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Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Manish Manrai, MD, DM, FRCP (Edinburgh), Professor, Department of Internal Medicine, Armed Forces Medical College, Pune, Maharashtra 411040, India. manishmanrai@yahoo.com

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OPINION REVIEW

Current approaches and questions yet to be resolved for the prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis

Hirokazu Saito, Atsushi Fujimoto, Kana Oomoto, Yoshitaka Kadowaki, Shuji Tada

Hirokazu Saito, Atsushi Fujimoto, Kana Oomoto, Yoshitaka Kadowaki, Shuji Tada, Department of Gastroenterology, Kumamoto City Hospital, Kumamoto City 862-8505, Kumamoto, Japan

Corresponding author: Hirokazu Saito, MD, Doctor, Department of Gastroenterology, Kumamoto City Hospital, 4-1-60, Higashimachi, Higashi-ku, Kumamoto City 862-8505, Kumamoto, Japan. arnestwest@yahoo.co.jp

Abstract

Prophylaxis is important for post-endoscopic retrograde cholangiopancreato-graphy (ERCP) pancreatitis (PEP), which is the most common and serious complication of ERCP. Although the current guidelines include independent patient- and procedure-related risk factors for PEP and available PEP prophylactic measures, the synergistic effect of these risk factors on PEP should also be considered, given that patients often harbor multiple risk factors. Furthermore, a combination of prophylactic measures is often selected in clinical practice. However, established methods estimating the synergistic effect of independent risk factors on PEP incidence are lacking, and evidence on the impact of combining prophylactic measures on PEP should be discussed. Selection of appropriate candidate patients for ERCP is also important to reduce the incidence of PEP associated with unnecessary ERCP. ERCP indications in patients with asymptomatic common bile duct stones (CBDSs) and in those with suspected CBDSs with no imaging-based evidence of stones are controversial. Further studies are warranted to predict the synergistic effect of independent risk factors on PEP, determine the best prophylactic PEP measures, and identify appropriate candidates for ERCP in patients with asymptomatic CBDSs and those with suspected CBDSs.

Key Words: Endoscopic retrograde cholangiopancreatography; Post-endoscopic retrograde cholangiopancreatography pancreatitis; Prophylaxis; Guidelines

Core Tip: To date, there are no established methods to estimate the synergistic effect of the independent risk factors on post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP), and evidence of the efficacy of the combination of prophylactic measures for PEP should be discussed. Furthermore, ERCP indications in patients with asymptomatic common bile duct stones (CBDSs) and patients with suspected CBDS without evidence of stones by imaging are controversial. Further studies are warranted to estimate the synergistic effect of independent risk factors on PEP and to determine the best prophylactic measures as well as the appropriate candidates for ERCP among patients with asymptomatic CBDS and those with suspected CBDS.

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is an essential therapeutic procedure for patients with biliopancreatic disorders. However, it is associated with high risks of procedure-related complications. Post-ERCP pancreatitis (PEP) is the most frequent complication, with an approximate rate of 3%-10%[1,2]. A meta-analysis of 108 randomized controlled trials revealed that the incidence of PEP was high at 14.7% [95% confidence interval (CI) 11.8%-17.7%] in high-risk patients, with one or more patient- and/or procedure-related risk factors for PEP[2]. Although most PEP cases are mild or moderate, severe PEP, which is potentially lethal, occurs in approximately 10% of the cases[1]. Therefore, it is important to reduce the incidence of PEP.

Recent guidelines published by the European Society of Gastrointestinal Endoscopy (ESGE) and the American Society for Gastrointestinal Endoscopy (ASGE) recommend prophylactic methods for reducing the incidence of PEP[3,4]. These guidelines encompass patient- and procedure-related risk factors associated with PEP and strategies for reducing the incidence of PEP, including patient selection, pharmacologic prophylaxis, and ERCP technique modifications. This opinion review discusses the current approaches used in PEP prevention and the questions yet to be resolved for the prophylaxis of PEP to further reduce the incidence of PEP.

RISK FACTORS FOR PEP

Table 1 summarizes the independent risk factors for PEP included in the ESGE and ASGE guidelines for ERCP-related adverse events[3,4]. Specifically, the ESGE guideline categorizes independent PEP risk factors into definitive and likely risk factors, and patients with at least one definitive or two likely patient- or procedure-related risk factors are defined as those at a high risk for PEP[3].

Patients often harbor multiple risk factors for PEP; therefore, the potential synergistic effect of independent risk factors for PEP should be considered. A prospective multicenter study revealed the escalation of PEP risk in patients with multiple risk factors for PEP. The odds ratios in female gender alone, female gender plus normal serum bilirubin, and female gender plus normal serum bilirubin plus difficult cannulation were 2.5, 4.8 and 16.2, respectively[5]. Although scoring systems may be useful for estimating this synergistic effect[6-10], no established scoring system exists due to the limited number of studies. Furthermore, estimating the risk for PEP before ERCP is important for advanced counseling of patients on the specific risk for PEP. A recent study suggesting a disease-based PEP risk stratification approach for choledocholithiasis reported that the incidence rates of PEP were 13.7%, 7.3%, and 1.8% in patients with asymptomatic common bile duct stones (CBDSs), obstructive jaundice without cholangitis, and acute cholangitis, respectively[11]. Disease-based risk stratification may be a useful method for easily estimating the average risk for PEP before ERCP in patients with biliary and pancreatic diseases as the synergistic effect of the independent risk factors for PEP may differ among the wide range of diseases requiring ERCP. Furthermore, a study demonstrated that a large pancreatic volume was associated with high risk and increased severity of PEP[12]. Pancreatic volume based on pre-ERCP images may also be useful for predicting the risk for PEP prior to ERCP.

In summary, although several independent risk factors for PEP have been identified[3,4,13], further studies are warranted to establish the methods for estimating the synergistic effect of independent risk factors for PEP. If possible, advanced prediction of PEP before ERCP is desirable to properly counsel patients on the specific risk for PEP and to perform aggressive prophylaxis prior to ERCP based on the

Table 1 Risk factors for post-endoscopic retrograde cholangiopancreatography pancreatitis in the European Society of Gastrointestinal Endoscopy and American Society for Gastrointestinal Endoscopy guidelines

ESGE guideline	ASGE guideline
Patient-related definitive risk factors	**Patient-related risk factors**
Suspected sphincter of Oddi dysfunction	Suspected sphincter of Oddi dysfunction
Female sex	Female sex
Previous pancreatitis	Previous recurrent pancreatitis
Previous post-ERCP pancreatitis	Previous post-ERCP pancreatitis
Procedure-related definitive risk factors	Younger age
Difficult cannulation	Absence of chronic pancreatitis
More than one pancreatic guidewire passage	Normal serum bilirubin
Pancreatic injection	**Procedure-related risk factors**
Patient-related likely risk factors	Difficult cannulation (> 10 min)
Younger age	Repeated pancreatic guidewire cannulation
Nondilated extrahepatic bile duct	Pancreatic injection
Absence of chronic pancreatitis	Endoscopic papillary large-balloon dilation of a native papilla
Normal serum bilirubin	
End-stage renal failure	
Procedure-related likely risk factors	
Precut sphincterotomy	
Pancreatic sphincterotomy	
Papillary balloon dilation	
Unsuccessful clearance of bile duct stones	
Intraductal ultrasound	

ASGE: American Society for Gastrointestinal Endoscopy; ERCP: Endoscopic retrograde cholangiopancreatography; ESGE: European Society of Gastrointestinal Endoscopy.

specific PEP risk of the patient.

PATIENT SELECTION

Selection of appropriate candidates for ERCP is important to reduce the incidence of PEP associated with unnecessary ERCP. Patients with biliary and pancreatic diseases requiring drainage, such as malignant biliary and pancreatic strictures and symptomatic choledocholithiasis with imaging-based evidence of CBDSs, are strong candidates for ERCP. However, determining ERCP candidates may be difficult in patients with asymptomatic CBDSs and suspected choledocholithiasis with no imaging-based evidence of stones.

The ASGE and ESGE guidelines for the evaluation and management of choledocholithiasis recommend strategies for selecting ERCP candidates in patients with suspected CBDSs based on stratification into low-, intermediate-, and high-PEP-risk groups[14,15]. The criteria and treatment strategy for each risk group are presented in Table 2. In these guidelines, proceeding with ERCP is recommended in high-risk patients regardless of the imaging-based evidence of CBDSs. However, the high-diagnostic ability of imaging modalities, such as magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasonography (EUS), has been recently described. Two meta-analyses reported that the sensitivity and specificity of EUS were 95%-97% and 87%-93%, and that the sensitivity and specificity of MRCP were 90%-97% and 92%-96%, respectively[16,17]. The rate of detecting even small CBDSs was high with EUS[16]. However, a systematic review and meta-analysis revealed that the mean sensitivity and specificity for the diagnosis of CBDSs were 23% (range, 18%-32%) and 89% (range, 70%-100%), respectively, when acute cholangitis was used to predict the presence of CBDSs in patients with suspected CBDSs[18]. Furthermore, one study reported that the sensitivity and specificity for the

Table 2 Recommended strategies for suspected common bile duct stones in patients with symptomatic cholelithiasis based on the ESGE and ASGE guidelines

ESGE guideline			ASGE guideline	
Likelihood	Predictors	Recommended strategy	Predictors	Recommended strategy
Low	Normal liver function tests and no CBD dilation at US	Proceed to cholecystectomy	No predictors	Cholecystectomy with/without laparoscopic cholangiography (IOC) or intraoperative US
Intermediate	Abnormal liver function tests and/or dilated CBD on US	Perform EUS/MRCP	Abnormal liver function tests or age > 55 years or dilated CBD on US/cross-sectional imaging	Perform EUS/MRCP, laparoscopic IOC, or intraoperative US
High	CBDSs identified at US or features of cholangitis	Proceed to ERCP	CBDSs identified at US/cross-sectional imaging	Proceed to ERCP
			or features of cholangitis or dilated CBD with total bilirubin > 4 mg/dL on US/cross-sectional imaging	

ASGE: American Society for Gastrointestinal Endoscopy; CBD: Common bile duct; CBDSs: Common bile duct stones; ERCP: Endoscopic retrograde cholangiopancreatography; ESGE: European Society of Gastrointestinal Endoscopy; EUS: Endoscopic ultrasonography; MRCP: Magnetic resonance cholangiopancreatography; US: Ultrasonography.

diagnosis of CBDSs were 19% and 96%, respectively, using the high-risk criteria of a total bilirubin level of above 4 mg/dL plus the presence of a dilated common bile duct (CBD) (> 6 mm in patients without cholecystectomy and > 8 mm in those with prior cholecystectomy)[19]. Therefore, high-risk criteria for diagnosis of CBDSs based on the clinical diagnosis, such as cholangitis features and dilated CBD with a total bilirubin level > 4 mg/dL without evidence of stones remains controversial. Patients with suspected CBDSs who exhibit imaging-based evidence of CBDSs are strong candidates for ERCP. However, it remains questionable whether ERCP is indicated in high-risk patients with no imaging-based evidence of stones, except for those with severe cholangitis requiring emergent biliary drainage.

Several studies have demonstrated that the incidence of PEP is significantly higher in patients with asymptomatic CBDSs, defined as the absence of abdominal symptoms and abnormal liver function tests, than in those with symptomatic CBDSs (12.5%-20.8% *vs* 3.7%-6.9%)[20-23], although only one study reported that the risk for PEP following ERCP performed by experienced endoscopists was comparable between patients with asymptomatic and symptomatic CBDSs[24]. Due to the absence of cholestasis, patients with asymptomatic CBDSs have normal total bilirubin levels and nondilated CBD, and can confound the assessment of patient-related risk factors for PEP[21]. Furthermore, floppy major duodenal papilla due to low bile duct pressure often results in difficult biliary cannulation in asymptomatic patients[21]. Therefore, the risk of PEP might be higher in patients with asymptomatic CBDSs, who are susceptible to the synergistic effect of the independent risk factors for PEP, than in those with symptomatic CBDSs.

Studies investigating the natural history of asymptomatic CBDSs have demonstrated that the cumulative incidence rate of biliary complications ranges from 0% to 29% during a median follow-up period of 30 days to 4.8 years[25-29]. Although available guidelines recommend endoscopic stone removal even in asymptomatic patients[14,15,30,31], prospective studies comparing the long-term outcomes between endoscopic treatment and the wait-and-see strategy for patients with asymptomatic CBDSs are warranted to determine whether routine endoscopic stone removal of asymptomatic CBDS is justified or not.

A recent study reported that the risk for PEP was lower in ERCP for choledocholithiasis with acute cholangitis than in ERCP for choledocholithiasis without acute cholangitis[32]. Although ESGE guideline for the endoscopic management of CBDS recommends elective ERCP for mild cholangitis, performing ERCP before improving cholangitis may be better in the view point of reducing the risk of PEP.

MODIFICATIONS IN ERCP TECHNIQUE AND PHARMACOLOGICAL PROPHYLAXIS TO REDUCE THE INCIDENCE AND SEVERITY OF PEP

PEP prophylaxis during ERCP
Recommendations for post-ERCP pancreatitis prophylaxis in ASGE and ESGE guidelines are presented in Table 3.

Table 3 Recommendations for post-endoscopic retrograde cholangiopancreatography pancreatitis prophylaxis in American Society for Gastrointestinal Endoscopy and European Society of Gastrointestinal Endoscopy guidelines

ASGE guideline	ESGE guideline
PEP prophylaxis during ERCP	**PEP prophylaxis during ERCP**
Pancreatic duct stenting in high-risk patients (high quality of evidence)	Pancreatic duct stenting in high-risk patients (strong recommendation, moderate quality of evidence)
Early precut sphincterotomy for difficult cannulation (moderate quality of evidence)	
Pharmacologic methods for PEP prophylaxis	**Pharmacologic methods for PEP prophylaxis**
Rectal NSAIDs in high-risk patients without contraindication (moderate quality of evidence)	Routine rectal NSAIDs of 100 mg of diclofenac or indomethacin immediately before in all patients without contraindication (strong recommendation, moderate quality of evidence)
Rectal indomethacin in average-risk patients without contraindication (moderate quality of evidence)	Hydration with lactated ringers in patients with contraindication to NSAIDs without at risk of fluid overload and without prophylactic pancreatic stenting (strong recommendation, moderate quality of evidence)
Hydration with lactated ringers (very-low quality of evidence)	Not suggested for the routine combination of rectal NSAIDs with other prophylactic measures (weak recommendation, low quality of evidence)
	Not recommended for protease inhibitors and epinephrine onto the papilla (strong recommendation, moderate quality of evidence)
	Somatostatin and octoreotide (no recommendation)

ERCP: Endoscopic retrograde cholangiopancreatography; ASGE: American Society for Gastrointestinal Endoscopy; ESGE: European Society of Gastrointestinal Endoscopy; PEP: Post-endoscopic retrograde cholangiopancreatography pancreatitis; NSAIDs: Nonsteroidal anti-inflammatory drugs.

Prophylactic pancreatic stent placement is a well-known effective method for PEP prophylaxis. Several meta-analyses have indicated that prophylactic pancreatic stent is associated with the decreased overall incidence of PEP (odds ratio, 0.22-0.39) and decreased incidence of severe PEP[33-38]. However, evidence for the benefit of salvage pancreatic stenting in patients with PEP is lacking. Two studies demonstrated that salvage pancreatic stenting might be useful for the rapid resolution of PEP and halting progression to severe PEP[39,40]. The ESGE guidelines recommend against the use of salvage pancreatic stenting in patients with PEP due to the limited evidence; however, this approach has been recommended in select patients, such as those with PEP accompanied by severe abdominal pain and those with more than 10-fold increase in serum amylase levels[3].

Pancreatic injection is a procedure-related definitive risk factor for PEP[3]. The use of low-osmolality contrast media, which might be less harmful for the epithelium of pancreatic duct compared with high-osmolality contrast media[41], may be a possible approach to prevent PEP. However, studies evaluating the efficacy of low-osmolality contrast medium for PEP prevention have reported contradictory findings [41-44].

Difficult biliary cannulation is another definitive risk factor for PEP[3,4]. Although the definition of difficult cannulation varies among the previous studies, the ESGE guidelines for papillary cannulation and sphincterotomy technique in ERCP define difficult cannulation as cases fulfilling one or more of several criteria, such as more than five contacts with the major duodenal papilla during the cannulation attempt, cannulation attempt lasting more than 5 min after the visualization of the papilla, and more than one unintended cannulation or opacification of the pancreatic duct[45]. In cases with difficult biliary cannulation, pancreatic guidewire-assisted cannulation and precut sphincterotomy are used as well-known rescue techniques. Several studies have demonstrated the safety and efficacy of early precut sphincterotomy in reducing the risk of PEP. A recent systematic review and network meta-analysis revealed that early precut sphincterotomy was associated with increased successful biliary cannulation and reduced incidence of PEP compared with the standard cannulation technique and pancreatic guidewire-assisted cannulation[46]. Furthermore, a retrospective study demonstrated that the second ERCP after the failure of initial biliary cannulation following precut sphincterotomy should be performed at least 4 days after the first ERCP[47]. However, a few studies investigated the efficacy and safety of the early use of double-guidewire technique. A randomized controlled trial revealed that the early use of double-guidewire technique increased the rate of successful biliary cannulation and that the incidence of PEP was similar between the double-guidewire technique and the repeated use of single-guidewire technique[48]. Another randomized controlled trial demonstrated that the early use of double-guidewire technique did not facilitate successful biliary cannulation and did not reduce the incidence of PEP[49]. Further studies are warranted to evaluate the efficacy and safety of early use of pancreatic guidewire-assisted cannulation. Furthermore, the optimal timing for the rescue cannulation technique is unclear, although one study suggested that attempting biliary cannulation for 5 min might be a valid cutoff for the implementation of the rescue technique[50].

Pharmacologic methods for PEP prophylaxis

Rectal nonsteroidal anti-inflammatory drugs (NSAIDs) are consistently recommended as pharmacologic prophylaxis for PEP in the current guidelines[3,4]. Rectal diclofenac and indomethacin are considered to have a similar beneficial effect for the prophylaxis of PEP, and the rectal NSAID dose of 100 mg is recommended in the ASGE and ESGE guidelines[3,4]. However, the rectal NSAID dose of 100 mg may be too high for elderly patients or those with low body weight, especially among Asian populations. A randomized controlled trial revealed that the incidence of PEP was significantly lower in patients who were administrated 25-50-mg rectal NSAIDs than in those who were not administered rectal NSAIDs [3.9% (2/51) *vs* 18.9% (10/53)][51]. However, several retrospective and prospective studies demonstrated that low-dose rectal NSAIDs were not useful for reducing the risk for PEP[52-54]. Further studies are warranted to determine the optimal rectal NSAID dose in elderly patients and in those with low body weight. Studies investigating the combination of rectal NSAIDs with other prophylactic approaches for PEP found no difference in the PEP incidence between rectal NSAIDs alone and rectal NSAIDs in combination with prophylactic pancreatic stenting[55-57]. However, a recent study demonstrated that the combined approach of rectal NSIADs and prophylactic pancreatic stenting was useful for preventing PEP in patients undergoing ERCP using the double-guidewire technique[58].

Aggressive hydration is recognized as a useful method for PEP prophylaxis[3]. Recent meta-analyses revealed that aggressive hydration with the lactated Ringer's solution of 35-45 mL/kg administered during 8-10 h contributed to reduce the incidence of PEP with odds ratios of 0.29–0.47[59-61]. Furthermore, aggressive hydration was associated with the decreased moderate to severe PEP with the odds ratio of 0.16[59], and there were no differences in fluid overload-related complications[60,61]. While several studies reported that rectal NSAIDs plus hydration was an effective combination for the prevention of PEP[37,62-65], others reported no benefit with this approach[66,67]. A recent network meta-analysis of 24 randomized controlled trials demonstrated that a combination of rectal indomethacin and aggressive hydration is the best conservative approach for prophylaxis of PEP with preventive efficacy 70%-99% higher than that of single prophylaxis[64]. In recent years, with the increasing implementation of prophylactic measures for PEP, the combination of various approaches is often selected in clinical practice[68]. Further studies are warranted to solve the dilemma of combining specific approaches for PEP prophylaxis.

CONCLUSION

Estimation of the PEP risk based on patient- and procedure-related risk factors, patient selection for ERCP, and technical and pharmacological prophylaxis for PEP are important aspects to be considered to reduce the incidence of PEP following ERCP. Although several independent patient- and procedure-related risk factors for PEP have been identified, methods for estimating the synergistic effect of these risk factors on PEP incidence should be established in future studies. Regarding patient selection, whether routine ERCP in cases of asymptomatic CBDSs and highly suspected CBDSs without imaging-based evidence of stones is warranted should be discussed. Furthermore, although independent prophylactic measures such as rectal NSAIDs and prophylactic pancreatic stenting have been implemented, further studies are warranted to determine the best prophylactic measures for PEP, including the combination of independent prophylactic measures.

FOOTNOTES

ORCID number: Hirokazu Saito 0000-0001-8729-9604; Atsushi Fujimoto 0000-0003-4222-8065; Kana Oomoto 0000-0002-9312-4015; Yoshitaka Kadowaki 0000-0003-0227-9802; Shuji Tada 0000-0001-9087-5457.

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MINIREVIEWS

Optimal traction direction in traction-assisted gastric endoscopic submucosal dissection

Mitsuru Nagata

Mitsuru Nagata, Department of Endoscopy, Shonan Fujisawa Tokushukai Hospital, Fujisawa 251-0041, Kanagawa, Japan

Corresponding author: Mitsuru Nagata, MD, Chief Doctor, Department of Endoscopy, Shonan Fujisawa Tokushukai Hospital, 1-5-1 Tsujidokandai, Fujisawa 251-0041, Kanagawa, Japan. mitsuru10jp@yahoo.co.jp

Abstract

Various traction devices have been developed to secure a visual field and sufficient tension at the dissection plane during endoscopic submucosal dissection (ESD). However, few large-scale studies have investigated the effectiveness of traction devices in gastric ESD. Clip-with-line (CWL) is one such traction device that is widely used in cases of gastric ESD. The CONNECT-G trial was the first multicenter randomized controlled trial to compare conventional ESD with CWL-assisted ESD (CWL-ESD) for superficial gastric neoplasms. Overall, no significant intergroup difference was observed in terms of the gastric ESD procedure time. However, subgroup analysis according to lesion location revealed a significant reduction in the procedure time of gastric ESD for the lesion located at the greater curvature of the middle and upper third of the stomach in the CWL-ESD group. In this subgroup analysis, lesion location was categorized as follows: anterior wall, posterior wall, lesser curvature, and greater curvature of the upper, middle, and lower thirds of the stomach. However, the gastric ESD procedure time showed no significant difference, except for lesions located at the greater curvature of the upper and middle thirds of the stomach. The traction direction of CWL in the stomach was limited to the cardia and changed depending on the lesion location. Therefore, outcomes of the CONNECT-G trail suggest that the effectiveness of CWL was influenced by lesion location, i.e., traction direction. Further studies are warranted to investigate the optimal traction direction in gastric ESD.

Key Words: Endoscopic submucosal dissection; ESD; Traction device; Clip-with-line; Traction direction; Vertical traction

Core Tip: Various traction devices have been developed for endoscopic submucosal dissection (ESD). However, few traction devices have been validated in large-scale studies thus far. The CONNECT-G trial was the first multicenter randomized controlled trial to compare conventional ESD with clip-with-line-assisted ESD for superficial gastric neoplasms. This study suggested that the effectiveness of traction devices in gastric ESD depends on the traction direction; in addition, the most optimal traction direction is vertical to the gastric wall.

INTRODUCTION

Endoscopic submucosal dissection (ESD) allows en bloc resection of superficial gastric neoplasms. However, gastric ESD is a challenging procedure. Surgeons can use their nondominant hand to generate traction for lesions while they resect using their dominant hand. Meanwhile, endoscopists cannot use their nondominant hand to generate traction because they cannot insert their hand into the stomach. Therefore, endoscopists occasionally cannot secure a visual field and sufficient tension at the dissection plane, resulting in a long ESD procedure time and a high perforation rate. Recently, many traction devices were reported to overcome these problems, but few large-scale studies investigated the effectiveness of traction devices in gastric ESD.

CONNECT-G TRIAL

The CONNECT-G trial was the first multicenter randomized controlled trial to compare conventional ESD with traction-assisted ESD for the treatment of superficial gastric neoplasms[1]. In this study, clip-with-line (CWL) was used as a traction device (Figure 1), and its traction direction is restricted to the direction where the line is drawn[2,3]. The primary endpoint was the mean gastric ESD procedure time, which was 58.1 min in the conventional ESD group and 60.7 min in the CWL-assisted ESD (CWL-ESD) group, with no significant difference ($P = 0.45$). R0 resection was not statistically significant in both groups (96.8% vs 97.8%, $P = 0.45$). However, the perforation rate was significantly lower in the CWL-ESD group (0.3% vs 2.2%, $P = 0.04$), suggesting that CWL may have improved the field of vision and reduced blind submucosal dissection.

For lesions located at the greater curvature of the middle and upper third of the stomach, the CWL-ESD group had a significantly shorter gastric ESD procedure time than the conventional ESD group (57.2 min vs 104.1 min, $P = 0.01$). This part of the stomach is a challenging area for conventional ESD because it is basically a gravitational lower side, so a mucosal flap is difficult to deploy, and the visual field tends to deteriorate due to fluid retention. Nevertheless, CWL-ESD is particularly useful in this area. In this subgroup analysis, lesion location was divided into the anterior wall, posterior wall, lesser curvature, and greater curvature of the upper, middle, and lower third of the stomach. However, no significant difference was found in the procedure time of gastric ESD, except for lesions located at the greater curvature of the middle and upper third of the stomach.

TRACTION DIRECTION OF CWL DIFFERS DEPENDING ON THE LESION LOCATION AND ENDOSCOPIC POSITION

The results of the CONNECT-G trail suggest that the effectiveness of CWL-ESD varies depending on the lesion location. Traction direction can be classified into five categories (Figure 2)[4]. Since CWL is a per-oral traction device, its traction direction is limited to the cardia and varies depending on the lesion location. Another consideration for the traction direction of CWL is the endoscopic position during submucosal dissection. Because of the large lumen of the stomach, there are two possible endoscopic positions: forward and retroflexed. Therefore, the traction direction also varies depending on the endoscopic position even if the lesion is in the same location. For example, for lesions located at the lesser curvature of the middle third of the stomach, CWL commonly provides a distal traction in retroflexed endoscopic position (Figure 3A) and proximal traction in forward endoscopic position (Figure 3B).
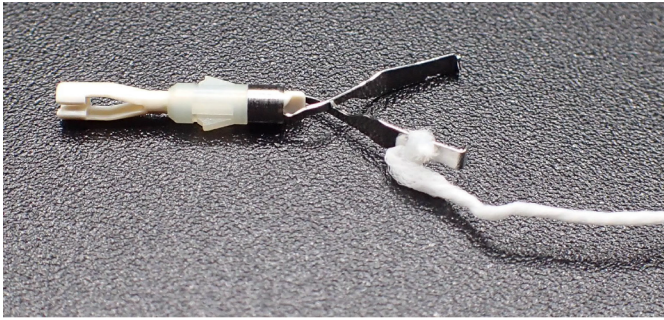
Figure 1 A clip-with-line was made by tying a commercially available dental floss to the arm section of the hemoclip.
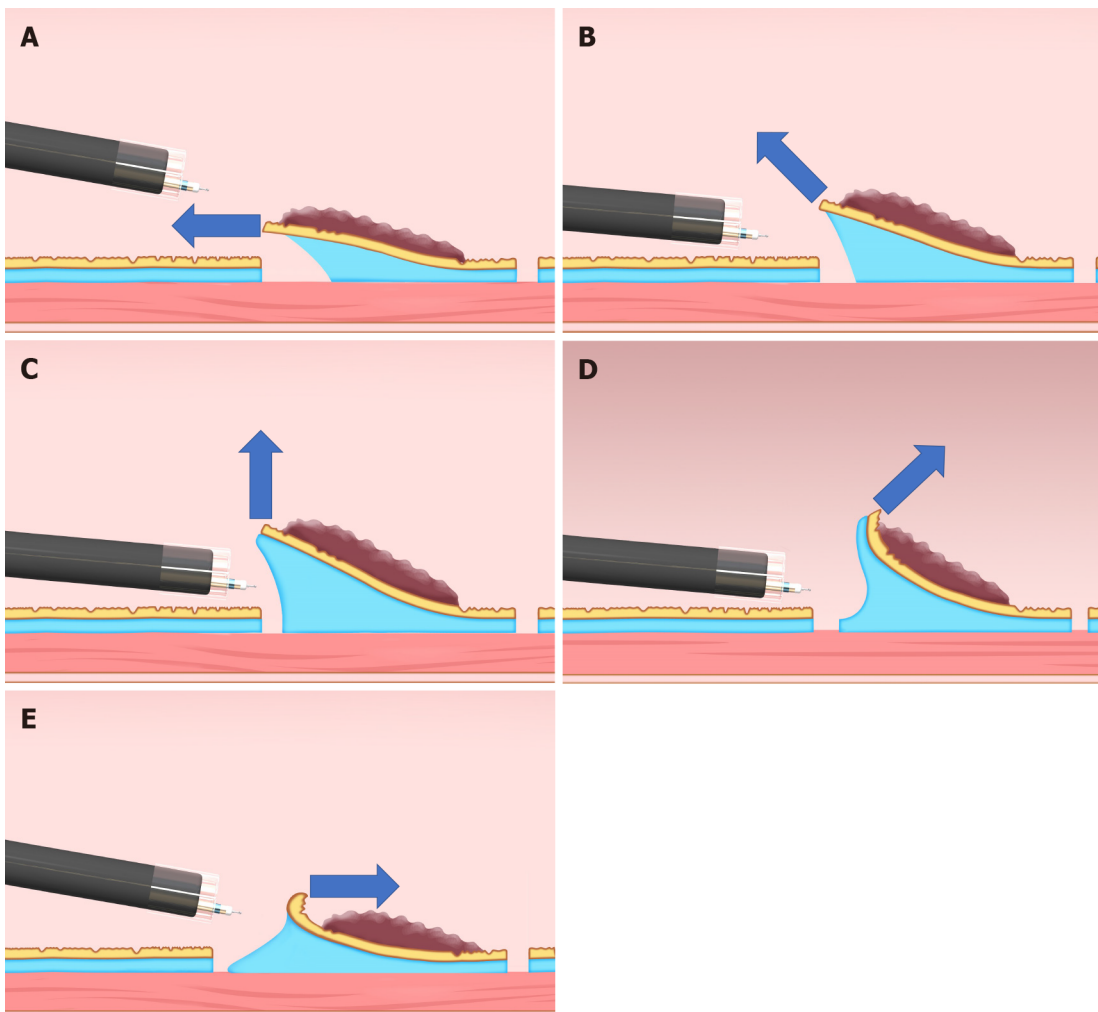
Figure 2 Classification of the traction direction. A: Proximal traction; B: Diagonally proximal traction; C: Vertical traction; D: Diagonally distal traction; E: Distal traction. Citation: Reprinted from Mitsuru Nagata. Advances in traction methods for endoscopic submucosal dissection: What is the best traction method and traction direction? *World Journal of Gastroenterology* 2022; 28(1): 1–22. Copyright ©Mitsuru Nagata 2022. Published by Baishideng Publishing Group Inc.

WHAT IS THE OPTIMAL TRACTION DIRECTION IN GASTRIC ESD?

The optimal traction direction in gastric ESD was not yet fully investigated. However, several studies indicated that a vertical traction is the optimal traction direction. The CONNECT-G trial suggests that CWL is effective for lesions located at the greater curvature of the upper and middle third of the stomach, and vertical traction is frequently performed in this area from an anatomical point of view (Figure 3C). CWL can essentially only provide vertical traction for lesions located at the greater curvature of the stomach, but multidirectional traction devices, such as a spring-and-loop with clip
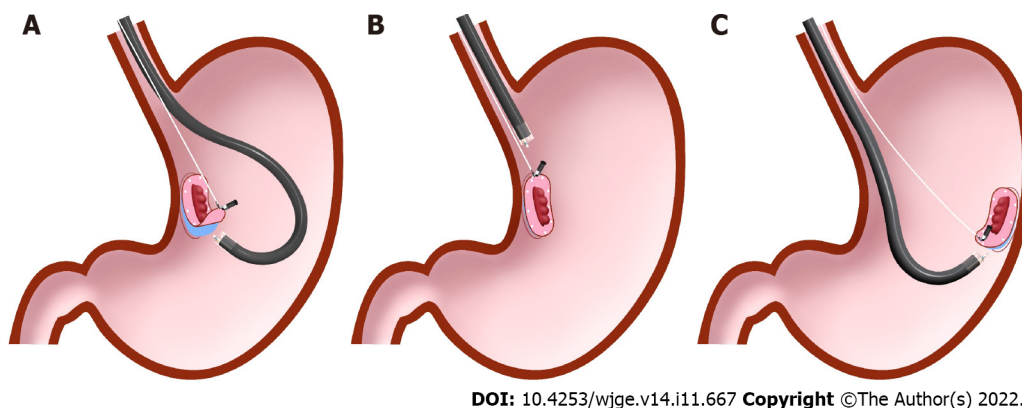
Figure 3 Differences in traction direction depending on the lesion location in clip-with-line–assisted endoscopic submucosal dissection.
A: Distal traction; B: Proximal traction; C: Vertical traction. Citation: Reprinted from Mitsuru Nagata. Advances in traction methods for endoscopic submucosal dissection: What is the best traction method and traction direction? *World Journal of Gastroenterology* 2022; 28(1): 1–22. Copyright ©Mitsuru Nagata 2022. Published by Baishideng Publishing Group Inc.

Figure 4 An S–O clip (Zeon Medical, Tokyo, Japan) was made of a 5 mm-long spring and 4 mm-long nylon loop on one side of the clip claws.

(Figure 4; SLC; S–O clip; Zeon Medical, Tokyo, Japan), may provide a vertical traction for lesions in other areas. The SLC allows the traction direction to be controlled in any direction. This clip was developed as a traction device to provide traction for colorectal ESD. Hence, we have devised a novel usage of the SLC with both forward and retroflexed endoscopic positions for gastric ESD[5,6]. A single-center randomized controlled trial comparing conventional ESD and SLC-assisted ESD (SLC-ESD) was conducted. In SLC-ESD, a vertical traction was selected using the multidirectional traction function. This study demonstrated that the median gastric ESD procedure time was significantly shorter in SLC-ESD than in conventional ESD (29.1 min *vs* 52.6 min; P = 0.005)[7]. However, SLC-ESD was not associated with a reduction in the gastric ESD procedure time for lesions > 20 mm. As submucosal dissection progresses, the distance between the SLC attachment site and the anchor site diminishes gradually, resulting in weaker traction force due to the spring shortening. For larger lesions, diagonally proximal traction may be preferable to vertical traction to maintain spring extension even as submucosal dissection progresses or an additional SLC should be considered when traction force becomes weaker. Overall, considering the results of these two randomized controlled trials, vertical traction may be the optimal traction direction for most cases of gastric ESD.

It is unclear whether other traction directions are effective in gastric ESD. Especially in distal traction, as the submucosal dissection progresses, the dissection plane falls toward a distal direction, which may be counterproductive because it may not provide an effective tension on the dissection plane. In CWL-ESD, a retroflexed endoscopic position occasionally results in a distal traction, and this position is common in gastric ESD. It is possible that a distal traction was provided for a relatively large number of cases in the CONNECT-G trial, and this could cause no significant difference in gastric ESD procedure time between conventional ESD and CWL-ESD in the total population of the CONNECT-G trial. However, the traction direction and endoscopic position were not reported, so this point should be

further investigated.

In CWL-ESD, combined with the pulley method[8,9], the traction direction can be controlled, and vertical traction can be obtained. Therefore, the pulley method may improve the gastric ESD procedure time in CWL-ESD. However, since the pulley method in gastric ESD has been reported mainly in case series studies or *ex-vivo* studies, its feasibility and effectiveness should be further investigated.

CONCLUSION

Vertical traction may be the optimal traction direction in traction-assisted ESD for gastric neoplasms. Further studies are needed to investigate the effectiveness of other traction directions.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Quality of colonoscopy performed by medical or surgical specialists and trainees in five Australian hospitals

Tsai-Wing Ow, Olga A Sukocheva, Vy Tran, Richard Lin, Shawn Zhenhui Lee, Matthew Chu, Bianca Angelica, Christopher K Rayner, Edmund Tse, Guru Iyngkaran, Peter A Bampton

Tsai-Wing Ow, Olga A Sukocheva, Vy Tran, Richard Lin, Christopher K Rayner, Edmund Tse, Peter A Bampton, Department of Gastroenterology and Hepatology, Royal Adelaide Hospital, Adelaide 5000, SA, Australia

Tsai-Wing Ow, Department of Gastroenterology and Hepatology, Flinders Medical Centre, Bedford Park 5042, SA, Australia

Shawn Zhenhui Lee, Matthew Chu, Department of Gastroenterology and Hepatology, The Queen Elizabeth Hospital, Woodville South 5011, SA, Australia

Bianca Angelica, Department of Gastroenterology, Royal Darwin Hospital, Darwin 0810, NT, Australia

Guru Iyngkaran, Department of Gastroenterology and Hepatology, Royal Melbourne Hospital, Parkville 3050, VIC, Australia

Corresponding author: Tsai-Wing Ow, FRACP, MBBS, Doctor, Department of Gastroenterology and Hepatology, Royal Adelaide Hospital, Port Road, Adelaide 5000, SA, Australia. tsai-wing.ow@sa.gov.au

Abstract

BACKGROUND
Ensuring colonoscopy procedure quality is vital to the success of screening and surveillance programmes for bowel cancer in Australia. However, the data on the performance of quality metrics, through adequate adenoma detection, bowel preparation, and procedure completion rates, in the Australian public sector is limited. Understanding these can inform quality improvement to further strengthen our capacity for prevention and early detection of colorectal cancer.

AIM
To determine the quality of colonoscopy in Australian teaching hospitals and their association with proceduralist specialty, trainee involvement, and location.

METHODS
We retrospectively evaluated 2443 consecutive colonoscopy procedure reports from 1 January to 1 April, 2018 from five public teaching tertiary hospitals in Australia (median 60 years old, 49% male). Data for bowel preparation quality,

procedure completion rates, and detection rates of clinically significant adenomas, conventional adenomas, and serrated lesions was collected and compared to national criteria for quality in colonoscopy. Participating hospital, proceduralist specialty, and trainee involvement indicators were used for stratification. Data was analysed using Chi-squared tests of independence, Mann-Whitney *U*, One-way ANOVA, and multivariate binary logistic regression.

RESULTS
Fifty-two point two percent (*n* = 1276) and 43.3% (*n* = 1057) were performed by medical and surgical proceduralists respectively, whilst 29.8% (*n* = 728) involved a trainee. Inadequate bowel preparation affected 7.3% of all procedures. The procedure completion rate was 95.1%, which increased to 97.5% after adjustment for bowel preparation quality. The pooled cancer, adenoma, and serrated lesion detection rates for all five hospitals were 3.5%, 40%, and 5.9% respectively. Assessed hospitals varied significantly by patient age (*P* < 0.001), work-force composition (*P* < 0.001), adequacy of bowel preparation (*P* < 0.001), and adenoma detection rate (*P* < 0.001). Two hospitals (40%) did not meet all national criteria for quality, due to a procedure completion rate of 94.5% or serrated lesion detection rate of 2.6%. Although lower than the other hospitals, the difference was not significant. Compared with surgical specialists, procedures performed by medical specialists involved older patients [65 years (inter-quartile range, IQR 58-73) *vs* 64 years (IQR 56-71); *P* = 0.04] and were associated with a higher adenoma detection rate [odds ratio (OR) 1.53; confidence interval: 1.21-1.94; *P* < 0.001]. Procedures involving trainee proceduralists were not associated with differences in the detection of cancer, adenoma, or serrated lesions, compared with specialists, or according to their medical or surgical background. On multivariate analysis, cancer detection was positively associated with patient age (OR 1.04; *P* < 0.001) and negatively associated with medical compared to surgical proceduralists (OR 0.54; *P* = 0.04). Conventional adenoma detection rates were independently associated with increasing patient age (OR 1.04; *P* < 0.001), positively associated with medical compared to surgical proceduralists (OR 1.41; *P* = 0.002) and negatively associated with male gender (OR 0.53; *P* < 0.001).

CONCLUSION
Significant differences in the quality of colonoscopy in Australia exist, even when national benchmarks are achieved. The role of possible contributing factors, like procedural specialty and patient gender need further evaluation.

Core Tip: We evaluated the quality of colonoscopy performed at five teaching hospitals in Australia, using bowel preparation quality, procedure completion, and detection of cancer, adenoma, and serrated lesions as main indicators. In our retrospective analysis of 2443 procedures, the collective performance met national benchmarks for quality. However, two hospitals individually failed to meet all national benchmarks and we observed significant differences in key metrics of adenoma detection and adequacy of bowel preparation for colonoscopy across all hospitals. Higher adenoma detection rates were also independently shown amongst medical compared with surgical proceduralists, and amongst female patients.

INTRODUCTION

Metrics conventionally used in the assessment of quality in colonoscopy are centred around its role in the prevention and early detection of colorectal cancer (CRC) and other gastrointestinal (GI) complications. These include the adenoma detection rate (ADR), generally considered the gold-standard indicator of quality, the adequacy of bowel cleansing and rate of procedure completion[1,2]. The im-

portance of the indicator to GI cancers screening and surveillance programs is highlighted by the association between lower ADRs and the development of interval cancers, whilst incomplete procedures or poor bowel preparation significantly increase the risk of subsequent advanced colonic lesions[3,4].

The Gastroenterological Society of Australia has recently implemented a recertification program using self-reported data to assess the performance of colonoscopy. Current nominated benchmarks include an ADR of 25% in eligible procedures, completion rate of at least 95% in patients with intact colons, and serrated lesion detection rate (SLDR) of 4%[5]. This can provide valuable data on adenoma detection, procedure completion, and bowel preparation rates. However, the data submitted for recertification typically relates to work performed for patients with private health insurance. This does not reflect the quality of procedures in government-funded universal healthcare, in which a quarter of all colonoscopies in Australia are performed[6]. Considering that patients of lower socio-economic background are not only at risk of the poorest outcomes of CRC and other GI complications, but are also reliant upon this pathway for access to healthcare, it is important to ensure its quality[6].

However, assessment of performance data from this section is limited to a handful of single-centre studies[7-10]. Furthermore, the quality of procedures performed by proceduralists-in-training in Australia remain unreported. Ensuring the quality of colonoscopy in this sector therefore also supports both current and future screening and surveillance practice. We measured the quality of colonoscopy performed in five public teaching hospitals in Australia. We aimed to assess not only the quality of the performed colonoscopies, but also key areas for further improvement and targeted solutions for potential problems.

MATERIALS AND METHODS

Study design and setting
We performed a retrospective, multicentre, cohort study across five hospitals (identified as Site 1-5) in South Australia and the Northern Territory with electronic records of colonoscopy and pathology data spanned over three months. Together, the catchment population for the five hospitals is estimated to be just over one million people. Ethical approval was granted by the Central Adelaide Local Health Network ethics committee.

Data collection
We searched GI endoscopy databases (ProVationMD) for colonoscopy procedures performed between 1 January, 2018 to 31 March, 2018 inclusive at each participating site. We excluded patients undergoing a flexible sigmoidoscopy, where only the left side of the colon was viewed. Patients younger than 18 years were also excluded as conventional quality metrics are not typically applied in the paediatric population. Endoscopy and linked pathology data was collected, anonymised, and managed using REDcap electronic data capture tools hosted at The University of Technology Sydney accessed through the Australian Access Federation[11,12].

We collected data including patient age, gender, proceduralist speciality, trainee participation, trainee specialty, and site for each procedure. We examined the records of each patient for a history of CRC, prior colonic resection, and inflammatory bowel disease (IBD). We evaluated the quality of bowel preparation according to the main validated scores used by the participating centres - either the Aronchick or the Boston Bowel Preparation Scale[13]. Histological diagnosis was confirmed by linked pathology reports accessed through site-specific electronic health records. Definitions for each outcome were outlined on the REDcap software to ensure consistency and quality in data collection amongst the authors.

Definitions
Adequacy of bowel preparation was defined by a description of fair, good, or excellent according to the Aronchick scale. Alternatively, a score of 6 or greater, with no individual segment less than 2, was used according to the Boston Bowel Preparation Scale[13]. The rate of inadequate bowel preparation was determined by the proportion of procedures which did not meet the above criteria when rated against either scale. The rate of indeterminate bowel preparation quality otherwise determined according to the proportion of procedures where an alternative or no scoring system was applied.

Procedure completion was defined by documented (either written or photographic) progress to the caecum or terminal ileum, in patients with an intact colon (the absence of a history of CRC or prior colonic resection). The procedure completion rate was defined by the proportion of procedures in which this was achieved. The adjusted procedure completion rate was defined by the proportion of colonoscopies with adequate bowel preparation where procedure completion was achieved.

We adapted conventional criteria for ADR to define the population (or eligible procedures) for which the detection rates for the various lesions (CRC, conventional adenomas, and serrated lesions) were determined. Typically this involves patients, aged 50 and over, who are undergoing their index colonoscopy following a positive bowel cancer screening test[14]. However, we also included procedures performed for other indications except for IBD and CRC or where prior colonic resection had occurred,

in line with definitions adopted nationally for recertification in colonoscopy[5]. Additionally, we excluded patients without adequate bowel preparation due to its impact on adenoma detection and its potential as a confounder.

The CRC detection rate was defined as the proportion of eligible procedures in which the cancer was identified and confirmed on histology. These cases were subsequently excluded for the calculation of detection rates for conventional adenomas and serrated lesions due to the possibility that a newly diagnosed CRC may influence proceduralists' further efforts to find and resect synchronous non-malignant lesions. The ADR and SLDR were thus defined by the proportion of procedures in which at least one conventional adenoma or serrated lesion respectively was identified on histology amongst the remaining procedures[15]. The clinically significant lesion detection rate (CSLDR) was determined according to the proportion of procedures where either a conventional adenoma, serrated lesion or both were identified amongst eligible procedures without a new CRC diagnosis.

Contemporary World Health Organisation histological definitions for conventional adenomas (tubular, tubulovillous, or villous adenoma) and serrated lesions (sessile serrated lesion, traditional serrated lesion or large hyperplastic polyp ≥ 10 mm) were used[16].

Assessment of outcomes

We determined the rates of inadequate bowel preparation and procedure completion for all hospitals, and stratified the results according to hospital, proceduralist specialty (medical/surgical), presence or absence of a trainee, and trainee specialty. Amongst eligible procedures, those with a new diagnosis were used to calculate the cancer detection rate. We analysed the remaining procedures to determine the ADR, SLDR, and CSLDRs. Lesions identified on colonoscopy without available histology were not counted when calculating detection rates. The detection rates for cancer, adenoma, serrated lesions, and clinically significant lesions were also stratified according to the same groups as above. We did not compare the outcomes of procedures performed by nurse endoscopists to those of medical or surgical specialists as they were only employed at a single hospital and thus subject to a significant risk of sampling bias.

The primary outcome was ADR. According to a recent meta-analysis showing an expected ADR of 40% with a confidence interval of 95% and a margin of error of 5%, we assessed a minimum sample of 369 patients[17].

Statistical analysis

Descriptive statistics was adapted to characterise the data. Chi-squared tests of independence were used to analyse nominal data. Mann-Whitney *U* test and one-way ANOVA tests were used for comparison of non-parametric data. Multivariate binary logistic regression was used to determine contributing factors for detection rates for cancer, adenomas, and serrated lesions. The significance level was set at 0.05. IBM SPSS Statistics version 27 was used.

RESULTS

A total of 2443 consecutive colonoscopies were performed from January to April of 2018. 49% (*n* = 1198) of the patients were male with a median age of 60 (inter-quartile range 50-70). Prior to exclusions, 69.1% (*n* = 1688) of procedures were performed on individuals aged 50 or greater; 6.4% (*n* = 156) of procedures were indicated for a personal history of CRC; 7.9% (*n* = 192) had undergone prior surgical resection; and 6.5% (*n* = 159) of procedures were indicated for IBD. Bowel preparation was documented as adequate in 86.9% (*n* = 2123), indeterminate in 5.8% (*n* = 142), and inadequate in 7.3% (*n* = 178) of procedures, respectively. Procedure completion was confirmed in 95.1% (*n* = 2114) after 9% (*n* = 220) of procedures were excluded for either a history of CRC or prior surgical resection. After excluding additional procedures for inadequate or indeterminate bowel preparation quality (*n* = 288), the adjusted procedure completion rate was 97.5%.

Of the total 2443 procedures, we excluded 600 that were conducted in patients under 50 years old; and a further 74 with IBD; 137 with CRC; 34 with prior bowel surgery; 77 incomplete procedures; and 181 with inadequate or indeterminate bowel preparations (Figure 1). Consequently, 1340 (54.9%) procedures were considered eligible for the determination of detection rates for cancer, conventional adenomas, and serrated lesions. Cancer was detected in 1.9% (*n* = 47) of patients. Conventional adenomas and serrated lesions were identified in 40% (*n* = 517) and 5.9% (*n* = 76) of the remaining procedures, respectively.

Our analysis indicated that 43.3% (*n* = 1057) and 52.2% (*n* = 1276) of procedures were performed by surgical and medical specialty groups, respectively. Nurse endoscopists conducted 4.5% (*n* = 106) of procedures at a single site. The specialty could not be determined in the remaining four cases where a proceduralist was not named on the colonoscopy report. Amongst all procedures, 29.8% (*n* = 728) of colonoscopies were attended by trainees. Of these, 45.9% (*n* = 334) of procedures were attended by a medical trainee.
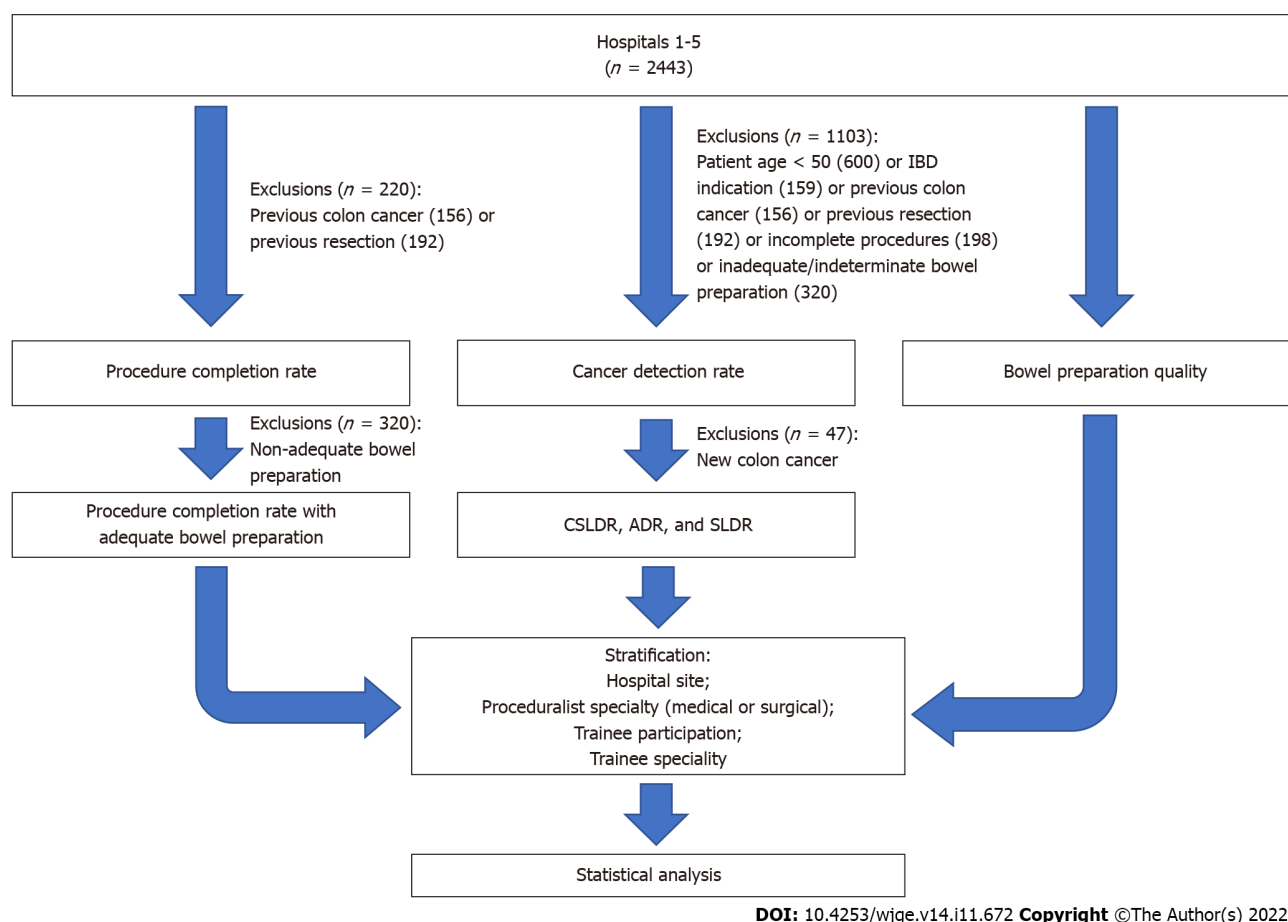
Figure 1 Study flow chart. IBD: Inflammatory bowel disease; CSLDR: Clinically significant lesion detection rate; ADR: Adenoma detection rate; SLDR: Serrated lesion detection rate.

On analysing outcomes according to specialty group, a total of 551 eligible procedures were performed by surgical proceduralists, with cancer detected in 4.7% (*n* = 26) of cases (Table 1). Of the remaining procedures, conventional adenomas and serrated lesions were identified in 34% (*n* = 178) and 4.6% (*n* = 24) respectively. In comparison, 716 eligible procedures were performed by medical proceduralists, with cancer detected in 2.7% (*n* = 19) of cases. After excluding new diagnoses of cancer, medical proceduralists identified conventional adenomas and serrated lesions in 44% (*n* = 307) and 6.6% (*n* = 46).

Further analysis indicated that, compared with medical specialists, surgeons performed their procedures on a significantly younger patient group (*P* = 0.04). The overall cancer detection rate was lower among medical compared to surgical specialists, although the difference was not found to be significant (*P* = 0.052). The odds of detecting a clinically significant polyp or adenoma, however, were significantly higher amongst medical than surgical specialists [*P* < 0.001, odds ratio (OR) 1.58, (95% confidence interval (CI): 1.25-1.99); *P* < 0.001, OR 1.53, (95%CI: 1.21-1.94)] (Table 1).

When we compared 370 eligible procedures performed with trainees present against 968 performed by specialists, no significant differences in the cancer, adenoma, and serrated lesion detection rates were found (Table 2). Similarly, no significant differences in the lesion detection rates were found amongst the procedures attended by trainees according to their background specialty (Table 3).

Following this, sites were compared for the quality of endoscopic procedures. Prior to exclusions (*n* = 2443), there were significant variations in the age of patients undergoing colonoscopy (*P* < 0.001); the procedure completion rate (*P* < 0.001); proportion of procedures performed by surgical or medical proceduralists (*P* < 0.001); degree of trainee involvement (*P* < 0.001); and bowel preparation quality (*P* < 0.001) (Table 4). Following univariate analysis, significant differences were observed in the detection of conventional adenomas (*P* = 0.01) and clinically significant polyps (*P* = 0.01), but not for cancer (*P* = 0.38) or serrated lesions (*P* = 0.31).

However, some differences were found to be no longer significant when multivariate analysis was performed (Tables 4 and 5). Our analysis indicates that two factors were associated with cancer detection: increasing patient age, and procedures performed by surgical specialists (Tables 4 and 5). Adenoma detection was increased with increasing patient age, female gender, and procedures performed by medical proceduralists. We also observed a trend towards the increased detection of serrated lesions amongst male patients, but this did not reach the significance level (*P* = 0.054).

Table 1 Comparison of key outcomes between eligible procedures performed by medical and surgical specialists

	Medical, *n* = 716	Surgical, *n* = 551	*P* value	OR (95%CI)
Patient age, median (IQR)	65 (58-73)	64 (56-71)	0.04	-
Patient gender (male %)	49.7 (*n* = 356)	48.8 (*n* = 269)	0.75	-
Cancer detection rate (%)	2.7 (*n* = 19)	4.7 (*n* = 26)	0.052	0.55 (0.30-1.01)
CSPDR (%)	46.6 (*n* = 325)	35.6 (*n* = 187)	< 0.001	1.58 (1.25-1.99)
ADR (%)	44 (*n* = 307)	34 (*n* = 178)	< 0.001	1.53 (1.21-1.94)
SLDR (%)	6.6 (*n* = 46)	4.6 (*n* = 24)	0.13	1.47 (0.89-2.45)

CSPDR: Clinically significant polyp detection rate; ADR: Adenoma detection rate; SLDR: Serrated lesion detection rate; CI: Confidence interval; OR: Odds ratio; IQR: Inter-quartile range.

Table 2 Comparison of outcomes between eligible procedures performed with and without trainees

	With trainees, *n* = 370	Without trainees, *n* = 968	*P* value	OR (95%CI)
Patient age, median (IQR)	64 (57-72)	64 (57-72)	0.83	-
Patient gender (male %)	53.5 (*n* = 198)	47.4 (*n* = 463)	0.06	-
Cancer detection rate (%)	4.1 (*n* = 15)	3.3 (*n* = 32)	0.51	1.24 (0.66-2.31)
CSPDR (%)	41.4 (*n* = 147)	42.7 (*n* = 400)	0.67	0.95 (0.74-1.21)
ADR (%)	38.9 (*n* = 138)	40.4 (*n* = 378)	0.62	0.94 (0.73-1.21)
SLDR (%)	4.8 (*n* = 17)	6.3 (*n* = 59)	0.30	0.74 (0.43-1.30)

CSPDR: Clinically significant polyp detection rate; ADR: Adenoma detection rate; SLDR: Serrated lesion detection rate; CI: Confidence interval; OR: Odds ratio; IQR: Inter-quartile range.

Table 3 Comparison of outcomes between eligible procedures performed with medical and surgical trainees

	Medical trainees, *n* = 370	Surgical trainees, *n* = 968	*P* value	OR (95%CI)
Patient age, median (IQR)	59.5 (47-71)	59 (48.75-69)	0.30	-
Patient gender (male %)	49.7 (*n* = 166)	52.3 (*n* = 206)	0.49	-
Cancer detection rate (%)	2.3 (*n* = 5)	3.3 (*n* = 10)	0.49	0.68 (0.23-2.02)
CSPDR (%)	38.2 (*n* = 81)	32.5 (*n* = 94)	0.19	1.28 (0.89-1.86)
ADR (%)	36.3 (*n* = 77)	29.1 (*n* = 84)	0.09	1.39 (0.95-2.03)
SLDR (%)	5.7 (*n* = 12)	5.2 (*n* = 15)	0.82	1.1 (0.5-2.39)

CSPDR: Clinically significant polyp detection rate; ADR: Adenoma detection rate; SLDR: Serrated lesion detection rate; CI: Confidence interval; OR: Odds ratio; IQR: Inter-quartile range.

DISCUSSION

Although heterogeneity of colonoscopy practice in Australia has been previously described, there are limited reports about its quality, or its association with proceduralist specialty or the involvement of trainees[6]. To our knowledge, this is the first paper to assess quality outcome measures in colonoscopy for surgical and medical specialists, and their trainees across multiple Australian hospitals.

While the collective rates for lesion detection, procedure completion, and adequacy of bowel preparation all met national criteria for quality in colonoscopy, this was only achieved at three sites independently. Limited rates of procedure completion and detection of serrated lesions affected the remaining two sites. When these key metrics were compared between hospitals, however, no significant differences were detected. This discrepancy may be explained by the comparatively low sample sizes at these individual sites with correspondingly wide confidence intervals. It is likely that individuals might be susceptible to the same issue given that submissions for recertification in Australia only require data

Table 4 Comparison of key outcomes between participating hospitals

	Site 1 (*n* = 254)	Site 2 (*n* = 396)	Site 3 (*n* = 604)	Site 4 (*n* = 790)	Site 5 (*n* = 399)	*P* value	Overall (*n* = 2443)
Patient age, median (IQR)	56 (46-66)	61 (50-71)	59.5 (49-70)	61 (50-71)	60 (50-71)	< 0.001	60 (50-70)
Patient gender (male %)	56.7 (*n* = 144)	45.7 (*n* = 181)	48.0 (*n* = 290)	48.4 (*n* = 382)	50.4 (*n* = 201)	0.08	49.0 (*n* = 1197)
Proceduralist							
Surgical (%)	87.4 (*n* = 222)	33.1 (*n* = 131)	35.6 (*n* = 215)	35.9 (*n* = 284)	51.4 (*n* = 205)	< 0.001	43.3 (*n* = 1057)
Medical (%)	12.6 (*n* = 32)	66.9 (*n* = 265)	64.1 (*n* = 387)	50.5 (*n* = 399)	48.4 (*n* = 193)	< 0.001	52.2 (*n* = 1276)
Trainee (%)	59.4 (*n* = 151)	38.9 (*n* = 154)	8.1 (*n* = 49)	28.1 (*n* = 222)	38.1 (*n* = 152)	< 0.001	29.8 (*n* = 728)
Medical (%)	0 (*n* = 0)	61.7 (*n* = 95)	91.8 (*n* = 45)	39.2 (*n* = 87)	70.4 (*n* = 107)	-	45.9 (*n* = 334)
Surgical (%)	100 (*n* = 151)	38.3 (*n* = 59)	8.2 (*n* = 4)	60.8 (*n* = 135)	29.6 (*n* = 45)	-	54.1 (*n* = 394)
Inadequate bowel preparation (%)	13.4 (*n* = 34)	8.1 (*n* = 32)	2.6 (*n* = 16)	7.2 (*n* = 57)	9.8 (*n* = 39)	< 0.001	7.3 (*n* = 178)
Indeterminate bowel preparation (%)	0.0 (*n* = 0)	2.8 (*n* = 11)	1.5 (*n* = 9)	4.3 (*n* = 34)	22.1 (*n* = 88)	< 0.001	5.8 (*n* = 142)
Procedure completion (%)	94.3 (*n* = 215)	92.2 (*n* = 319)	98.2 (*n* = 556)	95.1 (*n* = 686)	93.4 (*n* = 338)	< 0.001	95.1 (*n* = 2114)
Procedure completion (%) with adequate preparation	98.0 (*n* = 195)	94.5 (*n* = 294)	99.2 (*n* = 537)	98.0 (*n* = 627)	96.3 (*n* = 233)	0.99	97.5 (*n* = 1886)
Eligible procedures	121	216	381	462	160		1340
Cancer detection (%)	5.0 (*n* = 6)	2.3 (*n* = 5)	2.9 (*n* = 11)	3.5 (*n* = 16)	5.6 (*n* = 9)	0.38	3.5 (*n* = 47)
CSPDR (%)	30.4 (*n* = 35)	40.8 (*n* = 86)	48.6 (*n* = 180)	42.6 (*n* = 190)	41.1 (*n* = 62)	0.01	42.8 (*n* = 553)
ADR (%)	27.8 (*n* = 32)	39.3 (*n* = 83)	45.7 (*n* = 169)	39.5 (*n* = 176)	37.7 (*n* = 57)	0.01	40.0 (*n* = 517)
SLDR (%)	2.6 (*n* = 3)	5.2 (*n* = 11)	5.1 (*n* = 19)	7.4 (*n* = 33)	6.6 (*n* = 10)	0.31	5.9 (*n* = 76)

CSPDR: Clinically significant polyp detection rate; ADR: Adenoma detection rate; SLDR: Serrated lesion detection rate; IQR: Inter-quartile range.

from as few as 150 procedures. Although statistical comparisons with peers could provide an alternative method of assessment in this setting, the outcome ultimately requires further study with longer sampling times for low-volume centres.

One area where hospital sites differed significantly was in the quality of bowel preparation. The importance of this metric is attributable to its association with ADR and procedure completion[2,18]. The rates of inadequate preparation within our analysis were comparable with the 9%-13% previously observed in two Australian studies[19,20]. A validated scale for bowel preparation quality (Boston Bowel Preparation or Aronchick), however, was only adopted in one of these[19]. Although either scale was used in 94.2% of colonoscopy procedures assessed in our study, unvalidated approaches were used in up to 22.1% of procedures at individual sites. The exclusion of these procedures from the calculation of completion and detection rates may have been a significant source of bias, potentially limiting our analysis. Considering that suboptimal bowel preparations also justify the re-booking of procedures, ensuring the standardised adoption of validated scales in participating centres should be a priority for quality assurance.

The ADR across all sites in our study comfortably surpassed national benchmarks for quality. Although this was similar to rates reported in a recent meta-analysis of the international literature, direct comparisons should be interpreted with caution due to differences in the definitions used in our study[17]. Whilst ADR has traditionally been determined amongst patients over 50 undergoing an index colonoscopy for the indication of a positive bowel cancer screening test, we included all indications except IBD or prior colorectal surgery as per our national recertification program. However, we additionally excluded non-adequate bowel preparation and incomplete procedures so that the ADR might be a more accurate indicator of technical proficiency. Consequently, this would allow for quality improvement initiatives to be better targeted. Although ADR differed between sites, this was no longer significant on multivariate analysis.

Both patient and proceduralist factors can affect adenoma and lesion detection rates[21]. The medical proceduralists in our study demonstrated significantly higher ADRs compared to their surgical counterparts on both univariate (*P* < 0.001) and multivariate analyses (*P* = 0.002). The area is controversial with two other Australian studies reporting conflicting results. Lee *et al*[10] found no difference in ADR amongst 300 procedures completed by medical or surgical specialists in a single centre, whilst Zorron Cheng Tao Pu *et al*[8] showed a significantly higher ADR, of 36.8% and 30.4% (*P* < 0.001), amongst medical proceduralists. Our findings are, however, consistent with a recent meta-analysis of 36

Table 5 Multivariate regression analysis for detection rates of cancer, adenomas, and serrated lesions amongst eligible procedures

	Coefficient	OR (95%CI)	*P* value
Cancer			
Site	0.11	1.11 (0.87-1.43)	0.40
Patient age	0.04	1.04 (1.02-1.07)	< 0.001
Patient gender (male)	-0.45	0.64 (0.36-1.14)	0.13
Trainee (present)	-0.12	0.89 (0.46-1.73)	0.73
Proceduralist (medical)[1]	-0.61	0.54 (0.30-0.97)	0.04
Adenomas			
Site	-0.01	0.99 (0.90-1.09)	0.84
Patient age	0.04	1.04 (1.03-1.05)	< 0.001
Patient gender (male)	-0.65	0.53 (0.42-0.65)	< 0.001
Trainee (present)	0.22	1.24 (0.96-1.61)	0.10
Proceduralist (medical)[1]	0.34	1.41 (1.13-1.76)	0.002
Serrated lesions			
Site	0.08	1.08 (0.90-1.3)	0.42
Patient age	0.00	1.00 (0.99-1.02)	0.57
Patient gender (male)	0.41	1.51 (0.99-2.29)	0.05
Trainee (present)	0.26	1.29 (0.78-2.14)	0.33
Proceduralist (medical)[1]	0.28	1.32 (0.87-2.02)	0.19

[1]Surgical specialists were defined as the reference population.

CI: Confidence interval; OR: Odds ratio.

international studies which reported results which were similar to ours[22]. This raises important questions about whether the patients of surgical specialists are disadvantaged. However, the possibility of selection bias due to additional factors which influence ADR, such as procedure indication, should be considered[23]. Additional studies to understand the difference between medical and surgical specialists in Australia are thus required.

A higher cancer detection rate amongst surgical specialists was also observed in our multivariate analysis. Although such a finding would appear to contradict the lower ADR, it would most likely reflect a selection bias in the process of referral for colonoscopy. We assumed that patients with more conspicuous CRC diagnoses would more likely be referred to a surgical specialist. However, data on referral indication was not available in this dataset.

Another key finding of the multivariate analysis was the association between gender and ADR. Higher adenoma detection and CRC risk are usually seen in men and thus the finding of increased adenoma detection amongst female patients was unexpected[24,25]. Metabolic risk factors which increase the risk of adenoma development, including smoking, alcohol use, and low physical activity, have however been observed more frequently in women[26,27]. However, data on these lifestyle factors was not available. On the other hand, our findings may alternatively suggest better engagement of females in individuals with increased risk of adenoma and CRC development. Further studies to validate these results and understand the mechanism of increased ADR amongst women in Australia are therefore also required.

No significant differences were found in the primary outcomes between trainee and specialist proceduralists, the detection of serrated lesions, or procedure completion after adjustment for bowel preparation. Further analysis of trainees according to background speciality similarly showed no significant differences. Together, these findings suggest that the quality of procedures involving training proceduralists are comparable to those of specialists. These findings encouraging for patients who may have reservations about the quality of their procedures on teaching lists within the public sector in Australia. As the next generation of proceduralists in Australia, it is vital that good quality colonoscopy is a foundation of their clinical practice.

Limitations

The sample size at each individual site may be considered as a limitation of the current study which

incorporated five study sites (hospitals). Although the included sites represent both regional and metropolitan practice across two states and territories, it may not be reflective of the broader picture of public practice. To our knowledge, however, it is the first and largest multicentre dataset analysis providing an insight into the quality of colonoscopy in training hospitals in Australia.

One of the major limitations of this study is its retrospective design. Indeterminate outcomes resulting from shortfalls in the quality of the documentation were censored from the analyses but could have affected the results. Non-validated bowel preparation quality scoring systems could not be interpreted although it would have been expected that inadequate preparations would have been reported as such. Limited documentation of withdrawal times also meant that this could not be measured within this study, despite its accepted place as a marker of procedure quality. A prospective study design could account for these limitations and may provide more data reliable quality of documentation, however, would be susceptible to bias from the Hawthorne effect[28].

The exclusions for calculating key metrics in this study also differs from those used in prior studies or the National Recertification program[5,29]. Although this may limit the ability to compare the outcomes against national and internationally reported metrics, we would argue that the adjustments allow the metrics to reflect the aspects of practical interest more accurately. Our definitions separated the outcomes of procedure completion, quality of bowel preparation, and lesion detection which can inform targeted quality improvement efforts. This could include split preparations and shorter runway times to improve quality of bowel preparation, technical re-training for issues associated with procedure completion, or monitoring of withdrawal times for lesion detection. Caution should be taken in the assessment of lesion detection rates however due to the incorporation of multiple indications (screening; surveillance; symptomatic presentations) in the definition of the eligible population.

The definition for serrated lesions adopted within this study were in line with the most recent World Health Organization publication[16]. Repeated updates to these definitions have resulted in the reclassification of lesions in prior studies and remain dependent on the expertise of the reporting pathologist. The absence of a centralised expert pathologist for the assessment of resected lesions of the bowel may have resulted in the misclassification of some lesions, particularly serrated ones. Although we detected no differences in the detection of serrated lesions in our study, it is possible that this may have been masked by misclassification. Careful consideration of the definitions employed in colonoscopy is required for the interpretation of quality outcomes.

Despite potential limitations, our study offers novel clinical insights into the quality of procedures currently being performed in Australian public hospitals. These results highlight the need for quality procedural reporting and bowel preparation, as well as further research into factors which may result in lower ADRs amongst surgeons and men.

CONCLUSION

Our study indicates that the quality of colonoscopy collectively in the Australian public sector meets national benchmarks. Even when national benchmarks targets were achieved, significant differences in the quality of bowel preparation, and ADRs according to proceduralist specialty and patient gender were found. Two sites of the five assessed did not individually meet all the requirements. Improving bowel preparation should therefore be a key target for quality improvement initiatives. Our analysis suggested that sampling bias was a significant contributing factor which requires attention and control in future investigations. Additional studies to understand why surgical proceduralists detect fewer adenomas than their medical counterparts, and why women in Australia have higher rates of adenoma are required.

ARTICLE HIGHLIGHTS

Research background

There is increasing attention on the quality of colonoscopy performed in Australia due to its vital role in the prevention of colorectal cancer, and its relative under-utilisation among rural and lower socioeconomic communities. However, quality of colonoscopy in Australia has seldom been reported outside of single-centre studies. The largest database, the National Re-certification Program, attempts to address this but largely reflects the quality of work being performed in private hospital settings. Government funded procedures are not well represented in this data, yet accounts for 25% of colonoscopy work, and remains the main pathway for patients without private insurance and within the lowest socioeconomic strata to access this care. We sought to characterise the quality of colonoscopy in this sector, with the aim of informing quality improvement initiatives.

Research motivation

The key quality metrics for colonoscopy are bowel preparation quality, procedure completion rate, and

lesion detection rates (cancer, adenomas, and clinically significant serrated lesions). Serrated lesions have also received increasing attention recently, resulting in their incorporation within current national re-certification guidelines. We hope to determine if there are deficiencies in these metrics according to national guidelines and by comparison between participating hospital sites. We also sought to determine if there are significant differences in the detection rates of lesions according to consultant specialty (medical *vs* surgical), training level (specialist *vs* trainee), hospital site, and trainee background (medical *vs* surgical). The outcomes of this research can drive further inquiry into understanding the reasons for these differences and potential solutions.

Research objectives

We aimed to determine the lesion (cancer, adenoma, clinically significant serrated lesion) detection rates, quality of bowel preparation, procedure completion rates among teaching hospitals in Australia. Additionally, we wished to compare the outcomes according to proceduralist specialty, hospital, involvement of trainees, and trainee specialty. We were able to realize all these outcomes, however the analysis of outcomes according to sites was limited by the small sample sizes at some of the participating hospitals. Further studies to explore the link between proceduralist specialty, gender, and adenoma detection rates in Australia are warranted. Additional research regarding methods to improve these outcomes is also indicated.

Research methods

This was a retrospective cohort study involving consecutive colonoscopies performed over five publicly-funded teaching hospitals in Australia. Currently available colonoscopy quality metrics in Australia are either self-reported and reflect privately funded procedural work or pertain to fewer procedures at single centres. To our knowledge, this is the first study to describe colonoscopy quality across multiple large teaching endoscopy units in the public sector of Australia.

Research results

The overall quality of colonoscopy performed in participating hospitals met all specified national benchmarks (adenoma detection rate/procedure completion rate/serrated lesion detection rate). Two hospitals did not meet all benchmarks, due to either a low procedure completion or serrated lesion detection rate, when assessed individually. However, these results were not significantly different when compared with their peers. Significant differences between hospitals were identified on the remaining outcomes of bowel preparation, and detection of cancers and adenomas. Medical specialists detected adenomas in significantly more procedures than their surgical counterparts. In procedures attended by trainees, the detection rate of clinically significant lesions (cancer, adenoma, serrated lesions) was no different to those only involving specialists. Trainee specialty similarly did not affect lesion detection rates. The difference in adenoma detection rate between medical and surgical specialists was confirmed on multivariate analysis. An additional unexpected finding on the multivariate analysis was an association between female gender and adenoma detection. The findings highlight the need for further research to understand the differences between the colonoscopy procedures performed by medical and surgical specialists, and the reasons why female gender in this cohort of patients was an independent risk factor for adenoma detection. Furthermore, it suggests the need for additional sampling in lower-volume endoscopy units for the assessment of quality in colonoscopy.

Research conclusions

Our study suggests that although the overall quality of colonoscopy in publicly funded Australian hospitals reach national standards, significant variations exist between hospitals, according to procedural specialty, as well as patient gender. Understanding the reasons for these differences can provide additional insights on how quality in colonoscopy can be further improved. Although comparison with peer hospitals may provide an acceptable alternative for the assessment of outcomes in low-volume centres, larger studies are ideally required to assess their quality independently.

Research perspectives

Further research is required to explain the disparity in adenoma detection rates between medical and surgical specialists performing colonoscopy, and to determine why female, rather than male gender, is an independent predictor for adenoma in Australia.

FOOTNOTES

ORCID number: Tsai-Wing Ow 0000-0002-5405-7681; Olga A Sukocheva 0000-0003-1041-3311; Matthew Chu 0000-0002-8956-4691; Christopher K Rayner 0000-0002-5527-256X; Peter A Bampton 0000-0002-5873-4459.

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Retrospective Study

Effectiveness and safety of endoscopic resection for duodenal gastrointestinal stromal tumors: A single center analysis

Zhen-Zhen Wang, Xiao-Dan Yan, Hai-Deng Yang, Xin-Li Mao, Yue Cai, Xin-Yu Fu, Shao-Wei Li

Zhen-Zhen Wang, Shao-Wei Li, Key Laboratory of Minimally Invasive Techniques & Rapid Rehabilitation of Digestive System Tumor of Zhejiang Province, Taizhou Hospital Affiliated to Wenzhou Medical University, Linhai 315000, Zhejiang Province, China

Zhen-Zhen Wang, Xiao-Dan Yan, Hai-Deng Yang, Xin-Li Mao, Yue Cai, Shao-Wei Li, Department of Gastroenterology, Taizhou Hospital of Zhejiang Province affiliated to Wenzhou Medical University, Linhai 315000, Zhejiang Province, China

Zhen-Zhen Wang, Shao-Wei Li, Institute of Digestive Disease, Taizhou Hospital of Zhejiang Province affiliated to Wenzhou Medical University, Linhai 315000, Zhejiang Province, China

Xin-Yu Fu, Taizhou Hospital of Zhejiang Province affiliated to Wenzhou Medical University, Taizhou Hospital of Zhejiang Province affiliated to Wenzhou Medical University, Linhai 315000, Zhejiang Province, China

Corresponding author: Shao-Wei Li, MD, Associate Professor, Research Assistant Professor, Key Laboratory of Minimally Invasive Techniques & Rapid Rehabilitation of Digestive System Tumor of Zhejiang Province, Taizhou Hospital Affiliated to Wenzhou Medical University, Ximen Street No. 150 Linhai 315000, Zhejiang Province, China. li_shaowei81@hotmail.com

Abstract

BACKGROUND
Endoscopic resection for duodenal gastrointestinal stromal tumors (GISTs) is still considered a great challenge with a high risk of complications, including perforation, bleeding, tumor rupture, and residual tumor.

AIM
To assess the effectiveness and safety of endoscopic resection for duodenal GISTs.

METHODS
Between January 2010 and January 2022, 11 patients with duodenal GISTs were treated with endoscopic resection. Data were extracted for the incidence of complete resection, bleeding, perforation, postoperative infection, recurrence, and distant metastasis.

RESULTS
The incidence of successful complete resection of duodenal GISTs was 100%. Three cases (27.3%) had suspected positive margins, and the other 8 cases (72.7%)

had negative vertical and horizontal margins. Perforation occurred in all 11 patients. The success rate of perforation closure was 100%, while 1 patient (9.1%) had suspected delayed perforation. All bleeding during the procedure was managed by endoscopic methods. One case (9.1%) had delayed bleeding. Postoperative infection occurred in 6 patients (54.5%), including 1 who developed septic shock and 1 who developed a right iliac fossa abscess. All 11 patients recovered and were discharged. The mean hospital stay was 15.3 d. During the follow-up period (14-80 mo), duodenal stenosis occurred in 1 case (9.1%), and no local recurrence or distant metastasis were detected.

CONCLUSION
Endoscopic resection for duodenal GISTs appears to be an effective and safe minimally invasive treatment when performed by an experienced endoscopist.

Key Words: Duodenal tumor; Gastrointestinal stromal tumors; Treatment; Endoscopic resection; Effectiveness; Safety

Core Tip: This study presents the findings on endoscopic resection for duodenal gastrointestinal stromal tumors. Endoscopic resection of duodenal gastrointestinal stromal tumors is a great challenge. This study aimed to assess the effectiveness and safety of endoscopic resection for duodenal gastrointestinal stromal tumors. The rate of successful complete resection was 100%. Intraoperative perforation occurred in all 11 patients. The success rate of perforation closure was 100%. All 11 patients recovered. During the follow-up period (14-80 mo), duodenal stenosis occurred in 1 case (9.1%), and no local recurrence or distant metastases were detected.

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are rare digestive mesenchymal tumors, characterized by differentiation towards the interstitial cells of Cajal[1]. They can occur in any part of the gastrointestinal tract, most commonly in the stomach (60%) and small intestine (30%), but only 4%-5% occur in the duodenum [2]. GISTs have a variety of clinical behaviors with potentially malignant tendency. Currently, the treatment strategy for GISTs is somewhat controversial[3]. Some studies show that active surveillance was a safe option for GISTs smaller than 20 mm or even 30 mm (excision is only considered when the tumor grows)[4,5]. However, GISTs have inherent potential for malignancy, and the real risk stratification of the lesions is only known after resection[6]. Therefore, several societies recommend resection if a diagnosis of GIST is made, unless a major morbidity is expected[7-9].

In comparison to gastric GISTs, duodenal GISTs have a higher risk of malignancy. In addition, the duodenum has special anatomical features. Once the tumor grows, the difficulty of the operation increases accordingly, increasing the risk of combined organ resection. Therefore, resection should be performed for localized or potentially resectable duodenal GISTs. Traditional surgical treatment methods include pancreaticoduodenectomy and local resection of duodenal lesions. However, these operations are traumatic and prone to serious complications, such as delayed bleeding, pancreatic leakage, bile leakage, or abdominal infection[10,11]. Furthermore, pancreaticoduodenectomy or segmental duodenectomy will inevitably reduce the patient's quality of life. GISTs have unique biological characteristics and rarely have lymph node metastasis[9], which makes endoscopic resection of lesions an alternative. In recent years, the development of endoscopic minimally invasive technologies, such as endoscopic submucosal dissection, endoscopic submucosal excavation, and endoscopic full-thickness resection, has brought attention to endoscopic minimally invasive treatment of duodenal GISTs.

Thus far, there are few studies about endoscopic resection of duodenal GISTs, most of which have been case reports. A few studies have reported small series of cases[12,13]. The aim of this study was to evaluate the effectiveness and safety of endoscopic resection for duodenal GISTs.

MATERIALS AND METHODS

Patients

From January 2010 to January 2022, 11 consecutive patients with pathologically confirmed duodenal GIST underwent endoscopic resection in our center. All patients were examined preoperatively by computed tomography (CT) and endoscopic ultrasonography (EUS). In all cases, there were no signs of lymph node metastasis or distant metastasis, no other malignant tumors, and no coagulation dysfunction, and it was considered that the patient could tolerate endotracheal intubation and general anesthesia. Written informed consent was obtained from all patients. The study was reviewed and approved by the Institutional Ethics Committee of Taizhou Hospital of Zhejiang Province (Approval No. K20210611).

Endoscopic equipment and accessories

A single-accessory channel endoscope (Q260J; Olympus) and/or a dual-channel endoscope (GIF-2T240, Olympus) were used during the procedures. A transparent cap (ND-201-11802; Olympus) was attached to the tip of the endoscope. An insulated-tip knife (KD-611L, IT2; Olympus), hook knife (KD-620LR; Olympus), dual knife (KD-650Q; Olympus), or hybrid knife (ERBE, Tübingen, Germany) was used to dissect the submucosal layer and peel the tumor. A titanium clip (HX-600-135; Olympus and M00522600), an endoloop (Leo Medical Co., Ltd, Changzhou, China), and an over-the-scope clip (OTSC) (12/6 t-type, Ovesco Endoscopy AG) were used for wound closure. Other devices and accessories that were used included a high-frequency electronic cutting device (ICC 200; ERBE), an argon plasma coagulation unit (APC 300; ERBE, Tübingen, Germany), a hot biopsy forceps (FD-410LR; Olympus), a foreign body forceps (FG-B-24, Kangjin, Changzhou, China), a snare (SD-230U-20; Olympus), and a carbon dioxide insufflator (Olympus).

Endoscopic procedures and perioperative management

All operations were performed under general anesthesia with endotracheal intubation by experienced endoscopists. All patients were fasted for ≥ 6-8 h with no water for 2 h before the operation. Antibiotic prophylaxis was administered.

Endoscopic resection was conducted as follows (Figure 1A-K): (1) Several dots were marked around the lesion; (2) A mixture solution (100 mL normal saline +1 mL epinephrine + 2 mL indigo carmine) was then injected to elevate the submucosa; (3) Subsequently, a circumferential incision was made outside the border to expose the pseudo capsule; (4) Next, the submucosa and muscularis propria (MP) around the lesion were circumferentially dissected. After complete excision, the lesion was removed with a snare or foreign body forceps and sent for histopathological examination; and (5) The wound was closed with titanium clips, an OTSC, or an endoloop. If perforation occurred, a 20-gauge needle was used intraoperatively and postoperatively to relieve pneumoperitoneum.

A jejunal nutrition tube with the tip near the duodenal wound and a gastric tube were placed for drainage and detection of any postoperative hemorrhage. After the procedure, all patients were fasted and treated with a proton-pump inhibitor and prophylactic antibiotics. Oral intake was gradually resumed according to wound recovery.

Postoperative specimen management and pathological evaluation

After the operation, the resected specimens were observed and measured, and their size, shape, and envelope integrity were recorded. Then the specimens were immersed in 4% formaldehyde solution and fixed. Hematoxylin and eosin staining and immunohistochemistry were performed routinely. A diagnosis of GIST was confirmed if microscopic spindle cell proliferation was seen in the fasciculate, with staggered arrangement and positivity for CD117 or DOG-1 and CD34 (Figure 1L-R). The risk of recurrence after resection of GISTs was assessed according to the National Institutes of Health risk stratification system (2008 modified)[14].

Definition of terms and outcome assessment

Complete resection was considered if the lesion was resected en bloc with no obvious residual tumor at the resection site and with tumor-free margins according to histopathological examination[15]. Complications included intraoperative perforation, delayed perforation, intraoperative bleeding, delayed bleeding, and perioperative infection. Intraoperative perforation was considered if an extra-duodenal structure was visualized, retroperitoneal pneumatosis occurred, or free gas was detected by CT examination immediately after resection of the lesion[16]. Delayed perforation was considered if the patient experienced sudden abdominal pain after the procedure with a duodenal defect found under endoscopy or surgery. Intraoperative bleeding was regarded as a complication if one of the following criteria was met: (1) During the procedure, bleeding affected the visual field and could not be managed by endoscopic methods; (2) There was a significant reduction in hemoglobin (> 2 mg/dL); or (3) Blood transfusion was required[17]. Delayed bleeding was defined as hemorrhage from a post-procedure ulcer [18]. Local recurrence was defined as the detection of a lesion located on or adjacent to the scar of the previous endoscopic resection, which was then pathologically confirmed by biopsy[15].
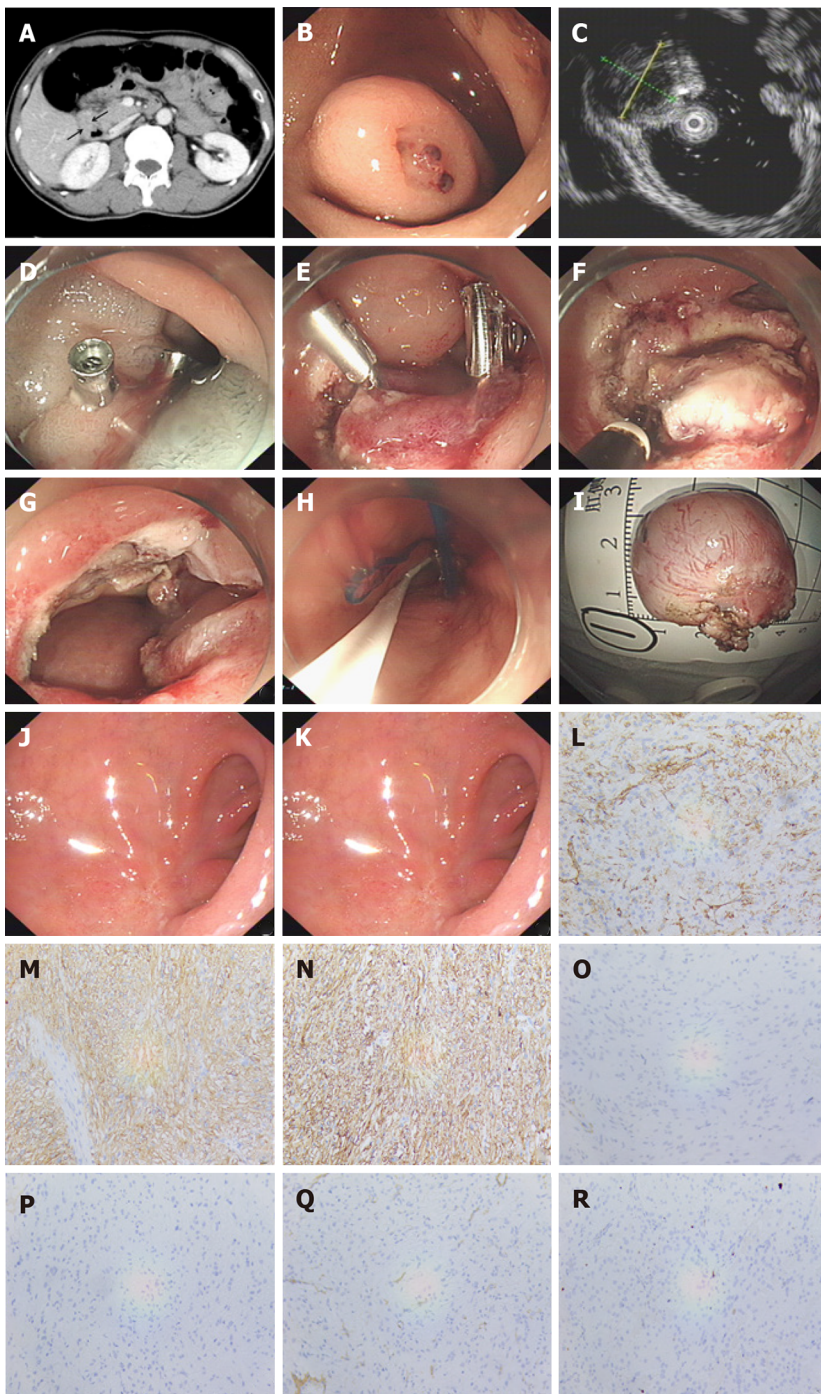
Figure 1 Endoscopic full-thickness resection for duodenal gastrointestinal stromal tumors in the descending junction of the duodenal bulb. A: Computed tomography revealed a tumor of approximately 3 cm in diameter, with enhancement in the arterial phase; B: A tumor located in the descending junction of the duodenal bulb with ulcer and exposed blood vessels on the surface. Titanium clips were used to stop the bleeding; C: The endoscopic ultrasonography showed that the lesion was a hypoechoic structure originating from the muscularis propria layer, with uniform echo and a clear boundary; D: Submucosal injection after making several marking dots around the lesion; E: A circumferential incision was made outside the border; F: The submucosa and muscularis propria around the lesion were circumferentially dissected; G: The duodenal defect after tumor resection; H: The wound was occluded with several titanium clips + an endoloop + an over-the-scope clip. A jejunal nutrition tube was placed near the wound for drainage; I: The resected tumor with the intact capsule; J: The wound healed well at 3 mo after the procedure; K: Hematoxylin and eosin staining (original magnification × 40); L: Immunohistochemistry showed that the tumor was positive for CD34; M: Immunohistochemistry showed that the tumor was positive for CD117; N: Immunohistochemistry showed that the tumor was positive for Dog-1; O: Immunohistochemistry showed that the tumor was negative for desmin; P: Immunohistochemistry showed that the tumor was negative for S-100; Q: Immunohistochemistry showed that the tumor was negative for SMA; and R: Immunohistochemistry showed that Ki67 was about 2%.

Follow-up

Every patient underwent EUS at 3 mo after the operation to evaluate wound healing and check for residual lesions. The second surveillance endoscopy procedure was performed at 6 mo. Subsequently,

gastroscopy and/or EUS was performed to detect tumor recurrence, and CT and/or abdominal ultrasound was used every 12 mo if any distant metastasis was detected; this was continued indefinitely.

Statistical analysis

Data were presented as the mean, median, number of cases, and percentage. All statistical analyses were performed using the SPSS software program (version 20.0; SPSS Inc, Armonk, NY, United States).

RESULTS

Clinical characteristics

The patient and tumor characteristics are summarized in Table 1. A total of 11 patients (male, n = 9; female, n = 2) with duodenal GISTs underwent endoscopic resection at our center. The median age was 55 years (range: 33–74 years). Eight patients (72.7%) were symptomatic at presentation, with melena in 6 patients (54.5%), abdominal pain in 1 patient (9.1%), and abdominal distension in 1 patient (9.1%). Three tumors (27.3%) were detected incidentally during endoscopy for other reasons. All patients were negative for immunologic series and tumor markers (AFP, CEA, CA199, and CA125). Patients with gastrointestinal hemorrhaging showed fecal occult blood positivity and had anemia, with a minimum hemoglobin level of 36 g/L. All patients showed duodenal mass on abdominal CT before operation, which was enhanced after enhancement.

The lesions were single in all 11 patients. The lesion was detected in the duodenal bulb in 2 cases (18.2%), in the descending junction of the duodenal bulb in 4 cases (36.4%), and in the descending part in 5 cases (45.4%). All lesions originated from the MP layer with intraluminal growth in 6 cases (54.5 %), partially extraluminal growth in 2 cases (18.2%), and mainly extraluminal growth in 3 cases (27.3%). EUS revealed hypoechoic structures in 10 cases (90.9%) and a mixed echoic structure in 1 case (9.1%). The median maximal diameter of these lesions was 3.0 cm (range: 1.5-5.0 cm). Immunohistochemistry of all lesions showed that CD34, CD117, and Dog-1 were positive, and Desmin and S-100 were negative. Nine cases (81.8%) were SMA positive. Four cases (36.4%) were Ki-67 < 1%, 3 cases (27.3%) were Ki-67 1%+, 3 cases (27.3%) were Ki-67 2%+, and 1 case (9.1%) was Ki-67 3%+.

Treatment outcomes

Complete resection was successful in 100% of cases. Four patients (36.4%) were classified as very low risk, and 7 patients (63.6%) were classified as low risk. Among the 11 patients, a positive resection margin was suspected in 3 cases (27.3%) (tumor tissue was found at the electrocautery margin); all cases were pathologically low risk. The remaining 8 cases (72.7%) had negative lateral and basal margins. All 11 patients recovered and were discharged.

Complications

Perforation was detected in all 11 patients during the operation. The duodenal wall defect was occluded with several titanium clips + an endoloop in 1 case (9.1%), an OTSC in 6 cases (54.5%), and an OTSC + several titanium clips + an endoloop in 4 cases (36.4%). Intraoperative perforation closure was successfully performed in 100% of cases. Delayed perforation was suspected in 1 patient (9.1%) (as described below).

All 11 patients had bleeding during the procedure and were treated successfully using argon plasma coagulation and a hot biopsy forceps. A little coffee-colored liquid was drained from the gastrointestinal decompression tube in 1 case (9.1%) on the 1st d after the procedure, which improved after strengthening the acid inhibition and using somatostatin.

Six patients (54.5%) developed postoperative abdominal infection, and their anti-infection treatment was strengthened. Among them, 1 patient developed severe abdominal pain and septic shock on the day after endoscopic resection of a 3.0 cm × 2.5 cm tumor in the descending junction of the duodenal bulb. Emergency surgical exploratory laparotomy was performed immediately for suspected delayed perforation. During the operation, obvious edema was observed on the wound, but no obvious perforation was detected. This patient received peritoneal lavage and distal subtotal gastrectomy with resection of the duodenal bulb. Another patient developed a right iliac fossa abscess, which improved after puncture and drainage. One patient (9.1%) suffered malignant arrhythmia 5 d after the procedure and was transferred to the intensive care unit. All 11 patients recovered and were discharged. The mean time to the recovery of food intake after the operation was 8.1 d (range: 4-14 d). The mean postoperative hospital stay was 15.3 d (range: 8-26 d).

Follow-up

The wound healed well in all patients, and no recurrence or distant metastasis was detected during the follow-up period (median: 36 mo; range: 14-80 mo). Duodenal stenosis occurred in 1 patient (9.1%) whose previous tumor was in the descending junction of the duodenal bulb, and the wound was closed by an OTSC. The OTSC was found to block the lumen, and the endoscope could not pass through at 3

Table 1 Clinical characteristics of 11 duodenal gastrointestinal stromal tumors cases

Patient	Sex	Age, yr	Clinical presentation	Location	Size of maximum diameter, cm	Growth pattern	EUS appearance	Risk assessment	Specimen margin	Postoperative hospital stay, d	Follow-up, mo
1	M	57	Melena	Duodenal bulb	2.2	Mainly extraluminal growth	MP, hypoecho, uniform echo	Low risk	Negative	9	14
2	M	56	No symptoms	Descending junction of duodenal bulb	2.0	Intraluminal growth	MP, hypoecho, uniform echo	Very low risk	Negative	15	19
3	M	68	No symptoms	Descending duodenum	3.0	Partially extraluminal growth	MP, hypoecho, uniform echo	Low risk	Negative	11	22
4	M	63	Melena	Descending duodenum	5.0	Mainly extraluminal growth	MP, hypoecho, uniform echo	Low risk	Suspiciously positive	16	30
5	M	52	Melena	Descending duodenum	1.5	Intraluminal growth	MP, mixed echo, uneven echo	Very low risk	Negative	8	33
6	M	53	Melena	Descending junction of duodenal bulb	3.5	Mainly extraluminal growth	MP, hypoecho, uniform echo	Low risk	Suspiciously positive	15	36
7	M	54	Melena	Descending duodenum	4	Intraluminal growth	MP, hypoecho, uniform echo	Low risk	Suspiciously positive	24	43
8	M	74	Melena	Descending junction of duodenal bulb	3.0	Intraluminal growth	MP, hypoecho, uniform echo	Low risk	Negative	26	50
9	F	33	Abdominal pain	Descending duodenum	3.0	Intraluminal growth	MP, hypoecho, uniform echo	Low risk	Negative	14	51
10	F	42	No symptoms	Descending junction of duodenal bulb	1.5	Intraluminal growth	MP, hypoecho, uniform echo	Very low risk	Negative	13	75
11	M	55	Abdominal distension	Duodenal bulb	2.0	Intraluminal growth	MP, hypoecho, uniform echo	Very low risk	Negative	12	80

EUS: Endoscopic ultrasonography; F: Female; M: Male; MP: Muscularis propria.

mo after the procedure. The patient was followed up, as he had no symptoms of obstruction. During endoscopic surveillance at 12 mo after the procedure, the OTSC detached spontaneously, and the lumen stenosis improved.

DISCUSSION

Endoscopic resection of duodenal lesions, especially subepithelial lesions, is still considered a challenging procedure due to the unique anatomical and endoscopic features of the duodenum. The duodenal lumen is rather narrow, and the initial part (bulbar to descending part) is an anti-c-shaped loop, which makes endoscopic operations difficult. The mucosa is difficult to lift after the injection due to the abundant Brunner's gland and blood vessels in the submucosa of the duodenum, which also increases the difficulty of treatment. Traditionally, the duodenum has been regarded as a forbidden zone for endoscopic excision of duodenal subepithelial lesions, especially for endoscopic full-thickness resection. The rapid de-velopment of endoscopic techniques and endoscopic devices makes endoscopic resection for duodenal GISTs another acceptable alternative to minimize morbidity.

For localized GISTs, complete excision is the standard treatment. R0 resection is the goal in any case. A post hoc observational study showed that among patients with GISTs, when tumor rupture was excluded, there was no significant difference in overall survival of patients who received R0 and R1 resection[19]. Some studies also indicated that the recurrence rate of patients who received R1 resection did not differ from that of patients who received R0 resection[20,21]. Thus, if R0 resection is difficult to achieve, R1 resection (microscopically positive margins) may also be performed for low-risk GISTs in unfavorable locations[7]. If R1 resection was already performed, routine re-excision is not recommended [7], and the microscopic margin status should not be used to dictate adjuvant medical therapy decisions [19]. In our study, there were 3 cases in which microscopic involvement of the resection margins was suspected; all were low risk. No recurrence or distant metastasis was found during follow-up (30 mo, 36 mo, and 43 mo) without re-excision or adjuvant medical therapy.

Tumor rupture is an important adverse prognostic factor for the recurrence of GIST. It is defined by tumor spillage or fracture in the abdominal cavity, piecemeal resection, incisional biopsy, gastric or intestinal perforation to the abdominal cavity, blood-stained ascites at laparotomy, or transperitoneal microscopic infiltration of an adjacent organ[7]. In our study, the maximal diameter of all tumors was ≤ 5 cm and were resected en bloc. When the tumor size is > 5 cm in diameter, it is very difficult to resect it completely and take it out as a whole through the cardia, esophagus, and pharynx. Thus, for tumors larger than 5 cm, especially in intermediate- and high-risk cases, conventional surgery or laparoscopic and endoscopic cooperative surgery may be more appropriate.

In comparison to other parts of the digestive tract, the muscular layer of the duodenum is much thinner, and intraoperative perforation is prone to occur during endoscopic operations. In addition, digestive fluids, such as bile and pancreatic juice, can corrode the wound, and delayed perforation may subsequently occur. Injury to the duodenal muscularis and serosa should be avoided as far as possible in the case of perforation. However, when the lesion is closely associated with the MP or serosal layer of the duodenum, perforation is almost inevitable. Most duodenal GISTs originate from the MP, and the strategy "active perforation" is often adopted, resulting in a well-defined edge and mild edema. In some studies, perforation that could be closed by endoscopic methods during the endoscopic operation was not regarded as a complication[22,23].

With the development of endoscopic suture technology and the invention of OTSC, the OverStitch endoscopic suturing (ES) device and other suture devices, the success rate of wound suturing has been greatly improved. An OTSC has the following advantages: (1) It has great holding strength[24,25]; thus, it can grasp more tissue and clamp the entire wall of the lumen; (2) It is a bear trap-like, large clip with a wingspan of 12 mm, which can close full-thickness perforations of up to 3 cm in diameter[26]; and (3) The gap between the teeth of an OTSC allows blood to pass through to avoid tissue necrosis.

A systematic review showed that the rate of successful closure of the perforation by OTSC closure was 85.3%[27]. In our previous study, OTSC successfully closed the perforation after endoscopic resection of duodenal subepithelial lesions in 100% of cases, without delayed perforation[28]. The OverStitch ES device is designed for tissue approximation and allows the creation of either interrupted or continuous running stitches. Thus, it can reliably close perforations[29]. In a study by Chung *et al* [30], the OverStitch ES device was applied in 7 cases after endoscopic mucosal resection of large duodenal adenomas, and all ES sessions were technically successful.

In addition, purse-string suture technique, which is also widely used in iatrogenic digestive tract perforation, shows a high rate of successful sealing. Our previous study suggested that the closure rate of purse-string suture in endoscopic treatment of duodenal subcutaneous lesions was 100% (including 5 cases of perforation)[31]. In this study, duodenal wall defects were all successfully closed using OTSC, titanium, or purse-string suture according to the size of wound and wall defect. We placed two tubes, one with the tip in the gastric cavity to attract gas and gastric juice, and the other with the tip next to the duodenal wound to attract pancreatic juice and bile. Lessening tension of the wound and reducing the corrosion of digestive juice to the wound could effectively decrease the occurrence of delayed perforation.

Another serious complication of endoscopic resection of duodenal GISTs is perioperative infection followed by perforation. In this study, 6 patients had postoperative abdominal infection, including 1 who developed septic shock and another who developed an abscess in the right iliac fossa. During the procedure, suction should be carried out in a timely manner in order to prevent excessive blood, intestinal contents, and digestive juices flowing into the retroperitoneum. The wound should be closed as soon as possible after the lesion is removed. When a large volume of liquid has overflowed into the retroperitoneum, timely flushing and drainage can also reduce the incidence of infection. Besides, if the lesion is really difficult to remove endoscopically, timely conversion to surgery or laparoscopic-assisted resection may be a wiser option.

In addition, it should be noted that the duodenal lumen is relatively narrow, especially in the descending junction of the duodenal bulb, and postoperative stricture may occur. In this study, 1 patient developed stricture after the wound was closed with an OTSC. When treating the wound, especially when placing the OTSC, attention should be paid to avoid grasping too much tissue in the case of duodenal lumen stenosis.

The present study was associated with some limitations. First, this was a single center retrospective study with a relatively small sample size, and a selection bias may have been present. Second, there was a lack of randomized and controlled samples. Third, the follow-up period of some cases was relatively short.

CONCLUSION

Endoscopic resection for duodenal GISTs appears to be effective and safe in selected cases. The procedure should be performed by a senior endoscopist who has rich experience in the management of complications of endoscopic operations for duodenal lesions. If the lesion is difficult to remove endoscopically or there are severe complications that cannot be managed by conservative treatment or an endoscopic method, surgery should be performed in a timely manner.

ARTICLE HIGHLIGHTS

Research background

Currently, endoscopic resection of duodenal gastrointestinal stromal tumors (GISTs) is a challenging procedure with a high risk of complications.

Research motivation

Traditional surgical treatment methods for duodenal GISTs are traumatic and prone to serious complications. Endoscopic resection of duodenal GISTs is an alternative. However, there are few reports on endoscopic treatment for duodenal GISTs.

Research objectives

We aimed to evaluate the effectiveness and safety of endoscopic resection for duodenal GISTs.

Research methods

This was a retrospective study. We collected data of 11 consecutive patients with duodenal GISTs who were treated with endoscopic resection and analyzed the rate of complete resection, bleeding, perforation, postoperative infection, recurrence, and distant metastasis.

Research results

All lesions were completely resected, while three cases (27.3%) had suspected positive margins. No local recurrence or distant metastasis were detected during the follow-up period in any of the patients.

Research conclusions

Endoscopic resection for duodenal GISTs appears to be an effective and safe treatment by an experienced endoscopist.

Research perspectives

We need to expand the sample size to further confirm the effectiveness and safety of endoscopic resection of duodenal GISTs. In addition, the long-term outcome should be observed by extending the follow-up time.

FOOTNOTES

K20210611).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

Data sharing statement: No additional data are available.

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Country/Territory of origin: China

ORCID number: Zhen-Zhen Wang 0000-0002-6274-2646; Xiao-Dan Yan 0000-0002-1493-6817; Xin-Li Mao 0000-0003-4548-1867; Yue Cai 0000-0002-7201-6525; Shao-Wei Li 0000-0002-3276-1037.

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ORIGINAL ARTICLE

Retrospective Study

Impact of looping on premalignant polyp detection during colonoscopy

Osamu Toyoshima, Toshihiro Nishizawa, Shuntaro Yoshida, Tatsuya Matsuno, Toru Arano, Ryo Kondo, Kazunori Kinoshita, Yuki Yasumi, Yosuke Tsuji, Mitsuhiro Fujishiro

Osamu Toyoshima, Shuntaro Yoshida, Tatsuya Matsuno, Toru Arano, Ryo Kondo, Department of Gastroenterology, Toyoshima Endoscopy Clinic, Tokyo 157-0066, Japan

Toshihiro Nishizawa, Department of Gastroenterology and Hepatology, International University of Health and Welfare, Narita Hospital, Narita 286-8520, Japan

Kazunori Kinoshita, Department of Obstetrics and Gynecology, Seijo Kinoshita Hospital, Tokyo 157-0066, Japan

Yuki Yasumi, Department of Internal Medicine, Yasumi Hospital, Morioka 028-4125, Japan

Yosuke Tsuji, Mitsuhiro Fujishiro, Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo 113-8655, Japan

Corresponding author: Toshihiro Nishizawa, MD, PhD, Professor, Department of Gastroenterology and Hepatology, International University of Health and Welfare, Narita Hospital, 852 Hatakeda, Narita 286-8520, Japan. nisizawa@iuhw.ac.jp

Abstract

BACKGROUND
The presence of premalignant polyps on colonoscopy is an indicator of metachronous colorectal cancer. Looping during colonoscopy is associated with old age, female sex, and colonoscopy insertion time. However, the clinical significance of looping is not fully understood. We aimed to clarify the effect of looping on colorectal premalignant polyp detection.

AIM
To assess the effects of looping on premalignant polyp detection using logistic regression analyses.

METHODS
We retrospectively investigated patients who underwent colonoscopy at Toyoshima Endoscopy Clinic between May, 2017 and October, 2020. From the clinic's endoscopy database, we extracted data on patient age, sex, endoscopist-assessed looping, colonoscopy duration, endoscopist experience, detection rate, and number of premalignant polyps.

RESULTS

We assessed 12259 patients (mean age, 53.6 years; men, 50.7%). Looping occurred in 54.3% of the patients. Mild and severe looping were noted in 4399 and 2253 patients, respectively. The detection rates of adenomas, advanced adenomas, high-risk adenomas, clinically significant serrated polyps (CSSPs), and sessile serrated lesions (SSLs) were 44.7%, 2.0%, 9.9%, 8.9% and 3.5%, respectively. The mean numbers of adenomas and SSLs were 0.82 and 0.04, respectively. The detection rates of adenomas, high-risk adenomas, and CSSPs increased with looping severity (all $P < 0.001$). The number of adenomas increased with looping severity ($P < 0.001$). Multivariate analyses found that detection of adenomas, high-risk adenomas, and CSSPs was associated with severe looping ($P < 0.001$, $P < 0.001$, and $P = 0.007$, respectively) regardless of age, sex, time required for colonoscope insertion and withdrawal, and endoscopist experience.

CONCLUSION
Looping severity was independently associated with high detection rates of premalignant polyps. Therefore, looping may predict the risk of metachronous colorectal cancer. Endoscopists should carefully examine the colorectum of patients with looping.

Key Words: Looping; Colorectal polyp; Colonoscopy; Adenoma; Serrated polyp; Colorectal neoplasm

Core Tip: This study aimed to clarify the effect of colonic looping on colorectal premalignant polyp detection during colonoscopy. We retrospectively investigated 12259 patients who underwent colonoscopies. Looping occurred in 54.3% (35.9% and 18.4% with mild and severe looping, respectively) of the cases. The detection rates of adenomas (44.7%), high-risk adenomas (9.9%), and clinically significant serrated polyps (CSSPs) (8.9%) increased with the looping severity. The number of adenomas per colonoscopy (0.82) increased with the looping severity. Multivariate analyses found that detection of adenomas, high-risk adenomas, and CSSPs was associated with severe looping regardless of age, sex, time required for colonoscope insertion and withdrawal, and endoscopist experience.

INTRODUCTION

Colorectal cancer mainly occurs because of adenomas or serrated polyps[1-3]. Colonoscopy is the gold standard for cancer screening and detection of premalignant polyps. The prevalence of metachronous colorectal cancer is high in patients with adenomas, especially high-risk adenomas, removed during colonoscopy[4]. Similarly, individuals with colonoscopically resected clinically significant serrated polyps (CSSPs) have a long-term risk of colorectal cancer[5-7]. Thus, the detection of adenomas and CSSPs on colonoscopy is a surrogate marker for the risk of metachronous colorectal cancer. Factors related to premalignant polyp detection include patient characteristics, such as age and sex[8,9], endoscopic procedure-related factors, such as cecal intubation time[10] and withdrawal time[11-14], and endoscopist experience[8].

Colonic looping is a common obstacle during routine colonoscopy[15,16]. Looping is associated with a redundant colon, older age, female sex, and cecal intubation time[17-20]. However, the clinical significance of looping is poorly understood. Therefore, this study aimed to clarify the effect of looping on colorectal premalignant polyp detection by using multivariate analysis to control for potential confounding factors.

MATERIALS AND METHODS

Study design and overview

This retrospective study was conducted at a single institute, Toyoshima Endoscopy Clinic, a representative outpatient endoscopy-specialized clinic located in an urban area of Japan. Toyoshima

Endoscopy Clinic performs 10000 endoscopies annually. The study design was described in a protocol prepared at Toyoshima Endoscopy Clinic and approved by the Certified Institutional Review Board of Yoyogi Mental Clinic on July 16, 2021 (Approval no. RKK227). We published this study's protocol on our institute's website (www.ichou.com). Thus, patients could opt out of the study if desired. All the authors approved the final manuscript. No funding was received for this study.

Patients

Patients who underwent colonoscopy at Toyoshima Endoscopy Clinic between May, 2017 and October, 2020 were enrolled in this study. The indications for colonoscopy included the examination of symptoms and abnormal findings, screening, and surveillance for colorectal diseases. Patients undergoing treatment, such as polypectomy and hemostasis, those with poor bowel preparation[21,22], and those with a history of colorectal surgery were excluded. Cases of colonoscopies with incomplete cecal intubation, withdrawal time of < 6 min[11], and those performed with an ultrathin colonoscope were also excluded[23].

Definition of looping

Common colonic looping patterns observed during colonoscopy have been described previously. Loops occur in the transverse and sigmoid colons, and sigmoid loops include alpha and N shapes[19,24]. When forming a loop, there is no one-to-one relationship between the transmission of the colonoscope shaft movement and colonoscope tip motion. In the case of looping, further insertion of the scope results in a larger loop size without de-looping the scope[24,25].

Cecal insertion without loop formation was defined as the absence of looping. Cecal insertion that required straightening of the colonic loop once was defined as mild looping. Cecal insertion that required straightening of the colonic loop two or more times was defined as severe looping.

Colonoscopy

Small and gentle shaking and jiggling of the colonoscope shaft were performed. Right-turn shortening maneuvers for straightening the shaft were used for colonoscope insertion. Water-assisted, carbon dioxide-assisted, and cap-assisted chromoendoscopies with sedation were performed[26]. Position changes and rectal retroflexion were performed[8,27]. When looping was formed, we usually controlled the colonoscope by changing the patient's position to supine or right lateral, and manual abdominal compression was performed by the assistant[15].

Thirty endoscopists with various levels of experience performed the colonoscopies[28,29]. This study defined experienced endoscopists as those with > 15 years of experience in performing endoscopy. We used a combination of the Elite system and CF-HQ290ZI, CF-HQ290I, or PCF-H290ZI colonoscopes (Olympus Corporation, Tokyo, Japan). Poor bowel preparation was defined as at least one colon segment that could not be examined because of the presence of remnant solid stool[9,16,27].

Colorectal polyps

All polyps suspected to be cancerous, adenomatous, or CSSP were removed or biopsied. All polyps were histologically diagnosed by an experienced gastrointestinal pathologist using the resected specimens and biopsy samples. Advanced adenomas included adenomas ≥ 10 mm in size, villous adenomas, and adenomas with high-grade dysplasia. A high-risk adenoma was defined as the presence of advanced adenoma and/or three or more adenomas. CSSPs comprise all sessile serrated lesions (SSLs), all traditional serrated adenomas, hyperplastic polyps of size ≥ 10 mm anywhere in the colorectum, and hyperplastic polyps of size ≥ 5 mm located between the cecum and descending colon[30-33].

Outcomes

We extracted data from the endoscopy database of Toyoshima Endoscopy Clinic, including patient age, sex, endoscopist-assessed looping, colonoscope insertion time, withdrawal time, endoscopists, detection rates of adenomas, advanced adenomas, high-risk adenomas, CSSPs, and SSLs, and numbers of adenomas and SSLs. Withdrawal time was defined as the time required to examine the colorectal mucosa and remove the polyps. The polyp detection rate was defined as the rate of colonoscopies that detected at least one polyp.

Statistical analysis

The significance of any orderly increase or decrease along the three stratifications (*i.e.,* no, mild, and severe looping) was assessed using Cochran-Armitage trend test or Jonckheere-Terpstra trend test for categorical and continuous variables, respectively. Because of the significant association between looping severity and polyp detection in the trend test, the effect of subject characteristics on polyp detection was analyzed using a multivariate analysis. Furthermore, a subgroup analysis, limited to experienced endoscopists, was performed. Multivariate analysis was performed using a binomial logistic regression model, with no, mild, and severe looping scores of 0, 1, and 2, respectively. Statistical significance was defined as a *P*-value < 0.05. The calculations were performed using Bell Curve for Excel version 3.22 (Social Survey Research Information Co., Ltd., Tokyo, Japan) and R version 4.1.2 (R Core

Team 2021, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients
During the study period, colonoscopies were performed on 13315 patients. We excluded 236 patients undergoing treatment, such as polypectomy and hemostasis, 77 with poor bowel preparation, 217 with previous colorectal surgery, 20 with incomplete cecal insertion (including 8 with stenosis caused by colorectal tumor and 6 with colonic looping), 22 with withdrawal time < 6 min, and 484 who were examined using an ultrathin colonoscope. Ultimately, 12259 patients were enrolled in this study. A patient flowchart is shown in Figure 1.

The mean patient age was 53.6 years. Men accounted for 50.7% of the participants. Looping occurred in 54.3% of the patients. There were 4399 and 2253 patients with mild and severe looping, respectively. The mean insertion and withdrawal times were 4.6 and 13.9 min, respectively. Experienced endoscopists performed 70.4% of the colonoscopies. The polyp detection rates for adenomas, advanced adenomas, high-risk adenomas, CSSPs, and SSLs were 44.7%, 2.0%, 9.9%, 8.9%, and 3.5%, respectively. The mean number of adenomas and SSLs was 0.82 and 0.04, respectively (Table 1).

Subject characteristics based on looping
Patients with severe looping tended to be older and more likely to be female (both $P < 0.001$). Cecal insertion and withdrawal times tended to be longer in severe looping (both $P < 0.001$). Experienced endoscopists performed cases with severe looping more often. The polyp detection rates of adenomas ($P < 0.001$), advanced adenomas, high-risk adenomas ($P < 0.001$), CSSPs ($P < 0.001$), and SSLs tended to increase with looping severity. However, the tendency of advanced adenoma and SSL detection rates were not statistically significant ($P = 0.166$ and $P = 0.064$, respectively). The number of adenomas increased with looping severity ($P < 0.001$, Table 2).

Multivariate analysis of effect on polyp detection
We investigated the effect of subject characteristics on the detection of adenomas, high-risk adenomas, and CSSPs using multivariate analyses. The detection of adenomas and high-risk adenomas was independently associated with severe looping (both $P < 0.001$), old age, male sex, short insertion time, long withdrawal time, and endoscopist experience. CSSP detection was independently associated with severe looping ($P = 0.007$), female sex, short insertion time, long withdrawal time, and endoscopist experience (Table 3).

Subgroup analysis limited to experienced endoscopists
We performed a subgroup analysis that was limited to experienced endoscopists. Multivariate analyses showed similar results to the all-case analyses, that is, severe looping was independently associated with high detection rates of adenomas, high-risk adenomas, and CSSPs ($P < 0.001$, $P < 0.001$, and $P = 0.008$, respectively; Table 4).

DISCUSSION

In this study, we found that the severity of looping during colonoscopy was positively associated with high detection rates of adenomas, high-risk adenomas, and CSSPs, independent of other confounding factors, such as patient age, sex, colonoscope insertion and withdrawal times, and endoscopist experience. To the best of our knowledge, this is the first study to demonstrate a relationship between looping and polyp detection. Adenomas, high-risk adenomas, and CSSPs are precancerous lesions[2]. Recent studies have also shown that adenoma, high-risk adenoma, and CSSP detection rates are associated with a high risk of metachronous colorectal cancer[4,6]. Therefore, looping may predict a high frequency of metachronous colorectal cancer; however, further analysis is needed. Colonoscopists should carefully examine the colorectal region of patients with looping considering the high premalignant polyp detection rate.

Magnetic endoscopic imaging, computed tomographic colonoscopy, and autopsy revealed that looping was more common in older adults and women. Loop formation is also associated with prolonged cecal insertion time[17-20]. In our study, looping severity was associated with older age, female sex, and longer insertion time. Our results were consistent with those of previous studies. Looping during colonoscopy mainly occurs in the intraperitoneal segments of the colon, such as the transverse and sigmoid colon[15,17,19,20,34,35]. Barium enema and computed tomographic colonoscopy revealed that older adults and women had longer colons and larger colonic surface areas than younger adults and men, respectively. Differences in the total length and surface area are predominantly due to differences in the transverse colon[36-38]. The increased length and surface area of the

Table 1 Characteristics of the study subjects

Characteristics	
n	12259
Age, mean (SD), yr	53.6 (12.2)
Male sex, %	50.7
Looping, none/mild/severe, *n*	5532/4399/2253
Insertion time, mean (SD), min	4.57 (2.66)
Withdrawal time, mean (SD), min	13.87 (4.19)
Experienced endoscopist, %	70.4
Polyp detection	
Adenoma DR, %	44.7
Advanced adenoma DR, %	2.0
High-risk adenoma DR, %	9.9
CSSP DR, %	8.9
SSL DR, %	3.5
Number of adenomas, mean (SD), *n*	0.82 (1.25)
Number of SSLs, mean (SD), *n*	0.04 (0.24)

SD: Standard deviation; DR: Detection rate; CSSP: Clinically significant serrated polyp; SSL: Sessile serrated lesion.

Table 2 Subject characteristics based on looping severity

	No looping	Mild looping	Severe looping	*P* value
n	5532	4399	2253	
Age, mean (SD), yr	51.5 (11.5)	54.2 (12.2)	56.7 (13.0)	< 0.001
Male sex, %	62.8	44.6	33.4	< 0.001
Insertion time, mean (SD), min	3.53 (1.89)	4.95 (2.41)	6.38 (3.44)	< 0.001
Withdrawal time, mean (SD), min	13.70 (4.30)	14.17 (4.29)	13.74 (3.66)	< 0.001[1]
Experienced endoscopist, %	61.1	73.7	87.6	< 0.001
Polyp detection				
Adenoma DR, %	42.2	45.0	50.2	< 0.001
Advanced adenoma DR, %	1.8	2.1	2.3	0.166
High-risk adenoma DR, %	8.4	9.8	13.5	< 0.001
CSSP DR, %	7.8	9.5	10.3	< 0.001
SSL DR, %	3.2	3.7	3.9	0.064
Number of adenomas, mean (SD), *n*	0.74 (1.16)	0.81 (1.25)	1.03 (1.44)	< 0.001
Number of SSLs, mean (SD), *n*	0.04 (0.22)	0.05 (0.26)	0.05 (0.26)	0.553

[1]There were 22065005 and 19833488 combinations of increasing and decreasing trends, respectively.
P values were calculated using Cochran–Armitage trend test and Jonckheere-Terpstra test for categorical and continuous variables, respectively. SD: Standard deviation; DR: Detection rate; CSSP: Clinically significant serrated polyp; SSL: Sessile serrated lesion.

colon may contribute to the formation of loops and high frequency of premalignant polyps.

Colonic redundancy is a major cause of looping during colonoscopy[39]. Colonic elongation and tortuosity appear to be related to redundancy of the colon, such as in the transverse and sigmoid colon [40,41]. Older adults and women often present with colonic redundancy and looping[41]. Raahave *et al* [42] reported that colonic transit time is associated with redundant colonic loops. Constipation increases

Table 3 Multivariate analysis of the effect on polyp detections				
	Odds ratio	95% confidence interval	DOF	*P* value
Adenoma				
Looping[1]	1.13	1.06-1.20	1	< 0.001
Age	1.05	1.04-1.05	1	< 0.001
Male sex	1.39	1.28-1.50	1	< 0.001
Insertion time	0.94	0.92-0.96	1	< 0.001
Withdrawal time	1.14	1.13-1.15	1	< 0.001
Endoscopist experience	1.68	1.53-1.85	1	< 0.001
High-risk adenoma				
Looping[1]	1.25	1.13-1.38	1	< 0.001
Age	1.05	1.05-1.06	1	< 0.001
Male sex	1.527	1.33-1.74	1	< 0.001
Insertion time	0.90	0.87-0.93	1	< 0.001
Withdrawal time	1.20	1.18-1.21	1	< 0.001
Endoscopist experience	3.91	3.17-4.82	1	< 0.001
Clinically significant serrated polyp				
Looping[1]	1.14	1.04-1.26	1	0.007
Age	1.00	0.99-1.01	1	0.999
Male sex	0.60	0.52-0.68	1	< 0.001
Insertion time	0.92	0.88-0.95	1	< 0.001
Withdrawal time	1.16	1.14-1.17	1	< 0.001
Endoscopist experience	2.04	1.71-2.43	1	< 0.001

[1]No, mild, and severe looping were scored 0, 1, and 2, respectively.

P value was calculated using binomial logistic regression model. DOF: Degree of freedom.
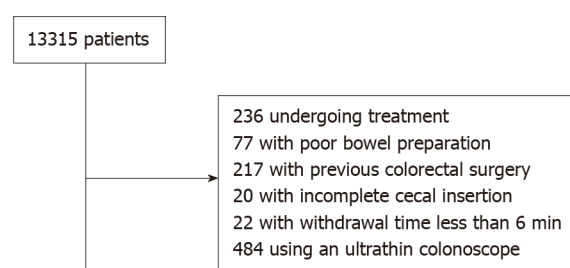
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Figure 1 Patient flowchart.

the risk of colorectal cancer[43]. This causes prolonged contact between the colonic mucosa and carcinogens in the stool.

Our study showed that adenoma detection was associated with old age, male sex, short insertion time, long withdrawal time, and endoscopist experience. These results are consistent with those of previous studies[8,10-12]. Female sex and longer withdrawal time, but not older age, were associated with CSSPs in our study. These findings are also concordant with those of previous studies[44-46]. The consistency of these results strengthens the credibility of this study.

Table 4 Multivariate analysis of the effect on polyp detections in the sub-analysis of experienced endoscopists

	Odds ratio	95% confidence interval	DOF	*P* value
Adenoma				
Looping[1]	1.14	1.07-1.23	1	< 0.001
Age	1.05	1.05-1.05	1	< 0.001
Male sex	1.42	1.29-1.56	1	< 0.001
Insertion time	0.93	0.91-0.95	1	< 0.001
Withdrawal time	1.13	1.11-1.14	1	< 0.001
High-risk adenoma				
Looping[1]	1.27	1.14-1.41	1	< 0.001
Age	1.05	1.05-1.06	1	< 0.001
Male sex	1.56	1.35-1.81	1	< 0.001
Insertion time	0.89	0.85-0.92	1	< 0.001
Withdrawal time	1.18	1.16-1.20	1	< 0.001
Clinically significant serrated polyp				
Looping[1]	1.15	1.04-1.28	1	0.008
Age	1.00	1.00-1.01	1	0.627
Male sex	0.66	0.57-0.77	1	< 0.001
Insertion time	0.92	0.89-0.96	1	< 0.001
Withdrawal time	1.13	1.11-1.15	1	< 0.001

[1]No, mild, and severe looping were scored 0, 1, and 2, respectively.

P value was calculated using binomial logistic regression model. DOF: Degree of freedom.

Limitations

This study had several limitations. First, this study was retrospectively conducted at a single institution; however, medical data were well-controlled. Second, although patients' body mass index, family history of colorectal cancer, and gynecological surgery are associated with the presence of premalignant polyps and looping[25,47], they were not examined. Third, since mucosal exposure can affect adenoma detection rate[48], the shape of looping, de-looping method, and successful de-looping after cecal intubation should be evaluated, not only the degree of looping during insertion. However, our data do not contain this information. Further verification is required in the future.

CONCLUSION

In conclusion, the severity of looping during colonoscopy was strongly associated with high detection rates of premalignant polyps, such as adenomas, high-risk adenomas, and CSSPs. Therefore, looping may predict the risk of metachronous colorectal cancer; however, further investigation is needed. Endoscopists should be more careful when examining for colorectal polyps in patients with looping.

ARTICLE HIGHLIGHTS

Research background

Colonic looping is a common obstacle during routine colonoscopy.

Research motivation

Looping is associated with a redundant colon, older age, female sex, and cecal intubation time. However, the clinical significance of looping is not fully understood.

Research objectives

We aimed to clarify the effect of looping on colorectal premalignant polyp detection.

Research methods

We extracted data from the clinic's endoscopy database on patient age, sex, endoscopist-assessed looping, colonoscopy duration, endoscopist experience, and premalignant polyp detection. The effects of looping on premalignant polyp detection were assessed using logistic regression analyses.

Research results

The detection rates of adenomas, high-risk adenomas, and clinically significant serrated polyps (CSSPs) increased with the severity of looping (all $P < 0.001$). The number of adenomas increased with looping severity ($P < 0.001$). Multivariate analyses found that detection of adenoma, high-risk adenoma, and CSSP was associated with severe looping ($P < 0.001$, $P < 0.001$, and $P = 0.007$, respectively) regardless of age, sex, and the time required for colonoscope insertion and withdrawal, and endoscopist experience.

Research conclusions

Looping severity was independently associated with high detection rates of premalignant polyps.

Research perspectives

Looping may predict the risk of metachronous colorectal cancer; however, further investigation is needed.

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FOOTNOTES

Author contributions: Toyoshima O, Nishizawa T, Yoshida S and Fujishiro M designed the study; Toyoshima O, Nishizawa T, Yoshida S, Matsuno T, Arano T, and Kondo R contributed to the endoscopic diagnosis; Toyoshima O wrote the article; Toyoshima O and Yoshida S were responsible to the statistical analysis; Nishizawa T edited the article; Yoshida S, Matsuno T, Arano T, Kondo R, Kinoshita K, Yasumi Y, Tsuji Y, and Fujishiro M involved in the critical review; and all authors approved the final manuscript.

Institutional review board statement: This study was approved by the Certificated Review Board, Yoyogi Mental Clinic on July 16, 2021 (approval no. RKK227).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. For full disclosure, the details of the study are published on the home page of Toyoshima Endoscopy Clinic.

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Country/Territory of origin: Japan

ORCID number: Osamu Toyoshima 0000-0002-6953-6079; Toshihiro Nishizawa 0000-0003-4876-3384; Shuntaro Yoshida 0000-0002-9437-9132; Tatsuya Matsuno 0000-0002-1935-3506; Toru Arano 0000-0003-3205-6669; Ryo Kondo 0000-0001-7939-5217; Kazunori Kinoshita 0000-0002-9222-8664; Yuki Yasumi 0000-0002-9028-6860; Yosuke Tsuji 0000-0001-9537-4993; Mitsuhiro Fujishiro 0000-0002-4074-1140.

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ORIGINAL ARTICLE

Retrospective Study

Self-expanding metal stent placement and pathological alterations among obstructive colorectal cancer cases

Keisuke Kosumi, Kosuke Mima, Kosuke Kanemitsu, Takuya Tajiri, Toru Takematsu, Yuki Sakamoto, Mitsuhiro Inoue, Yuji Miyamoto, Takao Mizumoto, Tatsuo Kubota, Nobutomo Miyanari, Hideo Baba

Keisuke Kosumi, Department of Gastroenterological Surgery, Kumamoto University, Kumamoto 860-8556, Japan

Kosuke Mima, Yuki Sakamoto, Mitsuhiro Inoue, Takao Mizumoto, Tatsuo Kubota, Nobutomo Miyanari, Department of Surgery, National Hospital Organization Kumamoto Medical Center, Kumamoto 860-0008, Japan

Kosuke Kanemitsu, Takuya Tajiri, Toru Takematsu, Yuji Miyamoto, Hideo Baba, Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, Honjo 860-8556, Kumamoto, Japan

Corresponding author: Keisuke Kosumi, MD, PhD, Doctor, Surgeon, Surgical Oncologist, Department of Gastroenterological Surgery, Kumamoto University, 1-1-1 Honjo, Chuo-ku, Kumamoto 860-8556, Japan. kosumi-kmm@umin.ac.jp

Abstract

BACKGROUND

Experimental studies suggest that self-expanding metal stents (SEMSs) enhance the aggressive behavior of obstructive colorectal cancer. The influence of SEMS placement on pathological alterations remains to be elucidated.

AIM

To determine whether SEMS placement is associated with molecular or pathological features of colorectal carcinoma tissues.

METHODS

Using a nonbiased molecular pathological epidemiology database of patients with obstructive colorectal cancers, we examined the association of SEMS placement with molecular or pathological features, including tumor size, histological type, American Joint Committee on Cancer (AJCC)-pTNM stage, and mutation statuses in colorectal cancer tissues compared with the use of transanal tubes. A multivariable logistic regression model was used to adjust for potential confounders.

RESULTS

SEMS placement was significantly associated with venous invasion ($P < 0.01$), but not with the other features examined, including tumor size, disease stage, mutation status, and lymphatic invasion. In both the univariable and mult-

ivariable models with adjustment for potential factors including tumor location, histological type, and AJCC-pT stage, SEMS placement was significantly associated with severe venous invasion (P < 0.01). For the outcome category of severe venous invasion, the multivariable odds ratio for SEMS placement relative to transanal tube placement was 19.4 (95% confidence interval: 5.24–96.2). No significant differences of disease-free survival and overall survival were observed between SEMS and transanal tube groups.

CONCLUSION
SEMS placement might be associated with severe venous invasion in colorectal cancer tissue, providing an impetus for further investigations on the pathological alterations by SEMSs in colorectal cancer development.

Key Words: Bridge to surgery; Colorectal carcinoma; Obstruction; Stent; Venous invasion

Core Tip: This study aimed to determine whether self-expanding metal stent (SEMS) placement is associated with molecular or pathological features of colorectal carcinoma tissues. As a result, SEMS placement was significantly associated with venous invasion (P < 0.01), but not with the other features examined, including tumor size, disease stage, mutation status, and lymphatic invasion. In both the univariable and multivariable models with adjustment for potential factors including tumor location, histological type, and American Joint Committee on Cancer-pT stage, SEMS placement was significantly associated with severe venous invasion (P < 0.01). For the outcome category of severe venous invasion, the multivariable odds ratio for SEMS placement relative to transanal tube placement was 19.4 (95% confidence interval: 5.24–96.2).

INTRODUCTION

Colorectal cancer is the third most common cancer in both men and women worldwide[1]. Despite remarkable advances in conventional multidisciplinary therapies for colorectal cancer, including surgery[2], radiotherapy, chemotherapy, and immunotherapy, improvements in clinical outcomes have been limited. Further developments of innovative treatment strategies are aggressively being sought, especially for colorectal cancer with complications, such as obstruction, perforation, and hemorrhage [3]. A considerable number of colorectal cancer patients present with a colonic obstruction, and the incidence is reported as high as 30%[4]. As colonic obstruction might endanger the life of patients, emergent decompression is urgently required. Emergency surgery might be associated with increased morbidity, mortality, stoma rate, and oncological suboptimal resection[4-6]. Therefore, a bridge to surgery approach could be a reasonable treatment strategy to allow for one-stage, or elective resection for obstructive colorectal cancer patients[7].

Self-expanding metal stents (SEMSs) have been used worldwide to rescue intestinal obstruction caused by colorectal cancer as well as benign diseases. Accumulating evidence suggests that SEMS placement results in marked advantages in short-term outcomes including the primary anastomosis rate, postoperative complications, and hospital stay after elective surgery because of patients' good general condition and adequate bowel preparation before surgery[8-11]. SEMSs might have a critical role of serving as a bridge to surgery for resectable colorectal carcinomas. Despite the efficacy and feasibility of SEMS placement in patients with obstructive colorectal cancer, there are several clinical concerns regarding SEMS placement. One of the major concerns is the risk of worse molecular or pathological malignancy by mechanical damage and pressure to the primary tumor by SEMS placement. In an *in vivo* experiment, peritoneal carcinomatosis and liver metastasis were more frequently observed in the stent group[12]. Additionally, human studies have indicated increased numbers of circulating tumor cells after SEMS placement but not after transanal decompression tube placement[13-15]. Based this evidence, we hypothesized that SEMS placement is associated with molecular or pathological malignancy in colorectal carcinoma tissues.

To test this hypothesis, we used a nonbiased molecular pathological epidemiology database of patients with obstructive colorectal cancer, and examined the molecular and pathological features of tumor tissue according to the decompression methods. Unlike previous studies[16,17], we first diagnosed lymphatic invasion (absent, minimal, moderate, or severe) and venous invasion (absent, minimal, moderate, or severe) in detail based on the Japanese Classification of Colorectal Carcinoma [18], and investigated the association between SEMS placement and molecular or pathological malignancy. We argue that the use of transdisciplinary integrated analyses to obtain a better understanding of the interaction between the decompression technique and tumor tissue characteristics will significantly help in the development of new treatment strategies for obstructive colorectal cancer.

MATERIALS AND METHODS

Study population

This study included 102 consecutive patients with obstructive colorectal cancer who underwent emergent colonic decompression at the National Hospital Organization Kumamoto Medical Center from July 2012 to December 2020. The main inclusion criteria were an age of > 18 years, histological confirmation of colorectal adenocarcinoma before or after the operation, no other active malignancy, and performance of emergent colonic decompression followed by surgery. The exclusion criteria were neoadjuvant chemotherapy and/or radiotherapy, perforation, peritonitis. The decompression method for each case was determined by tumor board. SEMS or transanal decompression tube placement was performed under both endoscopic and fluoroscopic guidance for obstructive colorectal cancer (CROSS scale 0, 1, or 2)[19]. Patients underwent cleansing enema for bowel preparation and received analgesia and sedation. The stent size and length were chosen according to the measured length of the obstruction. Tumor staging was performed according to the American Joint Committee on Cancer (AJCC) TNM classification (7th edition)[20]. Two institutional pathologists diagnosed histopathological differentiation (well, moderate, or others), lymphatic invasion (absent, minimal, moderate, or severe), and venous invasion (absent, minimal, moderate, or severe) based on the Japanese Classification of Colorectal Carcinoma[18]. Postoperative complications were recorded and graded as defined by the Clavien–Dindo classification system[21]. The term "prognostic marker'' is used throughout this article according to the REMARK Guidelines[22].

This study was approved by the Human Ethics Review Committee of the National Hospital Organization Kumamoto Medical Center, Kumamoto, Japan (institutional ethics committee number: 1061). The requirement for written informed consent was waived in view of the retrospective nature of the study.

Statistical analysis

All statistical analyses were conducted using the JMP program (version 10, SAS Institute, Cary, NC, United States). All P values were two-sided, and the two-sided α level of 0.05 was used for all testing.

Our primary analysis (hypothesis testing) involved examination of the associations of the decompression method used (SEMS *vs* transanal tube; as a predictor variable) with lymphatic invasion and venous invasion. All other analyses, including assessments of odds ratios (ORs), represented secondary analyses. We performed multivariable logistic regression analyses to control for potential confounders. The multivariable logistic regression model included variables showing a univariable association (P < 0.05) with lymphatic invasion or venous invasion from the decompression method (transanal tube *vs* SEMS), age (continuous), sex (female *vs* male), tumor location (cecum to transverse colon *vs* descending to sigmoid colon *vs* rectum), waiting period (continuous), tumor size (continuous), histological type (well differentiated *vs* moderately differentiated *vs* others), AJCC-pT (T2/T3 *vs* T4), and mutation (absent *vs* present).

To compare characteristics across strata of decompression methods, we used the chi-square test for categorical variables, and an analysis of variance, assuming equal variances for continuous variables. Each of the cross-sectional analyses was secondary.

Overall survival was defined as the time between the operation date and the date of death. Disease-free survival was defined as the time between the operation date and the date of recurrence. The survival time distributions were determined by the Kaplan–Meier method using a log-rank test.

RESULTS

Decompression methods and clinical, pathological, and molecular characteristics

Among the 102 patients with obstructive colorectal cancer in the nonbiased independent database, 53% were women and the median age was 72.6 years. The most frequent tumor location was descending to sigmoid colon (65 patients, 64%), followed by the rectum (21 patients, 21%) and cecum to transverse colon (16 patients, 16%). Table 1 summarizes the clinical, pathological, and molecular features of the

Table 1 Clinical and pathological features of patients with colorectal cancer according to decompression methods

Characteristic[1]	All cases (*n* = 102)	Decompression methods		*P* value[2]
		Transanal tube (*n* = 76)	SEMS (*n* = 26)	
Sex, *n* (%)				0.91
Female	54 (53)	40 (53)	14 (54)	
Male	48 (47)	36 (47)	12 (46)	
Age, mean ± SD (years)	72.6 ± 12.5	71.7 ± 12.9	75.1 ± 11.1	0.24
Tumor location, *n* (%)				0.24
Cecum to transverse colon	16 (16)	13 (17)	3 (12)	
Descending to sigmoid colon	65 (64)	45 (59)	20 (77)	
Rectum	21 (21)	18 (24)	3 (12)	
Tumor size, mean ± SD (mm)	40.7 ± 16.2	39.0 ± 14.9	45.4 ± 19.3	0.086
Time from decompression to operation, mean ± SD (days)	13.6 ± 12.9	12.0 ± 7.6	18.2 ± 21.7	0.035
Histological type, *n* (%)				0.35
Well	29 (28)	19 (25)	10 (38)	
Moderate	67 (66)	53 (70)	14 (54)	
Mucinous, poor, or signet-ring cell	6 (5.9)	4 (5.3)	2 (7.7)	
T stage (depth of tumor invasion), *n* (%)				0.57
T1 (submucosa)	-	-	-	
T2 (muscularis propria)	1 (1.0)	-	1 (3.9)	
T3 (subserosa)	67 (66)	54 (71)	13 (50)	
T4 (serosa or other organs)	34 (33)	22 (29)	12 (46)	
N stage (number of positive lymph nodes), *n* (%)				0.54
N0 (0)	49 (48)	36 (47)	13 (50)	
N1 (1-3)	39 (38)	28 (37)	11 (42)	
N2 (4-)	14 (14)	12 (16)	2 (7.7)	
AJCC disease stage, *n* (%)				0.40
I	1 (1.0)	-	1 (3.9)	
II	42 (41)	31 (41)	11 (42)	
III	36 (35)	27 (36)	9 (35)	
IV	23 (23)	18 (24)	5 (19)	
Mutation status, *n* (%)				0.51
KRAS mutated	34 (43)	26 (47)	8 (33)	
NRAS mutated	3 (3.8)	2 (3.6)	1 (4.2)	
BRAF mutated	0 (0)	0 (0)	0 (0)	
Absent	42 (53)	27 (49)	15 (63)	

[1]Percentage indicates the proportion of patients with a specific clinical characteristic among all patients or in strata of decompression methods.
[2]We used the chi-square test to compare categorical variables and analysis of variance to compare continuous variables. We adjusted the two-sided α level to 0.05.
AJCC: American Joint Committee on Cancer; SEMS: Self-expanding metal stent.

patients stratified according to decompression methods. Seventy-six (75%) patients underwent transanal tube placement, and 26 (25%) patients underwent SEMS placement. SEMS placement was significantly associated with a longer time between decompression and surgery (*P* = 0.035), but not with the other features examined, including tumor size, disease stage, and mutation status (all *P* > 0.08).

Table 2 summarizes the perioperative features of the patients stratified according to decompression methods. SEMS placement was significantly associated with a higher chance of reconstruction (*P* = 0.011), but not with the other features examined, including operation method, procedure, lymph node dissection, and short-term outcomes (all *P* > 0.07).

Decompression methods and lymphatic or venous invasion

Table 3 shows the distribution of patients according to the decompression methods and lymphatic invasion or venous invasion. SEMS placement was significantly associated with severe venous invasion (*P* < 0.0001). Table 4 shows the distribution of colorectal cancer cases according to decompression methods (transanal tube *vs* SEMS) and lymphatic or venous invasion in strata of AJCC-pT stage or tumor location. A similar association of SEMS placement with severe venous invasion was observed (*P* < 0.11).

Logistic regression analyses between decompression methods and venous invasion

To test our primary hypothesis, we used a logistic regression analysis to assess the association of the decompression method (SEMS *vs* transanal tube) with the degree of venous invasion (Table 5). In both the univariable and multivariable models, SEMS placement was significantly associated with severe venous invasion (*P* < 0.0001). For the outcome category of venous invasion, the univariable OR was 20.9 [95% confidence interval (CI): 5.78–101] for SEMS placement relative to transanal tube placement, and the multivariable OR was 19.4 (95%CI: 5.24–96.2). Similar findings were observed in the sensitivity analyses, in which we performed a multivariable analysis with adjustment for potential factors including tumor location, histological type, and AJCC-pT stage (multivariable OR: 36.7; 95%CI: 7.89–259; *P* < 0.0001). AJCC-pT was significantly associated with severe venous invasion in only the univariable model (*P* = 0.021), and the univariable OR was 3.72 (95%CI: 1.22–12.2) for AJCC-pT4 relative to AJCC-pT2/T3.

Among SEMS group, the waiting period for surgery did not have any association with venous invasion. For the outcome category of venous invasion, the univariable OR was 0.86 (95%CI: 0.46–1.14; *P* = 0.32) for waiting period (for 1-wk increment).

Exploratory analyses for the influence of stent diameter on lymphatic and venous invasion

As an exploratory analysis, we determined the influence of stent diameter on lymphatic and venous invasion (Table 6). A larger stent was significantly associated with venous invasion (*P* < 0.0001), and was possibly associated with lymphatic invasion (*P* = 0.055).

Decompression methods and long-term survival

As exploratory analyses, a Kaplan-Meier analysis was conducted to assess the influence of SEMS placement on long-term survival. No significant differences of disease-free survival and overall survival were observed (*P* = 0.56 for disease-free survival, *P* = 0.60 for overall survival).

DISCUSSION

Evidence indicates marked advantages in short-term outcomes by SEMS placement in patients with obstructive colorectal cancer because of these patients' good general condition and adequate bowel preparation before surgery[8,9]. Notably, other emerging evidence points to a link between SEMS placement and an increase in the number of circulating tumor cells by mechanical damage and pressure to the primary tumor[12-15]. However, the associations of SEMS placement with the molecular and pathological features of colorectal carcinoma tissues remain to be elucidated. The present study was performed to test the hypothesis that SEMS placement is associated with molecular or pathological malignancy in colorectal carcinoma tissues. We used a nonbiased molecular pathological epidemiology database of patients with obstructive colorectal cancer, and showed for the first time that SEMS placement is independently associated with severe venous invasion in colorectal cancer tissue. Although no significant differences of prognoses were observed, our findings suggest a possible influence of SEMS placement on pathological findings.

A growing body of evidence highlights associations between SEMS placement and short-term clinical outcomes among patients with obstructive colorectal cancer. A systematic review of randomized controlled trials showed that 81% of SEMS placements were technically successful, with 76% of patients achieving restoration of gastrointestinal function[23]. Additionally, a meta-analysis showed that SEMS placement helped to maintain quality of life by allowing food intake and temporal discharge, promoted laparoscopic one-stage surgery without stoma creation, and had morbidity and mortality rates equivalent to those of transanal decompression tube placement[9]. SEMS placement might decrease the rate of permanent stomas, especially in elderly patients[8]. Emerging evidence indicates the safety and feasibility of minimally invasive surgery combined with stent insertion for malignant colonic obstruction[24]. Collectively, colonic stenting followed by laparoscopy is safe and effective with high success rates and low complication rates. However, several points remain to be investigated, such as

Table 2 Perioperative features of patients with colorectal cancer according to decompression methods

Characteristic[1]	All cases (*n* = 102)	Decompression methods		*P* value[2]
		Transanal tube (*n* = 76)	SEMS (*n* = 26)	
Operation method, *n* (%)				0.31
Open	54 (53)	38 (50)	16 (62)	
Laparoscopy	48 (47)	38 (50)	10 (38)	
Conversion to laparotomy, *n* (%)				0.072
Absent	47 (98)	38 (100)	9 (90)	
Present	1 (2.1)	-	1 (10)	
Procedure, *n* (%)				0.17
Colectomy	58 (57)	44 (58)	14 (54)	
Anterior resection	37 (36)	25 (33)	12 (46)	
Hartmann procedure	5 (4.9)	5 (6.6)	-	
Abdominoperineal resection (Miles' operation)	2 (2.0)	2 (2.6)	-	
Lymph node dissection, *n* (%)				0.35
D1	3 (2.9)	3 (4.0)	-	
D2	10 (9.8)	8 (11)	2 (7.7)	
D3	89 (87)	65 (86)	24 (92)	
Reconstruction (except 2 abdominoperineal resection cases), *n* (%)				0.011
Absent	10 (10)	10 (14)	-	
Present	90 (90)	64 (86)	26 (100)	
Number of harvested lymph nodes, mean ± SD	21.6 ± 12.0	21.5 ± 11.8	21.7 ± 12.6	0.97
Operation time, mean ± SD (min)	241 ± 80	234 ± 79	263 ± 79	0.12
Blood loss, mean ± SD (g)	224 ± 364	229 ± 375	212 ± 336	0.84
Clavien-Dindo classification, *n* (%)				0.22
0	78 (76)	58 (76)	20 (77)	
1	5 (4.9)	5 (6.6)	-	
2	11 (11)	8 (11)	3 (12)	
3	7 (7.7)	5 (6.6)	2 (7.7)	
4	-	-	-	
5	1 (1.0)	-	1 (3.9)	
Postoperative hospitalization, mean ± SD (days)	18.8 ± 15.1	19.3 ± 17.0	17.2 ± 6.7	0.53
Postoperative chemotherapy, *n* (%)				0.36
Absent	51 (50)	36 (47)	15 (58)	
Present	51 (50)	40 (53)	11 (42)	

[1]Percentage indicates the proportion of patients with a specific clinical characteristic among all patients or in strata of decompression methods.

[2]We used the chi-square test to compare categorical variables and analysis of variance to compare continuous variables. We adjusted the two-sided α level to 0.05.

SEMS: Self-expanding metal stent.

postoperative chemotherapy[25], the SEMS-related perforation rate (5.0%–8.9%)[8,23,26], perforation-related recurrence[26], the SEMS diameter[27], and the optimal timing from stent placement to surgery [28,29].

Long-term survival of patients with complicated colorectal cancer remains poor despite advances in surgical techniques. Additionally, how SEMS placement impacts long-term survival compared with

Table 3 Pathological features of patients with colorectal cancer according to decompression methods

Characteristic[1]	All cases (*n* = 102)	Decompression methods		P value[2,3]
		Transanal tube (*n* = 76)	SEMS (*n* = 26)	
Lymphatic invasion, *n* (%)				0.12 (0.020)
Absent	11 (11)	10 (13)	1 (3.9)	
Minimal	41 (40)	33 (43)	8 (31)	
Moderate	32 (31)	23 (30)	9 (35)	
Severe	18 (18)	10 (13)	8 (31)	
Venous invasion, *n* (%)				< 0.0001 (0.0002)
Absent	19 (19)	17 (22)	2 (7.7)	
Minimal	45 (44)	37 (49)	8 (31)	
Moderate	23 (23)	19 (25)	4 (15)	
Severe	15 (15)	3 (4.0)	12 (46)	

[1]Percentage indicates the proportion of patients with a specific clinical characteristic among all patients or in strata of decompression methods.

[2]We used the chi-square test to compare as categorical variables. We adjusted the two-sided α level to 0.05.

[3]We used the Mann-Whitney U test to compare as nonparametric continuous variables. We adjusted the two-sided α level to 0.05.

SEMS: Self-expanding metal stent.

other procedures, including diverting stomas, transanal tubes, and emergency surgery, remains controversial. A retrospective single- or multicenter observational study and two meta-analyses showed no significant difference in long-term survival between the SEMS group and emergency surgery group among patients with obstructive left-sided colorectal cancer[30-33]. Additionally, one randomized controlled trial showed no prognostic difference between the two groups[34]. One retrospective observational study revealed no significant differences in long-term outcomes between patients with obstructive colorectal cancer who underwent SEMS placement and transanal decompression tube placement as a bridge to surgery[35]. In the current study, no significant differences of disease-free survival and overall survival were observed between SEMS and transanal tube groups. A national, population-based cohort study using propensity score matching suggested that SEMS placement has intermediate-term oncologic outcomes similar to those of a decompressing stoma as a bridge to resection of left-sided obstructive colon cancer[36]. While, a French surgical association multicenter cohort study utilizing a propensity score analysis suggested that SEMS placement might be associated with a worse prognosis than a diverting stoma or immediate surgery for obstructive left-sided colorectal cancer[37,38]. The CODOMO study showed that transanal decompression tube placement might be associated with a worse prognosis than surgery for obstructive left-sided colorectal cancer[30]. For obstructive right-sided colorectal cancer, another population-based observational study demonstrated that the prognosis was significantly better in the decompression tube group than in the SEMS group [39]. SEMS-related perforation or an increased bridging interval to surgery might be a significant risk factor for systemic recurrence[26,29]. With respect to operation methods, laparoscopic surgery after stent placement for obstructive colon cancer might be performed safely with long-term outcomes comparable with those of open surgery[40]. The diameter of the colonic stent might not impact long-term survival[27]. Further research is warranted to investigate the prognostic role of SEMS placement in obstructive colorectal cancer compared with other procedures.

Dissemination of tumor cells has been a major concern in patients who undergo SEMS placement for obstructive colorectal cancer, and several experimental studies have focused on circulating tumor cells in the bloodstream. In 2007, an increase in the level of CK20 mRNA in the peripheral circulation was confirmed after endoscopic colonic stent insertion in patients with colorectal cancer[41]. In an *in vivo* study using a mouse model, peritoneal carcinomatosis and liver metastasis were more frequently observed in the stent group[12]. Moreover, in patients with obstructive colorectal cancer, the plasma levels of cell-free DNA and circulating tumor DNA increased after SEMS placement but not after transanal decompression tube placement; this suggests an oncological risk of SEMS placement in terms of molecular analysis[13-15]. The no-touch isolation technique, which was first proposed in 1952[42], gives first priority to central vascular ligation followed by mobilization of the tumor-bearing segment of the colon. This technique might reduce the spread of circulating tumor cells from the primary tumor site to other organs by ligation of blood vessels first. One retrospective study showed prognostic improvement by the no-touch isolation technique[43], but a large-scale randomized controlled trial failed to confirm the superiority of the no-touch isolation technique in patients with colorectal cancer [44]. In the current study, we found an association of SEMS placement with high severe invasion, but we

Table 4 Pathological features of patients with colorectal cancer according to decompression methods in strata of American Joint Committee on Cancer-pT stage or tumor location

Characteristic[1]	All cases (*n* = 102)	Decompression methods		P value[2,3]
		Transanal tube (*n* = 76)	SEMS (*n* = 26)	
Lymphatic invasion				
AJCC-pT2/T3 cases, *n* (%)				0.024 (0.036)
Absent	8 (12)	8 (15)	-	
Minimal	31 (46)	25 (46)	6 (43)	
Moderate	20 (29)	17 (31)	3 (21)	
Severe	9 (13)	4 (7.4)	5 (36)	
AJCC-pT4 cases, *n* (%)				0.53 (0.56)
Absent	3 (8.8)	2 (9.1)	1 (8.3)	
Minimal	10 (29)	8 (36)	2 (17)	
Moderate	12 (35)	6 (27)	6 (50)	
Severe	9 (26)	6 (27)	3 (25)	
Venous invasion				
AJCC-pT2/T3 cases, *n* (%)				0.0031 (0.0025)
Absent	13 (19)	12 (22)	1 (7.1)	
Minimal	37 (54)	32 (59)	5 (36)	
Moderate	12 (18)	9 (17)	3 (21)	
Severe	6 (8.8)	1 (1.9)	5 (36)	
AJCC-pT4 cases, *n* (%)				0.0077 (0.042)
Absent	6 (18)	5 (23)	1 (8.3)	
Minimal	8 (24)	5 (23)	3 (25)	
Moderate	11 (32)	10 (45)	1 (8.3)	
Severe	9 (26)	2 (9.1)	7 (58)	
Lymphatic invasion				
Cecum to transverse colon cases, *n* (%)				0.21 (0.088)
Absent	3 (19)	3 (23)	-	
Minimal	7 (44)	6 (46)	1 (33)	
Moderate	4 (25)	4 (31)	-	
Severe	2 (13)	-	2 (67)	
Descending to rectum, *n* (%)				0.40 (0.096)
Absent	8 (9.3)	7 (11)	1 (4.4)	
Minimal	34 (40)	27 (43)	7 (30)	
Moderate	28 (33)	19 (30)	9 (39)	
Severe	16 (19)	10 (16)	6 (26)	
Venous invasion				
Cecum to transverse colon cases, *n* (%)				0.10 (0.078)
Absent	5 (31)	5 (38)	-	
Minimal	6 (38)	5 (38)	1 (33)	
Moderate	2 (13)	2 (15)	-	
Severe	3 (19)	1 (7.7)	2 (67)	

Descending to rectum, *n* (%)				0.0001 (0.0012)
Absent	14 (16)	12 (19)	2 (8.7)	
Minimal	39 (45)	32 (51)	7 (30)	
Moderate	21 (24)	17 (27)	4 (17)	
Severe	12 (14)	2 (3.2)	10 (43)	

[1]Percentage indicates the proportion of patients with a specific clinical characteristic among all patients or in strata of decompression methods.

[2]We used the chi-square test to compare as categorical variables. We adjusted the two-sided α level to 0.05.

[3]We used the Mann-Whitney U test to compare as nonparametric continuous variables. We adjusted the two-sided α level to 0.05.

AJCC: American Joint Committee on Cancer; SEMS: Self-expanding metal stent.

Table 5 Logistic regression analyses to assess the association of decompression method (predictor) with severe venous invasion (outcome)

Model for severe venous invasion (*n* = 102, as a binary outcome variable)	Univariable		Multivariable[1]		Multivariable[2]	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Decompression methods						
Transanal tube	1 (reference)	< 0.0001	1 (reference)	< 0.0001	1 (reference)	< 0.0001
SEMS	20.9 (5.78-101)		19.4 (5.24-96.2)		36.7 (7.89-259)	
Age (for 10-yr increment)	1.29 (0.82-2.20)	0.28				
Sex						
Female	1 (reference)	0.60				
Male	1.34 (0.44-4.14)					
Tumor location						
Cecum to transverse colon	1 (reference)	0.27			1 (reference)	0.27
Descending to sigmoid colon	0.88 (0.23-4.31)				0.38 (0.05-2.60)	
Rectum	0.22 (0.01-1.90)				0.11 (0.003-1.58)	
Waiting period (for 1-wk increment)	0.91 (0.47-1.22)	0.64				
Tumor size (for 10-mm increment)	1.10 (0.78-1.49)	0.55				
Histological type						
Well	1 (reference)	0.21			1 (reference)	0.065
Moderate	2.65 (0.65-17.9)				7.27 (1.27-64.5)	
Mucinous, poor, or signet-ring cell	6.75 (0.66-72.0)				10.7 (0.48-342)	
AJCC-pT						
T2/T3	1 (reference)	0.021	1 (reference)	0.084	1 (reference)	0.082
T4	3.72 (1.22-12.2)		3.17 (0.86-12.6)		3.76 (0.85-19.4)	
Mutation						
Absent	1 (reference)	0.81				
Present (*KRAS, NRAS*)	1.16 (0.33-4.07)					

[1]The multivariable logistic regression model included the decompression method (transanal tube *vs* SEMS), and AJCC-pT (T2/T3 *vs* T4).

[2]The multivariable logistic regression model included the decompression method (transanal tube *vs* SEMS), tumor location (cecum to transverse colon *vs* descending to sigmoid colon *vs* rectum), histological type (well-differentiated vs. moderately differentiated *vs* others), and AJCC-pT (T2/T3 *vs* T4).

AJCC: American Joint Committee on Cancer; CI: Confidence interval; OR: Odds ratio; SEMS: Self-expanding metal stent.

observed no significant differences of long-term survivals between two groups. Our findings need to be confirmed in future multicenter studies with a larger cohort.

Table 6 Pathological features of patients with colorectal cancer according to decompression methods (transanal tube *vs* 18-mm stent *vs* 22-mm stent)

Characteristic[1]	All cases (*n* = 102)	Decompression methods			P value[2,3]
		Transanal tube (*n* = 76)	18 mm stent (*n* = 11)	22 mm stent (*n* = 15)	
Lymphatic invasion, *n* (%)					0.055 (0.0060)
Absent	11 (11)	10 (13)	1 (9.1)	-	
Minimal	41 (40)	33 (43)	5 (45)	3 (20)	
Moderate	32 (31)	23 (30)	4 (36)	5 (33)	
Severe	18 (18)	10 (13)	1 (9.1)	7 (47)	
Venous invasion, *n* (%)					< 0.0001 (0.0006)
Absent	19 (19)	17 (22)	2 (18)	-	
Minimal	45 (44)	37 (49)	3 (27)	5 (33)	
Moderate	23 (23)	19 (25)	1 (9.1)	3 (20)	
Severe	15 (15)	3 (4.0)	5 (45)	7 (47)	

[1]Percentage indicates the proportion of patients with a specific clinical characteristic among all patients or in strata of decompression methods.

[2]We used the chi-square test to compare as categorical variables. We adjusted the two-sided α level to 0.05.

[3]We used the Mann-Whitney U test to compare as nonparametric continuous variables. We adjusted the two-sided α level to 0.05.

We acknowledge several limitations in our study. First, the sample size was small, and this was a retrospective observational study at a single center. However, our findings are quite significant despite of small sample size. Because the optimal treatment strategy for obstructive colorectal cancer has not been established, our findings should be verified with a larger cohort in a multi-institutional study. Second, the current study was cross-sectional in nature, and the exact mechanisms that underlie the relationship between SEMS placement and severe venous invasion remain uncertain. Our hypothesis was based on several lines of experimental and population-based evidence indicating that mechanical damage and pressure to the primary tumor by SEMS placement increase venous invasion. Comparison of the pathological features between before and after SEMS placement is quite challenging, and the current study which considered the tumor stage and molecular and pathological features must be valuable. Third, we did not investigate the relationship between venous invasion and circulating tumor cells in the bloodstream. Fourth, the pathological findings including the degree of venous invasion were diagnosed based on the Japanese Classification of Colorectal Carcinoma by two pathologists[18], but the diagnosis is assessed by subjective methods. That is another limitation. Future studies are needed to confirm our findings and examine the association of SEMS placement with molecular and pathological features and long-term survival of patients with obstructive colorectal cancer.

A major strength of our study is that it used a molecular pathological epidemiology[45,46] database of patients with colorectal cancer, forming an independent cohort. This database integrates epidemiologic data, clinicopathologic features, and tumor molecular features including the *KRAS*, *BRAF*, or *NRAS* mutation status in colorectal cancer tissue. Our multidisciplinary integrated study based on this human-population colorectal cancer database enabled us to rigorously investigate the association of SEMS placement with the molecular and pathological features of colorectal cancer tissues; we utilized multivariable logistic regression models after controlling for multiple potential confounders such as disease stage, tumor location, and tumor molecular features.

CONCLUSION

In conclusion, we have herein shown that SEMS placement might be associated with severe venous invasion in colorectal cancer tissue, providing an impetus for further investigation of the potential interactive roles of SEMS placement and pathological alterations in colorectal cancer tissues. Validation of our findings may provide insights for further investigations on strategies for obstructive colorectal cancer.

ARTICLE HIGHLIGHTS

Research background

Experimental studies suggest that self-expanding metal stents (SEMSs) enhance the aggressive behavior of obstructive colorectal cancer.

Research motivation

The influence of SEMS placement on pathological alterations remains to be elucidated.

Research objectives

This study aimed to determine whether SEMS placement is associated with molecular or pathological features of colorectal carcinoma tissues.

Research methods

Using a nonbiased molecular pathological epidemiology database of patients with obstructive colorectal cancers, we examined the association of SEMS placement with molecular or pathological feature.

Research results

SEMS placement was significantly associated with venous invasion ($P < 0.01$), but not with the other features examined, including tumor size, disease stage, mutation status, and lymphatic invasion. In both the univariable and mult-ivariable models with adjustment for potential factors including tumor location, histological type, and American Joint Committee on Cancer-pT stage, SEMS placement was significantly associated with severe venous invasion ($P < 0.01$).

Research conclusions

SEMS placement might be associated with severe venous invasion in colorectal cancer tissue.

Research perspectives

Future studies are needed to confirm our findings and examine the association of SEMS placement with pathological features and long-term survival of patients with obstructive colorectal cancer.

FOOTNOTES

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Antibiotic prophylaxis to prevent complications in endoscopic retrograde cholangiopancreatography: A systematic review and meta-analysis of randomized controlled trials

Maria Fernanda Shinin Merchan, Diogo Turiani Hourneaux de Moura, Guilherme Henrique Peixoto de Oliveira, Igor Mendonça Proença, Epifanio Silvino do Monte Junior, Edson Ide, Caroline Moll, Sergio A Sánchez-Luna, Wanderley Marques Bernardo, Eduardo Guimarães Hourneaux de Moura

Maria Fernanda Shinin Merchan, Diogo Turiani Hourneaux de Moura, Guilherme Henrique Peixoto de Oliveira, Igor Mendonça Proença, Epifanio Silvino do Monte Junior, Edson Ide, Caroline Moll, Wanderley Marques Bernardo, Eduardo Guimarães Hourneaux de Moura, Department of Gastroenterology, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo 05403-010, Brazil

Sergio A Sánchez-Luna, Department of Internal Medicine, University of Alabama at Birmingham Heersink School of Medicine, Birmingham, AL 35233, United States

Corresponding author: Guilherme Henrique Peixoto de Oliveira, MD, Medical Assistant, Department of Gastroenterology, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Dr Enéas de Carvalho Aguiar, 225, São Paulo 05403-010, Brazil. guilherme.hpoliveira@hc.fm.usp.br

Abstract

BACKGROUND

The prophylactic use of antibiotics in endoscopic retrograde cholangiopancreatography (ERCP) is still controversial.

AIM

To assess whether antibiotic prophylaxis reduces the rates of complications in patients undergoing elective ERCP.

METHODS

This systematic review and meta-analysis were performed following the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines. A comprehensive search of multiple electronic databases was performed. Only randomized controlled trials were included. The outcomes analyzed included bacteremia, cholangitis, sepsis, pancreatitis, and mortality. The risk of bias was assessed by the Cochrane revised Risk-of-Bias tool for randomized controlled trials. The quality of evidence was assessed by the Grading of Recommendation Assessment, Development, and Evaluation. Meta-analysis was performed using the Review Manager 5.4 software.

RESULTS
Ten randomized controlled trials with a total of 1757 patients that compared the use of antibiotic and non-antibiotic prophylaxis in patients undergoing elective ERCP were included. There was no significant difference between groups regarding incidence of cholangitis after ERCP [risk difference (RD) = -0.02, 95% confidence interval (CI): -0.05, 0.02, $P = 0.32$], cholangitis in patients with suspected biliary obstruction (RD = 0.02, 95%CI: -0.08 to 0.13, $P = 0.66$), cholangitis on intravenous antibiotic prophylaxis (RD = -0.02, 95%CI: -0.05 to 0.01, $P = 0.25$), septicemia (RD = -0.02, 95%CI: -0.06 to 0.01, $P = 0.25$), pancreatitis (RD = -0.02, 95%CI: -0.06 to 0.01, $P = 0.19$), and all-cause mortality (RD = 0.00, 95%CI: -0.01 to 0.01, $P = 0.71$). However, the antibiotic prophylaxis group presented a 7% risk reduction in the incidence of bacteremia (RD= -0.07, 95%CI: -0.14 to -0.01, $P = 0.03$).

CONCLUSION
The prophylactic use of antibiotics in patients undergoing elective ERCP reduces the risk of bacteremia but does not appear to have an impact on the rates of cholangitis, septicemia, pancreatitis, and mortality.

Key Words: Endoscopy; Antibiotics; Endoscopic retrograde cholangiopancreatography; Cholangitis; Infection

Core Tip: There is controversy about antibiotic prophylaxis in patients undergoing elective endoscopic retrograde cholangiopancreatography. This is a systematic review and meta-analysis based on randomized controlled trials that analyzed whether the use of antibiotic prophylaxis is beneficial in preventing complications after this procedure. Outcomes evaluated include the rate of cholangitis, bacteremia, sepsis, pancreatitis, and mortality. Based on this meta-analysis, antibiotic prophylaxis reduces the risk of bacteremia but does not impact the rate of cholangitis, septicemia, pancreatitis, and mortality.

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is one of the most technically challenging procedures in digestive endoscopy, associated with high rates of adverse events (AEs), reported in up to 18.9% of cases[1-3]. The most common adverse events include bacteremia, cholangitis, and pancreatitis occurring in about 6.5% to 18.0%[4], 3.0%[5,6], and 5.5%[7] respectively.

Prophylactic antibiotics are used with the intent to prevent complications of ERCP. Their use is controversial and is currently being recommended in patients with incomplete biliary drainage, such as hilar tumors and primary sclerosing cholangitis[8] due to the potential risk of septic complications from the manipulation of obstructed bile ducts that could serve as a source of bacterial colonization, thus increasing the risk of bacteremia[4] and cholangitis.

The European Society for Gastrointestinal Endoscopy[9] and the American Society for Gastrointestinal Endoscopy[10] guidelines do not recommend routine antibiotics prophylaxis before elective ERCP in low-risk groups. Both guidelines recommend antibiotic prophylaxis in specific situations such as liver transplant[11], severe neutropenia, the impossibility of complete biliary drainage, use of cholangioscopy[12], and in patients with primary sclerosing cholangitis[13].

Although both guidelines regarding antibiotic prophylaxis for ERCP do not recommend its routine use, the data to support this recommendation is not robust. Therefore, we performed a systematic review and meta-analysis to evaluate whether the use of antibiotic prophylaxis has an impact on the rate of complications related to elective ERCP.

MATERIALS AND METHODS

Protocol and registration
The study protocol was registered in the International Prospective Register of Systematic Reviews under the file number CRD42022289127 and was approved by the Ethics Committee of Hospital das Clínicas, Faculty of Medicine at The University of São Paulo. This systematic review and meta-analysis were performed in conformity with the recommendations from the Cochrane Handbook of Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines[14].

Information source and literature search
Individualized searches of multiple electronic databases (MEDLINE, Embase, Cochrane, LILACS, clincaltrials.gov, and gray literature) were performed based upon a standardized protocol from their inception through February 2022. The search included the following Medical Subject Headings: "(Endoscopy OR Endoscopic) AND (Anti-Bacterial Agents OR Antibacterial Agents OR Antibacterial Agent OR Antibiotics OR Antibiotic) AND [prophylaxis OR preventive OR (prevention and control)]." A further literature search was conducted with the Reference Citation Analysis engine, an artificial intelligence technology-based open multidisciplinary citation analysis database (https://www.re ferencecitationanalysis.com). Following a search within the Reference Citation Analysis database no further studies were identified that fit our inclusion criteria.

Study selection
Two researchers independently conducted the eligibility screening. From the initial search results, duplicate articles were excluded, and the titles and abstracts of all potentially relevant studies were screened for eligibility. Any disagreements were settled by consensus or by consulting a third reviewer.

Only randomized controlled trials (RCTs) comparing antibiotic prophylaxis *vs* no use of prophylactic antibiotics in patients undergoing elective ERCP regardless of publication date or language were considered.

Patients with cholangitis or other types of active infection, history of antibiotic allergy, and immunosuppressed were excluded.

Data extraction and definitions
Items included in data extraction were first author, year of publication, study design, and outcomes of interest such as cholangitis, bacteremia, septicemia, pancreatitis, and mortality. We defined cholangitis as the presence of fever (> 38.5 °C), abdominal pain, leukocytosis, and elevated C-reactive protein. Blood cultures and bile samples were taken to evaluate for bacteremia. Bacteremia was defined as a positive culture with no evidence of systemic inflammatory response. Blood culture samples were taken before and after the ERCP procedure and in the presence of fever. In one of the studies a blood culture was obtained only if the patients presented signs of cholangitis. Septicemia was defined as a positive blood culture with systemic inflammatory response (fever, hypotension, tachycardia, leukocytosis > 10 g/dL, leukopenia < 3 g/L, and chills). The diagnosis of pancreatitis was based on clinical findings, increased serum amylase or lipase three-fold or more over the normal upper range. Antibiotic prophylaxis is defined as administering antibiotics to patients who underwent invasive procedures without evidence of infection at the time of the procedure. The goal of such prophylaxis was to reduce the risk of infection.

Risk of bias and quality of evidence
We assessed the risk of bias using the Cochrane Risk of Bias tool version 2[14].

The quality of evidence was assessed utilizing the objective criteria from Grading Recommendations Assessment, Development, and Evaluation for each of the prespecified results and outcomes using the GRADEpro-Guideline Development Tool software (McMaster University, 2015; Evidence Prime, Inc., Ontario, Canada)[15].

Statistical analysis
Continuous variables were analyzed using mean difference and standard deviation with a 95% confidence interval. For categorical variables, the risk difference (RD) was used, with a 95% confidence interval. The RD and mean difference were considered statistically significant at a value of $P \leq 0.05$. If a study provided medians and interquartiles or ranges, they were attributed to means, and standard deviation was estimated as described by the McGrath *et al*[16] method.

The inconsistency index was evaluated using the Higgins I^2 method[17], in which the presence of heterogeneity can be observed. The random effect was used for all analyses. The meta-analysis was performed using the RevMan software (Review Manager Software version 5.4-Cochrane Collaboration Copyright© 2020).

RESULTS

Study selection

The initial search strategy identified 5594 articles. Through the evaluation by title and abstract, 2999 articles were excluded, yielding 165 studies. Of these, 10 RCTs, including 1757 patients (843 in the control group and 914 in the intervention group) met the eligibility criteria and were included in this systematic review and meta-analysis (Figure 1). The characteristics and results of the included studies are summarized in Table 1.

Risk of bias and quality of evidence

All 10 studies[18-27] were RCTs. Three studies presented a low risk bias[19,20,22]. Three studies presented a moderate risk of bias[18,24,27]. Four studies presented a serious risk of bias[21,23,25,26]. Detailed information concerning the risk of bias for each outcome is described in Figure 2.

The overall quality of evidence was moderate for the outcomes of bacteremia, cholangitis, septicemia, pancreatitis, and cholangitis in patients with suspected biliary obstruction. The quality of evidence was high for the outcomes of cholangitis in patients on intravenous antibiotic prophylaxis and mortality. Detailed information on the quality of evidence (Grading Recommendations Assessment, Development, and Evaluation) is described in Figure 3.

Outcomes

Bacteremia: Data from seven studies[20-22,24-27] were evaluated in a total of 758 patients: 371 in the intervention group and 378 in the control group. The intervention group presented a bacteremia rate of less than 7% with a statistical difference compared to the control group (RD = -0.07, 95%CI: -0.14 to -0.01, P = 0.03) (Figure 4A).

Cholangitis: Analysis of nine studies[18-23,25-27], totaling 1658 patients (794 in the intervention group and 864 in the control group) showed no significant differences between the groups (RD = -0.02, 95%CI: -0.05 to 0.02, P = 0.32) (Figure 4B).

Septicemia: Septicemia was evaluated in seven studies[19-22,24,25,27], totaling 1152 patients (568 assigned to the intervention group and 584 to the control group) and showed no significant differences between the groups (RD = -0.02, 95%CI: -0.06 to 0.01, P = 0.18) (Figure 4C).

Pancreatitis: Pancreatitis was evaluated in five studies[18,21-23,26], totaling 798 patients (371 assigned to the intervention group and 427 to the control group) and showed no significant differences between the groups (RD = -0.02, 95%CI: -0.06 to 0.01, P = 0.19) (Figure 4D).

Cholangitis in patients with suspected biliary obstruction: Data from three studies[18,19,26] were evaluated in a total of 838 patients (302 assigned to the intervention group and 536 to the control group) and showed no significant difference between the groups (RD = 0.02, 95%CI: -0.08 to 0.13, P = 0.66) (Figure 5A).

Cholangitis in patients on intravenous antibiotic prophylaxis: Analysis of eight studies[18-22,24,26, 27], totaling 1540 patients (755 assigned to the intervention group and 785 to the control group) showed no significant difference between the groups (RD = -0.02, 95%CI: -0.05 to 0.01, P = 0.25) (Figure 5B).

Mortality: Mortality rate was evaluated in nine studies[18-22,24-27], totaling 1638 patients (804 of the intervention group and 834 of the control group) and showed no significant difference between the groups (RD = 0.00, 95%CI: -0.01 to 0.01, P = 0.71) (Figure 4E).

DISCUSSION

We analyzed 10 RCTs to assess whether antibiotic prophylaxis positively impacts patients undergoing elective ERCP, thus preventing complications after the procedure. Including a total of 1757 patients, this meta-analysis showed no statistical difference in the rates of cholangitis, septicemia, pancreatitis, and mortality. However, our study showed a lower bacteremia rate in the antibiotic group.

Although our systematic review and meta-analysis revealed less risk of bacteremia in the group that underwent antibiotic prophylaxis, there are doubts about whether this finding has any clinical relevance. Antibiotics are highly prescribed drugs in clinical practice. It is estimated that about 50% of antibiotic use in hospitals (both outpatient and inpatient) is not appropriately prescribed[28]. A meta-analysis published in 2009, which evaluated ERCP-induced cholangitis as an outcome, showed that antibiotics do not prevent cholangitis[29]. However, another meta-analysis from 2010 showed that prophylactic antibiotics could reduce bacteremia rates and may prevent cholangitis in patients undergoing elective ERCP[30]. Nonetheless, due to conflicting findings in the literature, it is not possible to state that reducing bacteremia rates leads to less cholangitis. Another critical point is that the

Table 1 Characteristics of included studies

Ref.	Year	Type of study	Intervention	Participants	Bacteremia	Cholangitis	Pancreatitis	Septicemia	Mortality
Brandes *et al* [23]	1981	RCT	Minocycline 300 mg orally	Total: 118 Antibiotics: 39 Control: 79	N/A	Intervention: 0/39 Control: 1/79	Intervention: 1/39 Control: 2/79	N/A	N/A
Sauter *et al* [22]	1990	RCT	Cefotaxime 2 g IV, 15 min before ERCP	Total: 100 Antibiotics: 50 Control: 50	Intervention: 1/50 Control: 8/50	Intervention: 1/50 Control: 2/50	Intervention: 0/50 Control: 0/50	Intervention: 0/50 Control: 0/50	Intervention: 0/50 Control: 0/50
Niederau *et al*[21]	1994	RCT	Cefotaxime 2 g IV. 15 min before ERCP	Total: 100 Antibiotics: 50 Control: 50	Intervention: 0/50 Control: 4/50	Intervention: 0/50 Control: 4/50	Intervention: 2/50 Control: 3/50	Intervention: 0/50 Control: 8/50	Intervention: 0/50 Control: 0/50
Byl *et al*[20]	1995	RCT	Piperacillin, 4 g IV, 3/d	Total: 68 Antibiotics: 34 Control: 34	Intervention: 0/30 Control: 7/32	Intervention: 2/34 Control: 10/34	N/A	Intervention: 0/30 Control: 5/32	Intervention: 0/34 Control: 5/34
Finkelstein *et al*[27]	1996	RCT	Cefonicid 1 g IV, 1 h before ERCP	Total: 179 Antibiotics: 88 Control: 91	Intervention: 3/88 Control: 2/91	Intervention: 7/88 Control: 2/91	N/A	Intervention: 0/88 Control: 0/91	Intervention: 0/88 Control: 0/91
Lorenz *et al* [24]	1996	RCT	Cefuroxime 1.5 g IV, 30 min before ERCP	Total: 99 Antibiotics: 49 Control: 50	Intervention: 3/49 Control: 8/50	N/A	N/A	Intervention: 3/49 Control: 5/50	Intervention: 0/49 Control: 0/50
van den Hazel *et al* [19]	1996	RCT	Piperacillin 4 g IV, 30 min before ERCP	Total: 551 Antibiotics: 270 Control: 281	N/A	Intervention: 12/170 Control: 17/281	N/A	Intervention: 2/170 Control: 3/281	Intervention: 3/170 Control: 2/281
Räty *et al*[18]	2001	RCT	2g of ceftazidime IV, 30 min before ERCP	Total: 315 Antibiotics: 155 Control: 160	N/A	Intervention: 0/155 Control: 7/160	Intervention: 4/155 Control: 15/160	N/A	Intervention: 1/155 Control: 0/160
Spicak *et al* [26]	2002	RCT	Amoxicillin – clavulanic acid 2.4 g IV	Total 165 Antibiotics: 77 Control: 88	Intervention: 18/73 Control: 24/84	Intervention: 4/77 Control: 3/88	Intervention: 6/77 Control: 10/88	N/A	Intervention: 2/77 Control: 2/88
Llach *et al* [25]	2006	RCT	Clindamycin 600 mg and gentamicin 80 mg IM, 1 h before ERCP	Total: 62 Antibiotics: 31	Intervention: 2/31 Control: 2/30	Intervention: 1/31 Control: 1/31	N/A	Intervention: 0/31 Control: 0/30	Intervention: 0/31 Control: 0/30

Control: 31

3/d: Three times a day; ERCP: Endoscopic retrograde cholangiopancreatography; IM: Intramuscular; IV: Intravenous; N/A: Not available; RCT: Randomized controlled trial.

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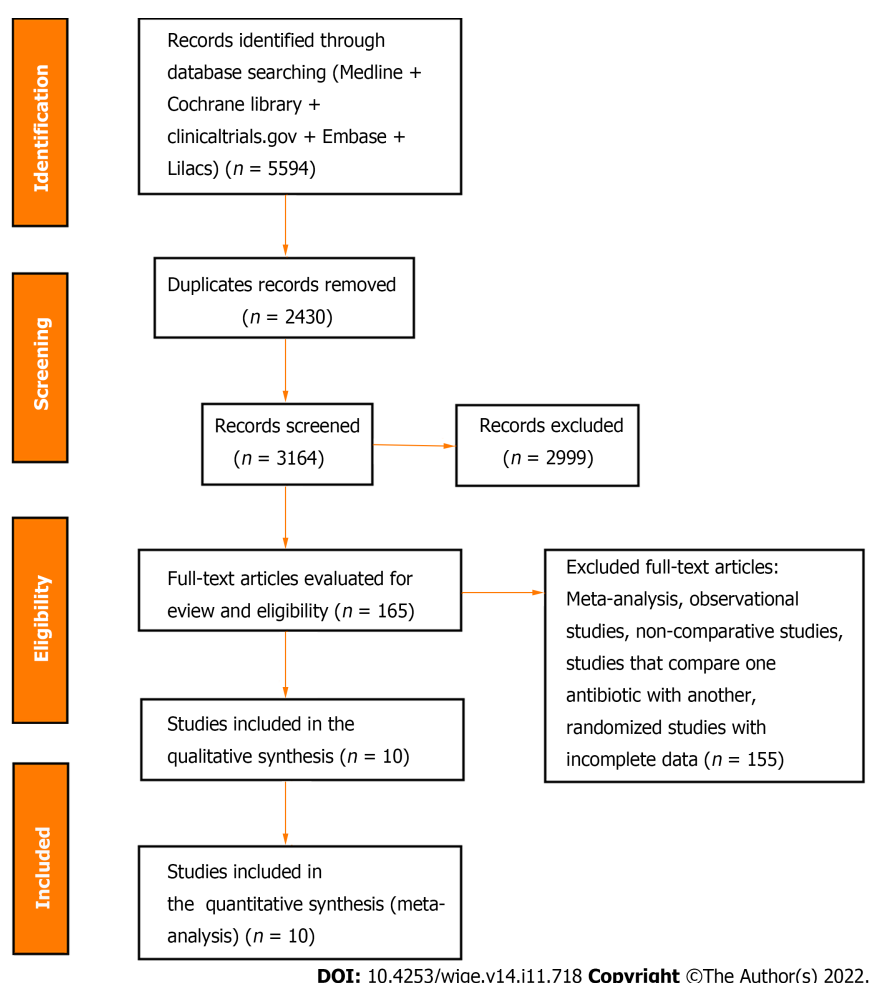
Figure 1 Flow diagram showing the article selection process.

indiscriminate use of antibiotics has the potential to increase bacterial resistance and lead to the emergence of multiresistant germs[31]. Antimicrobial drug resistance is a global health problem that causes a high impact and inflicts an enormous economic burden worldwide. The World Health Organization reported that the ratio of morbidity and mortality rate of diseases due to the spreading of multidrug resistant strains will lead to a substantial economic loss of approximately 100 trillion US Dollars by 2050[32].

Post-ERCP cholangitis, although infrequent, is a significant concern due to its 3% mortality rate. It is mainly associated with incomplete drainage of the bile ducts, equipment contamination[8], or an immunosuppressed state[4]. Many studies[18-23,25-27] demonstrated that prophylactic antibiotics administered in patients undergoing elective ERCP do not reduce the risk of cholangitis. A prospective study that analyzed antibiotic prophylaxis in patients undergoing elective ERCP published[33] in 2014 with 138 patients who underwent this procedure showed that cholangitis was greater when incomplete biliary drainage was present. They concluded there was no benefit in using prophylactic antibiotics to reduce cholangitis and sepsis in patients with satisfactory biliary drainage. Another retrospective study published in 2008[11], with 11484 patients over 11 years to identify post-ERCP infections, was performed in patients with biliary obstruction and immunosuppression. This study showed that the higher risk of infection was in the group who underwent ERCP after liver transplantation.

Sepsis is a significant cause of morbidity and mortality worldwide[34]. Antibacterial therapy is the cornerstone treatment for infection[35], reducing the risk of septic complications and the length of stay. However, prophylactic use of antibiotic agents is not a consensus in terms of minimizing infection risk after some procedures. In ERCP, the main factor for developing clinically relevant sepsis appears to be biliary obstruction. The presumed mechanism by which obstruction leads to sepsis is increased biliary

Risk of bias domains

Domains
D1: Bias arising from the randomization process.
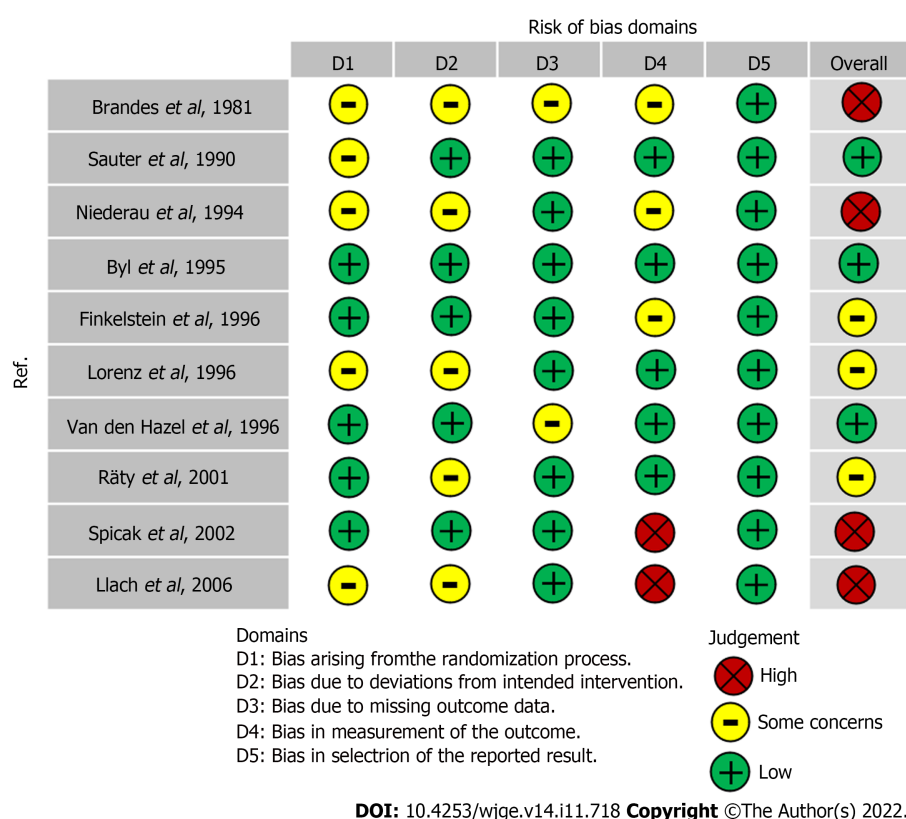D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selectrion of the reported result.

Judgement

❌ High

➖ Some concerns

➕ Low

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Figure 2 Risk of bias according to the ROB-2 tool.

pressure leading to bile-venous reflux. The manner this manifests clinically depends on the content of the bile: whether it contains a contrast medium during ERCP or percutaneous transhepatic cholan-giography[36]. The use of prophylactic antibiotics to prevent bacterial colonization in an unobstructed biliary system is not recommended because bacteria in the bile (bacterobilia) are clinically silent. On the other hand, using prophylactic antibiotics appears to be beneficial for patients with biliary obstruction and known or suspected bacterobilia. Antibiotics should be continued until the obstruction is relieved. In addition, antibiotic prophylaxis to prevent biliary colonization that can lead to systemic sepsis is warranted in particular circumstances of an immunocompromised patient or a patient with primary sclerosing cholangitis[37]. When analyzing specific trials of patients with suspected biliary obstruction [18,19,26], they also showed no significant effect in antibiotic prophylaxis to prevent cholangitis, especially when drainage was effective. The study published in 2007 by Thawee *et al*[38], including patients who underwent complete biliary drainage, showed that antibiotic prophylaxis did not reduce the rate of cholangitis.

Studies[18-22,24,26,27] that used the intravenous route of administration of prophylactic antibiotics found no significant differences in the incidence of cholangitis. The type of antibiotic also did not influence the prevention of infectious complications. It should be noted that many classes of antibiotics were used, so it is not possible to determine which of them may be indicated for antibiotic prophylaxis. Besides, it is important to study the best antibiotic regimen and dosage when indicated, which is still not clear in the current literature.

In the present study, there was no significant difference in the incidence of pancreatitis in patients undergoing ERCP. The most recent study[39] from 2015 demonstrated that antibiotic prophylaxis did not influence the rate of pancreatitis in patients with risk factors such as choledocholithiasis, primary sclerosing cholangitis, and incomplete biliary drainage.

Also, there was no significant difference between the intervention and control groups regarding mortality. In general, mortality rates in the analyzed studies were low. The deaths were related to bleeding from percutaneous transhepatic drainage, cholangitis, severe sepsis, and pancreatic cancer.

Despite this being the largest study on the subject and included only RCTs, our study was not exempt from limitations. Some of the included studies[21,23,25,26] presented a high risk of bias. Also, in some studies[27], some high-risk groups (patients with incomplete biliary drainage) were not excluded when analyzing the results of cholangitis and sepsis. The absence of a homogeneous antibiotic regimen protocol and standardized methods to assess bacterial resistance may also limit the interpretation of the results. Also, the studies included in this meta-analysis are not recent, but this could be explained because during our literature search we found randomized studies that did not reach the estimated sample size of patients and thus were not included for this reason. Others are still under development.

Antibiotic treatment compared to non-antibiotic in patients undergoing ERCP eletive
Bibliography:

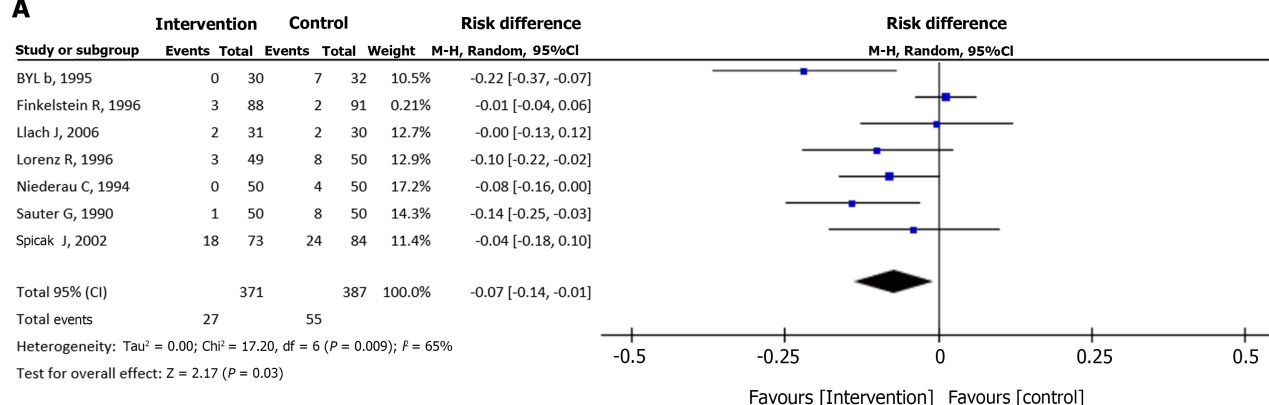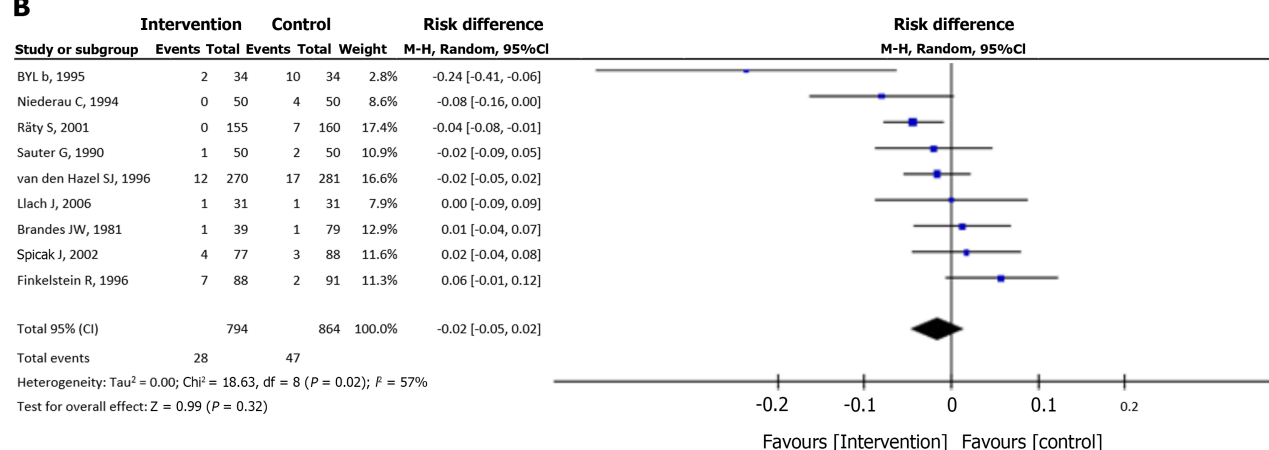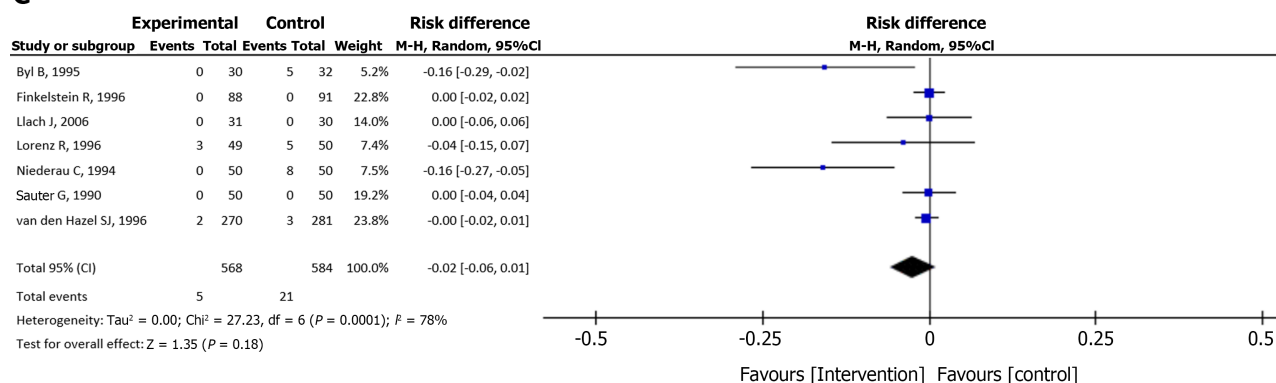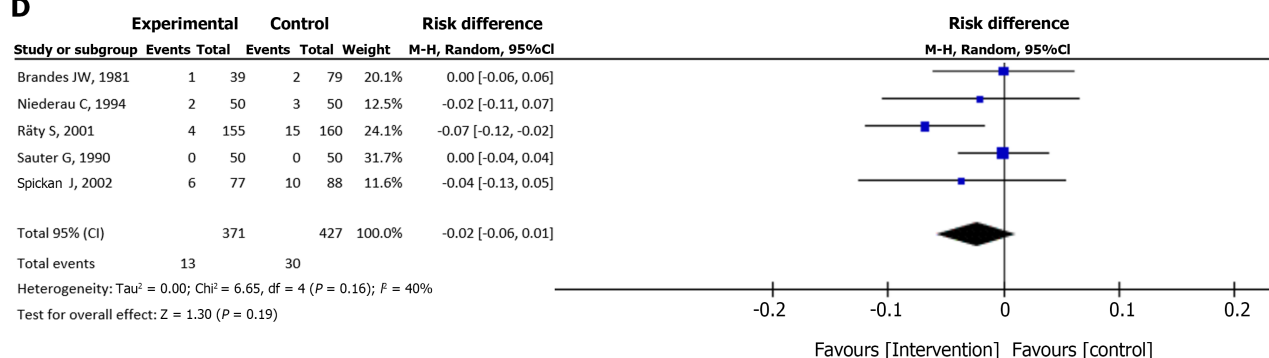| Certainty assessment							Summary of findings				
Participants (studies) follow-up	Risk of bias	Inconsisten-cy	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95%CI)	Anticipated absolute effects	
							With non-antibiotic	With antibiotic treatment		Risk with non-antibiotic	Risk difference with antibiotic treatment
Bacteremia											
758 (7 Rictos)	Serious[1]	Not serious	Not serious	Not serious	None	⊕⊕⊕○ Moderate	55/387 (14.2%)	27/371 (7.3%)	**RR 0.50** (0.23 to 1.08)	142 per 1.000	**70 more per 1.000** (from 10 more to 140 more)
Cholangitis											
1658 (9 RCTs)	Serious[1]	Not serious	Not serious	Not serious	None	⊕⊕⊕○ Moderate	47/864 (5.4%)	28/794 (3.5%)	**RR 0.69** (0.32 to 1.49)	54 per 1.000	**17 fewer per 1.000** (from 37 fewer to 27 more)
Septicemia											
1152 (7 RCTs)	Not serious	Serious[2]	Not serious	Not serious	None	⊕⊕⊕○ Moderate	21/584 (3.6%)	5/568 (0.9%)	**RR 0.35** (0.11 to 1.11)	36 per 1.000	**20 more per 1.000** (from 10 fewer to 60 more)
Pancreatitis											
798 (5 RCTs)	Serious[1]	Not serious	Not serious	Not serious	None	⊕⊕⊕○ Moderate	30/427 (7.0%)	13/371 (3.5%)	**RR 0.51** (0.27 to 0.97)	70 per 1.000	**20 more per 1.000** (from 10 fewer to 60 more)
Suspected biliary obstruction											
838 (3 RCTs)	Not serious	Serious[2]	Not serious	Not serious	None	⊕⊕⊕○ Moderate	27/536 (5.0%)	16/302 (5.3%)	**RR 1.05** (0.18 to 6.14)	50 per 1.000	**20 fewer per 1.000** (from 130 fewer to 80 more)
Effect of intravenous antibiotics on post-ERCP cholangitis											
1540 (8 RCTs)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ High	46/785 (5.9%)	27/755 (3.6%)	**RR 0.64** (0.28 to 1.45)	59 per 1.000	**20 more per 1.000** (from 10 fewer to 50 more)
Mortality											
1638 (9 RCTs)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ High	4/834 (0.5%)	4/804 (0.5%)	**RR 1.19** (0.30 to 4.73)	5 per 1.000	**0 fewer per 1.000** (from 10 fewer to 10 more)

Figure 3 Quality of evidence assessed by Grading Recommendations Assessment, Development, and Evaluation. [1]There was risk of bias in selection of the reported result according to ROB-2; [2]High heterogeneity. CI: Confidence interval; ERCP: Endoscopic retrograde cholangiopancreatography; RCT: Randomized controlled trials; RR: Risk ratio.

However, for our systematic review and meta-analysis, we relied on current clinical guidelines with recommendations on the use of antibiotic prophylaxis as well as references from recent prospective clinical studies that also analyzed its use.

Overall, antibiotic prophylaxis for ERCP reduces the rate of bacteremia without affecting other complications. Bacteremia is defined as the presence of bacteria in the bloodstream[40]. Among hospitalized patients, the incidence of bacteremia is highest within a few days of admission and varies according to clinical and patient characteristics[41]. Bacteremia related to endoscopic procedures can result in local infections due to contamination of "sterile" bile ducts by an endoscopic accessory and contrast material[42]. Patients undergoing ERCP may develop infectious complications depending on their comorbidities, especially in those in whom immunity is compromised and in patients with incomplete biliary drainage. In these patients, the use of prophylactic antibiotics is recommended. Appropriate use of antibiotics will reduce hospitalization time, health care costs, and the risk of mortality. On the other hand, the indiscriminate and inappropriate use of antibiotics is of concern, and bacterial resistance has become an increasing challenge. Also, the profile of procedure-related pathogens has evolved in recent years and multidrug resistant organisms have been reported[42]. Therefore, appropriate and timely selection of empiric antimicrobial treatment has become difficult. The clinical relevance and bacterial resistance should be weighed before routinely using antibiotic prophylaxis for ERCP. Considering the findings of our meta-analysis and in agreement with previous studies[29,30], the recommendation to not use antibiotic prophylaxis is maintained.

CONCLUSION

Prophylactic antibiotics reduce the rate of bacteremia in patients undergoing elective ERCP. However, its use does not have an impact on other associated complications such as cholangitis, septicemia, pancreatitis, and mortality.

A

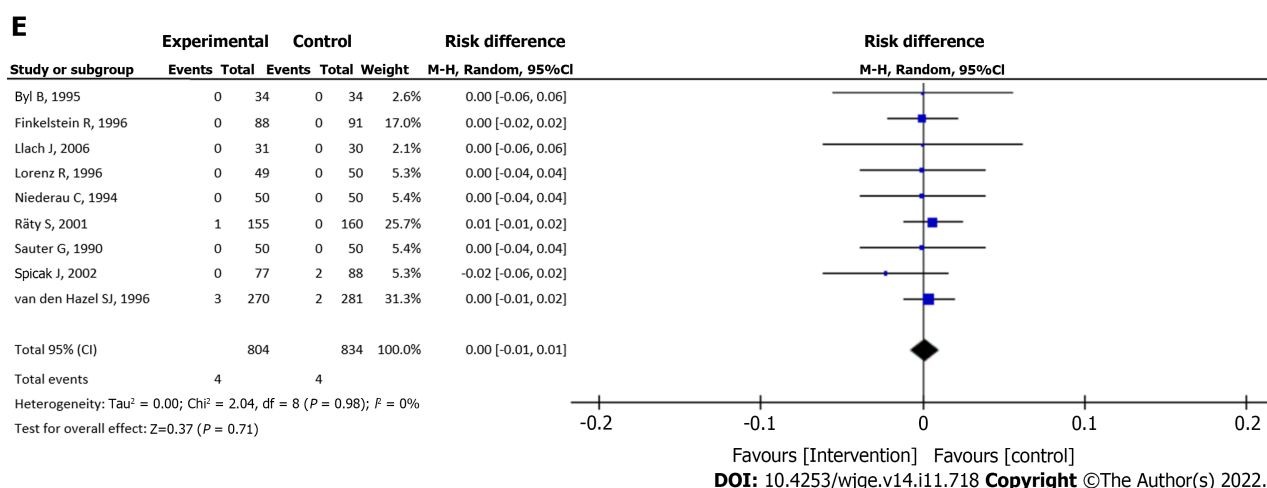| Study or subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk difference M-H, Random, 95%CI
BYL b, 1995	0	30	7	32	10.5%	-0.22 [-0.37, -0.07]
Finkelstein R, 1996	3	88	2	91	0.21%	-0.01 [-0.04, 0.06]
Llach J, 2006	2	31	2	30	12.7%	-0.00 [-0.13, 0.12]
Lorenz R, 1996	3	49	8	50	12.9%	-0.10 [-0.22, -0.02]
Niederau C, 1994	0	50	4	50	17.2%	-0.08 [-0.16, 0.00]
Sauter G, 1990	1	50	8	50	14.3%	-0.14 [-0.25, -0.03]
Spicak J, 2002	18	73	24	84	11.4%	-0.04 [-0.18, 0.10]
Total 95% (CI)		371		387	100.0%	-0.07 [-0.14, -0.01]
Total events	27		55			

Heterogeneity: Tau^2 = 0.00; Chi^2 = 17.20, df = 6 (P = 0.009); I^2 = 65%
Test for overall effect: Z = 2.17 (P = 0.03)

Favours [Intervention] Favours [control]

B

Study or subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk difference M-H, Random, 95%CI
BYL b, 1995	2	34	10	34	2.8%	-0.24 [-0.41, -0.06]
Niederau C, 1994	0	50	4	50	8.6%	-0.08 [-0.16, 0.00]
Räty S, 2001	0	155	7	160	17.4%	-0.04 [-0.08, -0.01]
Sauter G, 1990	1	50	2	50	10.9%	-0.02 [-0.09, 0.05]
van den Hazel SJ, 1996	12	270	17	281	16.6%	-0.02 [-0.05, 0.02]
Llach J, 2006	1	31	1	31	7.9%	0.00 [-0.09, 0.09]
Brandes JW, 1981	1	39	1	79	12.9%	0.01 [-0.04, 0.07]
Spicak J, 2002	4	77	3	88	11.6%	0.02 [-0.04, 0.08]
Finkelstein R, 1996	7	88	2	91	11.3%	0.06 [-0.01, 0.12]
Total 95% (CI)		794		864	100.0%	-0.02 [-0.05, 0.02]
Total events	28		47			

Heterogeneity: Tau^2 = 0.00; Chi^2 = 18.63, df = 8 (P = 0.02); I^2 = 57%
Test for overall effect: Z = 0.99 (P = 0.32)

Favours [Intervention] Favours [control]

C

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk difference M-H, Random, 95%CI
Byl B, 1995	0	30	5	32	5.2%	-0.16 [-0.29, -0.02]
Finkelstein R, 1996	0	88	0	91	22.8%	0.00 [-0.02, 0.02]
Llach J, 2006	0	31	0	30	14.0%	0.00 [-0.06, 0.06]
Lorenz R, 1996	3	49	5	50	7.4%	-0.04 [-0.15, 0.07]
Niederau C, 1994	0	50	8	50	7.5%	-0.16 [-0.27, -0.05]
Sauter G, 1990	0	50	0	50	19.2%	0.00 [-0.04, 0.04]
van den Hazel SJ, 1996	2	270	3	281	23.8%	-0.00 [-0.02, 0.01]
Total 95% (CI)		568		584	100.0%	-0.02 [-0.06, 0.01]
Total events	5		21			

Heterogeneity: Tau^2 = 0.00; Chi^2 = 27.23, df = 6 (P = 0.0001); I^2 = 78%
Test for overall effect: Z = 1.35 (P = 0.18)

Favours [Intervention] Favours [control]

D

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk difference M-H, Random, 95%CI
Brandes JW, 1981	1	39	2	79	20.1%	0.00 [-0.06, 0.06]
Niederau C, 1994	2	50	3	50	12.5%	-0.02 [-0.11, 0.07]
Räty S, 2001	4	155	15	160	24.1%	-0.07 [-0.12, -0.02]
Sauter G, 1990	0	50	0	50	31.7%	0.00 [-0.04, 0.04]
Spickan J, 2002	6	77	10	88	11.6%	-0.04 [-0.13, 0.05]
Total 95% (CI)		371		427	100.0%	-0.02 [-0.06, 0.01]
Total events	13		30			

Heterogeneity: Tau^2 = 0.00; Chi^2 = 6.65, df = 4 (P = 0.16); I^2 = 40%
Test for overall effect: Z = 1.30 (P = 0.19)

Favours [Intervention] Favours [control]

E

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk difference M-H, Random, 95%CI
Byl B, 1995	0	34	0	34	2.6%	0.00 [-0.06, 0.06]
Finkelstein R, 1996	0	88	0	91	17.0%	0.00 [-0.02, 0.02]
Llach J, 2006	0	31	0	30	2.1%	0.00 [-0.06, 0.06]
Lorenz R, 1996	0	49	0	50	5.3%	0.00 [-0.04, 0.04]
Niederau C, 1994	0	50	0	50	5.4%	0.00 [-0.04, 0.04]
Räty S, 2001	1	155	0	160	25.7%	0.01 [-0.01, 0.02]
Sauter G, 1990	0	50	0	50	5.4%	0.00 [-0.04, 0.04]
Spicak J, 2002	0	77	2	88	5.3%	-0.02 [-0.06, 0.02]
van den Hazel SJ, 1996	3	270	2	281	31.3%	0.00 [-0.01, 0.02]
Total 95% (CI)		804		834	100.0%	0.00 [-0.01, 0.01]
Total events	4		4			

Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.04, df = 8 (P = 0.98); I^2 = 0%
Test for overall effect: Z=0.37 (P = 0.71)

Favours [Intervention]   Favours [control]

Figure 4 Forrest plot studies reporting the rate of bacteremia (A), cholangitis (B), septicemia (C), pancreatitis (D), and mortality (E). CI: Confidence interval.

A

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk difference M-H, Random, 95%CI
Räty S, 2001	0	155	7	160	36.9%	-0.04 [-0.08, -0.01]
Spicak J, 2002	4	77	3	88	33.7%	0.02 [-0.04, 0.08]
van den Hazel SJ, 1996	12	70	17	288	29.4%	0.11 [0.02, 0.20]
Total 95% (CI)		302		536	100.0%	0.02 [-0.08, 0.13]
Total events	16		27			

Heterogeneity: Tau^2 = 0.01; Chi^2 = 17.75, df = 2 (P = 0.0001); I^2 = 89%
Test for overall effect: Z = 0.44 (P = 0.66)

Favours [Intervention]   Favours [control]

B

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk difference M-H, Random, 95%CI
Byl B, 1995	2	34	10	34	3.4%	-0.24 [-0.41, -0.06]
Finkelstein R, 1996	7	88	2	91	13.1%	0.06 [-0.01, 0.12]
Lorenz R, 1996	1	31	1	31	9.3%	0.00 [-0.09, 0.09]
Niederau C, 1994	0	50	4	50	10.1%	-0.08 [-0.16, 0.00]
Räty S, 2001	0	155	7	160	19.4%	-0.04 [-0.08, -0.01]
Sauter G, 1990	1	50	2	50	12.6%	-0.02 [-0.09, 0.05]
Spicak J, 2002	4	77	3	88	13.4%	0.02 [-0.04, 0.08]
van den Hazel SJ, 1996	12	270	17	281	18.7%	-0.02 [-0.05, 0.02]
Total 95% (CI)		755		785	100.0%	0.02 [-0.05, 0.01]
Total events	27		46			

Heterogeneity: Tau^2 = 0.00; Chi^2 = 17.25, df = 7 (P = 0.02); I^2 = 59%
Test for overall effect: Z = 1.15 (P = 0.25)

Favours [Intervention]   Favours [control]

Figure 5 Forrest plot studies reporting the rate of cholangitis in patients with suspected biliary obstruction (A) and on intravenous antibiotic prophylaxis (B). CI: Confidence interval.

ARTICLE HIGHLIGHTS

Research background

The prophylactic use of antibiotics in endoscopic retrograde cholangiopancreatography (ERCP) is controversial. The most common adverse events include bacteremia, cholangitis, and pancreatitis. Although recent guidelines regarding antibiotic prophylaxis for ERCP do not recommend its routine use, the data to support this recommendation is not robust.

Research motivation

Antimicrobial drug resistance is a global health problem that causes a high impact and inflicts an

enormous economic burden worldwide. The World Health Organization reported that the ratio of morbidity and the mortality rate of diseases due to the spreading of multidrug resistant strains will lead to a substantial economic loss by 2050. Due to the lack of data in the literature, we performed a systematic review and meta-analysis to evaluate whether antibiotic prophylaxis impacts the rate of complications related to elective ERCP.

Research objectives

This systematic review and meta-analysis aimed to assess whether antibiotic prophylaxis reduced the rates of complications such as bacteremia, cholangitis, sepsis, pancreatitis, and mortality in patients undergoing elective ERCP.

Research methods

This systematic review and meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines. A comprehensive search of multiple electronic databases was performed only including randomized controlled trials.

Research results

Ten randomized clinical trials with a total of 1757 patients that compared the use of antibiotic and non-antibiotic prophylaxis in patients undergoing elective ERCP were included. There was no significant difference between groups regarding the incidence of cholangitis [risk difference (RD) = -0.02, 95% confidence interval (CI): -0.05 to 0.02, $P = 0.32$], cholangitis in patients with suspected biliary obstruction (RD = 0.02, 95%CI: -0.08 to 0.13, $P = 0.66$), cholangitis on intravenous antibiotic prophylaxis (RD = -0.02, 95%CI: -0.05 to 0.01, $P = 0.25$), septicemia (RD = -0.02, 95%CI: -0.06 to 0.01, $P = 0.25$), pancreatitis (RD = -0.02, 95%CI: -0.06 to 0.01, $P = 0.19$), and all-cause mortality (RD = 0.00, 95%CI: -0.01 to 0.01, $P = 0.71$). However, the antibiotic prophylaxis group presented a 7% risk reduction in the incidence of bacteremia (RD= -0.07, 95%CI: -0.14 to -0.01, $P = 0.03$).

Research conclusions

Considering our findings, antibiotic prophylaxis in patients undergoing elective ERCP reduces the risk of bacteremia. Still, it does not appear to impact the rate of other adverse events.

Research perspectives

Antibiotics are highly prescribed drugs in clinical practice, but they can have adverse effects. Larger randomized controlled trials regarding the use of prophylactic antibiotics on ERCP in specific populations of patients are still warranted.

FOOTNOTES

ORCID number: Maria Fernanda Shinin Merchan 0000-00020713-8518; Diogo Turiani Hourneaux de Moura 0000-0002-7446-0355; Guilherme Henrique Peixoto de Oliveira 0000-0002-1057-2390; Igor Mendonça Proença 0000-0003-0274-038X; Epifanio

Silvino do Monte Junior 0000-0001-7304-8222; Edson Ide 0000-0003-4533-6117; Caroline Moll 0000-0001-8488-4322; Sergio A Sánchez-Luna 0000-0001-6870-2226; Wanderley Marques Bernardo 0000-0002-8597-5207; Eduardo Guimarães Hourneaux de Moura 0000-0003-1215-5731.

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LETTER TO THE EDITOR

Minimally invasive colorectal surgery learning curve

Serafino Vanella, Enrico Coppola Bottazzi, Giancarlo Farese, Rosa Murano, Adele Noviello, Tommaso Palma, Maria Godas, Francesco Crafa

Serafino Vanella, Enrico Coppola Bottazzi, Giancarlo Farese, Rosa Murano, Adele Noviello, Tommaso Palma, Maria Godas, Francesco Crafa, Department of General and Oncology Surgery, A.O.R.N. San Giuseppe Moscati, Avellino 83100, Italy

Corresponding author: Serafino Vanella, MD, PhD, Surgical Oncologist, Department of General and Oncology Surgery, A.O.R.N. San Giuseppe Moscati, Avellino 83100, Italy. nekroma@yahoo.it

Abstract

The learning curve in minimally invasive colorectal surgery is a constant subject of discussion in the literature. Discordant data likely reflects the varying degrees of each surgeon's experience in colorectal, laparoscopic or robotic surgery. Several factors are necessary for a successful minimally invasive colorectal surgery training program, including: Compliance with oncological outcomes; dissection along the embryological planes; constant presence of an expert tutor; periodic discussion of the morbidity and mortality rate; and creation of a dedicated, expert team.

Key Words: Learning curve; Colorectal surgery; Laparoscopy; Robotic surgery; Minimally invasive surgery; Cusum method

Core Tip: Minimally invasive techniques, such as laparoscopy and robotic surgery, are increasingly used in the treatment of colorectal cancer. The learning curve for minimally invasive surgery is not well-defined and subject to several influences. A successful operation depends on the preparation of the surgical team to imagine and contemplate the specific details for each step. The principal objective of treating the pathologic condition through the appropriate extent of resection must be clearly defined.

TO THE EDITOR

We read with interest the article of Perivoliotis *et al*[1] regarding the change point analysis of the learning curve (LC) in laparoscopic colorectal surgery. Hermann Ebbinghaus[2], in 1885, and Theodore Paul Wright[3], in 1936, introduced the term "learning curve" to express the average learning rate for a procedure for the aviation industry. This term is now used extensively, including in laparoscopic colorectal surgery. Proficiency is obtained when predefined variables reach a plateau and results are comparable with those in the literature[4,5]. Multiple parameters define proficiency in laparoscopic colorectal surgery, but the total number of cases required to complete the LC and obtain proficiency is not conclusively known[6,9,11]. Current reports vary between 11 cases to 152 cases[6,9,11-13].

The LC process from learning to competence to mastery has been analyzed by the cumulative summation method. This method does not require a large sample size or grouping. Therefore, it is very practical and precise[14,15]. Reports have shown that the surgeon's experience correlates significantly with the safety and feasibility of laparoscopic colorectal surgery. Case selection is another factor that affects the LC because it has not yet been standardized during training[7].

Oncologic efficacy of the laparoscopic colorectal procedure is a crucial parameter in the assessment of learning. This goal is measured by negative surgical distal and circumferential margins and an adequate number of harvested lymph nodes. However, oncologic efficacy should not be compromised and inappropriate resection is not justified regardless of the stage of the training period[6]. The use of well-structured and standardized intra- and perioperative protocols ensures that all patients can benefit from the advantages of minimally invasive surgery[16-19].

We agree with the authors that a specialized team dedicated to colorectal surgery is important. This team must be composed of surgeons, anesthetists, pathologists and nurses and must be supported by specialists with high levels of expertise in colorectal surgery from the diagnostic step to the perioperative period to the follow-up.

The site of colorectal surgery also has an effect on the LC. We would like to emphasize the difference between the LC of colonic surgery and the LC of rectal surgery, particularly the low rectum. Rectal cancer surgery underwent a major breakthrough with the introduction of the circular stapler in the 1970s that facilitated lower anastomoses[20]. This revolutionary tool has greatly facilitated the preservation of the sphincter. In 1988, Heald[21] described the "holy plane" of rectal surgery, which lead to the realization of the importance of tumor-free circumferential margins. Understanding of the fundamental role of total mesorectal excision (TME) in cancer success has steadily grown to become the standard approach for rectal cancer treatment. It has been 30 years since the introduction of the concepts of TME and tumor-free circumferential resection margins. Numerous surgical technological advances have developed over these three decades, improving the ability to perform surgeries with less invasive measures[22].

Adequate margin resection and specific postoperative morbidity (anastomotic leakage) are critical issues in the care of patients with lower rectal cancer. Morbidity following large bowel anastomosis can impact the hospital course of patients undergoing colon resection. Additionally, anastomotic morbidity is quite often influenced by the distance of the suture line from the anal verge. The double-stapled technique is one of the commonly used methods to construct low colorectal or coloanal anastomosis after low anterior resection of rectal cancer[23].

Anastomotic leak ranges from less than 1% to approximately 25%[24]. It is associated with serious short-term morbidity and mortality and long-term functional compromise. It may also have a negative impact on the oncologic outcomes of colorectal cancer[25,26]. Multiple stapler firings, low tumor location, longer operation time, perioperative blood transfusion and male sex were the most common risk factors of anastomotic leak after the double-stapled technique. Different methods have been devised to improve the outcome of the double-stapled technique, including elimination of dog-ears using sutures, transanal reinforcement of anastomosis, single-stapled transanal transection, transanal pull-through with single-stapling technique, natural orifice intracorporeal anastomosis with extraction of specimen procedure, hand-sewn colonic J pouch and vertical division of the rectum[22,25].

Transanal visual inspection obtained through endoscopy or self-retaining anal retractors may be the only reliable means to assure bowel transection at a proper distance from the distal tumor margin. In 2015, we proposed an original technique of low colorectal anastomosis with transanal control after TME with the removal of the rectal stump suture line avoiding dog-ear formations[27], as described in the TICRANT study[28]. The same technique can be applied to partial mesorectal excision and proximal colorectal anastomosis. The ability to perform low rectal anastomosis with an adequate transanal assessment of distal resection margins, technical adequacy, and transanal repair of any resulting anastomotic defects was a clinical necessity[29-32]. We continue to utilize transanal control after anastomosis fashioning with the reverse air leak test and endoscopic control with fluorescence. These controls are useful because problems can be identified early and repaired intraoperatively, thus reducing the number of complications and ostomies.

Colorectal surgery training programs should also distinguish between colonic surgery and rectal surgery as well as between surgery of the right and left colon. In accordance with what the authors wrote, complete mesocolic excision follows the principles of TME with central vascular ligation and dissection along the embryological planes[33].

Over the past 30 years, there have been tremendous innovations in minimally invasive colorectal surgery with countless new technologies and approaches[34,35]. Numerous studies have confirmed that laparoscopic surgery is equal to or superior to open surgery. Further studies have focused on single incision, transluminal endoscopic surgery of the natural orifice and most recently on robotic surgery[36, 37]. The comparison between the LCs of laparoscopic and robotic colorectal surgery is still under investigation.

A shorter LC in robotic colorectal surgery compared to laparoscopic surgery has been reported. A plateau has been reached after 15-25 cases[12,38]. This is likely due to reducing the differences between laparoscopy and robotics. In our center, we use a robotic approach in colorectal and low rectal cancer surgery. Robotic surgery appears to be less invasive due to three-dimensional vision and better visualization of the anatomical structures; the EndoWrist® (Intuitive, Sunnyvale, CA, United States) allows accurate movements in confined spaces and other intrinsic characteristics of the robotic platform[13,39-42].

For experienced laparoscopists, the LC of robotic surgery seems to be shorter[43]. Flynn *et al*[44] showed that operating times for robotic surgery might be faster than laparoscopy when surgeons are inexperienced with both platforms. This may be related to a superior baseline performance rather than a shorter LC. A selection of the most suitable patients can help surgeons in the early stages of training. A small primary tumor, no previous adjuvant chemoradiotherapy, appropriate body mass index, and few medical comorbidities are ideal characteristics for robotic surgery[45].

In the early stages of learning there are still many difficulties, despite the numerous advantages of the da Vinci robot: Preoperative times are longer; the freedom of movement of the robotic arms during the operation is limited by the relatively fixed angle and position; and the lack of force feedback from the robotic arm, which limits the sensitivity of the operator who must judge the effect of pulling and cutting by sight[46-49]. Of note, the rates of disease-free survival and overall survival on a small sample size were similar for robotic and laparoscopic surgery[50].

All innovative techniques with clinical advantages will also have disadvantages when compared to established methods. The key is continued refinement and modification by masters of the craft. More extensive comparative studies are needed to give definitive conclusions regarding the LC in minimally invasive colorectal surgery. Regardless of the approach used, dissection along the embryological planes, correct knowledge of the anatomical and vascularization variants, respect for oncological outcomes, regular tutoring, variation of the surgical approach based on the results, and a dedicated team are essential prerequisites for a colorectal surgery training program.

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FOOTNOTES

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ORCID number: Serafino Vanella 0000-0002-6599-8225; Maria Godas 0000-0002-3777-5788; Francesco Crafa 0000-0002-2038-625X.

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CORRECTION

Correction to "Laparoscopy-assisted resection of colorectal cancer with situs inversus totalis: A case report and literature review"

Wei Chen, Jing-Lin Liang, Jun-Wen Ye, Yan-Xin Luo, Mei-Jin Huang

Wei Chen, Jing-Lin Liang, Jun-Wen Ye, Yan-Xin Luo, Mei-Jin Huang, Department of Colorectal Surgery, The Six Affiliated Hospital, Sun Yat-sen University, Guangzhou 510655, Guangdong Province, China

Corresponding author: Mei-Jin Huang, PhD, Academic Fellow, Doctor, Department of Colorectal Surgery, The Six Affiliated Hospital, Sun Yat-sen University, No. 26 Yuancun Er Heng Road, Guangzhou 510655, Guangdong Province, China. 13924073322@139.com

Abstract

Correction to "Laparoscopy-assisted resection of colorectal cancer with situs inversus totalis: A case report and literature review" *World J Gastrointest Endosc* 2020; 12: 310-316. In this article, we have replaced the previous TNM stage of colorectal cancer (T4aN0M0) and the revised TNM stage is provided (T4aN1cM1c).

Key Words: Colorectal cancer; Situs inversus totalis; Hyperthermic intraperitoneal chemotherapy; Case report; Correction

Core Tip: This is a correction to "Laparoscopy-assisted resection of colorectal cancer with situs inversus totalis: A case report and literature review" *World J Gastrointest Endosc* 2020; 12: 310-316. In this article, the previous TNM stage of colorectal cancer is T4aN0M0, which has been replaced by the revised TNM stage (T4aN1cM1c).

TO THE EDITOR

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Correction to "Laparoscopy-assisted resection of colorectal cancer with situs inversus totalis: A case report and literature review"[1]"(ID: Manuscript NO. 77875, Correction). Those comments are all valuable and very helpful for our paper.

The previous TNM stage of colorectal cancer is T4aN0M0, which has been replaced by the revised TNM stage (T4aN1cM1c). Since the specific number of versions of tumor staging was not indicated in our previous text, the staging of the tumor was different from the latest one. Therefore, we would like to modify the postoperative staging of tumors, which should be T4aN1cM1c.

FOOTNOTES

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