum	540	509	94.30	31	5.70
GIST	872	737	84.50	135	15.50
Other/unspecified	1322	1228	92.90	94	7.10
Liver	33452	29111	87.00	4341	13.00
HCC	27601	23877	86.50	3724	13.50
Other primary liver	5988	5357	89.50	631	10.50
Bile ducts	18706	17577	94.00	1129	6.00
Intrahepatic	12515	11749	93.90	766	6.10
Extrahepatic	2749	2608	94.90	141	5.10
Ampulla of Vater	2143	2008	93.70	135	6.30
Other/unspecified	1464	1368	93.40	96	6.60
Gallbladder	4268	4049	94.90	219	5.10
Pancreas	63636	59063	92.80	4573	7.20
Head	17643	16469	93.30	1174	6.70
Body	3077	2882	93.70	195	6.30
Tail	3892	3630	93.30	262	6.70
Ducts	774	718	92.80	56	7.20
Endocrine	589	548	93.00	41	7.00
Other/unspecified	38379	35489	92.50	2890	7.50
Colon and rectum	148943	135410	90.90	13533	9.10
Cecum	12171	10863	89.30	1308	10.70
Appendix	3967	3835	96.70	132	3.30

Ascending	16104	14458	89.80	1646	10.20
Hepatic flexure	3280	2916	88.90	364	11.10
Transverse	7439	6687	89.90	752	10.10
Splenic flexure	2033	1851	91.00	182	9.00
Descending	4239	3862	91.10	377	8.90
Sigmoid	17602	15976	90.80	1626	9.20
Rectosigmoid	17199	15527	90.30	1672	9.70
Rectum	29634	26730	90.20	2904	9.80
Other/unspecified	40531	37341	91.50	3190	8.50

GI: Gastrointestinal; GIST: Gastrointestinal stromal tumor; HCC: Hepatocellular carcinoma.

endoscopic procedure, *i.e.*, upper endoscopy or colonoscopy. Figure 2 displays a significant decrease in mortality associated with endoscopy performance in patients with GIH and GIC (mortality with endoscopy: 5.5% *vs* no endoscopy: 14.9%, $P < 0.001$). Multivariate adjusted analysis (Table 6) shows a mortality reduction associated with endoscopy [OR = 0.42 (0.38-0.46)]. This association also applied to cancer subtypes, particularly esophageal, gastric, primary hepatic, biliary, pancreatic, and colorectal cancer. Gallbladder and small bowel cancer patients did not show a statistically significant association between mortality and endoscopy.

Colorectal cancer had a sufficient patient population to study the types of endoscopy performed and their association with inpatient mortality. Figure 3 shows that, in colorectal cancer patients with GIH, the lowest mortality was reported in patients who underwent either colonoscopy (2.6%) or dual (upper and lower) endoscopy (2.6%). This was significantly lower compared to mortality in patients who underwent upper endoscopy (6.5%) or no endoscopy (9.0%) ($P < 0.001$ for colonoscopy or dual endoscopy *vs* upper endoscopy or non-endoscopy group). Eight percent of all GIH causes in colorectal cancer patients were attributed to upper GIH, including 4.1% peptic ulcer disease and 0.9% esophageal varices.

Surgery

Out of 30507 inpatients with GIC who also had GIH, 4568 (15.0%) underwent surgical exploration with or without bowel resection during hospitalization. Unadjusted analysis displays a significant decrease in mortality associated with the performance of surgery in GIH patients with GIC (total) (5.6% *vs* 10.6%, $P < 0.001$) and colorectal cancer (4.6% *vs* 6.5%, $P < 0.001$). On multivariate (adjusted) analysis shown in Table 6, results were different from unadjusted analysis. Surgery was not associated with any statistical difference decrease in mortality in GIC (total) but had increased odds of mortality in patients with gastric [OR = 1.73 (1.00-3.00)] and colorectal cancer [OR = 1.33 (1.09-1.62)]. Small bowel, hepatic, and pancreatic cancer patients did not show a statistical difference between surgery and non-surgery groups.

Trans-arterial embolization

Out of 30507 inpatients with GIC who also had GIH, 516 (1.7%) underwent trans-arterial embolization. Unadjusted analysis displays a significant increase in mortality associated with the performance of trans-arterial embolization in GIH patients with GIC (total) (14.7% *vs* 9.8%, $P < 0.001$). Gastric cancer (15.1% *vs* 8.7%, $P = 0.01$) and colorectal cancer (21.9% *vs* 5.9%, $P < 0.001$) were also associated with increased mortality in patients who underwent embolization. Similarly, on multivariate (adjusted) analysis in Table 6, embolization was associated with increased odds of mortality in GIC (total) [OR = 1.35 (1.02-1.80)] and colorectal cancer [OR = 2.52 (1.23-5.15)]. Gastric, hepatic, and pancreatic cancer patients did not show a statistical association between embolization and mortality on multivariate analysis.

Radiation therapy

Out of 30507 inpatients with GIC who also had GIH, radiation therapy was performed in 210 (0.7%) patients during the hospitalization. On bivariate analysis, the inpatient mortality of patients who underwent inpatient radiation therapy was lower than those who did not undergo radiation therapy (5.7% *vs* 9.9%, $P = 0.04$). On multivariate

Table 4 Bivariate analysis comparing various factors based on gastrointestinal hemorrhage status in a population of inpatients with gastrointestinal cancer

Inpatients with GI cancer		No GI hemorrhage		GI hemorrhage		*P* value
		n = 291115		*n* = 30507		
		Count/mean	Column%/SD	Count/mean	Column%/SD	
Demographic factors						
Age (yr)		66.2	± 12.8	**68.2**	**± 13.2**	< 0.001
Female		**125898**	**43.30**	11543	37.80	< 0.001
Race	White	**192544**	**68.30**	18633	63.00	< 0.001
	Black	37986	13.50	**4727**	**16.00**	< 0.001
	Hispanic	29010	10.30	**3462**	**11.70**	< 0.001
	Asian or Pacific Islander	11482	4.10	**1562**	**5.30**	< 0.001
	Native American	1494	0.50	**189**	**0.60**	0.015
	Other	9345	3.30	999	3.40	0.543
Socioeconomic factors						
Insurance	Medicare	161272	55.50	**18371**	**60.30**	< 0.001
	Medicaid	33523	11.50	**3859**	**12.70**	< 0.001
	Private	**81599**	**28.10**	6483	21.30	< 0.001
	Self-pay	6348	2.20	**894**	**2.90**	< 0.001
	No charge	628	0.20	71	0.20	0.544
	Other	7379	2.50	799	2.60	0.373
Median household income for patient ZIP Code	1st quartile	78840	27.60	**8905**	**29.70**	< 0.001
	2nd quartile	73759	25.80	7733	25.80	0.965
	3rd quartile	**69806**	**24.40**	7072	23.60	0.003
	4th quartile	**63693**	**22.30**	6241	20.80	< 0.001
Comorbidities						
Acute kidney injury		55007	18.90	**7849**	**25.70**	< 0.001
Chronic kidney disease		38425	13.20	**5766**	**18.90**	< 0.001
Heart failure		8704	3.00	**1289**	**4.20**	< 0.001
Cirrhosis and liver failure		32194	11.10	**6154**	**20.20**	< 0.001
Intestinal infection		6694	2.30	753	2.50	0.06
Cancer related						
Metastasis		**125345**	**43.10**	12120	39.70	< 0.001
Chemo and Immunotherapy		**57005**	**19.60**	4314	14.10	< 0.001
Radiation gastroenteritis/proctitis		849	0.30	**189**	**0.60**	< 0.001
Palliative care		38129	13.10	**5318**	**17.40**	< 0.001
Nutritional status						
Severe malnutrition and cachexia		41008	14.10	**4952**	**16.20**	< 0.001
Obesity		**32691**	**11.20**	3127	10.30	< 0.001
Use of antithrombotic/anticoagulants						
Aspirin/antiplatelets		30778	10.60	**3605**	**11.80**	< 0.001
Anticoagulants		22753	7.80	**3345**	**11.00**	< 0.001

Bold values represent a statistically significant higher column proportion. GI: Gastrointestinal.

analysis (Table 6), inpatient radiation therapy for GI bleeding patients with GIC was not significantly associated with any inpatient mortality difference. Analysis was not performed on individual GIC types (esophageal, gastric, small bowel, …) due to insufficient sample in the radiation group.

DISCUSSION

This was a retrospective review of the 2016-2018 NIS database, which is one of the largest national inpatient databases. Our results, as presented in Table 2, our results showed that hospitalized patients with GIC have a significantly higher prevalence of GIH (9.5%) compared to that of the general inpatient population (3.4%). This estimate underscores that GIH is a common complication of GIC and corroborates this study's importance.

Our study showed that GIH is note common in GIC patients and varies significantly based on the anatomical location of cancer. The highest to lowest GIH rates are listed in the following order: stomach cancer (15.7%), liver cancer (13.0%), small bowel cancer (12.7%), esophageal cancer (9.1%), colorectal cancer (9.1%), pancreatic cancer (7.2%), bile duct cancer (6.0%), and gallbladder cancer (5.1%). Figure 1 shows a more detailed representation of GIH rates based on the anatomical location of GIC. The rate of GIH can significantly vary with different tumor locations, even for locations within the same organ. The pattern of bleeding, displayed in Figure 1, shows the highest GIH rate in gastric cancers (ranging between 14.8% in the cardia and 25.5% in cancers of the fundus) followed by cancers adjacent to the stomach, such as cancer of the duodenum (15.6%) and lower third of the esophagus (10.7%). This could be related to the effect of the stomach's acidic medium that can cause erosion and ulceration of the friable intraluminal cancerous tissue and subsequently bleeding. Thus, the further the cancerous tissue from the stomach, the less risk of GIH. Following the same logic, jejunal (11.1%) and ileal cancers (5.7%) have lower GIH rate than duodenal cancers (15.6%), and cancers of the upper (6.2%) and middle third (8.0%) of the esophagus have lower GIH than lower third cancers (10.7%). The correlation between the high incidence of GIH in hepatocellular carcinoma and underlying severe liver cirrhosis with resultant variceal hemorrhage has been demonstrated in previous studies.[16] Colorectal cancer's GIH rates based on different anatomical locations were relatively comparable in the range between 9% to 11%. Appendiceal cancer was an exception with 3.3% GIH, which is similar to the general inpatient population (3.4%).

While our study reports the prevalence of GIH among GIC patients, prior studies have reported the reciprocal prevalence of GIC among patients with GIH[3,17,18]. For example, Sheibani *et al*[6] stated that tumor bleeding comprised 5% (106 cases) of all upper GIH with gastric cancer representing 73%, esophageal cancer 16%, and duodenal cancer 11%. The aforementioned study serves another purpose and cannot estimate the rates of GIH as it examines another parameter. In addition, the large sample size of our patients (30507 bleeding GIC) robustly increases the power of our GIH estimates and analysis.

Notable findings were also reported in the study of the predictors of GIH in GIC. Multivariate analysis results are shown in Table 5. A closer look at the prevalence of GIH in GIC, stratified by race, raises concerning questions on healthcare disparities. Compared to the White race, certain minority races (Black, Hispanic, Asian, and Native American) were predictors of GIH. Lower median household income was also a concerning predictor of GIH. GIH outcomes, stratified by race, have been studied before in various contexts. One study of patients hospitalized for upper GIH found that rebleeding rates were significantly lower in White patients than in Hispanic or Black patients[19]. In the instance of cancer, healthcare disparities also play a significant role in disease onset and outcome. Black patients are observed to have the highest incidence and mortality of many GI tract malignancies, including esophageal, gastric, small bowel, pancreas, colorectal, and anal cancer[20]. Despite the decline in colorectal cancer mortality rates in the past years, the reduction is not as prominent in Black patients. The causes of this are likely multifactorial, many of which are modifiable risk factors such as socioeconomic status, insurance coverage, education level, and consistent access to medical care[21]. The results of this study potentially reinforce these conclusions, as Medicaid patients and non-White patients with GIC

Table 5 The results of multivariate analysis showing the predictors of gastrointestinal hemorrhage in a population of patients with gastrointestinal cancer

Predictors of GI hemorrhage				
		aOR	95%CI	*P* value
Demographic factors				
Age (yr)		**1.01**	**(1.01-1.02)**	**< 0.001**
Female		0.84	(0.81-0.86)	< 0.001
Race	White- Reference	1.00	-	-
	Black	**1.27**	**(1.22-1.31)**	**< 0.001**
	Hispanic	**1.19**	**(1.14-1.24)**	**< 0.001**
	Asian or Pacific Islander	**1.42**	**(1.34-1.50)**	**< 0.001**
	Native American	**1.24**	**(1.06-1.46)**	**0.007**
	Other	**1.13**	**(1.05-1.21)**	**0.001**
Socioeconomic factors				
Insurance	Medicare- Reference	1.00	-	-
	Medicaid	**1.17**	**(1.12-1.22)**	**< 0.001**
	Private	0.91	(0.88-0.94)	< 0.001
	Self-pay	**1.44**	**(1.34-1.56)**	**< 0.001**
	No charge	1.21	(0.94-1.56)	0.148
	Other	1.03	(0.95-1.12)	0.468
Median household income for patient ZIP Code	1st quartile- Reference	1.00	-	-
	2nd quartile	0.98	(0.95-1.01)	0.246
	3rd quartile	0.96	(0.93-0.99)	0.022
	4th quartile	0.94	(0.90-0.97)	< 0.001
Comorbidities				
Acute kidney injury		**1.17**	**(1.13-1.20)**	**< 0.001**
Chronic kidney disease		**1.22**	**(1.18-1.26)**	**< 0.001**
Heart failure		**1.19**	**(1.12-1.27)**	**< 0.001**
Cirrhosis and liver failure		**1.84**	**(1.78-1.90)**	**< 0.001**
Cancer related				
Metastasis		0.93	(0.90-0.95)	< 0.001
Chemo and Immunotherapy		0.74	(0.72-0.77)	< 0.001
Radiation gastroenteritis/proctitis		**2.39**	**(2.02-2.81)**	**< 0.001**
Palliative care		**1.21**	**(1.17-1.26)**	**< 0.001**
Nutritional status				
Severe malnutrition and cachexia		**1.12**	**(1.08-1.15)**	**< 0.001**
Obesity		0.94	(0.90-0.98)	0.001
Use of antithrombotic/anticoagulants				
Aspirin/antiplatelets		**1.09**	**(1.05-1.13)**	**< 0.001**
Anticoagulants		**1.48**	**(1.42-1.54)**	**< 0.001**

Bold values represent a statistically significant odds ratio > 1 [in favor of gastrointestinal hemorrhage (GIH)]; multivariate logistic regression of outcome (GIH) was performed using the backward stepwise method to determine statistically significant factors; variables included in the analysis: Age, female, race, insurance, income, acute kidney injury, chronic kidney disease, heart failure, cirrhosis and liver failure, intestinal infection, metastasis, chemotherapy

and immunotherapy, radiation gastroenteritis, palliative care, severe malnutrition and cachexia, obesity, aspirin/antiplatelet, and anticoagulant; intestinal infection was a statistically non-significant factor; GI: Gastrointestinal; CI: Confidence interval; OR: Odds ratio.

Table 6 The results of multivariate analysis showing the odds ratio of inpatient mortality associated with different interventions (endoscopy, surgery, embolization, radiation)

		GI bleeding patients with cancer								
		All GI Ca	Esophageal Ca	Gastric Ca	Hepatic Ca	Biliary Ca	Gallbladder Ca	Pancreatic Ca	Small bowel Ca	Colorectal Ca
Mortality aOR (95%CI)	Endoscopy	**0.42 (0.38-0.46)**	**0.42 (0.31-0.57)**	**0.42 (0.32-0.54)**	**0.36 (0.29-0.43)**	**0.43 (0.28-0.66)**	0.71 (0.24-2.11)	**0.36 (0.29-0.44)**	1.19 (0.59-2.43)	**0.45 (0.38-0.54)**
	Surgery	0.97 (0.84-1.13)	-	**1.73 (1.00-3.00)**	1.30 (0.67-2.53)	-	-	0.85 (0.49-1.48)	2.26 (0.95-5.36)	**1.33 (1.09-1.62)**
	Trans-arterial embolization	**1.35 (1.02-1.80)**	-	1.46 (0.81-2.62)	1.12 (0.55-2.30)	-	-	0.98 (0.56-1.69)	-	2.52 (1.23-5.15)
	Radiation therapy	0.55 (0.29-1.05)	-	-	-	-	-	-	-	-

Bold values: Statistically significant ($P < 0.05$). Adjusted odds ratio with 95% confidence interval; empty cells indicate that analysis for the corresponding intervention was not performed due to the insufficient sample size; multivariate logistic regression of outcome (mortality) was performed using the backward stepwise method to determine statistically significant factors; variables included in the analysis: Age, female, race, income, acute kidney injury, chronic kidney disease, heart failure, cirrhosis and liver failure, intestinal infection, metastasis, chemotherapy and immunotherapy, radiation gastroenteritis, palliative care, hypovolemic shock, endoscopy, surgery, embolization, and radiation therapy. GI: Gastrointestinal. CI: Confidence interval; Ca: Cancer; OR: Odds ratio.

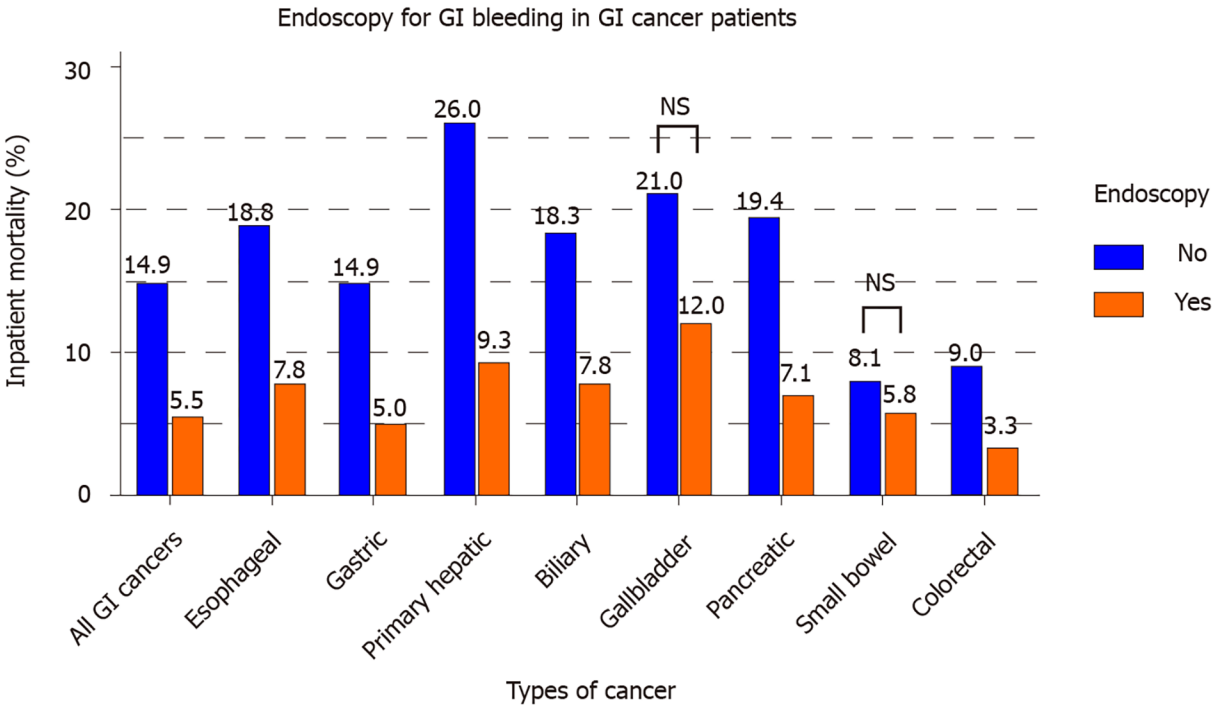

Figure 2 The mortality outcomes of endoscopy in gastrointestinal cancer patients who have gastrointestinal hemorrhage. GI: Gastrointestinal; NS: Not significant.

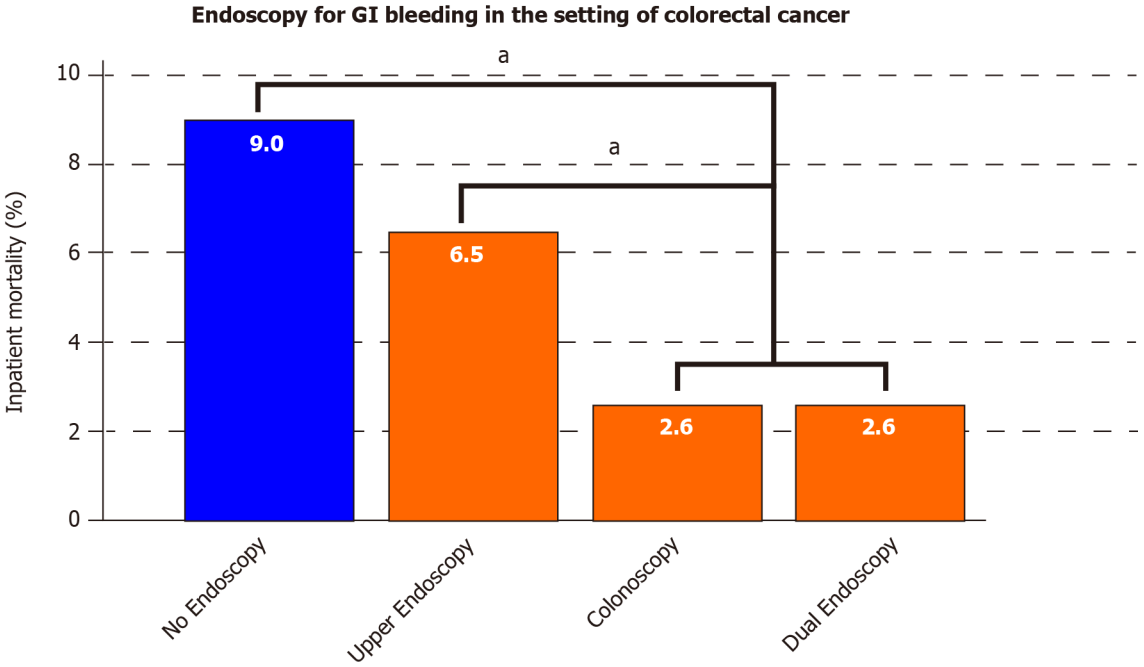

Figure 3 The mortality outcomes of different endoscopic approaches (upper, colonoscopy, or dual) in colorectal cancer patients who have gastrointestinal hemorrhage. [a]*P* < 0.05. GI: Gastrointestinal.

experienced higher rates of GIH. Future studies should continue to examine outcomes of GIH in cancer patients, stratified by factors that would affect access to quality healthcare. Such data would be important in driving targeted screening and prevention efforts to high-risk populations. Our analysis also found other significant predictors of GIH, including cancer-related factors. Chemotherapy and immunotherapy were associated with lower risk for GIH [OR = 0.74 (0.72-0.77), *P* < 0.001]. We speculate that the associated decreased risk is related to tumor involution in response to chemotherapy. Radiation gastroenteritis and proctitis was the strongest predictor of GIH [OR = 2.39 (2.02-2.81), *P* < 0.001]. The presence of metastasis was associated with a lower risk of GIH [OR = 0.93 (0.90-0.95), *P* < 0.001]. This could be confounded by other factors that are not retrospectively available for analysis in this database, such as patients' prior surgical history related to the malignancy.

In examining interventions for GIH in the setting of GIC, our data support that endoscopic therapy is associated with a substantial reduction in mortality. Figure 2 highlights the marked difference in mortality between endoscopy and non-endoscopy groups in various GICs (esophageal, gastric, liver, biliary, pancreatic, and colorectal cancer). There was no statistical difference in the subset of gallbladder and small bowel cancers. The type of endoscopy was studied particularly in our cohort of bleeding colorectal cancer patients. Performing either dual endoscopy or colonoscopy resulted in a statistically significant reduction in mortality compared to no endoscopy or upper endoscopy alone (Figure 3). We also have reported that eight percent of all GIH causes in colorectal cancer patients were attributed to upper GIH, including 4.1% peptic ulcer disease and 0.9% esophageal varices. From this standpoint, we can argue in favor of performing dual endoscopy, as upper endoscopy is a fast procedure that can generally be performed with ease along with colonoscopy. As discussed before, endoscopic therapy for GIH may decrease overall morbidity and the need for surgical intervention[14]. Multiple endoscopic methods such as injection, mechanical, and ablative therapies were suggested to stop bleeding from GI tumors; however, literature is mainly based on limited small sample size (10-100 patients) studies[22,23]. Based on our current knowledge, this current study has the largest analysis of endoscopy in bleeding GIC patients. Future studies should examine the different modalities of endoscopic therapy for the treatment of hemorrhage in the specific setting of cancer.

Trans-arterial embolization for GIH in GIC patients was associated with increased inpatient mortality, particularly for colorectal cancers. Surgical exploration with or without resection was not associated with mortality difference in bleeding GIC total population. However, it was associated with increased gastric and colorectal cancer mortality on multivariate analyses (Table 6). Surgery is usually reserved as a last resort

for rebleeding or hemorrhage refractory to endoscopic therapy, and these cancer patients usually have an initial poor prognosis or advanced disease[12]. Radiation therapy was not associated with mortality difference in patients with GIH and GIC. The limitations are mainly due to the retrospective nature of the study. Important factors, such as the severity of GIH, intensive care admission, rebleeding rates, tumor's size, and the stage and grade of cancer, were also not available for analysis in this database. Therefore, prospectively studying this patient population in the future would instead decrease potential information bias and would be able to fill in the gaps of the current research. However, our study's strength is numerous and related to its uniqueness, novelty, and robust analysis. The current study provides a detailed and comprehensive examination of the subject of GIH in GIC and provides evidence to support the use of endoscopy in this patient population.

CONCLUSION

The prevalence of GIH in patients with GIC varies significantly based on the anatomical location of the tumor. GICs with the highest to the lowest likelihood of GIH are stomach cancer, liver cancer, small bowel cancer, esophageal cancer, colorectal cancer, pancreatic cancer, bile duct cancer, and lastly, gallbladder cancer. Endoscopy is associated with a substantial reduction in inpatient mortality and therefore should be offered to GIH patients with GIC. Nevertheless, the decision on intervention in the GIC population should be tailored to individual patient's goals of care, the benefit on overall care, and long-term survival.

ARTICLE HIGHLIGHTS

Research background

Gastrointestinal hemorrhage (GIH) is a common complication with gastrointestinal cancers (GIC).

Research motivation

There is no comprehensive research that examines GIH in different types of GIC. Furthermore, endoscopic therapy is insufficiently studied in this setting.

Research objectives

We aim to study the prevalence, predictors, and interventions of GIH based on the anatomical location of GIC.

Research methods

This is a retrospective analysis of the 2016-2018 National Inpatient Sample database, the largest inpatient care database in the United States. Adult inpatients were evaluated for the prevalence and predictors of GIH in the setting of GIC. In addition, inpatient mortality was compared between patients who underwent or did not undergo endoscopy.

Research results

The highest to lowest GIH rates are listed in the following order: stomach cancer (15.7%), liver cancer (13.0%), small bowel cancer (12.7%), esophageal cancer (9.1%), colorectal cancer (9.1%), pancreatic cancer (7.2%), bile duct cancer (6.0%), and gallbladder cancer (5.1%). Inpatient mortality was significantly lower in patients who underwent endoscopy compared to no endoscopy [5.5% *vs* 14.9%, OR = 0.42 (0.38-0.46)], $P < 0.001$).

Research conclusions

The prevalence of GIH in patients with GIC varies significantly based on the tumor's anatomical location. Endoscopy appears to be associated with a substantial reduction in inpatient mortality and should be offered to GIC patients with GIH.

Research perspectives

Future studies, prospective and randomized trials, would help confirm the effectiveness of endoscopic therapy for GIH in patients with GIC.

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ORIGINAL ARTICLE

Observational Study

Clinical characteristics and prognosis of patients with ulcerative colitis that shows rectal sparing at initial diagnosis

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Author contributions: Choi YS designed the research study and wrote the manuscript; Kim JK and Kim WJ analyzed the data; all authors have read and approve the final manuscript.

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Conflict-of-interest statement: All authors disclosed no conflict of interest or financial relationships relevant to this publication.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at [yschoi427@naver.com]. Participants gave informed consent for data sharing.

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Abstract

BACKGROUND

Ulcerative colitis (UC) is characterised by mucosal inflammation from the rectum to its proximal area in a symmetric and continuous fashion. However, although uncommon, we encounter cases of UC with rectal sparing in the initial stage.

AIM

To evaluate the clinical characteristics and clinical course for rectal sparing UC compared with typical UC.

METHODS

We looked at records from 2004 to 2015, and selected patients who were newly diagnosed with UC, and who could be followed up for at least 5 years in our hospital. We then retrospectively analysed the medical records and endoscopic findings of those patients. To compare the clinical course and prognosis, we matched each patient with rectal sparing UC 1:3 with controls by age, sex, and disease extent.

RESULTS

Of 619 UC patients, 24 (3.9%) showed rectal sparing at diagnosis. During the follow-up period (median 8 years), in two (8.3%) of the 24 patients, rectal sparing remained through follow-up inspections; but for the other 22 (91.7%) patients, obvious rectal inflammation was found at follow-up endoscopy. Of the 24 patients, 8 (33.3%) were initially misdiagnosed with infectious colitis. No diagnosis was changed to Crohn's disease. The uses of corticosteroid or biologic agents, hospitalisation rate, and colectomy rates were not different between the rectal sparing UC group and typical UC group.

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CONCLUSION
Some patients with UC can reveal atypical patterns of disease distribution, such as rectal sparing in its initial stage; but despite this, the clinical course and prognosis may not differ from those of typical UC patients.

Key Words: Ulcerative colitis; Rectal sparing; Clinical characteristics; Prognosis; At diagnosis; Adult

Core Tip: Ulcerative colitis (UC) is characterised by mucosal inflammation from the rectum to its proximal area in a symmetric and continuous fashion. However, the atypical distribution of UC, such as skip inflammation or rectal sparing can be encountered at initial stage, making diagnosis difficult in usual practice although it is uncommon. As a matter of fact, some studies concerning pediatric UC patients were reported, but its clinical significance and incidence is not known well in adult UC patients. Our study is the only study that evaluated the clinical characteristics and prognosis of adult rectal sparing-typed UC compared with typical UC.

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INTRODUCTION

Ulcerative colitis (UC) is an idiopathic inflammatory bowel disease that is characterised by mucosal inflammation in a continuous and symmetrical fashion from rectum to colon. Recently, however, together with the easy availability and technical advance of colonoscopy, some reports have demonstrated atypical disease distribution of UC, such as skipped lesion, rectal sparing, and upper gastrointestinal tract involvement of ulcerative colitis[1-6]. Moreover, early and increasing diagnosis of UC may also raise the possibility of this diagnostic perplexity, and make it more difficult to differentiate UC from other colitis that can show similar endoscopic findings, such as infectious colitis (*i.e.*, bacterial, amoebic, tuberculous, *etc.*), ischemic colitis, radiation-induced colitis, drug-induced colitis, eosinophilic colitis, lymphoma, and solitary rectal ulcer syndrome[7].

Atypical distribution of UC, such as rectal sparing, can be encountered in patients with UC during treatment, when the mucosal healing of ulcerative proctitis is achieved by topical treatment with mesalamine or corticorsteroids[8]. This condition can also be found more frequently in paediatric UC patients[9-11]. Nevertheless, although uncommon, it can be noted even in adult patients, even at the initial UC diagnosis. In fact, challenging cases of UC with rectal sparing can be encountered at initial diagnosis, which may lead to misdiagnosis.

The clinical characteristics and significance of rectal sparing UC are not known well. Some previous reports have suggested that rectal sparing UC was associated with primary sclerosing cholangitis[12,13]. However, the clinical study concerning its clinical courses and prognosis is still insufficient, although some Japanese studies reported that rectal sparing type UC was related to poor prognosis[14,15]. The aim of the present study was to evaluate the clinical characteristics and clinical course for rectal sparing UC, compared to typical UC.

MATERIALS AND METHODS

Patients' inclusion

We looked at the records of 905 patients [median age: 39 years; range: (16-81) years]

who were newly diagnosed with UC at Daehang Hospital, Seoul, Korea, from January 2004 to December 2015; all UC patients were initially diagnosed and regularly followed for at least 5 years in our clinic.

We then retrospectively investigated a number of baseline patient demographics, which included sex and age, time of diagnosis, symptom duration, perinuclear antineutrophil cytoplasmic antibody status, white cell count, erythrocyte sedimentation rate, C-reactive protein levels, initial disease extent, endoscopic findings (new development of rectal inflammation on follow-up endoscopy as well as initial findings), clinical courses including hospitalisation or colectomy, and medication history.

Study design and definitions

To compare the clinical course and prognosis, we matched each patient with rectal sparing UC (n = 24) 1:3 with controls who had typical continuous and symmetric pattern of UC without rectal sparing (n = 72) to reduce bias; we matched the controls with the cases by age, gender, and disease extent. Primary study outcomes were the cumulative use of corticosteroid. Secondary outcomes were the use of biologic agents (including infliximab, adalimumab, golimumab, vedolizumab, or tofacitinib), hospitalisation of patients, and colectomy in patients with UC with and without rectal sparing at diagnosis. We collected and retrospectively analysed all data through December 31, 2015, or until loss to follow-up. The UC patients who were not on follow-up for less than 5 years were excluded from the analysis. The study was approved by the ethics committee of Daehang Hospital.

UC was definitively diagnosed in those who met the following criteria: (1) Typical history of diarrhea, blood and pus in the stool, or both, for longer than four weeks; (2) Typical sigmoidoscopic or colonoscopic picture with loss of vascularity, friability, granularity, and/or ulcerations of the colorectal mucosa in a continuous and circumferential pattern in the rectum; and (3) Characteristic histopathologic signs of inflammation on biopsy, such as chronic inflammation or distortion of crypt architecture, inflammation of crypts, crypt abscesses, increased chronic inflammatory cells in the lamina propria, erosions, and/or ulcers[16]. Proctitis was categorised when disease extent was limited to the rectum (E1), left-sided colitis when disease extent was limited to the proportion of the colon distal to the splenic flexure (E2), and extensive disease when the disease extended proximal to the splenic flexure, including pancolitis (E3) [17,18]. In the case of UC with rectal sparing, left-sided colitis (E2) and pancolitis (E3) were defined as the same without rectal involvement. We defined rectal sparing as no evidence of mucosal inflammation of the rectal mucosa by colonoscopy, such as normal transparent mucosa with visible capillary vasculature. Endoscopic findings were reviewed by two experienced endoscopists in random order (Kim JK and Choi YS).

Statistical analysis

We used the χ^2 test to compare the categorical variables, and the independent t test to compare the continuous variables. We calculated the cumulative rates of corticosteroids use using the Kaplan-Meier method, and we used the log-rank test to compare the categorical variables. We considered $P < 0.05$ to be statistically significant, and conducted all calculations using SPSS version 15.0 statistical software package (SPSS Inc., Chicago, IL, United States).

RESULTS

Clinical characteristics at diagnosis

Of 619 UC patients, 24 (3.9%) showed rectal sparing by colonoscopy at initial diagnosis (Figures 1 and 2). Of the 24 patients, 16 (66.7%) had a disease extent beyond splenic flexure (E3), while 8 (33.3%) of the 24 patients were limited before splenic flexure (E2) with rectal sparing. During the follow-up period [median 9 years, range (5-15) years], in two (8.3%) of the 24 patients, rectal sparing remained through follow-up inspections; but for the other 22 (91.7%) patients, obvious rectal inflammation was found at follow-up endoscopy. Of the 24 patients, 8 (33.3%) were initially misdiagnosed with infectious colitis, and empirical antibiotics were administered. No diagnosis was changed from ulcerative colitis to Crohn's disease (Table 1).

Table 1 Clinical characteristics of rectal sparing ulcerative colitis at diagnosis

	Rectal spring UC at diagnosis (*n* = 24)
Age (yr)	35.8 ± 11.0
Sex (male:female)	19:5
Disease distribution	
Extensive colitis (E3) with rectal sparing	16 (66.7%)
Left-sided colon (E2) with rectal sparing	8 (33.3%)
Initial Diagnosis	
IBD-U	8 (33.3%)
Infectious colitis	7 (29.2%)
UC	7 (29.2%)
Nonspecific	2 (8.3%)
Symptom duration	2 mo (2 wk to 60 mo)
Laboratory findings	
WBC (count/mm^3)	6475.9 ± 2273.4
ESR (mm/h)	17.4 ± 13.9
CRP (mg/dL)	0.4 ± 0.7
p-ANCA positive	4 (16.7%)
Follow-up endoscopy (follow-up period median 9 yr, 5-15 yr)	
Persistence of rectal sparing	2 (8.3%)
Appearance of proctitis	22 (91.7%)

UC: Ulcerative colitis; IBD: Inflammatory bowel disease; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; ANCA: Anti-neutrophil cytoplasmic antibodies; WBC: White blood cell.

Clinical courses and prognosis

During the follow-up period [median: 115 mo; range: (60-194) mo], in the UC with rectal sparing group, 11 of 24 patients (45.8%) were treated with systemic corticosteroid therapy; in the control group, 38 of 72 patients (52.8%) were treated with systemic corticosteroid. The median time to use corticosteroids were 91 mo in rectal sparing group and 87 mo in control group, respectively. The cumulative rates of ever use of corticosteroid in rectal sparing group and in the control were 35.3%, 46.0% and 53.8% *vs* 34.7%, 41.8% and 61.1% at 3, 5 and 10 years, respectively (log rank: $P = 0.77$) (Figure 3).

In the UC with rectal sparing group, 4 patients (16.7%) were treated with biologic agents; in the control group, 10 patients (13.9%) with biologic agent, which did not significantly differ (Table 2). In the UC with rectal sparing group, 4 patients (16.7%) received hospital treatment, and 2 patients (8.3%) underwent total colectomy at maximal follow-up; in the control group, 16 patients (22.2%) were hospitalised, and 2 patients were colectomised, which also did not significantly differ (Table 3).

DISCUSSION

Although "rectal involvement" and "continuous and symmetric fashion" are known well as typical colonoscopic findings of ulcerative colitis, rectal sparing or non-continuous distribution of mucosal inflammation can be found by colonoscopy in usual practice. For example, it is common in patients with UC who receive local therapy, such as suppository, enema, or foam type of mesalamine, or corticosteroid enema. However, unfortunately, if it is at the moment of initial diagnosis, it is a challenge to an endoscopist, although clinical or pathologic correlation is necessary for the definitive diagnosis of UC. In any event, is it possible to encounter rectal sparing in a newly diagnosed UC patient? If so, how often? Is the prognosis of this case different

Table 2 Summarized clinical history of ulcerative colitis patients who used biologics in both study and control group

No.	Age at diagnosis	Sex	Initial endoscopic finding	No. of systemic steroid use	Indication for biologics	History of biologics	Colectomy
1	21	F	RS	4	Steroid dependent	infliximab	-
2	30	F	RS	2	Steroid refractory	Infliximab (failed)	+
3	31	F	RS	9	Steroid dependent	golimumab	-
4	35	M	RS	2	Steroid refractory	Infliximab (failed)	+
5	15	F	RI	3	Steroid refractory	golimumab	
6	22	F	RI	1	Steroid refractory	Infliximab (failed)	+
7	20	F	RI	7	Steroid dependent	golimumab topacitinib	-
8	33	M	RI	4	Steroid refractory	infliximab	-
9	34	M	RI	2	Steroid refractory	Infliximab (failed)	+
10	35	M	RI	4	Steroid refractory	golimumab	-
11	39	M	RI	3	Steroid refractory	golimumab	-
12	41	F	RI	4	Steroid dependent	golimumab	-
13	44	M	RI	5	Steroid refractory	golimumab	-
14	48	M	RI	2	Steroid refractory	golimumab	-

RS: Rectal sparing; RI: Rectal involvement.

Table 3 Clinical prognosis of ulcerative colitis with rectal sparing versus without rectal sparing (control)

	Rectal sparing UC (*n* = 24)	Control (*n* = 72)	*P* value
Age	35.8 ± 11.0	36.6 ± 10.6	Matched
Sex (male:female)	19:5	57:15	Matched
Disease extent (E2/E3)	8/16	24/48	Matched
Follow-up period (mo)	103.4 ± 41.3	109.4 ± 41.6	0.5
Clinical outcomes			
Use of systemic corticosteroid			0.77
3-yr cumulative rate	35.3%	34.7%	
5-yr cumulative rate	46.0%	41.8%	
10-yr cumulative rate	53.8%	61.1%	
Use of biologics	4 (16.7%)	10 (13.9%)	0.74
Hospitalization	4 (16.7%)	16 (22.2%)	0.77
Colectomy	2 (8.3%)	2 (2.8%)	0.26

UC: Ulcerative colitis.

from a typical one?

To the best of our knowledge, our study is the only study that evaluated the clinical prognosis of adult UC patients who showed rectal sparing at the stage of initial diagnosis. In fact, the studies analysing the incidence of rectal sparing UC are very rare, because initial endoscopic data can be modified by prior treatment in tertiary or referred hospital, and differential diagnostic methods from infectious colitis, such as culture, serologic test, or PCR, have limitations in primary practice. In one Korean data, eight (3.3%) of the 240 patients had rectal sparing at initial colonoscopy[3]. They suggested that the atypically-distributed UC, including rectal sparing UC, seemed to be uncorrelated with poor prognosis, in terms of rates of remission, relapse, disease

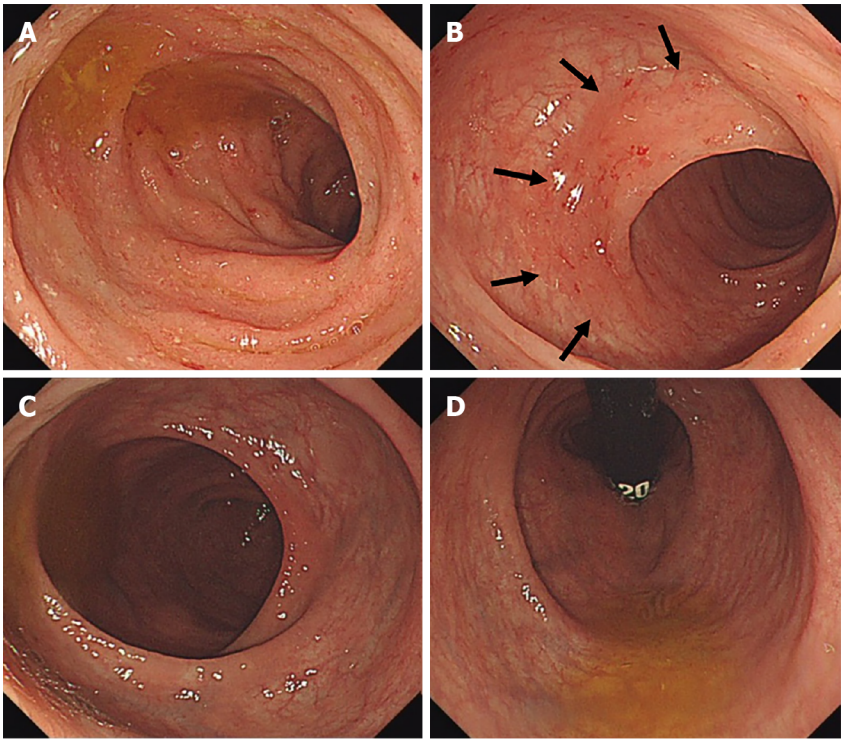

Figure 1 Colonoscopy at initial diagnosis. A: On descending and sigmoid colon, continuous and symmetric micro-erosive inflammation with friability was noted; B: At distal sigmoid colon, transitional zone was noted (arrow); C: On the rectum, normal transparent mucosa with visible vascularity was noted; D: At retroflexion view, there was no evidence of mucosal inflammation.

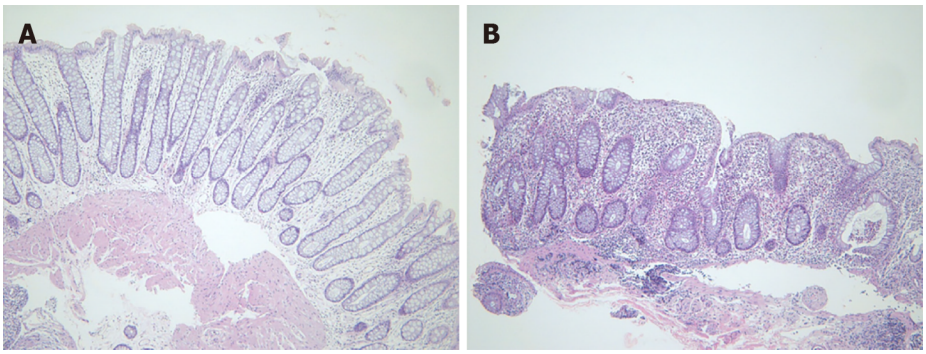

Figure 2 Hematoxylin and eosin stain. A: Rectum: No architectural distortion or neutrophilic inflammation; B: Sigmoid colon: Crypt abscess, crypt distortion, and lymphoplasmacytic infiltration in lamina propria (hematoxylin and eosin stain × 100).

extension, colectomy, and mortality. However, the prognosis of rectal sparing UC is still debatable, because in the previous study, the number of patients with rectal sparing was too small (n = 8), and follow-up data was insufficient, because of relatively short follow-up period [median 69 mo, range (2 to 238) mo].

In contrast to prior clinical studies suggesting the unfavourable prognosis of UC with rectal sparing, our result concluded that clinical course and prognosis were not different from those of typical UC patients. Oshitani *et al*[14] suggest that rectal sparing may be associated with intractability or a tendency to relapse; but that data included the patients with relapsing type of UC, which means that study demonstrated the clinical courses of moderate to severe UC patients with rectal sparing during or after medical treatment, and not the patients at the time of diagnosis. Horio *et al*[15] also reported that rectal sparing UC was an independent risk factor for surgery in the analysis of colectomy specimens of 46 surgically treated patients with UC. However, the subjects of that study were not selected by their initial colonoscopic finding, but selected by pathologic review after colectomy.

In contrast to adult UC, paediatric UC patients seem to have different clinical patterns. Rajwal *et al*[19] reported that rectal sparing was more frequent, and found in

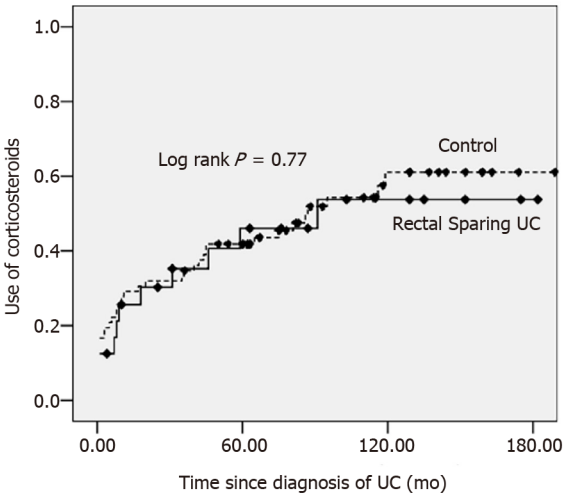

Figure 3 Cumulative rate of corticosteroids use in rectal sparing group (*n* = 24) *vs* control group (*n* = 72). UC: Ulcerative colitis.

23% of children with newly diagnosed and untreated UC; and that the presence of rectal sparing may be related to less responsiveness to conventional medical treatment. Glickman *et al*[11] reported that the endoscopic rectal sparing was found in 9% (6 of 73) and pathologic rectal sparing in 30% (absolute 3% *vs* relative 27%) of paediatric patients with newly diagnosed UC. Interestingly, according to their result, in the adult control group (*n* = 38), no patient showed endoscopic rectal sparing, but one patient revealed pathologic relative rectal sparing.

Already in the 1980s, one report demonstrated 12 cases of rectal sparing UC, in which double-contrast barium enema showed an apparently normal rectum but an abnormal colon; but in all cases, the author reported that rectal biopsy showed changes compatible with ulcerative colitis[20]. Although the study subjects were different from ours, because those cases included the patients after and during medical treatment, their study suggested that rectal sparing of UC had been challenging diagnostically. As early detection of ulcerative colitis is possible thanks to the easy availability of colonoscopy and advanced imaging techniques, we can hypothesise that atypical pattern of colonoscopic findings in a patient with ulcerative colitis can be observed more frequently. In fact, in our data, most of the UC patients with rectal sparing showed rectal lesion during the follow-up examination, which means that the atypical distribution of mucosal inflammation may be found temporarily at an early stage. In one of our cases (Figure 2), a biopsy obtained at rectal sparing area demonstrated normal pathologic finding, although it is not certain whether normal-looking mucosa by colonoscopy is really pathologically intact, because pathologic evaluation at skipped lesion was not performed in all cases.

We should think outside the box, and reconsider the stereotype of ulcerative colitis, such as rectal involvement with continuity, and symmetricity in colonoscopy. In the present study, a third of patients were initially diagnosed with infectious colitis, because the results of stool and pathologic examination were nonspecific, and so proper management was delayed. However, there was no case of diagnostic change to Crohn's disease in our data. In two of 24 cases, rectal sparing has persisted for more than 10 years; one 30-year-old male has mucosal inflammation on cecum and ascending colon, while a 46-year-old female showed mucosal inflammation on ascending, transverse, and descending colon in a homogenous, symmetric, and continuous fashion. In cases like this, definitive diagnosis of ulcerative colitis is still not easy. Both are being kept stable on mesalamine therapy during the follow-up period.

There are some limitations to this study. First, the definition of rectal sparing was ambiguous. For example, in this study, it is based only on endoscopical findings, and additional pathologic correlation was insufficient. However, at initial diagnosis, biopsies tend to be obtained only at grossly inflamed mucosa, because the extent of UC is generally classified according to endoscopic features, rather than histologic features. To define the rectal sparing more with more confidence, prospective designed study is needed. Second, the number of patients with rectal sparing UC was relatively small, so survival analysis in comparison with the control group was impossible. Long-term survival analysis is required to draw a more reliable conclusion. To minimise this

limitation inevitably caused by retrospective analysis, we included the patients who could be followed up for more than five years [medium follow-up period was 115 mo; range (60 to 194) mo], and matched each UC patient with rectal sparing with controls.

CONCLUSION

In conclusion, adult patients with UC can reveal atypical patterns of disease distribution, such as rectal sparing; and the incidence at initial diagnosis was rare, but existed in 3.9%. The clinical course and prognosis that we can assume through the need for advanced treatment, hospitalisation, and colectomy did not differ from that of typical UC patients. We trust that this information can be useful in making an accurate diagnosis, and understanding the various disease phenotypes of UC.

ARTICLE HIGHLIGHTS

Research background

In practice, atypical pattern of ulcerative colitis (UC) such as rectal sparing UC is a challenge to endoscopist in timely diagnosis of UC, therefore we retrospectively reviewed the data of our clinic to study the clinical feature of these atypical pattern of UC, and their prognosis as well.

Research motivation

As early diagnosis and progression of diagnostic tools such as endoscopic, imaging techniques become possible, the detection of atypical pattern of inflammatory bowel disease seems to be possible. If we clarify the clinical characteristics, it will be helpful to understand the pathophysiology of inflammatory bowel disease.

Research objectives

The main object of this study is to predict the clinical course of these atypical pattern of UC. There are very rare report concerning this subject. A few reports demonstrated the poorer prognosis, but our experiences were out of accord.

Research methods

As atypical pattern of UC is very rare and difficult to define in the early stage of UC, prospectively-designed study seems to be impossible, therefore, we (three different inflammatory bowel disease experts) inevitably analyzed the chart, pathologic report and mainly endoscopic images, and reached agreement.

Research results

Some reports suggested that the atypical pattern of UC may have a poor clinical outcome such as higher rate of colectomy, but we demonstrated the different results because the patient selection was not similar to the previous studies. Advanced treatment, hopitalization and colectomy rates did not different between rectal sparing UC and typical UC patients.

Research conclusions

According to a few previous reports, the prognosis of UC showing atypical pattern is debatable. Our data propose that various form of UC phenotype can be possible and their prognosis seems to be similar to the typical one. Further study is needed to predict the prognosis of UC.

Research perspectives

In the future, further prospective studies to clarify the pathophysicology as well as prognosis of other various atypical patterns of UC is warranted.

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ORIGINAL ARTICLE

Observational Study

COVID-19 in the endoscopy unit: How likely is transmission of infection? Results from an international, multicenter study

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Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) significantly affected endoscopy practice, as gastrointestinal endoscopy is considered a risky procedure for transmission of infection to patients and personnel of endoscopy units (PEU).

AIM

To assess the impact of COVID-19 on endoscopy during the first European lockdown (March-May 2020).

METHODS

Patients undergoing endoscopy in nine endoscopy units across six European countries during the period of the first European lockdown for COVID-19 (March-May 2020) were included. Prior to the endoscopy procedure, participants were stratified as low- or high- risk for potential COVID-19 infection according to the European Society of Gastrointestinal Endoscopy (ESGE) and the European Society of Gastroenterology and Endoscopy Nurses and Associates (ESGENA) joint statement, and contacted 7-14 d later to assess COVID-19 infection status. PEU were questioned regarding COVID-19 symptoms and/or infection *via* questionnaire, while information regarding hospitalizations, intensive care unit-admissions and COVID-19-related deaths were collected. The number of weekly endoscopies at each center during the lockdown period was also recorded.

RESULTS

A total of 1267 endoscopies were performed in 1222 individuals across nine European endoscopy departments in six countries. Eighty-seven (7%) were excluded because of initial positive testing. Of the 1135 pre-endoscopy low risk or polymerase chain reaction negative for COVID-19, 254 (22.4%) were tested post endoscopy and 8 were eventually found positive, resulting in an infection rate of 0.7% [(95%CI: 0.2-0.12]. The majority (6 of the 8 patients, 75%) had undergone esophagogastroduodenoscopy. Of the 163 PEU, 5 [3%; (95%CI: 0.4-5.7)] tested positive during the study period. A decrease of 68.7% (95%CI: 64.8-72.7) in the number of weekly endoscopies was recorded in all centers after March 2020. All centers implemented appropriate personal protective measures (PPM) from the initial phases of the lockdown.

CONCLUSION

COVID-19 transmission in endoscopy units is highly unlikely in a lockdown setting, provided endoscopies are restricted to emergency cases and PPM are implemented.

Key Words: COVID-19; SARS-CoV-2; Gastrointestinal endoscopy; Personal protection measures; Transmission; Lockdown

Core Tip: The Coronavirus disease 2019 (COVID-19) pandemic outbreak caused an unprecedented disruption in everyday endoscopy practice worldwide, with recent guidelines advocating suspension of nonemergency endoscopies, implementation of strict personal protection measures (PPM) and post-endoscopy evaluation of patient COVID-19 status. This was an international multicenter study seeking to evaluate the impact of COVID-19 on endoscopy during the first European lockdown (March-May 2020). COVID-19 transmission across endoscopic units proved to be highly unlikely in lockdown circumstances as long as endoscopy performance was restricted to emergency cases and sufficient PPM are available.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has spread throughout the world in a short period of time, rapidly affecting medical practice. Although the disease usually manifests with respiratory symptoms, gastrointestinal (GI) symptoms are not rare and, in some cases, constitute the basic clinical manifestations[1,2]. GI endoscopy is considered a risky procedure for transmission of the infection. During endoscopy, close contact of the endoscopist with the patient takes place, respiratory droplets and aerosols are generated, and contact with contaminated material, body fluids, and feces is likely to occur. Moreover, endoscopy also involves the assisting personnel of the unit (PEU). The PEU include not only the endoscopist, but also nurses and paramedical staff. In light of these considerations, specific protective measures and disinfection procedures have been recommended by scientific societies and recognized experts[3-5]. Endoscopic societies such as the European Society of Gastrointestinal Endoscopy (ESGE) and the European Society of Gastroenterology and Endoscopy Nurses and Associates (ESGENA) recently published a joint position statement for GI endoscopy during the COVID-19 pandemic regarding safe endoscopies for patients and PEU[3]. The statement suggests minimizing nonemergency endoscopies, implementation of personal protection measures (PPM), and post-endoscopy calls to patients 7 d and 14 d after the endoscopy to check their COVID-19 status. In a study from the heavily affected north of Italy, the number of post-endoscopy COVID-19 infections was negligible and the number of infected PEU was very small[6]. The aim of this European multicenter study was to evaluate the impact of endoscopic procedures on the risk of transmission for patients and PEU using the telephone as contact tool as suggested by ESGE and ESGENA.

MATERIALS AND METHODS

Study design

This was an international, multicenter study conducted during the period of the first European lockdown for COVID-19 (March-May 2020) in nine high-volume endoscopy departments across six European countries: Athens, Greece (two centers), Foggia/Verona, Italy (two centers), Brussels, Belgium, Skopje, Republic of North Macedonia, Zagreb/Rijeka, Croatia (two centers), and Belgrade, Serbia. The centers were included based on their high volume of endoscopic procedures prior to the COVID-19 outbreak and because they represented regions with a high prevalence of the disease on one side of the spectrum (Verona and Brussels) as well as regions with a lower prevalence of COVID-19 in southern Europe. This was an analysis of retrospectively collected data within a prospectively built database.

Inclusion criteria

All consecutive patients undergoing any endoscopic procedure, including upper and lower GI endoscopy (colonoscopy or rectosigmoidoscopy), endoscopic retrograde cholangiopancreatography (ERCP), or endoscopic ultrasonography (EUS) during the aforementioned period and involving each of the abovementioned PEU were considered eligible for inclusion.

Study population

Patients undergoing endoscopy: Following the triage protocol at each center, on the day of the endoscopy or the day before, all patients were questioned by the predetermined local study coordinator for symptoms and contacts that could be linked to COVID-19 and then stratified as low- or high-risk of potential COVID-19 infection, according to the ESGE/ESGENA joint statement[3]. Demographic data and procedural information regarding the endoscopy performed as well as previous performance of

testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were also recorded. Following the ESGE/ESGENA joint statement recommendation regarding post-procedure risk management[3], local study coordinators contacted the patients by telephone on day 7 and day 14 after the endoscopy to inquire about any new COVID-19 diagnosis, or development of COVID-19 symptoms. The calls were carried out using a structured questionnaire that was identical across all centers (Supplementary Table 1) and filled out for each patient. Polymerase chain reaction (PCR) testing *a posteriori* was possible at physician's discretion after the endoscopic procedure on a case-by-case basis, taking into account each patient's clinical status. For those who tested positive after the endoscopic procedure, additional information regarding need for hospitalization, intensive care unit (ICU) admission for COVID-19 and COVID-19-related deaths were also collected.

PEU: The PEU were questioned regarding potential COVID-19 symptoms and/or SARS-CoV-2 infection with the use of a structured questionnaire (Supplementary Table 2). PEU included not only medical and nursing staff, but also assisting staff working in the unit who could contact patients or material potentially infected by SARS-CoV-2, *i.e.* cleaning personnel, transporters, and secretarial staff. For those positive for SARS-CoV-2, information regarding hospitalization, ICU admission and COVID-19-related deaths were collected. Additionally, the final part of the questionnaire recorded the total number of endoscopies conducted pre-, during and post-implementation of COVID-19-transmission preventative measures.

Study endpoints

The primary endpoint of the study was the incidence of infection among patients who underwent endoscopy during the established time period. Secondary endpoints were: (1) Incidence and outcome of hospitalization, ICU admission for COVID-19, and COVID-19-related deaths among patients who tested positive; (2) Prevalence of COVID-19 symptoms and/or positive SARS-CoV-2 testing among PEU; (3) Incidence and outcome of hospitalization, ICU admission for COVID-19, and COVID-19-related deaths among PEU who tested positive; and (4) Percentage decrease in the overall number of endoscopies before and after implementation of lockdown measures and implementation of PPM in the study centers. For the purposes of this study, only PCR testing was deemed adequately accurate for confirmation of infection. Rapid tests, when performed, needed to be confirmed by PCR.

Statistical analysis

Categorical data were reported as numbers and percentages (%) with their 95%CIs. The distribution of quantitative data was evaluated for normality by the Kolmogorov–Smirnov statistic and reported as means ± SD or means and interquartile range (IQR) depending to their distribution. A P value < 0.05 was considered significant. A statistical review of the study was performed by a biomedical statistician (IP).

Ethical approval

The protocol of this study was reviewed and approved by the local institutional review board (ΒΠΠΚ ΕΒΔ 320/10-6-20). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and in compliance with good clinical practice.

RESULTS

Overall, 1267 endoscopies were performed in 1222 patients during the study time period. Of those, 87 (7%) were excluded because of initial positive testing. The remaining 1135 patients were enrolled in the study (Figure 1). Baseline patient baseline characteristics and recruitment at center are presented in Table 1.

Primary endpoint

Among the 1135 enrolled patients, 254 (22.4%) were retested the days following endoscopy because of the onset of new symptoms that could indicate a potential COVID-19 infection. Eight (n = 8) were eventually found positive. The incidence of infection among patients undergoing endoscopy was thus 0.7% (95%CI: 0.2-0.12). Of those eight patients, the majority had undergone upper GI endoscopy (n = 6/8, 75%). A negative pre-endoscopy PCR test was available in only 1 case. A detailed overview

Table 1 Baseline characteristics of patients

Patients characteristics	
Male/female	678 (59.7)/457 (40.3)
Age (mean ± SD), yr	63.4 ± 14.5
Inpatient	506 (44.6)
Outpatient	598 (52.7)
Referral	31 (2.7)
Recruitment per center	
"Attikon" Hospital, Athens, Greece	236 (20.8)
Aretaieio Hospital, Athens, Greece	42 (3.7)
Foggia, Italy	215 (18.9)
Verona, Italy	235 (20.7)
Belgrade, Serbia	19 (1.7)
Brussels, Belgium	143 (12.6)
Skopje, Republic of North Macedonia	149 (13.1)
Zagreb/Rijeka, Croatia	96 (8.5)
Type of endoscopy[1]	
Upper GI-endoscopies	587 (46.3)
Colonoscopies/rectosigmoidoscopies	444 (35.1)
ERCP	178 (14.1)
EUS	57 (4.5)

Data are n (%) unless noted otherwise.
[1]A total of 1266 endoscopies. ERCP: Endoscopic retrograde cholangiopancreatography; EUS: Endoscopic ultrasonography; GI: Gastrointestinal; SD: Standard deviation.

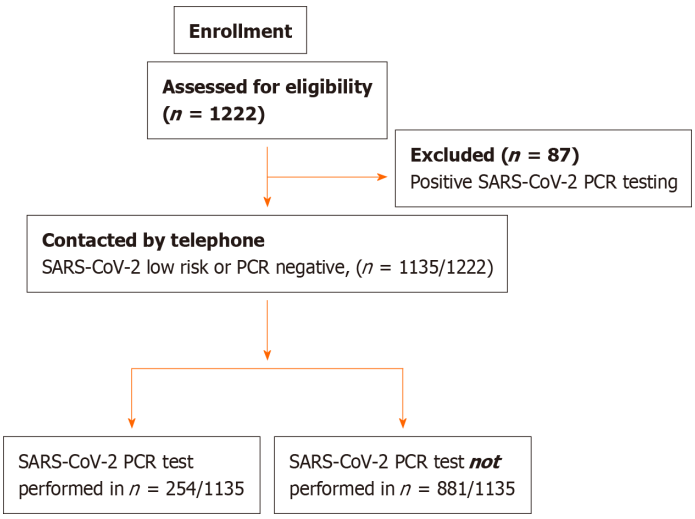

Figure 1 Study flowchart. PCR: Polymerase chain reaction; SARS-CoV2: Severe acute respiratory syndrome coronavirus 2.

of the infected characteristics of the patients is presented in Table 2.

Secondary endpoints

Of the 8 SARS-CoV-2-positive cases, 2 (25%) presented with a very mild illness and did not require hospitalization at all; the other 6 (75%) were hospitalized at some point, with 2 of them (33.3%) ultimately dying of COVID-19. Another 2 patients

Table 2 Baseline characteristics and outcomes of patients positive for severe acute respiratory syndrome coronavirus 2 after endoscopy

Case	Patient, age	Endoscopy	Date of endoscopy	COVID PCR test before endoscopy	Contact of suspected or confirmed COVID 19 case after endoscopy	Symptoms	COVID PCR test after endoscopy	Outcome of those hospitalized	Case related to endoscopy
1	Female, 66 yr	Upper GI	March 12, 2020	No	No	Fever and cough	Tested positive March 18, 2020	Death/deceased due to COVID-19	Cannot reasonably exclude
2	Male, 81 yr	Upper GI	April 8, 2020	No	No	Fever, cough and sore throat since April 17 for 42 d	Hospital admission April 12, 2020, tested positive and had Pneumonia	Death May 4/deceased due to COVID-19	Cannot reasonably exclude
3	Male, 66 yr, head/neck cancer and arterial disease	Upper GI	March 18, 2020	No	Yes with suspected case	Fever and Diarrhea since March 27, 2020	Tested positive March 28, 2020	Death May 7 due to cancer	Cannot reasonably exclude
4	Male, 55 yr, cancer esophagus	Upper GI	March 18, 2020	No	Yes with suspected case	Cough since March 16, 2020	Tested positive March 24, 2020	Discharge	No
5	Male, 76 yr, cancer stomach, 2, COPD	EUS	March 24, 2020	No	Yes with suspected case	Cough since March 19, 2020	Tested positive Apirl 23, 2020	Became negative/remained at nursing home	No
6	Female, 66 yr, AML	Lower GI	Apirl 1, 2020	Yes March 30, 2020negative	Yes with suspected case	Fever since April 3, 2020 for 6 d	Tested positive Apirl 10, 2020	Death May 4 due to cancer/at home	Cannot reasonably exclude
7	Male, 48 yr	Upper GI	March 27, 2020	No	No	Fever and cough since April 8, 2020 for 4 d	Tested positive Apirl 12, 2020	Not hospitalized	No
8	Male, 63 yr, diabetes, lung disease, IBD	Upper GI	March 30, 2020	No	Yes with suspected case	Fever and cough since April 22, 2020 for 2 d	Tested positive Apirl 22, 2020	Not hospitalized	No

AML: Acute myeloid leukemia; Chronic obstructive pulmonary disease; COPD; EUS: Endoscopic ultrasonography; GI: Gastrointestinal; IBD: Inflammatory bowel disease; PCR: Polymerase chain reaction.

(33.3%) died, but the cause of death was considered to be their underlying cancer. The remaining 2 (33.3%) were discharged to home and to a nursing residency.

Overall, the data included the COVID-19 infection status of 163 PEU from all 9 PEU. Eighty-four of the 163 (51.5%) were physicians (attendings as well as trainees), 62/163 (38%) were nurses and 17/163 (10.4%) were assisting staff working exclusively (or mostly) in the PEU (*i.e.* cleaning personnel, transporters, and secretarial staff of the units). Overall, 5/163 of the total PEU tested positive during the study period (2 physicians and 3 nurses), giving a 3% (95%CI: 0.4-5.7) incidence of infection. The majority of the infections (n = 4, 80%) were considered to be associated with the work environment. Those cases represent 2.3% (4/163) of the total PEU in our study and 7% and 16.6% of the PEU of their own units, respectively. None (0/5) of the infected PEU developed severe disease, none required hospitalization, and no COVID-19-related deaths occurred in the PEU who were included in our study.

PPM in accord with the ESGE/ESGENA position statement regarding reduction of cases to focus on emergency therapies, *i.e.* gowns, goggles, and masks, were implemented and adhered to in all participating centers during the initial phase of the study, which continued from 9 to 23 March, 2020. Overall, a significant reduction in the number of endoscopies was evident in all the participating centers after March 2020 (Figure 2). In detail, 1 wk before implementation of the ESGE/ESGENA position statement suggestions, the total number of endoscopies across all centers was 534 (246

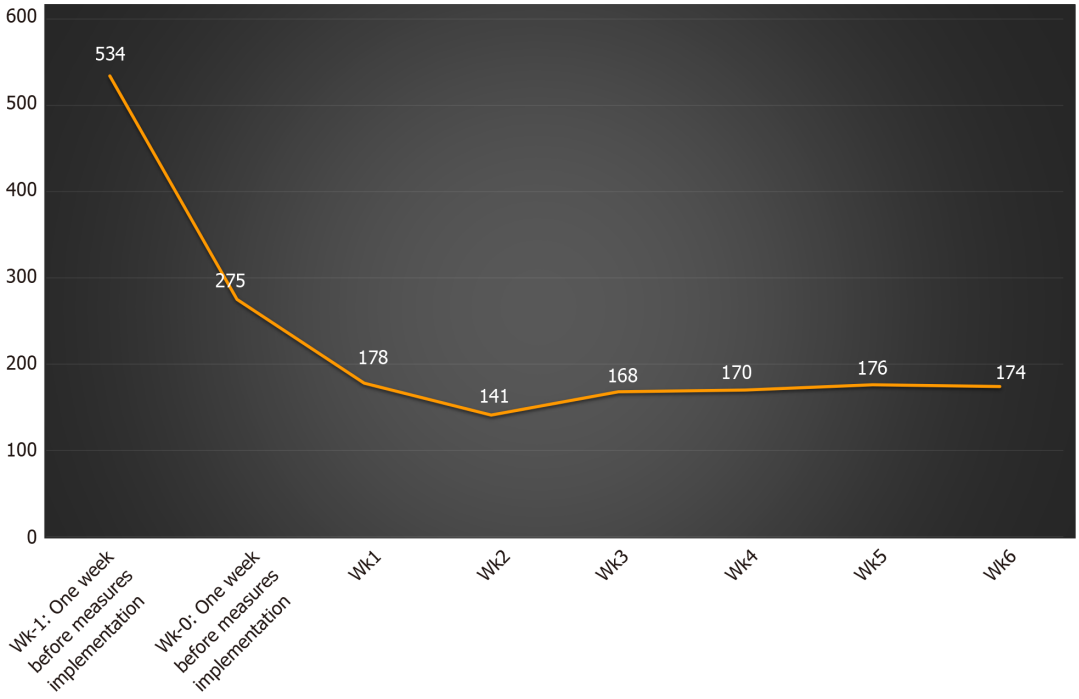

Figure 2 Overall endoscopies 1 wk before and in the weeks during lockdown.

upper GI-endoscopies, 209 colonoscopies/rectosigmoidoscopies, 56 ERCPs and 23 EUS). During the following 6 wk, the number gradually dropped, reaching a plateau with a mean of 167 ± 14 endoscopies per week, an estimated 68.7% (95%CI: 64.8-72.7) decrease in the performance of endoscopic procedures.

DISCUSSION

Endoscopic procedures were deemed as risky procedures for bidirectional COVID-19 infection transmission[1,2,7,8]. In this analysis of retrospectively collected data within a prospectively built database conducted across nine European endoscopic facilities, we showed that the risk of COVID-19 infection for patients undergoing GI endoscopy was extremely low in a lockdown setting. The results underline the value of following ESGE/ESGENA recommendations to address the danger of COVID-19 infection in everyday, real-world clinical practice.

Although COVID-19 infection and its potential implications have been at the focal point of ongoing research worldwide, evidence regarding this risk of healthcare professional and patient infection after endoscopy remain scarce[9]. In one of the few studies, Repici *et al*[6] retrospectively analyzed data from 802 patients and 968 PEU in 41 hospitals in northern Italy. Their results suggested that the number of post-endoscopy patient infections was negligible, *i.e.* 1 infection in 802 patients for a confirmed infection rate of 0.12%. Similarly in a much smaller multicenter, retrospective study that evaluated patients who underwent stent placement for upper GI obstruction[10]; only 1 of 29 patients (3.4%) tested positive for SARS-CoV-2 after the procedure. All the medical staff involved in the stenting procedures remained COVID-19 free 14 d later. The results of our multicenter study are also in line with those, as only 8 of the 1135 patients who were deemed pre-endoscopy SARS-CoV-2 low risk or negative, became positive. The results are further corroborated by the findings of a recent cross-sectional study. In a high-volume Japanese endoscopic facility, not a single positive result was detected among 783 PCR-analyzed saliva samples from patients undergoing endoscopic procedures[11].

Regarding PEU infection after endoscopy, our study is consistent with that of Repici *et al*[6], who found a very low risk of PEU contamination. Indeed, the Italian study reported a very small number of infected PEU (42 cases, or only 4.3% of the PEU population in their study), with 85.7% of the infections occurring before PPM were introduced. Even for the PEU who were infected, fewer than 1% needed hospitalization and none required admission in ICU or died[6]. Outside Europe, the risk of

COVID-19 infection of PEU may be higher, up to 23.9%, especially in endoscopy technicians[12]. Our study had even more impressive results, with only 5 PEU testing positive during the study period, representing a 3% of the total PEU involved in the endoscopies that were performed in the study. In only 4 of the total PEU, 1 physician and 3 nurses, was the infection considered to be linked to their work. As in the Italian study, none of the infected PEU in our study developed severe disease, required hospitalization, or died, compared with 2 COVID-19-related deaths that occurred in the 8 patients who became positive post endoscopy. Whether that was merely a random association or a result of the younger age and better health status of the PEU compared with that of our patient population, who were severely ill individuals undergoing emergency endoscopies, remains unclear. Published data suggest that PEU, when affected, experience relatively mild disease, but as the numbers were extremely small, we cannot provide further insights[5,6]. Notably, a case-by-case analysis revealed a clustering of infections, as all PEU found positive worked in a unit performing almost exclusively ERCPs. A possible explanation could be based on the longer duration of those particular examinations compared with standard upper GI-endoscopies, resulting in increased risk for transmission.

Pre-endoscopic testing for COVID-19 was available only for one-fourth of the patients of our study (326/1222, 26.7%). One might consider that to be a low percentage; however, it should be noted that this policy is in accordance with the ESGE/ESGENA recommendations that do not advocate SARS-CoV-2 tests as a prerequisite for GI endoscopy. On the contrary, they put a spotlight on appropriate triaging of nonemergency endoscopies and PPM. Our low post-endoscopy infection rates of both patients and PEU seem to justify those suggestions.

The finding that the COVID-19 pandemic led to a significant reduction in the volume of endoscopic procedures is not novel. Beyond patient stratification as low- or high-risk of COVID-19 infection, the position ESGE/ESGENA statement for GI endoscopy during the COVID-19 pandemic also clearly lists which endoscopic procedures should be definitely performed and which can be postponed. That policy was uniformly applied at all the participating centers of our study. Thus, all the endoscopies performed in our series, if not emergency, were nevertheless completely necessary; none were purely elective. Still, the optimal policy, when resumption of endoscopy services comes into question, remains to be elucidated. In that regard, a stepwise approach that takes: (1) The regional prevalence of COVID-19 with stricter guidelines in endoscopy and use of PPE in high-prevalence (> 2%) areas[13]; (2) Patient stratification for procedures that should be performed immediately or postponed, as well as low- or high-risk of infection[3]; and (3) Modifications in PEU working schedules to prevent hospital-based transmission into account seems the most appropriate[14,15].

A number of study strengths should be cited. First, this iteration is one of the few studies addressing the question of the safety of endoscopy during the COVID-19 pandemic. Second, we enrolled patients in different countries, giving a more representative overview of the impact of COVID-19 outbreak on endoscopy units. Third, our questionnaire content was guided by the ESGE/ESGENA position statement. Finally, our population was homogenous, including patients who underwent endoscopic procedures involving both the upper and lower GI tract as well as the respective participating PEU.

On the other hand, there are also limitations that merit attention. The lack of SARS-CoV-2 testing of patients presenting for endoscopy without COVID-19 symptoms and heterogeneity of PEU testing can initially be seen as such; but that practice was in accord with endoscopy society recommendations including those of the ESGE/ESGENA). The practice should therefore be considered unavoidable, but it undoubtedly had an impact on our epidemiological data, as the percentage of asymptomatic patients in our group remains unknown and hinders the complete tracking of the infection. Another shortcoming is the possibility of recall bias, given that the study data was acquired by asking patients to recall their symptoms. Again, that was unavoidable, as it complied with the ESGE/ESGENA directive stating that patients should be contacted 7 d and 14 d post endoscopy. Finally, the small number of positive cases and study design prevent a definitive causal relationship to be established. However, aim of the study was not to address issues related to potential routes of infection, but rather to investigate the actual possibility of COVID-19 transmission in endoscopy units when established guidelines are implemented.

CONCLUSION

In conclusion, COVID-19 transmission in endoscopy units is a highly unlikely event for both patients and PEU in a lockdown setting, provided endoscopies are effectively restricted to emergency cases and appropriate, stringent PPM are implemented. In the extremely rare cases of PEU infection in our series, the disease was relatively mild, with no hospitalizations or COVID-19-related deaths.

ARTICLE HIGHLIGHTS

Research background

The coronavirus disease 2019 (COVID-19) outbreak significantly affected endoscopic practice, as gastrointestinal endoscopy is considered as a risky procedure for transmission of infection. The ESGE and ESGENA published a position statement for endoscopy during the COVID-19 pandemic regarding the safety of endoscopies for patients and the personnel of endoscopy units (PEU). However, the incidence and outcome of infection among patients undergoing endoscopy and PEU remains to be determined.

Research motivation

Currently, there is insufficient data regarding the incidence and outcomes of COVID-19 infection among patients undergoing endoscopy and in PEU.

Research objectives

We aimed to evaluate the impact of endoscopic procedures on the risk of transmission to patients and PEU in a European multicenter study, using telephone contact as a tool as suggested by the ESGE and ESGENA.

Research methods

Patients undergoing endoscopy in nine endoscopy departments across six European countries during the period of the first European lockdown for COVID-19 (March-May 2020) were included. Participants were stratified as low- or high-risk for potential COVID-19 infection according to the ESGE/ESGENA joint statement were contacted 7 d and 14 d later to assess COVID-19 infection status. PEU were questioned regarding COVID-19 symptoms and/or infection by questionnaire. Information on hospitalizations, ICU-admissions, and COVID-19-related deaths were collected. The number of weekly endoscopies during the lockdown period was also recorded.

Research results

A total of 1267 endoscopies were performed in 1222 individuals; 87 (7%) were excluded following initial positive PCR testing. The remaining 1135 individuals were at low risk or PCR negative for COVID-19 before endoscopy, and of 254 (22.4%) who were tested post endoscopy, eight were eventually found positive, resulting in an infection rate of 0.7% (95%CI: 0.2-0.12). The majority, (6/8, 75%) had undergone esophagogastroduodenoscopy. Data were available for 163 PEU, and 5 (3%; 95%CI: 0.4-5.7) tested positive during the study period. In 4 of the 5, or 2% of the total, the infection was deemed relevant to their work environment. A decrease of 68.7% (95%CI: 64.8-72.7) in the number of endoscopies was recorded.

Research conclusions

This study showed that COVID-19 transmission in endoscopic units was highly unlikely during a lockdown setting, provided endoscopies were restricted to emergency cases and PPM were implemented.

Research perspectives

More robust data are definitely warranted to identify various clinical factors that contribute to an increased risk of endoscopy-related COVID-19 infection.

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ORIGINAL ARTICLE

Observational Study

Enlarged folds on endoscopic gastritis as a predictor for submucosal invasion of gastric cancers

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Institutional review board statement: This retrospective study was approved by Certificated Review Board, Hattori Clinic on September 4, 2020 (approval No. S2009-U04).

Informed consent statement: Patients were not required to give

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Abstract

BACKGROUND

Accurate diagnosis of the depth of gastric cancer invasion is crucial in clinical practice. The diagnosis of gastric cancer depth is often made using endoscopic characteristics of the tumor and its margins; however, evaluating invasion depth based on endoscopic background gastritis remains unclear.

AIM

To investigate predicting submucosal invasion using the endoscopy-based Kyoto classification of gastritis.

METHODS

Patients with gastric cancer detected on esophagogastroduodenoscopy at

Toyoshima Endoscopy Clinic were enrolled. We analyzed the effects of patient and tumor characteristics, including age, sex, body mass index, surveillance endoscopy within 2 years, current *Helicobacter pylori* infection, the Kyoto classification, and Lauren's tumor type, on submucosal tumor invasion and curative endoscopic resection. The Kyoto classification included atrophy, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness. Atrophy was characterized by non-reddish and low mucosa. Intestinal metaplasia was detected as patchy whitish or grayish-white flat elevations, forming an irregular uneven surface. An enlarged fold referred to a fold width ≥ 5 mm in the greater curvature of the corpus. Nodularity was characterized by goosebump-like multiple nodules in the antrum. Diffuse redness was characterized by uniform reddish non-atrophic mucosa in the greater curvature of the corpus.

RESULTS

A total of 266 gastric cancer patients (mean age, 66.7 years; male sex, 58.6%; mean body mass index, 22.8 kg/m^2) were enrolled. Ninety-three patients underwent esophagogastroduodenoscopy for surveillance within 2 years, and 140 had current *Helicobacter pylori* infection. The mean Kyoto score was 4.54. Fifty-eight cancers were diffuse-type, and 87 cancers had invaded the submucosa. Multivariate analysis revealed that low body mass index (odds ratio 0.88, P = 0.02), no surveillance esophagogastroduodenoscopy within 2 years (odds ratio 0.15, P < 0.001), endoscopic enlarged folds of gastritis (odds ratio 3.39, P = 0.001), and Lauren's diffuse-type (odds ratio 5.09, P < 0.001) were independently associated with submucosal invasion. Similar results were obtained with curative endoscopic resection. Among cancer patients with enlarged folds, severely enlarged folds (width ≥ 10 mm) were more related to submucosal invasion than mildly enlarged folds (width 5-9 mm, P < 0.001).

CONCLUSION

Enlarged folds of gastritis were associated with submucosal invasion. Endoscopic observation of background gastritis as well as the lesion itself may help diagnose the depth of cancer invasion.

Key Words: Gastric cancer; Gastritis; Enlarged fold; Endoscopy; Kyoto classification

Core Tip: We investigated predicting submucosal invasion using the endoscopy-based Kyoto classification of gastritis. We analyzed the effects of patient and tumor characteristics, including the Kyoto classification, on submucosal tumor invasion. Two hundred sixty-six gastric cancer patients were enrolled. Multivariate analysis revealed that low body mass index, no surveillance esophagogastroduodenoscopy within 2 years, endoscopic enlarged folds of gastritis, and Lauren's diffuse-type were independently associated with submucosal invasion. Among cancer patients with enlarged folds, severely enlarged folds (width ≥ 10 mm) were more related to submucosal invasion than mildly enlarged folds (width 5-9 mm). Enlarged folds of gastritis were associated with submucosal invasion.

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informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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INTRODUCTION

Gastric cancer is the third most common cause of cancer mortality worldwide, making

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it an important disease[1,2]. The depth of gastric cancer invasion is associated with lymph node metastasis[3,4], recurrence[5], and survival[6,7] and has a great influence on therapeutic strategy[8-10]. This means that the diagnosis of invasion depth is crucial.

At present, the diagnosis of gastric cancer depth is often made using the endoscopic characteristics of the tumor and its margins. For example, an irregular surface, marked marginal elevation, and clubbing/abrupt cutting/fusion of converting folds are useful for the diagnosis of submucosal invasion[11]. Similarly, using nodular mucosal changes, deep depression, and fold convergence for the diagnosis of signet ring cell carcinoma with submucosal invasion[12], and the non-extension sign[13], size > 30 mm, margin elevation, uneven surface[14], remarkable redness[14,15], and abrupt cutting converging folds[15] for the diagnosis of deeper submucosal invasion (SM2: ≥ 500 μm in depth) have also been reported. For the last decade, the depth of gastric cancer has been predicted using magnifying narrow-band imaging, which is an image-enhanced endoscopy, in addition to conventional white-light imaging[16]. Findings such as non-structure, scattering, or multi-caliber vessels[17], D-vessels[18], and the vessel plus surface classification[19] were found to be useful for depth diagnosis. Furthermore, various modalities, including endoscopic ultrasonography[20] and computed tomography[21], have been found to assist in depth diagnosis. Thus, research on the depth of invasion is being vigorously conducted.

On the other hand, artificial intelligence is now overwhelming human intelligence. Artificial intelligence defeated the world champion in chess in 1997 and in the East Asian game of go in 2017. The style of play used by artificial intelligence was of a different dimension unimaginable to humans. Recently, artificial intelligence has been used for endoscopic diagnosis[22]. In the future, artificial intelligence may be used to diagnose the depth of invasion based not only on the tumor itself but also on background gastritis. However, there are few reports on the evaluation of invasion depth based on endoscopic background gastritis. Therefore, we decided to investigate predictions for submucosal invasion using the endoscopy-based Kyoto classification of gastritis, for which evidence has been accumulated recently[23-25].

MATERIALS AND METHODS

Patients and overview

This study involved those patients who underwent esophagogastroduodenoscopy (EGD) between January 2008 and August 2020 at Toyoshima Endoscopy Clinic, in whom gastric cancers were detected. Exclusion criteria were cancer located in the esophagogastric junction or in the residual stomach after surgery, or unavailable EGD images. We also excluded patients with unavailable *Helicobacter pylori* (*H. pylori*) status. In this study, curative endoscopic resection of gastric cancer was performed according to the guidelines of the Japanese Gastric Cancer Association[26].

This retrospective study was approved by the Certificated Review Board, Hattori Clinic on September 4, 2020 (approval No. S2009-U04). Written informed consent was obtained from all participants. All clinical evaluations were conducted in accordance with the ethical guidelines of the Declaration of Helsinki. This study had no financial support.

Endoscopy

The Japan Gastroenterological Endoscopy Society advocated the endoscopy-based Kyoto classification of gastritis in 2013 with the aim of matching endoscopic findings and pathology. The Kyoto classification of gastritis comprises atrophy, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness. Endoscopic atrophy is characterized by non-reddish and low mucosa, identified by an atrophic border, according to the Kimura-Takemoto classification[27]. Endoscopic intestinal metaplasia is detected as patchy whitish or grayish-white flat elevations, forming an irregular uneven surface[28]. An enlarged fold refers to a fold with width ≥ 5 mm in the greater curvature of the corpus, which is not flattened or only partially flattened by stomach insufflation. Endoscopic nodularity is characterized by goosebump-like multiple nodules that appear mainly in the antrum and represent a collection of lymphoid follicles. Diffuse redness is characterized by uniform reddish non-atrophic mucosa located mainly in the greater curvature of the corpus and representing superficial gastritis.

The Kyoto score is the sum of the following five parameters: atrophy, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness score and ranges from 0 to 8. Kimura-Takemoto classification gradings of C0 and CI are defined as an atrophy score of 0, CII and CIII have an atrophy score of 1, and OI to OIII have an atrophy score of 2. Absence of intestinal metaplasia was defined as an intestinal metaplasia score of 0, intestinal metaplasia limited to the antrum was given 1, and intestinal metaplasia extending into the corpus received an intestinal metaplasia score of 2. The absence and presence of enlarged folds were defined as enlarged fold scores of 0 and 1, respectively. The absence and presence of nodularity were defined as nodularity scores of 0 and 1, respectively. Diffuse redness scores were defined as 0, 1, and 2 for no diffuse redness, mild redness, and severe redness, respectively. The Kyoto score has been proven to be associated with the presence of gastric cancer[23], the risk of gastric cancer[25], and *H. pylori* infection[24].

In this study, enlarged folds were divided into two groups: severely enlarged folds with widths ≥ 10 mm and mildly enlarged folds with widths of 5-9 mm[29,30]. Fold width was measured by placing a closed or opened forceps, which has a width of 2 mm or 7mm, against enlarged folds.

One expert endoscopist retrospectively reviewed the EGD images and evaluated the Kyoto score. Surveillance EGD was defined as such only if the patients had undergone a previous EGD at our institution within the last 2 years[31].

Pathology

The depth of the tumor was diagnosed using the resected specimen or if unresectable, from computed tomography images. Tumor type was evaluated according to the Lauren classification (diffuse- or intestinal-type)[32].

H. pylori status

We divided the *H. pylori* infection status into two groups: current infection and negative for current infection. The current infection group included patients in whom *H. pylori* eradication therapy had failed. The group of negative for current infection included *H. pylori*-uninfected patients and *H. pylori*-past infected patients who had undergone successful eradication therapy or in whom *H. pylori* had spontaneously disappeared[33].

Data collection and outcomes

The T-File System (STS-Medic Inc., Tokyo, Japan) was used to file the endoscopic images and for documentation of the endoscopic findings. We collected data on age, sex, interval from previous EGD, and endoscopic images from the T-File System, and data on body mass index (BMI), *H. pylori* status, treatment for the cancer, and Lauren type of the tumor from electronic medical records.

Statistical analysis

Univariate and multivariate analyses for the effect on submucosal invasion and curative endoscopic resection were performed using a binomial logistic regression model. Variables with a P value < 0.1 in the univariate analysis were entered into the multivariate analysis and calculated using the all-possible-regressions procedure. We used a complete analysis for missing data. We evaluated the frequency of submucosal invasion among patients with negatively enlarged folds and mildly and severely enlarged folds using the Cochran-Armitage trend test.

Statistical significance was indicated by a P value of < 0.05. Calculations were performed using the statistical software Ekuseru-Toukei 2015 (Social Survey Research Information Co., Ltd., Tokyo, Japan).

RESULTS

Patient enrollment

A total of 300 patients with gastric adenocarcinomas were observed at the Toyoshima Endoscopy Clinic during the study period. We excluded nine cancers located at the esophagogastric junction, seven cancers located in the residual stomach after surgery, nine cancers with unavailable EGD images, and nine cancers with unavailable *H. pylori* status. Finally, 266 gastric cancers were enrolled. Figure 1 presents the patient flowchart of this study.

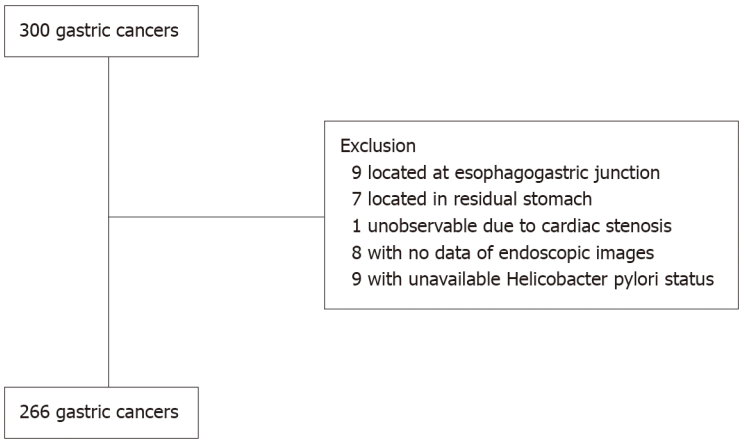

Figure 1 Patient flowchart.

Patient characteristics

Table 1 shows the patient characteristics of the study. The mean age was 66.7 (range, 37-89) years. Of the patients, 58.6% were male. The mean BMI was 22.8 kg/m^2. Ninety-three patients (35.0%) underwent EGD for surveillance within 2 years. Current *H. pylori* infection was identified in 52.6% (including 129 patients without past eradication therapy and 11 patients with failed eradication therapy) of the study patients. Cases negative for current *H. pylori* infection included 13 uninfected and 113 past-infected patients. The mean Kyoto score was 4.54 (atrophy score, 1.75; intestinal metaplasia, 1.32; enlarged folds, 0.24; nodularity, 0.08; diffuse redness score, 1.15). The proportion of diffuse-type adenocarcinoma on the Lauren classification was 21.8%. With respect to the depth of gastric cancer, 179 (67.3%) were in the mucosa, 51 (19.2%) were in the submucosa, and 36 (13.5%) were in the muscularis propria or deeper.

Effects on submucosal invasion of gastric cancer

We analyzed the effects on submucosal invasion of gastric cancer using univariate and multivariate analyses (Table 2). Multivariate analysis showed that low BMI (odds ratio 0.88, $P = 0.02$), non-surveillance EGD (odds ratio 0.15, $P < 0.001$), enlarged folds (odds ratio 3.39, $P = 0.001$), and Lauren's diffuse-type adenocarcinoma (odds ratio 5.09, $P < 0.001$) were associated with submucosal invasion.

Next, we analyzed the effects on patients who underwent curative treatment with endoscopic resection without surgery. In addition to the mucosal depth of gastric cancer, patients who underwent curative endoscopic resection were associated with high BMI, surveillance EGD, no enlarged folds, and Lauren's intestinal-type adenocarcinoma (Supplementary Table 1).

Sub-analysis of patients with enlarged folds

We divided gastric cancer patients with enlarged folds into two categories: mildly and severely enlarged folds. Submucosal invasion was observed in 49 of 203 cancers without enlarged folds, 14 of 30 cancers with mildly enlarged folds, and 24 of 33 cancers with severely enlarged folds. Figure 2 shows the proportions of submucosal invasion based on the severity of the enlarged folds. The severity of the enlarged folds was related to the depth of the tumor ($P < 0.001$, Cochran-Armitage trend test).

Representative images of enlarged fold gastritis and coexisting gastric cancer are shown in Figure 3.

DISCUSSION

In this study, we found that the enlarged folds of background gastritis were related to submucosal invasion of gastric cancer. Furthermore, the severity of the enlarged folds was associated with the depth of the tumor. We showed that cancer invasion may be predicted based on background gastritis. The strength of this study is that background gastritis, under the new criterion of the Kyoto classification, is related to the depth of invasion and not limited to observation of the lesions themselves. However, comprehensive endoscopic diagnosis is required in clinical practice because of advances in

Table 1 Patient characteristics of this study

Patient characteristics	
n	266
Age, mean (SD), yr	66.7 (12.1)
Male sex	58.6%
Body mass index, mean (SD), kg/m^2	22.8 (3.3)
Surveillance endoscopy within 2 yr	35.0%
Current *Helicobacter pylori* infection	52.6%
Endoscopic findings	
Atrophy score, mean (SD)	1.75 (0.54)
Intestinal metaplasia score, mean (SD)	1.32 (0.84)
Enlarged folds score, mean (SD)	0.24 (0.43)
Nodularity score, mean (SD)	0.08 (0.27)
Diffuse redness score, mean (SD)	1.15 (0.92)
Kyoto score, mean (SD)	4.54 (1.84)
Lauren's diffuse-type	21.8%
Depth of gastric cancer, M/SM/MP or deeper, *n*	179/51/36

M: Mucosa; MP: Muscularis propria; SD: Standard deviation; SM: Submucosa.

Table 2 Effect on submucosal invasion of gastric cancer

	Univariate analysis		Multivariate analysis		
	Odds ratio	*P* value	Regression coefficient	Odds ratio (95% confidence interval)	*P* value
Age	0.96	< 0.001	0.003	1.00 (0.97-1.03)	0.82
Male sex	1.17	0.56			
Body mass index	0.85	< 0.001	-0.130	0.88 (0.79-0.98)	0.02
Surveillance endoscopy within 2 yr	0.12	< 0.001	-1.913	0.15 (0.06-0.38)	< 0.001
Current *Helicobacter pylori* infection	2.55	< 0.001	-0.387	0.68 (0.21-2.24)	0.52
Endoscopic findings					
Atrophy score	0.58	0.11			
Intestinal metaplasia score	0.71	0.03	-0.014	0.99 (0.65-1.49)	0.95
Enlarged folds score	4.76	< 0.001	1.222	3.39 (1.61-7.14)	0.001
Nodularity score	1.57	0.33			
Diffuse redness score	1.48	0.01	-0.020	0.98 (0.54-1.78)	0.95
Kyoto score	1.14	0.08			
Lauren's diffuse-type	7.61	< 0.001	1.627	5.09 (2.22-11.64)	< 0.001

P values were calculated using binomial logistic regression analysis.

technology such as artificial intelligence.

Enlarged folds have been well studied for their biological characteristics. Enlarged folds have been shown to be associated with the tumor necrosis factor-alpha gene polymorphism as a genetic predisposition[34]. Genome wide hypomethylation and regional hypermethylation have been shown to occur in enlarged folds[35,36]. The production of interleukin 1 beta and hepatocyte growth factor caused by *H. pylori* infection reportedly contributes to fold enlargement in the stomach by stimulating

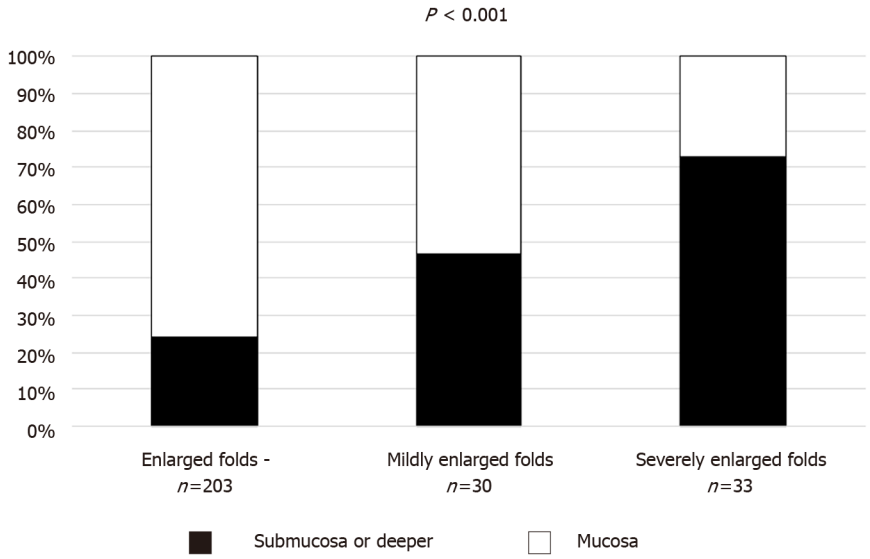

Figure 2 Proportion of submucosal invasion based on severity of enlarged folds. The *P* value was calculated using the Cochran-Armitage trend test.

epithelial cell proliferation and inhibiting acid secretion[37,38]. Morphological changes in parietal cells associated with *H. pylori* infection have been reported to be functionally related to the inhibition of acid secretion seen in patients with enlarged folds[39]. In addition, enlarged folds are strongly associated with *H. pylori* infection and have been shown to improve with eradication[24,29,34]. Enlarged folds are considered to be at high risk of gastric cancer, especially diffuse cancer, which is closely related to highly active inflammation[36,40]. These biological behaviors of the enlarged folds may be attributed to the depth of the cancer.

Yasunaga *et al*[29] divided enlarged folds into two categories (severe and mild) and found that severely enlarged folds suppressed acid secretion and had higher serum gastrin, pepsinogen I, and pepsinogen II levels compared to mildly enlarged folds[30]. Such differences may contribute to active inflammation of the mucosa and depth of cancer.

Invasion depth has already been reported to be associated with Lauren's histological type[41], surveillance endoscopy[31], and BMI[42]. Consistent with these previous reports, the multivariate analysis of the present study demonstrated that submucosal invasion was associated with pathology, surveillance, and BMI.

This study has some limitations. First, this was a single-institute retrospective study. However, the quality of the data was well-controlled. In the future, a prospective, multicenter design is needed. Second, because the number of events was small, the variables that could be entered into multivariate analysis were limited. It is desirable to increase the number of events and investigate factors such as family history, drinking and smoking history, and aspirin use. Third, we did not endoscopically evaluate the tumor itself. Comprehensive analyses of the tumor itself and background gastritis are warranted.

CONCLUSION

Endoscopy-based enlarged folds of gastritis were associated with submucosal invasion of the tumor. Endoscopic observation of background gastritis as well as the lesion itself may help diagnose the depth of cancer invasion in clinical practice. Therefore, further comprehensive investigations are required.

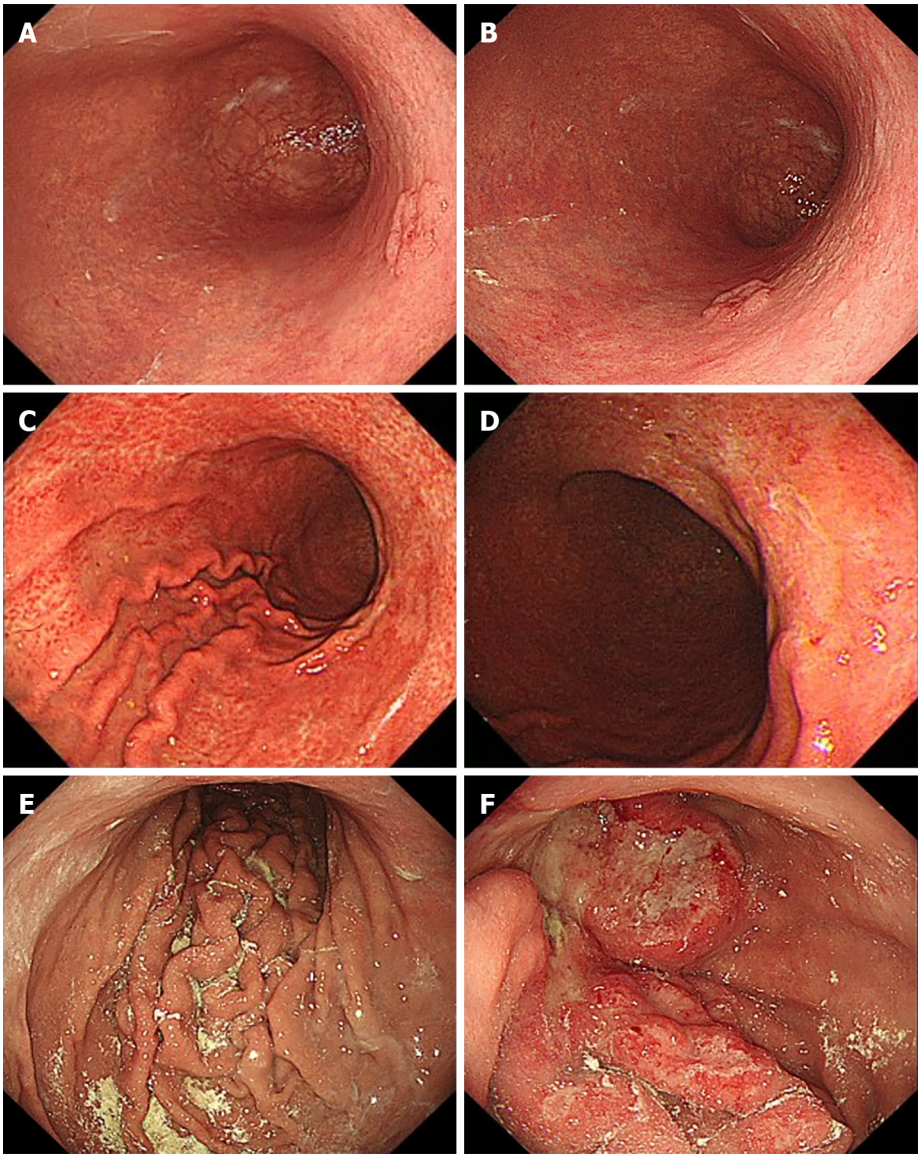

Figure 3 Representative images of enlarged folds and coexisting gastric cancer. A and B: Enlarged fold-negative; 74-year-old man with current *Helicobacter pylori* (*H. pylori*) infection. The cancer was limited to the mucosa and was intestinal-type; C and D: Mildly enlarged folds; 40-year-old woman with current *H. pylori* infection. The cancer invaded the submucosa and was diffuse-type; E and F: Severely enlarged folds; 60-year-old man with current *H. pylori* infection. The cancer invaded the serosa and was diffuse-type. A, C and E: Greater curvature of the body; B, D and F: Gastric cancer.

ARTICLE HIGHLIGHTS

Research background

The diagnosis of gastric cancer depth is often made using endoscopic characteristics of the tumor and its margins.

Research motivation

In the future, artificial intelligence may be used to diagnose the depth of invasion based not only on the tumor itself but also on background gastritis.

Research objectives

We investigated predicting submucosal invasion based on endoscopic background gastritis.

Research methods

Patients with gastric cancer detected on esophagogastroduodenoscopy were enrolled. We analyzed the effects of patient and tumor characteristics including the Kyoto classification.

Research results

Endoscopic enlarged folds of gastritis (odds ratio 3.39, $P = 0.001$) was independently associated with submucosal invasion. Among cancer patients with enlarged folds, severely enlarged folds (width ≥ 10 mm) were more related to submucosal invasion than mildly enlarged folds (width 5-9 mm, $P < 0.001$).

Research conclusions

Enlarged folds of gastritis were associated with submucosal invasion.

Research perspectives

Endoscopic observation of background gastritis as well as the lesion itself may help diagnose the depth of cancer invasion.

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CASE REPORT

Ectopic pancreas at the ampulla of Vater diagnosed with endoscopic snare papillectomy: A case report and review of literature

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Abstract

BACKGROUND

Ectopic pancreas is a rare developmental anomaly that results in a variety of clinical presentations. Patients with ectopic pancreas are mostly asymptomatic, and if symptomatic, symptoms are usually nonspecific and determined by the location of the lesion and the various complications arising from it. Ectopic pancreas at the ampulla of Vater (EPAV) is rare and typically diagnosed after highly morbid surgical procedures such as pancreaticoduodenectomy or ampullectomy. To our knowledge, we report the first case of confirmed EPAV with a minimally invasive intervention.

CASE SUMMARY

A 71-year-old male with coronary artery disease, presented to us with new-onset dyspepsia with imaging studies revealing a 'double duct sign' secondary to a small subepithelial ampullary lesion. His hematological and biochemical investigations were normal. His age, comorbidity, poor diagnostic accuracy of endoscopy, biopsies and imaging techniques for subepithelial ampullary lesions, and suspicion of malignancy made us acquire histological diagnosis before morbid surgical intervention. We performed balloon-catheter-assisted endoscopic snare papillectomy which aided us to achieve *en bloc* resection of the ampulla for histopathological diagnosis and staging. The patient's post-procedure recovery was uneventful. The *en bloc* resected specimen revealed ectopic pancreatic tissue in the ampullary region. Thus, the benign histopathology avoided morbid surgical intervention in our patient. At 15 mo follow-up, the patient is asymptomatic.

CONCLUSION

EPAV is rare and remains challenging to diagnose. This rare entity should be included in the differential diagnosis of subepithelial ampullary lesions.

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Endoscopic *en bloc* resection of the papilla may play a vital role as a diagnostic and therapeutic option for preoperative histological diagnosis and staging to avoid morbid surgical procedures.

Key Words: Ectopic pancreas; Heterotopic pancreas; Ampulla of Vater; Endoscopic snare papillectomy; Ampullary tumors; Case report

Core Tip: Ectopic pancreas at the ampulla of Vater (EPAV) is an extremely rare condition, usually mimicking malignancy and presents as abdominal pain and obstructive jaundice. This rare entity should be included in the differential diagnosis of subepithelial ampullary lesions. The diagnosis of EPAV remains very challenging despite several endoscopic and radiological advances. The diagnosis is usually based on morbid surgical interventions such as pancreaticoduodenectomy/ampullectomy or autopsy. Endoscopic *en bloc* resection of the papilla with endoscopic snare papillectomy may play a vital role as a diagnostic and therapeutic option for preoperative histological diagnosis and staging to avoid morbid surgical procedures.

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INTRODUCTION

Ectopic or heterotopic pancreas is a rare developmental anomaly with an estimated frequency of 0.6% to 13.7% at autopsy. It is mostly an incidental finding in the upper gastrointestinal tract, the most typical sites being the stomach (25%-38%), duodenum (17%-36%), and jejunum (15%-21.7%). It has been noted occasionally in the esophagus, gallbladder, common bile duct (CBD), spleen, mesentery, mediastinum and fallopian tubes[1,2]. The clinical manifestations of ectopic pancreas are usually nonspecific and are determined by the location of the lesion and the various complications arising from it.

Ectopic pancreas at the ampulla of Vater (EPAV) is extremely rare and usually presents as obstructive jaundice or abdominal pain, and hence, mimicking ampullary malignancy. Despite several advances in endoscopic and radiological techniques, the diagnosis of EPAV remains challenging and is mostly identified post-surgery or at autopsy.

Endoscopic snare papillectomy (ESP) is a minimally invasive technique that helps to achieve *en bloc* resection of the ampulla for preoperative histopathological diagnosis and staging, and thus avoids morbid surgical intervention. To our knowledge, we report the first case of this rare and challenging entity diagnosed by *en bloc* resection of the ampulla with ESP.

CASE PRESENTATION

Chief complaints

A 71-year old male presented in the outpatient department in August 2019 with the chief complaint of epigastric pain of 3 mo duration.

History of present illness

The epigastric pain was mild to moderate, localized, continuous, with no relation to meals. There was no relief with proton pump inhibitors. There was no history of jaundice, pruritus, clay-colored stools, anorexia, weight loss, dysphagia, gastrointestinal bleeding or vomiting.

History of past illness

The patient had undergone coronary angioplasty for coronary artery disease in 2010 and was on dual antiplatelet drugs.

Personal and family history

He had no addictions, and his family history was non-contributory.

Physical examination

The patient was conscious and oriented. His pulse rate was 80 bpm and regular, and blood pressure was 110/70 mmHg. There was no pallor, icterus, or lymphadenopathy. Abdominal examination and other systemic examinations did not reveal any abnormalities.

Laboratory examinations

His blood investigations were as follows: Hb 13.9 g/ dL, white blood cell count 4600/μL, platelet count 166000/μL, prothrombin time 16.5 s, serum bilirubin 0.42 mg/dL, ALT 18 U/L, AST 17 U/L, ALP 83 U/L (< 129 U/L), gamma glutamyl transferase - 33 U/L (< 71 U/L), and serum creatinine 1.22 mg/dL (< 1.4 mg/dL).

Imaging examinations

At the local medical center, he had undergone ultrasonography of the abdomen that revealed dilatation of the CBD (15 mm) and pancreatic duct (PD) (5 mm). He was referred to our center for further management. Abdominal magnetic resonance imaging and magnetic resonance cholangiopancreatography (MRCP) showed dilated CBD (15 mm) and PD (6 mm) with abrupt cut-off at the level of the ampulla. No other abnormalities were noted (Figure 1). Endoscopic ultrasonography (EUS) revealed a subepithelial, hypoechoic mass lesion at the ampulla 7 mm in size, causing upstream dilation of the CBD and PD. The lesion was free from duodenal muscularis propria. There was no regional lymphadenopathy.

Diagnostic and therapeutic intervention

The age and comorbidity of the patient, the limitations and diagnostic accuracy of endoscopy, biopsies and imaging for ampullary lesions, and suspicion of malignancy made us acquire the histological diagnosis of ampullary lesion before a highly morbid surgical intervention. EUS-guided biopsy was not possible due to technical difficulties of the tiny mobile lesion. Hence, ESP was considered a diagnostic and therapeutic intervention for the subepithelial ampullary lesion. ESP aids in achieving *en bloc* resection of the ampulla for histopathological diagnosis and staging. Thus, *en bloc* ESP was performed with a balloon-catheter-assisted technique as described by Aiura *et al* [3]. ESP was carried out with a therapeutic duodenoscope (TJF Q 180V, Olympus Medical Systems Corp., Tokyo, Japan) with a 4.2 mm diameter accessory channel. Selective CBD cannulation was achieved with a 0.035" guidewire using a sphincterotome. The linked stone extraction balloon catheter (Fusion Quattro Extraction Balloon, Wilson Cook Medical Inc., Winston-Salem NC, USA) and a 5 Fr snare were inserted over the guidewire through the accessory channel side by side. The balloon catheter alone was advanced into the bile duct, and then the balloon was expanded with distilled water mixed with contrast. The balloon was pulled back gently towards the duodenal lumen, at which point the snare was opened so that it grasped the base of the papilla next to the inflated balloon. Pulling the balloon catheter toward the duodenal lumen made it easier to snare the papillary lesion entirely by lifting the papilla from the duodenal wall and towards the lumen[3]. *En bloc* papillectomy was performed with a monopolar electrosurgical current (ERBE Vio3, Endocut Q mode). A 5 Fr X 7 cm single pigtail pancreatic plastic stent was placed prophylactically, and a 10 Fr X 10 cm biliary plastic stent was placed after biliary sphincterotomy (Figure 2).

FINAL DIAGNOSIS

Histopathological examination of the retrieved specimen showed ampullary-type mucosa with the central area of erosion associated with mild acute on chronic inflammation in the lamina propria. There was a lobular arrangement of normal looking exocrine pancreatic tissue on the deeper aspect of the lamina propria consistent with the ectopic pancreatic tissue (Gasper Fuentes Classification - Type III) (Figure 3). Thus, the final diagnosis in the presented case was EPAV.

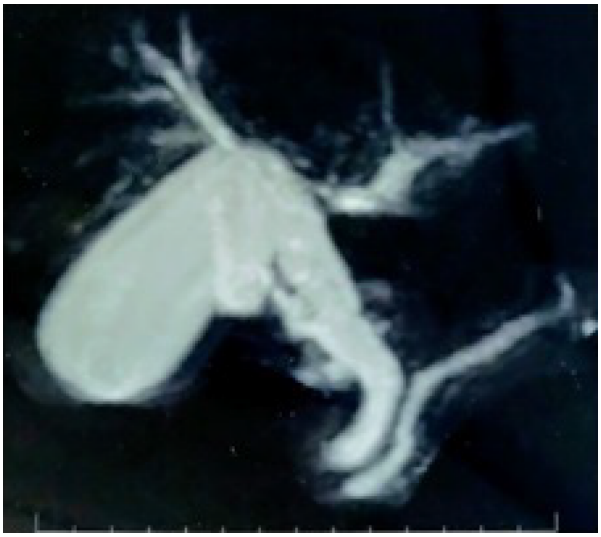

Figure 1 Magnetic resonance cholangiopancreatography showing the dilated common bile duct and pancreatic duct with abrupt cut-off at the ampulla.

TREATMENT

ESP (as described in section 'Diagnostic and Therapeutic intervention') played a vital role as a diagnostic and therapeutic modality in this case.

OUTCOME AND FOLLOW-UP

Post-procedure recovery was uneventful. Both stents were removed after ten days. The patient was asymptomatic at the 15 mo follow-up.

DISCUSSION

Ectopic pancreas is an uncommon developmental anomaly where pancreatic tissue has grown outside its usual location and shows no vascular or anatomical connections to the pancreas. The prevalence of ectopic pancreas is estimated to range from 0.6% to 13.7% of autopsies. It is mostly identified as an incidental finding within the upper gastrointestinal tract, the most typical sites being the stomach (25%-38%), duodenum (17%-36%), and jejunum (15%-21.7%)[1]. Ectopic pancreas is found in all age groups, with most cases in the 4th to 6th decade of life with a male preponderance (male:female ratio is 3:1).

In 1909, Heinrich described the first histological classification system for ectopic pancreas that Gasper Fuentes subsequently modified in 1973[4,5] (Table 1).

The exact incidence of EPAV is unknown. The autopsy series by Dolzhikov *et al*[6] found 48 cases (14.7%) of ectopic pancreatic tissue in 327 routine autopsies of the ampulla of Vater. Notably, the ectopic pancreatic tissue was detected macroscopically in one case only (2.1%) where it was suspected as a tumor of the ampulla of Vater. All other 47 cases had no macroscopic changes. The ectopic pancreatic tissue was positioned in the medial wall of the major duodenal papilla (37.5%), interductular septum (37.5%), lateral wall (16.7%) and the parapapillary area of the duodenum (8.3%). The autopsy findings further stated that the most common site of EPAV was in the walls of the ampulla of Vater and the base of the interductular septum (39.6%) followed by mucosa and the muscular glandular layer of the ampulla of Vater (27.1%). The exocrine variety of ectopic pancreas was the most typical variant (72.9%)[6].

EPAV is an infrequent entity presenting with clinical symptoms in the form of jaundice or abdominal pain. We found only 43 cases of EPAV (excluding bile duct ectopic pancreatic tissue) after an extensive literature search (Table 2)[7-31]. The most extensive series was fourteen cases by Vankemmel and Houcke[12] in 1977. They found these cases after undertaking a systematic study with multiple sections of the region of the ampulla of Vater in a total of 50 pancreaticoduodenectomies (49 – chronic

Table 1 Histological classification of ectopic pancreas

Heinrich classification (1909)
Type I - Contains acini, ducts and islands of Langerhans
Type II - Contains acini and ducts, but lacks endocrine elements
Type III Comprises proliferating ducts, exhibiting neither acini nor endocrine elements
Gasper Fuentes Classification (1973)
Type I - typical pancreatic tissue with acini, ducts, and islet cells similar to the normal pancreas.
Type II (canalicular variety) - pancreatic ducts only.
Type III (exocrine pancreas) - acinar tissue only.
Type IV (endocrine pancreas) - islet cells only.

pancreatitis; 1 – benign ampullary tumor). The age of the 43 cases of EPAV ranged from 32 years to 72 years with almost equal sex distribution. The most common symptoms were jaundice and abdominal pain. Eighty-two percent of cases revealed some degree of biliary dilatation, but it was shown that jaundice did not correlate with the size of the lesion. The size of the tumor ranged from 1 mm to 40 mm. The precise mechanism of CBD obstruction by ectopic pancreas is not known but may be due to mechanical obstruction (pressure by ectopic pancreatic tissue or surrounding tissue edema) or functional obstruction (spasm due to irritative secretions).

The important differential diagnoses for an ampullary lesion in addition to adenomatous lesions are neuroendocrine tumors, adenomyomas, gangliocytic paraganglioma, duodenal duplication cyst, inflammatory pseudotumor and infrequently ectopic pancreas[32-34]. Despite several advances in endoscopic and radiological techniques, the diagnosis of EPAV remains challenging. The unique finding of central umbilication on endoscopy is seldom seen at the ampulla of Vater. An endoscopic biopsy is unhelpful due to the subepithelial nature of the lesion. Radiological techniques such as CT scan and MRCP do not appear to be useful for preoperative diagnosis. Although very few cases had been subjected to EUS according to the previously reported cases, EUS appears to assist in determining the dimensions, layer of origin, adherence to the muscularis propria of the ampullary lesion and any regional lymphadenopathy. EUS-guided fine needle aspiration may help to clarify the diagnosis[35].

Thus, almost all the reported cases of EPAV in the literature are diagnosed after surgical intervention (95%), either in the form of pancreaticoduodenectomy (80%) or transduodenal ampullectomy (10%) or other interventions (10%). This appears to be due to in preoperative diagnosis and suspicion of malignancy. Similar findings were reported in the literature review by Biswas *et al*[26] in 2007. Surgical intervention carries a high rate of morbidity (pancreaticoduodenectomy – 25%-50% and transduodenal ampullectomy – 20%-30%) and mortality (pancreaticoduodenectomy 3-9% and transduodenal ampullectomy – 0%-6%)[36].

ESP is a minimally invasive technique that helps achieve *en bloc* resection of the ampulla for accurate preoperative histology and thus avoids morbid surgical procedures. ESP is a safe procedure that has low morbidity and mortality rates (9.7%–20% and 0.09%–0.3%, respectively)[36]. Lesions less than 5 cm, with no evidence of intraductal growth and no evidence of malignancy on endoscopic appearance (spontaneous bleeding, ulceration) are considered suitable for ESP. However, with advances in endoscopic techniques and armamentarium, the indications are expanding[37]. ESP can provide accurate histology and grading, tumor and lymphovascular invasion staging in cases of malignancy. There are plenty of debatable issues such as the use of submucosal injection, cautery current settings, and the use of prophylactic pancreatic stents *etc.*, in ESP. However, ESP seems to be a feasible and safe modality to achieve *en bloc* resection of ampullary lesions for accurate histology after pre-procedure work up in expert hands.

Our patient presented with new-onset dyspepsia with a ‘double duct sign’ on imaging, giving rise to the suspicion of ampullary malignancy. The age and comorbidity of the patient, the limitations and diagnostic accuracy of endoscopy, biopsies and imaging for ampullary lesions, and suspicion of malignancy made us acquire the histological diagnosis of ampullary lesion before considering a highly morbid surgical intervention. Hence, we carried out endoscopic *en bloc* resection of the

Table 2 Summary of clinical features of patients with ectopic pancreas at the ampulla of Vater

Author	Number of cases	Age (yr)/sex	Symptoms	Tumor size (mm)	CBD dilation	Treatment
Hoelzer[7], 1940	1	54/F	Abdominal pain, jaundice	12	Yes	Inoperable
Mitchell and Augrist [8], 1943	1	68/F	N/A	5	No	N/A
Varay[9], 1946	1	44/F	Jaundice	3	Yes	Pancreaticoduodenectomy
Pearson[10], 1951	1	43/F	Abdominal pain, jaundice	25	Yes	Pancreaticoduodenectomy
Weber *et al*[11], 1968	1	46/F	Abdominal pain, jaundice	8	Yes	Pancreaticoduodenectomy
Vankemmel and Houcke[12], 1977	14	32-53/ NA	13 cases – chronic pancreatitis1 case – ampullary tumor	1-10 mm	NA	14 cases - Pancreaticoduodenectomy
Bill *et al*[13], 1982	1	64/M	Abdominal pain	40	Yes	Pancreaticoduodenectomy
O'Reilly *et al*[14], 1983	1	61/M	Jaundice	8	Yes	Pancreaticoduodenectomy
Laughlin *et al*[15], 1983	1	54/F	Abdominal pain	5	Yes	Ampullectomy
Xu[16], 1991[1]	6	35-60 /5M/1F	6 cases - Jaundice	NA	NA	6 cases - Pancreaticoduodenectomy
Kubota *et al*[17], 1996	1	71/M	Abdominal pain	NA	Yes	Pancreaticoduodenectomy
Hammarström and Nordgren[18], 1999	1	NA/F	Acute pancreatitis	4	No	ERCP, Sphincterotomy & biopsy
Molinari *et al*[19], 2000	1	42/M	Abdominal pain, jaundice, weight loss	4	Yes	Pancreaticoduodenectomy
Chen *et al*[20], 2001	1	59/F	Abdominal pain	12	Yes	Ampullectomy
Contini *et al*[21], 2003	1	72/F	Abdominal pain, jaundice	8	Yes	Ampullectomy
Obermaier *et al*[22], 2004	1	46/M	Jaundice	2	Yes	Pancreaticoduodenectomy
Wagle *et al*[23], 2005	1	70/F	Abdominal pain, jaundice	NA	Yes	Pancreaticoduodenectomy
Filippou *et al*[24], 2006	1	69/F	Jaundice, weight loss	NA	Yes	Ampullectomy
Karahan *et al*[25], 2006	1	67/M	Abdominal pain, jaundice	10	Yes	Laparotomy, biopsy, Choledochojejunostomy
Biswas *et al*[26], 2007	1	47/M	Abdominal pain, jaundice	15	Yes	Pancreaticoduodenectomy
Hsu *et al*[27], 2008	1	54/M	Abdominal pain, jaundice	NA	Yes	Pancreaticoduodenectomy
Rao *et al*[28], 2011	1	48/M	Jaundice	1.5	Yes	Pancreaticoduodenectomy
Ciesielski *et al*[29], 2015	1	54/M	Abdominal pain, jaundice	NA	No	Cholecystectomy with intraoperative CBD BX
Kang *et al*[30], 2016[2]	1	39/F	-	14	No	Endoscopic resection
Nari *et al*[31], 2019	1	49/M	Abdominal pain, Jaundice	NA	Yes	Cholecystectomy with CBD Exploration and Bx; Papillo - Sphincterotomy
Present case, 2021	1	71/M	Abdominal pain	8	Yes	Endoscopic snare papillectomy
Total no of cases	44					

[1]Article in Chinese language.
[2]Article in Korean language.
Ampullary gangliocytic paraganglioma along with ectopic pancreas. CBD: Common bile duct; N/A: Not applicable; NA: Not available.

subepithelial ampullary lesion using a balloon-catheter-assisted ESP. The benign histopathology of the resected specimen avoided morbid surgical intervention in our case.

To our knowledge, this is the first reported case of EPAV managed with minimally invasive ESP.

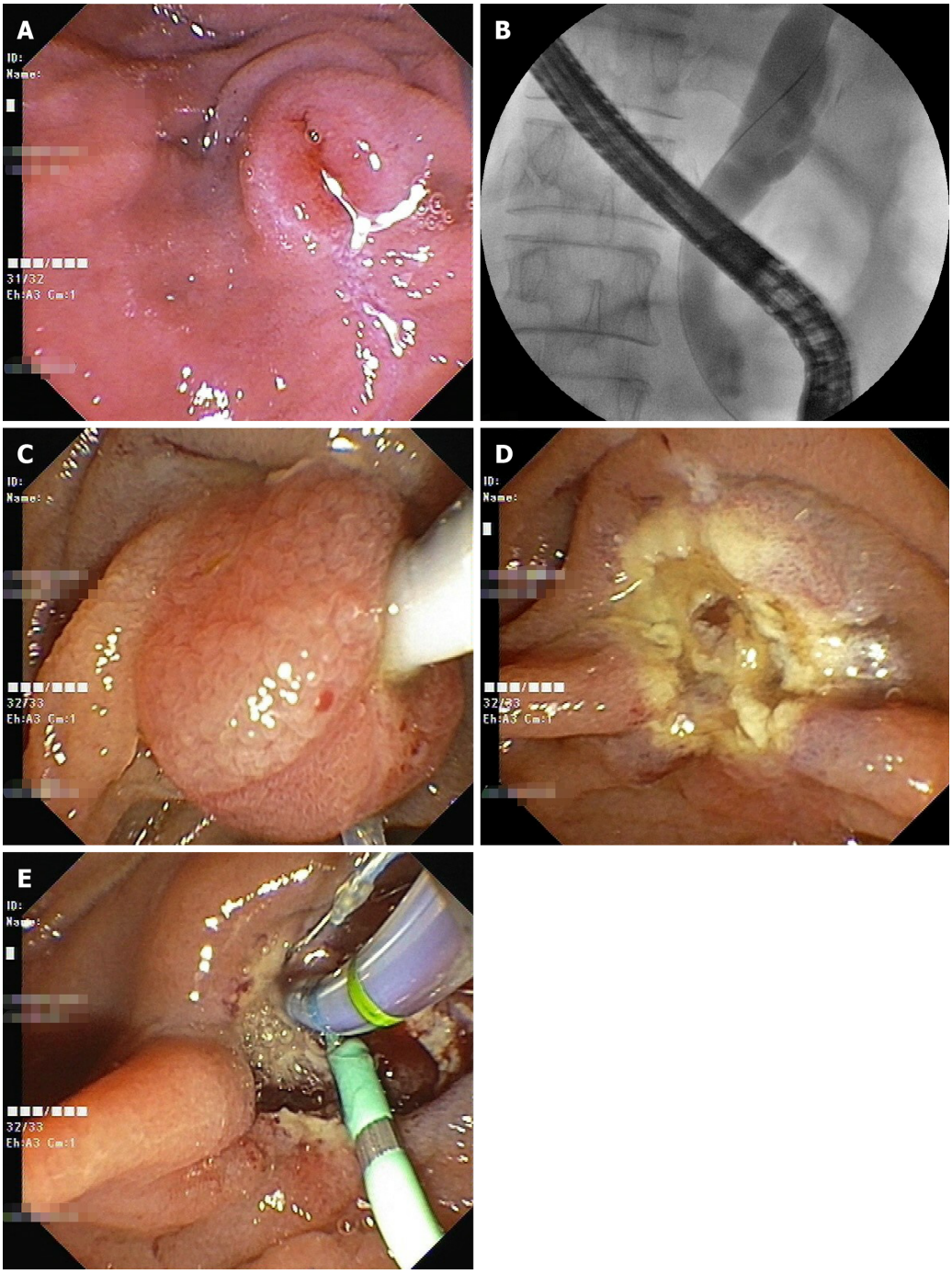

Figure 2 Endoscopic snare papillectomy. A: Endoscopic view of the sub-epithelial ampullary lesion; B: Cholangiogram showing terminal common bile duct (CBD) stricture with upstream dilated CBD after selective CBD cannulation; C: Endoscopic view showing snaring of the papilla while pulling back the expanded balloon within the CBD towards the duodenal lumen; D: Endoscopic view after endoscopic snare papillectomy; E: Endoscopic view of the biliary sphincterotomy and pancreatic stent in place.

CONCLUSION

EPAV mimicking malignancy with a 'double duct sign' is an extremely rare condition. The diagnosis remains challenging even with advances in endoscopic and radiological techniques. Hence, the diagnosis rests totally on morbid surgical interventions or autopsy. This rare entity should be included in the differential diagnosis of subepithelial ampullary lesions. ESP which helps to achieve *en bloc* resection of the ampulla may play a vital role as a diagnostic and therapeutic option for preoperative histological diagnosis and staging to avoid morbid surgical procedures.

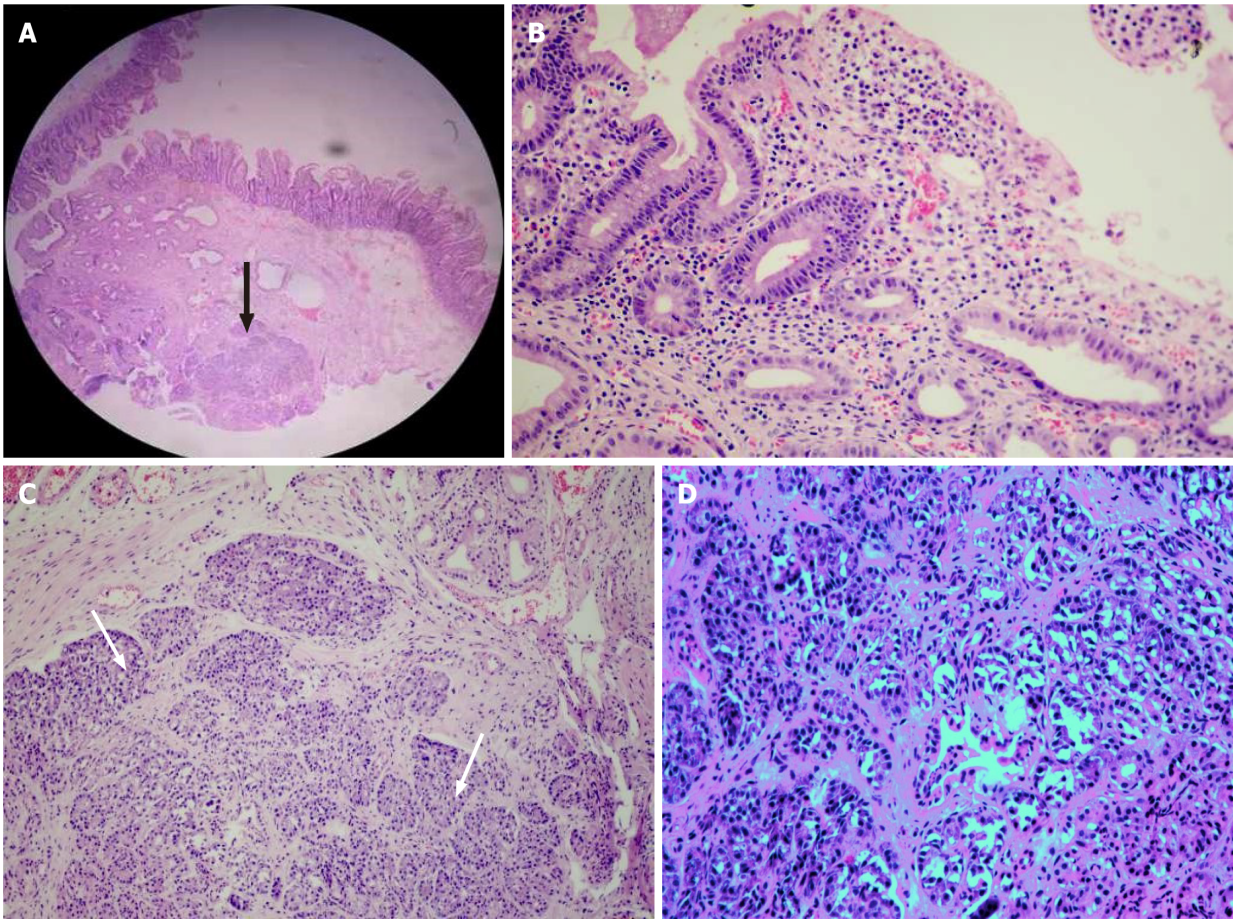

Figure 3 Ectopic pancreas at the ampulla of Vater–histopathology. A: Hematoxylin and eosin (HE) staining showing ampullary mucosa with ectopic pancreatic tissue (arrow) on low power view; B: Ampullary mucosa with inflammatory infiltrates in the lamina propria; C: HE staining showing ectopic exocrine pancreatic tissue (arrows) (20 ×); D: Pancreatic acini (40 ×).

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LETTER TO THE EDITOR

Ethical dilemma of colorectal screening: What age should a screening colonoscopy start and stop?

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Abstract

Many advanced age patients who are diagnosed with colorectal cancer are often not offered surgical treatment due to presumed high risks of the procedure. While there is data to support surgical treatment of colorectal cancer in advanced age patients, screening colonoscopy is not currently recommended for patients older than 85 years. Moreover, recent studies concluded that the incidence of colorectal cancer in patients 80 years and older is increasing. This raises the concern that the current guidelines are withholding screening colonoscopy for healthy elderly patients. Another concern contrary to this would be the new trend of growing incidence of advanced colorectal cancer in the younger patient population. Together they raise the ethical dilemma of how to best utilize colonoscopies as well as surgical intervention, as they are limited resources.

Key Words: Colonoscopy; Colorectal cancer; Screening; Advanced age patient; Screening colonoscopy

Core Tip: Flynn *et al* collected data on surgery in colorectal cancer patients who are 85 years or older. They concluded that surgery in this patient population is safe, and that age alone is not a reason to withhold surgery. The incidence of colorectal cancer in patients 80 years and older is increasing. This raises the concern that the current

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guidelines are withholding screening colonoscopy for healthy elderly patients. On the other hand, a greater number of younger patients are being diagnosed with colorectal cancer. This raises an inevitable ethical dilemma of how to best utilize screening and treatment resources.

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TO THE EDITOR

Continuous development and new advances in medical treatment have extended the life expectancy of the average patient. As a result, the advanced age population is increasing worldwide, with the United States Census Bureau estimating that 16.5 percent of the population in the United States in 2019 is 65 years of age or older[1]. The prevalence of colorectal cancer is increasing alongside extended life expectancies[2,3]. The significance of this is that an increasing number of individuals over the age of 65 years have colorectal cancer and must be screened and treated appropriately. Colorectal cancer continues to be the fourth most common cancer and is the second leading cause of cancer-related deaths worldwide, with many cases diagnosed between 50 and 70 years old[4]. While there are many advanced age patients that are diagnosed with colorectal cancer[5], surgery is frequently withheld due to presumed high risks associated with it given scarce data on surgical treatment outcomes in this patient population. Given this gap in epidemiological data, Flynn *et al*[6] sought to evaluate the post-operative outcomes for patients 85 years or older following colorectal cancer resection as well as compare outcomes in patients who underwent laparoscopic procedures *vs* open abdominal procedures.

Flynn *et al*[6] performed a single institution, retrospective cohort study of patients at The Prince Charles Hospital who underwent resection of colorectal cancer from January 2010 to December 2018. A total of 533 patients were identified: 136 patients were between the ages of 75-85 years old, and 48 patients were 85 years of age at the time of the surgery. Short-term post-operative outcomes were assessed in patients over the age of 85 in terms of operative technique, that being laparoscopic *vs* open colorectal resection. They found that 30-d mortality was similar between the open surgery (9 percent) and laparoscopic intervention (0 percent) groups. They also found no significant difference between the two age groups regarding short-term surgical outcomes in terms of length of stay, grading of complications, and 30-d mortality. Flynn *et al*[6] concluded that resection of colorectal cancer in patients over the age of 85 is safe and effective, and that age alone is not a sufficient reason to withhold surgical treatment in this patient population.

The study had a long follow up period and is well powered with 533 patients. However, only 136 patients were of age 75-85 years old and only 48 patients were at least 85 years old, and therefore were included in the analysis. There were disproportionately more women in the age group 85 years and older, which may have affected the results of the study. The study included analysis on the most common surgical interventions for colorectal cancer, using t-tests, chi squared tests, and Fisher's exact tests with statistically significant results having $P < 0.05$. The study, however, was retrospective as well as a single institution study which may introduce some unknown geographical variables and therefore affect this study's external validity. Lastly, when comparing 30-d mortality between laparoscopic and open methods, it was not accounted for that many of the open cases were more likely to be emergent cases. While Flynn *et al*[6] proposed that surgical intervention is safe in the older patient population with colorectal cancer, this is yet to be confirmed by a larger scale prospective randomized controlled study.

Recent studies concluded that the incidence rate of colorectal cancer in patients who are 80 years or older is increasing[1,2]. Despite that, the American Gastroenterological Association (AGA) 2020 guidelines for colorectal cancer screening suggest that screening should be discontinued once a patient reaches 75 years of age or had less

than ten years of life expectancy, given they have been up to date with screening and have had negative results[7]. The screening remains optional for 75 to 85 years of age and depends on risk factors and comorbidities[7]. AGA also expressed concerns about increasing incidence of colorectal cancer in the younger patient population, and it is now recommended to do a thorough diagnostic evaluation for persons under 50 years of age with colorectal bleeding[7]. Mauri *et al*[8] also discussed how colorectal cancer incidence in individuals younger than 50 years has been increasing by two percent per year since 1994. As of this year, routine screening of the average risk individual should begin at 50 years old, except in African Americans, in whom limited evidence suggests screening at 45 years old[7]. Currently, only patients with significant family history are considered for colorectal cancer screening at 40 years old or earlier[7]. The United States Preventive Services Task Force supported AGA's guidelines to screen adults ages 50 years to 75 years[9]. They concluded with moderate certainty that screening for colorectal cancer in adults of 45 years to 49 years has moderate benefit and that screening of adults of 75 years to 85 years has a small net benefit[9].

It remains unclear how to best utilize colonoscopies, as they are a limited resource. Given the recent concerning trend of a growing number of younger patients being diagnosed with advanced colorectal cancer[10,11], the question is raised whether younger patients could benefit from earlier screening and whether resources should be diverted to a younger patient group. It is important to note that patients of 35 years or younger are more likely to be diagnosed with stage III or IV colorectal cancer[4]. Interestingly, the 5 and 10-year overall survival is also decreased in patients younger than 35 years old[4]. Overall, younger patients diagnosed with colorectal cancer have a worse prognosis because of a higher proportion of advanced stage tumors.

In conclusion, it is evident that elderly individuals are still suffering from colorectal cancer in spite of current screening guidelines. Flynn *et al*[6] emphasized how the elderly population beyond age 85 years are indeed good surgical candidates for resection of colorectal cancer and that age should not be considered when determining surgical risk. With this being said, we propose that screening should be continued in adults over 85 years old despite no available recommendations for screening. Additionally, there is a concerning trend in younger individuals being diagnosed with colorectal cancer prior to initiation of screening at 50 years of age. The increasing incidence of colorectal cancer in the elderly population beyond 75 years of age as well as the increasing incidence of advanced stage colorectal cancer in patients younger than 50 years of age raises an important concern of whether colorectal cancer screening is being done appropriately. If elderly patients do well undergoing surgery, should colorectal cancer screening be stopped and/or reduced at 75 years of age? Likewise, should colorectal cancer screening be initiated prior to age 50 years old? While Flynn *et al*[6] provided no data on long term outcomes and on increase in life expectancy, screening and treatment for the very elderly, or those who are 86 years and older, may not necessarily provide a large gain in additional life-years, especially in comparison to those who are 76-85 years of age. Long term outcomes and effects on the life expectancy is something that still needs to be investigated. We propose that colorectal cancer screening, with colonoscopies in particular, should be extended to both the younger population of 40 years of age as well as patients 75 years or older based on risk factors and patient profile rather than on age as a number alone. By creating a scale or grading system, patients over 75 years and under 45 years could be stratified into high risk *vs* low risk for development of colorectal cancer. This would allow for diverging of resources towards the population(s) that would have the most benefit from screening[12,13]. This idea remains to be proven with prospective large scale randomized controlled studies.

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