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REVIEW

Endoscopic evaluation in diagnosis and management of inflammatory bowel disease

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Abstract

Endoscopy is a keystone in the management of patients with inflammatory bowel disease (IBD). It is the fundamental diagnostic tool for IBD, and can help discern between ulcerative colitis and Crohn's disease. Endoscopic assessment provides an objective end point in clinical trials, and identifies patients in clinical practice who may benefit from treatment escalation and may assist risk stratification in patients seeking to discontinue therapy. Recent advances in endoscopic assessment of patients with IBD include video capsule endoscopy, and chromoendoscopy. Technological advances enable improved visualization and focused biopsy sampling. Endoscopic resection and close surveillance of dysplastic lesions where feasible is recommended instead of prophylactic colectomy.

Key words: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Endoscopy; Capsule endoscopy; Cancer surveillance; Colonoscopy

Core tip: Ileo-colonoscopy remains the most important test in the diagnosis and monitoring of inflammatory bowel disease (IBD). Video capsule endoscopy shows very high sensitivity for small bowel mucosal lesions not accessible to conventional flexible endoscopes. Both techniques facilitate monitoring of response to treatment. Endoscopic activity indices are important for monitoring treatment response and can help identify patients who may benefit from treatment escalation. Colorectal cancer surveillance in patients with IBD is shifting from high frequency random biopsies, to that of high quality visual inspection and targeted biopsies of suspected dysplasia, enabled by technological advances including chromoendoscopy and high-definition endoscopes.

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INTRODUCTION

Endoscopy plays an integral role in the diagnosis and management of patients with inflammatory bowel disease (IBD). In patients with lower gastro-intestinal symptoms suggestive of IBD, colonoscopy with intubation, evaluation and biopsies of the terminal ileum enables assessment of disease activity and extent, severity and histological evaluation (Figure 1). Detailed real-time endoscopic examination can help in delineating between ulcerative colitis (UC) and Crohn's disease (CD), and assessing disease behavior in patients with CD. Upper gastrointestinal (GI) endoscopy enables assessment and diagnosis of upper GI CD. The diagnosis of CD can be difficult, small bowel and upper gastrointestinal investigations are recommended after ileo-colonscopy[1]. Video capsule endoscopy (VCE) is useful in the diagnosis and evaluation of patients with IBD, especially non-stricturing small bowel disease.

Endoscopy enables objective measurement of disease response to medical and surgical therapies. Colorectal cancer (CRC) surveillance is imperative in patients with longstanding colonic IBD, except in patients with proctitis or colonic CD limited to only involving one segment of the colorectum[2]. Although essential in the management of patients with IBD, endoscopy is invasive and expensive, placing a burden on patients[3] and healthcare systems. Newer, less invasive tests have not replaced the use of endoscopy in our patients, but rather are used in tandem. Endoscopic ultrasound, and therapeutic endoscopic techniques such as stent placement and balloon dilation are covered elsewhere[4]. This review will focus on paramount roles that endoscopy plays in the management of adults with IBD.

ENDOSCOPIC ASSESSMENT OF DISEASE

Ileo-colonoscopy is the gold standard investigation for the diagnosis of UC and ileo-colonic CD. Real time endoscopic assessment can help delineate between CD and UC, although no endoscopic feature is specific for either. The key features that suggest a diagnosis of CD include perianal disease (careful examination of the perianal region at the time of endoscopy, prior to scope insertion, can reveal fistula tract openings, fissures, strictures and tags), skip lesions, cobblestoning, fistula and strictures, as well as isolated ileal disease. A diagnosis of UC is favoured by continuous colonic inflammation in affected bowel, with obvious demarcation between inflamed and non-inflamed bowel[2]. Patients with UC can be mistaken to have CD secondary to backwash ileitis and "skip lesions"; attributed to a caecal patch[5], characterised by localized peri-appendiceal inflammation, and from treatment effect giving the impression of a spared distal colon[6]. To avoid this pitfall, it is recommended to document endoscopic features in each colonic segment and terminal ileum at index ileo-colonoscopy, in addition to taking serial segmental biopsies (from affected mucosa and any raised lesions, and normal appearing mucosa)[2,4]. The presence of fistulae and strictures increase the index of suspicion for CD rather than UC, however these need to fully investigated (to outrule mimics and to ensure that a CRC associated with UC is not dismissed).

In patients with acute severe colitis, a flexible sigmoidoscopy without purgatives is recommended as initial endoscopic investigation[2], to confirm the presence, extent and severity of inflammation, to outrule pseudomembranes (although this may be absent in IBD patients with co-morbid *Clostridium difficile* infection) and obtain tissue for histological analysis (which is useful to outrule cytomegalovirus infection in immune suppressed patients). Early endoscopic assessment can help identify patients at risk of needing rescue medical therapy[7].

One must be aware of conditions that can masquerade as flares of IBD (Table 1)[8-24]. Endoscopic assessment can be useful; however many conditions such as infective colitis, the findings can be non-specific and overlap with features of IBD. The founding tenets of medical practice: History taking (including a careful drug and travel history) and clinical examination are to be used in tandem with other laboratory, endoscopic and histologic assessment.

ENDOSCOPIC SCORING SYSTEMS

Endoscopic evaluation is the gold standard to assess objective signs of mucosal inflammation and healing, frequently used in clinical trials. However, inter-observer variability in the assessment of endoscopic findings in patients with IBD has led to the development of several endoscopic scoring systems for both CD and UC, few of which have been validated. Scoring systems aim to interpret endoscopic disease appearance and translate these findings into a quantified score. Baron *et al*[25] introduced the first scoring system for UC in 1964, they recognised the importance of discontinuous variables in describing endoscopic findings to reduce inter-observer variability[25]. With time numerous other scoring systems[26,27] have been introduced, mainly for use as outcome measures in clinical trials, Table 2 lists some of the commonly used endoscopic indices. Ensuring objective endoscopic evidence of baseline disease activity in clinical trials is associated with reduced placebo remission rates[28,29].

Endoscopic scoring systems can be used in clinical practice to identify patients who may benefit from escalation of medical therapy. In acute severe colitis (ASC), the UCEIS helps predict patient outcomes. Nearly 80% of patients admitted to a single institution with ASC, recording a UCEIS score $\geqslant$ 7 required rescue medical therapy with infliximab or ciclosporine[7]. When UCEIS was $\geqslant$ 5, 33% of patients required colectomy during follow-up, compared with 9% of patients with UCEIS $\leqslant$ 4[7].

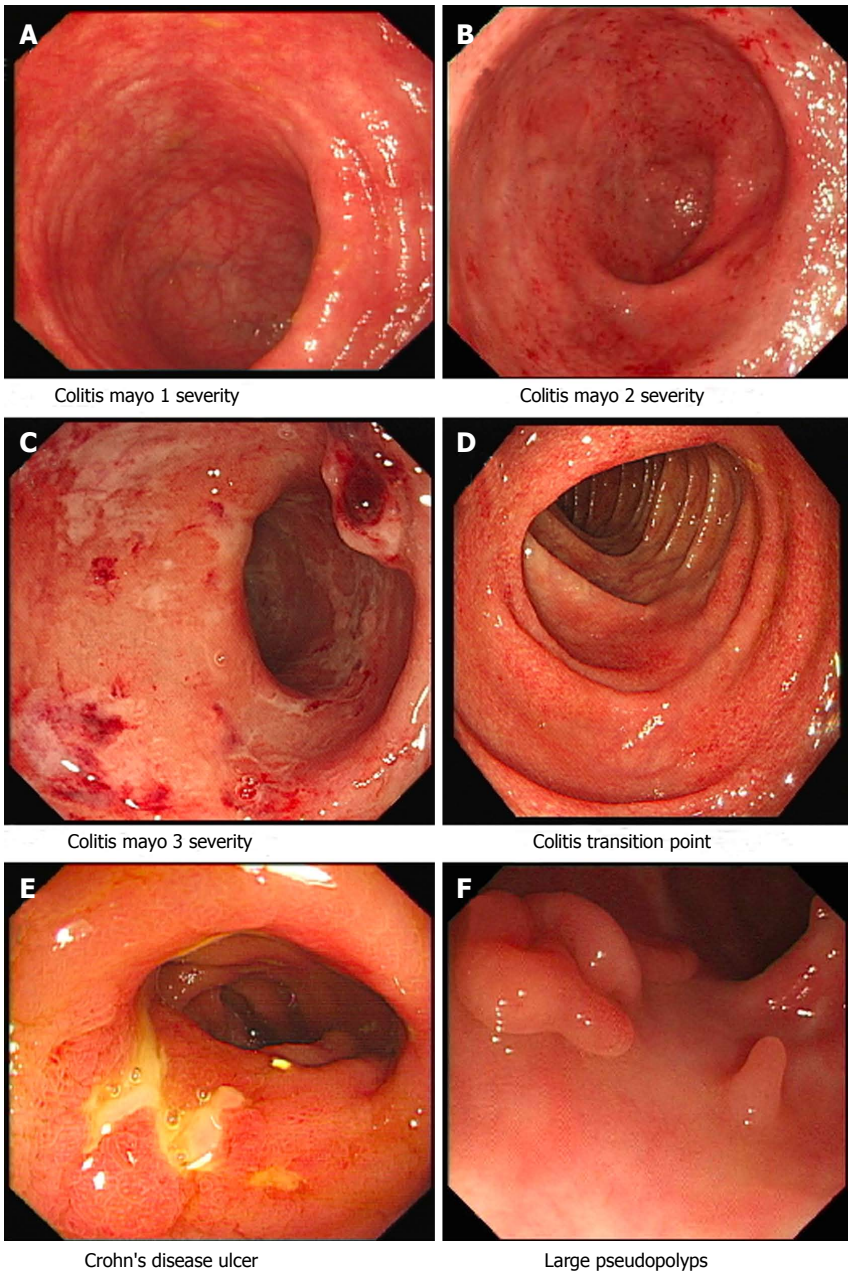

Figure 1 Common endoscopic findings in patients with inflammatory bowel disease.

Early post-operative endoscopic assessment, using the Rutgeert's score, in patients with CD who undergo intestinal resection is useful in predicting the risk of clinical relapse and need for future surgery[30]. Recent data suggest the Rutgeerts score, which quantifies the degree of recurrent mucosal lesions in the pre-anastomotic ileum, can improve selection of patient's who require escalation of treatment to reduce risk of post-operative disease recurrence[31]. A recent study escalated treatment of patients with a Rutgeert's score of i2 or greater, this was associated with significant improvements in mucosal healing and endoscopic recurrence, compared to standard treatment[31]. Prophylactic postoperative Azathioprine use was not superior to endoscopic driven therapy in a study of patients with CD deemed to be high risk for recurrence, in which the primary endpoint was endoscopic remission (i0-i1) at week 102 post-op[32].

Endoscopic response can also help predict patient outcomes. The International Organization for the study of IBD recommends defining endoscopic response as a decrease from baseline in CDEIS or SES-CD score of at least 50%[33]. Mucosal healing and endoscopic response at 26 wk, was predictive of corticosteroid free remission at week 50 in a subgroup analysis of 172 patients from the SONIC trial[34].

CAPSULE ENDOSCOPY

When CD is diagnosed at ileo-colonoscopy, it is recom-

Table 1 Mimics of active inflammatory bowel disease

Condition	Comment	Ref.
ITB	Skip lesions, cobblestoning of mucosa, apthous and linear ulcers are found more frequently in patients with CD compared to ITB	[8,9]
	Patulous ileocaecal valve, transverse ulcers more common in ITB	[9,10]
Segmental colitis associated with diverticulosis	Inflammatory changes limited to the segment of bowel containing the diverticula with rectal sparing	[11]
CMV colitis superimposed in IBD	Mucosal bleeding on light contact, wide mucosal defects and punched out ulcers more common in UC complicated by CMV	[12]
	The presence of ulcers helps predict CMV in patients with UC but not CD	[13]
	Other studies could not identify striking differences on endoscopy	[14]
	Biopsies of inflamed mucosa needed assess for inclusion bodies characteristic for CMV colitis	
Clostridium difficile associated disease	Pseudomembranes seldom occur in patients with IBD and *Clostridium difficile* infection	[15]
Campylobacter colitis	Can produce similar appearences to that of UC, detailed endoscopic assessment can help discern from IBD, in addition to stool cultures and biopsies	[16,17]
Ischaemic colitis	Typically a segmental disease, with normal mucosa proximal and distal to affected region of colon	[18]
	Rectum usually spared	[19]
Medication effects	Endoscopic assessment of Ipilimumab induced colitis reveals absent vascular pattern, and erythema in most patients. Variety of endoscopic features described in recent retrospective study	[20]
	NSAID induced colopathy can affect the whole colon, but has a right sided predominance. Colonic findings include ulceration, strictures and diaphragm like strictures	[21]
Solitary rectal ulcer syndrome	Ulcerative lesions (either single or multiple) most common finding, however can present with erythema or polypoid lesions	[22]
Behçet disease	Predilection for ulcers in the ileo-caecal region. Ulcers are typically larger than 1 cm, deep and have discrete margins	[23]
Amebic colitis	Endoscopic findings can vary from procto-sigmoiditis to right colonic involvement, biopsy and microscopic identification of Entamoeba species useful in evaluation of suspected amebiasis	[24]

IBD: Inflammatory bowel disease; ITB: Intestinal tuberculosis; CMV: Cytomegalovirus; CD: Crohn's disease; NSAID: Non-steroidal anti-inflammatory drug.

Table 2 Endoscopic activity indices

Endoscopic score	Comment	Variables	Ref.
Ulcerative colitis endoscopic index of severity	Easy to use. Scoring based on area of bowel most severely affected. Correlates well with patient reported symptoms	Vascular pattern, bleeding, ulcers/erosions	[83-85]
Mayo endoscopic score	Commonly used in clinical practice, four point scale (0-3) (Figure 1)	Vascular pattern, erythema, bleeding, friability, erythema, erosions and ulcers	[86]
Modified mayo endoscopic score	Total endoscopic mucosal activity accounted. Easy to use. Correlates well with clinical and histological activity	Combines disease extent with MES severity	[87]
Ulcerative colitis colonoscopic index of severity	Total score based on parameters throughout the colon. Validated	Vascular pattern, ulceration, granularity, friability/bleeding	[88]
CDEIS	Complex scoring system, time consuming. Validated. Utilised to monitor endoscopic response to treatment	Deep and superficial ulceration, surface of ulcerations, surface of lesions	[33,89]
SES-CD	Correlates well with CDEIS and clinical parameters Utilised to monitor endoscopic response to treatment	Ulcer size, stenosis, ulcerated and affected surfaces	[34,90]
Rutgeerts' score	To assess degree of postoperative recurrence at ileo-colonic anastomosis in Crohn's disease. Easy to use in clinical practice	Apthous ulceration, large ulcers, stenosis, nodularity and ileitis	[30]

SES-CD: Simple endoscopic score for Crohn's disease; CDEIS: Crohn's disease endoscopic index of severity.

mended to assess the extent of small bowel disease. VCE can be useful in the management of patients with known[35,36] or suspected IBD[37], by visualising mucosa not readily accessible by standard endoscopy. VCE is generally safe in patients with CD[35], the main complication of VCE is that of capsule retention. This can be reduced by excluding patients with known or suspected obstruction, and testing with patency capsule (although recent retrospective study of patients with CD capsule retention was not reduced by use of patency capsule in all patients, compared to selective use of patency capsule[38]). Imaging studies or patency capsule is recommended prior to capsule endoscopy in patients with known small bowel CD[4].

A prospective, multi-centered, blinded cohort study of patients with suspected CD found that VCE is equivalent

to ileo-colonoscopy in detecting ileo-caecal inflammation, and is superior to small bowel follow through studies[37]. In patients with suspected inflammatory phenotype CD, VCE is safe and can confirm diagnosis of CD in the presence of a normal ileo-colonoscopy[37]. VCE was superior to MRE and CTE in detecting mucosal lesions proximal to the terminal ileum, in a blinded prospective study of patients with suspected or newly diagnosed CD[39]. However, some authors have suggested that there is a trade-off between sensitivity and specificity with VCE. In particular, while VCE has greater sensitivity for small bowel mucosal lesions in individuals with suspected CD, there is a risk that presence of minor mucosal erosions can give rise to "false positive" diagnosis[40]. This underlines the importance of use of a scoring system (the Lewis index[41], is validated[42] and is comprised of three parameters: stenosis, ulceration and mucosal oedema).

A recent retrospective study of CD patients with isolated small bowel disease, undergoing VCE at diagnosis, found that moderate to severe disease as defined by the Lewis Score[41]; was associated with need for hospitalisation and corticosteroid use after 12 mo follow-up[43]. Conversely a retrospective study of patients with suspected CD, a low Lewis score (defined as < 135) is associated with a low probability CD diagnosis being confirmed on follow-up[44]. VCE also enables assessment of mucosal healing after initiating immunomodulator or biological therapy[45].

VCE may be contraindicated in patients with stricturing CD. MRE and CTE are utilized inpatients with complicated phenotype CD requiring small bowel evaluation, although their use can be limited by patient factors and local availability. Recently the magnetic resonance index of activity has been shown to correlate well with the SES-CD in the assessment of ileal lesions[46].

CRC SURVEILLANCE

Following index endoscopy, endoscopic re-evaluation to guide treatment is typically repeated every few years. Endoscopic surveillance is recommended to commence after 8[2,4,47] to 10[48] years from initial symptoms in patients with colonic disease, as some patients are at increased risk of developing CRC[49]. Patients with extensive colonic disease, concomitant PSC[50], young age at diagnosis, history of sporadic CRC in first degree relative, advanced age[51], severe inflammation[52] and longer duration of disease are at increased risk of developing CRC[53,54]. The optimal surveillance interval is uncertain, the major gastrointestinal societies have differing recommendations[2,4,47,48] but most now increasingly recognize that surveillance efforts are best focused on those at highest risk.

The goal of surveillance is to reduce CRC related mortality and morbidity, by detecting asymptomatic CRC and premalignant lesions. The risk of CRC in patients with IBD is less than previously reported (meta-analysis of population based studies described a pooled standardized incidence ratio of 1.7[53]), and is not increased in all patients. The incidence of CRC in patients with UC has decreased in the last few decades[55]. A nationwide Danish cohort found that patients diagnosed with UC in the 1980s were at increased risk of CRC, however that excessive risk of CRC has declined and no longer exceeds that of the general population[54]. CRC pathogenesis in patients with IBD is thought to occur mainly from dysplasia rather than adenoma to CRC sequence. Patients with colonic CD (3.9%) and UC (6.3%) were found to have reduced risk of developing sporadic adenomatous polyps compared to control population (25.9%)[56]. Interestingly patients with small bowel CD had similar rate of adenomas as control population[56].

The development of flat dysplasia in patients with colonic IBD makes endoscopic surveillance challenging. Traditionally surveillance consisted of numerous random biopsies (4 quadrant biopsies every 10 cm, minimum of 32 biopsies[47]), in addition to any suspicious lesions. The aim of random biopsy sampling is to detect dysplasia, often without visible mucosal abnormalities, before to progresses to CRC. However the principle that dysplasia in patients with IBD occurs usually occurs without visible mucosal abnormalities, has been challenged[57,58].

In patients with UC diagnosed with LGD, risk factors for progression to HGD or CRC include lesions greater than 1 cm, and lesions invisible on endoscopy[59]. Patients with UC were found to have a low risk of progression to CRC after resection of polypoid dysplasia, in a meta-analysis not including any studies using chromoendoscopy[60]. This finding supports current practice of resection and surveillance of raised lesions with dysplasia[49] (although non-adenoma like raised lesions with dysplasia are usually difficult to resect by polypectomy). In a prospective study of patients with undergoing surveillance colonoscopy, CE was superior to random biopsy or WLE in detecting dysplasia[61]. These findings contrast with a large retrospective study, which found no difference between CE and WLE with random and targeted biopsies, in detection rates for dysplasia[62]. Narrow band imaging has not been shown to be superior to white light endoscopy for detecting dysplasia in patients with IBD[63,64]. CE with targeted biopsies are more cost effective than traditional WLE endoscopy with random biopsies[65], and are recommended as preferred method of surveillance in recent guidelines[2,4,48].

The incidence of CRC amongst patients with IBD enrolled in regular surveillance appears to be lower than previously reported[52,66], likely reflecting improvements in medical care and quality of endoscopies performed; with both of this factors benefiting from technological advances. In patients with IBD who develop CRC, those involved in surveillance programmes have better survival rates than those not enrolled in regular surveillance[67].

MUCOSAL HEALING

Clinical remission and endoscopic remission correlate poorly[68], especially in CD. VCE reveals that in patients with small bowel CD in clinical remission, mucosal healing (defined as a Lewis score < 135) is rare[69]. Mucosal healing has become an important treatment target in managing patients with IBD, and is associated with improved outcomes[70,71]. A recent meta-analysis found that mucosa healing was associated with long-term clinical remission, corticosteroid free remission and avoidance of colectomy[71]. Mucosal healing at 26 wk was predictive of corticosteroid free remission at week 50 in a subgroup analysis of 172 patients from the SONIC trial[34]. Considerations influencing the choice of modality to assess mucosal healing are discussed in a recent review[72], colonoscopy is the gold standard in ileo-colonic disease. Faecal calprotectin has been proposed as a surrogate non-invasive marker for mucosal healing, which may rationalize the use of endoscopy in assessing mucosal healing[73]. Faecal markers may not, however, have adequate negative predictive value in all patients, especially those with limited, small bowel disease.

There is a discrepancy between the endoscopic and histological assessment in UC[74], especially mild disease[75]. Endoscopic mucosal healing or inactivity, does not always equate to quiescent microscopic disease[76]. Histological remission is not yet a routinely sought objective in the management of IBD[77], however histological remission better predicts need for hospitisation and corticosteroid use in patients with UC compared to endoscopic remission[78]. A recent prospective study of 179 patients with UC in clinical remission, revealed an association between baseline histology grade and risk of clinical relapse[79]. Patients with an elevated histological grade (Geboes[80] grade $\geqslant$ 3.1) at baseline had a relative risk of clinical relapse, over 12 mo follow-up, of 3.5 (95%CI: 1.9-6.4, P < 0.0001)[79]. To aid assessment of histological disease activity in patients with IBD, there needs to be close co-operation between endoscopists and histopathologists[81].

Confocal laser endomicroscopy has the potential to provide real-time microscopic assessment ("endopathology"), which can help predict disease relapse in patients with endoscopic and clinical remission[82].

CONCLUSION

Endoscopy remains integral in the diagnosis and management of IBD, endoscopic disease assessment is essential for objective monitoring of treatment response. Endoscopic severity scores facilitate monitoring of endoscopic response to treatment, and help identify patients who may benefit from escalation of therapy.

The paradigm of CRC surveillance in patients with IBD is shifting from high frequency random biopsies, to that of high quality visual inspection and targeted biopsies of suspected dysplasia, enabled by technological advances including CE and high-definition endoscopes. Current practice in the management of dysplasia entails resection of dysplastic lesions where possible, rather than colectomy.

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REVIEW

Colorectal cancer screening: Opportunities to improve uptake, outcomes, and disparities

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Abstract

Colorectal cancer screening has become a standard of care in industrialized nations for those 50 to 75 years of age, along with selected high-risk populations. While colorectal cancer screening has been shown to reduce both the incidence and mortality of colorectal cancer, it is a complex multi-disciplinary process with a number of important steps that require optimization before tangible improvements in outcomes are possible. For both opportunistic and programmatic colorectal cancer screening, poor participant uptake remains an ongoing concern. Furthermore, current screening modalities (such as the guaiac based fecal occult blood test, fecal immunochemical test and colonoscopy) may be used or performed suboptimally, which can lead to missed neoplastic lesions and unnecessary endoscopic evaluations. The latter poses the risk of adverse events, such as perforation and post-polypectomy bleeding, as well as financial impacts to the healthcare system. Moreover, ongoing disparities in colorectal cancer screening persist among marginalized populations, including specific ethnic minorities (African Americans, Hispanics, Asians, Indigenous groups), immigrants, and those who are economically disenfranchised. Given this context, we aimed to review the current literature on these important areas pertaining to colorectal cancer screening, particularly focusing on the guaiac based fecal occult blood test, the fecal immunochemical test and colonoscopy.

Key words: Fecal occult blood test; Fecal immunochemical test; Colonoscopy; Neoplasia; Polyp

Core tip: Colorectal cancer (CRC) screening has become a standard of care in industrialized nations for those aged 50 to 75 years. While CRC screening has been shown to reduce the incidence and mortality of CRC, it is a complex multi-disciplinary process that frequently presents challenges to implementation. This is a focused review on 3 pivotal areas of CRC screening that require improvement: (1) suboptimal uptake of CRC screening; (2) poor outcomes manifesting as missed lesions and adverse events during the screening process; and (3) ongoing disparities among marginalized populations.

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INTRODUCTION

Colorectal cancer (CRC) is a critical health concern. It is the second most commonly diagnosed cancer in women and the third most commonly diagnosed cancer in men[1,2], with North America, Europe and Australia having the highest incidence rates worldwide[2,3]. In part due to the increasingly widespread adoption of Western dietary and lifestyle behaviors, the incidence of CRC is also rising in developing nations[3,4]. Therefore, CRC represents a significant economic burden globally, with Medicare treatment costs within the United State estimated at over $7 billion dollars[5]. This highlights the importance of effective CRC screening with the intent to minimize the CRC disease burden through the removal of adenomatous neoplasia and the detection of CRC at an earlier stage at which point treatment is more successful. CRC screening has been shown to be effective at reducing the incidence and mortality of CRC[6-13]. In addition, economic analyses[14-18] evaluating CRC screening have highlighted it as a cost-effective, and possibly cost-saving, intervention[18]. Consequently, many North American organizations including the Canadian Association of Gastroenterology (CAG)[19], the American College of Gastroenterology (ACG)[20], the Canadian Task Force on Preventative Health Care (CTFPHC)[21], the United States Preventative Services Task Force (USPSTF)[22] and the United States Multi-Society Task Force[23] have endorsed multiple different screening methods including: Fecal occult blood tests (FOBTs) such as the guaiac-based (gFOBT) as well as fecal immunochemical (FIT) tests, fecal DNA tests, flexible sigmoidoscopy (FSIG), colonoscopy (CSPY), and computed tomographic colonography (Table 1).

Although the concept of screening is intuitively simplistic, the implementation of population-based CRC screening is a complex interdisciplinary process. Most notably, participation in initial and subsequent CRC screening have still not reached well-recognized benchmarks[24,25]. Moreover, screening test performance is an ongoing area of concern, given the potential for missed neoplasia as well as procedure-related adverse events. These issues are further exacerbated by persistent disparities in CRC screening among marginalized populations[26]. Considering these issues, we sought to review these important areas and propose opportunities for optimization. For the purposes of this article, we will focus on the two predominant methods for CRC screening used in Canada and the United States, namely FOBTs (including gFOBT and FIT) and CSPY.

UPTAKE AND RETENTION

For CRC screening to be effective, high levels of participation in initial and subsequent CRC screening are required. Likewise, when gFOBT or FIT are used, abnormal results must be promptly followed by an evaluation with CSPY[27]. Failure at any of these steps carries with it the potential to impair the effectiveness of CRC screening.

Initial CRC screening

In the United States, CRC screening uptake appears to be increasing[28]. Unfortunately, estimates still remain below national targets[28]. Based on findings derived from the 2010 National Health Interview Survey, a United States-based survey assessing a representative sample of the United States civilian population, only 59% of those aged 50 to 75 years were up-to-date with CRC screening as per the 2008 USPSTF recommendations (high-sensitivity FOBT every year; or FSIG every 5 years and high-sensitivity FOBT every 3 years; or CSPY every 10 years)[24]. In comparison, estimates gathered from the 2012 Behavioral Risk Factor Surveillance System survey, another United States-based survey assessing a representative sample of the United States civilian population, close to 65% of those aged 50 to 75 years were up-to-date with CRC screening as per the same USPSTF recommendations[28]. Of note, a concerning finding was that 28% stated they had never been screened for CRC.

In Canada, CRC screening rates also appear to be increasing, but they are similarly below current national benchmarks[27]. Estimates from the 2012 Canadian Community Health Survey, a Canadian-based survey assessing a representative sample of the Canadian population, only 55% of those aged 50 to 74 years were up-to-date with CRC screening (FOBT every 2 years; or FSIG or CSPY every 10 years)[25]. In recent years, Canada has made a concerted effort to transition to nationwide programmatic screening. Emerging data from 5 Canadian provinces between 2009 and 2011 collated by the Canadian Partnership Against Cancer (CPAC) revealed that participation in programmatic CRC screening (either gFOBT or FIT) ranged from 5% to 37% only[27]. These estimates captured programmatic CRC screening alone whereas CRC utilization considers both programmatic and non-programmatic CRC

Table 1 Colorectal cancer screening recommendations for guaiac-based fecal occult blood test, fecal immunochemical test and colonoscopy among asymptomatic average-risk adults

	USPSTF[22]	CTFPHC[21]	CAG[19]	USMSTF[23]	ACG[20]
Publication year	2016	2016	2010	2008	2008
Country	United States	Canada	Canada	United States	United States
Age cut-off	50 to 75[2]	50 to 74	50 to 75[2]	Start at 50	Start at 50
gFOBT	Every year	Every 2 yr	Every 1 or 2 yr[3]	Every year	Every year
FIT	Every year	Every 2 yr	Every 1 or 2 yr[3]	Every year	Every year
CSPY	Every 10 yr	Not recommended	Not recommended[4]	Every 10 yr	Every 10 yr
Preferred test[1]	No preference	No preference	FIT[5]	CSPY	CSPY

[1]Preferred test considering gFOBT, FIT and CSPY as potential CRC screening tests; [2]CRC screening can be considered between ages 76 to 85 years on an individual basis; [3]Frequency of testing dependent on jurisdictional resources; [4]Recommendation against CSPY for population-based CRC screening. CSPY was a recommended option for opportunistic screening; [5]Preference in the setting of programmatic CRC screening. ACG: American College of Gastroenterology; CAG: Canadian Association of Gastroenterology; CRC: Colorectal cancer; CSPY: Colonoscopy; CTFPHC: Canadian Task Force on Preventative Health Care; FIT: Fecal immunochemical test; gFOBT: Guaiac-based fecal occult blood test; USMSTF: United States Multi-Society Task Force; USPSTF: United States Preventative Services Task Force.

screening. FIT or gFOBT utilization ranged from 6% to 44% in 2009, and increased to 12% to 58% in 2011[27].

Confirmatory testing with CSPY

Follow-up CSPY after an abnormal gFOBT or FIT result has also been highlighted as an area requiring further optimization. In 2001, a prospective study of 2410 participants aged ⩾ 70 years were assessed, of which 212 has a positive gFOBT result[29]. After 6 mo and 1 year, only 22% and 42%, respectively, had undergone endoscopic evaluation. In Canada between 2009 and 2011, 45% of subjects participating in programmatic screening underwent CSPY within 60 d and 81% underwent CSPY within 180 d after an abnormal gFOBT or FIT[27]. There were significant variations between provinces whereby estimates ranged from 68% to 90%.

Serial screening at subsequent intervals

To benefit from CRC screening, retention during subsequent screening cycles is required. In a United States-based cohort of 11110 participants who had undergone gFOBT for CRC screening, only 44% completed repeat testing in the next 2-year follow-up period[30]. In another large United States-based retrospective cohort of over 1 million participants across 136 Veteran Affairs medical centers, only 41% of men and 44% of women received adequate screening over a 5-year period (FOBT in 4 of the 5 years or ⩾ 1 FOBT as well as CSPY, FSIG or double-contrast barium enema)[31]. When stratifying outcomes based on the 384527 men and 10469 women who only used FOBT, only 14% (both groups) completed FOBT testing in 4 of the 5 years.

While findings from programmatic screening are more optimistic, they are still not ideal. Two studies from the Netherlands that assessed gFOBT and/or FIT showed that participation in the second round of testing ranged between 63% to 86%[32,33]. In the evaluation of an Italian FIT-based CRC screening program over 4 rounds in a 7-year period, participation ranged between 56% to 63%[34].

POOR OUTCOMES

Test performance is a major determinant of health outcomes, especially considering the potential clinical and economic implications of false positive and false negative results. In the setting of CRC screening, false negative findings equate to missed neoplastic lesions. This delay in diagnosis can have a profound impact on outcomes whereby potentially curable disease is rendered palliative. Likewise, false positive results can lead to additional healthcare resource use in the form of unnecessary CSPYs. Although CSPY is a generally safe procedure, it is not without adverse events, specifically post-polypectomy bleeding and perforation.

Fecal occult blood test performance

In comparing FIT and gFOBT, FIT has clearly emerged as the superior option for CRC screening[35,36], which is now reflected in both national[19] and international[37] guidelines. However, FIT still has some inherent limitations. In a recent meta-analysis of 19 unique evaluations, FIT sensitivity was 79%[38]. However, with adjustment of the FIT cut-off, sensitivity ranged from 67% to 86%. Interestingly, single sample FIT had similar sensitivity as several sample FIT. Aside from modifying the quantitative threshold to define test positivity, other factors have been identified that affect FIT sensitivity. For example, the version of FIT being used has been implicated in test performance variability. In the Taiwanese nation-wide screening program, 956005 participants underwent CRC screening using either OC-Sensor (Eiken Chemical Co, Tokyo, Japan) or HM-Jack (Kyowa Medex Co Ltd, Tokyo, Japan). Even though identical positive test cut-offs (20 μg hemoglobin/g feces) were used[39], significant differences between the two quantitative FITs were found when examining the positive predictive value for cancer and rates of interval cancer. Additional factors that affect FIT performance include processing time and temperature. As FIT is based on the detection of the protein globin, it is susceptible to false-negative results secondary to protein degradation. In a 2009 study, van Rossum

et al[40] compared FIT performance based on time between sampling and laboratory delivery (< 5 d *vs* ⩾ 5 d). There was a significant reduction in adenoma detection rate (ADR) when samples were returned after ⩾ 5 d. Moreover, it was found that mean fecal hemoglobin values decreased by 29 ng hemoglobin/mL buffer solution per day. In regards to the effect of temperature on FIT result, an Italian FIT CRC screening program found that an increase in temperature of one degree Celsius reduced the likelihood of FIT positivity by 0.7%[41]. Similarly, there was a 13% reduction in detecting CRC or advanced adenomas in the summer compared to the winter.

Missed lesions on CSPY

It is well documented that CSPY may not reliably prevent CRC[42-47] because of the potential of missed lesions[47,48] or incomplete polypectomy[49,50] at initial procedure. This is further compounded by variations in CRC tumorigenesis[51]. In a recent meta-analysis that characterized the miss rates of polyps which were corroborated by tandem CSPY, the pooled miss rate for polyps of any size was 22%[48]. For adenomas, the pooled miss rates were 2.1% for adenomas ⩾ 10 mm, 13% for adenomas 5 to 10 mm and 26% for adenomas 1 to 5 mm. Moreover, there is marked variability in ADR between endoscopists[52-55] in which estimates have ranged from 7% to 44%[52-55]. In a 2010 study that evaluated 186 endoscopists alongside 45026 patients (188788 person-years), ADR was significantly associated with the risk of interval cancer[56]. In comparing ADR < 20% *vs* ADR ⩾ 20%, the hazard ratios were > 10 for interval CRC. In a 2014 study of 136 endoscopists, it was determined that a 1% increase in ADR was associated with a 3% decrease in risk of CRC[57]. The aforementioned evidence underscores the importance of ADR and reinforces its value as an important CSPY quality indicator. This has been endorsed by multiple societies[58,59], with the American Society for Gastrointestinal Endoscopy (ASGE) recommending an ADR of ⩾ 25% (⩾ 30% in men, ⩾ 20% in women) among asymptomatic average-risk individuals[59].

Another limitation of CSPY pertains to proximal CRC (lesions proximal to the splenic flexure)[42,45,60]. Proximal lesions are different from those that are distal in many ways. For instance, proximal masses can be missed secondary to inadequate bowel preparation[59], complicated by incomplete CSPY[61], and prone to suboptimally removed lesions. Further, CRC tumorigenesis between proximal and distal lesions can be different[51,62]. In a 2009 study of 10292 patients who died of CRC and 51460 matched-controls, it was shown that receipt of a complete CSPY was significantly associated with less death secondary to left-sided CRC; however, a similar relationship was not found for right-sided CRC[42]. In a subsequent 2010 study, amongst 54803 patients who underwent index CSPY, a 29% reduction in overall CRC mortality was identified[45]. However, there was no reduction in CRC mortality for proximal CRC. In another 2010 study that investigated 3287 individuals undergoing screening CSPY, a preceding CSPY within 10 years decreased the prevalence of advanced colorectal neoplasms, but this had little, if any, effect on reducing the prevalence of proximal advanced colorectal neoplasms[60].

CSPY - adverse events

Serious adverse events secondary to CSPY are well-recognized. Although they are relatively infrequent, they remain a concern, particularly in settings where CSPYs are performed outside current recommendations for screening and surveillance[63]. It is estimated that the risk of serious adverse events, specifically perforation and post-polypectomy bleeding, is approximately 1 per 1000 CSPYs[64,65].

Perforation is the most serious adverse event associated with CSPY. In a 2008 study[64], using administrative-level data among 97091 individuals who underwent outpatient CSPY, the rate of perforation was 0.85/1000 and the rate of death was 0.074/1000. Factors associated with increased risk of perforation were older age, male sex, polypectomy, and having the CSPY performed by a low-volume endoscopist. These findings were supported by a 2009 study[65] of 53220 CSPYs performed in a Medicare population, highlighting a perforation rate of 0.6/1000. In terms of post-polypectomy bleeding, two studies described rates to be 1.64/1000[64] and 6.4/1000[65] respectively. Similar risk factors were observed to increase the likelihood of post-polypectomy bleeding, including older age, male sex, polypectomy and having the CSPY performed by a low-volume endoscopist[64]. In addition, large polyp size, proximal location, and use of anti-coagulation[66] worsened the risk

In the recent ASGE quality indicators for colonoscopy guidelines, performance targets for perforation have been set at < 1:500 (all examinations), < 1:1000 (screening examinations) and < 1% for post-polypectomy bleeding. As per the ASGE, it was recommended that rates exceeding these recommendations should prompt a review of CSPY technique of the endoscopist in question.

ONGOING DISPARITIES

Disparities in CRC screening are an unfortunate reality. With an estimated 49190 deaths due to CRC within the United States in 2016, a disproportionate burden will occur within marginalized populations[1]. People of specific ethnic minorities, immigrants, and those in lower socioeconomic backgrounds are less likely to receive screening[24,67]. For United States and Canada to successfully achieve their respective screening targets, these disparities need to be addressed and minimized.

Ethnic and immigrant minorities

Ethnic minorities have been found to have lower CRC screening uptake. This is apparent across multiple ethnicities including African Americans[68], Hispanics[1],

Asians[69], and Indigenous populations (American Indians and Alaska Natives within the United States; First Nations and Metis within Canada)[70]. Multiple factors have been implicated as drivers of this disparity. A lack of knowledge concerning CRC and poor awareness of the concept and importance of CRC screening are key drivers, but fear of discomfort, anxiety of waiting for results, and general mistrust of healthcare professionals have been cited in the literature as reasons why selected patient subgroups fail to seek screening[71-73]. The latter is especially concerning since it can lead to decreased physician engagement and poor continuity of care. Similar to other factors associated with treatment disparities, ethnic populations may also be more vulnerable to the effects of lower socioeconomic status[74], a lack of health insurance[75] and barriers in communication[75]. Lastly, differences in CRC tumorigenesis[76] may play a further role whereby a CRC diagnosis affects patients at younger ages when screening is generally not recommended. Likewise, immigrants[75,77] represent another subgroup of patients who are less likely to undergo CRC screening. In a 2013 study[75] that compared United States-born citizens to non-citizens who participated in the California Health Interview Survey, 67% *vs* 46% underwent CRC screening. Potential factors contributing to this disparity were living in rural areas, a lack of health insurance, and not being proficient in the English language.

Socioeconomic status

There is notable interplay between drivers of disparity and socioeconomic status. Individuals with low socioeconomic status have poorer uptake of CRC screening[78,79]. In a 2009 study assessing Medicare enrollees ages 65 to 80 years, individuals less educated or belonging to low-income groups were less likely to undergo CRC screening[80]. Unfortunately, even when the cost of CRC screening is alleviated, disparity still persists[81]. In England, the Bowel Cancer Screening Program does not pose any financial costs to participants because it is operated by the National Health Service since 2006. Despite this fact, there were marked variations in CRC screening uptake among the first 2.1 million participants. In the least socially and economically deprived areas, uptake was highest at 61% whereas uptake was lowest at 35% in the most deficient areas[81,82]. To a large extent, the ongoing drivers of these differences remain unclear within this subgroup; however, it is postulated that stress, low social supports, competing life demands, and literacy are strongly implicated[72,83] and thus challenging to mitigate systematically.

CONCLUSION

In conclusion, while CRC screening has clearly proven its ability to reduce the incidence and mortality of CRC, there are critical areas requiring further improvements. For the benefits of CRC screening to materialize, increased uptake and retention during subsequent screening cycles is paramount. Additionally, refinement of current screening test performance measures along with optimization of CSPY quality to prevent procedure-related adverse events are essential as an increasing number of jurisdictions continue to introduce and implement programmatic CRC screening. Lastly, effective interventions that target and consider the unique needs of the marginalized subsets of our population is crucial if our goal is to enhance outcomes for all. With universal adoption of programmatic CRC screening and continued advances in screening modalities, it is our hope that CRC screening can provide meaningful morbidity and mortality benefits to patients in an equitable and cost-effective manner.

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REVIEW

Evidence based review of the impact of image enhanced endoscopy in the diagnosis of gastric disorders

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Abstract

Gastric cancer is the third most common cause of cancer-related death. Advanced stages of gastric cancers generally have grim prognosis. But, good prognosis can be achieved if such cancers are detected, diagnosed and resected at early stages. However, early gastric cancers and its precursors often produce only subtle mucosal changes and therefore quite commonly remain elusive at the conventional examination with white light endoscopy. Image-enhanced endoscopy makes mucosal lesions more conspicuous and can therefore potentially yield earlier and more accurate diagnoses. Recent years have seen growing work of research in support of various types of image enhanced endoscopy (IEE) techniques (*e.g.*, dye-chromoendoscopy; magnification endoscopy; narrow-band imaging; flexible spectral imaging color enhancement; and I-SCAN) for a variety of gastric pathologies. In this review, we will examine the evidence for the utilization of various IEE techniques in the diagnosis of gastric disorders.

Key words: Gastritis; Gastric cancer; Image enhanced endoscopy; Chromoendoscopy; Narrow band imaging

Core tip: Image-enhanced endoscopy is useful for an accurate real-time diagnosis of a variety of gastric diseases. But, good prognosis can be achieved if such cancers are detected, diagnosed and resected at early stages. However, early gastric cancers and its precursors often produce only subtle mucosal changes and therefore quite commonly remain elusive at the conventional examination with white light endoscopy. Image-enhanced endoscopy makes mucosal lesions more conspicuous and can therefore potentially yield earlier and more accurate diagnoses. Recent years have seen growing work of research in support of various types of image enhanced endoscopy (IEE) techniques (*e.g.*, dye-chromoendoscopy; magnification endoscopy; narrow-band imaging; flexible spectral imaging color enhancement; and I-SCAN) for a variety of gastric

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INTRODUCTION

In 1957, Hirchowitz *et al*[1] pioneered the use of flexible endoscope to visualize the gastrointestinal (GI) tract. These early fibreoptic endoscopes were cumbersome to use and had dim views of the GI tract. Diagnosis of frank gastric pathologies (*e.g.,* ulcer or malignant tumor) was straightforward. However, subtle abnormalities in the mucosa often got missed or misdiagnosed. This is especially relevant in stomach where early and confident detection of subtle pre-malignant features has potential to save the organ and life of a patient[2].

Recent years have witnessed tremendous progress in various novel endoscopic techniques. These techniques claim easy and confident detection, diagnosis and assistance in endoscopic resection of gastric subtle mucosal abnormalities. Simplistically, these techniques make a GI mucosal lesion appear more conspicuous. In a consensus methodological classification (in year 2008), such techniques were classified into five categories by Tajiri *et al*[3]: (1) conventional white light endoscopy (WLE); (2) image-enhanced endoscopy (IEE); (3) magnification endoscopy (ME); (4) microscopic endoscopy; and (5) tomographic. As these technologies offer different advantages and disadvantages, some have become indispensable tools inside every endoscopy room while others remain research tools.

Like in any disease, the endoscopic assessment of a mucosal abnormality also follows the logical sequence comprising "identification (or screening)", "characterization", "confirmation" by a gold standard (*e.g.,* histology), and finally "treatment". Explicit identification or screening of significant lesions is important to achieve low false miss-rates during endoscopy. At the same time, an accurate characterization, before histological assessment, is equally crucial to enable endoscopic resection for a significant lesion while leaving behind benign findings. Various IEE techniques have been studied for "identification" and "characterization" of gastric pathologies. In this review, we will study various IEE techniques and review their respective evidences for utilization in stomach.

METHODOLOGY

Publications in English language, limited to humans, were searched in the databases of "PUBMED/MEDLINE", "the Cochrane Library", and "Google Scholar". The studies were searched between January 1995 and January 2016. Only studies published in peer-reviewed journals were taken into consideration. Relevant studies from the references of selected articles were also screened. The search keywords were: "Endoscopy, digestive system", "Narrow band", "Narrow-band imaging (NBI)", "White light", "Image enhance", "Image enhanced", "Endoscopy/methods", "Gastroscopy/methods", "White light endoscopy", "Chromoendoscopy (CE)", "Blue laser", "Fujinon intelligent", "Flexible spectral imaging color enhancement (FICE)", "I-SCAN", "Methylene blue", "Indigo carmine", "Acetic acid", "Dye endoscopy", "Helicobacter", "Gastric atrophy", "atrophic gastritis (AG)", "Intestinal metaplasia", "Gastric tumor", "Gastric cancer", "Stomach cancer", and "Gastric neoplasm". The two sets of keywords were combined individually. The studies were searched as free texts and as Medical Subject Headings terms.

WHITE-LIGHT ENDOSCOPY

The last decades of 20th century saw the advent of video-endoscopes equipped with charge-coupled devices (CCDs). These CCD chips produced image signal of 100000 to 400000 pixels, allowing clear images of GI mucosa[4]. Each pixel represents a unit of sample image, and therefore higher pixel-density meant greater spatial resolution and sharper images. Although good in detecting significant lesions in the GI tract, these standard definition (SD) video-endoscopes still had high miss-rates for subtle mucosal abnormalities.

The currently available high-definition (HD) endoscopes produce images with resolution of up to a million pixels and can magnify the mucosal image by 30- to 35 fold. These images can be further magnified optically by having an in-built motor-driven optical lens at the tip of endoscope. The lens can be focused upon an area-of-interest to provide a genuinely close-up image without sacrificing any pixel or image resolution. Contrary to the electronic magnification, the optical zoom produces a truly magnified (up to 150-times) and sharp image. Since the lens needs to be focused 2-3 mm away from the lesion, it is almost essential to have short hood or cap at the tip of magnifying-endoscope to maintain the focal length. These advances in endoscopic resolution have accompanied the considerable improvements in endoscope processors, which can convert tremendous amount of photonic data into a high-definition image without many artefacts. To get such HD images, it is imperative to have a compatible set of HD endoscopes, processor, monitors and transmission cables. Figure 1 illustrates cases of EGC detected by HD-WLE. They appear as a mildly depressed lesion with discoloration compared to adjacent normal mucosa.

Very few studies have directly compared HD-endoscopy with SD-endoscopy. For example in colon, these HD endoscopes showed marginal benefit in a meta-analysis

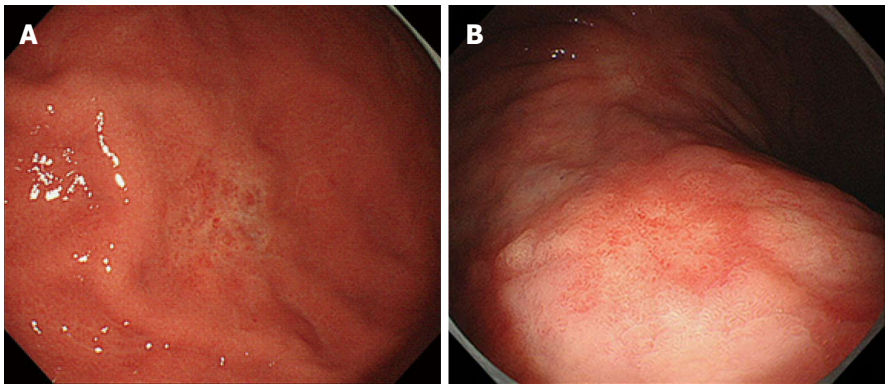

Figure 1 High definition white light endoscopy view. A: A depressed lesion with mucosal discoloration due to early gastric cancer; B: High definition white light endoscopy view of early gastric cancer.

with a number needed to treat of 25 to identify one additional polyp or adenoma[5]. Such objective data are not available for the upper GI tract but the expectation is similar.

WLE WITH MAGNIFICATION

WLE with magnification has potential to provide detailed mucosal views. In 1978, Sakaki *et al*[6] described classification of the stomach mucosa according to the "minute gastric mucosal patterns". Since 1999, true magnifying endoscopes (for example, GIF-Q240Z by Olympus Corporation or EG-450ZH by Fujinon) were introduced which could optically zoom the image by up to 80 times. Such spatially resolved and magnified images revealed surface and microvascular patterns of stomach mucosa in great details. These studies are summarized in Table 1.

Appearance of normal gastric mucosa with "only ME"

Magnified views of normal gastric mucosa have been classified and named differently by various authors. In a preliminary study in 2001, Yao *et al*[7] described the magnifying views of antrum as coil-shaped network with rare collecting venules, and of corpus as honey-comb pattern with interspersed collecting venules. Absence of sub-epithelial capillary network (SECN) along with proliferation of irregular microvessels was observed in differentiated early gastric cancer (EGC). Similarly, Yagi *et al*[8] studied the mucosal patterns in normal stomach without *Helicobacter pylori* (*H. pylori*) infection. The study concluded that the presence of regular arrangement of collecting venules (RAC) could predict the absence of *H. pylori* gastritis with 95.5% accuracy. Moreover, the presence of well-defined ridge pattern (wDRP) in antrum had 100% specificity for the absence of *H. pylori* gastritis, although its sensitivity was relatively low at 54.5%. In another study, the ME views of corpus were grouped into four types (Z-0 to Z-3) and almost all patients without *H. pylori* gastritis had Z-0 pattern[9].

H. pylori assessment with "only ME"

Six prospective studies have reported the use of "only ME" in predicting the gastritis (especially *H. pylori* gastritis)[8-13]. However, a variety of different mucosal classifications were used and proposed to correlate with *H. pylori* status. As mentioned in the earlier section, Yagi *et al*[8,9] correlated *H. pylori* status with RAC in corpus, wDRP in antrum and Z0-Z4 classification in corpus with good success. Based on the same Z0-Z4 classification, a group from Turkey showed superior results with *H. pylori* detection when compared with standard endoscopy[10]. In another study, Anagnostopoulos *et al*[11] grouped ME views of corpus (GIF Q240-Z, 115 × magnifications) into four types with high inter-observer agreement. Their classification identified *H. pylori* gastritis with sensitivity and specificity of 100% and 92.7% respectively. Similarly, other authors have reported excellent results with other classifications.

Worldwide, *H. pylori* gastric infection is considered the primary carcinogen for development of gastric adenocarcinoma[14]. Real-time diagnosis of *H. pylori* and other types of gastritis with ME may be beneficial in a sense that detection of such types of abnormal mucosal patterns may make an endoscopist more vigilant to the possibility of dysplastic gastric lesions. However it should be emphasized that there are inherent difficulties in interpretation of these subjective classifications and all studies have been done by experts. Moreover, given the widespread availability of relatively cheap, objective and sensitive tests to detect *H. pylori* gastritis (*e.g.,* rapid urease test), routine utilization of ME alone for diagnosis of *H. pylori* should be undertaken with caution and biopsy based tests remain the standard for diagnosis.

Characterization of EGC with "only ME"

As the area of mucosal view is small with ME, its role for screening or identification of pre or early malignant lesions in stomach is limited. However, ME has a role in characterization of subtle gastric lesions which are detected by screening WLE. A variety of patterns have been described to differentiate EGC from benign

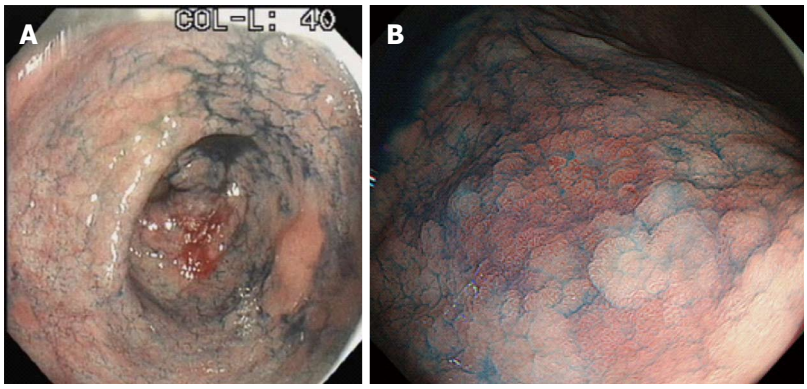

Figure 2 Mucosal irregularities and boundaries of a lesion. A: Gastric adenoma accentuated by indigo carmine; B: Early gastric cancer accentuated by indigo carmine.

Table 1 Summary of studies using magnification with white light

Use in stomach	Type of evidence	Description	Remarks
Identification of normal gastric mucosa	Descriptive study[7]; Cross-sectional study with comparison to histology[8]	Normal corpus: Regular honeycomb pattern Normal antrum: Coil-shaped network with rare collecting venules	Different descriptive classifications have been used, but all emphasize on regular and uninterrupted mucosal and vascular patterns
Diagnosis of *H. pylori* gastritis	Six prospective studies with histology as the comparator[8-13]	High sensitivities and specificities for diagnosis of *H. pylori*	Multiple and varied pattern classifications with different endoscopes. Inherent subjectivity in classifications is an issue
Characterization of EGC	Six prospective studies with histology as the comparator[15-20]	Better results as compared to the traditional white light endoscopy	Multiple classifications bring inherent subjectivity; the most prevalent classification is the "VS" classification[17] which describes: Differentiated EGC: Irregular microvessels with a demarcation line Undifferentiated EGC: Absent demarcation line and absent sub-epithelial capillary networks

H. pylori: *Helicobacter pylori*; EGC: Early gastric cancer.

gastric mucosa. A variety of patterns have also been described for characterization of differentiated EGC from undifferentiated EGC. There have been six prospective studies using ME-alone for characterization of EGC[15-20]. In 2001, Tobita[15] from Japan first described ME findings in 103 depressed gastric lesions (including 63 malignant lesions) using Fujinon, EG-410CR at × 60 magnification. It was concluded that the findings of "irregular protrusion" and "minute vessels in amorphia" were specific for malignancy. However, the classification had inherent subjectivity as it was assessed by one expert and was not been validated externally. In another prospective study in 2002, Tajiri *et al*[16] compared WLE-examination with ME (Olympus, GIF-Q240Z) in 211 consecutive gastric lesions. The authors found 89 EGC (58 depressed-type, 31 elevated-type). Using their classification, the accuracy of ME-examination was significantly superior to WLE-examination for any type of small (⩽ 1 cm) EGC. In the same year, Yao *et al*[17] proposed a classification of magnified views of gastric mucosa which subsequently became the most widely utilized classification in studies of ME with IEE techniques. The mucosa was classified based on "microvascular" and "microsurface" patterns, later known as the "VS classification". Non-cancerous mucosa were found to have regular appearances of SECN, all differentiated EGC had a demarcation line and irregular microvessels, while all undifferentiated EGC had absent demarcation line with absent or reduced SECN. In 2007, Yao *et al*[18] validated their classification on a larger sample. For characterization of EGC with ME, other authors have used varied classification with good results[19,20].

Overall, the efficacy of ME-alone in the stomach has been studied by a few authors, mainly from Japan. The various uses of ME-alone in stomach are summarized in Table 1. However as will be discussed later, the majority of studies of ME in stomach have been performed in combination with other IEE techniques.

CONVENTIONAL CHROMOENDOSCOPY

Introduced in the 1990s, CE refers to spraying of harmless dyes to stain the mucosal surface. This is usually done after a preliminary inspection with WLE. The staining of surface makes subtle mucosal patterns more obvious. A variety of stains have been used in the GI tract and these are classified into three types

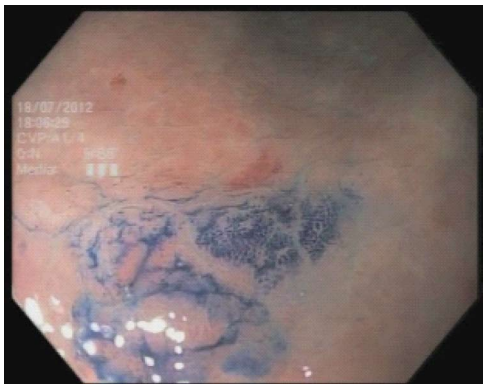

Figure 3 Gastric intestinal metaplasia highlighted by methylene blue.

based on their actions: Absorptive (or vital) stains, contrast stains, and reactive stains. Absorptive stains (*e.g.,* Lugol's iodine, methylene blue) have property of differential absorption into different cell types, thus highlighting one type of tissue over other. For example, methylene blue is absorbed by cells of small intestine and colon, and therefore a stained focus in the stomach theoretically indicates IM. On the contrary, the contrast stains (*e.g.,* indigo carmine) do not react with the cells, but accumulate in the pits and crevices of a mucosal lesion thus accentuating the surface pattern (or the topography), mucosal irregularities and boundaries of a lesion (Figure 2). The last category, the reactive stains (*e.g.,* acetic acid, phenol red) change color by coming in contact with a particular protein on the surface. For example, Phenol red and Congo red are reactive stains which turn red in an alkaline gastric environment signalling infection with *H. pylori*.

CE can be performed in two ways: (1) pan-CE, which involves spraying the dye blindly and voluminously to screen for any abnormal areas; or (2) targeted staining, where a dye is sprayed over a lesion of interest to further characterize it. Several studies have attempted a variety of stains in the stomach, either alone or in combination, to identify, characterize and outline focal lesions (*e.g.,* IM or EGC). CE is technically easy to perform and has shown significant advantages in detecting flat colorectal neoplasia and colitis-associated neoplasia[21].

Use of acetic acid in stomach

Acetic acid causes a reversible and transient alteration in the tertiary structure of the cellular proteins which leads to temporary opacification of mucosal surface. This produces a vivid mucosal image with crypts turning brown while the intervening epithelial surface appearing white. While the non-cancerous mucosa changes into white, the dysplastic and cancerous cells remain unstained, producing a good contrast. After spray of acetic acid, the mucosal details are visualized with magnification. This combination of acetic acid instillation and ME is often termed as "Enhanced-magnification endoscopy (EME)", which allows visualization of villi and crypts. In 2005, Yagi *et al*[22] studied the value of EME in stomach in 45 patients. The mean duration of whitening differed with each histologic type: Low-grade adenoma, 94 s; high-grade adenoma, 24.3 s; non-invasive carcinoma, 20.1 s; invasive intramucosal carcinoma, 3.5 s; and submucosal carcinoma or beyond, 2.5 s. Therefore, the acetic-acid with ME was useful in differentiating between neoplasia and non-neoplasia based on duration of whitening.

One year later in 2006, Tanaka *et al*[23] proposed a classification of EME findings in stomach based on forty seven consecutive patients, into five categories: Type Ⅰ, small round pits; type Ⅱ, slit-like pits; type Ⅲ, gyrus and villous patterns; type Ⅳ, irregular arrangements and sizes; type Ⅴ, destructive patterns. Elevated gastric carcinomas showed type Ⅲ or Ⅳ patterns; while depressed carcinomas showed type Ⅳ or Ⅴ patterns. Later the same group, in a separate observational study, found that the surface patterns were evident in 100% of lesions by EME as compared to only 66.4% with conventional or magnification endoscopies[24]. The type Ⅳ-Ⅴ lesions were strongly associated with gastric cancer with a sensitivity of 100% and specificity of 89.7%.

Use of congo-red and phenol-red in stomach

Utilizing its tendency to turn red in an alkaline environment, this Congo-red has been used for detection of AG, *H. pylori* infection and IM. Data are limited. Phenol-red has been used in old studies to map the gastric mucosa for *H. pylori* infection. With phenol red spraying endoscopy, Kohli *et al*[25] identified *H. pylori* infection with sensitivity and specificity of 100% and 84.6% respectively.

Use of methylene-blue in stomach

Methylene blue is absorbed by intestinal cells and thus highlights gastric IM (Figure 3). Dinis-Ribeiro *et al*[26] examined and proposed a classification in 136 patients using ME after methylene blue (1%) spray and could identify IM and dysplasia with 84% and 83% accuracy respectively. The findings were externally validated at another centre in Portugal in forty two patients with AG with or without IM, and the results showed excellent reproducibility for the classification[27]. In a tandem study with only thirty-three patients, Taghavi *et al*[28] compared conventional endoscopy against CE with methylene blue. The CE group yielded more IM lesions compared to conventional endoscopy.

Use of haematoxylin in stomach

Haematoxylin is a common stain used in histological assessment since it stains the nuclei of cells. To date, there is only a single study utilizing haematoxylin as CE on a heterogeneous sample of gastric abnormalities[29]. Although high sensitivity (92.9%) and specificity (89.3%) for diagnosing gastric neoplasia were reported, there were only three cases of cancer.

Use of "acetic acid plus indigo carmine" in stomach

Acetic acid whitens the non-cancerous gastric mucosal epithelial cell while the cancerous cells remain unstained.

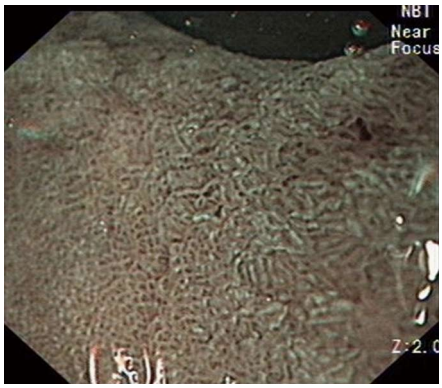

Figure 4 Gastric intestinal metaplasia highlighted by narrow band imaging using the EXERA III system with dual focus.

As detailed above, multiple studies have utilized acetic acid with ME in technique known EME. However, some authors believe that the use of ME may be cumbersome for neoplastic lesions (especially if lesion is large or located at a difficult position). Therefore, CE using a sequential combination of acetic acid spray followed by another spray with indigo carmine (AI) has been proposed for examination of a mucosal neoplastic lesion. Multiple studies have shown the efficacy of AI for delineating the margins of EGC before endoscopic resection. In the first published study on AI use with 114 patients, AI was much more effective in delineating the lateral spread of cancers as compared to indigo carmine alone[30]. In another prospective comparative study, Sakai *et al*[31] used AI in 53 consecutive gastric lesions before endoscopic submucosal dissection and good interobserver agreement was reported between the two endoscopists (kappa = 0.764). The diagnostic performance of AI was significantly better than either indigo carmine or acetic acid alone. In another prospective study on 108 EGC lesions, Kawahara *et al*[32] compared WLE, indigo-carmine and AI for delineation of margins before ESD. All endoscopic examinations were performed by one endoscopist. When correlated with pathological specimens, the diagnostic accuracy of AI was higher when compared to WLE or indigo-carmine (90.7% *vs* 50.0% *vs* 75.9%, respectively).

Overall, the studies with AI have shown an excellent efficacy in demarcation of EGC before endoscopic resection. The technique does not require additional equipment (*e.g.,* magnification endoscope).

NARROW BAND IMAGING

NBI is a proprietary optical image-enhancement technology launched by the Olympus Corporation (Tokyo, Japan) in year 2005. NBI is the most widely utilized electronic IEE technique with demonstrated scientific evidence for its efficacy in GI diseases. Normally, the wavelengths of white light range from 400 to 700 nm. During conventional WLE, the illuminating white light travels from the xenon lamp *via* a rotating red-green-blue (RGB) rotatory filter. In NBI, an additional filter is placed between the xenon lamp and the RGB filter[33]. This whole NBI system is simply activated by a push of button on the control handle of the endoscope without interrupting the views on monitor. By this additional NBI filter, the light is converted from a broad RGB into narrow bands of blue and green at 415 (± 15) nm and 540 (± 15) nm wavelengths respectively. The narrow wavelengths of illuminating light increase the saturation. Moreover, biological tissues behave differently at different wavelengths of light due to their characteristic patterns of absorption and scattering of light. Since haemoglobin molecule has two absorption peaks at 415 nm and 540 nm, the mucosal microvascular patterns are highlighted in extensive detail with NBI[34].

NBI can diagnose the subtle and flat mucosal GI lesions which are often missed or remain uncharacterized on WLE. Since the sub-epithelial capillaries of stomach have minimum diameter of 8 μm[17], combining ME with NBI has been studied for detailed examination of capillary patterns in stomach. As described below, most of the published studies have utilized a simultaneous combination of ME and NBI. It must be recognized that there are two NBI systems in use, the EVIS EXERA and the EVIS LUCERA systems. For the EXERA system, the magnification achieved is by digital magnification and a specific technique called "Dual Focus" which allows near mode imaging; in contrast, the LUCERA system allows optical magnification and this is the main system used in prior studies of magnifying NBI. An overview of NBI studies are provided in Table 2.

NBI for screening of gastric pathologies

At narrow wavelengths of light with NBI, the intensity of illumination is compromised resulting in darker images when compared to images during WLE. This is especially relevant while examining the stomach, a capacious organ, where dark views result in NBI being not so useful for screening of focal gastric lesions. However, NBI can be utilized as a second-look method to focus on lesions detected upon screening with WLE. This technique appears to increase detection rate of gastric focal lesions. At least five prospective studies have studied NBI using this approach[35-39]. In a prospective study on an unselected population, our group screened for focal gastric lesions using WLE followed by characterization of detected lesions by magnified NBI (M-NBI)[34]. Additional 15% lesions (mostly IM) were detected with M-NBI (Figure 4). In another multicentre prospective study using the similar sequence (WLE followed by M-NBI), the accuracy of M-NBI for high confidence diagnoses of gastric lesions was 98%[35]. In a recent prospective study with more than three thousands non-selected patients, gastric examinations were performed with high-definition white light (HD-WLE) followed by ME and then with M-NBI[36]. Using such strategy to detect EGC, ME and M-NBI had significantly higher sensitivities when compared to HD-WLE. However, there were no differences among specificities of the techniques.

Table 2 Summary of studies using narrow band imaging in stomach

Use in stomach	Type of evidence	Description	Remarks
Screening of focal lesions in stomach	Five prospective studies[35-39] studied screening with WLE followed by characterization of detected lesions with NBI Single randomized prospective study with bright-NBI[40]	WLE followed by characterization with NBI seems to increase confidence in taking targeted biopsies New generation "bright-NBI" appears promising to increase yield of FGL as single step examination in stomach	Majority of the detected FGLs are intestinal metaplasia Due to small sample sizes in these studies, it is unclear whether such strategy will improve detection of subtle malignant gastric lesions
Diagnosis of *H. pylori* gastritis	Two prospective trials[41,42] using M-NBI with histology as comparator	Subjective classifications of mucosal microvascular patterns showed high sensitivity and specificity for real-time diagnosis of *H. pylori* gastritis	Inherent subjectivity in the classification is an issue
Diagnosis of IM	Multiple prospective studies and one recent meta-analysis[44] using M-NBI for diagnosis of IM	Multiple patterns have been assigned for diagnosis of IM. The most prevalent is the "LBC" sign The pooled sensitivity and specificity of LBC for diagnosis of IM are 84% and 93% respectively	LBC sign with M-NBI appears easy to learn and reliable for real-time diagnosis of IM
Characterization of an EGC	Multiple prospective studies including two recent meta-analyses[52,53] using M-NBI for characterization of an EGC	Various pattern-classification systems with M-NBI have been used in different studies to characterize a lesion as EGC. The pooled sensitivity: 0.83-0.85 The pooled specificity: 0.96	Inherent subjectivities in a variety of classifications remain an issue Significant heterogeneity were observed in both meta-analyses
Prediction of histological differentiation of an EGC	At least two prospective studies[54,55]	Subjective pattern assignments were given; Only moderate sensitivities and specificities to determine histological differentiation of an EGC	Inherent subjectivities in the classification system. Currently, histology is still required to determine histological differentiation of an EGC
Determination of horizontal extent of an EGC	Few studies with small sample sizes	One study[58] showed better accuracy than indigo carmine chromoendoscopy	Real-time estimation of an EGC is useful before endoscopic resection. However, the histology still remains the gold-standard
Determination of depth of an EGC	Two prospective[61,62] studies	Subjective classifications but with excellent accuracy	Inherent subjectivities in the classification system. Currently, histology is still required to determine depth of an EGC

FGL: Focal gastric lesion; *H. pylori*: *Helicobacter pylori*; EGC: Early gastric cancer; M-NBI: Magnifying narrow band imaging; IM: Intestinal metaplasia; LBC: Light blue-crest; WLE: White light endoscopy.

The new generation NBI system introduced in 2012 (*e.g.*, the "EVIS EXERA III" or "EVIS LUCERA" from Olympus Corporation) attempt to overcome the drawback of dark views by having an upgraded xenon light source. Besides this, the new systems also have two filters for blue light and one filter for green light in contrast with previous NBI system where only one filter each is used for blue and green. Thus, this new generation NBI system (sometimes known as bright-NBI) produces brighter NBI images even from a distance. In a recent multicentre prospective randomized study, our group compared the HD-WLE with the new generation bright-NBI system (either 190-NBI or 290-NBI) for screening of focal gastric lesions (FGL)[40]. The detection rate of FGL was higher with bright-NBI than with HD-WLE (41% *vs* 29%; $P = 0.003$).

Magnifying-NBI for diagnosis of H. pylori gastritis

Since *H. pylori* infection produces alterations in the microsurface structures and microvascular patterns of gastric mucosa, it is postulated that the magnified NBI views may be helpful for real-time diagnosis of *H. pylori* gastritis. For this pathology, there has been considerable interest by researchers for two reasons. First, the high-confidence real-time diagnosis of *H. pylori* may stimulate an endoscopist to be more vigilant for concomitant pre-malignant and malignant lesions of stomach. Also, the real-time gastric mucosal pattern analyses may theoretically help in obtaining targeted biopsies instead of routine practice of blind-biopsies for *H. pylori* check. In a prospective study in 2009, Tahara *et al*[41] attempted to correlate gastric mucosal patterns on magnifying-NBI (M-NBI) with *H. pylori* gastritis. At M-NBI, the normal gastric corpus pattern was identified as small, round pits with regular subepithelial capillary networks (SECN). The abnormal patterns were classified into three (type 1 to 3) categories. The sensitivity and specificity of abnormal patterns (type 1 + 2 + 3) for *H. pylori* gastritis were 95.2% and 82.2%, respectively. In a comparative trial in 2014, Yagi *et al*[42] compared conventional WLE with M-NBI for detection of *H. pylori* gastritis in patients diagnosed with EGC. For diagnosis of *H. pylori* gastritis, the sensitivity and specificity in M-NBI group were higher than in WLE group.

M-NBI for diagnosis of AG and IM

AG and IM represent significant milestones in the sequence of gastric carcinogenesis[14]. On conventional WLE, corpus AG is suspected based on a paucity of gastric rugae with more marked appearances of sub-mucosal vessels; while IM appears as patchy, white, raised or flat spots. However, WLE is considered

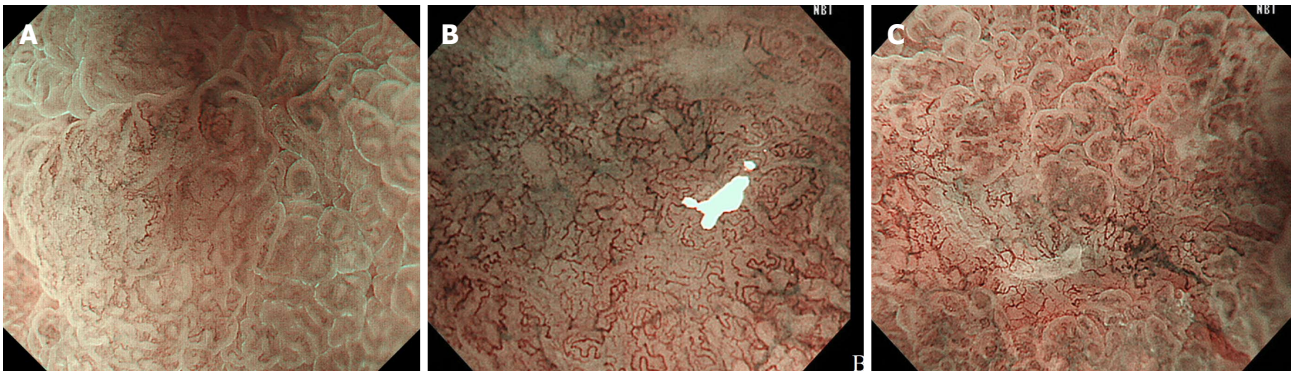

Figure 5 Best visualized with optical magnification. A: Magnifying narrow band image of gastric intestinal metaplasia showing, the light blue crest sign, surrounding central area of early gastric cancer; B: Magnifying narrow band image of early gastric cancer; C: Magnifying narrow band image of early gastric cancer.

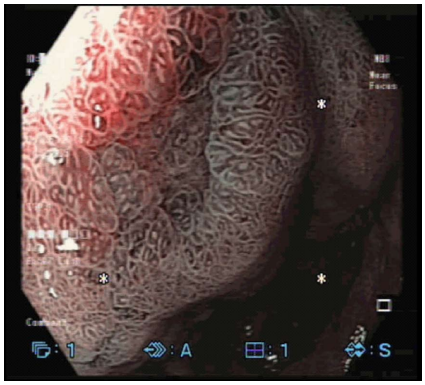

Figure 6 Image of early gastric cancer visualized using narrow band imaging with digital magnification and dual focus imaging.

insensitive for diagnosis of AG and IM. On NBI, AG is characterized by a complete loss of pit-pattern and SECN, with presence of only collecting venules. In a randomized, prospective and crossover study by Dutta *et al*[38] NBI was superior to WLE for detection of AG. With NBI various appearances have been proposed for characterization of IM. The most important of these is the identification of light blue crests (LBC).

In 2006, Uedo *et al*[43] first described LBC as fine blue-white lines on the crests of the epithelial surface/gyri, similar to a light reflected from mirror. In this seminal study, the sensitivity and specificity of LBC for diagnosis of IM were 89% and 93% respectively. Similarly, high diagnostic values of LBC for characterization of IM have been shown by other authors (Figure 5A). A recent meta-analysis by Wang *et al*[44], which included four prospective studies without significant heterogeneity, documented that the pooled sensitivity and specificity of LBC for diagnosis of IM were 84% and 93% respectively. In a pilot feasibility trial, Bansal *et al*[45] found sensitivity and specificity of "ridge/villous pattern" for IM to be 80% and 100% respectively.

M-NBI for characterization of EGC

Perhaps the most important and most extensively investigated use of NBI in the stomach is for the characterization of EGC. The accurate identification of EGC is important since endoscopic resection for such early cancers achieves > 90% five-year survival. Morphologically EGC are categorized mainly into three types by the Paris classification[46]: Superficial elevated (0-IIa), superficial flat (0-IIb), and superficial depressed (0-IIc). EGCs often produce subtle mucosal changes (sometimes known as "gastritis-like cancers") and can be easily missed on conventional WLE. The major contribution of M-NBI lies in accurate differentiation of such lesions from normal or inflamed gastric mucosa.

The most widely studied and utilized classification is the "VS classification" by Yao *et al*[47] where "V" stands for microvascular patterns while "S" stands for surface microstructures. In this classification, an EGC is accurately identified based on two features: (1) a demarcation line (DL) with loss of SECN; and (2) an irregular microvascular pattern (IMVP) or an irregular microstructural pattern. These features are best visualized with optical magnification (Figure 5). Digital magnification combined with dual focus imaging may provide an adequate view of the demarcation line and microstructural pattern, but will not be able to clearly visualize the microvascular pattern (Figure 6).

In 2010, Ezoe *et al*[48] prospectively compared diagnostic efficacies of ME with M-NBI using VS classification in a sample of 57 depressed gastric lesions (including 27 malignant). For accurate diagnosis of EGC, the diagnostic accuracy and sensitivity were significantly higher for M-NBI as compared to ME. Subsequently, the same comparison was studied in much larger sample in a randomized and multicentre trial[49]. Again for diagnosis of depressed-type EGC, the M-NBI was superior to ME. The sensitivity and specificity of M-NBI were 95.0% and 96.8% respectively.

In the recent post-hoc analysis of this study, a sequential strategy for diagnosing a cancerous gastric lesion was proposed[50]. For a depressed gastric lesion on white-light examination, M-NBI was suggested to look for a DL first since presence of DL had high sensitivity and high negative predictive value for a malignant lesion. In lesions with DL, an absence of IMVP was proposed to rule out malignant lesions because of high specificity of IMVP. In another prospective study, Kato

et al[51] surveyed 111 high-risk patients for EGC based on a triad of findings on M-NBI: (1) disappearance of mucosal pattern; (2) microvascular dilatation; and (3) heterogeneity. Although only 14 gastric cancers were detected, the sensitivity and specificity of M-NBI (92.9% and 94.7% respectively) were superior to WLE (42.9% and 61.0% respectively).

In a recent meta-analysis by Zhang *et al*[52] the pooled sensitivity and specificity of M-NBI for diagnosis of EGC were 0.83 and 0.96 respectively. However, there were significant heterogeneity among the studies and also, a combination of retrospective and prospective studies were pooled together. Another recent meta-analysis, which only included six prospective studies, also showed high pooled sensitivity (0.85) and specificity (0.96) for M-NBI diagnosis of EGC[53]. A significant heterogeneity among studies was also observed in this meta-analysis.

M-NBI for histological differentiation of EGC

Besides differentiating between cancerous and non-cancerous lesions, several studies have attempted to use M-NBI for prediction of histologic differentiation of EGC. During the early years of NBI technique, Nakayoshi *et al*[54] studied 165 depressed-type of EGC with M-NBI. The microvascular patterns were divided into three patterns: Fine network, corkscrew and unclassified. The fine network patterns were seen more commonly in differentiated EGC as compared to the undifferentiated type (66.1% *vs* 3.7%), whereas corkscrew patterns were seen more commonly in undifferentiated-type (85.7% *vs* 3.6%; $P = 0.0011$). However, the conclusion was that the real-time optical diagnosis with M-NBI, although beneficial, was still not sufficient to replace histopathological confirmation.

Similarly, Yokoyama *et al*[55] studied 257 consecutive EGC with M-NBI and divided the microvascular patterns into four categories: Fine-network, corkscrew, intra-lobular loop-1, and intra-lobular loop-2. When correlated with histopathology, differentiated-type EGC mostly had fine-network pattern or intra-lobular loop patterns. On the contrary, the undifferentiated-type of EGC had intra-lobular loop-2 pattern and corkscrew pattern in almost all patients (41.2% and 58.2% respectively).

M-NBI to determine the horizontal extent of EGC

Delineating the horizontal extent of EGC is important for margin-free endoscopic resection. Traditionally, CE with indigo-carmine has been used to highlight abnormal mucosal patterns before endoscopic resection. In 2002, Yao *et al*[56] published a case report where demarcation of a well-differentiated EGC was made with an image-enhanced technology using "hemoglobin index".

Subsequently in a sample of twelve EGC, Sumiyama *et al*[57] used a combination of M-NBI and a multibending endoscope for *en bloc* endoscopic mucosal resection. Using this combination, 91.7% (11/12) *en bloc* resections were made feasible as compared to 35% in conventional endoscopy group. However, authors stated that it was unclear as to which of these factors (*i.e.,* either NBI or multibending endoscope or both) led to this satisfactory outcome.

Kiyotoki *et al*[58] compared M-NBI with indigo-carmine based CE in 118 EGC. For delineating margins of EGC, the accuracy was higher in M-NBI group as compared to the indigo-carmine (97.4% and 77.8% respectively; $P = 0.009$). Another prospective study by Nagahama *et al*[59] documented 72.6% accuracy for identifying margins of EGC which could not be delineated with acetic acid CE.

Overall, studies have shown beneficial results with M-NBI for delineation of margins only in the differentiated-type of EGC. Demarcation of undifferentiated-type of EGC is considered difficult since the malignant growth seems to creep more into the lamina propria which may not always produce endoscopically visible mucosal changes. For example in the study by Nagahama *et al*[59] the endoscopic delineation remained difficult for undifferentiated lesions. However one prospective study also showed high accuracy (81.6%) using M-NBI for demarcation of undifferentiated-type of EGC[60].

It can be concluded that there is good evidence with prospective trials in support of M-NBI for demarcation of differentiated EGC before performing endoscopic resection. However it should also be noted that the trials have generally included a small number of patients in whom experts have performed endoscopic examination while utilizing various types of classification for pattern categorization. Although histopathology is still considered the gold-standard for retrospective confirmation of clearance of margins, the real-time estimation of horizontal margins with M-NBI is helpful as a prospective guide for accurate *en-bloc* resection.

M-NBI to determine the depth of EGC

According to the Japanese Gastric Cancer Handling Codes, the submucosal EGC are divided into three types (SM1 to SM3) based on the depth of cancer invasion. The differentiated-type of SM1 (*i.e.,* vertical depth up to 500 μm) EGC can be considered as an expanded indication for endoscopic resection. But, surgical resection should be considered for SM2 and SM3 cancers as the probability of lymph node metastatic disease is high. Prospective estimation of the depth of invasion is difficult and therefore endoscopic resection is considered complete only after histopathological assessment of the resected specimen. Knowledge of deep invasion will avoid unwarranted endoscopic resection. Presence of ulceration on standard WLE suggests deep invasion. But, it may be especially difficult to estimate depth of invasion in flat (Paris 0-IIa, 0-IIb and 0-IIc) EGC.

In 2008, Yagi *et al*[61] correlated the M-NBI patterns of 72 differentiated-type EGC (10 elevated, 27 flat, and 35 depressed-type) with histopathology. All endoscopic examinations were performed by one expert and the patterns were classified into three types: Mesh, loop and interrupted. The mesh or loop pattern were seen

in 94.9% of mucosal EGC while 92.3% of submucosal EGC had interrupted patterns. In another prospective study from China, Li *et al*[62] reported findings of M-NBI in 164 suspected gastric lesions. The patterns of M-NBI were categorized into three groups (A, B and C) based on both surface pattern and microvascular architecture. Besides excellent diagnostic values for characterization and differentiation of EGC, M-NBI classification was able to accurately predict the depth of invasion in 37 out of 39 differentiated adenocarcinomas (95%).

Two retrospective studies have also attempted correlation of M-NBI images (taken before the resection) with histopathology of resected specimens. In the first study by Kobara *et al*[63] it was concluded that the presence of non-structure, scattery vessels and multi-caliber vessels can possibly serve as indicators of SM2 invasion in differentiated-type of EGC. In the second study by Kikuchi *et al*[64] M-NBI images were examined for dilated vessels (D-vessels) which were defined as vessels with diameter 3 times larger than that of the irregular microvessels. The sensitivity and specificity of D-vessels for SM2 invasion were 37.5% and 88.3% respectively.

FICE

This technology is also known as "optimal band imaging" or "multi-band imaging". FICE was introduced by Fujinon (Tokyo, Japan) in year 2005 and is currently its proprietary technology. In FICE, the ordinary white-light images are captured by the CCD and are mathematically processed in the processor by assigning specific ranges of wavelengths. Thereafter, electronically enhanced and reconstructed color images are displayed on the monitor[65]. This is in contrast with the NBI where raw and enhanced images are captured by putting an optical filter in the path of illuminating light. Since FICE processes well-illuminated white-light images, this means that the FICE can provide enhanced images without compromising on brightness. At present, there are ten pre-settings of FICE which can be instantaneously activated by pushing a button on an accompanying keyboard. A total of three presets can also be assigned to the buttons on the control handle of the endoscope to ease the switching of the different FICE images. In recent years, several studies have claimed superior efficacy of FICE as compared to WLE for various pathologies of esophagus, colon and stomach. Only a few studies have studied FICE in stomach, with most performed for delineation of margins of EGCs. However, a learning curve for pattern recognition, a requirement for separate endoscopic equipment and lack of consensus for objective diagnostic criteria has restricted use of FICE.

Use of FICE in EGC

In the management of EGC, the use of FICE has been limited to demarcation of already identified lesions. FICE has not been objectively studied as a screening tool to pick up early malignant lesion. In 2008, Osawa *et al*[66] published the first clinical study in stomach. In this real-time prospective study with a small sample of twenty-seven patients, four endoscopists, in real-time demarcated the depressed type of EGC with accuracy of 96%. In the same year, another study by the same group claimed efficacy in demarcation of elevated and depressed type of EGC[67]. However in this study, the objective results of efficacy of this method were not reported. In another study from the same group, it enabled delineation of elevated-type of ECG in the background of AG[68].

Since a variety of wavelengths were being used for gastric examination with FICE, the most effective wavelength was studied in a retrospective fashion by another group in Japan[69]. Previously captured white-light images of EGC were processed by the FICE processor and analysed. It was noted that the wavelength of 530 nm generated maximal difference in spectral reflectance between EGC and normal mucosa and there was significant improvement from the WLE images to the FICE images. FICE is proposed as a potential alternative to conventional CE because it provides contrast enhancement of tissue surface structures. However at present, the evidence for its support has come from a few studies with small sample. Since the technology requires a new set of equipment, further external and large-scale validation will be required before its widespread use.

Use of FICE for other gastric pathologies

In one study, FICE was studied for differentiation of non-neoplastic lesions, adenomas and cancers in the stomach[70]. A total of 171 gastric lesions were examined and FICE performed better than magnifying-WLE. Another study examined the role of FICE for diagnosis of gastric intestinal metaplasia[71]. FICE had sensitivity and specificity of IM diagnosis of 60% and 87% based on histological confirmation. Although this study might have diagnosed IM based on LBC, there is still no consensus on diagnostic criteria for IM on FICE.

Small-caliber gastroscope with FICE

Small-caliber endoscope has lower resolution but is more comfortable for the patients, especially if used as a screening tool for gastric pathologies. Theoretically, FICE combined with small-caliber gastroscope can enhance the color contrast of gastric pathologies. To date, there are two studies, from Japan, which have evaluated this hypothesis. Tanioka *et al*[72] retrospectively examined 50 gastric lesions which were previously identified on screening endoscopy with Ultraslim endoscope (Fujinon EG-530N2). After conversion into FICE images, superior visibility was seen in 54.7% upper GI lesions as compared to conventional images. In another study by Osawa *et al*[73] 82 depressed-type EGC (which were already diagnosed with conventional normal-caliber

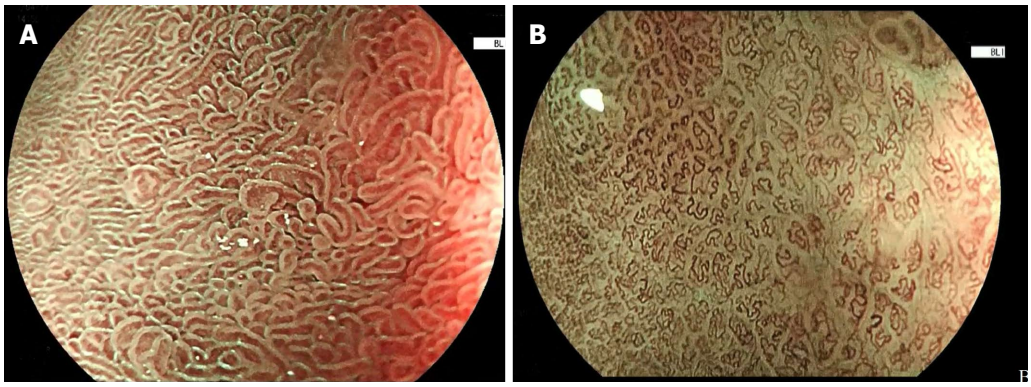

Figure 7 Performance characteristics. A: Image of gastric intestinal metaplasia visualized by blue laser imaging with optical magnification; B: Image of early gastric cancer visualized by blue laser imaging with optical magnification.

Table 3 Summary of image-enhanced endoscopy in stomach

Technique	Use	Evidence	Remarks
High-definition WLE	Standard of care for initial examination of gastric mucosa	Not available	
WLE with magnification	Helpful in describing normal mucosal patterns in corpus and antrum. Appears useful in predicting real-time diagnosis of *H. pylori* infection. Better than WLE for characterization of EGCs	Multiple prospective comparative studies for identifying *H. pylori* infection and for characterization of EGCs	A variety of classifications in describing the normal and abnormal mucosal pattern makes interpretation difficult for widespread use
Dye-based chromoendoscopy	Traditionally used for demarcation of EGC before resection	Few prospective studies are available, and more data will be needed	There are heterogeneity in the types of stain, technique of staining, classification in defining mucosal patterns
NBI	Good for characterization of a focal lesion detected on WLE May be useful for real-time diagnosis of *H. pylori* Appears reliable for diagnosis of intestinal metaplasia High specificity for characterization of EGCs May be useful for prediction of histological differentiation, prediction of depth of invasion, and in determination of horizontal extent of EGCs	Multiple prospective comparative study show good evidence in support of NBI for diagnosis of intestinal metaplasia and characterization of EGCs More evidence will be needed for other indications	Identifying intestinal metaplasia appears straightforward A variety of classifications for different mucosal pattern bring difficulty in generalization of NBI
FICE	May be useful for diagnosis of focal gastric lesions	Not much comparative prospective data is available	
I-SCAN		No comparative data for use of I-SCAN in stomach	
Blue-laser imaging	Is expected to be used in similar manner as NBI	Data mainly based on case series rather than comparative studies	Based on anecdotal experience it is similar to NBI and therefore would be expected to provide similar outcomes

WLE: White light endoscopy; EGC: Early gastric cancer; NBI: Narrow-band imaging; FICE: Flexible spectral imaging color enhancement; BNI: Narrow band imaging; *H. pylori*: *Helicobacter pylori*.

endoscopy) were examined with small-caliber (Fujinon EG-530N2) endoscopy and FICE by endoscopists who were blinded of the locations of the lesions. Most EGC could be detected as reddish lesions on FICE with clear demarcation.

FICE combined with indigo carmine in stomach

A single study from Japan has evaluated the usefulness of adding indigo-carmine to FICE examination (I-FICE)[74]. In a small sample of 29 well-differentiated EGC, I-FICE was superior for demarcation of the lesion when compared to WLE, FICE and indigo-carmine CE.

I-SCAN

Conceptually similar to FICE, I-SCAN is a post-processing image-enhancement technology introduced by Pentax Corporation (Tokyo, Japan) in year 2007, allowing detailed views of mucosal vascular patterns[75]. Special processors (EPKi high-definition, Pentax)

are required for I-SCAN. The white-light images are processed arithmetically into three types of enhancements: Surface enhancement (SE), contrast enhancement (CE), and tone enhancement (TE). The SE and CE are suggested useful for screening of early GI lesions, while TE is proposed for further characterization of identified lesions. The modes can be switched back and forth by pressing a button on the endoscope, and two modes can be displayed simultaneously. A small number of studies have explored this technique for colonic and esophageal pathologies, where equivocal benefits have been seen. Till date, there is only one study of I-SCAN's use in stomach. Using magnified I-SCAN in a small sample of 43 patients, Li *et al*[76] performed a feasibility trial. Magnified I-SCAN was attempted to characterize a heterogeneous variety of small superficial gastric lesions. With histology as gold-standard, the specificity of real-time magnified I-SCAN was only 77% for neoplastic lesions. Therefore at present, the data for gastric use of I-SCAN is almost non-existent and further work will be required before routine use in stomach.

BLUE-LASER IMAGING

Introduced in year 2012 by Fujifilm Corporation (Tokyo, Japan), this is the latest addition to the field of IEE. Contrary to NBI which, in the process of producing a narrow bandwidth, darkens the image, blue-laser imaging (BLI) generates brighter and sharper images. BLI utilizes two laser sources: One at 410 nm for illumination of superficial mucosa and another at 450 nm to visualize deep vascular mucosal image. Therefore, BLI produces more vivid mucosal and microvascular architectural details. In 2014, first in-human clinical trial with BLI in stomach was reported by Kaneko *et al*[77] from Japan. Out of a variety of GI lesions, 14 patients had EGC. BLI-bright produced better far-field view as compared to the first generation NBI. Since the BLI technology is new, more extensive work is warranted before any conclusion can be drawn. However, it would appear to be very promising, and be similar to NBI in terms of performance characteristics (Figure 7).

CONCLUSION

Especially in last 15 years, there has been a proliferation of research for use of IEE in detection and characterization of gastric pathologies. The role of IEE in screening is still limited and WLE should still be used as first line method of examination. However, there is large amount of data in support of M-NBI for diagnosis, delineation and depth-estimation of EGC. M-NBI also has excellent diagnostic characteristics for IM. It is important to emphasize that almost all studies have been done by experts in IEE highlighting the importance of a proper training in pattern recognition before general use. The published data for other IEE techniques are more limited. Since the principle of BLI is the same as NBI, it would be expected to provide similar efficacy as NBI, especially with optical magnification. In contrast, it is probably not possible to extrapolate the NBI data to FICE and I-SCAN, since these are processed images without optical magnification (Table 3).

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MINIREVIEWS

Clinical problems with antithrombotic therapy for endoscopic submucosal dissection for gastric neoplasms

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Abstract

Endoscopic submucosal dissection (ESD) is minimally invasive and thus has become a widely accepted treatment for gastric neoplasms, particularly for patients with comorbidities. Antithrombotic agents are used to prevent thrombotic events in patients with comorbidities such as cardio-cerebrovascular diseases and atrial fibrillation. With appropriate cessation, antithrombotic therapy does not increase delayed bleeding in low thrombosis-risk patients. However, high thrombosis-risk patients are often treated with combination therapy with antithrombotic agents and occasionally require the continuation of antithrombotic agents or heparin bridge therapy (HBT) in the perioperative period. Dual antiplatelet therapy (DAPT), a representative combination therapy, is frequently used after placement of drug-eluting stents and has a high risk of delayed bleeding. In patients receiving DAPT, gastric ESD may be postponed until DAPT is no longer required. HBT is often required for patients treated with anticoagulants and has an extremely high bleeding risk. The continuous use of warfarin or direct oral anticoagulants may be possible alternatives. Here, we show that some antithrombotic therapies in high thrombosis-risk patients increase delayed bleeding after gastric ESD, whereas most antithrombotic therapies do not. The management of high thrombosis-risk patients is crucial for improved

outcomes.

Key words: Antithrombotic therapy; Endoscopic submucosal dissection; Heparin bridge therapy; Dual antiplatelet therapy; Delayed bleeding

Core tip: It is unclear if antithrombotic therapy increases delayed bleeding after endoscopic submucosal dissection (ESD) of gastric neoplasms. With appropriate cessation, antithrombotic therapy does not increase delayed bleeding in low thrombosis-risk patients. However, high thrombosis-risk patients are often treated with combination therapy with antithrombotic agents, such as dual antiplatelet therapy (DAPT), and occasionally require the continuation of antithrombotic agents or heparin bridge therapy (HBT) in the perioperative period. Both patients with DAPT and HBT have a high risk of delayed bleeding. The management of these antithrombotic therapies is important in the perioperative period of ESD.

Yoshio T, Nishida T, Hayashi Y, Iijima H, Tsujii M, Fujisaki J, Takehara T. Clinical problems with antithrombotic therapy for endoscopic submucosal dissection for gastric neoplasms. *World J Gastrointest Endosc* 2016; 8(20): 756-762 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i20/756.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i20.756

INTRODUCTION

Endoscopic resection of early gastric cancer (EGC) has been developed and applied to many patients since the establishment of criteria for node-negative cancers[1] and the advancement of endoscopic submucosal dissection (ESD)[2,3]. In multicenter studies, we have reported that ESD is a feasible method for the treatment of EGC[4] and that the long-term outcome of gastric ESD is satisfactory[5]. A risk of metachronous gastric cancer exists following ESD or endoscopic mucosal resection, even when the procedure is curative[6,7]. The cumulative 3-year risk is 5.9%[7]. However, we also demonstrated that nearly all secondary cancers after ESD (97%) were treatable by repeated ESD following scheduled endoscopic surveillance[5]. Consequently, ESD can preserve the entire stomach and improve patient post-operative quality of life. Therefore, ESD has become a more acceptable treatment option for EGC than gastrectomy, particularly for patients with comorbidities[8].

Delayed bleeding is one of the major complications of gastric ESD, and the delayed bleeding rate is 3.1%-6.5%[4,9,10]. In most cases, delayed bleeding is treated successfully by endoscopic hemostasis; however, some patients require transfusion or surgery, and these situations can be fatal[11]. The reported risk factors for delayed bleeding include larger lesions[10], lesions with ulceration[10,12], and longer procedure time[1,13]. The risk is highest for lesions in the middle and lower third[9]. Electronic coagulation of vessels in the ulcer bed after ESD was reported to decrease delayed bleeding[9]. In our analysis, half of delayed bleeding occurred the day of ESD or the next day, and the remainder occurred within 2 wk, with the exception of 1 case that occurred 22 d after ESD[14]. It has been argued that second-look endoscopy after ESD prevents delayed bleeding. However, Goto *et al*[15] showed that second-look endoscopy did not decrease delayed bleeding in a retrospective analysis. A prospective randomized control study also denied a preventive effect of second-look endoscopy for delayed bleeding[16].

Antithrombotic therapy, including antiplatelet agents and anticoagulants, is increasingly used worldwide to prevent cerebro-cardiovascular events[17,18]. These prophylactic agents reduce the risks of thromboembolic events but simultaneously increase the risk of bleeding complications. Most patients with EGC are elderly, and these patients commonly exhibit several comorbidities that require medical treatment, particularly antithrombotic therapy. Risks for delayed bleeding after ESD in patients with antithrombotic therapy depend on the type of endoscopic treatment and the use of antithrombotic therapy.

In this review, we discuss the problems of antithrombotic therapy associated with delayed bleeding after gastric ESD. This review is not a systematic review because of the limited evidence and the variety of patients with various comorbidities receiving many types of antithrombotic agents. However, we searched the entire MEDLINE database to identify the literature on antithrombotic therapy and gastric ESD and included as many studies as possible.

EFFECT OF ANTIPLATELET AGENTS ON GASTRIC ESD

Antiplatelet agents are used to prevent platelet aggregation for prophylaxis of secondary cerebro-cardioembolic events after the occurrence of stroke or ischemic heart disease[19]. Antiplatelet agents include thienopyridines, protease-activated receptor-1 inhibitors, glycoprotein IIb/IIIa receptor inhibitors, aspirin and non-steroidal anti-inflammatory drugs. When patients exhibit a low risk of thrombosis, antithrombotic agents can be discontinued. Antithrombotic therapy with appropriate cessation is not considered to increase delayed bleeding rates[14,20]. In some high thrombosis-risk patients, it is difficult to discontinue antithrombotic therapy during the perioperative period of ESD. Administration of these antithrombotic agents in combination further complicates the management of these agents. In these patients, the continuous use of minimum antithrombotic agents during ESD is an option.

The recent guidelines of the American Society for Gastrointestinal Endoscopy (ASGE) in 2016[21] and

the Japan Gastroenterological Endoscopy Society in 2014[22] recommend the continuous use of aspirin during endoscopic procedures in high thrombosis-risk patients, even if the procedures carry a high risk of bleeding. For gastric ESD, a multivariate analysis[23-25] found that the continuous use of aspirin did not increase delayed bleeding, supporting the application of this treatment; however, the delayed bleeding rate was slightly increased (3.6%-21.1%)[23-26]. Moreover, the delayed bleeding rate was considerably higher in patients receiving dual antiplatelet therapy (DAPT) with continuous aspirin and cessation of thienopyridines (35.5%) than in patients who did not receive antithrombotic medications[25].

For patients with coronary artery stents, DAPT with aspirin plus thienopyridines is recommended for 30 d after placement of a bare metal stent and for one year after placement of a drug-eluting stent (DES)[27]. Cessation of these agents within the period resulted in a high risk of stent thrombosis[28]. Thus, according to the consensus statement from the American College of Cardiology Foundation and the American College of Gastroenterology, it is recommended to defer elective endoscopic procedures up to 12 mo from the time of DES placement and perform endoscopic procedures 5 to 7 d after thienopyridine cessation[29]. In addition, aspirin should be continued throughout the perioperative period, and thienopyridine should be resumed once hemostasis is achieved[29]. The timing of ESD for EGC should be decided based on the balance of cancer progression and bleeding risk. EGC often remains in the early stage for a period[30]. Thus, ESD can be delayed in patients with DES placement, provided that the EGC lesion is still considered resectable after the completion of required DAPT.

The management of patients with DAPT for ESD is difficult. A delayed bleeding rate as high as 35.5%[25] was reported when ESD was performed with continuous aspirin and cessation of thienopyridines following the guidelines[21,22,29]. Moreover, patients receiving DAPT for ESD face thrombotic risk from the cessation of thienopyridines, and this thrombotic risk can be increased if delayed bleeding occurs[11,14]. However, it is sometimes necessary to perform ESD in patients with DAPT with continuous aspirin and cessation of thienopyridines who have a risk of delayed bleeding and thrombosis. Care must be taken to identify the initial symptoms of delayed bleeding and thrombotic events. There is insufficient evidence for methods to minimize both bleeding risk and thrombotic risk during DAPT, and we have no data on cases of continuous administration of both aspirin and thienopyridines or cessation of aspirin and continuous thienopyridines.

EFFECTS OF ANTICOAGULANTS ON GASTRIC ESD

Anticoagulants prevent thrombotic events in patients with conditions such as arterial fibrillation (AF) and deep vein thrombosis by interfering with the native clotting cascade. Anticoagulants include oral warfarin, direct oral anticoagulants (DOACs: Dabigatran, rivaroxaban, apixaban, and edoxaban), and heparin derivatives.

The risk of thromboembolism associated with withdrawal of anticoagulants varies considerably. AF is the most common reason for the use of anticoagulant therapy, and the risk of thrombotic events is approximately 1% when anticoagulation is interrupted for 4 to 7 d[31,32]. Thrombotic events can cause serious complications and can be fatal. Thus, all patients on anticoagulant therapy are recommended to be treated as having a high risk of thrombosis[22]. Thus, for the cessation of anticoagulants, heparin bridge therapy (HBT) is required to prevent thrombotic events during the perioperative period[33-35]. However, ESD with HBT carries an extremely high risk of delayed bleeding, with a delayed bleeding rate of 23.8%-37.5% as we previously reported[14,36-38].

DOACs are administered without the need to monitor their effects due to their rapid action and effectiveness in preventing cerebrovascular events[39-42]. Before endoscopic procedures, 1 to 3 d of cessation is recommended in patients without renal dysfunction according to the ASGE guideline[21] based on the half-lives of the agents (8-15 h)[39-42]. According to the British Society of Gastroenterology and ESGE guidelines, at least 2 d of cessation is recommended before endoscopic procedures[43]. By contrast, warfarin requires 5 d of cessation to cancel the effect[44], and HBT is required during this period. After the procedure, DOACs should be re-administered without heparin because DOACs achieve their maximum effect shortly (1-4 h) after re-administration, in contrast to warfarin[39-42,45]. Thus, shorter perioperative periods of controlling anticoagulant effects can be applied for DOACs compared with warfarin.

Unfortunately, no study has examined the effect of DOACs on endoscopic procedures except our following conference paper. For gastric ESD for patients, we observed a delayed bleeding rate of 16.7% (3/18) in patients using DOACs, which did not differ significantly from the delayed bleeding rate of 23.5% (4/17) observed in patients using warfarin during the same period[46]. However, the hospitalization period was significantly shorter in patients on DOACs compared with those on warfarin (8 d *vs* 14 d: $P < 0.01$) because the period of HBT was shorter[46]. Further investigations are needed to understand the effect of DOACs on endoscopic procedures.

In high thrombosis-risk patients with comorbidities, combination use of antiplatelet agents and anticoagulants is occasionally required, which also increases delayed bleeding[14].

TIMING OF DELAYED BLEEDING

Koh *et al*[47] reported that antithrombotic therapy was a risk factor for late bleeding [later than post-operative

Table 1 Multivariate analysis of risk factors for delayed bleeding: Antithrombotic therapy and patient and lesion characteristics

Ref.	No. of patients	Risk factor identified by multivariate analysis	OR (95%CI)	Risk factors identified by univariate analysis
Furuhata *et al*[36]	1781	HBT Multiple antithrombotic agents Lower third location Operation time longer than 100 min	10.04 (4.35-23.16) 5.44 (2.00-14.79) 2.17 (1.32-3.58) 2.00 (1.25-3.20)	HBT, multiple antithrombotic agents, tumor size greater than 20 mm, lower third location, UL+ tumors, operation time longer than 100 min, and cardiovascular disease
Matsumura *et al*[37]	413	CKD undergoing hemodialysis HBT Lesion size greater than 40 mm	33.86 (4.72-242.74) 5.77 (1.67-19.96) 3.70 (1.09-12.52)	HBT, tumor size over 40 mm, CKD undergoing hemodialysis

HBT: Heparin bridge therapy; CKD: Chronic kidney disease.

day (POD) 5]. Tounou *et al*[25] reported late bleeding (later than POD 8) was significantly more frequent in cases with DAPT but not cases with single aspirin therapy. In cases with HBT, the timing of delayed bleeding was later than in cases without HBT (POD 3.8 ± 4.1 *vs* POD 8.0 ± 5.7, $P < 0.05$)[14]. In cases without HBT, half of delayed bleeding cases occurred on POD 0 and 1; however, in cases with HBT, only 10% of the cases occurred on POD 0 and 1[14].

IS HBT FEASIBLE FOR GASTRIC ESD?

A recent, randomized control study compared discontinued anticoagulant use with or without HBT in 1884 surgical cases and revealed that HBT did not reduce perioperative arterial thromboembolism but significantly increased major bleeding complications[48]. A meta-analysis of studies of elective invasive procedures or surgeries revealed that warfarin-treated patients receiving bridge therapy with low-molecular-weight heparin appear to be at an increased risk of both overall and major bleeding and exhibited a similar risk of thromboembolic events as non-bridged patients[49].

Another randomized control study involving 681 cases of pacemaker or defibrillator surgery revealed that bleeding complications occurred less frequently in patients with continuous warfarin use than in patients in whom warfarin was discontinued with HBT[50]. Additional meta-analyses supported these results[51].

Considering these findings together, continuous use of warfarin throughout the perioperative period is a better choice than HBT because continuous use of warfarin likely does not increase bleeding complications and exhibits the same risk for thrombosis. None of them are originated of the outcome of endoscopic procedures nor gastric ESD, these results will change our treatment. Tounou *et al*[52] reported a case of gastric ESD safely performed with continuous use of warfarin; however, further investigation is needed, such as a randomized study comparing gastric ESD with continuous ESD and with HBT.

For patients requiring HBT, continuous use of warfarin and switching warfarin to DOACs are candidate new strategies, although data to support their use are lacking.

ANALYSIS OF BLEEDING RISK IN ANTITHROMBOTIC THERAPY BY COMPARING PATIENT AND LESION CHARACTERISTICS

High thrombosis-risk patients are often at a high risk of delayed bleeding under antithrombotic therapy with multiple agents, particularly patients with HBT and accompanying comorbidities. The antithrombotic therapies, patient comorbidities and EGC characteristics with the highest risks for delayed bleeding remain unclear.

Furuhata *et al*[36] conducted a multivariate analysis of these factors and identified HBT (OR = 10.04), multiple antithrombotic agents (OR = 5.44), the lower third of the stomach (OR = 2.17), and an operation time longer than 100 min (OR = 2.00) as independent risk factors. Matsumura *et al*[37] identified chronic kidney disease (CKD) undergoing hemodialysis (OR = 33.86), HBT (OR = 5.77) and a lesion size greater than 40 mm (OR = 3.70) as risk factors (Table 1).

We performed a bleeding risk analysis in 1563 consecutive patients with 1671 gastric neoplasms treated by ESD[53] as an extended analysis of our previous study[11] (unpublished data). This study included 283 (18%) patients receiving antithrombotic agents who all discontinued the agents before ESD. The delayed bleeding rates were similar between patients receiving no antithrombotic therapy and those who discontinued antithrombotic agents without HBT (5.6% *vs* 4.9%); however, the delayed bleeding rate was significantly higher (21.9%) in patients with HBT ($P < 0.01$). Moreover, the delayed bleeding rate increased in proportion to the number of discontinued drugs (two drugs: 15.6%, $P < 0.01$; three drugs: 27.3%, $P < 0.05$). Patients on warfarin or ticlopidine had a significant risk of delayed bleeding compared with patients receiving no antithrombotic agent. In a univariate analysis of tumor and patient factors, tumor size greater than 30 mm, tumor in the middle third of the stomach, tumor with ulceration, patients with CKD and male gender were identified as risk factors for delayed bleeding.

Multivariate analysis showed that HBT (OR = 6.14), lesion in the middle third of the stomach (OR = 2.21),

ulceration in tumor (OR = 1.97) and tumor size greater than 30 mm (OR = 1.75) were significant, independent risk factors for delayed bleeding. HBT (OR = 16.43) and CKD (OR = 6.34) were identified as significant risk factors for blood transfusions by multivariate analysis.

The results of these studies show that HBT is the most significant independent factor for delayed bleeding compared with other factors involving patient and lesion characteristics.

THROMBOTIC EVENTS

Few studies of the relationship between thrombotic events and endoscopic procedures have been conducted, and incidence rates of thrombotic events related to gastric ESD of 0%-4.2% have been reported[14,20,23,54]. We observed one patient who developed a thrombotic event[14]. This patient received HBT during the peri-operative period and exhibited delayed bleeding on POD 10. After successful endoscopic hemostasis, we restarted heparin, and his activated partial thromboplastin time was sufficiently prolonged on POD 11. However, a cerebral infarction developed on POD 13. This case suggests that delayed bleeding can lead to thrombotic events by reducing intravascular volume and causing hypercoagulability after bleeding. Numata *et al*[11] also reported a case of femoral artery infarction consequent to delayed bleeding after gastric ESD that led to death. These findings suggest that the prevention of delayed bleeding is important for preventing thrombotic events in patients at a high risk for thromboembolism.

CONCLUSION

Most antithrombotic therapies do not increase the risk of delayed bleeding during gastric ESD; however, patients receiving multiple antithrombotic agents, including DAPT, and patients on anticoagulants requiring HBT have a high risk for delayed bleeding. These high thrombosis-risk patients with accompanying comorbidities may have a high risk of delayed bleeding under strong antithrombotic therapy.

To prevent the exposure of these patients to a serious risk of acute ischemic events, new strategies should be developed to replace HBT and to address DAPT. Well-designed prospective and comparative clinical studies are needed to obtain further evidence regarding the management of antithrombotic therapy.

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ORIGINAL ARTICLE

Retrospective Study

Outcomes of submucosal (T1b) esophageal adenocarcinomas removed by endoscopic mucosal resection

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Abstract

AIM

To investigate the outcomes and recurrences of pT1b esophageal adenocarcinoma (EAC) following endoscopic mucosal resection (EMR) and associated treatments.

METHODS

Patients undergoing EMR with pathologically confirmed T1b EAC at two academic referral centers were retrospectively identified. Patients were divided into 4 groups based on treatment following EMR: Endoscopic therapy alone (group A), endoscopic therapy with either chemotherapy, radiation or both (group B), surgical

resection (group C) or no further treatment/lost to follow-up (< 12 mo) (group D). Pathology specimens were reviewed by a central pathologist. Follow-up data was obtained from the academic centers, primary care physicians and/or referring physicians. Univariate analysis was performed to identify factors predicting recurrence of EAC.

RESULTS

Fifty-three patients with T1b EAC underwent EMR, of which 32 (60%) had adequate follow-up ⩾ 12 mo (median 34 mo, range 12-103). There were 16 patients in group A, 9 in group B, 7 in group C and 21 in group D. Median follow-up in groups A to C was 34 mo (range 12-103). Recurrent EAC developed overall in 9 patients (28%) including 6 (38%) in group A (median: 21 mo, range: 6-73), 1 (11%) in group B (median: 30 mo, range: 30-30) and 2 (29%) in group C (median 21 mo, range: 7-35. Six of 9 recurrences were local; of the 6 recurrences, 5 were treated with endoscopy alone. No predictors of recurrence of EAC were identified.

CONCLUSION

Endoscopic therapy of T1b EAC may be a reasonable strategy for a subset of patients including those either refusing or medically unfit for esophagectomy.

Key words: Esophageal cancer; Submucosal; T1b; Endoscopic mucosal resection; Chemotherapy; Esophagectomy

Core tip: Endoscopic eradication therapy (EET) is reported as safe and effective for low risk T1b esophageal adenocarcinomas (EAC), but overall data is lacking. We retrospectively evaluated patients with T1b EAC treated with EET, EET with chemotherapy and/or radiation therapy and surgical resection. The overall recurrence rate was 28% at median 21 mo (range: 6-73) following EMR. In those treated with endoscopic mucosal resection alone, recurrence rate was 38% at median 21 mo (range: 6-73). Six of the 9 recurrences were local; 5 were treated with endoscopy alone. EET of T1b EAC may be a reasonable treatment strategy for a subset of these patients.

Ballard DD, Choksi N, Lin J, Choi EY, Elmunzer BJ, Appelman H, Rex DK, Fatima H, Kessler W, DeWitt JM. Outcomes of submucosal (T1b) esophageal adenocarcinomas removed by endoscopic mucosal resection. *World J Gastrointest Endosc* 2016; 8(20): 763-769 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i20/763.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i20.763

INTRODUCTION

Due to the inherent morbidity and rare mortality associated with esophagectomy and lymph node dissection, endoscopic eradication therapy [including endoscopic mucosal resection (EMR) and ablative techniques] has been increasingly used as a safe, effective and potentially curative organ-sparing procedure to treat high grade dysplasia (Tis lesions) and intramucosal esophageal cancer (T1a lesions)[1-5]. When complete resection or eradication of T1a cancers is confirmed, disease is generally considered cured due to the low rate of reported lymph node metastasis (< 2%) in these patients[6]. Tumors that penetrate the submucosa of the esophagus (T1b cancers), however metastasize to regional lymph nodes in up to 30% of cases and the likelihood for metastases increases the further the tumor penetrates from the first third (sm1) into the lower two thirds (sm2 and sm3) of the submucosal layer[7-11]. Therefore, endoscopic eradication therapies (EET) have generally not been employed in patients with T1b cancers.

The use of EET for primary treatment of T1b tumors was initially reported in patients with "low risk" submucosal esophageal cancers (macroscopically polypoid or flat, invasion limited to the upper 1/3 of the submucosa, no invasion of the vessels or lymphatic system, well to moderate tumor differentiation); this has more recently been updated in a larger series (*n* = 66) from the same group with similar characteristics showing recurrent or metachronous carcinomas developed in 19% of patients with an estimated 5 year survival rate of 84%[12,13]. A study from two referral centers in the Netherlands examined EET of deep T1a and T1b EAC (*n* = 75) with an overall recurrence rate of 9%[14]. A study from a tertiary center in the United States reported a group of patients (*n* = 29) with T1b EAC with sm1 (46%) and sm2-3 (54%) invasion that underwent either EET, chemo/radiation or a combination of both and showed mean survival of 34.8 mo with a 38% mortality rate[15].

To our knowledge, there are no studies examining the outcomes and predictors of disease recurrence in patients with pathologically staged T1b esophageal cancer treated with EET alone, surgery, or adjuvant therapy following endoscopic resection. Identification of predictive factors for recurrence and outcomes following endoscopic therapy in this population would help to identify and tailor appropriate treatment. For this reason, we aimed to (1) retrospectively evaluate the clinical outcomes of pT1b esophageal cancers following EMR; (2) to compare the recurrence rates of cancer when patients are treated with EET alone, EET in association with chemotherapy, radiation therapy or both and surgical resection; and (3) to evaluate the predictors of recurrence of T1b esophageal cancer following EMR.

MATERIALS AND METHODS

Study population and design

All patients age ⩾ 18 years of age who underwent EMR of the esophagus from 2001 to 2013 at India-

na University Medical Center and the University of Michigan were retrospectively identified from institutional endoscopic databases. Patient charts were then reviewed to identify the subset of patients with pathologically (p) staged T1b esophageal cancer that comprised the study population. Patients with treatment by endoscopic submucosal dissection or ⩽ 12 mo of follow-up after resection were excluded. Approval for this study was obtained by the institutional review boards at both participating institutions prior to any study activities.

Pre-procedure imaging with CT and/or PET scans was initially obtained in all patients to exclude distant metastasis. Endoscopic ultrasound (EUS) was also used in selected patients to assess the depth of any visualized mass or detect and sample any suspicious lymph nodes. Prior to EMR, all patients underwent EGD with a detailed exam of the mucosa of the esophagus and gastric cardia. The use of advanced imaging techniques such as narrow band imaging and chromoendoscopy was at the discretion of the endoscopist. After identification of the site(s) for resection, either cap-assisted (Olympus America Inc., Center Valley, PA) or band ligation-assisted EMR (Cook Medical Inc., Winston Salem, NC) was performed. The specimens retrieved were placed into formalin and sent to pathology for evaluation for examination by an experienced gastrointestinal pathologist.

Treatment groups

Treatment after identification of a pT1b esophageal cancer at each institution was at the discretion of the endoscopist as well as referring physicians based on the pathology findings, patient comorbidities and patient wishes. For study purposes, treatment after EMR was classified as utilizing endoscopy alone (group A), endoscopy with either chemotherapy, radiation or both (group B), surgical resection alone (group C), or no further treatment or lost to follow-up (group D). Patients in group A underwent additional EMR with or without ablation, surveillance endoscopies and cross-sectional imaging as determined by the treating physicians.

Pathology assessment

Endoscopic resection specimens from both institutions were initially reviewed by local pathologists. For the current study, slides from both institutions were re-reviewed by a single gastrointestinal pathologist at Indiana University for the following characteristics: Depth of tumor invasion (sm1 *vs* sm2/3), tumor differentiation (well, moderate and poor), presence or absence of lymphatic or perineural invasion (LPI) and the status of deep and lateral margins following resection. A T1b esophageal cancer was defined as tumor extending beyond the muscularis mucosa and into tissue which contains submucosal glands or tumor adjacent to large caliber arteries which would not be present in the mucosa. Tumors classified as sm1 had invasion of tumor into the upper 1/3 of the submucosa and sm2/3 depth of invasion was defined as invasion into the lower 2/3 of the submucosa. Tumor differentiation was determined based on standard histologic features such as growth pattern, gland formation and degree of atypia. LPI was defined as the presence of malignant tumor cells within a lymphatic channel or neural bundle.

Follow-up

Follow-up cross-sectional imaging and endoscopy were performed at the discretion of the endoscopist and consulting physicians at each institution. These data on the study population were obtained both from the treating institution as well as referring physicians and primary care physicians and consisted of endoscopic procedures, imaging studies and clinic visits. The end point of follow-up for study patients included: Death, surgery for esophageal cancer, or loss of patient contact. Patient death was identified by reviewing medical records or by searching the Social Security Death Index. Tumor recurrence was diagnosed when biopsies from the previous or adjacent esophageal EMR site or from either regional or metastatic sites demonstrated pathology consistent with the primary cancer. A univariate analysis was performed in order to identify factors predicting recurrence of cancer after EMR and associated treatment. Variables analyzed in the analysis included: method of EMR (cap *vs* band), pathology depth (sm1 *vs* sm2/3), initial tumor location (proximal 2/3 *vs* distal 1/3 of the esophagus), lymphovascular and/or perineural invasion, degree of tumor differentiation, positive *vs* negative deep and lateral EMR margins, and primary treatment modality (endoscopic ± chemotherapy and/or radiation therapy *vs* surgery).

Statistical analysis

The data were analyzed descriptively using means, medians, ranges and standard deviations. The variables between groups were compared using Fisher's exact tests (GraphPad). $P < 0.05$ was considered statistically significant.

RESULTS

Sixty patients who underwent EMR were found to have pT1b esophageal cancer, including 53 (88%) with adenocarcinoma and 7 (12%) with squamous cell carcinoma. Of the 53 patients with adenocarcinomas, 32 patients (60%) had adequate follow-up after EMR of ⩾ 12 mo (median 34 mo, range 12-103). There were 16 patients in group A, 9 patients in group B, 7 patients in group C and 21 patients in group D (8 with no further treatment and 13 without required 12 mo follow-up). Demographics, EMR method (cap *vs* band), pathology findings and follow-up are summarized in Table 1. Pathology in patients who underwent esophagectomy (group C) showed no residual dysplasia or malignancy in 2, adenocarcinoma with negative nodes in 1, dysplasia in 3 and 1 with unknown findings.

No recurrence of carcinoma developed in 23 patients

Table 1 Characteristics of T1b esophageal adenocarcinoma by treatment modality following endoscopic mucosal resection

	Group A (*n* = 16)	Group B (*n* = 9)	Group C (*n* = 7)	Group D (*n* = 21)	Overall (*n* = 53)
Average age, yr	75 ± 78	70 ± 14	62 ± 5	72 ± 13	71 ± 12
Median follow-up after EMR, mo (range)	34 (12-102)	27 (12-56)	49 (13-103)	N/A	34 (12-103) (for groups A-C, *n* = 32)
EMR method, *n* (%)					
Cap	6 (38)	0 (0)	2 (29)	4 (19)	12 (23)
Band	10 (62)	9 (100)	5 (71)	17 (81)	41 (77)
Pathology depth, *n* (%)					
sm1	6 (38)	4 (44)	1 (14)	2 (10)	13 (25)
sm2/3	10 (62)	5 (56)	6 (86)	19 (90)	40 (75)
Tumor location, *n* (%)					
Proximal two-thirds	2 (13)	1 (11)	1 (14)	5 (24)	9 (17)
Distal one-third	14 (88)	8 (89)	6 (86)	16 (76)	44 (83)
LPI, *n* (%)					
Yes	1 (6)	1 (11)	0 (0)	3 (14)	5 (9)
No	15 (94)	8 (89)	7 (100)	18 (86)	48 (91)
Differentiation, *n* (%)					
Well-moderate	14 (88)	6 (67)	7 (100)	15 (71)	42 (79)
Poor	2 (13)	3 (33)	0 (0)	6 (29)	11 (21)
EMR margins for cancer, *n* (%)					
Deep -/lateral -	6 (38)	2 (22)	1 (14)	2 (10)	11 (21)
Deep -/lateral +	5 (31)	1 (11)	1 (14)	4 (19)	11 (21)
Deep +/lateral +	4 (25)	6 (66)	5 (71)	13 (62)	28 (53)
Deep +/lateral -	1 (6)	0 (0)	0 (0)	2 (10)	3 (6)
Recurrences, *n* (%)					
Yes	6 (38)	1 (11)	2 (29)	N/A	9 (28)
No	10 (63)	8 (88)	5 (71)		23 (72)
Median time to recurrence (mo, range)	21 (6-73)	30 (30-30)	21 (7-35)		21 (6-73) (for groups A-C, *n* = 32)
Location of recurrence					
Local	5	0	1	N/A	6
Metastatic	1	1	1		3

EMR: Endoscopic mucosal resection; LPI: Lymphatic/perineural invasion.

Table 2 Recurrence rates of esophageal adenocarcinoma investigated risk factors of esophageal adenocarcinoma (*n* = 3 *n* (%)

Variable	Recurrence rates	*P* value
EMR method		
Cap	4/8 (50)	0.18
Band	5/24 (21)	
Pathology depth		
sm1	3/11 (27)	0.11
sm2/3	6/21 (29)	
Tumor location		
Proximal 2/3 esophagus	2/4 (50)	0.56
Distal 1/3 esophagus	7/28 (25)	
LPI		
Yes	0/2 (0)	1.00
No	9/30 (30)	
Differentiation		
Well-moderate	8/27 (30)	1.00
Poor	1/5 (20)	
Deep EMR margins		
Positive	4/16 (25)	1.00
Negative	5/16 (31)	
Lateral EMR margins		
Positive	6/22 (27)	1.00
Negative	3/10 (30)	
Primary treatment		
Endoscopic +/- CRT	7/25 (28)	1.00
Surgical	2/7 (29)	

EMR: Endoscopic mucosal resection; LPI: Lymphatic/perineural invasion; CRT: Chemoradiation.

Table 3 Endoscopic ultrasound staging/path accuracy for T1b esophageal adenocarcinoma

EUS staging (*n* = 51)	Pathologic staging		
	pT1sm1 (*n* = 12)	pT1sm2/3 (*n* = 39)	Overall (all pT1b) (*n* = 51)
uT0 Nx	0	1	1
uT1 Nx	11	36	47
uT2 Nx	1	2	3
T staging accuracy	91.7%	92.3%	92.2%

(72%) during a median follow-up of 31 mo (range 12-103). Recurrent adenocarcinoma developed in 9 (28%) patients among all 3 groups. There was no statistically significant differences between recurrences in group A (*n* = 6; 38%), group B (*n* = 1; 11%) and group C (*n* = 2; 29%). Median time to recurrence was 21 mo (range 6-73) in group A, 30 mo in group B, and 9 mo (range 8-10) in group C. Of the recurrences in group A, 5 were local and 1 was metastatic. These local recurrences in group A were treated with further EET alone in two, EET and radiation in one, EET with chemotherapy with radiation in one and radiation in one. The single metastatic recurrence in group A was treated with chemotherapy and radiation. The single recurrence in group B was metastatic and had no further treatment. The two recurrences in group C were

Table 4 Studies evaluating endoscopic management of T1b esophageal adenocarcinoma

Ref.	# Patients	Depth of invasion	Histology	Margins	Remission	Recurrence	Survival
Manner *et al*[12]	21	sm1	Well to moderately differentiated, no lymphovascular invasion	Lateral margins negative in 12	95% at mean 5.3 mo	28% at mean 62 mo (range 45-89)	67% estimated 5-yr survival
Alvarez Herrero *et al*[14]	18	sm1 and sm2/3	Well, moderately and poorly differentiated, some with lymphovascular invasion	Not reported	Not reported	17%	Not reported
Tian *et al*[15]	29	sm1 and sm2-3	Not reported	Not reported	Not reported	Not reported	62% with median duration 34.8 mo
Manner *et al*[13]	66	sm1	Well to moderately differentiated, no lymphovascular invasion	Not reported	84% at mean 4.5 mo	21% at mean 22 mo (range 6-60)	84% estimated 5-yr survival

local in one and metastatic in one. The local recurrence in group C was treated with chemotherapy and the metastatic recurrence in group C was treated with local resection of a hepatic metastasis. No predictors of recurrence of adenocarcinoma were identified on univariate analysis (Table 2).

Of the 32 patients in groups A, B and C, 7 died within 3 years of EMR giving an overall 3 year mortality for all causes of 22%. Specifically within each group, 3 year mortality rates were 13% in group A (2/16), 44% in group B (4/9), and 14% in group C (1/7).

EUS was performed prior to EMR in 51 (96%) of the 53 patients with T1b EAC. T staging accuracy (for T1 malignancy) on EUS for pT1b tumors overall was 92%; specifically for pT1sm1 tumors was 92% and for pT1sm2/3 tumors was 92% (Table 3).

DISCUSSION

Endoscopic therapy is an alternative to esophagectomy for mucosal EAC in select populations[1] and has been included in national guidelines as a curative form of treatment[16]. More recently, "low risk" T1b EAC have been treated with EET as primary therapy in Germany with recurrence rates ranging from 19% to 28% and estimated five-year survival rates up to 84%[12,13]. Two small studies from the United States (n = 15) and the Netherlands (n = 18) showed a recurrence rate of 21% and 17% respectively, with all recurrences in the latter study having initial sm2/3 depth of invasion[14,15].

In our study, we aimed to retrospectively evaluate and compare outcomes of various treatments for T1b EAC after EMR and to evaluate predictors of recurrence after those treatments. We found an overall recurrence rate of 28%, which was not statistically different between those treated with endotherapy alone (38%), chemotherapy, radiation or both (11%) or those undergoing esophagectomy (29%). The overall observed rate of recurrence in our study for those undergoing EET alone is higher than previously reported in patients undergoing EET as primary therapy (Table 4). These differences likely reflect differences in population between most other series (which included primarily low risk T1bsm1 EAC) and our study which evaluated outcomes for all T1b patients. The rate of recurrence in our study does compare favorably to that previously reported for a small cohort of patients with sm2/3 invasion of 33%[14].

We found that most recurrences following EMR in those treated at least partly endoscopically (groups A and B) were localized. Of the patients who underwent EET alone, there were 6 recurrences (38%), five of which were localized to the esophagus with only 1 having metastatic disease 21 mo following EMR. Of the patients who underwent EET + chemotherapy and/or radiation, 1 (11%) had metastatic recurrence 30 mo after resection. Therefore, EET with or without chemotherapy or radiation, may be a reasonable initial treatment strategy for a subset of patients with T1b EAC, especially those that refuse or are unfit for surgical intervention due to medical comorbidities or home support since most recurrences appear to be localized.

In those that underwent esophagectomy, we identified 2 recurrences out of 7 patients (29%). Our recurrence rate is similar to a recent retrospective study including 26 patients with T1b EAC undergoing surgical resection which showed a 23% recurrence rate[17]. Recurrence or metastatic disease discovered after resection may be related to micrometastatic disease that was unable to be identified prior to esophagectomy.

Overall, we found a 3-year survival rate of 78% when evaluating the patients in our study; more specifically a rate of 87% in those treated with EET only and 56% in those treated with EET + chemotherapy and/or radiation. When combining those treated at least partly endoscopically, the survival rate at 3 years was 76%. Manner *et al*[13] previously have shown an estimated 5-year survival rate of 84% in those treated with EET with "low risk" T1b. Our lower survival rate is likely reflected in our patient population, as we evaluated all patients with T1b EAC and not only those with "low risk" disease. Tian *et al*[15] reported on a group of patients (n = 29) more similar to our cohort including "low risk" and higher risk T1b EAC patients [sm1 (46%) and sm2-3 (54%) invasion] that underwent either EET, chemo/radiation or a combination of both and showed a

survival rate of 72% at mean 34.8 mo.

We failed to identify any individual predictors of cancer recurrence in this population. A previous retrospective study with 39 patients with T1b EAC treated with EET alone showed decreased survival in patients with older age and lymphovascular invasion, although it did not specifically assess for predictors of cancer recurrence[18]. In our study, we were unable to identify lymphatic and perineural invasion as predictors of recurrence.

A recent prospective study from Germany evaluated the risk of lymph node metastases when comparing "low risk" (sm1 invasion) to "high risk" (sm2/3 invasion) T1b EAC in patients treated both surgically and with EET, and found a 2% risk of lymph node metastasis in pT1bsm1 tumors and 9% in pT1bsm2/3 tumors, which is lower than has generally been reported in prior studies[19]. In our study which includes both sm1 and sm2/3 invasion, we similarly found 6% of patients with metastatic lymph nodes either on initial staging or on surveillance (one each with sm1 and sm2/3 tumors).

Previous studies have shown excellent accuracy for staging both T1a and T1b esophageal cancers. Specifically, a previous meta-analysis showed good accuracy with area under the curve > 0.93 for both T1a and T1b esophageal cancers[20]. We also demonstrated overall diagnostic accuracy of 91% for pT1 lesions in our cohort.

Our study has several strengths including data from all T1b cancers removed by EMR from two tertiary care referral centers, re-review of all pathology by a single pathologist, and evaluation of outcomes of medical and surgical therapy for these patients. However, our study is limited by the number of patients who refused further therapy or were lost to follow-up which may limit the ability to compare outcomes from various treatments after resection.

In conclusion, our study shows that endoscopic therapy alone following EMR of a T1b cancer is associated with a recurrence rate of 38%. Therefore, treatment with adjuvant therapy appears reasonable in this population when possible. No particular variable is predictive of recurrence following EMR of T1b adenocarcinomas. Therefore, future research into the management and risk stratification of these patients after EMR is warranted.

COMMENTS

Background

Endoscopic eradication therapy (EET) (including endoscopic mucosal resection and ablative techniques) have become standard of care for high grade dysplasia and T1a esophageal cancer. The use of EET for T1b cancers is more controversial due to the higher risk of lymph node involvement and data is lacking.

Research frontiers

Recent studies have shown that "low risk" T1b esophageal cancer can be treated safely and effectively with EET. Many of these studies include relatively small numbers of patients, and do not address higher risk T1b esophageal cancers or the use of EET in conjunction with other treatment modalities such as chemotherapy or radiation.

Innovations and breakthroughs

In the current study, the authors attempted to evaluate the clinical outcomes and recurrence rates of T1b esophageal cancers treated with EET alone, as well as those treated with EET in conjunction with chemotherapy and/or radiation as well as those undergoing surgical resection. In addition, the authors attempted to identify factors that may predict recurrence.

Applications

For patients with T1b esophageal cancer and treated with EET alone, the recurrence rate was 38%; therefore treatment with adjuvant therapy in conjunction with EET seems reasonable in patients that are either unable to or refuse to undergo esophagectomy. No particular variables were identified that predict recurrence of cancer in this population following EMR. Further research in these areas regarding management and risk stratification will be required.

Terminology

T1b esophageal adenocarcinoma - cancer which invades into but not through the submucosal layer; Endoscopic eradication therapy - Endoscopic treatment including endoscopic mucosal resection and ablative techniques such as radiofrequency ablation and cryotherapy.

Peer-review

A retrospective study is reported to investigate outcomes and recurrences of T1b esophageal adenocarcinomas following EMR. The topic is relevant, and the data collection done by the authors are very useful.

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ORIGINAL ARTICLE

Retrospective Study

Identification of factors associated with sedation tolerance in 5000 patients undergoing outpatient colonoscopy: Canadian tertiary center experience

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Author contributions: Shingina A and Enns R designed the project; Shingina A and Svarta S designed ethics proposal; Shingina A, Ou G, Svarta S, Kwok R, Donaldson K collected the data; Takach O and Lam E analyzed the data; Shingina A, Ou G, Svarta S, Lam E and Enns R wrote the manuscript.

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Abstract

AIM

To develop a prediction model aimed at identifying patients that may require higher than usual sedation doses during colonoscopy.

METHODS

A retrospective chart review on 5000 patients who underwent an outpatient colonoscopy at St. Paul's Hospital from 2009 to 2010 was conducted in order to develop a model for identifying patients who will require increased doses of sedatives. Potential predictor variables including age, gender, endoscopy indication, high sedation requirements during previous endoscopies, difficulty of the procedure, bowel preparation quality, interventions, findings as well as current use of benzodiazepines, opioids and alcohol were analyzed. The outcome of study was the use of

high dose of sedation agents for the procedure. In particular, the high dose of sedation was defined as fentanyl greater than 50 mcg and midazolam greater than 3 mg.

RESULTS

Analysis of 5282 patients (mean age 57 ± 12, 49% female) was performed. Most common indication for the procedure was screening colonoscopy (57%). Almost half of our patients received doses exceeding Fentanyl 50 mcg and Midazolam 3 mg. Logistic regression models identified the following variables associated with high sedation: Younger age (OR = 0.95 95%CI: 0.94-0.95; $P < 0.0001$); abdominal pain (OR = 1.45, 95%CI: 1.08-1.96); $P = 0.01$) and Inflammatory Bowel Disease (OR = 1.45, 95%CI: 1.04-2.03; $P = 0.02$) as indications for the procedure; difficult procedure as defined by gastroenterologist (OR = 1.73, 95%CI: 1.48-2.03; $P < 0.0001$); past history of abdominal surgery (OR = 1.33, 95%CI: 1.17-1.52; $P < 0.0001$) and previous colonoscopy (OR = 1.39, 95%CI: 1.21-1.60; $P = 0.0001$) and alcohol use (OR = 1.26, 95%CI: 1.03-1.54; $P = 0.02$). Age and gender adjusted analysis yielded inflammatory bowel disease as an indication (OR = 3.17, 95%CI: 1.58-6.37; $P = 0.002$); difficult procedure as defined by an endoscopist (OR = 5.13 95%CI: 2.97-8.85; $P = 0.0001$) and current use of opioids, benzodiazepines or antidepressants (OR = 2.88, 95%CI: 1.74-4.77; $P = 0.001$) having the highest predictive value of high sedation requirements. Our prediction model using the following pre-procedural variables including age, indication for the procedure, medication/substance use, previous surgeries yielded an area under the curve of 0.76 for Fentanyl $\geqslant$ 100 mcg and Midazolam $\geqslant$ 3 mg.

CONCLUSION

Pre-procedural planning is the key in conducting successful, efficient colonoscopy. Logistic regression analysis of 5000 patients who underwent out-patient colonoscopy revealed the following factors associated with increased sedation requirement: Younger age, female gender, difficult endoscopy, specific indications as well as cardiopulmonary complications and current use of opioids/benzodiazepines. Age and gender adjusted analysis yielded similar results. These patients are more likely to need a longer recovery periods post-endoscopy, which could result in additional time and personnel requirements. The final predictive model has good predictive ability for Fentanyl $\geqslant$ 100 mcg and Midazolam $\geqslant$ 3 mg and fair predictive ability for Fentanyl $\geqslant$ 50 mcg and Midazolam $\geqslant$ 2 mg. The external validity of this model is planned to be tested in another center.

Key words: Colonoscopy; Sedation; Sedation tolerance; Fentanyl; Midazolam; Predictive model

Core tip: This manuscript explores patient specific characteristics that are associated with increased sedation tolerance based on retrospective review of 5000 patients that underwent outpatient colonoscopies. Using a logistic regression analysis, we developed a predictive model that can identify patients requiring higher than usual sedation doses using pre-procedurally available patient parameters. The final prediction model that includes age, indication for the procedure, medication/substance use, previous surgeries yielded an area under the curve of 0.76 for Fentanyl $\geqslant$ 100 mcg and Midazolam $\geqslant$ 3 mg. This modelling could help optimize periprocedural planning and potentially identify patients who would benefit from alternative sedation methods, *e.g.*, propofol.

Shingina A, Ou G, Takach O, Svarta S, Kwok R, Tong J, Donaldson K, Lam E, Enns R. Identification of factors associated with sedation tolerance in 5000 patients undergoing outpatient colonoscopy: Canadian tertiary center experience. *World J Gastrointest Endosc* 2016; 8(20): 770-776 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i20/770.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i20.770

INTRODUCTION

Lower gastrointestinal endoscopy remains a key modality for colorectal cancer evaluation and polyp detection. Patient satisfaction with colonoscopies remains an important area for quality improvement and have been linked to the ability to achieve adequate sedation in the endoscopy suite[1]. Several prospective studies evaluated patient characteristics that influence endoscopy satisfaction and identified younger age, female gender, high levels of pre-procedure anxiety and current use of benzodiapines/opioids as risk factors for decreased procedure tolerance[2-5]. Currently a combination of benzodiazepines (*e.g.,* Midazolam) with opioids (*e.g.,* Fentanyl) is recommended for sedation during colonoscopic procedures. However, few predictive tools have been developed to accurately identify patients who will require higher than routine doses of procedural sedation.

Recently, one model using a retrospective database was used to evaluate patient pain thresholds included such variables as younger age, procedure indication, gender, trainee participation, psychiatric history and benzodiazepine and opioid use[5]. However, this model reached only moderate discriminative ability with a receiver operating characteristic (ROC) area under the curve (AUC) of 0.648. The development of an accurate predictive model could simplify procedure planning, eliminate unnecessary patient discomfort thereby improving patient satisfaction. It can also decrease peri-procedural time associated with administration of additional doses of sedatives and ultimately lead to a potentially increased diagnostic yield of the procedure.

In an attempt to address the paucity of data on factors associated with increased sedation rates in

colonoscopy we reviewed our experience in a large tertiary care hospital and developed a predictive tool that could be used for this purpose.

MATERIALS AND METHODS

Patient population and data gathering

A retrospective chart review was conducted on 5282 consecutive patients who underwent a non-urgent, outpatient colonoscopy within a two-year period between January 2009 and December 2010. Patients undergoing upper endoscopy on the same day were excluded. The final analysis included 5064 patients after patients with missing information and duplicate entries were excluded. Charts were reviewed and the following patient related variables were recorded: (1) age at the time of procedure; (2) gender; (3) indication for the procedure; (4) use of sedatives as well as doses; (5) past surgical history; (6) previous endoscopy; (7) high sedation requirements during previous endoscopy; (8) current use of benzodiazepines/opiods/antidepressants; and (9) current alcohol use. Furthermore, peri-procedural factors including: (1) quality of preparation; (2) difficulty of procedure as commented by the endoscopist; (3) finding on endoscopy; (4) interventions; and (5) cardiopulmonary complications.

Definitions

Increased sedation rates were defined as Fentanyl doses > 50 mcg and Midazolam doses > 3 mg a priori at the discretion of the endoscopists at our center. Increased sedation rates during previous endoscopic procedures followed the same definition. However, variable dose cut offs were subsequently tested in predictive models. Mild alcohol use was defined as less than 4 drinks/wk with moderate/severe defined as over 4 drinks/wk. Alcohol use was subsequently excluded from final analysis due to large proportion of missing data. Indication for the procedure was classified into one of five categories: (1) screening/surveillance; (2) abdominal pain; (3) inflammatory bowel disease (IBD); (4) lower gastrointestinal bleeding bleeding; (5) change in bowel movements.

Statistical analysis

Summary statistics were used to describe the characteristics of the study cohort. In particular, the data were summarized as mean, standard deviation, for continuous variables and count and percentage for categorical variables. We used a logistic regression model in an attempt to identify variables associated with higher than expected doses for midazolam and fentanyl. These variables were then included in the multivariate regression model.

In order to create a clinical prediction model of increased does of sedation, multivariable logistic regression model with backward elimination based on Akaike Information Criterion was applied[7]. The performance of the final model was evaluated from two aspects, discrimination (the ability to discriminate patients who need high does and those that do not) and calibration (the agreement between observed outcomes and model predictions). The discrimination of the model was measured with the use of the area under ROC curves. Discrimination is assumed to be useful if AUC $\geqslant$ 0.75[6]. Furthermore, we applied bootstrapping technique to account for model over-fitting as internal model validation. Three hundred bootstrapping samples were created. A biased corrected AUC and calibration plot were generated. All statistical analysis was performed using SAS software. The statistical methods of this study were reviewed by Oliver Takach, Dr. Eric Lam, Terry Lee and Hong Qian.

Table 1 Study population characteristics

Variable		No. (%)
Age (mean ± standard deviation)		56.94 ± 13.06
Female gender		2306 (50.1%)
Indication of the procedure	Screening/ surveillance	2892 (57.15%)
	Bleeding	1036 (20.4%)
	Abdominal pain	240 (4.72%)
	Change in bowel movements	690 (13.64%)
	Inflammatory bowel disease	210 (3.99%)
Previous history of surgery	No	2343 (50.7%)
	Yes	2363 (49.26%)
Previous history of colonoscopy and of increased dose of sedation for colonoscopy	Colonoscopy with high dose(Fent > 50 mcg, Midazolam > 3 mg)	3300 (64.1%)
	Colonoscopy with standard dose	470 (9.1%)
	Colonoscopy with unknown sedation dose	305 (5.9%)
	No previous colonoscopy	1076 (20.9%)
Current use of opioids		243 (4.8%)
Current use benzodiazepines		254 (5%)
Current use antidepressants		589 (11.6%)
Current use of opioids or benzodiazepines or antidepressants		826 (16.96%)
Difficult procedure		1038 (19%)
Cardiopulmonary complications		23 (0.4%)
Findings	Any	4139 (78%)
	Polyps	3439 (83%)
	Haemorrhoids	1970 (48%)
	Diverticuli	1050 (35%)
	Colitis	72 (1.7%)
	Stricture	71 (1.7%)
Intervention	Any	3231 (61%)
	Biopsy	2139 (66%)
	Polypectomy	1621 (50%)
Current use alcohol		1930 (46.9%)
Fentanyl dose > 50 mcg		2244 (46%)
Midazolam dose > 3 mg		3000 (62%)
Fentanyl dose > 50 mcg and midazolam > 3 mg		1959 (40%)

Table 2 Multivariate logistic regression analysis for Fentanyl dose > 50 mcg

Variable for fentanyl > 50 mcg	Coefficient	*P* value	OR (95%CI)
Age	-0.04	0.0001	0.957 (0.952-0.963)
Indication for endoscopy			
Bleeding	-0.04	0.62	0.96 (0.82-1.12)
Abdominal pain	0.29	0.06	1.34 (0.99-1.81)
Change in BM	0.07	0.44	1.08 (0.88-1.31)
IBD	0.46	0.009	1.59 (1.22-2.49)
Intraprocedural characteristics			
Difficult procedure	0.45	0.0001	1.57 (1.34-1.81)
Intervention	0.15	0.013	1.17 (1.033-1.32)
Bad preparation	0.16	0.14	1.17 (0.94-1.45)
Past history			
Abdominal surgery	0.33	0.0001	1.40 (1.23-1.59)
Colonoscopy	0.26	0.0002	1.30 (1.13-1.49)
Current medications/substance use			
Opioids	0.34	0.028	1.40 (1.03-1.91)
Benzodiazepines	0.37	0.017	1.45 (1.06-1.98)
Antidepressants	0.26	0.009	1.30 (1.06-1.60)
Alcohol (any *vs* none)	0.23	0.022	1.26 (1.03-1.54)

IBD: Inflammatory bowel disease; BM: Bowel movements.

Table 3 Multivariate logistic regression analysis for midazolam dose > 3 mg

Variable for midazolam > 3 mg	Coefficient	*P* value	OR (95%CI)
Age	-0.05	0.0001	0.94 (0.939-0.95)
Female gender	-0.06	0.0004	0.78 (0.68-0.89)
Indication for endoscopy (reference - screening)			
Bleeding	-0.41	0.0001	0.65 (0.56-0.77)
Abdominal pain	0.38	0.032	1.46 (1.03-2.08)
Change in BM	0.02	0.849	1.02 (0.82-1.25)
IBD	0.19	0.346	1.21 (0.81-1.80)
Intraprocedural characteristics			
Difficult procedure	0.50	0.0001	1.64 (1.38-1.96)
Past history			
Abdominal surgery	0.31	0.0001	1.37 (1.20-1.57)
Medication/substance use			
Opioids	0.38	0.025	1.47 (1.04-2.07)
Antidepressants	0.33	0.018	1.39 (1.11-1.73)

IBD: Inflammatory bowel disease; BM: Bowel movements.

RESULTS

Characteristics of study population

The study population consisted of 50.1% females, mean age of 56 years (Table 1). The most common indication for colonoscopy was malignancy screening/surveillance that accounted for 57% of procedures. Approximately half of the population had some history of abdominal surgery (49%) and colonoscopy (79%). The use of opioids, benzodiazepines and antidepressants was identified in 4.8%, 5% and 11.6% of patients respectively or 17% of all patients on any of the three drugs. There was a significant proportion of alcohol use data missing (30%); of patients on whom the data was available 46% used alcohol on a regular basis.

The procedure was identified as difficult in 19% by a gastroenterologist. The most common cause for difficult procedure was identified as "tortuous colon" accounting for almost 50%, followed by looping of the colonoscope in 20% of patients. Poor preparation and patient discomfort was identified as a reason in 2% and 3% respectively. Cardiopulmonary complications were recorded in 0.4% of procedures. Presences of any findings were seen in 78% of procedures with polyps being the most common one (83%). Interventions were carried out in 61% of all colonoscopies, most common of those being a biopsy (66%).

Logistic regression analyses to identify variables predicting high sedation doses

Univariate logistic regression analysis revealed that younger age, indication for colonoscopy, intraprocedural characteristics such as difficult procedure, interventional procedure, poor preparation, past history of abdominal surgery as well as substance use were independently predictive of increased Fentanyl doses defined as more than 50 mcg (data not shown). Including these variables in the multivariate regression model showed that younger age (OR = 0.95, 95%CI: 0.95-0.96), presence of IBD (OR = 1.59, 95%CI: 1.22-2.49), difficult procedure (OR = 1.57, 95%CI: 1.34-1.81), presence of intervention (OR = 1.17, 95%CI: 1.03-1.32), past history of surgery (OR = 1.4, 95%CI: 1.23-1.59) and colonoscopy(OR = 1.3, 95%CI: 1.13-1.49) were predictors of Fentanyl doses over 50 mcg (Table 2).

Similar multivariate analysis of Midazolam dosages over 3 mg revealed female gender (OR = 0.78, 95%CI: 0.68-0.89) in addition to younger age (OR = 0.94, 95%CI: 0.93-0.95), presence of bleeding (OR = 0.65, 95%CI: 0.56-0.77) and abdominal pain (OR = 1.46, 95%CI: 1.03-2.08) as indications for the procedure, difficulty of the procedure (OR = 1.64, 95%CI: 1.38-1.96), history of abdominal surgery (OR = 1.37, 95%CI: 1.20-1.57) as well as opioid (OR = 1.47, 95%CI: 1.04-2.07) and antidepressant use (OR = 1.39, 95%CI: 1.11-1.73) (Table 3).

Multivariate regression analysis of patients requiring both Fentanyl dose of over 50 mcg and midazolam dose over 3 mg revealed the following significant variables: Younger age (OR = 0.95, 95%CI: 0.94-0.95), abdominal pain (OR = 1.45, 95%CI: 1.08-1.96) and IBD (OR = 1.45, 95%CI: 1.04-2.03) as indications for the procedure, difficult procedure (OR = 1.73, 95%CI: 1.48-2.03), past history of abdominal surgery (OR = 1.33, 95%CI: 1.17-1.52) and colonoscopy (OR = 1.39, 95%CI: 1.21-1.60) as well as alcohol use (OR = 1.26, 95%CI: 1.03-1.53) (Table 4).

Age and gender adjusted analysis

Since previously published literature identified younger age and female gender as predictors of high sedation requirements, we also carried out age and gender

Table 4 Multivariate regression analysis of both Fentanyl > 50 mcg and Midazolam > 3 mg

Variable for Fentanyl > 50 mcg and midazolam > 3 mg	Coefficient	*P* value	OR (95%CI)
Age	-0.04	< 0.0001	0.95 (0.94-0.95)
Indication for endoscopy (reference - screening)			
Bleeding	-0.11	0.18	0.89 (0.76-1.05)
Abdominal pain	0.37	0.01	1.45 (1.08-1.96)
Change in BM	0.13	0.18	1.14 (0.93-1.40)
IBD	0.37	0.02	1.45 (1.04-2.032)
Intraprocedural characteristics			
Difficult procedure	0.55	< 0.0001	1.73 (1.48-2.03)
Interventions	0.1	0.12	1.10 (0.97-1.25)
Past history			
Abdominal surgery	0.30	< 0.0001	1.33 (1.17-1.52)
Colonoscopy	0.33	0.0001	1.39 (1.21-1.60)
Medication/substance use			
Opioids	0.41	0.46	0.49 (0.07-3.36)
Benzodazepines	0.36	0.36	3.76 (0.21-64)
Antidepressants	0.22	0.6	0.48 (0.03-7.76)
Alcohol	0.23	0.02	1.26 (1.03-1.54)

BM: Bowel movements; IBD: Inflammatory bowel disease.

adjusted analyses (Supplemental Table 1). Significance of only one variable changed: Abdominal pain as an indicator for the procedure was no longer statistically impacting the higher dose of sedation medications (P = 0.03 in unadjusted *vs* P = 0.06 in age/gender adjusted analysis).

Development of predictive model

To predict patients who will require higher than routine doses of procedural sedation before the procedure, a prediction model was created using patient characterisers recorded at admission. Age, gender, previous history of surgery, previous history of colonoscopy with high dose, indication of the procedure and current use of opioids, benzodiazepines, antidepressants or alcohol were included in the final model for predicting the use of fentanyl > 50 mcg plus midazolam > 3 mg (Table 5).

In our model the probability of high dose correlated negatively with younger age, with proportional decrease for every 10 years of life, female gender, previous colonoscopies, and history of surgical procedures, composite of current use of opioids/benzodiazepines/antidepressants as well indications for the procedure. The bootstrapping bias corrected ROC AUC of the final prediction model was 0.66 for Midazolam > 3 mg and Fentanyl > 50 mcg doses indicating moderate discriminative ability (supplemental matetial).

We analysed the predictive ability of our model in variable higher Fentanyl and Midazolam doses (Table 6). The model using Fentanyl > 100 mcg and Midazolam > 3 and 4 mg reached the acceptable level of discrimination ability of 0.7 and remained under 0.8 indicating its moderate discrimination ability.

Table 5 Multivariable prediction model for high Fentanyl and Midazolam doses

Pre-procedural variables	Measurement units	Odds ratio, 95%CI; *P* value
Age	10-yr	0.62, 0.52-0.73; P < 0.0001
Gender	Female *vs* male	2.31, 1.32-4.05; P = 0.01
Previous colonoscopy	Yes *vs* no	1.98, 1.15-3.42; P = 0.02
Previous surgery	Yes *vs* no	1.33, 0.78-2.25; P = 0.25
Current use of opioids, benzodiazepines or antidepressants	Yes *vs* no	2.50, 1.47-4.27; P = 0.004
Indications (reference - screening)	Bleeding	1.90, 1.03-3.51; P = 0.04
	Abdominal pain	3.07, 1.29-7.31; P = 0.01
	Change in BM	1.45, 0.71-2.97; P = 0.30
	IBD	3.01, 1.43-6.35; P = 0.01

BM: Bowel movements; IBD: Inflammatory bowel disease.

DISCUSSION

Pre-procedural planning is key for successful and efficient colonoscopy. Identifying patients requiring higher sedation rates could optimize sedation methods and use of scheduling with improved efficiency in addition to better tolerated procedures.

Our analysis of over 5000 patients yielded several prediction variables of high sedation rates. These included: Younger age, indication for the procedure, difficulty of the procedure, previous history of high endoscopy sedation requirements and substance use. A predictive model including patients' age, indication for procedure, medication/substance use, previous surgeries as well as previously high sedation requirements yielded a good predictive model. These factors can help physicians in planning endoscopy slates and ensure appropriate time can be booked for procedure completion.

To our knowledge, this is the first and the largest study using Canadian data that describes sedation tolerance in outpatient colonoscopies. Another predictive model was recently described by Braunstein *et al*[5] after reviewing data on 13711 EGDs and 21763 colonoscopies using a retrospective database in the United States. In contrast to our study, the stratifying clinical outcomes prior to endoscopy (SCOPE) scoring system included inpatient colonoscopies as well as used a composite endpoint of sedation doses in top quintile stratified per endoscopist plus endoscopist report of patient discomfort or agitation during the procedure. The SCOPE model did not evaluate previous surgical or endoscopic history of the patients, however it did include the use of tobacco and lower BMI. Despite these differences, the final model for colonoscopy prediction tool was similar to ours perhaps validating our findings despite a smaller sample size. The predictive value of the SCOPE class model remained only moderate with areas under the ROC curves of 0.648 and comparable to ours at 0.7. It is possible that the moderate predictive ability of both models is attributed to variables that

Table 6 Performance of prediction model using variable sedation doses cut-offs

Fentanyl (mcg)	Midazolam (mg)	AUC	Prevalence rate
> 50	> 3	0.67	43%
> 50	> 4	0.70	22%
> 75	> 3	0.68	23%
> 75	> 4	0.70	18%
> 100	> 3	0.76	2%
> 100	> 4	0.77	2%

AUC: Area under the curve.

could not be extracted from retrospective data, such as the patient's pre-procedural anxiety as well as the subjective discretion of the endoscopist. Nevertheless, these models may help in pre-identifying patients that may benefit from deeper sedation (*e.g.,* propofol) and may serve as a starting point in pre-endoscopic assessment.

This study has several limitations. First, our experience is limited to one tertiary care center with eight endoscopists. As such, it may have limited generalizability to other centers and perhaps could reflect the specific sedation preferences of individual endoscopists. Second, a large proportion of substance and alcohol use data was missing which could otherwise improve the discriminatory ability of our predictive model. Third, this was a retrospective review study and the model needs to be prospectively evaluated. Finally, propofol was not assessed in this study as it is not commonly used in a Canadian population and as such this study may not be applicable to this patient population.

Further prospective studies are needed to test the model in order to increase its generalizability and also potentially incorporating subjective variables such as patient anxiety and endoscopist subjective judgement.

ACKNOWLEDGMENTS

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COMMENTS

Background

Patient satisfactions with colonoscopies remain an important area for quality improvement and have been linked to the ability to achieve adequate sedation in the endoscopy suite. Predicting which patients may require high doses of opioid/benzodiazepine combination may help with periprocedural planning (*e.g.,* accounting for longer recovery times, using alternative sedation methods such as propofol) and improve overall patient experience.

Research frontiers

Recently, one model using a retrospective database was used to evaluate patient pain thresholds included such variables younger age, procedure indication, gender, trainee participation, psychiatric history and benzodiazepine and opioid use. However, this model reached only moderate discriminative ability with a receiver operating characteristic (ROC) area under the curve (AUC) of 0.648.

Innovations and breakthroughs

This is the first and the largest study using Canadian data that describes sedation tolerance in outpatient colonoscopies to our knowledge. In this model the probability of high dose correlated negatively with younger age, with proportional decrease for every 10 years of life, female gender, previous colonoscopies, and history of surgical procedures, composite of current use of opioids/benzodiazepines/antidepressants as well indications for the procedure. The model for predicting patients requiring Fentanyl > 100 mcg and Midazolam > 3-4 mg reached the acceptable level of discrimination ability of 0.7 and remained under 0.8 indicating its moderate discrimination ability.

Applications

The analysis of over 5000 patients yielded a moderately predictive model for identifying patients requiring high opioid/benzodiazepine doses. This is in concordance with previously reported models in SCOPE study. It is possible that the moderate predictive ability of both models is attributed to variables that could not be extracted from retrospective data, such as the patient's pre-procedural anxiety as well as the subjective discretion of the endoscopist. Nevertheless, these models may help in pre-identifying patients that may benefit from deeper sedation (*e.g.,* propofol) and may serve as a starting point in pre-endoscopic assessment.

Terminology

To assess the ability of the prediction model to discriminate patients who need high does with those don't, the concordant statistics (C-index) was calculated. The C-index is equivalent to the area under ROC curve and ranges from 0 to 1. A value of 0.5 is considered as no discrimination ability. As a general rule, a value between 0.7 and 0.8 is considered the threshold for acceptable discriminatory performance and a value of > 0.8 is considered to be the threshold for excellent discriminatory performance.

Peer-review

This paper presents the results of retrospective analysis of sedation dose requirement of benzodiazepine with opiates used for colonoscopy. The basic objective of the study was to provide the data as to the optimization of sedation conditions for patients undergoing colonoscopy. The data obtained with 5000 patients support the notion that the predictive model can help to identify patients requiring higher than usual sedation doses. Statistical analyses were conducted in detail and authors have led a conclusion based on the findings. That was helpful for us to identify patients that may require higher sedation doses for successful and efficient colonoscopy.

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ORIGINAL ARTICLE

Retrospective Study

Combination of two-hour post-endoscopic retrograde cholangiopancreatography amylase levels and cannulation times is useful for predicting post-endoscopic retrograde cholangiopancreatography pancreatitis

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Author contributions: All authors contributed to this manuscript.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Board of Toyonaka Municipal Hospital.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis retrospectively used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. However, this study was announced on the website at our hospital for a certain period and subjects who did not want to be used their data in this study were guaranteed the right to refuse.

Conflict-of-interest statement: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

Data sharing statement: Dataset is available from the corresponding author at hayashishiro1976@yahoo.co.jp, when data sharing was anonymized and the project was approved by the Institutional Review Board of Toyonaka Municipal Hospital.

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Abstract

AIM

To estimate the efficacy of 2 h post-endoscopic retrograde cholangiopancreatography (ERCP) serum amylase levels and other factors for predicting post-ERCP pancreatitis.

METHODS

This was a retrospective, single-center cohort study of consecutive patients who underwent ERCP from January 2010 to December 2013. Serum amylase levels were measured 2 h post-procedure, and patient- and procedure-related pancreatitis (PEP) risk factors were

analyzed using a logistic model.

RESULTS

A total of 1520 cases (average age 72 ± 12 years, 60% male) were initially enrolled in this study, and 1403 cases (725 patients) were ultimately analyzed after the exclusion of 117 cases. Fifty-five of these cases developed PEP. We established a 2 h serum amylase cutoff level of two times the upper limit of normal for predicting PEP. Multivariate analysis revealed that a cannulation time of more than 13 min [odds ratio (OR) 2.28, 95%CI: 1.132-4.651, P = 0.0210] and 2 h amylase levels greater than the cutoff level (OR = 24.1, 95%CI: 11.56-57.13, P < 0.0001) were significant predictive factors for PEP. Forty-seven of the 55 patients who developed PEP exhibited 2 h amylase levels greater than the cutoff level (85%), and six of the remaining eight patients who developed PEP (75%) required longer cannulation times. Only 2 of the 1403 patients (0.14%) who developed PEP did not exhibit concerning 2 h amylase levels or require longer cannulation times.

CONCLUSION

These findings indicate that the combination of 2 h post-ERCP serum amylase levels and cannulation times represents a valuable marker for identifying patients at high risk for PEP.

Key words: Serum amylase levels; Cannulation time; Post-endoscopic retrograde cholangiopancreatography pancreatitis; Predictor

Core tip: Serum amylase levels have a high negative predictive value (NPV; 95%-100%) and have therefore previously been used to predict post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) to facilitate patient discharges. However, the positive predictive value (PPV) of serum amylase is highly variable (4%-62%); therefore, a more useful PEP predictor is needed. In this retrospective study, we identified useful predictive factors *via* multivariate analysis and the combination 2 h amylase levels and cannulation times. The 2 h amylase levels exhibited a good NPV (99%) and a poor PPV (22%) similar to those of previous reports but exhibited a sensitivity of only 86% with respect to PEP detection. However, the combined use of the above two variables increased the sensitivity to 96%; thus, this combination may enable clinicians to detect patients at high risk for PEP during the early phase of treatment.

Hayashi S, Nishida T, Shimakoshi H, Shimoda A, Amano T, Sugimoto A, Takahashi K, Mukai K, Matsubara T, Yamamoto M, Nakajima S, Fukui K, Inada M. Combination of two-hour post-endoscopic retrograde cholangiopancreatography amylase levels and cannulation times is useful for predicting post-endoscopic retrograde cholangiopancreatography pancreatitis. *World J Gastrointest Endosc* 2016; 8(20): 777-784 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i20/777.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i20.777

INTRODUCTION

Acute pancreatitis is a common post-endoscopic retrograde cholangiopancreatography (ERCP) complication and is therefore known as post-ERCP pancreatitis (PEP). PEP may result in procedure-related death and is often unpreventable. Moreover, no medications appear to be effective with respect to acute pancreatitis treatment[1,2]. Andriulli *et al*[3] conducted a systematic review of 21 selected surveys involving 16855 patients exhibiting a 3.5% incidence of PEP and observed that 0.11% of those patients died. Although many PEP prophylactic treatments have been reported[4-6], only prompt aggressive intravenous hydration is reportedly effective at reducing morbidity and mortality[7-10]. Therefore, early PEP identification is important, as it facilitates early intervention and may prevent disease progression and death.

Many studies have investigated the factors that increase the risk of PEP[7-10]. Those risk factors can generally be divided into the following two types: Patient-related factors and procedure-related factors. The patient-related risk factors for PEP reportedly include previous PEP, female gender, younger age, normal serum bilirubin levels, and the absence of chronic pancreatitis, whereas the procedure-related risk factors for PEP reportedly include cannulation attempt duration, pancreatic guidewire passage, pancreatic injection, precut sphincterotomy, biliary balloon sphincter dilatation, and failed bile duct stone clearance. No evidence exists indicating that hospital ERCP volume influences PEP occurrence[11,12]. The aforementioned risk factors synergistically increase PEP risk. Serum amylase levels less than 1.5 times the upper limit of normal (ULN) at 2-4 h post-ERCP have a very negative predictive value (NPV) for PEP. The European Society of Gastrointestinal Endoscopy (ESGE) guidelines recommend testing serum amylase or lipase levels 2-6 h after ERCP in patients presenting with pain. Patients exhibiting amylase or lipase values less than 1.5 and 4 times the ULN, respectively, may be discharged on the day of ERCP without concern regarding PEP risk[5]. However, very few tests with good positive predictive values (PPVs) for PEP exist. This study aimed to estimate the efficacy of 2 h post-ERCP serum amylase levels and other risk factors for predicting PEP.

MATERIALS AND METHODS

This study was a retrospective single-center cohort study of consecutive hospitalized patients who underwent ERCP or ERCP-related procedures at Toyonaka Municipal Hospital, certified as a teaching hospital by the Japan Gastroenterological Endoscopy Society (JGES)

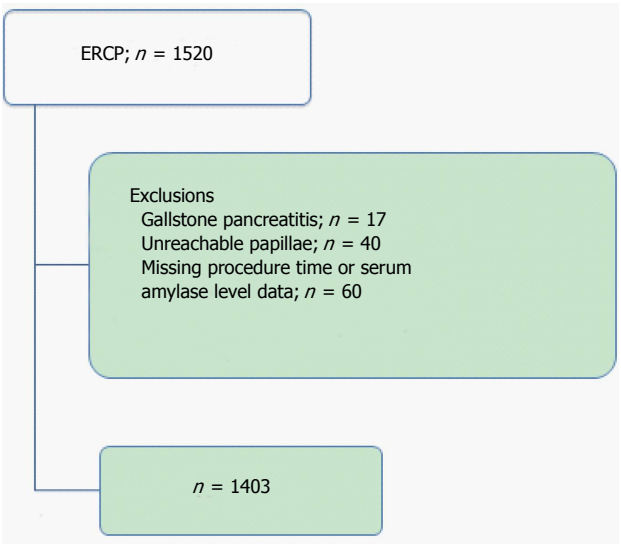

Figure 1 Study flow chart. ERCP: Endoscopic retrograde cholangiopancreatography.

(No. 1239), from January 2010 to December 2013. A total of 1520 procedures were enrolled in this study. Of these cases, 117 procedures with the following conditions were excluded: (1) gallstone pancreatitis, *n* = 17; (2) unreachable papillae, *n* = 40; and (3) missing procedure time or serum amylase level data, *n* = 60 (including cases with pancreatitis before ERCP). A total of 1403 procedures were ultimately analyzed in the present study (Figure 1).

The following demographic and clinical data were collected: Age and sex, ERCP indications, ERCP history, and 2 h post-ERCP serum amylase levels (after scope removal from the patient). The following procedural data were retrospectively collected from patient medical records: Biliary and pancreatic sphincterotomy with and without stent placement, procedure time, cannulation time, and complications. This study was approved by the Institutional Review Board of Toyonaka Municipal Hospital.

ERCP and pharmacological prophylaxis

Trainees or experts performed ERCP because our hospital is a JGES-certified teaching hospital, and trainees were assisted by experts as needed to avoid complications and ensure procedural quality when performing ERPC. We did not use a strict cannulation protocol. Cannulation was attempted *via* the wire-loaded cannulation method, which entails the use of contrast and wire-guided cannulation using a side-viewing duodenoscope (JF260 V: Olympus Optical Co. Tokyo, Japan). Procedure times were measured using a stopwatch, and images were recorded at key points and subsequently reviewed. Patients underwent routine blood tests 2 h after the procedure and the following day and received routine protease inhibitor (200 mg gabexate mesilate × 2/d) treatments until the day after the procedure. No patients received rectal diclofenac or indomethacin for PEP prophylaxis during this period.

Complications

PEP was diagnosed based on consensus criteria[13]. Briefly, PEP was defined as the combination of abdominal pain persisting for at least 24 h after the procedure and a high serum amylase level equivalent to 3 times the ULN at 24 h after the procedure. Bleeding was defined as blood loss requiring emergency endoscopic hemostasis or a transfusion or a hemoglobin level decrease greater than 2 g/dL following ERCP. Perforation was diagnosed endoscopically during ERCP or based on the observation of free air on post-ERCP plain radiography or computed tomography. Procedure-related mortality was defined as any death within 30 d of ERCP.

Analysis of PEP predictive factors

Patient- and procedure-related PEP risk factors were analyzed *via* logistic regression using the following factors: Sex, native papilla, cannulation time, total procedure time, endoscopic nasobiliary drainage, endoscopic biliary stent (EBS) placement, precut sphincterotomy, endoscopic sphincterotomy (EST), endoscopic papillary balloon dilation (EPBD), pancreatic duct brush cytology, and 2 h amylase levels. Cannulation time was defined as the time from papilla identification until successful biliary cannulation, and procedure time was defined as the time from papilla identification until the scope was removed from the patient. PEP development was analyzed in relation to the following factors *via* univariate logistic regression: Patient-related factors (sex, age, and native papilla), procedure-related factors (cannulation time, total procedure time, endoscopic nasal pancreatic drainage, EBS, endoscopic metallic stent, endoscopic pancreatic stent, precut sphincterotomy, EST, EPBD, and pancreatic duct brush cytology), and 2 h post-ERCP amylase levels.

Statistical analysis

All continuous variables are expressed as the mean ± SD, except for the nonparametric variables, which are expressed as the median and range. Categorical variables are expressed as the number in each category or the frequency. Continuous variables were compared using student's *t* test, whereas categorical variables were compared using a χ^2 test or Fisher's exact test when appropriate. Receiver operating characteristic (ROC) curve analysis was used to determine the 2 h amylase level cutoff, the cannulation times, and the procedure times for predicting PEP. Univariate and multivariate logistic regression analyses were performed to identify complication-related factors. A *P*-value less than 0.05 was considered statistically significant. All statistical analyses were performed using JMP software (ver. 11.1.1, SAS Institute Inc., Cary, NC, United States).

RESULTS

Patients and ERCP procedures

Patient characteristics are summarized in Table 1. A total

Table 1 Patient characteristics

Patients	*n*
Male, %	846, 60%
Age, median (range)	73 (12-99)
Native papilla	668, 47.6%
Indication	
Malignancy	522
Choledocholithiasis	771
Others	110
Cannulation time, median (range)	5 min (1-185)
Procedure time, median	37 min (3-185)
2 h amylase median (range)	97 IU/mL (10-3502)
ERCP and related procedures	
Total ERCP	1403
ENBD	362
EBS	380
EMS	42
EPS	124
Precut	35
EST	505
EPBD	20
EPLBD	38
Pancreatic duct brush	15

ERCP: Endoscopic retrograde cholangiopancreatography; EBS: Endoscopic biliary stent; EMS: Endoscopic metallic stent; EPS: Endoscopic pancreatic stent; EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; EPLBD: Endoscopic papillary large balloon dilation; ENBD: Endoscopic nasobiliary drainage.

of 1403 procedures (725 patients) were analyzed in the present study. The median age of the study population was 73 years, and 846 patients were male (60%). A total of 688 patients (59%) exhibited naive papillae. ERCP was performed for choledocholithiasis (n = 771); biliary malignancies from pancreatic cancer (n = 203); biliary malignancies from common bile duct cancer (n = 161); other biliary malignancies, including gallbladder cancer, intrahepatic bile duct cancer and other metastatic cancers (n = 158); and other conditions (n = 110). The median cannulation time was 5 min (range 1-185), and the median procedure time was 37 min (range 3-185 min). Primary cannulation was successful in 97.7% of cases. The median 2 h post-ERCP amylase level was 97 IU/L.

Complications

The overall complication rate was 4.8%. PEP developed in 55 patients (4.5%, 95%CI: 3.02-5.07), and perforation and bleeding occurred in 5 (0.35%, 95%CI: 0.15-0.83) and 8 patients (0.57%, 95%CI: 0.28-1.12), respectively (Table 2). All the patients who developed PEP improved with conservative therapy. The 2 h amylase cutoff value for predicting PEP was 264 IU/L (AUC: 0.93) (Figure 2) and remained 264 IU/L when limited to naïve papilla cases (n = 688). This cutoff level was 2.2 times the ULN at our hospital; thus, we established a serum amylase cutoff level of 2 times the ULN (240 U/L) for predicting PEP. Patients with an amylase level greater than 2 times the ULN (47/238, 19.8%) exhibited a significantly higher PEP rate than patients with a lower amylase level (8/1165, 0.7%) (P < 0.0001). Two-hour post-ERCP amylase levels greater than 2 times the ULN exhibited an NPV and a PPV for PEP of 99.3% and 19.8%, respectively.

Table 2 Complications

Complications	*n*, % (95%CI)
Bleeding	8, 0.57 (0.28-1.12)
Perforation	5, 0.35 (0.15-0.83)
Pancreatitis	55, 3.9 (3.02-5.07)
(severe pancreatitis)	[3, 0.2 (0.073-0.64)]
Procedure-related death	0, 0

The cannulation and procedure time cutoff values for predicting PEP were 13 (AUC: 0.93) and 54 min (AUC: 0.72), respectively (Figure 2), and similar results (13 and 55 min) were observed in naïve cases. Patients with cannulation times ⩾ 13 min exhibited a significantly higher PEP rate (34/327, 10.4%) than patients with shorter cannulation times (21/1075, 2.0%) (P < 0.0001), and patients with procedure times ⩾ 54 min exhibited a significantly higher PEP rate (33/359, 9.2%) than patients with shorter procedure times (22/1044, 2.1%) (P < 0.0001).

Logistic regression analysis of PEP predictors

We analyzed the ability of patient- and procedure-related risk factors to predict PEP. Univariate analysis identified 10 significant predictive factors for PEP: Female sex, native papillae, cannulation time, total procedure time, EBSs, precut sphincterotomy, EST, EPBD, pancreatic duct brush cytology, and 2 h amylase levels (Table 3).

Multivariate analysis adjusted for age revealed that cannulation times longer than 13 min (OR = 2.28, 95%CI: 1.132-4.651, P = 0.0210) and 2 h amylase levels 2 times the ULN (OR = 24.1, 95%CI: 11.56-57.13, P < 0.0001) were significant predictive factors for PEP (Table 4).

DISCUSSION

The consensus PEP definition and severity grading system developed by Cotton *et al*[13] has been used for more than 20 years, but PEP remains a primary concern for endoscopists performing ERCP, as it is the most frequent post-ERCP complication, with an incidence of 3.5% in unselected patients[3,5]. Approximately 90% of cases are of mild-to-moderate in severity; however, PEP results procedure-related death in 3% of PEP cases[3]. Many prophylactic treatments have been reported, and the most recent ESGE guidelines recommend rectal NSAID administration for PEP prophylaxis[5]. However, PEP is difficult to prevent, and few medications are effective at treating PEP once it develops. Only prompt aggressive intravenous hydration is reportedly effective with respect to decreasing morbidity and mortality[2,7,8,10]. Appropriate and early fluid therapy can mitigate PEP severity[14]; therefore, PEP must be diagnosed, and

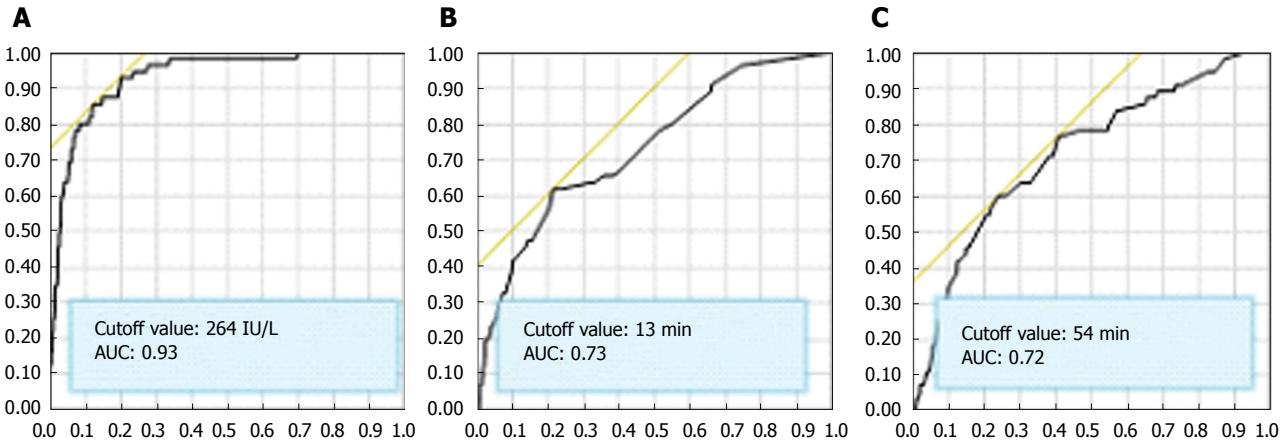

Figure 2 Receiver operating characteristic curve of 2 h amylase levels (A), cannulation times (B), and procedure times (C). AUC: Area under the curve.

Table 3 Univariate analysis of pancreatitis predictors

Predictors	Odds ratio	95%CI	*P* value
Sex (female)	0.53	0.31-0.92	0.0245
Native papilla	5.62	2.73-11.6	< 0.0001
ENBD	0.77	0.43-1.38	0.4313
EBS[1]	2.62	1.18-5.85	0.0129
EMS	0.37	0.13-1.08	0.0784
EPS	0.47	0.22-1.00	0.0528
Precut	0.23	0.08-0.61	0.0102
EST	0.49	0.28-0.84	0.0099
EPBD	0.22	0.06-0.78	0.0405
EPLBD	-	-	0.3983
Pancreatic duct brush	6.42	1.75-23.5	0.0186
2 h amylase ⩾ 2 times ULN	36.6	17.6-76.3	< 0.0001
Cannulation time ⩾ 13 min	5.82	3.33-10.2	< 0.0001
Procedure time ⩾ 54 min	4.70	2.70-8.18	< 0.0001

[1]EBS: Including with and without EST. EBS: Endoscopic biliary stent; EMS: Endoscopic metallic stent; EPS: Endoscopic pancreatic stent; EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; ULN: Upper limit of normal; EPLBD: Endoscopic papillary large balloon dilation; ENBD: Endoscopic nasobiliary drainage.

Table 4 Age-adjusted multivariate analysis of pancreatitis predictors

Predictors	Odds ratio	95%CI	*P* value
Sex (female)	1.46	0.77-2.75	0.2431
Native papilla	1.78	0.75-4.48	0.1908
Endoscopic biliary stent	0.61	0.23-1.45	0.2810
Precut	1.71	0.43-6.00	0.4288
EST	1.18	0.60-2.35	0.6278
EPBD	1.94	0.34-8.91	0.4296
Pancreatic duct brush	3.15	0.54-15.5	0.1870
2 h amylase ⩾ 2 times ULN	25.4	12.2-59.9	< 0.0001
Cannulation time ⩾ 13 min	2.63	1.34-5.23	0.0051
Procedure time ⩾ 54 min	1.23	0.389-3.67	0.7183

EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; ULN: Upper limit of normal.

treatment must be initiated during the early phase of the disease to prevent severe acute pancreatitis development and progression.

Numerous studies have identified factors that increase PEP risk. Among these factors, the measured amylase levels after ERCP have been evaluated for the prediction of PEP[15-17]. Many reports have shown the effectiveness of the 2-8 h amylase measurement. Generally, the NPVs are 95%-100%, the PPVs are 4%-62%, the sensitivity values are 23%-100% and the specificities are 63%-98%, although some differences in the definition of PEP and amylase cutoff levels exist across studies (Table 5).

Consequently, the ESGE guidelines indicate that 2-4 h amylase levels have very high NPVs but do not demonstrate sufficient PPVs (evidence level 2+)[4] and therefore recommend measuring serum amylase or lipase levels 2-6 h after ERCP in patients presenting with pain who are to be discharged on the day of their ERCP procedure (recommendation grade B). In this study, 2 h amylase levels exhibited a good NPV of 99% and a poor PPV of 20%, findings consistent with the above results, as well as a good sensitivity (84%) for the diagnosis of PEP. Previous studies have reported values of 70%-90%, particularly studies using the Consensus Criteria PEP definition. A PPV of 20% is not sufficient to identify PEP but may be suitable for identifying patients at high risk for developing PEP. Moreover, 2 h amylase levels may enable clinicians to identify high-risk patients requiring early acute PEP treatments, such as infusion therapy.

Previous studies have demonstrated that difficult cannulation is a risk factor for PEP[12,18,19]. Tian *et al*[20] reported that cannulation time is a more accurate measure of cannulation difficulty in ERCP than other parameters. Moreover, Halttunen *et al*[21] reported that cannulation attempts lasting > 5 min may increase the incidence of PEP and that procedures lasting less than 5 min had a lower PEP rate (2.6%) than longer procedures (11.8%). The most recent ESGE guidelines state that PEP risk factor analyses have demonstrated that cannulation attempts lasting > 10 min had an odds ratio (OR) of 1.76 (1.13-2.74) with respect to PEP development and that the pooled incidences of PEP in patients with and without this risk factor were

Table 5 Previous reports of hourly variations in post-endoscopic retrograde cholangiopancreatography amylase levels

Ref.	Year	*n*	Time[1] (h)	Amylase cut off	Sensitivity	Specificity	PPV	NPV	Definition of PEP
LaFerla *et al*[23]	1986	20	2	800	n.d.	n.d.	n.d.	Unlikely	Amy > 1200
Gottlieb *et al*[24]	1996	231	2	276	82	76	15	98	Consensus criteria
Testoni *et al*[25]	1999	409	2	5 ×	23.1	98.2	46.2	94.9	Amy > 5 × ULN
			4	5 ×	53.8	95	42.4	96.8	
			8	5 ×	76.9	96.9	62.5	98.4	
Testoni *et al*[26]	2001	1185	6-8	3 ×	n.d.	n.d.	n.d.	100	Pancreatic type pain
Thomas *et al*[27]	2001	263	4	2 ×	90	92.9	24.3	99.6	Consensus criteria
			4	3 ×	70	95.3	36.8	98.8	
Kapetanos *et al*[28]	2007	97	2	3 ×	72	79	32	95	Consensus criteria
			6	3 ×	82	75	30	97	
Ito *et al*[16]	2007	1291	3	3 ×	77	n.d.	29	n.d.	Amy > 1 × ULN,
			6	3 ×	85	n.d.	24	n.d.	with pain at 24 h
Nishino *et al*[29]	2009	1631	4	3 ×	89.8	72.9	12.7	99.4	Consensus criteria
			4	4 ×	84.7	80.4	16	99.2	
Artifon *et al*[30]	2010	300	4	1.5 ×	77	63	26	94	Consensus criteria
Sutton *et al*[15]	2011	959	4	2.5 ×[2]	80	80.4	11.1	99.2	Consensus criteria
			4	2.5 ×[3]	100	91.8	4.3	100	(mod/severe only)
Our study	2015	1403	2	2 ×	85.5	85.8	19.8	99.3	Consensus criteria
			2	2 ×[4]	96.4	68.8	11.2	99.8	

[1]Hourly variations in serum amylase measurements after the procedure; [2]With pancreatogram; [3]Without pancreatogram; [4]Longer cannulation time. Consensus criteria: Amy > 3 × ULN with pain at 24 h. n.d.: Not described; ULN: Upper limit of normal.

10.8% and 3.8%, respectively. ROC curve analysis was performed in the present study and demonstrated that the cannulation and the procedure time cutoff values for predicting PEP were 13 (AUC: 0.93) and 54 min (AUC: 0.72), respectively. The incidences of PEP in patients with and without cannulation attempts lasting > 13 min were 10.4% and 2.0%, respectively, and the incidences of PEP in patients with and without cannulation times lasting > 10 min were 9.6% and 2.1%, respectively (data not shown), findings similar to those reported by Halttunen *et al*[21]. Multivariate analysis indicated that cannulation time is another significant PEP risk factor; therefore, we propose that cannulation time is a reliable marker for predicting PEP, in addition to 2 h post-ERCP amylase levels.

Based on above findings, we used the following markers to predict PEP development: 2 h post-ERCP amylase levels greater than 2 times the ULN and cannulation times greater than 13 min. Figure 3 includes a flowchart depicting these markers. A total of 238 patients (17%) in the present study exhibited 2 h post-ERCP amylase levels greater than 2 times the ULN, 47 of whom (20%) developed PEP, whereas a total of 1165 patients (83%) exhibited 2 h post-ERCP amylase levels less than 2 times the ULN. Eight patients (0.7%) in the latter group developed PEP; however, six of these patients required more than 13 min for cannulation. Thus, only 2 of the 1403 patients (0.14%) who developed PEP did not exhibit concerning 2 h post-ERCP amylase levels or require longer cannulation times. This study demonstrated that cannulation time inclusion may rescue 75% (6/8) of patients with non-concerning 2 h amylase levels and that the combination of 2 h post-ERCP levels and cannulation times exhibited a 96% sensitivity and an 11.2% PPV for the identification of PEP. The latter percentage is not sufficient to identify PEP but may be useful for identifying high-risk patients in whom early treatments, such as aggressive infusions, are necessary.

The present study had several limitations because of its retrospective design. Routine protease inhibitor administration without rectal diclofenac or indomethacin administration may have influenced the frequency of PEP. However, nonsteroidal anti-inflammatory drugs (NSAIDs) were reportedly used infrequently for PEP prevention in clinical practice in Japan until the publication of the 2015 Japanese Guideline[22], which recommends prophylactic NSAID administration to prevent PEP. In addition, we did not strictly evaluate certain PEP risk factors, such as the number of cannulation attempts, pancreatic guidewire, and pancreatic injection, because of the retrospective design of this study. The number of cannulation attempts represents the degree of cannulation difficulty; the most recent ESGE guidelines recommend keeping this number as low as possible[21]. The degree of cannulation difficulty during ERCP is positively correlated with PEP[18]. The degree of cannulation difficulty during ERCP procedures may differ when different methods are used (total cannulation time *vs* number of attempts); thus, grading scales used to evaluate the difficulty of performing ERCP *via* different methods should not be used interchangeably. Tian *et al*[20] reported that cannulation time is a more objective and accurate means of grading cannulation difficulty than the number of papilla cannulation attempts. The ESGE guidelines categorize pancreatic guidewire use and pancreatic injection as definite PEP risk factors. However, it is sometimes difficult to establish if either

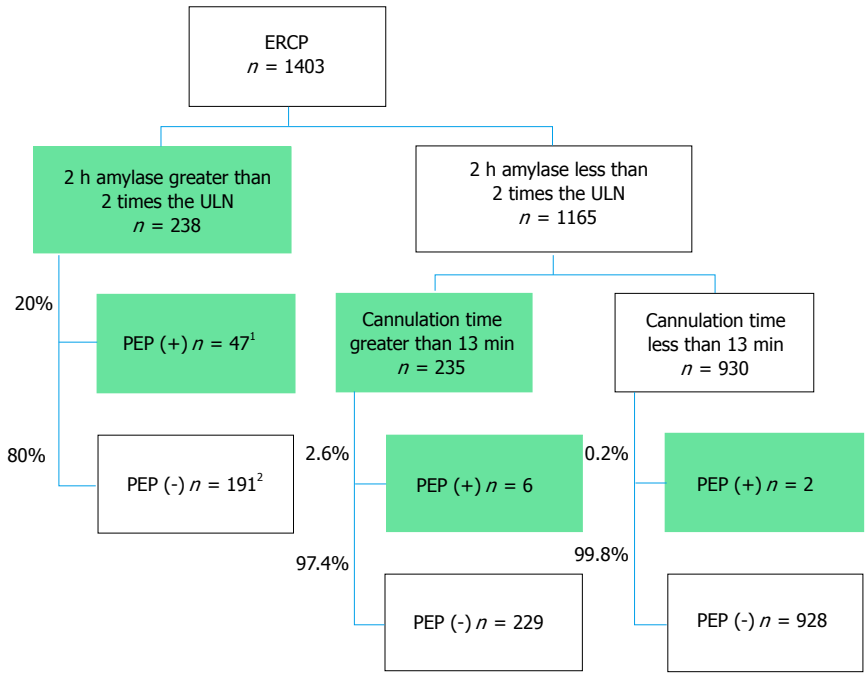

Figure 3 Flow chart using two-hour amylase levels and cannulation times for predicting pancreatitis. [1]Includes cannulation times greater than 13 min, *n* = 28; [2]Includes cannulation times greater than 13 min, *n* = 64. ERCP: Endoscopic retrograde cholangiopancreatography; PEP: Post ERCP Pancreatitis; ULN: Upper limit of normal.

procedure has been performed, particularly cannulation, which is performed *via* contrast and wire-guided methods at our institution. In addition, the ESGE guidelines recommend that prophylactic pancreatic stent placement should be strongly considered in patients at high risk for PEP. Prophylactic pancreatic stents were placed in 124 patients in the present study, 9 of whom (7.3%) developed PEP. However, multivariate analysis demonstrated that stent placement did not significantly prevent PEP, perhaps because pancreatic stents tend to be used in patients at high risk for PEP, in accordance with the above guidelines. Therefore, we must target patients at high risk for PEP to evaluate the efficacy of prophylactic pancreatic stent placement. Because of the above limitations, in the present study, we evaluated cannulation time and procedure time as surrogate markers of procedure-related risk factors in the present study. Despite these limitations, we believe that this study has effectively demonstrated that Two-hour post-ERCP amylase levels and cannulation times are useful PEP predictors.

In conclusion, 2 h post-ERCP serum amylase levels and cannulation times may be useful markers for predicting PEP development. We plan to conduct prophylactic interventions to reduce the incidence of PEP in high-risk patients exhibiting 2 h post-ERCP amylase levels greater than 2 times the ULN or requiring cannulation times greater than 13 min.

COMMENTS

Background

Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) may result in procedure-related death and is often unpreventable. So it is important to predict and treat in early phase.

Research frontiers

Post-ERCP serum amylase levels are known as a predictor of PEP, which have good negative predictive value (NPV) and poor positive predictive value (PPV). The aim of this study was to estimate the efficacy of post-ERCP 2 h serum amylase levels and other factors for predicting PEP.

Innovations and breakthroughs

The 2-h amylase levels exhibited a good NPV (99%) and a poor PPV (22%) similar to previous reports but exhibited a sensitivity of 86%, and the combined use with cannulation time increased the sensitivity to 96%.

Applications

Combination of Two-hour post-ERCP amylase levels and cannulation times may be simple useful markers for predicting PEP development in early phase.

Terminology

PEP is one of the major adverse events of ERCP. It is most frequent and sometimes results in death, so that it has been the most concern still now.

Peer-review

This retrospective study was performed to identify the risk factors for PEP, and the authors revealed that two factors of serum amylase levels 2 h after ERCP and cannulation time were significant independent factor. This is well designed study which revealed interesting results.

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ORIGINAL ARTICLE

Observational Study

Current state of practice for colonic diverticular bleeding in 37 hospitals in Japan: A multicenter questionnaire study

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Author contributions: Nagata N and Doyama H conceived and designed the experiments; Niikura R and Ota R analyzed the data; Niikura R and Nagata N wrote the paper; Nagata N, Doyama H, Ishii N, Mabe K, Nishida T, Hikichi T, Sumiyama K, Nishikawa J, Uraoka T, Kiyotoki S, Fujishiro M and Koike K contributed to editing the manuscript.

Institutional review board statement: Owing to the anonymous nature of the data in this retrospective questionnaire survey of endoscopists, institutional review board approval was waived.

Informed consent statement: Informed consent was waived because this study included no personal information about patients.

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Abstract

AIM

To clarify the current state of practice for colonic diverticular bleeding (CDB) in Japan.

METHODS

We conducted multicenter questionnaire surveys of the practice for CDB including clinical settings (8 questions), diagnoses (8 questions), treatments (7 questions), and outcomes (4 questions) in 37 hospitals across Japan. The answers were compared between hospitals with high and low number of inpatient beds to investigate which factor influenced the answers.

RESULTS

Endoscopists at all 37 hospitals answered the questions, and the mean number of endoscopists at these hospitals was 12.7. Of all the hospitals, computed tomography was performed before colonoscopy in 67% of the hospitals. The rate of bowel preparation was 46.0%. Early colonoscopy was performed within 24 h in 43.2% of the hospitals. Of the hospitals, 83.8% performed clipping as first-line endoscopic therapy. More than half of the hospitals experienced less than 20% rebleeding events after endoscopic hemostasis. No significant difference was observed in the annual number of patients hospitalized for CDB between high- ($\geqslant$ 700 beds) and low-volume hospitals. More emergency visits (P = 0.012) and endoscopists (P = 0.015), and less frequent participation of nursing staff in early colonoscopy (P = 0.045) were observed in the high-volume hospitals.

CONCLUSION

Some practices unique to Japan were found, such as performing computed tomography before colonoscopy, no bowel preparation, and clipping as first-line therapy. Although, the number of staff differed, the practices for CDB were common irrespective of hospital size.

Key words: Colonic diverticular hemorrhage; Lower gastrointestinal bleeding; Computed tomography; Endoscopy; Bowel preparation

Core tip: Colonic diverticular bleeding (CDB) is increasing in Asia. There are no practice guidelines for CDB, and it is important to determine which recommendation is acceptable to a majority of hospitals. We conducted multicenter questionnaire surveys of 37 hospitals in Japan regarding management of CDB including clinical settings, diagnosis, treatment, and clinical outcomes, and made comparisons between hospitals with different patient volumes and between hospitals in different regions. Thus, practice styles unique to Japan such as performing computed tomography before colonoscopy, no bowel preparation, and clipping as first-line therapy were identified. However, management of CDB was common among hospitals irrespective of hospital size and region.

Niikura R, Nagata N, Doyama H, Ota R, Ishii N, Mabe K, Nishida T, Hikichi T, Sumiyama K, Nishikawa J, Uraoka T, Kiyotoki S, Fujishiro M, Koike K. Current state of practice for colonic diverticular bleeding in 37 hospitals in Japan: A multicenter questionnaire study. *World J Gastrointest Endosc* 2016; 8(20): 785-794 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i20/785.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i20.785

INTRODUCTION

Colonic diverticular bleeding (CDB) is a major cause of lower gastrointestinal bleeding, and is estimated to cause 25% to 40% of all cases of lower gastrointestinal bleeding[1-3]. In Japan, CDB was found in 427 (1.5%) of 28192 patients who underwent colonoscopy at an emergency hospital[4]. Its occurrence has increased in Japan as well as in Western countries[4-7]. CDB results in hemorrhagic shock requiring blood transfusion[8,9], and has a high recurrence rate of 20% within 1 year[10,11]. As a result, patients are often burdened by the frequent examinations, hospitalization, repeated blood transfusions, and a consequent decrease in their quality of life. Furthermore, these practices for CDB may be different between Western countries and Japan. For example, Western countries perform purged colonoscopy using polyethylene glycol as the first diagnostic procedure, and perform endoscopic hemostasis using clipping[12]. In contrast, Japanese hospitals have good access to computed tomography (CT)[13] and may select CT as the first diagnostic procedure. In addition, diagnostic tools, endoscopic environment, and treatment strategy may potentially differ among hospitals in Japan. Moreover, the practice for CDB may differ according to hospital patient volume and region, as is seen in the practice for other lower gastrointestinal disease[14,15]. Some studies have reported significant associations between hospital volume and clinical outcome, and between hospital region and diagnosis methods[14,15]. Today, there are no practice guidelines for CDB, and it is

important to determine what recommendations would be acceptable to a large number of hospitals.

Therefore, we conducted a multicenter questionnaire survey of the practice for CDB in 37 hospitals across Japan to elucidate the current state of the clinical settings, diagnosis, treatment, and clinical outcomes of patients with CDB, and to compare these findings according to hospital volumes and regions.

MATERIALS AND METHODS

Contents of the questionnaire

First, 1 endoscopist (Doyama H) developed the questionnaire on practice for CDB. Then, 3 endoscopists (Ota R, Niikura R and Nagata N) reviewed and edited the questionnaire regarding the length, clarity, and contents. Finally, 27 survey questions on practice for CDB were developed. The questionnaire consisted of 4 parts (clinical settings, diagnosis, treatment, clinical outcomes) as follows. In part (Ⅰ), there were 9 questions for clinical settings on: (1) the clinical database for CDB such as gastrointestinal bleeding database, inpatient database, or endoscopy database; (2) institution-specific strategy for CDB; (3) number of CDB admissions; (4) number of emergency ambulance visits; (5) number of endoscopists performing early colonoscopy within 24 h of patient arrival; (6) number of expert endoscopists with hemostatic technical skills; (7) nursing staff who monitored vital signs during bowel preparation; (8) nursing staff assisting early colonoscopy; and (9) use of a water-jet colonoscope. For part (Ⅱ), there were 8 questions for diagnoses of CBD on (10) the first choice diagnostic examination; (11) early contrast-enhanced CT within 3 h of patient arrival; (12) early colonoscopy; (13) bowel preparation; (14) cap-assisted colonoscopy; (15) how to improve the identification of stigmata of recent hemorrhage (SRH); (16) availability of small bowel examinations in case of negative colonoscopy; and (17) modality for small bowel examinations. For part (Ⅲ), there were 6 questions for treatment of CDB on (18) first-line endoscopic therapy; (19) selection of non-endoscopic therapy; (20) first-line therapy among non-endoscopic therapies; (21) how to prevent rebleeding; (22) discontinuation of antithrombotic drugs on admission; and (23) strategy for restarting antithrombotic drugs. In part (Ⅳ), there were 4 questions for clinical outcomes of CDB on (24) identification rate of SRH; (25) rebleeding rate after endoscopic hemostasis; (26) rebleeding rate after interventional radiology; and (27) rebleeding rate after barium impaction therapy.

Questionnaire survey

The questionnaire survey was conducted by e-mail that was sent to 1 or 2 endoscopists at each of the 37 hospitals with different numbers of inpatient beds and in different regions in Japan between May 2015 and June 2015. Selection of the hospitals was made by Fujishiro M, who knew that the representative endoscopists would be interested in this topic from his personal communications. To assess the reproducibility of questionnaire, we conducted a blinded secondary questionnaire survey 2 mo after using the same 16 questionnaire items. Selection of these questionnaire items was made by Niikura R and Nagata N. because these items were found to be related to the practice for CDB. These 37 hospitals were located in East or West Japan and have 100 to 1000 inpatient beds (Appendix).

Statistical analysis

The data from the first questionnaire survey were analyzed, and the intra-observer agreement between the first and second questionnaires was analyzed using kappa statistics. Kappa values were evaluated as follows: > 0.80, excellent agreement; > 0.60 to 0.80, good agreement; > 0.40 to 0.60, moderate; > 0.20 to 0.40, fair; and ≤ 0.20, poor[16].

A high-volume hospital was defined as one with over 700 beds, because the median number of beds in our data was 700 beds per hospital. Expert endoscopists were defined as those who were able to perform endoscopic hemostatic treatment by themselves. We evaluated the clinical settings, diagnosis methods, treatment, and outcomes between the groups of hospital separated by hospital volume and region (East Japan, West Japan) using a χ^2 test or Fisher's exact test as appropriate. Continuous variables were compared using the Mann-Whitney *U* test. We also evaluated the associations of the rates of SRH identification and rebleeding with type of procedure from questionnaire answers using a nonparametric trend test. A *P* value < 0.05 was considered statistically significant. All statistical analyses were performed using the STATA version 13 software (StataCorp, College Station, TX, United States).

RESULTS

The number of beds per hospital in each region of Japan is shown in Figure 1. There were 18 high-volume hospitals (≥ 700 beds) and 19 low-volume hospitals. Twenty-one of the 37 (56.8%) hospitals were located in East Japan, and 16 hospitals (43.2%) were located in West Japan (Figure 1). All 37 hospitals completed the first questionnaires, and 35 of the hospitals completed the second questionnaires. Intra-observer agreement for each question between the first and second surveys was excellent (mean κ, 0.83, 95% confidence interval 0.78-0.87) (Supplementary Table 1).

Questionnaire items for clinical settings

Questions and answers regarding clinical settings are shown in Table 1. Of all the hospitals, 86.5% answered the questionnaire based on the clinical database of each hospital. Only 13.5% of hospitals had an institution-specific strategy for CDB. The number of CDB patients who received therapy, and the number of emergency ambulance visits, differed among hospitals. The mean

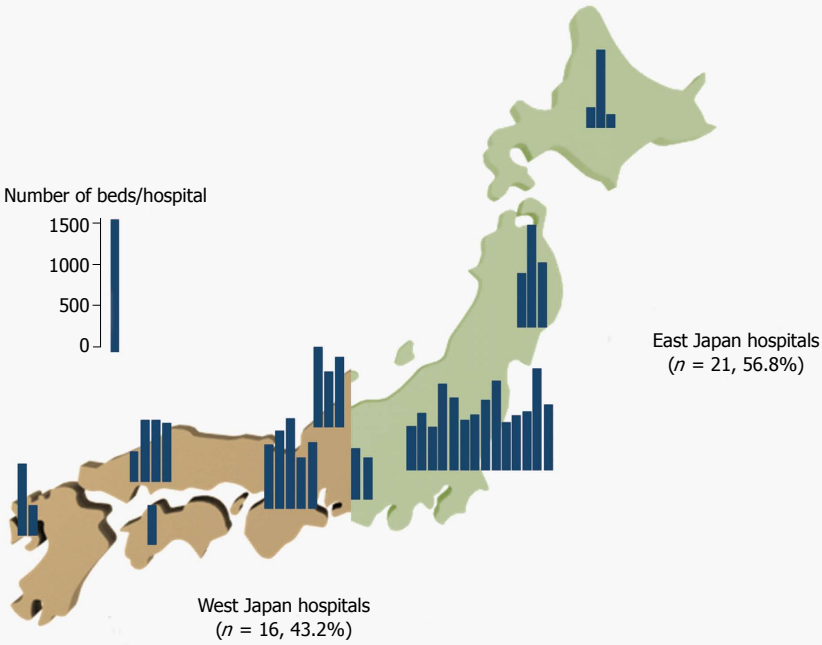

Figure 1 Number of beds per hospital in East and West Japan.

Table 1 Questions and answers regarding clinical settings in 37 hospitals *n* (%)

No.	Question	Answer (*n* = 37)	High volume (*n* = 18)	Low volume (*n* = 19)	*P* value	East Japan (*n* = 21)	West Japan (*n* = 16)	*P* value
1	Did you answer the questions based on a clinical database?							
	Yes	31 (83.8)	16 (51.6)	15 (48.4)		18 (58.1)	13 (41.9)	
	No	6 (16.2)	2 (33.3)	4 (66.7)	0.660	3 (50.0)	3 (50.0)	1.000
2	Do you have a specific institutional strategy for CDB?							
	Yes	5 (13.5)	0	5 (100)		2 (40.0)	3 (60.0)	
	No	32 (86.5)	18 (56.3)	14 (43.7)	0.046	19 (59.4)	13 (40.6)	0.634
3	How many patients are hospitalized for CDB annually?							
	1-10	12 (32.5)	7 (58.3)	5 (41.7)		7 (58.3)	5 (41.7)	
	11-20	10 (27.0)	4 (40.0)	6 (60.0)		4 (40.0)	6 (60.0)	
	21-30	5 (13.5)	2 (40.0)	3 (60.0)		1 (20.0)	4 (80.0)	
	⩾ 31	10 (27.0)	2 (50.0)	5 (50.0)	0.824	9 (90)	1 (10)	0.035
4	How many emergency ambulance visits do you receive annually?[1]							
	< 2000	15 (44.1)	5 (33.3)	10 (66.7)		8 (53.3)	7 (46.7)	
	2000-6000	11 (32.3)	4 (36.4)	7 (63.6)		5 (45.5)	6 (54.5)	
	6000-10000	6 (17.7)	6 (100)	0		3 (50.0)	3 (50.0)	
	⩾ 10000	2 (5.9)	0	2 (100)	0.012	2 (100)	0	0.724
5	How many endoscopists perform early colonoscopy within 24 h after patient arrival at your hospital?							
		12.7 ± 9.4	17.0 ± 11.6	8.8 ± 4.4	0.015	10.4 ± 5.7	15.8 ± 12.5	0.296
6	How many are expert endoscopists with endoscopic hemostasis technical skills are there at your hospital?							
		10.1 ± 7.5	13.1 ± 9.5	7.3 ± 3.3	0.019	7.9 ± 3.3	13.0 ± 10.2	0.143
7	Do you have nursing staff who monitor the patients' vital signs during bowel preparation?							
	Yes	33 (89.2)	17 (51.5)	16 (48.5)		19 (57.6)	14 (42.4)	
	No	4 (10.8)	1 (25.0)	3 (75.0)	0.604	2 (50.0)	2 (50.0)	1.000
8	Do you have nursing staff for early colonoscopy examinations within 24 h after patient arrival at the hospital?							
	Yes	23 (62.2)	8 (34.8)	15 (65.2)		13 (56.5)	10 (43.5)	
	No	14 (37.8)	10 (71.4)	4 (28.6)	0.045	8 (57.1)	6 (42.9)	1.000
9	Do you have a water-jet colonoscope?							
	Yes	34 (91.9)	17 (50.0)	17 (50.0)		20 (58.9)	14 (41.1)	
	No	3 (8.1)	1 (33.3)	2 (66.7)	1.000	1 (33.3)	2 (66.7)	0.568

[1]Missing data included. The values in parentheses are percentages, and continuous data are shown as mean ± standard deviation. CDB: Colonic diverticular bleeding.

number of endoscopists and expert endoscopists were 12.7 and 10.1, respectively. Of all the hospitals, 89.2% and 62.2% had nursing staff for monitoring vital signs during bowel preparation and early colonoscopy examination, respectively. Ninety-one percent of hospitals had a water-jet colonoscope.

Comparing hospital with high and low patient volumes, more emergency visits (P = 0.012), endoscopists (P = 0.015), and expert endoscopists (P = 0.019), and less institution-specific management for CDB (P = 0.046) and frequent participation of nursing staff in early colonoscopy (P = 0.045) were observed

Table 2 Questions and answers regarding diagnosis of colonic diverticular bleeding in 37 hospitals *n* (%)

No.	Question	Answer (*n* = 37)	High volume (*n* = 18)	Low volume (*n* = 19)	*P* value	East Japan (*n* = 21)	West Japan (*n* = 16)	*P* value
10	What do you use as the first-line diagnostic method for hematochezia and suspected CDB?							
	Non-contrast-enhanced CT	3 (8.1)	0	3 (100)		0	3 (100)	
	Contrast-enhanced CT	22 (59.5)	11 (50.0)	11 (50.0)		12 (54.6)	10 (45.4)	
	Colonoscopy	10 (27.0)	6 (60.0)	4 (40.0)		7 (70.0)	3 (30.0)	
	Contrast-enhanced CT and colonoscopy	2 (5.4)	1 (50.0)	1 (50.0)	0.359	2 (100)	0	0.101
11	Can you perform urgent contrast-enhanced CT within 3 h after patient arrival at hospital?[2]							
	Yes	22 (61.1)	12 (54.6)	10 (45.4)		13 (59.1)	9 (40.9)	
	No	14 (38.9)	6 (42.9)	8 (57.1)	0.494	7 (50.0)	7 (50.0)	0.593
12	Can you perform early colonoscopy within 24 h after patient arrival at hospital?							
	Yes	16 (43.2)	9 (56.3)	7 (43.7)		10 (62.5)	6 (37.5)	
	No	21 (56.8)	9 (42.9)	12 (57.1)	0.419	11 (52.4)	10 (47.6)	0.538
13	Do you request bowel preparation?							
	Yes	17 (46.0)	6 (35.3)	11 (64.7)		13 (76.5)	4 (23.5)	
	No	3 (8.1)	3 (100)	0		2 (66.7)	1 (33.3)	
	Case by case	17 (45.9)	9 (52.9)	8 (47.1)	0.105	6 (35.3)	11 (64.7)	0.046
14	Do you use a cap-assisted colonoscopy for early colonoscopy?							
	Yes	24 (64.9)	11 (45.8)	13 (54.2)		15 (62.5)	9 (37.5)	
	No	13 (35.1)	7 (53.9)	6 (46.1)	0.642	6 (46.2)	7 (53.8)	0.338
15	How do you perform colonoscopy to improve identification of SRH?[1]							
	Cap-assisted colonoscopy	17 (46.0)	10 (58.8)	7 (41.2)	0.254	10 (58.8)	7 (41.2)	0.815
	Long cap-assisted colonoscopy	13 (35.1)	6 (46.2)	7 (53.8)	0.823	7 (53.9)	6 (46.1)	0.793
	Inverting diverticulum *via* suction of colonoscopy	18 (48.7)	11 (61.1)	7 (38.9)	0.140	11 (61.1)	7 (38.9)	0.603
	Wash out with water	36 (97.3)	18 (50.0)	18 (50.0)	1.000	21 (58.3)	15 (41.7)	0.432
	Colonoscopy by multiple doctors	3 (8.1)	1 (33.3)	2 (66.7)	1.000	2 (66.7)	1 (33.3)	1.000
	Colonoscopy under X-ray	3 (8.1)	1 (33.3)	2 (66.7)	1.000	1 (33.3)	2 (66.7)	0.568
16	Do you examine the small bowel when you are unable to diagnose definite CDB by colonoscopy?							
	Yes	18 (48.7)	11 (61.1)	7 (38.9)		10 (55.6)	8 (44.4)	
	No	7 (18.9)	1 (14.3)	6 (85.7)		4 (57.1)	3 (42.9)	
	Case by case	12 (32.4)	6 (50.0)	6 (50.0)	0.145	7 (58.3)	5 (41.7)	1.000
17	Which modality do you select for the small bowel examination?[2]							
	Capsule endoscopy	29 (85.3)	17 (58.6)	12 (41.4)		18 (62.1)	11 (37.9)	
	Balloon-endoscopy	2 (5.9)	0	2 (100)		1 (50.0)	1 (50.0)	
	Case by case	3 (8.8)	1 (33.3)	2 (66.7)	0.301	1 (33.3)	2 (66.7)	0.776

[1]Duplicated data allowed; [2]Missing data included. Parenthesis shows percentage. CT: Computed tomography; CDB: Colonic diverticular bleeding; SRH: Stigmata of recent hemorrhage.

in high-volume hospitals (Table 1). No significant differences were observed in other questionnaire items such as number of patients hospitalized for CDB between the two groups (Table 1). Comparing hospitals in East and West Japan, a higher number of patients hospitalized for CDB was observed in East Japan hospitals (P = 0.035) (Table 1). No significant difference was observed in other questionnaire items between the two groups (Table 1).

Questionnaire items for diagnoses

Questions and answers regarding diagnosis are shown in Table 2. Of all the hospitals, 59.5% selected contrast-enhanced CT as first examination of choice. The rates of urgent CT, early colonoscopy, bowel preparation, cap-assisted colonoscopy were 61.1%, 43.2%, 46.0%, and 64.9%, respectively. Ninety-one percent of hospitals washed out with water to improve identification of SRH. There was a wide variation among hospitals in small bowel intestinal examination, but 85.3% of hospitals selected capsule endoscopy as the tool of choice when it was unable to diagnose definite CDB.

No significant differences between hospitals with high and low patient volumes were observed in all questionnaire items (Table 2). Comparing hospitals in East and West Japan, East Japan hospitals performed more frequent bowel preparation compared with West Japan hospitals (P = 0.046) (Table 2). No significant differences were observed in other questionnaire items between the two groups (Table 2).

Questionnaire items for treatments

Questions and answers regarding treatment are shown in Table 3. In endoscopic treatment, clipping, band ligation, and epinephrine injection were performed as first-line therapy in 83.8%, 13.5%, and 2.7% of hospitals. Seventy-three percent and 67% of hospitals selected non-endoscopic therapy for patients with rebleeding and hemorrhagic shock, and 77.4% of hospitals performed interventional radiology as first-line non-endoscopic therapy. Fifty-nine percent of hospitals discontinued antithrombotic drugs on admission and only 15% of hospitals had a strategy for restarting these drugs.

Table 3 Questions and answers regarding treatments of colonic diverticular bleeding in 37 hospitals *n* (%)

No.	Question	Answer (*n* = 37)	High volume (*n* = 18)	Low volume (*n* = 19)	*P* value	East Japan (*n* = 21)	West Japan (*n* = 16)	*P* value
18	What kind of endoscopic treatment do you perform as first-line therapy?							
	Clipping	31 (83.8)	15 (48.4)	16 (51.6)	1.000	17 (54.8)	14 (45.2)	
	Endoscopic band ligation	5 (13.5)	3 (60.0)	2 (40.0)		3 (60.0)	2 (40.0)	
	Epinephrine injection	1 (2.7)	0	1 (100)		1 (100)	0	1.000
19	What kinds of patient undergo non-endoscopic therapy?[1]							
	Patients with an unidentified bleeding source	18 (48.7)	10 (55.6)	8 (44.4)	0.413	8 (44.4)	10 (55.6)	0.141
	Patients with rebleeding	27 (73.0)	15 (55.6)	12 (44.4)	0.269	17 (63.0)	10 (37.0)	0.274
	Patients with hemorrhagic shock	25 (67.6)	15 (60.0)	10 (40.0)	0.079	13 (52.0)	12 (48.0)	0.491
20	What kind of non-endoscopic therapy do you perform as first-line therapy or when you are unable to identify SRH at endoscopy?							
	IVR	24 (77.4)	2 (50.0)	2 (50.0)	0.253	10 (41.7)	14 (58.3)	
	Surgery	3 (9.7)	14 (58.3)	10 (41.7)		3 (100)	0	
	Barium impaction therapy	4 (12.9)	0	3 (100)		3 (75.0)	1 (25.0)	0.145
21	What kind of treatment do you perform to prevent rebleeding?[1]							
	Treatment of diabetes mellitus	0	0	0	NA	0	0	NA
	Treatment of hypertension	6 (17.1)	2 (33.3)	4 (66.7)	0.658	3 (50.0)	3 (50.0)	1.000
	Discontinuation NSAIDs	14 (40.0)	7 (50.0)	7 (50.0)	0.890	10 (71.4)	4 (28.6)	0.296
	Discontinuation antithrombotic drugs	22 (62.9)	11 (50.0)	11 (50.0)	0.826	15 (68.2)	7 (31.8)	0.086
	Administrating vitamin D	0	0	0	NA	0	0	NA
	Treatment of constipation	14 (40.0)	9 (64.3)	5 (35.7)	0.129	6 (42.9)	8 (57.1)	0.163
	Administrating a low fiber diet	5 (14.3)	2 (40.0)	3 (60.0)	1.000	3 (60.0)	2 (40.0)	1.000
22	Do you discontinue antithrombotic drugs on admission?							
	Yes	22 (59.5)	10 (45.5)	12 (54.5)		12 (54.6)	10 (46.4)	
	No	12 (32.4)	7 (58.3)	5 (41.7)		6 (50.0)	6 (50.0)	
	Case by case	3 (8.1)	1 (33.3)	2 (66.7)	0.693	3 (100)	0	0.398
23	Do you have a strategy for restarting antithrombotic drugs?[2]							
	Yes	4 (15.4)	4 (100)	0		0	4 (100)	
	No	22 (84.6)	6 (27.3)	16 (72.7)	0.014	15 (68.2)	7 (31.8)	0.022

[1]Duplicated data allowed; [2]Missing data included. Values in parentheses are percentages. IVR: Interventional radiology; NSAIDs: Non-steroidal anti-inflammatory drugs; SRH: Stigmata of recent bleeding.

Comparing hospitals with high and low patient volume, low-volume hospitals had more strategies for restarting antithrombotic drugs (P = 0.014) than low-volume hospitals (Table 3). No significant differences were observed in other questionnaire items between the two groups (Table 3). Comparing hospitals in East and West Japan, East Japan hospitals had less strategies for restarting antithrombotic drugs than West Japan hospitals (P = 0.022) (Table 3). No significant differences were observed in other questionnaire items between the two groups (Table 3).

Questionnaire items for clinical outcomes

Questions and answers regarding clinical outcomes are shown in Table 4. The rate of identification of SRH varied widely among hospitals. No significant association between SRH identification rate and type of procedure was observed from questionnaire answers (Table 5). Forty-one percent of hospitals experienced less than 20% rebleeding events after endoscopic hemostasis, interventional radiology, and barium impaction therapy. No significant association was observed between rebleeding rate and endoscopic treatments from questionnaire answers (Table 5). No significant differences between hospitals with high and low patient volumes were observed in all questionnaire items (Table 4). Comparing hospitals in East and West Japan, East Japan hospitals experienced less rebleeding events after barium impaction therapy than West Japan hospitals (P = 0.005). No significant differences were observed in other questionnaire items between the two groups (Table 4).

DISCUSSION

Our questionnaire-based study was the first investigation to evaluate the current practice for CDB such as clinical settings, diagnoses, treatments, and clinical outcomes in 37 hospitals nationwide in Japan. Although the clinical setting such as the number of endoscopists and nursing staff were different between hospitals with high and low patient volumes, the practice for CDB was almost the same throughout Japan, such as performing CT before colonoscopy, various procedures to improve SRH identification rate, and clipping as first-line endoscopic therapy, irrespective of hospital size.

In regard to clinical settings, a high number of emergency visits, endoscopists, and expert endoscopists were observed in high-volume hospitals compared with low-volume hospitals. CDB is a major cause of acute lower gastrointestinal bleeding, and CDB patients experience severe bleeding and require transfusion and intensive care because of their advanced age or comorbidities[8,17-19]. Therefore, the management of CDB

Table 4 Questions and answers regarding clinical outcomes of colonic diverticular bleeding in 37 hospitals *n* (%)

No.	Question	Answer (*n* = 37)	High volume (*n* = 18)	Low volume (*n* = 19)	*P* value	East Japan (*n* = 21)	West Japan (*n* = 16)	*P* value
24	How often do you identify SRH in patients who undergo colonoscopy?[1]							
	0%-20%	15 (41.7)	6 (40.0)	9 (60.0)		7 (46.7)	8 (53.3)	
	21%-40%	16 (44.4)	7 (43.8)	9 (56.2)		10 (62.5)	6 (37.5)	
	41%-60%	4 (11.1)	4 (100)	0		3 (75.0)	1 (25.0)	
	61%-80%	1 (2.8)	0	1 (100)		0	1 (100)	
	81%-100%	0	0	0	0.122	0	0	0.658
25	How often do you experience rebleeding events after endoscopic hemostasis?[1]							
	0%-20%	22 (61.1)	10 (45.5)	12 (54.6)		13 (59.1)	9 (40.9)	
	21%-40%	10 (27.8)	4 (40.0)	6 (60.0)		7 (70.0)	3 (30.0)	
	41%-60%	3 (8.3)	2 (66.7)	1 (33.3)		1 (33.3)	2 (66.7)	
	61%-80%	1 (2.8)	1 (100)	0		0	1 (100)	
	81%-100%	0	0	0	0.721	0	0	0.458
26	How often do you experience rebleeding events after IVR?[1]							
	0%-20%	27 (90.1)	15 (55.6)	12 (44.4)		16 (59.3)	11 (40.7)	
	21%-40%	0	0	0		0	0	
	41%-60%	1 (3.3)	0	1 (100)		0	1 (100)	
	61%-80%	1 (3.3)	1	1 (100)		0	1 (100)	
	81%-100%	1 (3.3)	1 (100)	0	0.448	0	1 (100)	0.090
27	How often do you experience rebleeding events after barium impaction therapy?[1]							
	0%-20%	10 (71.6)	6 (60.0)	4 (40.0)		9 (90.0)	1 (10.0)	
	21%-40%	1 (7.1)	0	1 (100)		0	1 (100)	
	41%-60%	1 (7.1)	0	1 (100)		0	1 (100)	
	61%-80%	1 (7.1)	1 (100)	0		0	1 (100)	
	81%-100%	1 (7.1)	0	1 (100)	0.559	0	1 (100)	0.005

[1]Missing data included. Values in parentheses are percentages. SRH: Stigmata of recent hemorrhage; IVR: Interventional radiology.

Table 5 Association between procedures and outcomes *n* (%)

Procedure[1] (Question No. 15)	Answer (*n* = 37)	SRH identification rate[2] 0%-20% (*n* = 15)	21%-40% (*n* = 16)	41%-60% (*n* = 4)	61%-80% (*n* = 1)	81%-100% (*n* = 0)	*P* for trend
Cap-assisted colonoscopy	17 (46.0)	4 (25.0)	9 (56.3)	2 (12.5)	1 (6.2)	0	0.081
Long cap-assisted colonoscopy	13 (35.1)	6 (46.2)	5 (38.5)	2 (15.3)	0	0	0.735
Inverting diverticulum *via* suction of colonoscopy	18 (48.7)	5 (29.4)	10 (58.8)	2 (11.8)	0	0	0.588
Wash out with water	36 (97.3)	14 (40.0)	16 (45.7)	4 (11.4)	1 (2.9)	0	0.323
Colonoscopy by multiple doctors	3 (8.1)	2 (66.7)	1 (33.3)	0	0	0	0.328
Colonoscopy under X-ray	3 (8.1)	2 (66.7)	1 (33.3)	0	0	0	0.328
	Answer			Rebleeding rate[2]			
Endoscopic treatment (Question No. 18)	(*n* = 37)	0%-20% (*n* = 22)	21%-40% (*n* = 10)	41%-60% (*n* = 3)	61%-80% (*n* = 1)	81%-100% (*n* = 0)	*P* for trend
Clipping	31 (83.8)	19 (63.3)	8 (26.7)	3 (10.0)	0	0	0.290
Endoscopic band ligation	5 (13.5)	2 (40.0)	2 (40.0)	0	1 (20.0)	0	0.142
Epinephrine injection	1 (2.7)	1 (100)	0	0	0	0	0.489

[1]Duplicated data allowed; [2]Missing data included. Values in parentheses are percentages. SRH: Stigmata of recent bleeding.

patients requires an adequate number of medical staff and expert endoscopists, and a careful nursing system during the nighttime and weekend. However, there was no significant difference in the number of CDB patients who received treatment between high- and low-volume hospitals, which indicated that low-volume hospitals also need to treat CDB patients as well as high-volume hospitals regardless of the small number of endoscopists. Therefore, action is needed to handle an increasing number of CDB patients, such as transfer of CDB patients to core hospitals in each region.

In regard to diagnostic methods, most Japanese hospitals performed CT before colonoscopy for CDB diagnosis, and there were no significant differences between the groups separated by hospital volume and region. In contrast, Western countries may perform colonoscopy or scintigraphy, not CT[20]. This is probably because there were some studies from Japan that showed the usefulness of CT for the diagnosis of CDB, which had a sensitivity of 20.0%-42.9% and specificity of 78.6%-87.5%[13,21]. Only 46% of hospitals performed bowel preparation, and there was a significant difference between East and West Japan in this respect. This is probably because some physicians are concerned

that bowel preparation potentially increases the risk of aspiration pneumonia, volume overload, and a change in vital signs with blood loss[22]. However, the presence of colonic diverticula with poor visualization was a risk factor for perforation in screening colonoscopy[23]. Recent studies have shown that bowel preparation during acute lower gastrointestinal bleeding did not increase adverse events compared with non-gastrointestinal bleeding[24], and bowel preparation for early colonoscopy was safe as well as for elective colonoscopy[25]. In addition, bowel preparation contributes to excellent SRH identification rates[24,26]. Therefore, we may need to expand awareness of the safety of full bowel preparation in CDB diagnosis in Japan. Moreover, the rate of early colonoscopy was 43.2%. Now, we are conducting a randomized control study to resolve these unclarified issues in the diagnostic methods (UMIN 000021129).

In endoscopic treatment, clipping, band ligation, and epinephrine injection were performed as first-line therapy in 83.8%, 13.5%, and 2.7% of cases, which might be different from Western countries[27]. Some reports have indicated that Western countries usually performed thermal contact therapy[18,26,28,29]; however, this therapy is not approved in Japan[30]. Several reports from Western countries showed that clipping was a useful hemostasis treatment[12,31,32], and clipping may be performed as a common endoscopic treatment for CDB patients. On the other hand, in Japan, endoscopic band ligation was reported as useful for hemostasis in CDB, and therapeutic options for CDB have been expanding in Japan[33].

There was very limited data on the strategy for antithrombotic drugs in patients with acute gastrointestinal bleeding. The American Society for Gastrointestinal Endoscopy guidelines reported[34] that endoscopic hemostasis was considered as a procedure with a high risk of bleeding, and recommended that: (1) patients requiring endoscopic hemostasis taking non-steroidal anti-inflammatory drugs or low-dose aspirin continue these medications; (2) those taking thienopyridine should have the medication discontinued; and (3) those taking anticoagulants should consider bridging therapy. In contrast, Japan and European countries have no guidelines on the management of antithrombotic drugs in patients with gastrointestinal bleeding. Only 15% of hospitals have a strategy for antithrombotic drugs, and the timing of discontinuation and restart of antithrombotic drugs were individualized. Physicians considered discontinuation of antithrombotic therapy in patients following a hospitalization for gastrointestinal bleeding[35,36]. Discontinued use of antithrombotic drugs may decrease the risk of gastrointestinal bleeding, but discontinuation of these drugs was associated with an increased risk of thrombosis and mortality[37,38]. Although there is no consensus, we believed that patients with antithrombotic drugs need to have these medications continued, or restarted as soon as possible if patients discontinued antithrombotic drugs.

Our study has several strengths. First, our data were obtained from a large number of hospitals, so the generalizability of the results is high. Second, we evaluated intra-observer agreement, and our data showed a high level of reproducibility. However, our study has limitations. Our study was based on data from a questionnaire, and not based on patient data, so caution should be exercised in the interpretation of our results. In addition, our study has the potential of selection bias.

In conclusion, compared with Western countries, some practice styles unique to Japan such as performing CT before colonoscopy, no bowel preparation, and clipping as first-line endoscopic therapy were found. Although the number of endoscopists and nursing staff were different, the practices for CDB were almost the same, irrespective of the size of the hospital in Japan.

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COMMENTS

Background

Colonic diverticular bleeding (CDB) is increasing in Asia however there are no practice guidelines for CDB. It is important to determine which recommendation is acceptable to a majority of hospitals.

Research frontiers

To clarify the current state of the clinical settings, diagnosis, treatment, and clinical outcomes of patients with CDB.

Innovations and breakthroughs

The authors conducted multicenter questionnaire surveys of 37 hospitals in Japan regarding management of CDB such as the clinical settings, diagnosis, treatment, and clinical outcomes, comparing them between hospitals with different patient volumes and between hospitals in different regions. As a result, some practice styles unique to Japan such as performing computed tomography before colonoscopy, no bowel preparation, and clipping as first-line therapy were found. However, the management of CDB was common among hospitals irrespective of hospital size and region.

Applications

These data were obtained from a large number of hospitals, so the generalizability of the results is high.

Peer-review

This multicenter trial by questionnaire is very useful for assessment of current state of diagnosis and treatment of CDB.

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