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WJGE mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal endoscopy and covering a wide range of topics including capsule endoscopy, colonoscopy, double-balloon enteroscopy, duodenoscopy, endoscopic retrograde cholangiopancreatography, endosonography, esophagoscopy, gastrointestinal endoscopy, gastroscopy, laparoscopy, natural orifice endoscopic surgery, proctoscopy, and sigmoidoscopy.

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EDITORIAL

How to establish an endoscopic bariatric practice

Daniel B Maselli, Lauren L Donnangelo, Brian Coan, Christopher E McGowan

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Abstract

Obesity is a chronic, progressive, and relapsing disease of excess adiposity that contributes to more than two hundred medical conditions and is projected to affect more than half the adult population of the United States by the year 2030. Given the limited penetrance of traditional bariatric surgery, as well as the cost and adherence barriers to anti-obesity medications, there is growing interest in the rapidly evolving field of endoscopic bariatric therapies (EBTs). EBTs are minimally invasive, same-day, per-oral endoscopic procedures and include endoscopic sleeve gastroplasty, intragastric balloons, and endoscopic bariatric revisional procedures. This field represents an exciting and innovative subspecialty within gastroenterology. However, building a successful endoscopic bariatric practice requires intentional, coordinated, and sustained efforts to overcome the numerous obstacles to entry. Common barriers include acquisition of the technical and cognitive skillset, practice limitations including the availability of nutrition counseling, facility capabilities, direct-to-consumer marketing, and financial pressures such as facility and anesthesia fees. As the highest-volume center for metabolic and bariatric endoscopy in the United States, we provide insights into successfully establishing an endoscopic bariatric program.

Key Words: Obesity; Endoscopic bariatric therapies; Bariatric endoscopy; Endoscopic sleeve gastroplasty; Intragastric balloon; Practice management

Core Tip: In this editorial, we outline and examine the key components of building an endoscopic bariatric program including the endoscopic skillset, the cognitive approach, equipment needs, marketing and financial considerations, program infrastructure, and the practice model.

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INTRODUCTION

Obesity is a chronic, progressive, relapsing, and multifactorial disease[1]. It is characterized by excess adiposity that leads to metabolic and mechanical dysfunction, driving over two hundred weight-related medical conditions[2]. By 2030, nearly one in two adults in the United States will be affected by obesity, which underscores the pressing need for acceptable treatment options[3]. Patients with obesity warrant multiple therapeutic options that can be tailored to their specific needs and risk tolerance. The therapeutic landscape is evolving but still faces certain challenges. Metabolic and bariatric surgery reaches only 1%-2% of the eligible adult population in the United States, primarily due to concerns about invasiveness and risk[4-6]. Incretin-based agents have revolutionized anti-obesity pharmacotherapy but have limitations of cost, tolerability, reliable access, and high probability of weight recurrence following discontinuation[7-10].

Endoscopic bariatric therapies (EBTs) have emerged in the past decade as a viable alternative within the multidisciplinary approach to obesity management, particularly for those seeking a less invasive option than surgery[11,12]. EBTs are minimally-invasive, same-day, per-oral procedures that facilitate clinically meaningful weight loss in adults with obesity. These include primary obesity therapies, including intragastric balloons (IGBs)[13,14] and endoscopic sleeve gastroplasty (ESG)[15,16], as well as revisional therapies for weight return after metabolic and bariatric surgery, such as transoral outlet reduction (TORe)[17,18] and vertical sleeve gastrectomy revision (VSG-R)[19] (Table 1). The commercially available EBTs have been thoroughly presented in recent reviews[20,21]. Existing procedures target gastric restriction, acting through viscerocceptive pathways to enhance satiety and satiation to facilitate weight loss[22-25]. The future of EBT will very likely additionally involve metabolically-oriented small bowel-targeted therapies[26,27].

The metabolic and bariatric endoscopy field (or "endobariatrics") represents an exciting and growing subspecialty of gastroenterology; however, thoughtful, disciplined, and methodical effort is required to build a successful endobariatric program while overcoming the frequent barriers that may arise (Table 2). As the highest-volume center for metabolic and bariatric endoscopy in the United States, we provide insights into this endeavor.

MAIN BODY

The bariatric endoscopist

Nearly every aspect of the gastrointestinal tract has pathology directly or indirectly impacted by obesity[28,29] and endobariatrics transforms the gastroenterologist from bystander to facilitator in improving those pathways. An appeal of EBT is the interplay between complex medical management and highly technical advanced endoscopic procedures. The bariatric endoscopist must be adept in both areas.

The endoscopic skillset centers on endoscopic suturing. Presently, this is conducted using the Overstitch Endoscopic Suturing System (Boston Scientific, Marlborough, MA, United States). For many gastroenterologists, endoscopic suturing represents an entirely new and different skill set. Mastering endoscopic suturing will present the first challenge in pursuing a career in EBTs. With a dearth of formalized fellowships in EBT, a reasonable way to achieve these skills is through precepted/proctored cases with experts and dedicated suturing courses. Existing courses run by device manufacturers and professional societies, including the American Society for Gastrointestinal Endoscopy, offer structured didactic and wet-lab training. After learning the fundamentals of endoscopic suturing, proficiency, in our experience, requires between 30 and 50 cases per procedure type (*e.g.*, ESG, TORe, and VSG-R), consistent with existing literature [30]. In contrast, IGB placement and extraction can be mastered with a significantly more abbreviated training process, given the overlap with fundamental endoscopic skills. Until more formal EBT fellowship programs develop, training and education in EBTs are likely to remain mostly independent and self-driven[31,32].

The cognitive skillsets of a bariatric endoscopist center around knowledge of obesity, its pathogenesis, pathophysiology, and medical management. Given that obesity affects every organ system, with patients frequently carrying concomitant chronic health conditions, we recommend that the gastroenterologist maintain board certification in internal medicine through the American Board of Internal Medicine. Further, we contend that any gastroenterologist seeking to practice endobariatrics to become board-certified by the American Board of Obesity Medicine (ABOM). This step ensures the acquisition of foundational and specialized knowledge in obesity as a chronic disease state and helps ensure well-rounded, holistic patient care beyond the performance of a procedure. The ABOM curriculum also addresses weight stigma and bias, which is regrettably rampant in medicine and should be well-understood by physicians and procedur-

Table 1 Current commercially-available endoscopic bariatric therapies within the United States

Endoscopic bariatric therapies
Food and Drug Administration authorized
ESG with Apollo ESG™
Transoral outlet reduction with Apollo revise™
Orbera® intragastric balloon
Spatz3 intragastric balloon
Off-label or experimental procedures
Endoscopic gastroplasty with Endomina®*
Primary obesity surgery endoluminal 2.0 procedure with incisionless operating platform®*
Endoscopic revision of vertical sleeve gastrectomy (with Apollo OverStitch™, Endomina®, or the incisionless operating platform®)

ESG: Endoscopic sleeve gastroplasty.

Table 2 Common barriers to establishing an endoscopic bariatric therapy program

Common barriers
Lack of practice, administration, departmental, or partner support
Endoscopist skillset, specifically endoscopic suturing
Facility limitations, particularly the need for general anesthesia capability
Cost-prohibitive facility fees
Difficulty establishing a cash-pay model
Need for nutrition support
Inadequate marketing (limited patient awareness)
Poor patient intake process
External pressures (anti-obesity medication growth and competitive forces)

alists practicing obesity medicine in any form[33,34].

It is incumbent on the bariatric endoscopist to rigorously track outcomes longitudinally for patients undergoing EBTs, including both safety and efficacy data. These should satisfy, at a minimum, the expert consensus thresholds for clinical adoption of EBT: a serious adverse event rate < 5% and an excess weight loss (EWL) exceeding 25%[12]. While EBTs are safely performed at higher ranges of body mass index (BMI)[15,17,35], it is more commonly performed in class I and II obesity. At this BMI range, EWL may outpace total body weight loss (TBWL); therefore, we recommend tracking TBWL and targeting > 10% TBWL at one year, as this threshold is associated with substantial improvement in obesity-related comorbidities and mortality[36,37]. For a high-volume center, this degree of weight loss is readily achievable with ESG [15,16,38], TORe[17] and VSG-R[19].

While increased physician skillset and longitudinal follow-up can augment the likelihood of sustained success, patients undergoing EBT are not immune from non-response, weight loss plateau, and weight recurrence[39]. The bariatric endoscopist must be comfortable with this reality, the attendant patient dissatisfaction associated with these outcomes in a self-pay model, and the appropriate management steps. ABOM certification can increase one's ability to recognize contributing medical and behavioral factors and discuss and manage anti-obesity medications. Repeat suturing (for ESG) [40], conversion to ESG (after IGB)[41], and repeat ablation and/or suturing (for TORe)[17,42] are all feasible in these circumstances for the bariatric endoscopist comfortable with such techniques; however, this does present challenges with how to select candidates judiciously based on initial success and their willingness to adhere to strict nutritional follow up [40,41]. Finally, conversion from restrictive gastric EBTs to metabolic and bariatric surgeries is also an option, underscoring the importance of maintaining strong working relationships with bariatric surgeons as part of the multidisciplinary care model for obesity[43,44].

The endobariatric patient

Demographically, patients seeking EBTs resemble those who seek traditional metabolic and bariatric surgery. In a survey of 101 consecutive adults seeking ESG or IGB at our center, nearly 9 in 10 were women, the mean age was 43.2 ± 9.7 years, the mean BMI was 38.8 ± 5.6 kg/m^2, and 76.2% had at least one obesity-associated medical problem[11]. The respondents'

Table 3 Key components of an endoscopic bariatric therapy program

Key components
Medical personnel
Bariatric endoscopist with obesity medicine certification and sufficient procedural training
Advanced practice provider(s)
Longitudinal nutrition support
Licensed and registered dietitian(s)
Certified health and wellness coach(es)
Patient intake coordinator(s)
Marketing support
Facilities
General anesthesia capability
Experienced pre-op and recovery nurses
Anesthesiologist/anesthetists skilled in managing patients with obesity
Endoscopy technician

weight loss history was also instructive: 63.7% had attempted weight loss ten or more times, 66.3% had used commercial weight loss programs, 66.3% had used over-the-counter weight loss drugs, and 70.3% had used prescription anti-obesity medications. These observations underscore the intractable, chronic, and relapsing nature of obesity, the distressing effects it can have on both health and well-being, and the compassion and understanding that bariatric endoscopists must have to meet patients where they are.

This survey also revealed the importance of a thorough consultation with an experienced medical professional to provide patients with realistic expectations of EBT. Patients may overestimate the weight loss outcomes of EBT treatments, with nearly two-thirds believing they are as effective as traditional bariatric surgery, a view that is not supported by the literature[15,45,46]. Additionally, patients may underestimate risk, with approximately half of respondents failing to recognize that EBTs could induce serious adverse events. Thus, in our practice, about half of the duration of a consult is spent systematically disclosing the technical aspects, benefits, risks, recovery, and alternatives to EBT therapy. These are then provided in detail in a written consent form that patients review and sign before procedure day.

The practice model

Incorporation of EBT into the gastroenterologist's practice may be dictated by the existing practice structure. Reasonable approaches include the mixed practice of general gastroenterology and EBTs (perhaps suited for ambulatory private practices) or interventional endoscopy (common in academic/hospital-affiliated centers). Alternatively, the "all in" approach entirely focuses on EBT at the exclusion of other routine endoscopic procedures. We favor the all-in approach as this facilitates a high-volume clinical practice and allows the physician to focus on the medical management of obesity. However, this approach may be impractical or financially unfeasible until one's practice is well established. Notably, the gastroenterologist should avoid the temptation to "dabble" in EBTs, which may pose diminished efficacy and heightened risk to patients due to inconsistent experience, harming both the patient and the field of EBT.

Regardless of practice type, universal features should be consistent across venues (Table 3). At a minimum, these ought to include: (1) ABOM-certified physician(s) to provide a comprehensive approach to obesity management; (2) consistent volume of EBTs to ensure safety and efficacy; and (3) longitudinal support with a nutrition team[47]. Finally, while safe, EBTs do have rare but serious risks, including gastrointestinal bleeding, which may require emergent endoscopic intervention, as well as interventions that a gastroenterologist cannot typically manage alone—such as a gastric leak, intraabdominal abscess, or perforation—and the need for these services should influence whether EBT can be responsibly offered in the context of any particular call system and practice model[48,49]. While complications from suture-based EBTs are rare beyond the first three weeks from the procedure, IGBs may present with adverse events (*e.g.*, ulceration, gastrointestinal bleeding, hyperinflation, migration with small bowel obstruction, and viscus perforation) at any point during the dwell time; we therefore recommend that centers offering IGBs have unfettered direct access to an on-call physician who can help triage concerning signs of symptoms[13,46,50,51].

Equipment

EBT is a dynamic, rapidly evolving field, and equipment needs will evolve. For now, most endoscopic suturing procedures are performed using the OverStitch™ or OverStitch SX™ Endoscopic Suturing Systems (Boston Scientific, Marlborough, MA, United States). The former is compatible with specific dual-channel endoscopes, and the latter is compatible with single-channel endoscopes. For optimal performance of the TORe procedure, argon plasma coagulation is necessary for ablation of the gastrojejunal anastomosis prior to suturing. Additional EBT-specific equipment

Table 4 Equipment commonly used in endoscopic bariatric therapy

Equipment commonly used
Required
Dual-channel endoscope(s) or single-channel gastroscope(s) (if using OverStitch SX™)
Carbon dioxide insufflator
Argon plasma coagulation
Endoscopic scissors
Hemostatic clips for control of intraprocedural bleeding
Endoscopic retrieval net (for removal of foreign bodies or large clots)
Through-the-scope esophageal balloons (for transoral outlet reduction and subsequent dilations of stenotic outlets if needed)
Grasping forceps (for foreign body removal or suturing assistance)
Optional but recommended
Endoscopic overtube
Hemostatic powder or similar agent (*e.g.*, Hemospray®, PuraStat®)
Infiltration pump for intragastric balloon insertion
Sequential compression devices for venous thromboembolism prevention

requirements are listed in Table 4.

While no current Food and Drug Administration-authorized procedure requires fluoroscopy, the evolution of EBT to target the metabolically-enriched region of the small intestine suggests that the bariatric endoscopist should reasonably consider fluoroscopic capabilities as an advantage in the coming years[26,52].

Program infrastructure

In the abovementioned survey study of patients seeking EBTs at our center, the properties of an endobariatric practice that respondents deemed "very important" included physician experience (81.2% of respondents), ease of communication with the facility (74.3%), trust in medical staff (73.3%), quality of nutritional support (67.3%), the online reputation of the facility (67.3%), quality of psychological support (58.4%), self-pay price (52.4%), and wait time to procedure (45.5%)[11]. Emerging EBT programs can use these priorities as a rubric for successful patient recruitment and retention.

The patient intake model will be distinct from traditional gastroenterology and surgical centers, primarily due to the self-pay nature of EBT and the current lack of medical provider familiarity with the field[52]. The largely self-referral, self-pay model demands a more tailored level of service from team members who are personable, available, and skilled, as patients often require multiple touchpoints and significant time investment from their initial point of contact to their procedure day, regardless of practice setting. To facilitate the consultation process, this may require additional and intensive medical training of employees without medical background such that patients can be: (1) Appropriately screened for the correct procedure(s); (2) appropriately screened out for absolute contraindications; and (3) provided a basic overview of EBT procedures, as many patients may lack familiarity with the specialty. Beyond managing intake, scheduling, and financing, these team members also facilitate pre-procedural steps, including bloodwork, organization of peri-procedural medications, and subspecialty evaluations/clearances when needed for comorbid disease.

The initial patient consultation can be conducted with the bariatric endoscopist or an advanced practice provider. It should focus on the patient's medical, surgical, and social history, with emphasis on their history of obesity and prior weight loss endeavors, as well as concomitant issues that can impact and potentially contraindicate EBT, which are similar to those of metabolic and bariatric surgery, such as disordered eating, substance use disorders, untreated mood/psychiatric disorders, and significant end-organ dysfunction[53]. The technical aspects, benefits, risks, recovery, and logistical components of the EBT of interest should be discussed, as well as alternative options (other EBTs, anti-obesity medications, and metabolic and bariatric surgery, when appropriate). The need for behavioral change and longitudinal follow-up should be emphasized, as well as realistic expectations for the degree and trajectory of weight loss. Our published experience showed that patients tend to overestimate weight loss and underestimate risk prior to consultation with an EBT provider[42].

The procedure-day clinical care team should involve a bariatric endoscopist, registered nurses (pre-procedure intake nurse, circulating nurse, recovery nurse), an anesthesia provider, and an endoscopy technician. Additional staff may be needed to coordinate patient arrivals/departures and to clean endoscopes. After the procedure, medical follow-up can be balanced between the bariatric endoscopist and advanced practice providers to monitor patients' recovery during the early post-procedural course and for non-response, weight loss plateaus, or weight recurrence over the long term.

As emphasized above, we believe registered dieticians are mandatory members of an EBT practice[54]. Obesity is a chronic, progressive, multifactorial, relapsing condition, and any intervention aimed at weight loss should be offered and supported in conjunction with longitudinal aftercare focused on behavior change[1]. While many gastroenterologists

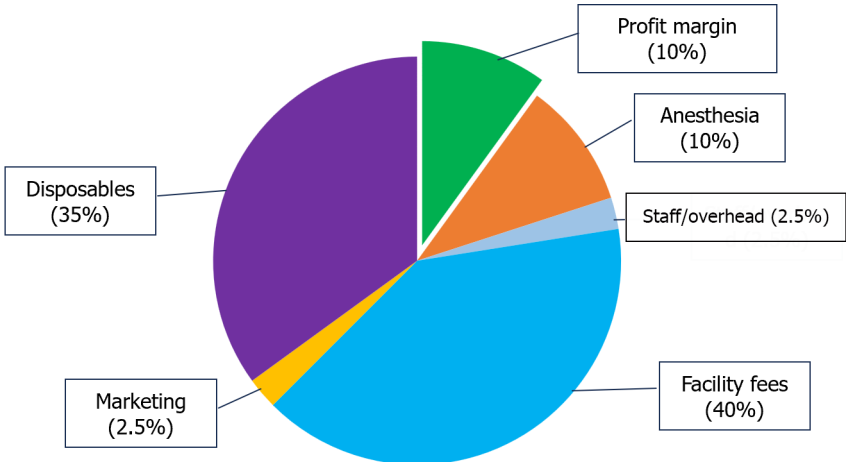

Figure 1 Estimated per-procedure cost breakdown in endoscopic bariatric therapy.

have experience with nutrition, dieticians bring an additional, practical skillset that goes beyond understanding physiology to help patients enact meaningful lifestyle changes. In a study of 284 patients undergoing TORe at our practice, the strongest predictor of weight loss at one year, out of a variety of procedural, patient, and practice components, was the number of follow-up visits the patient attended[17]. Registered dieticians can be integrated into a practice through virtual outsourcing, local outsourcing (*e.g.*, hospital nutrition department), or internal hiring. While these appear in order of increasing difficulty to arrange, their long-term cost decreases, volume permitting. We recommend that all patients considering undergoing an EBT meet with a dietician individually to review expectations of modified diets that follow the procedure to facilitate tissue healing, as well as to provide additional methods of screening for relevant elements of a patient's history that may impact their recovery and weight loss, such as concomitant disordered eating or alcohol use disorder.

Marketing and financial considerations

The self-pay nature of EBT and the existing lack of familiarity with EBT within the medical field[52] make marketing a critical and challenging aspect of an EBT program. Referrals from other medical professionals tend to be lower yield than in traditional gastroenterology practice, though this may change as provider familiarity increases and insurance coverage for EBT becomes possible. For now, the direct-to-patient approach has proven most fruitful. This should include a dedicated website or program-specific landing page that describes the available procedures and aftercare and heavy investment in social media, Google advertisements, and targeted digital marketing. Traditional marketing with print, signage, or radio may be helpful, but depends on the local market. Marketing may require a significant time and effort commitment from the bariatric endoscopist but is pivotal to building trust and rapport with patients exploring a relatively novel field.

The combination of disposable equipment, marketing, and infrastructure contributes to an EBT program's financial considerations. A significant aspect of cost per procedure is the facility fee and anesthesia costs (general anesthesia capabilities are required for EBT). These must be rigorously negotiated to keep costs low. The sum of these elements for a particular patient—their procedure and aftercare—make the margins in EBT far narrower than one might expect for a self-pay procedure (Figure 1).

CONCLUSION

EBT is an exciting and evolving opportunity for gastroenterologists to care for patients impacted by obesity through both endoscopic and cognitive skills. For the metabolic and bariatric endoscopist, it requires an effortful dedication to specific procedural skills (*e.g.*, full-thickness suturing technique, recognition of anatomy, management of intra-procedural adverse events) to maximize safety and efficacy, as well as a commitment to the cerebral aspects of obesity physiology (*e.g.*, through ABOM certification and continuing obesity education) to ensure patients are receiving comprehensive, longitudinal care. The success of the patient and practice requires the involvement of multiple team members, especially registered dieticians, as well as an engaging, adaptable patient intake team. As the field continues to evolve in reimbursement and toward applications beyond obesity to related comorbidities and novel technologies (*e.g.*, small bowel therapies), the bariatric endoscopist and EBT practice should be prepared to adapt to a rapidly changing landscape.

FOOTNOTES

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EDITORIAL

Colonoscopy in the diagnosis and management of appendiceal disease

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Abstract

In this editorial, we comment on the article published in the recent issue of the *World Journal of Gastrointestinal Endoscopy*. We focused on the understanding of appendiceal disease, and the various options for diagnosis and treatment *via* endoscopy. Some factors affecting the diagnosis and management of appendiceal diseases are also discussed. The existence of any organ has its natural rationality, and the appendix is such a magical organ. A growing number of experts and scholars have gradually come to a consensus that the appendix is not a useless evolutionary relic. There are many lymphocytes and lymph nodes in the appendix wall, which has a strong immune function, and this function is particularly important for children and adolescents. Many intestinal probiotics in the appendix are very helpful for maintaining the balance of the intestinal flora. With the continuous progress of endoscopic technology, endoscopic treatment involving preservation of the appendix has shown great advantages over surgery. In the diagnosis of appendiceal inflammation and neoplasms, colonoscopy, endoscopic retrograde appendicography and choledochoscopy help assess conditions of the appendix. Endoscopic retrograde appendicitis therapy, abscess drainage under colonoscopy, fenestration of abscess under colonoscopy, and endoscopic or natural orifice transluminal endoscopic surgery resection of appendiceal neoplasms are safe and effective endoscopic treatments for appendiceal disease. New breakthroughs in the application of endoscopy in the appendix are expected to occur in the near future.

Key Words: Appendicitis; Appendiceal neoplasms; Colonoscopy; Endoscopic ultrasonography

Core Tip: With the popularization of the concept of minimally invasive surgery and in-depth research on the function of the appendix, methods for preserving the appendix have emerged, and endoscopic diagnosis and treatment of appendiceal diseases have gradually become the first-line treatments. We summarize the current state of colonoscopic management of appendiceal disease, with an emphasis on reconsideration of the function of the appendix and endoscopic treatment. We also put forward our own views on how to improve the diagnosis and treatment of appendiceal diseases.

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INTRODUCTION

In this editorial, we comment on the article published in the recent issue of the *World Journal of Gastrointestinal Endoscopy* by Zhang *et al*[1]. The appendix is a structurally unique organ which should not be ignored[1].The human appendix is a narrow, blind tube with an average length of approximately 9 cm that is located between the cecum and ileum, communicating with the intestinal cavity[2]. It can be detected at 8 wk of gestation, and lymphoid tissue appears at 14 to 15 wk of gestation, begins to develop at 2 wk after birth, and rapidly matures within a few years[3]. The appendix has several important functions, mainly including immune function, maintenance of intestinal microbial homeostasis and coordination between them[4]. An increasing number of studies have shown that the role of the appendix needs to be viewed dialectically. On the one hand, the appendix can be a safe house for the gut microbiome. The excised appendix was found to contain a large number of aerobic and anaerobic bacteria, mainly Escherichia coli and Bacteroides[5]. On the other hand, it can be called the "tonsils" of the abdomen. It is rich in a large amount of lymphoid tissue, which begins to appear after birth and reaches its peak at 12-20 years of age[4]. Because of the abundant lymphoid tissue in the appendix, it can "trap" pathogens in the early stage and then develop inflammation. It is involved in the formation of intestinal IgA-secreting cells[6]. Epidemiological studies have also shown that appendectomy is associated with a variety of diseases, such as inflammatory bowel disease and colon cancer, as well as cardiovascular diseases, bacterial liver abscess and systemic lupus erythematosus[7-10]. Appendiceal inflammation can be divided into acute appendicitis (simple acute appendicitis, acute suppurative appendicitis, gangrenous and perforated appendicitis, and periappendiceal abscess) and chronic appendicitis. Appendiceal neoplasms can be divided into those of epithelial origin (*e.g.*, adenoma or adenocarcinoma) and those of nonepithelial origin (*e.g.*, neuroendocrine tumors or lymphomas)[11,12]. In this editorial, we discuss the current and emerging role of endoscopic management of appendiceal diseases.

Reconsideration of the function of the appendix

The appendix wall consists of the mucosa layer, submucosa layer, muscularis propria layer and serosal layer. The appendix has abundant lymphoid tissue that is rich in germinal centers of B cells, lymphodendritic cells and macrophages. Many plasma cells in the lamina propria of the mucosa can produce IgA and IgB, agglutinate with pathogens, promote phagocytosis by phagocytes, and activate complement. Ig A is the major immunoglobulin in gastrointestinal-associated lymphoid tissues. The secreted immunoglobulin A produced by the appendix plays an important role in repairing colonic biofilms when it is destroyed[4]. Mucosal intraepithelial lymphocytes (IELs) are composed mainly of CD8+ regulatory T cells and M cells and play important roles in the recognition and transport of antigens. IELs are considered to have innate immune response functions and are immune activation areas. In addition, the appendix is rich in natural killer T cells, which rapidly produce cytokines and chemokines after immune activation.

Previous studies have indicated that there are abundant and diverse microbial populations in both inflammatory and noninflammatory appendices. There are abundant intestinal beneficial bacteria in the appendix biofilm. When the intestine loses many beneficial bacteria due to pathogen invasion, the appendix quickly participates in the reconstruction of the intestinal microecology. In 2013, Guinane *et al*[13] conducted the first comprehensive analysis of the human appendiceal microbiota by using 16S rRNA high-throughput sequencing (HTSeq) and reported that the microbial composition was highly diverse with obvious individual differences. The hypothesis that the appendix is a reservoir of beneficial bacteria in the human body was preliminarily verified. Subsequently, more researchers have used 16S rRNA HTSeq to analyze the microbial composition of the appendix in different populations[14,15]. When the body is infected by pathogenic bacteria or antibiotics are applied, resulting in intestinal flora imbalance, diarrhea and other symptoms, the beneficial bacteria in the appendix cavity are released into the intestine to participate in the balanced reconstruction of the intestinal microecology[16].

The appendix is associated with many intestinal diseases. Appendectomy is thought to be a risk factor for recurrent Clostridium difficile infection[5]. However, some researchers hold the opposite view that appendectomy is not associated with recurrent Clostridium difficile infection[17]. The appendix is likely to be a preventive factor for colorectal cancer [18]. The mechanism may be related to the abundance of lymphoid tissue, immune-secreting cells and beneficial intestinal bacteria in the appendix. Appendectomy is closely related to age, the sequence of acute appendicitis and ulcerative colitis (UC)[4,19]. The incidence of UC and UC-related colectomy decreases after appendectomy in patients younger than 20 years without UC. For non-intestinal diseases, the risks of acute myocardial infarction and ischemic heart disease are

related to appendectomy[20,21]. It is possible that the operation changes the function of the immune system, leading to an increased risk of cardiovascular disease. Appendectomy is an independent risk factor for gallstones and drug resistance in patients with biliary tract infections and is closely related to the occurrence of pyogenic liver abscess[22-24]. Recently, large-sample cohort study has indicated that appendectomy increases the risk of autoimmune diseases[25]. There is clearly a correlation between appendectomy and immune inflammation.

Endoscopic diagnosis of appendiceal disease

Endoscopy is helpful in the diagnosis of appendicitis. When considering inflammatory diseases of the appendix, colonoscopy allows direct observation of the opening of the appendix, helps biopsy suspicious lesions and excludes ileocecal inflammation, diverticula or tumors. Currently, endoscopic retrograde appendicography (ERA) helps the appendix located, and indirectly reflects the conditions (stenosis, dilatation, filling defect and perforation) in the lumen of the appendix[26]. In addition, the condition of the lumen of the appendix can be observed directly, and appendix luminal biopsy can be performed *via* choledochoscopy. Endoscopic findings of acute appendicitis include deformation of the appendiceal orifice; varying degrees of congestion, edema, erosion, granularity, brittleness, or irregular shallow ulcers with yellow-white exudate on the surface; repeated stimulation of inflammation, which often leads to abnormal appendiceal contraction and relaxation, and its opening is usually in a state of continuous contraction; and obvious pain in the right lower abdomen when the appendix is touched with biopsy forceps. In addition to obvious congestion and edema at the appendiceal opening, the appendiceal abscess also showed a narrow, deformed and deviated opening, locally protruding into the intestinal cavity in a hemispherical shape and often surrounded by a raised appendiceal crease, resembling a tumor in appearance; moreover, there may be compression of the medial or posterior wall of the cecum.

The traditional diagnosis of appendiceal neoplasms relies mainly on imaging, including abdominal ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI). Current studies suggest that when an appendiceal tumor grows into the intestinal cavity, it has a characteristic colonoscopic appearance, that is, an intraluminal bulge at the opening of the appendix. Low-grade appendiceal mucinous neoplasms generally manifest as hemisphere-like protrusions at the ostium of the appendix, with a good mucosa surface and displacement and occlusion of the ostium of the appendix. Adenocarcinoma of the appendix was characterized by rough, erosive, stiff mucosa at the opening of the appendix and obvious oozing of blood after inflation or during biopsy. Colonoscopy and ultrasound colonoscopy can be used to evaluate the nature of the appendiceal eminence, extent of extraluminal lesions and extent of lymph node involvement before operation. Compared with the traditional diagnostic methods for appendiceal neoplasms, colonoscopy not only detects appendiceal neoplasms at an early stage but also has diagnostic value for low-grade appendiceal mucinous neoplasms and appendiceal adenocarcinoma and is highly helpful in evaluating tumor staging and performing preoperative biopsy[3]. To improve the diagnosis and treatment of appendiceal neoplasms, additional attention should be given to obtaining a detailed history. If the patient presented with chronic right lower abdominal pain that did not disappear after treatment and could not be explained by appendicitis, sufficient attention was given to the patient, and colonoscopy was performed as much as possible. The cecum, the opening of the appendix and the end of the ileum were carefully observed during colonoscopy. Once an abnormal appendiceal opening is found by colonoscopy, biopsy should be performed as much as possible. If conditions permit, ultrasound colonoscopy should be performed.

Endoscopic treatment of appendiceal disease

Endoscopic retrograde appendicitis therapy (ERAT) is a new and minimally invasive alternative method for the diagnosis and treatment of acute appendicitis. Liu *et al*[27] first introduced and implemented the technique in 2012. ERAT was inspired by endoscopic retrograde cholangiopancreatography technology. This novel technique requires direct endoscopic imaging or fluoroscopic ERA to distinguish between suspected acute appendicitis and actual acute appendicitis. For patients with uncomplicated acute appendicitis, ERAT is currently recommended, especially for patients with luminal stenosis and fecalith. The advantages of ERAT include the absence of scarring on the body surface; a reduced incidence of postoperative pain; surgical incision-related complications such as incisional hernia, incisional infection, postoperative peritoneal reaction, intestinal adhesion, and intestinal obstruction; and the preservation of potential physiological function of the appendix.

The appendiceal abscess is a complex appendicitis, which is an abscess or inflammatory mass formed by the exudation of the appendix, the adhesion of the greater omentum and the surrounding intestinal canal. Abscess drainage under colonoscopy and fenestration of abscess under colonoscopy help in the treatment of appendiceal abscess[28]. The advantages of stent drainage for appendiceal abscess treatment include reducing the use of antibiotics and accelerating recovery, causing relatively little trauma, and preserving the potential function of the appendix.

When ERAT or, conservative drug conservative treatment or acute complicated appendicitis such as gangrene and perforated appendicitis, the incidence of serious complications, such as acute diffuse peritonitis and sepsis will increase, and the appendix cannot be preserved, and appendectomy should be performed in time. There are several types of resection: Natural orifice transluminal endoscopic surgery (NOTES), the transgastric approach, the transvaginal approach and the transcaecal approach, and appendectomy under colonoscopy. Most appendiceal neoplasms have no obvious symptoms and can manifest as symptoms and signs of acute or chronic appendicitis. Some larger cases show a mass in the right lower abdomen, which may have been accompanied by intestinal obstruction. The advantages of endoscopic or NOTES resection of appendiceal neoplasms include the absence of scars on the body surface, the presence of minimal trauma, less occurrence of postoperative complications and the significant reduction in the anesthesia burden.

Several factors associate with the diagnosis and management of appendiceal disease

At present, the appendix is recognized to be closely related to immunity and thus related to some autoimmune diseases, although the mechanism has not been fully elucidated. Understanding this point can help us find a breakthrough in diagnosis when encountering atypical appendiceal disease. Combined with targeted biopsy, the diagnosis can be more precise. With the improvements in the endoscopic diagnosis and understanding of appendiceal disease, UC combined with peri-appendiceal inflammation (PAI) is becoming increasingly common. The main endoscopic manifestations of PAI are appendiceal orifice inflammation (AOI) and a peri-appendiceal red patch[29]. Many retrospective and prospective studies have shown that the endoscopic findings of PAI are consistent with those of UC, revealing mucosal granular changes, mucopurulent changes, mucosal bleeding, mucosal friability, erosion or ulceration[30,31]. The local manifestations of the appendix under endoscopy are diverse and need to be distinguished and diagnosed more carefully when combined with pathological biopsy and other technical methods. A case report from Japan suggested that the endoscopic manifestations of UC combined with AOI could be similar to those of lymphoma and that extranodal marginal zone lymphoma was suspected of being gastric mucosa-associated lymphoid tissue lymphoma, with slightly raised reddish lesions and microvascular dilatation but no erosions or ulcerations. However, flow cytometry and pathological analysis led to the diagnosis of UC with AOI[32]. Therefore, when the above atypical manifestations are found under endoscopy, the possibility of an AOI could also be considered.

In the treatment of infectious appendiceal inflammation, antibiotics play an important role. However, self-drug resistance, intestinal microbiome changes, and recurrent appendicitis are inevitable, which poses a problem for the treatment[33,34]. Studies have shown that patients treated with antibiotics for the first time have a recurrence rate of appendicitis of 27.3% within 1 year and 39.1% after 5 years, after which the appendix is removed by surgery[35]. Therefore, how to reduce the long-term recurrence rate of patients during antibiotic treatment is urgently needed. According to the current literature, the recurrence rate of simple acute appendicitis in patients treated with ERAT is lower than that in patients treated with antibiotics within 1 year[27,36], and the combination of ERAT and antibiotics for the treatment of simple acute appendicitis has not been considered. Although this will increase the short-term hospitalization cost, it can accelerate the recovery rate of patients and reduce the length of hospital stay, which is beneficial in the long run. However, additional research is needed to support this evidence.

Due to the low incidence of appendiceal neoplasms, the general early clinical symptoms are atypical, and the misdiagnosis rate is high. Clinicians should pay more attention to patients with suspected appendiceal neoplasms and improve the diagnosis rate so that patients can receive effective treatment as soon as possible. Adequate preoperative evaluation is helpful for determining treatment plan and follow-up strategy. Preoperative serological examination, endoscopic examination, B-ultrasound, CT/MRI and molecular immunological examination provide effective diagnostic methods for clinicians[37,38]. During the operation, surgeons need to be careful to completely remove the tumor tissue during the one-stage operation, avoid destroying the localized tumor and causing abdominal implantation metastasis, and achieve negative surgical margins as much as possible. For patients with other abdominal organ metastases, additional treatment is needed according to the actual situation. Patients who are unable to undergo surgery can also receive palliative chemotherapy according to their condition. Intraoperative frozen sectioning and postoperative routine pathology are helpful for determining the type of tumor. It is worth noting that pathologists need to clearly distinguish the tissue sources of appendiceal tumors and ileocecal tumors to improve diagnostic accuracy. In the course of this disease, it is necessary to improve the perioperative management of patients with appendiceal neoplasms, reduce surgical complications, improve the survival rate, and perform good long-term follow-up to record the prognosis of appendiceal neoplasms.

CONCLUSION

In this editorial, we have summarized the current state of colonoscopic management of appendiceal disease, with an emphasis on the reconsideration of the function of the appendix and endoscopic treatment. Understanding the immune function of the appendix helps us to better understand the impact of appendiceal diseases on the overall function of the body, which also facilitates us to better identify lesions. The combination of current powerful endoscopic or endoscopic ultrasonography methods, as well as pathological and molecular tests, can help us to accurately diagnose the lesions. In the treatment of appendiceal diseases, the patient's constitution and pathological characteristics should be fully considered, and a treatment method involving complete effect, less trauma and a good prognosis should be chosen. We are encouraged by the refinement of techniques for treating appendicitis and appendiceal neoplasms. We hope that more endoscopic research will be devoted to this tiny organ.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Long-term outcomes after endoscopic removal of malignant colorectal polyps: Results from a 10-year cohort

Anna Fábián, Renáta Bor, Béla Vasas, Mónika Szűcs, Tibor Tóth, Zsófia Bősze, Kata Judit Szántó, Péter Bacsur, Anita Bálint, Bernadett Farkas, Klaudia Farkas, Ágnes Milassin, Mariann Rutka, Tamás Resál, Tamás Molnár, Zoltán Szepes

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Abstract

BACKGROUND

Choosing an optimal post-polypectomy management strategy of malignant colorectal polyps is challenging, and evidence regarding a surveillance-only strategy is limited.

AIM

To evaluate long-term outcomes after endoscopic removal of malignant colorectal polyps.

METHODS

A single-center retrospective cohort study was conducted to evaluate outcomes after endoscopic removal of malignant colorectal polyps between 2010 and 2020. Residual disease rate and nodal metastases after secondary surgery and local and distant recurrence rate for those with at least 1 year of follow-up were investigated. Event rates for categorical variables and means for continuous variables with 95% confidence intervals were calculated, and Fisher's exact test and Mann-Whitney test were performed. Potential risk factors of adverse outcomes were

determined with univariate and multivariate logistic regression models.

RESULTS

In total, 135 lesions (mean size: 22.1 mm; location: 42% rectal) from 129 patients (mean age: 67.7 years; 56% male) were enrolled. The proportion of pedunculated and non-pedunculated lesions was similar, with en bloc resection in 82% and 47% of lesions, respectively. Tumor differentiation, distance from resection margins, depth of submucosal invasion, lymphovascular invasion, and budding were reported at 89.6%, 45.2%, 58.5%, 31.9%, and 25.2%, respectively. Residual tumor was found in 10 patients, and nodal metastasis was found in 4 of 41 patients who underwent secondary surgical resection. Univariate analysis identified piecemeal resection as a risk factor for residual malignancy (odds ratio: 1.74; $P = 0.042$). At least 1 year of follow-up was available for 117 lesions from 111 patients (mean follow-up period: 5.59 years). Overall, 54%, 30%, 30%, 11%, and 16% of patients presented at the 1-year, 3-year, 5-year, 7-year, and 9-10-year surveillance examinations. Adverse outcomes occurred in 9.0% (local recurrence and dissemination in 4 patients and 9 patients, respectively), with no difference between patients undergoing secondary surgery and surveillance only.

CONCLUSION

Reporting of histological features and adherence to surveillance colonoscopy needs improvement. Long-term adverse outcome rates might be higher than previously reported, irrespective of whether secondary surgery was performed.

Key Words: Malignant colorectal polyps; T1 tumor; Endoscopic removal; Outcomes; Long-term; Surveillance

Core Tip: Despite recent advancements in endoscopy and the ability to perform optical diagnoses, submucosal invasion in colorectal polyps is often diagnosed at post-polypectomy histological evaluations. The reporting of high-risk histological features cannot serve as the sole basis of optimal post-polypectomy management strategy. Long-term adverse outcomes after endoscopic resection of malignant colorectal polyps might be more common than previously reported, irrespective of whether secondary surgery was performed. Therefore, adherence to post-polypectomy surveillance colonoscopy should be improved.

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INTRODUCTION

Colorectal cancer is the third most frequently diagnosed malignancy and the second leading cause of cancer-related deaths. Hungary is among the countries with the highest global reported incidence rates[1,2]. Introduction of colorectal screening programs results in malignancies being recognized at an earlier stage, and consequently the number of malignant polyps [submucosal invasion (SMI) on histologic examination (pT1 stage according to the TNM classification), independent from lymph node involvement] is rising[3,4]. The prevalence of malignant polyps is estimated to be between 0.75%-5.60% of endoscopically removed polyps in the general population but can be as high as 15.00% in the screening population[3,5,6].

These lesions can appear macroscopically benign, and up to 40% of these lesions are not identifiable with optical macroscopic diagnostic tools[7,8]. Often, invasive adenocarcinoma is revealed by post-polypectomy histological examination. By this time, there is a risk for lymphovascular invasion and metastasis formation due to SMI. Lymph node metastases can occur in 6%-13% of T1 colorectal tumors[9], but the exact rate depends on various endoscopic and histological prognostic factors. The following histological features have been associated with a higher risk of adverse outcomes: Poorly differentiated adenocarcinoma; involvement of resection margins; deep SMI (at least 1 mm); vascular, lymphatic, and perineural invasion; and tumor budding[4,9,10].

The definition of a positive resection margin after polypectomy varies in the literature. Although most guidelines use the 1 mm cutoff value, recently some authors have proposed that resection margins should only be considered positive when tumor cells are found at the cautery line[4,11-13]. The 2023 update of National Comprehensive Cancer Network (NCCN) guidelines recommends surgical resection for both colon and rectum malignancies if one of the following features are present: Fragmented polypectomy sample; unassessable resection margins; or the presence of at least one of the histological prognostic features suggestive of an adverse outcome (lymphovascular invasion, positive resection margin, or tumor budding)[14,15].

Suboptimal reporting of histological features can make the decision-making process over further management strategy (completion surgery *vs* surveillance only) challenging[4,16]. The risk of surgery due to patient age and comorbidities, as well as patient preferences and tumor location, also need to be considered[17]. Evidence of long-term outcomes of a surveillance-only strategy after polypectomy is limited. Currently, there is no consensus on the timing of surveillance colonoscopies and the need for additional cross-section imaging modalities[4].

Therefore, we aimed to evaluate the long-term outcomes of endoscopic removal of malignant colorectal polyps by assessing residual malignancy and lymph node involvement rate after secondary surgery (first endpoint; Figure 1) and local and distant recurrence rate throughout the follow-up period both in cases of secondary surgery and a surveillance-only strategy (second endpoint; Figure 2).

MATERIALS AND METHODS

Study design and ethical considerations

This retrospective cohort study investigated outcomes after endoscopic resection of malignant colorectal polyps resected between January 1, 2010 and December 31, 2020 in the tertiary endoscopic center of University of Szeged. This study was carried out in accordance with the Helsinki Declaration and was approved by the Regional and Institutional Human Medical Biological Research Ethics Committee of University of Szeged (clinical trial registration number: 4137/2018).

Inclusion and exclusion criteria

Lesions were enrolled if the following inclusion criteria applied: (1) No invasive malignancy was suspected with pre-polypectomy examinations (histology, virtual chromoendoscopy, rectal endosonography, if performed); (2) Lesions appeared to be suitable for endoscopic resection based on their macroscopic appearance and adequate lifting sign; (3) Invasive adenocarcinoma was revealed by post-polypectomy histology; and (4) Depth of invasion was limited to the submucosa (T1). Lesions were excluded if polypectomy was not completed due to suspicion of an invasive tumor. Long-term outcomes were only assessed for lesions in cases that had least 1 year of follow-up data available. Patients with inflammatory bowel disease-associated neoplasia as well as those with a clinically suspected or verified polyposis syndrome or hereditary non-polyposis colorectal cancer based on the Amsterdam II criteria were excluded from the analysis. During the study period, tumor testing for microsatellite instability was not routinely available for early-stage colorectal cancer.

Investigated parameters

Demographic data of patients, polyp characteristics [size, location and morphology (pedunculated *vs* non-pedunculated, Paris classification)], method of endoscopic resection, completeness of resection based on endoscopic assessment, and rate of adverse events were collected from the electronic medical record system. Post-polypectomy histological reports were reviewed for the following features considered to be related to high risk of adverse outcomes: Determinability and involvement of resection margins (tumor cells in the cautery line, distance from resection margin reaching 1 mm), absolute depth of SMI (superficial SMI < 1mm, deep SMI ≥ 1 mm), tumor differentiation [low grade (well or moderately differentiated) *vs* high grade (poorly differentiated)], tumor budding (Bd1: 1-4 buds, Bd2: 5-9 buds, Bd3: ≥ 10 buds at the invasion front), and lymphovascular invasion (possibly assessing lymphatic and vascular invasion separately). Reporting of Haggitt and Kikuchi classification was also assessed, but because of their limited determinability due to the common lack of muscular propria in polypectomy specimens, these were not included in quantitative analyses. Tumor markers [carcinoembryonic antigen (CEA) and cancer antigen (CA) 19-9] at the time of endoscopic polyp removal were also assessed as potential predictors of adverse outcomes.

Outcome measures

Patients were divided into two groups according to the post-polypectomy management strategy applied (secondary surgery for completion *vs* surveillance only). The decision between the two strategies was made on tumor board discussions considering post-polypectomy histological results, age, comorbidities, and preferences of patients. The rate of residual malignancy and lymph node involvement was investigated in patients undergoing secondary surgery. Local and distant recurrence during the follow-up period were investigated as adverse outcome measures in cases of both secondary surgery and surveillance-only strategies. Adverse outcome rates were compared between the two strategies to assess the potential risk derived from not having completion surgery after endoscopic resection of malignant polyps.

Definitions

The follow-up period was defined as the time interval between the polypectomy date and the last registered date of a patient visit recorded in the electronic medical record system. Cause of death (if available) was registered for patients who died during the follow-up period. Length of colonoscopic surveillance (*i.e.* last registered colonoscopy date) was also assessed. Clinical data of patients with distant metastases were reviewed searching for other, more advanced malignancies as a potential primary focus of dissemination.

Statistical analysis

Categorical variables were reported as event rates and relative frequencies, and continuous variables as the means with 95% confidence intervals (CI). Fisher's exact test was used to analyze categorical data, whereas the Mann-Whitney test

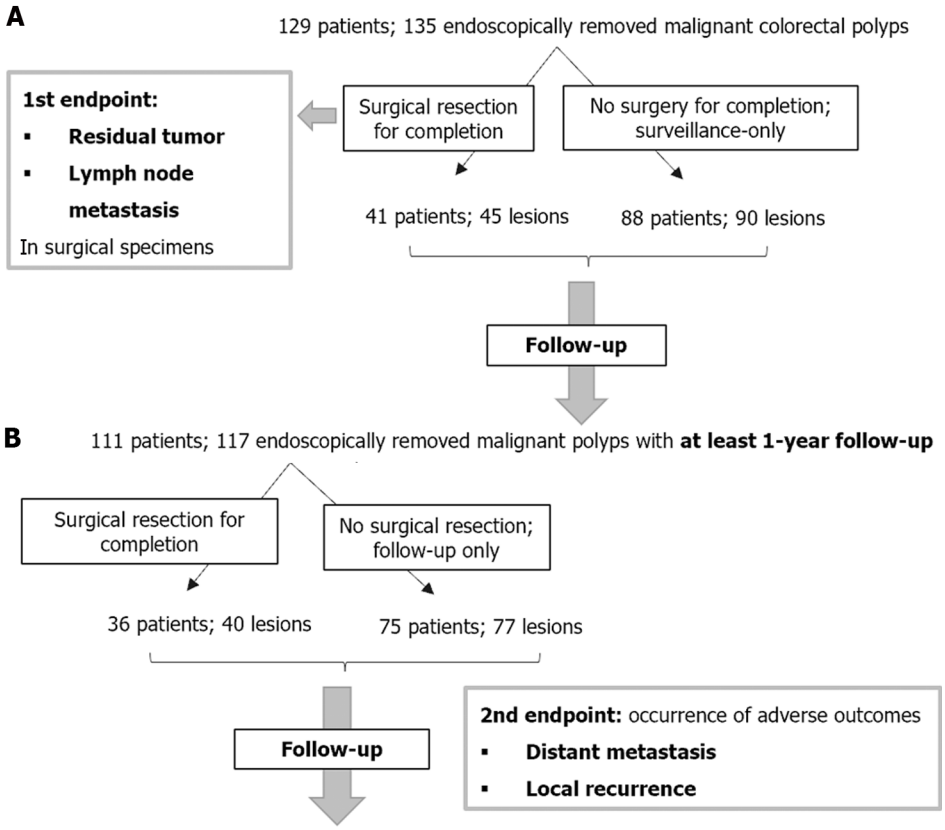

Figure 1 Study design and endpoints. A: First endpoint: residual tumor and lymph node metastasis rate in surgical specimens; B: Second endpoint: occurrence of adverse outcomes during follow-up.

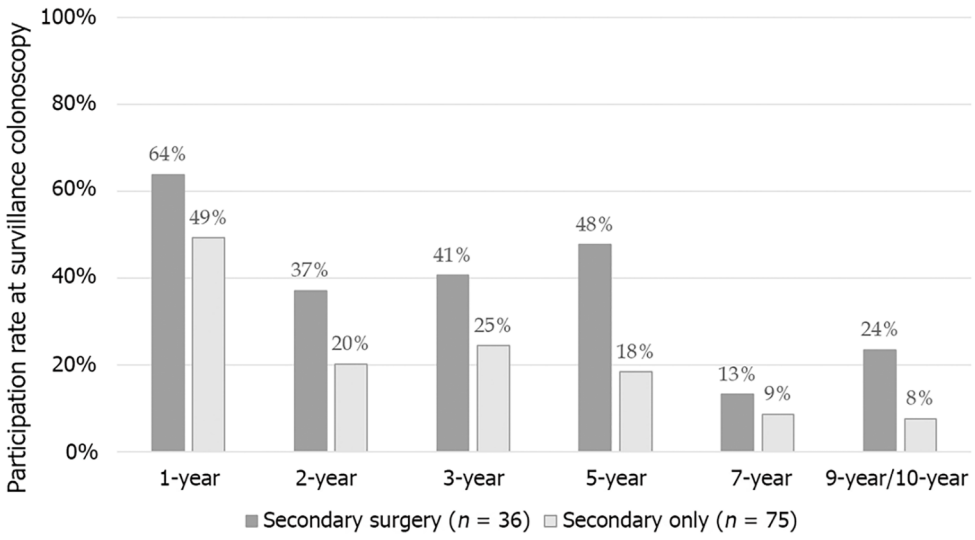

Figure 2 Participation rate at surveillance colonoscopy in the patient groups.

was used in cases of continuous data. Potential risk factors of adverse outcomes were determined with univariate and multivariate logistic regression models. Statistical tests were performed using R statistical software version 3.1.2 (R Foundation, Vienna, Austria) and jamovi software version 2.3.24[18,19]. *P* values < 0.05 were considered significant.

RESULTS

Demographic data, polyp characteristics

In total, 135 endoscopically resected malignant colorectal polyps from 129 patients [age: 67.7 years (95%CI: 66.0–69.4

years); 56% male] were enrolled during the 10-year study period. The proportion of pedunculated and non-pedunculated lesions was similar (48% *vs* 45%). En bloc resection could be achieved in 82% of pedunculated polyps, whereas it was feasible in only 47% of non-pedunculated lesions. Polyp characteristics are summarized in Table 1. Endoscopic polypectomy was performed with snare polypectomy and endoscopic mucosal resection in most of the cases. Endoscopic submucosal dissection (ESD) and endoscopic full-thickness resection were not routinely available in our institution during the study period.

Adverse events occurred in 21 cases (15.6%) and included post-polypectomy bleeding in 14 cases (transfusion was required in 2 cases), perforation in 6 cases (surgical intervention was necessary in 3 cases, the others could be managed by endoscopic closure), and post-polypectomy syndrome requiring antibiotics in 1 case.

Tumor marker values (CEA or CA 19-9) were available for 37 out of the 129 patients at the time of endoscopic polyp removal. CEA and CA 19-9 were elevated in 5 and 3 patients, respectively, and both were elevated in 1 patient. It should be noted that the latter patient also had a synchronous advanced-stage colorectal tumor in addition to the T1 stage malignant colorectal polyp. Elevated tumor marker values did not exceed 2× the upper limit of normal values for CEA and CA 19-9.

Post-polypectomy histologic results

Although endoscopic removal was considered complete based on endoscopic assessment in 87% of the cases, histology revealed complete resection in only 56%. Completeness of resection could not be determined in 26 cases (19%) due to thermal injury of resection margins, tissue fragmentation, or lack of adequate specimen orientation after piecemeal resection.

Throughout the entire study period, high-risk histologic features were adequately reported as follows: Tumor differentiation in 89.6%; tumor distance from resection margins in 45.2%; absolute depth of SMI in 58.5%; Haggitt/Kikuchi classification in 31.9%; lymphovascular invasion in 31.9%; and tumor budding in 25.2%. Reporting of all features (except Haggitt/Kikuchi classification) was adequate in only 26 cases (19%). Only one feature was reported in 36 cases (27%) and no features in 3 cases (2%).

Based on the available data, at least one high-risk histological feature was present in 60 cases (44%). If considering only R1 resection margin cases (tumor cells can be detected at the cautery line) as high risk (as proposed by recent studies[11]), this rate changed to 39% (53 cases). If unassessable resection margins and piecemeal resection were considered high-risk features as well, 77 cases (57%), and 88 cases (65%), respectively, were in the high-risk category.

Rate of residual malignancy and lymph node involvement in patients undergoing secondary surgery (first endpoint)

Secondary surgery was performed for 45 lesions (33.3%) in 41 patients (31.8%) 90 d (95%CI: 22.4–158.9 d) after the polypectomy on average. Overall, 53% of these lesions were located in the rectum and 47% in the colon. At least one high risk feature was present in 82.2% (including unassessable resection margins as high-risk features as well). This percentage increased to 91.1% if piecemeal resection was also considered a high-risk feature according to the most recent NCCN guideline[14,15]. On the other hand, only 48% of lesions (37/77 cases) with at least one high-risk feature (considering unassessable margins as high-risk as well) underwent secondary surgery for completion.

Surgery-related adverse events occurred in 5 cases (12.2%) and included postoperative confusion in 1 case, necessary reoperation in 3 cases because of mechanical occlusion due to adhesions, wound dehiscence, and enterocutaneous fistula, and 1 patient death due to aspiration-induced bronchopneumonia as a consequence of paralytic bowel obstruction. Therefore, surgical mortality was 2.4% in our cohort.

Histological examination of surgically resected specimens revealed residual malignancy in 15 lesions in 10 patients (24.4%) and lymph node involvement in 4 patients (9.8%) [3 of them (6.7%) had residual malignancy as well]. All patients with residual malignancy (in whom endoscopic resection margins were assessable) had tumor cells in the cautery line (R1) after endoscopic resection. In univariate logistic regression analysis, piecemeal resection was found to be a risk factor for residual malignancy [odds ratio (OR): 1.74, $P = 0.042$], but the multivariate model did not confirm this (Tables 2 and 3).

Follow-up

As described above, 45 lesions from 41 patients underwent secondary surgery, and surveillance-only strategy was chosen for the other 90 lesions from 88 patients. However, only 117 lesions from 111 patients had at least 1 year of follow-up data available and were taken into consideration when assessing long-term outcomes. The mean follow-up period for this subgroup was 5.59 years [95%CI: 5.02–6.16 years]. In total, 40 lesions from 36 patients underwent secondary surgery for completion, and surveillance-only strategy was chosen for 77 lesions from 75 patients.

During the follow-up period, participation rates at surveillance colonoscopy showed a gradually decreasing tendency. While 54% of patients presented at the 1-year surveillance colonoscopy, participation rates for 3-year, 5-year, 7-year, and 9-10-year examinations were 30%, 30%, 11%, and 16%, respectively. For each time point, participation rate was determined as the number of patients who underwent surveillance colonoscopy compared to the number of patients for whom follow-up information was available and who were alive. Remarkably, patients undergoing secondary surgery were more likely to participate in surveillance colonoscopies than those with a surveillance-only strategy after polypectomy (Figure 2).

Long-term adverse outcomes (second endpoint)

During the follow-up period, distant metastasis without any other, more advanced malignancy as a potential primary focus was detected in 9 patients (8.1%). Local recurrence was also detected in 3 of these patients and was reported in 1

Table 1 Characteristics of endoscopically removed malignant colorectal polyps, *n* = 135

Characteristic	*n*	Value
Location, *n* (%)		
Colon	80 (59)	
Right colon	12 (9)	
Left colon	68 (50)	
Rectum	55 (41)	
Morphology (Paris classification), *n* (%)		
Pedunculated		
0-Ip	65 (48)	
Non-pedunculated	60 (45)	
0-Is	34 (25)	
0-Isp	3 (2)	
0-IIa	13 (10)	
0-IIb	3 (2)	
0-IIc	7 (5)	
Not available	10 (7)	
Polyp size in mm, mean (95%CI)	22.1 (20.0–24.2)	
Pedunculated	20.7 (18.0–23.4)	$P = 0.004$[1]
Non-pedunculated	24.6 (21.0–28.2)	
***En bloc* resection, *n* (%)**	89 (66)	
Pedunculated	53 (82)	
Non-pedunculated	28 (47)	
Polyp morphology not available	8	

[1]Mann-Whitney test.
CI: Confidence interval.

additional patient without distant metastasis (local recurrence rate: 3.6%). The mean occurrence of local recurrence was 3.98 years (range: 1.84–7.53 years). The total rate of adverse outcomes (dissemination or local recurrence) in the entire study population was 9.0%. Cancer-related deaths were reported in 2 patients; therefore, tumor progression-related mortality rate was 1.8%. There was no significant difference in adverse outcome rates between the two patient groups (*i.e.* secondary surgery *vs* surveillance only) (Table 4).

Non-pedunculated polyp morphology was determined as a risk factor of distant metastases with logistic regression (OR: 2.51, $P = 0.020$), although it was not confirmed by multivariate analysis (Tables 5 and 6). None of the patients with elevated initial tumor marker values presented with adverse outcomes.

Long-term outcomes in view of the current NCCN guideline

It was also investigated how outcomes would have been affected if the need for resection surgery following endoscopic polypectomy during the study period had been assessed according to the current NCCN recommendation[14,15]. Overall, 64% of patients were managed according to the NCCN recommendation (resection surgery or surveillance only). However, of the patients for whom surgical resection was recommended, only 53% underwent resection surgery. No significant difference was observed in adverse event rates between the groups (Table 7).

DISCUSSION

To the best of our knowledge, the results from this single-center, retrospective cohort study are the first data from the Central-European region regarding long-term outcomes of endoscopic removal of malignant colorectal polyps. The relatively longer follow-up period in our study compared to that reported in the majority of previous studies[20-25] and inclusion of only those with at least 1 year of follow-up allowed for adequate assessment of adverse outcomes. Patient selection limited to those with a submucosally invasive malignant polyp was another strength of our study, as inclusion

Table 2 Risk factors for residual malignancy and lymph node involvement detected at secondary surgery: Univariate analysis

Investigated parameter	Residual malignancy		Lymph node involvement	
	OR	*P* value	OR	*P* value
Size	0.05	0.055	0.003	0.936
Location: Rectum	1.10	0.148	1.34	0.268
Morphology: Non-pedunculated	1.74	0.116	17.90	0.995
En bloc resection: No	1.74	0.042	1.10	0.362
Tumor differentiation	NA		NA	
Positive resection margins: Negative-R1	17.60	0.998	17.20	0.998
Positive resection margins: Negative-critical	3.58E-08	1.000	-6.93E-09	1.00
Depth of submucosal invasion: Deep	-1.18	0.227	-0.32	0.773
Lymphatic invasion	2.40	0.173	-17.80	0.997
Vascular invasion	-16.96	0.997	-16.06	0.997
Tumor budding	5.17E-15	1.000	-16.62	0.998

NA: Not available; OR: Odds ratio.

Table 3 Risk factors for residual malignancy and lymph node involvement detected at secondary surgery: Multivariate analysis

Investigated parameter	Residual malignancy		Lymph node involvement	
	OR	*P* value	OR	*P* value
Size	0.04	0.179	-0.02	0.654
Location: Rectum	0.48	0.602	0.82	0.518
Morphology: Non-pedunculated	1.32	0.332	17.45	0.996
En bloc resection: No	0.81	0.409	0.96	0.477
At least one high-risk feature	17.7	0.994	-0.48	1

OR: Odds ratio.

Table 4 Adverse outcome rates in the patient groups, *n* (%)

Feature	Secondary surgery for completion, *n* = 36	Surveillance-only strategy, *n* = 75	*P* value
Adverse outcomes: Dissemination and/or local recurrence	5 (13.9)	5 (6.7)	0.289
Dissemination	5 (13.9)	4 (5.3)	0.147
Local recurrence	2 (5.6)	2 (2.7)	0.594
Both	2 (5.6)	1 (1.3)	
Tumor progression	1 (2.8)	1 (1.3)	0.546

of intramucosal cancer (pTis) might falsely result in more favorable long-term outcomes.

Prepolypectomy identification of SMI in colorectal polyps is often challenging, even with the application of advanced optical diagnostic tools, *e.g.*, virtual chromoendoscopy[7,8]. In the community setting, the availability, feasibility, and minimum standard of advanced imaging use are unknown according to the current European Society of Gastrointestinal Endoscopy guidelines on performance measures for lower gastrointestinal endoscopy[26]. In our tertiary center, advanced imaging techniques were not routinely available and applied during the study period, which might have resulted in underassessment of SMI, resulting in suboptimal resection choice. Macroscopic assessment of completeness of endoscopic resection of malignant colorectal polyps is often unreliable, especially in cases of non-pedunculated lesions (the majority of which were resected with the piecemeal technique).

Table 5 Risk factors for long-term adverse outcomes: Univariate analysis

Investigated parameter	Distant metastasis		Local recurrence	
	OR	*P* value	OR	*P* value
Size	0.03	0.278	0.001	0.985
Location: Rectum	0.70	0.276	1.35	0.251
Morphology: Non-pedunculated	2.51	0.020	18.30	0.995
En bloc resection: No	0.19	0.776	-0.55	0.641
Tumor differentiation	-13.16	0.993	NA	
Positive resection margins: Negative-R1	0.43	0.715	1.75E-14	1.000
Positive resection margins: Negative-critical	-17.26	0.995	-8.97E-30	1.000
Depth of submucosal invasion: Deep	-0.486	0.578	-17.41	0.995
Lymphatic invasion	-16.62	0.995	-7.37E-14	1.000
Vascular invasion	1.70	0.212	5.19E-15	1.000
Tumor budding	-17.17	0.997	NA	
Surgery for completion: No	-0.61	0.343	-0.429	0.677

NA: Not available; OR: Odds ratio.

Table 6 Risk factors for long-term adverse outcomes: Multivariate analysis

Investigated parameter	Distant metastasis		Local recurrence	
	OR	*P* value	OR	*P* value
Size	-0.02	0.572	1.26E-15	1.000
Location: Rectum	0.32	0.648	19.5	0.998
Morphology: Non-pedunculated	1.19	0.136	17.7	0.998
At least one high-risk feature	0.59	0.514	18.0	0.999
Surgery for completion	-0.39	0.613	-19.4	0.998

OR: Odds ratio.

Table 7 Long-term outcomes in view of the current National Comprehensive Cancer Network recommendations

Recommendation according to NCCN guideline	Surgery for completion, *n* = 70		Surveillance was sufficient, *n* = 41	
Resection was performed?	Yes	No	Yes	No
	33	37	3	38
Adverse outcome: Dissemination or local recurrence	5 (15)	2 (5.4)	0	3 (7.9)
Dissemination	5	2	0	2
Local recurrence	2	0	0	2

Data are *n* or *n* (%). NCCN: National Comprehensive Cancer Network.

Selecting the optimal post-polypectomy management strategy is mainly based on the presence of histological risk factors, but their reporting shows great variations[16,27]. In our study, only tumor differentiation was reported in most of the cases, and reporting of histological features was inadequate in 30% of cases (maximum one feature was reported). A recent large volume study assessing the quality of histological reports after endoscopic resection of malignant polyps also highlighted the incomplete reporting of high-risk features. Tumor differentiation, distance from resection margins, and lymphovascular invasion was reported in 82.4%, 86.8%, and 75.6% of cases, respectively. Tumor budding was only reported in 14.4% of cases.

As quantification of the depth of SMI is not required routinely by histologic guidelines, sufficient information for making an optimal post-polypectomy management decision may be lacking, even in cases of reports containing otherwise complete and adequate information on the other high-risk features[12]. Recently, there has been a shift regarding the type of information on the depth of SMI where absolute depth of invasion is preferred over Haggitt/Kikuchi classification. This is also reflected in the availability of information in our study. The Haggitt/Kikuchi classification was reported in only 33.8% of cases. Absolute depth of SMI was proposed by Ueno *et al*[28] and was reported in 56.6% of cases.

The definition of a positive resection margin varies greatly in the literature. In our study, residual malignancy and lymph node involvement could only be detected in cases when post-polypectomy histology revealed tumor cells in the cautery line. Although the difference was not statistically significant, this seems to support the proposition that tumor involvement of the cautery line alone carries a high risk. Brown *et al*[11] also detected no residual carcinoma in surgical specimens of malignant polyps previously endoscopically resected with a 0.1-1.0 mm distance from resection margins. Berg *et al*[12] found significantly higher lymph node involvement in cases of tumor involvement of endoscopic resection margins than in cases of tumors approaching but not reaching the cautery line. The residual malignancy and lymph node involvement rate during secondary surgery for completion was found to be in accordance with literature data[17,27-31].

In our study, only piecemeal resection was found to be a potential risk factor for residual malignancy, although it was not confirmed by multivariate analysis. Richards *et al*[30] identified incomplete polypectomy as a high-risk factor for residual tumor detection, and only lymphovascular invasion was found to be a risk factor for lymph node involvement. Systematic review and meta-analysis by Dykstra *et al*[9] identified lymphovascular invasion, tumor differentiation, and tumor budding as independent risk factors of lymph node involvement. In terms of depth of SMI, 1500 μm depth was found to have the strongest association (OR = 4.37). A multicentric study investigating the role of lymphatic and vascular invasion stated that lymphatic invasion is a stronger predictor of lymph node involvement than vascular invasion or histological differentiation[32].

Neither initial CEA nor CA 19-9 (at the time of the endoscopic polypectomy) can serve as a basis for outcome prediction of malignant colorectal polyps based on our data, as none of the patients with adverse outcomes had elevated markers. On the other hand, none of the patients with elevated markers presented with adverse outcomes.

The adverse outcome rate was somewhat higher than the one reported in the literature. Local recurrence rate after endoscopic resection of malignant polyps was found to be 2.2% over a 100-mo follow-up in the study by Asayama *et al*[20]. It should be underlined that intramucosal adenocarcinoma cases without SMI were also included in this study; this may explain the lower adverse outcome rate. The adverse outcome rate was 4.6% over a median 36.5-mo follow-up by Backes *et al*[31]. The 5-year cumulative rate of recurrence was determined to be 5.1% (2.0-13.1%) by Lopez *et al*[33] among patients treated only with endoscopic polypectomy. According to Dang *et al*[34], the pooled cumulative incidence rate of recurrence after endoscopic removal of T1 colorectal cancer was 3.3% (95%CI: 2.6%-4.3%, I^2 = 54.9%) based on meta-analytic calculations, with similar rates for local and distant recurrence (1.9% and 1.6%, respectively). However, the recurrence rate can be higher in cases of high-risk T1 tumors [7.0% (95%CI: 4.9-9.9%, I^2 = 48.1%)]. Recurrence was detected within 72 mo in 95.6% of the cases.

Differences in polypectomy techniques might also serve as an explanation to variations in adverse outcome rates. Most of the previously mentioned studies involved cases of endoscopic mucosal resection and ESD, whereas ESD was not routinely performed in our institute during the study period. Tumor testing for microsatellite instability was also not routinely available for early-stage colorectal cancer during the study period. Therefore, in order to homogenize the patient population, those with suspected hereditary colorectal tumor or polyposis syndrome, as well as those with inflammatory bowel disease-associated neoplasia, were excluded. Therefore, the relatively higher adverse outcome rate in our study cannot be contributed to these.

Based on these results, the follow-up time of our study can be considered appropriate to assess adverse outcomes. However, it should be highlighted that local recurrence was detected more than 7 years after the polypectomy in one of our cases, even with adequate participation in surveillance colonoscopies. No uniform recommendation is available for the timing of surveillance examinations during the follow-up of malignant colorectal polyps undergoing endoscopic resection only. The European Society of Gastrointestinal Endoscopy guidelines published in 2019 recommend a surveillance strategy similar to that of other colorectal cancers after R0 endoscopic resection of low-risk T1 stage colorectal cancers[10]. For malignant polyps with high-risk features that were endoscopically resected and no consequent completion surgery, most authors recommend the initial surveillance colonoscopy to be performed within 3-6 months, and further follow-up should be based on these results. However, no additional advice on surveillance examinations is given[3].

Recently, based on their meta-analysis, Dang *et al*[34] recommended initial surveillance colonoscopy for low-risk lesions with complete endoscopic resection 1 year after the polypectomy and advised against the use of cross-sectional imaging modalities in this group. Individualized follow-up strategy was advocated for high-risk lesions, both in terms of surveillance colonoscopies and cross-sectional imaging modalities. The authors call for intensive surveillance strategies (surveillance colonoscopy at 3 months, 6 months, 12 months, semiannually in the second year, then annually from year 2 to year 5).

A recent questionnaire-based study investigating follow-up strategies applied in the Scandinavian countries reported the use of 3-year (38%-59%) and 5-year (26%-38%) surveillance strategies in most of the institutes with a different strategy applied based on tumor location (mainly in terms of the use of cross-sectional imaging modalities). They found that 34% of respondents would consider a surveillance strategy for malignant polyps removed endoscopically with ≤ 1 mm resection margin[6]. Although a surveillance-only strategy was applied in the majority of our patients, only half of these patients presented at the 1-year follow-up, and less than 20% showed up at the 5-year follow-up. Given the recurrence patterns detailed above, this should be considered insufficient. However, participation rates on follow-up are still more

favorable than those in the United Kingdom cohort reported by Sharma *et al*[27], where only 61% of patients had a 3-months surveillance colonoscopy, and information at the 1-year follow-up was available only in 6.6%.

Limitations

The greatest limitation of our study was its retrospective nature, in terms of data on endoscopic polypectomies, surveillance colonoscopies, and histological data. Many high-risk histological features were identified during the study period, and histological guidelines for their reporting were also published in this period. This may account for incomplete histological data in the initial study period. Virtual chromoendoscopy that may assist the recognition of deep SMI was not available in our institute at the earlier study period. Tumor testing for microsatellite instability was not routinely available for early-stage colorectal cancer during the study period. Therefore, the potential differences in adverse outcomes of sporadic and hereditary malignant colorectal polyps could not be assessed. The single center nature of the study reflects only local practice and might be contributed to the relatively smaller sample size compared to multicentric studies; on the other hand, it guarantees uniform management strategies.

CONCLUSION

Adequate knowledge of high-risk histological features is essential for the selection of the optimal post-polypectomy management strategy after endoscopic resection of malignant colorectal polyps. Appropriate reporting of high-risk endoscopic and histological features is necessary to improve the quality of endoscopic and histological reports and is expected to optimize the selection of post-polypectomy management strategy. Secondary surgery for completion was only performed for half of the cases with high-risk histological features. The residual malignancy and lymph node involvement rates were 25% and 10% of these cases, respectively. Considering that residual malignancy and lymph node involvement could exclusively be detected in surgical specimens after R1 endoscopic resection, revision of the definition of a positive resection margin needs to be considered.

The adverse outcome rate during the follow-up period was found to be somewhat elevated compared to literature data, irrespective of whether secondary surgery for completion after endoscopic polypectomy was performed. This might be attributed to suboptimal prepolypectomy assessment and therefore suboptimal polypectomy choice. Routine use of advanced optical diagnostic tools and implementation of advanced polypectomy techniques (*e.g.*, ESD and endoscopic full-thickness resection) for en bloc resection is expected to reduce adverse outcome rates and needs to be encouraged. Tumor markers cannot serve as a basis of adverse outcome prediction after endoscopic removal of malignant colorectal polyps.

Improving reduced patient adherence to surveillance colonoscopy is essential to detect adverse outcomes as soon as possible. In selected cases, extension of the follow-up period and incorporating cross-sectional imaging studies into the follow-up strategy to detect the disseminated process may be considered. There is a pressing need for further, long-term, multicentric studies considering optimal timing and participation rate of surveillance examinations.

ARTICLE HIGHLIGHTS

Research background

The incidence of malignant colorectal polyps is increasing with the introduction of colorectal screening programs. Even with the application of optical diagnostic tools, many of these lesions are diagnosed only after endoscopic polyp removal. Submucosal invasion that is already present by this time can result in lymphovascular invasion and metastasis formation. Choosing the management strategy (completion surgery *vs* surveillance only) is mainly based on histological prognostic factors.

Research motivation

Suboptimal reporting of prognostic histological features might lead to inadequate post-polypectomy management choice (including both over-treatment resulting in unnecessary bowel resection and under-treatment leading to an increased risk of disease recurrence and dissemination). The decision over post-polypectomy management is further complicated by the fact that evidence about long-term outcomes of a surveillance-only strategy is limited.

Research objectives

This study aimed to assess the long-term outcomes of endoscopic removal of malignant colorectal polyps by comparing local and distant recurrence rates between the two post-polypectomy management strategies (completion surgery and surveillance-only strategy). We also assessed the residual malignancy and lymph node involvement rate after secondary surgery as well as the adequacy of reporting of post-polypectomy prognostic histological features and investigated the adherence to post-polypectomy surveillance colonoscopies.

Research methods

A retrospective cohort study over a 10-year study period was conducted. Residual disease rate and nodal metastases after secondary surgery and local and distant recurrence rates for those with at least 1 year of follow-up were investigated. The

relatively longer follow-up period in our study compared to previous reports allowed for adequate assessment of adverse outcomes.

Research results

Reporting of high-risk histological features varies greatly. While tumor differentiation was reported in almost 90% of cases, budding was only reported in 25% of cases. The residual malignancy and lymph node involvement rates were 25% and 10%, respectively, but could only be detected in surgical specimens after R1 endoscopic resection. The long-term post-polypectomy adverse outcome rate was 9.0%, which was somewhat elevated compared to previously reported rates. Secondary surgery for completion after endoscopic polypectomy did not affect the occurrence of adverse outcomes. Adherence to surveillance colonoscopy was low with only half of the patients presenting at the 1-year follow-up.

Research conclusions

Reporting of high-risk features is often inadequate to serve as a basis for the decision of the optimal management strategy and needs to be improved. The definition of a positive resection margin after endoscopic resection needs to be reconsidered, as residual malignancy and lymph node involvement were found only in surgical specimens after R1 endoscopic resection. The relatively higher long-term adverse outcome rate draws attention to the importance of adequate prepolypectomy assessment and implementation of advanced polypectomy techniques. Tumor markers cannot serve as a basis of adverse outcome prediction. Improving adherence to surveillance colonoscopy is essential.

Research perspectives

There is a pressing need for further, long-term, multicentric studies considering optimal timing and participation rate of surveillance examination. Our study mainly focused on sporadic malignant colorectal polyps, but any potential differences between adverse outcomes of hereditary and sporadic lesions might further be investigated.

FOOTNOTES

Author contributions: Fábián A, Bor R, and Szepes Z designed the study; Tóth T, Bősze Zs, Szántó K, Bacsur P, Bálint A, Farkas B, Farkas K, Milassin Á, Rutka M, and Resál T collected and analyzed the data; Vasas B provided pathological revision of histological samples; Fábián A, and Szűcs M performed the statistical analysis; Fábián A drafted the manuscript; Bor R, Vasas B, Bősze Zs, Molnár T, and Szepes Z provided critical revision; All authors read and approved the final manuscript.

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Informed consent statement: As this was a retrospective cohort study, consent from patients was unnecessary.

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ORIGINAL ARTICLE

Prospective Study

In vivo pilot study into superficial microcirculatory characteristics of colorectal adenomas using novel high-resolution magnifying endoscopy with blue laser imaging

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Abstract

BACKGROUND

No studies have yet been conducted on changes in microcirculatory hemodynamics of colorectal adenomas *in vivo* under endoscopy. The microcirculation of the colorectal adenoma could be observed *in vivo* by a novel high-resolution magnification endoscopy with blue laser imaging (BLI), thus providing a new insight into the microcirculation of early colon tumors.

AIM

To observe the superficial microcirculation of colorectal adenomas using the novel magnifying colonoscope with BLI and quantitatively analyzed the changes in hemodynamic parameters.

METHODS

From October 2019 to January 2020, 11 patients were screened for colon adenomas with the novel high-resolution magnification endoscope with BLI. Video images were recorded and processed with Adobe Premiere, Adobe Photoshop and Image-pro Plus software. Four microcirculation parameters: Microcirculation vessel density (MVD), mean vessel width (MVW) with width standard deviation (WSD), and blood flow velocity (BFV), were calculated for adenomas and the surrounding normal mucosa.

RESULTS

A total of 16 adenomas were identified. Compared with the normal surrounding mucosa, the superficial vessel density in the adenomas was decreased (MVD: 0.95 ± 0.18 *vs* 1.17 ± 0.28 μm/μm², $P < 0.05$). MVW (5.11 ± 1.19 *vs* 4.16 ± 0.76 μm, $P <$

0.05) and WSD (11.94 ± 3.44 *vs* 9.04 ± 3.74, $P < 0.05$) were both increased. BFV slowed in the adenomas (709.74 ± 213.28 *vs* 1256.51 ± 383.31 μm/s, $P < 0.05$).

CONCLUSION

The novel high-resolution magnification endoscope with BLI can be used for *in vivo* study of adenoma superficial microcirculation. Superficial vessel density was decreased, more irregular, with slower blood flow.

Key Words: Adenoma; Microcirculation; High-resolution magnification endoscopy; Blue laser imaging

Core Tip: No studies have yet been conducted on changes in microcirculatory hemodynamics of colorectal adenomas *in vivo* under endoscopy. Through our study, we found that the novel high-resolution magnification endoscope with BLI can be a tool for in-vivo study of adenoma superficial microcirculation. The superficial vessel density in the adenoma was decreased with more irregularity and slower blood flow. This is the first and pilot study to observe the microcirculatory hemodynamics of colorectal adenomas *in vivo* under endoscopy, and we believe that other doctors will be inspired by our article.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignancies in humans, ranking third in morbidity and second in mortality worldwide. The incidence of CRC is rising rapidly in the Asia–Pacific region[1]. Nearly half of the patients have a life span of < 5 years due to late diagnosis and potentially progressive disease. The majority of CRCs arise from adenomas; that is, the classical adenoma–carcinoma sequence (ACS)[2]. ACS is a series of events by which colorectal adenomas develop, initially showing low-grade dysplasia, and some progress to high-grade dysplasia and eventually invasive carcinoma[3]. Prior research has shown that identifying premalignant stage lesions (adenomas) of CRC by colonoscopy and subsequent endoscopic resection can prevent disease progression and reduce CRC-associated morbidity and mortality[4,5].

Angiogenesis, the secondary growth of blood vessels, plays an important role in tumor development[6]. Angiogenesis mediates the transition from hyperplasia to dysplasia and is a necessary condition for the growth of solid tumors[7]. The surface capillaries of colorectal tumors often show morphological changes, such as heterogeneity in vessel diameter or density and loss of hierarchical structure[8]. Although the importance of tumor angiogenesis is well known, conventional endoscopic images cannot be used to display these changes in capillaries due to inadequate resolution. No studies have yet been conducted on changes in microcirculatory hemodynamics of colorectal adenomas *in vivo* under endoscopy. In clinical practice, we found that a novel high-resolution magnifying colonoscope (Fujifilm EC-760ZP) with blue-laser imaging (BLI) can clearly display mucosal surface capillary networks *in vivo* and in real time.

In this study, we observed the superficial microcirculation of colorectal adenomas using the novel magnifying colonoscope with BLI and quantitatively analyzed the changes in hemodynamic parameters, thus providing a new insight into the early colorectal tumors.

MATERIALS AND METHODS

Research design

In this prospective study, the novel magnifying colonoscopy at the endoscopic center of Beijing Tsinghua Changgung Hospital between October 2019 and January 2020 diagnosed 11 patients with colorectal adenomas. All patients gave signed informed consent and the study was approved by the Medical Ethics Committee of Beijing Tsinghua Changgung Hospital and registered in the Chinese Clinical Trial Registry (ChiCTR2000031294). All research was performed in accordance with relevant guidelines and regulations.

Image acquisition

The patients were examined by the same endoscopist (YR) with the same high-resolution magnifying endoscope (EC-760ZP; Fujifilm, Japan). Standard bowel preparation and intravenous anesthesia were conducted in all the patients. Before each endoscopic examination, a soft black rubber cap (Olympus, Japan) was attached to the tip of the endoscope,

Table 1 Characteristics of patients (*n* = 11) with colorectal polyps (*n* = 16)

Variables	*n* (%)
Sex	
Male	5 (45.5)
Female	6 (54.5)
Age (mean ± SD) (yr)	59.94 ± 7.40
Lesion size (mean ± SD) (mm)	8.19 ± 3.95
Polyp morphology	
0-Isp	4 (25)
0-IIa	11 (68.7)
SSL	1 (6.3)
JNET classification	
JNET 2a	13 (81.2)
JNET 2b	3 (18.8)
Pathology tubular adenoma	16 (100)

SSL: Sessile serrated lesions; JNET: Japanese narrow-band imaging expert team.

and a microscopic ruler on a transparent glass plate (div=100 μm, Cossim, China) was used for measurement calibration at maximal magnification (145×).

Once a polyp was discovered, it was initially observed by conventional white-light imaging. A fully opened biopsy forceps (width 6 mm) was used to estimate the lesion size. Under BLI with low magnification, Japanese narrow-band imaging Expert Team (JNET) classification was used to evaluate the microsurface and microvessels of the polyps[9]. The transparent cap was attached to the surface of the polyp and the surrounding mucosa. The superficial capillary network was observed at maximal magnification (145×). The calibration and examination procedures were recorded as high-resolution videos (.mp4, 1080p, 30 frames/s) for at least 5 s and stored in a hard disk for further analysis. After observation, all polyps were resected under endoscopy and sent for pathological evaluation.

Image calculation

Adobe Premiere Pro 2019 software was used to export the recorded video images at 30 frames/s. Clear images were selected and the surface capillaries were identified and highlighted by Image-pro Plus 6.0 (Media Cybernetics, JNET). Mean vessel width (MVW) with width standard deviation (WSD) and microcirculation vessel density (MVD) (total vessel length per image area) were calculated with microscopic ruler calibration in Image-pro Plus software[10,11].

Time-sequential surface capillary images of each frame were imported in Adobe Photoshop CS4. The route of capillary flow was identified, marked and merged into one image without resolution loss. The distance between two marks suggested the blood flow within a certain time. The emergent image was imported in Image-pro Plus. The blood flow velocity (BFV) was calculated as the distance between two marks divided by the time between the two given sequential frames (1/30-2/30 s). BFV in three different areas were averaged.

Statistical analysis

Continuous data were expressed as mean ± SD and categorical data as percentages. The paired *t* test was used to compare the means. $P < 0.05$ was considered statistically significant. STATA 17.0 software was used for statistical analysis.

RESULTS

A total of 16 adenomas were discovered in the 11 patients. The mean age of the patients was 59.9 ± 7.4 years and there were six women and five men (Table 1). The average adenoma size was 8.2 ± 4.0 mm. There were four 0-Isp, 11 0-IIa adenomas and one sessile serrated lesions. Thirteen adenomas were classified as JNET type 2a and three as JNET type 2b. Pathology showed that all the adenomas were tubular.

The surface blood flow in the capillaries could be clearly seen under BLI with maximal magnification, both in the adenoma and surrounding mucosa (Figure 1A and B, Videos 1 and 2). The capillaries within the adenoma appeared to be wider and more tortuous than those in the surrounding mucosa. The surface capillaries were automatically identified as red and calculated (Figure 1C and D). Mark the position of blood flow in certain time, so as to obtain the blood flow advance distance, and then calculate the BFV (Figure 2A and B).

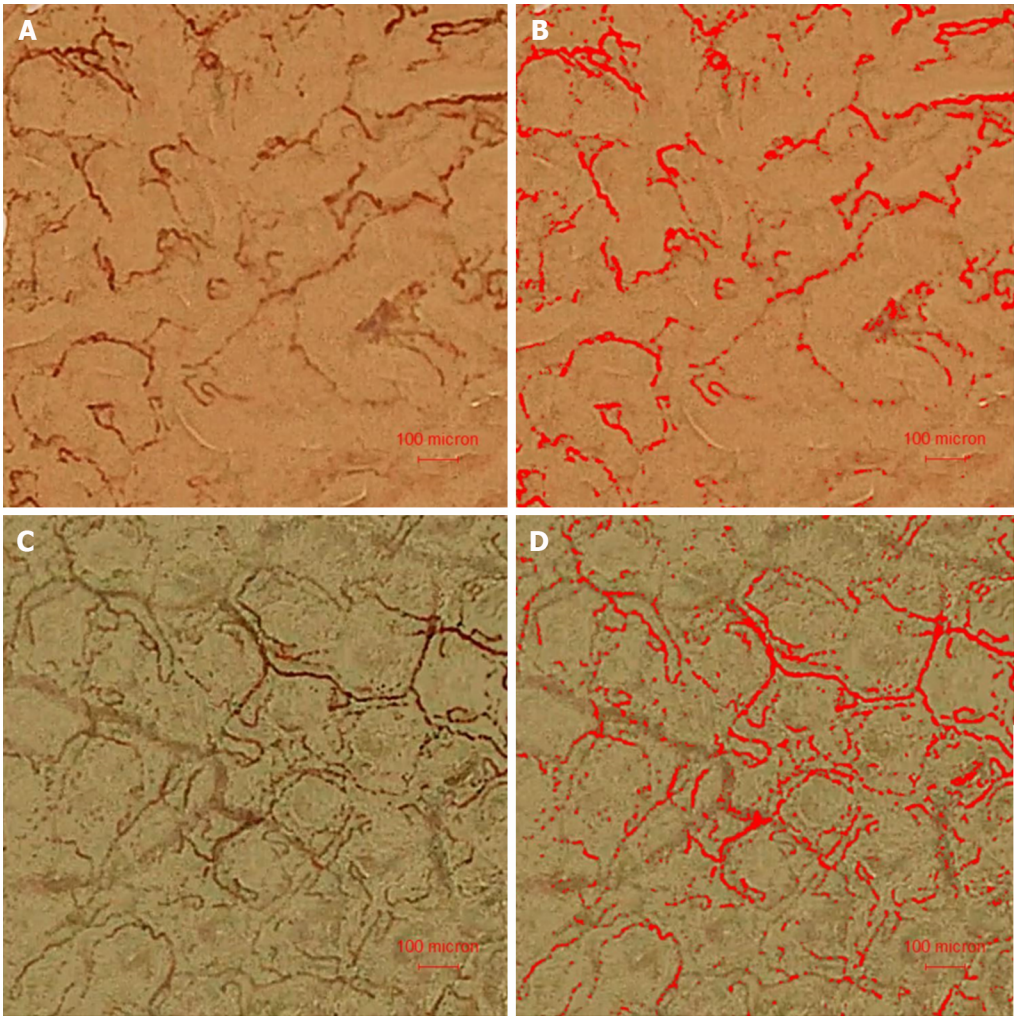

Figure 1 Superficial capillaries in an adenoma and surrounding normal mucosa observed under high-resolution magnifying endoscope with blue-laser imaging, and then identified by Image-pro plus software. A: Blue laser imaging (BLI) observed the surface vessels of adenomas; B: BLI observed normal mucosal surface vessels around the adenoma; C: Image-pro plus identified the blood vessels on the surface of adenoma as red; D: Image-pro plus identified normal mucosal surface blood vessels around the adenoma as red. BLI: Blue-laser imaging.

Compared with the surrounding normal mucosa, the superficial vessel density of the adenomas was significantly decreased (MVD: 0.95 ± 0.18 *vs* 1.1 ± 0.28 μm/μm², $P < 0.05$). MVW (5.11 ± 1.19 *vs* 4.16 ± 0.19 μm, $P < 0.05$) and WSD (11.94 ± 3.44 *vs* 9.04 ± 3.74, $P < 0.05$) were increased. The superficial blood flow slowed down remarkably in the adenomas (BFV: 709.74 ± 213.28 *vs* 1256.51 ± 383.31 μm/s, $P < 0.05$) (Table 2).

DISCUSSION

The pathway of CRC progression through ACS is well known, so early diagnosis and treatment of colorectal adenoma are crucial to reduce the risk of CRC development[4]. Various enhanced imaging techniques have been developed to improve the ability of doctors to recognize neoplastic lesions such as narrow-band imaging (NBI) (Olympus), i-SCAN (Pentax, Tokyo, Japan) and flexible spectral imaging color enhancement (Fujifilm)[12]. BLI (Lasereo System; Fujifilm) is another form of NBI. Instead of using filters for white light to produce narrow bandwidths, the BLI system is equipped with light sources that emit two different wavelengths of laser light. A laser with a wavelength of 450 nm can stimulate phosphors to produce white light illumination, while a BLI mode laser with a wavelength of 410 nm can be used as a high-contrast signal to obtain information on mucosal vascular patterns and surface patterns, thus achieving visual enhancement of surface vessels and structures[13,14].

Although the importance of neoplastic angiogenesis is widely recognized, there is strong evidence that induction of angiogenesis may occur early in the ACS, with angiogenic conversion occurring at the same time as tumor invasion[2,15,16]. However, there are no quantitative data on the indexes of capillary microcirculation of colorectal adenoma under endoscopy and in the surrounding normal mucosa. Blood flow in capillaries on the mucosal surface of the colon can be clearly observed under high-resolution magnification endoscopy with BLI, which provides a possibility for quantitative analysis of microcirculatory changes in colorectal adenomas.

Table 2 Comparison of superficial microcirculatory characteristics between adenoma and surrounding mucosa

	Adenoma	Surrounding mucosa	*t*	*P* value
MVD (μm/μm^2)	0.95 ± 0.18	1.17 ± 0.28	2.640	0.019
MVW (μm)	5.11 ± 1.19	4.16 ± 0.76	5.503	< 0.001
WSD (μm)	11.94 ± 3.44	9.04 ± 3.74	4.494	< 0.001
BFV (μm/s)	709.74 ± 213.28	1256.51 ± 383.31	4.986	< 0.001

MVD: Microcirculation vessel density; MVW: Mean vessel width; WSD: Width standard deviation; BFV: Blood flow velocity.

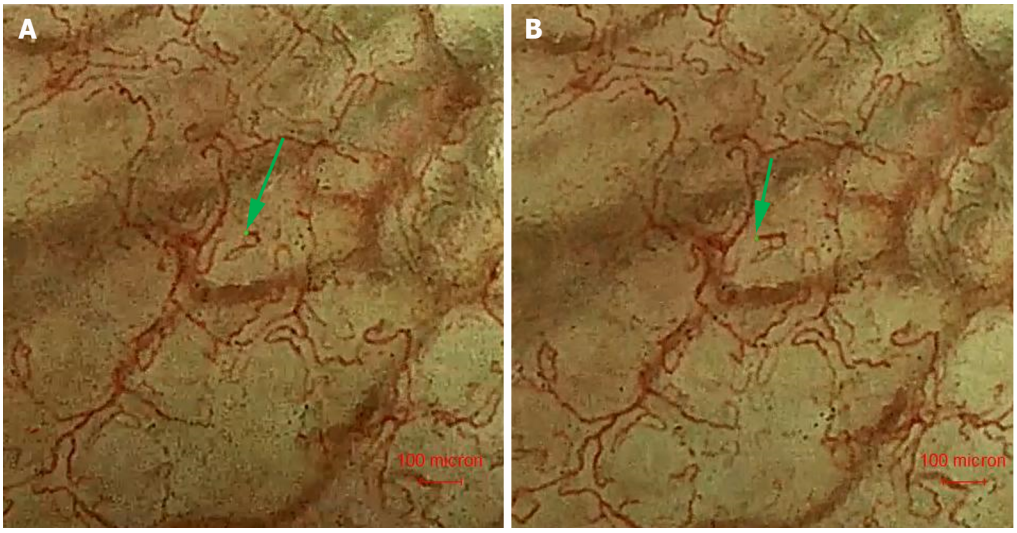

Figure 2 The green marks represent the blood flow progression in 1/30 s. A: The green mark represents the blood flow position at a certain time; B: The green mark represents the blood flow position after 1/30 s.

We found that capillaries on the normal colorectal mucosal surface were arranged around the annular adenoid tube, while capillaries on the surface of the adenoma lost their normal structure. The capillary length per unit area on the surface of adenoma was shortened and vessel density was reduced. In addition, compared with the surrounding normal mucosa, the vessel width on the surface of the adenoma was increased and BFV was decreased. Nowadays, endoscopists usually use the JNET classification for microsurface structure and microvascular pattern. It is subjective in nature, and there is still some disagreement[17]. However, through our quantitative calculation with high-resolution magnifying endoscopy with BLI, we found that the width and variability of capillaries on the surface of the adenomas increased, which could confirm the rationality of the (JNET) classification. Further studies are warranted.

Previous studies have shown that image-enhanced endoscopy using NBI and BLI can be used to characterize known lesions by enhancing mucosal vessels and structures[18]. The use of BLI can significantly improve identification of adenomas, but there are no studies on microcirculation of colorectal adenoma under endoscopy[19,20]. To date, the only study on tumor vessels is a scanning electron microscopy study of cast colorectal vessels, which has provided spatial tissue information of tumor vessels, as well as quantitative results of morphological characteristics and diameter of individual vessels[21,22]. The normal mucosal capillaries of the colorectum presented a honeycomb arrangement around the mucosal glands, while the vascular layer in the adenoma was lost, which was consistent with our endoscopic observations. Further quantitative analysis showed that the vascular space in the adenoma was narrowed, the density was increased, the vascular width was increased, and the dispersion was greater. However, the vascular density of colorectal adenomas was decreased in our study. The difference in vascular density between the two studies may be related to different definitions. In the previous study, vascular density was defined as the spatial density of blood vessels in the lesion, which was related to the volume of blood vessels and the distance between them. We defined vascular density as the length of microcirculation capillary blood vessels on the adenoma surface within a unit area[11]. We only studied the changes in surface vessel length and did not involve deeper vessels. Figure 1D clearly shows that the software automatically recognized the capillaries on the surface of the adenoma, while the deeper and thicker vessels were not included in the analysis.

For the first time, we quantitatively analyzed the changes in capillary BFV of the colorectal adenomas, and the decreased velocity in the tumor may explain the failure of tumor drug therapy, because slower blood flow affects the delivery of drugs to the tumor, thus reducing their effectiveness. We found that these changes were largely related to the progress in endoscopic imaging technology. The emergence of high-resolution magnification endoscopy provides us with the possibility to study the changes in microcirculation-related indicators of colorectal adenoma.

One limitation of our study was the small sample size, which means that the results are not widely representative. In the next study, we will increase the sample size and further analyze the changes in hemodynamic indicators related to the surface vascular microcirculation of polyps, adenomas and adenocarcinomas. This will provide a new theoretical basis for the diagnosis of early colorectal tumors and the possibility of active recognition of colorectal lesions with AI technology under endoscopy.

In conclusion, high-resolution magnifying endoscopy can be used to quantitatively analyze the microcirculation on the surface of colorectal adenomas. The superficial vessel density in the adenomas was decreased, with more irregularity and slower blood flow.

CONCLUSION

The novel high-resolution magnification endoscope with BLI can be a tool for the *in vivo* study of adenoma superficial microcirculation. The superficial vessel density in the adenoma was decreased, with more irregularity and slower blood flow.

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer (CRC) is one of the most common malignancies in humans. Prior research has shown that identifying premalignant stage lesions (adenomas) of CRC by colonoscopy and subsequent endoscopic resection can prevent disease progression and reduce CRC-associated morbidity and mortality. Angiogenesis, the secondary growth of blood vessels, plays an important role in the development of tumors. The surface capillaries of colorectal tumors often show morphological changes, such as heterogeneity in vessel diameter or density and loss of hierarchical structure.

Research motivation

Although the importance of tumor angiogenesis is well known, conventional endoscopic images cannot be used to show these changes in capillaries due to inadequate resolution. No studies have yet been conducted on changes in microcirculatory hemodynamics of colorectal adenomas *in vivo* under endoscopy. In clinical practice, we found that a novel high-resolution magnifying colonoscope (Fujifilm EC-760ZP) with blue-laser imaging (BLI) clearly revealed the mucosal surface capillary network *in vivo* and in real time.

Research objectives

In this study, we observed the superficial microcirculation of colorectal adenomas using the novel magnifying colonoscope with BLI and quantitatively analyzed the changes in hemodynamic parameters, thus providing a new insight into early colorectal tumors.

Research methods

From October 2019 to January 2020, 11 patients were screened for colon adenomas with the novel high-resolution magnification endoscope with BLI. Video images were recorded and processed with Adobe Premiere, Adobe Photoshop and Image-pro Plus software. Four microcirculation parameters: Microcirculation vessel density, mean vessel width with width standard deviation, and blood flow velocity, were calculated respectively for adenoma and the surrounding normal mucosa.

Research results

A total of 16 adenomas were identified. Compared with the normal surrounding mucosa, the superficial vessel density in the adenomas was decreased; the mean vessel width and vessel width deviation were both increased; and blood flow slowed down in the adenomas.

Research conclusions

The novel high-resolution magnification endoscope with BLI can be a tool for the *in vivo* study of adenoma superficial microcirculation. The superficial vessel density in the adenoma was decreased, with more irregularity and slower blood flow.

Research perspectives

High-resolution magnifying endoscopy can be used to quantitatively analyze the microcirculation on the surface of the colorectal adenomas. It provide the possibility of active recognition of colorectal lesions with AI technology under endoscopy.

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FOOTNOTES

Co-first authors: Hai-Bin Dong and Tao Chen.

Co-corresponding authors: Yu-Tang Ren and Bo Jiang.

Author contributions: Zhang XF contributed to statistical analysis of data; Dong HB contributed to drafting of the article; Dong HB and Chen T contributed to analysis and interpretation of the data; Ren YT and Jiang B, as co-corresponding authors, played an important role in the design, progress and summary of the study. Ren YT found that the new endoscope could be used for the study of blood microcirculation, and personally completed all endoscopic operations and designed the analysis indicators. Jiang B introduced new endoscopes, controlled the whole research concept and design, critically revised important contents of the paper, and finally approved the paper.

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SYSTEMATIC REVIEWS

Role of second look endoscopy in endoscopic submucosal dissection and peptic ulcer bleeding: Meta-analysis of randomized controlled trials

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Abstract

BACKGROUND

Second-look endoscopy (SLE) to prevent recurrent bleeding in patients with peptic ulcer disease (PUD) and those undergoing endoscopic submucosal dissection (ESD) is routinely being performed. Conflicting evidence exists regarding efficacy, risk, benefit, and cost-effectiveness.

AIM

To identify the role and effectiveness of SLE in ESD and PUD, associated

rebleeding and PUD-related outcomes like mortality, hospital length of stay, need for endoscopic or surgical intervention and blood transfusions.

METHODS

A systematic review of literature databases PubMed, Cochrane, and Embase was conducted from inception to January 5, 2023. Randomized controlled trials that compared patients with SLE to those who did not have SLE or evaluated the role of prophylactic hemostasis during SLE compared to other conservative interventions were included. The study was conducted per PRISMA guidelines, and the protocol was registered in PROSPERO (ID CRD42023427555:). RevMan was used to perform meta-analysis, and Mantel-Haenszel Odds ratio (OR) were generated using random effect models.

RESULTS

A total of twelve studies with 2687 patients were included in our systematic review and meta-analysis, of which 1074 patients underwent SLE after ESD and 1613 patients underwent SLE after PUD-related bleeding. In ESD, the rates of rebleeding were 7% in the SLE group compared to 4.4% in the non-SLE group with OR 1.65, 95% confidence intervals (CI) of 0.96 to 2.85; $P = 0.07$, whereas it was 11% in the SLE group compared to 13% in the non-SLE group with OR 0.8 95%CI: 0.50 to 1.29; $P = 0.36$. The mean difference in the blood transfusion rates in the SLE and no SLE group in PUD was OR 0.01, 95%CI: -0.22 to 0.25; $P = 0.91$. In SLE *vs* non-SLE groups with PUD, the OR for Endoscopic intervention was 0.29, 95%CI: 0.08 to 1.00; $P = 0.05$ while it was OR 2.03, 95%CI: 0.95 to 4.33; $P = 0.07$, for surgical intervention. The mean difference in the hospital length of stay was -3.57 d between the SLE and no SLE groups in PUD with 95%CI: -7.84 to 0.69; $P = 0.10$, denoting an average of approximately 3 fewer days of hospital stay among patients with PUD who underwent SLE. For mortality between SLE and non-SLE groups in PUD, the OR was 0.88, 95%CI: 0.45 to 1.72; $P = 0.70$.

CONCLUSION

SLE does not confer any benefit in preventing ESD and PUD-associated rebleeding. SLE also does not provide any significant improvement in mortality, need for interventions, or blood transfusions in PUD patients. SLE decreases the hospital length of stay on average by 3.5 d in PUD patients.

Key Words: Endoscopy; Endoscopic submucosal dissection; Peptic ulcer; Gastrointestinal bleeding

Core Tip: Second-look endoscopy (SLE) has been a common practice to prevent recurrent bleeding in patients with peptic ulcer disease (PUD) and those undergoing endoscopic submucosal dissection (ESD). Current guidelines by American college of gastroenterology and American society of gastrointestinal endoscopy do not advocate routine SLE for nonvariceal upper gastrointestinal (GI) bleeding but recommend its consideration in cases of recurrent bleeding or higher recurrence risk. Conflicting evidence exists regarding the cost-effectiveness, efficacy, and potential risks of SLE in non-variceal upper GI bleeds. Second look endoscopy does not have any benefit in preventing ESD and PUD-associated rebleeding. SLE also does not have any significant improvement in mortality, need for interventions, or blood transfusions in PUD patients. SLE reduced the hospital length of stay on average by 3.5 d in PUD patients.

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INTRODUCTION

Peptic ulcer disease (PUD) and endoscopic submucosal dissection (ESD) are distinct clinical entities, yet they share a common concern-the management of gastrointestinal bleeding. PUD is a prevailing cause of acute upper gastrointestinal (GI) bleeding, entailing significant morbidity and mortality[1], while ESD is a well-established technique for the resection of gastric neoplasms[2]. Despite their differences, both clinical scenarios require careful consideration of the role of second-look endoscopy (SLE).

ESD, while effective in providing high en-bloc resection rates for gastric neoplasms, is associated with the concern of post-procedural bleeding, which can be life-threatening[3]. Efforts have been made to prevent such bleeding, including prophylactic coagulation during ESD[4]. SLE, often performed with or without prophylactic hemostasis, has been a common practice in many institutions. However, recent evidence, including a meta-analysis of randomized controlled

trials (RCTs), has cast doubt on the efficacy of SLE in reducing the incidence of post-ESD bleeding[5]. The unpredictability of post-ESD bleeding sites and the limited applicability of prophylactic measures during SLE have further complicated its role.

On the other hand, for PUD, endoscopic treatment is effective in achieving initial hemostasis, but recurrent bleeding poses a substantial risk with potentially severe consequences[1,6,7]. The utility of planned SLE has been a topic of discussion, as it has shown promise in reducing the risk of recurrent bleeding in certain RCTs. However, conflicting results have also emerged, raising questions about the cost-effectiveness and potential risks associated with routine SLE [8].

Therefore, we conducted a systematic review and meta-analysis to assess the role of SLE in ESD and peptic ulcer bleeding to provide a comprehensive evaluation of the role of SLE in both settings by synthesizing evidence from RCTs and addressing the need for high-quality evidence to guide the further decision-making process.

MATERIALS AND METHODS

We conducted this review following the PRISMA statement as indicated in the PRISMA checklist and registered our protocol with PROSPERO (CRD42023427555; www.crd.york.ac.uk/prospero).

Data sources, search strategy, inclusion and exclusion criteria

A comprehensive literature search was performed in three databases, PubMed, Embase, and Cochrane, from inception until January 5, 2023. The search included keywords and subject-specific medical headings for SLE combined with gastrointestinal bleeding. We used vocabulary related to ('second look endoscopy' OR 'repeat endoscopy' OR 'prophylactic hemostasis') AND ('bleed' OR 'endoscopic submucosal dissection'/exp OR 'endoscopic submucosal dissection' OR 'ESD') AND (randomized OR randomized). Five authors were involved in the study selection process (Kogilathota Jagirdhar GS, Perez JA, Banga A, Qasba RK, Qasba RK). After removing duplicates using Endnote reference manager software, four authors independently performed title and abstract screening using the Rayyan software (https://rayyan.ai/)[9]. Studies that satisfied the inclusion criteria were retrieved and screened for full-text eligibility. Conflicts between authors on study selection were resolved through mutual discussion by an additional third arbiter if a consensus could not be reached. We have included studies that were: (1) Only RCTs; (2) patients who had initial endoscopy (EGD) for various reasons (peptic ulcer bleeding, submucosal dissection of polyps, dissection of tumor.), and (3) patients who had intervention such as SLE or prophylactic hemostasis during SLE. These studies compared patients who had SLE to those who did not have SLE, prophylactic hemostasis during SLE, or other conservative interventions.

We excluded the following studies: (1) Case reports; (2) case series; (3) literature reviews; (4) systematic reviews; (5) meta-analyses; (6) single arm studies; (7) non-randomized studies such as retrospective or prospective studies; (8) studies without SLE intervention groups; (9) animal studies; (10) unpublished studies; and (11) publications in a language other than English.

Data extraction

Three authors independently (Perez JA, Banga A, Qasba RK) extracted data including general information (Authors, DOI, Title, Journal, year of publication), Characteristics of studies and participants (site/ country, period of study, number of centers, study design, SLE/no SLE related numbers) and outcomes (SLE/no SLE Rebleeding number, types of treatment, Mean number of units blood transfused, type of intervention, need for surgery, all-cause mortality and hospital length of stay). All this data was transferred into a pre-piloted extraction form in Google Sheets. A Fourth author (GJ) checked the extracted data independently for validity.

Our outcomes were: (1) Recurrent bleeding; (2) all-cause mortality, (3) need for surgery; (4) mean number of units of blood transfused; and (5) mean number of hospital days.

Statistical analysis

We used RevMan 5.4.1 version, the Cochrane Collaboration, 2020, to assess all results[10], and Microsoft Excel to interpret and assess all results. After extracting raw data for events and non-events from each RCT, we calculated crude odds ratio (OR) using the Mantel-Haenszel method for each study with corresponding 95% confidence intervals (CI) using the random-effects model[11]. Differences were considered statistically significant at a P-value < 0.05. For continuous outcomes, a previously proven technique was used to convert the median to mean[12], and then estimates for mean differences were produced using the random effects model[11]. Further forest plots were generated to present the results of a meta-analysis. Cochrane Q and I^2 statistics were used to measure heterogeneity and a low-level heterogeneity was defined as I^2 of 20%[11]. The stability of the results was assessed using sensitivity analysis. Funnel plots were used to determine the likelihood of publication bias (Supplementary Figures 1-7)[13].

Quality assessment

We used the Cochrane Risk of Bias Assessment Tool (ROB1) to assess the bias in included studies[14]. Two authors (Rakhtan KQ and Ruman KQ) conducted separate evaluations of the risk of bias for each included study. Any discrepancies were deliberated among all authors, and a unanimous decision was reached. The assessment was conducted in the following domains: Sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data risk of bias, selective reporting, and other sources of risk of bias. Each domain was categorized under high risk, low risk, and unclear risk of bias.

RESULTS

Search and selection

A total of 271 records were identified from the initial search; 121 were excluded as duplicates, and 150 articles were selected for the screening of title and abstract. Twenty-seven were chosen for full-text screening, and a total of 12 studies met the inclusion criteria and were included. These papers were eligible for qualitative and quantitative synthesis. Figure 1 shows the PRISMA diagram for the study selection process. We included studies that included patients who had initial endoscopy (EGD) for various reasons (PUD, submucosal dissection of polyps, dissection of tumors) followed by bleeding or complications post EGD and patients who had intervention such as SLE or prophylactic hemostasis during SLE.

Characteristics of the included studies

A total of 2687 patients from twelve studies were included in the meta-analysis, of which 1074 patients from four studies belonged to the group of patients who underwent SLE[15-18] after ESD and 1361 patients from eight studies belonged to the group of patients who underwent SLE after PUD[19-27]. The studies observed outcomes of gastrointestinal bleeding in those with and without a SLE. The outcomes recorded were the number of events of gastrointestinal bleeding in the SLE and no-SLE groups, the timing of SLE, and risk factors for the occurrence of bleeding. The main characteristics of the included studies are summarized in Table 1.

Rebleeding in ESD

A total of 1074 patients from four RCTs were included in the qualitative analysis. The rates of rebleeding were 7% (SLE) 37/534 and 4.4% (no SLE) 24/540. The OR was 1.65 for ESD rebleeding with a 95%CI: 0.96 to 2.85; P = 0.07, I^2 = 0%. Figure 2A shows the Forest plot and meta-analysis for ESD rebleeding. Risk factors for delayed post-ESD bleeding were Lesions with a large size > 20 mm, ulcerative lesions, and a longer procedure time.

Endoscopic intervention in ESD

A total of 1074 patients from four RCTs were included in the qualitative analysis, of which 534 patients belonged to the SLE group and 540 belonged to no SLE group. The number of patients who underwent interventions in the SLE group was 12% (69/534). Commonly performed interventions in ESD were prophylactic hemostasis using hemostatic clips, hemostatic forceps, Argon plasma coagulation, and endoscopic injection therapy. The number of patients who underwent interventions in the no SLE group was 0.3% (2/540). The intervention method was Hemostatic forceps and hemostatic clips, Argon plasma coagulation, and endoscopic injection with epinephrine.

Rebleeding in PUD

A total of 1361 patients from eight RCTs were included in the qualitative analysis. The rates of rebleeding were 11% (SLE) 74/678 and 13% (no SLE) 89/683. The OR was 0.8 for PUD rebleeding with a 95%CI: 0.50 to 1.29; P = 0.36, I^2 = 44%. Figure 2B shows the forest plot and meta-analysis for PUD rebleeding. Figure 2C shows the sensitivity analysis for PUD rebleeding. Risk factors for delayed post-PUD rebleeding were higher Baylor bleeding score, active bleeding before initial endoscopy, larger amounts of transfused blood, unsatisfactory initial endoscopic hemostasis, and use of nonsteroidal anti-inflammatory drugs (NSAIDs).

Blood transfusions in PUD

A total of 1073 patients from five RCTs were included in the qualitative analysis. 537 patients were in the SLE group and 536 patients in the no SLE group. A qualitative synthesis showed that the mean difference in blood transfusion rates in PUD was 0.01 between the SLE and no SLE group and a 95%CI: -0.22 to 0.25; P = 0.91, I^2 = 72%. Figure 2D shows the forest Plot and meta-analysis for blood transfusion in PUD. Figure 2E shows sensitivity analysis for blood transfusion in PUD.

Endoscopic intervention in PUD

A total of 1113 patients from six RCTs were included in the qualitative analysis. A total of 556 patients were in the SLE group and 557 in the no SLE group. The number of patients who underwent SLE and required intervention in PUD was 17% (SLE) 95/556. The intervention number in patients with no SLE was 7% 41/557. The OR was 0.29 for Endoscopic intervention in PUD with a 95%CI: 0.08 to 1.00; P = 0.05, I^2 = 85%. Figure 2F shows the first plot and meta-analysis for endoscopic intervention in PUD. Commonly performed interventions were hemoclip application or thermal (heat probe) coagulation, endo-clips ± 1:10000 epinephrine, fibrin glue injection therapy, hemospray, second emergency adrenaline injection, sequential injection of epinephrine (1:10000v/v) and up to 2 mL of fibrin/ thrombin.

Surgical intervention in PUD

A total of 1218 patients from seven RCTs were included in the qualitative analysis. A total of 608 patients were in the SLE group, and 610 patients were in the no SLE group. The number of patients that required surgical intervention after SLE was 2% (SLE) 11/608, and the number of patients who required surgical intervention without undergoing prior SLE was 4% (no SLE) 23/610. The OR was 2.03 for surgical intervention in PUD with a 95%CI: 0.95 to 4.33; P = 0.07, I^2 = 0%. Figure 2G shows the forest plot and meta-analysis for surgical intervention in PUD.

Table 1 Main characteristics of the included studies in the systematic review and meta-analysis

No.	Ref.	Country	Year of publication	Study design	Number of participants in SLE	Number of participants in No SLE	GIB symptoms in SLE total	GIB symptoms In No SLE total	Timing of SLE	Risk factors for the occurrence of post-procedural bleeding
Endoscopic submucosal dissection for gastric neoplasm										
1	Ryu *et al*[15]	Korea	2013	Prospective, randomized, controlled trial study	74	81	15	11	> 24 h	Longer procedure: (41.4 ± 28.2 min *vs* 32.1 ± 25.8 min; $P < 0.048$)
2	Kim *et al*[16]	Korea	2014	Prospective, randomized, single-blind, controlled trial	220	217	8	6	> 48 h	Large tumor size > 20 mm
3	Mochizuki *et al*[17]	Japan	2015	Multicenter prospective randomized controlled non-inferiority trial	130	132	7	5	> 24 h	Large tumor size > 40 mm
4	Jee *et al*[18]	Korea	2016	Multicenter prospective randomized-controlled study	110	110	7	2	> 24 h	Ulcerative lesions finding
Peptic ulcer bleeding										
1	Chiu *et al*[19]	China	2003	Single center, prospective, randomized, controlled trial	100	94	5	13	16-24 h	N/A
2	Chiu *et al*[20]	China	2016	Single center, prospective, randomized, controlled trial	152	153	12	10	16-24 h	Baylor bleeding score
3	Park *et al*[21]	Japan	2018	Multicenter, prospective, randomized, controlled trial	158	161	16	9	24 to 36 h	N/A
4	Pittayanon *et al*[22]	Hong Kong	2022	Multicenter, prospective, randomized, controlled trial	75	76	9	14	24 h	N/A
5	Villanueva *et al*[23]	Spain	1994	Prospective, randomized, controlled trial	52	52	11	15	24 h	N/A
6	Messmann *et al*[24]	Germany	1998	Multicenter, prospective, randomized, controlled trial	52	53	14	11	16-24 h	N/A
7	Saeed *et al*[25]	United States	1996	Single-center, prospective, randomized, controlled trial	19	21	0	5	24 h	Active bleeding, visible vessel, fresh adherent clot
8	Lee[26]	-	2005	Randomized, controlled trial	70	73	7	12	-	NA

SLE: Second-look endoscopy.

In patients who underwent SLE and no SLE, the rates of angiographic embolization were similar, with 5 patients in each group. Figure 2H shows the forest Plot and meta-analysis for angiographic embolization in PUD.

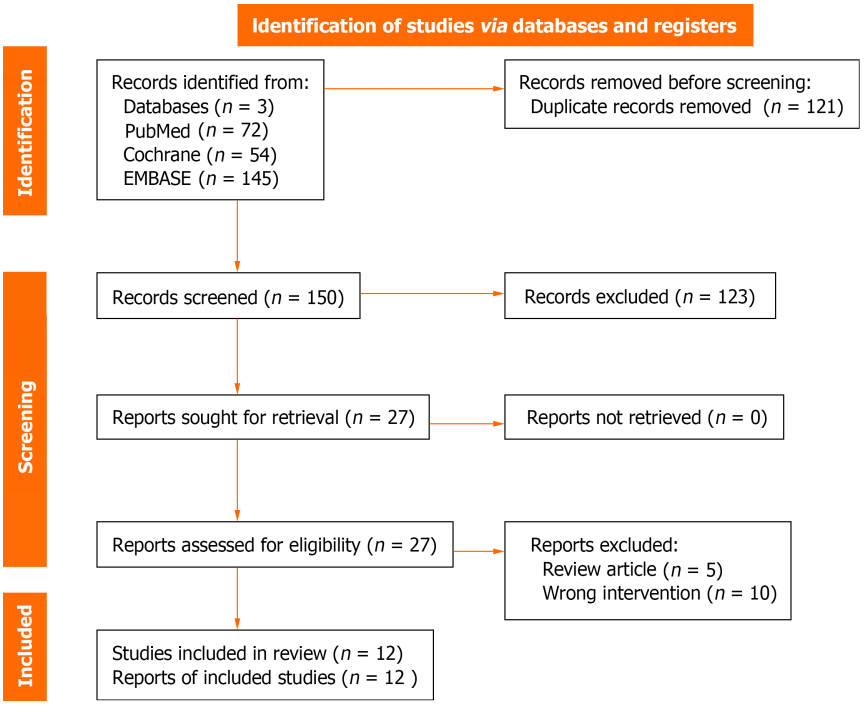


Figure 1 PRISMA flowchart outlining the study search.

Hospital length of stay in PUD

A total of 574 patients from three RCTs were included in the qualitative analysis. A total of 285 patients were in the SLE group, and 289 patients were in the no SLE group. A qualitative synthesis showed that the mean difference in the hospital length of stay was -3.57 d between the SLE and no SLE groups and a 95%CI: -7.84 to 0.69; P = 0.10, I^2 = 74%. Figure 2I shows the forest plot and meta-analysis for hospital length of stay in PUD. Figure 2J shows the sensitivity analysis for Hospital length of stay. This denotes an average of approximately 3 fewer d of hospital stay among patients with PUD (no-SLE).

Mortality in PUD

A total of 1218 patients from seven RCTs were included in the qualitative analysis. A total of 608 were from the SLE group and 610 patients from the no SLE group. The number of patients that underwent mortality in SLE was 3% (SLE) 18/608, and the number of patients that underwent mortality without SLE was 3% (no SLE) 21/610. The OR was 0.88 for mortality in PUD with a 95%CI: 0.45 to 1.72; P = 0.70, I^2 = 0%. Figure 2K shows the forest plot for mortality in PUD.

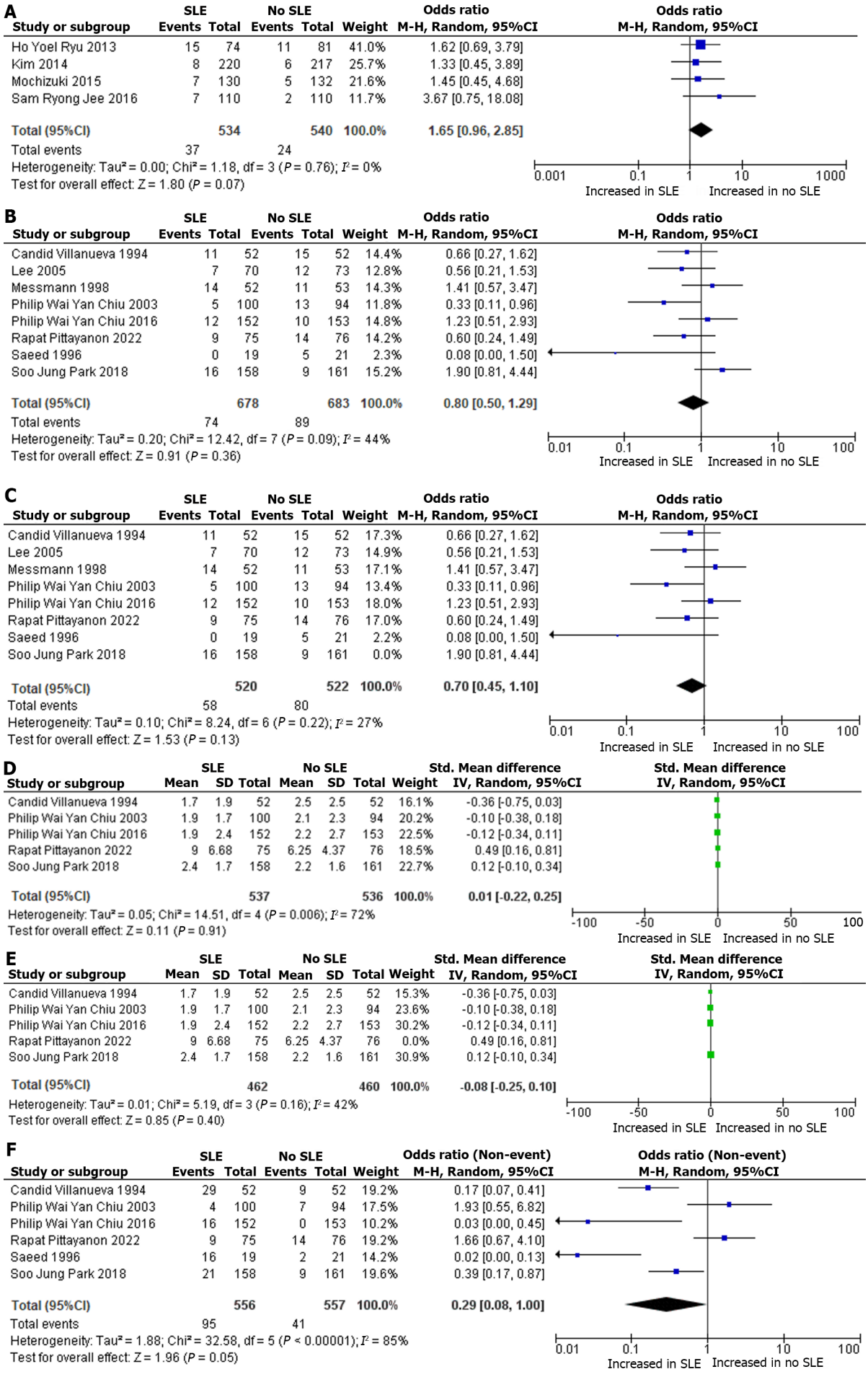
Quality assessment

The Cochrane Collaboration tool was used to assess the methodological quality of all included studies, with the summarized outcomes detailed in Figures 3 and 4. All studies were randomized. All of the thirteen studies reported adequate sequence generation and concealment. Only Mochizuki *et al*[17] did not report blinding of participants and personnel. Additionally, Kim *et al*[16] and Mochizuki *et al*[17] did not report blinding of the outcome assessments. In eight of the studies, intent-to-treat analyses were done. Out of thirteen, only seven studies met all criteria for low risk of bias.

DISCUSSION

Our systematic review and meta-analysis of 12 RCTs, which included 1074 and 1361 patients with ESD and PUD, respectively, aimed to evaluate the role of SLE in preventing gastrointestinal rebleeding and improving outcomes such as mortality, hospital length of stay, need for surgical interventions and blood transfusions in patients who had undergone initial endoscopy.

Our findings suggest that SLE does not affect the rebleeding rate in upper GI bleeding due to ESD or PUD. Interestingly, there was an observed rise in rebleeding incidents in the SLE group compared to the non-SLE group among patients with PUD. However, the trend was the opposite in patients undergoing ESD although neither reached statistical significance. However, PUD patients who underwent SLE had a significantly higher likelihood of undergoing endoscopic interventions. Notably, PUD patients in the SLE group had lower rates of surgical intervention, but this did not reach statistical significance. Furthermore, in PUD patients, SLE also lacks a statistically significant impact on mortality, the requirement for blood transfusions, and angiographic embolization when compared to the non-SLE group. Nevertheless, individuals with PUD who underwent SLE experienced, on average, a reduction in hospital stay by three and a half days.


A
SLE
No SLE
Odds ratio
Odds ratio
Study or subgroup Events Total Events Total Weight M-H, Random, 95%CI
M-H, Random, 95%CI
Ho Yoel Ryu 2013 15 74 11 81 41.0% 1.62 [0.69, 3.79]
Kim 2014 8 220 6 217 25.7% 1.33 [0.45, 3.89]
Mochizuki 2015 7 130 5 132 21.6% 1.45 [0.45, 4.68]
Sam Ryong Jee 2016 7 110 2 110 11.7% 3.67 [0.75, 18.08]
Total (95%CI) 534 540 100.0% 1.65 [0.96, 2.85]
Total events 37 24
Heterogeneity: Tau² = 0.00; Chi² = 1.18, df = 3 (P = 0.76); I² = 0%
Test for overall effect: Z = 1.80 (P = 0.07)
0.001 0.1 1 10 1000
Increased in SLE Increased in no SLE
B
SLE
No SLE
Odds ratio
Odds ratio
Study or subgroup Events Total Events Total Weight M-H, Random, 95%CI
M-H, Random, 95%CI
Candid Villanueva 1994 11 52 15 52 14.4% 0.66 [0.27, 1.62]
Lee 2005 7 70 12 73 12.8% 0.56 [0.21, 1.53]
Messmann 1998 14 52 11 53 14.3% 1.41 [0.57, 3.47]
Philip Wai Yan Chiu 2003 5 100 13 94 11.8% 0.33 [0.11, 0.96]
Philip Wai Yan Chiu 2016 12 152 10 153 14.8% 1.23 [0.51, 2.93]
Rapat Pittayanon 2022 9 75 14 76 14.2% 0.60 [0.24, 1.49]
Saeed 1996 0 19 5 21 2.3% 0.08 [0.00, 1.50]
Soo Jung Park 2018 16 158 9 161 15.2% 1.90 [0.81, 4.44]
Total (95%CI) 678 683 100.0% 0.80 [0.50, 1.29]
Total events 74 89
Heterogeneity: Tau² = 0.20; Chi² = 12.42, df = 7 (P = 0.09); I² = 44%
Test for overall effect: Z = 0.91 (P = 0.36)
0.01 0.1 1 10 100
Increased in SLE Increased in no SLE
C
SLE
No SLE
Odds ratio
Odds ratio
Study or subgroup Events Total Events Total Weight M-H, Random, 95%CI
M-H, Random, 95%CI
Candid Villanueva 1994 11 52 15 52 17.3% 0.66 [0.27, 1.62]
Lee 2005 7 70 12 73 14.9% 0.56 [0.21, 1.53]
Messmann 1998 14 52 11 53 17.1% 1.41 [0.57, 3.47]
Philip Wai Yan Chiu 2003 5 100 13 94 13.4% 0.33 [0.11, 0.96]
Philip Wai Yan Chiu 2016 12 152 10 153 18.0% 1.23 [0.51, 2.93]
Rapat Pittayanon 2022 9 75 14 76 17.0% 0.60 [0.24, 1.49]
Saeed 1996 0 19 5 21 2.2% 0.08 [0.00, 1.50]
Soo Jung Park 2018 16 158 9 161 0.0% 1.90 [0.81, 4.44]
Total (95%CI) 520 522 100.0% 0.70 [0.45, 1.10]
Total events 58 80
Heterogeneity: Tau² = 0.10; Chi² = 8.24, df = 6 (P = 0.22); I² = 27%
Test for overall effect: Z = 1.53 (P = 0.13)
0.01 0.1 1 10 100
Increased in SLE Increased in no SLE
D
SLE
No SLE
Std. Mean difference
Std. Mean difference
Study or subgroup Mean SD Total Mean SD Total Weight IV, Random, 95%CI
IV, Random, 95%CI
Candid Villanueva 1994 1.7 1.9 52 2.5 2.5 52 16.1% -0.36 [-0.75, 0.03]
Philip Wai Yan Chiu 2003 1.9 1.7 100 2.1 2.3 94 20.2% -0.10 [-0.38, 0.18]
Philip Wai Yan Chiu 2016 1.9 2.4 152 2.2 2.7 153 22.5% -0.12 [-0.34, 0.11]
Rapat Pittayanon 2022 9 6.68 75 6.25 4.37 76 18.5% 0.49 [0.16, 0.81]
Soo Jung Park 2018 2.4 1.7 158 2.2 1.6 161 22.7% 0.12 [-0.10, 0.34]
Total (95%CI) 537 536 100.0% 0.01 [-0.22, 0.25]
Heterogeneity: Tau² = 0.05; Chi² = 14.51, df = 4 (P = 0.006); I² = 72%
Test for overall effect: Z = 0.11 (P = 0.91)
-100 -50 0 50 100
Increased in SLE Increased in no SLE
E
SLE
No SLE
Std. Mean difference
Std. Mean difference
Study or subgroup Mean SD Total Mean SD Total Weight IV, Random, 95%CI
IV, Random, 95%CI
Candid Villanueva 1994 1.7 1.9 52 2.5 2.5 52 15.3% -0.36 [-0.75, 0.03]
Philip Wai Yan Chiu 2003 1.9 1.7 100 2.1 2.3 94 23.6% -0.10 [-0.38, 0.18]
Philip Wai Yan Chiu 2016 1.9 2.4 152 2.2 2.7 153 30.2% -0.12 [-0.34, 0.11]
Rapat Pittayanon 2022 9 6.68 75 6.25 4.37 76 0.0% 0.49 [0.16, 0.81]
Soo Jung Park 2018 2.4 1.7 158 2.2 1.6 161 30.9% 0.12 [-0.10, 0.34]
Total (95%CI) 462 460 100.0% -0.08 [-0.25, 0.10]
Heterogeneity: Tau² = 0.01; Chi² = 5.19, df = 3 (P = 0.16); I² = 42%
Test for overall effect: Z = 0.85 (P = 0.40)
-100 -50 0 50 100
Increased in SLE Increased in no SLE
F
SLE
No SLE
Odds ratio (Non-event)
Odds ratio (Non-event)
Study or subgroup Events Total Events Total Weight M-H, Random, 95%CI
M-H, Random, 95%CI
Candid Villanueva 1994 29 52 9 52 19.2% 0.17 [0.07, 0.41]
Philip Wai Yan Chiu 2003 4 100 7 94 17.5% 1.93 [0.55, 6.82]
Philip Wai Yan Chiu 2016 16 152 0 153 10.2% 0.03 [0.00, 0.45]
Rapat Pittayanon 2022 9 75 14 76 19.2% 1.66 [0.67, 4.10]
Saeed 1996 16 19 2 21 14.2% 0.02 [0.00, 0.13]
Soo Jung Park 2018 21 158 9 161 19.6% 0.39 [0.17, 0.87]
Total (95%CI) 556 557 100.0% 0.29 [0.08, 1.00]
Total events 95 41
Heterogeneity: Tau² = 1.88; Chi² = 32.58, df = 5 (P < 0.00001); I² = 85%
Test for overall effect: Z = 1.96 (P = 0.05)
0.01 0.1 1 10 100
Increased in SLE Increased in no SLE

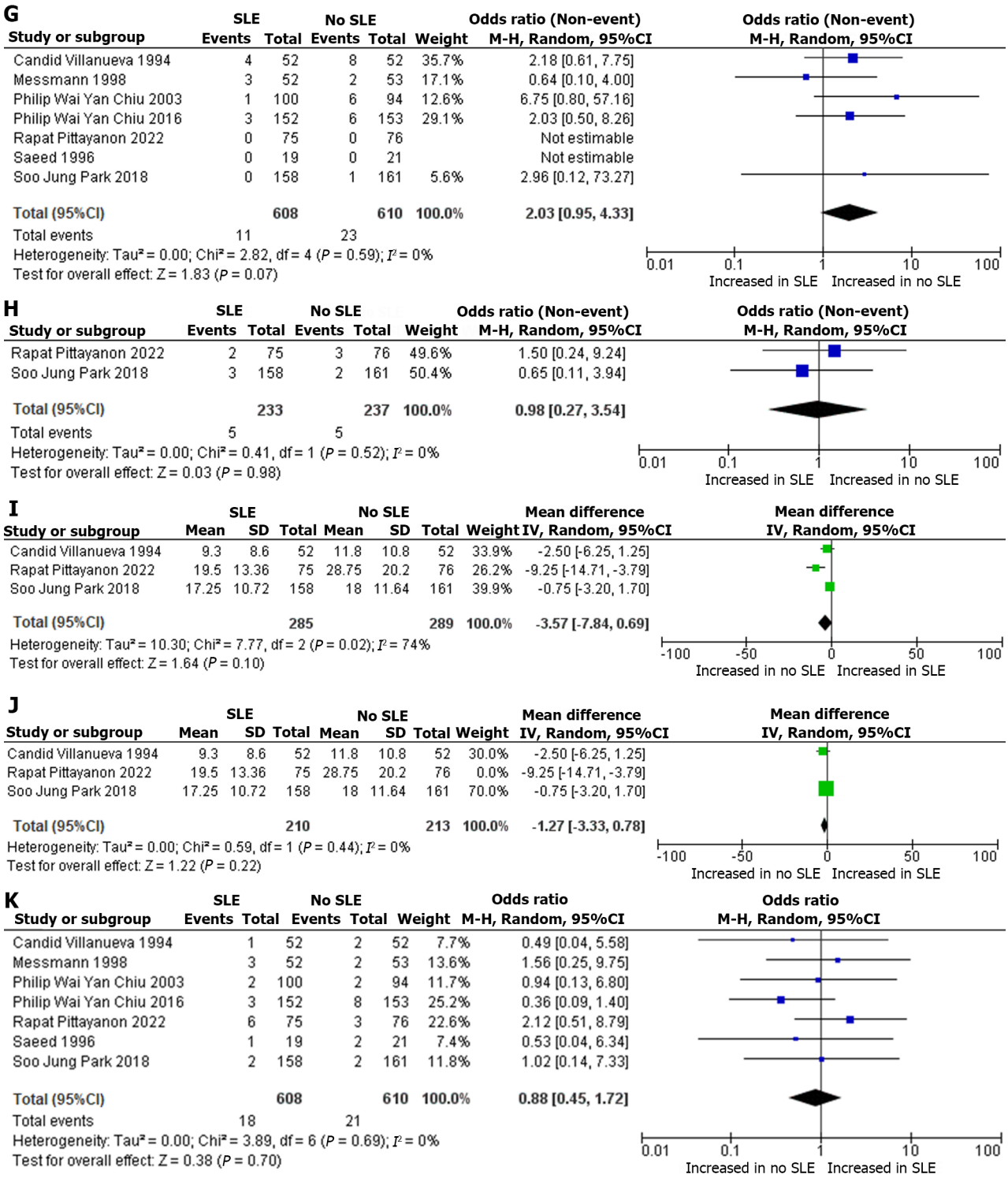


Figure 2 Forest plot and meta-analysis. A: Endoscopic submucosal dissection rebleeding; B: Peptic ulcer rebleeding; C: Rebleeding in peptic ulcer disease after excluding Park *et al*[21]; D: Blood transfusion in peptic ulcer disease; E: Blood transfusion in peptic ulcer disease after excluding Pittayanon *et al*[22]; F: Endoscopic intervention in peptic ulcer disease; G: Surgical intervention in peptic ulcer disease; H: Angiographic embolization in peptic ulcer disease; I: Hospital length of stay in peptic ulcer disease; J: Hospital length of stay in peptic ulcer disease after excluding Pittayanon *et al*[22]; K: Mortality in peptic ulcer disease. SLE: Second-look endoscopy.

A 2017 meta-analysis by Kim *et al*[16] reported that SLE after ESD did not reduce the risk of post-ESD bleeding (pooled OR =1.27, 95%CI: 0.80 to 2.00). Patients who were found to be at high risk for post-ESD bleeding during SLE underwent prophylactic hemostasis. These patients ended up with high rates of delayed post-ESD bleeding compared to those who were not prophylactically treated [pooled OR = 3.40, 95%CI: 1.87 to 6.18]. This is an interesting observation, wherein being aggressive with early/prophylactic intervention led to higher rebleeding rates and, hence, worse outcomes. SLE encourages higher rates of interventions without improved outcomes which may not be in the best interest of patients. In our research, patients treated with SLE showed notably increased rates of endoscopic interventions, but these did not lead

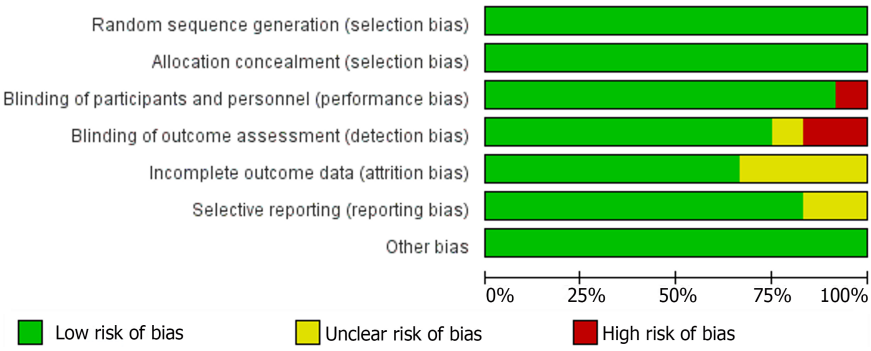


Figure 3 Risk of bias graph of included randomized controlled trials based on the Cochrane risk-of-bias (RoB) assessment tool version 1.

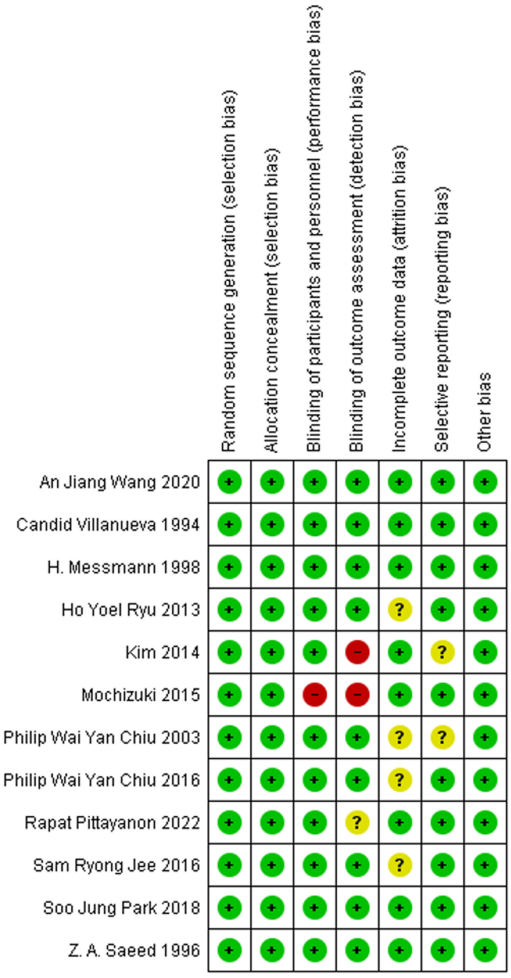


Figure 4 Risk of bias summary of included randomized controlled trials based on the Cochrane risk-of-bias (RoB) assessment tool version 1.

to improved outcomes such as mortality or decreased blood transfusion units.

In our study, SLE and non-SLE groups had no difference in the rebleeding rates after ESD. This is corroborated by a meta-analysis of risk factors for bleeding after gastric ESD by Libânio *et al*[28], which suggested that SLE was not associated with decreased post-procedural bleeding. Similarly, for PUD, SLE did not affect rebleeding, mortality, or the need for surgical intervention in our analysis, which is supported by previous studies[8,29]. However, SLE has been shown to reduce rebleeding if the risk of rebleeding is greater than or equal to 31%[8]. However, from a cost-effectiveness point of view, SLE in PUD patients who are not at an exceedingly high risk of bleeding is discouraged, especially in the current era of high-dose PPI[8,30,31].

More than half of bleeding episodes occur before SLE, and even prophylactic hemostasis on SLE was not capable of reducing bleeding[27]. Risk factors that contribute to delayed rebleeding like large size lesions, ulcerative lesions, and longer procedure time in the setting of ESD; higher bleeding score, active bleeding before initial endoscopy, a large amount of transfused blood, unsatisfactory initial endoscopic hemostasis, and use of NSAID's in the setting of PUD. This evidence suggests that the creation of risk stratification models to assess post-procedural bleeding based on patient, procedure, and high-risk lesion needs to be researched and practiced. These models can allow a cost-effective strategy by categorizing patients so that SLE can be performed in high-risk categories only[27].

According to a meta-analysis by Kamal *et al*[29], which included 9 RCTs, there was no significant difference in recurrent bleeding, need for surgery, or mean units of blood transfused. In our study, the bleeding rates were higher in the no-SLE group, although this was not statistically significant. There was no statistical difference in the mean number of transfusions nor the need for surgical intervention. There was no difference in mortality rate in our study. Interestingly, our study showed a statistically decreased length of stay in patients with PUD who had SLE. From a cost-effectiveness perspective, this is interesting as hospital systems continue to improve and address strategies to decrease the cost of care for patients and healthcare entities.

Additional research is required to assess the actual efficacy of SLE in patients with PUD and to investigate the factors contributing to a reduced hospital length of stay without a concurrent decrease in adverse outcomes.

In the study by Kim *et al*[16], for every 25 patients who stay longer in the hospital after getting preventive treatment for post-ESD bleeding during a SLE, one patient promptly received treatment for delayed bleeding.

Based on the available literature, there are no established guidelines on whether a SLE is beneficial in upper GI bleeding due to non-variceal bleeding. Studies report inconclusive results regarding its benefits. In regard to the recommendations in the setting of non-variceal bleeding by the American College of Gastroenterology (ACG) and the European Society of Gastrointestinal Endoscopy (ESGE), they do not recommend a routine SLE in patients with non-variceal upper GI bleeding unless there is recurrent bleeding[32,33]. The recommendation from the ACG is that patients with recurrent bleeding after endoscopic therapy for a bleeding ulcer undergo repeat endoscopy and endoscopic therapy rather than surgery or transcatheter arterial embolization[33,34].

The current consensus on SLE is reflected by the guidelines laid down by the ACG and the ESGE[32-34], which do not recommend performing routine SLE in patients with nonvariceal-upper-GI-bleeding. However, they recommend using SLE in cases of recurrent bleeding or in those who demonstrate a higher risk of recurrence. ACG guidelines also advise caution in choosing the type of endoscopic therapy, particularly heated probes, during SLE due to the demonstrated higher risk of perforation[33]. These recommendations are further bolstered by the findings of the International Consensus Group[35,36]. The National Institute for Health and Care Excellence, United Kingdom guidelines recommend considering SLE in all patients with a high risk of re-bleeding with emphasis on those patients whose initial endoscopic therapy was found to be inadequate to achieve hemostasis[37]. This is supported by an Asia-Pacific working group that recommends SLE in patients at high risk for recurrent bleeding[38]. In summary, the general care practice is to avoid a repeat endoscopy, to avoid iatrogenic injury in patients as non-invasive modality such as high-dose proton pump therapy is considered first line.

Strengths and limitations of our study

Our meta-analysis followed PRISMA guidelines, and our study was duly registered in PROSPERO. All the studies included in our meta-analysis were prospective RCTs, thus offering the highest grade of evidence and lending high confidence and low risk of bias to their results and, by extension, to our findings.

No previous study has conducted such an extensive meta-analysis of twelve studies, which were all prospective RCTs evaluating both ESD and PUD. We also discussed in detail the risk factors for delayed post-ESD and PUD bleeding and provided a comprehensive view of associated clinical outcomes through forest plots.

The studies included in our analysis were majorly from Asia with two from Europe and one from North America. However, given that Asia has the highest age-standardized prevalence rate of PUD[39] more studies are expected from this region. Due to a limited number of studies from the initial pool, it might be underpowered to assess their summary statistics. We consider the results of our study to be generalizable globally as they reflect the global burden of the disease.

Implications for clinical practice

For individuals with ESD and PUD, considering patient factors such as comorbidities, prior use of anticoagulants and antiplatelets, clinical status, hemoglobin levels, and units of blood transfused can guide decision-making for SLE. This personalized and individualized approach to decision-making can enhance cost-effectiveness, prevent unnecessary procedures, and reduce procedural complications.

Implication for research

Future studies should focus on types of high-risk lesions predisposing to rebleeding and patient factors that influence worse outcomes. Larger and more robust RCTs are necessary to find the true relationship between SLE and patient outcomes. Our study suggests the importance of developing risk stratification models to evaluate the risk of post-procedural bleeding, considering patient characteristics, procedural factors, and high-risk lesions. Implementing such models could facilitate a cost-effective strategy by classifying patients and ensuring that SLE is conducted specifically in high-risk categories.

CONCLUSION

Second look, endoscopy seems to offer no advantage in the prevention of ESD and PUD-associated rebleeding. The decision to perform a SLE must be personalized and individualized, despite SLE decreasing the hospital length of stay on average by 3.5 d in PUD patients.

FOOTNOTES

Author contributions: Kogilathota Jagirdhar GS, Perez JA, Banga A, Qasba RK, Qasba RK, Hussain M, Bains Y, Surani S, Kogilathota Jagirdhar GS contributed to conception and design; Kogilathota Jagirdhar GS contributed to administrative support; Kogilathota Jagirdhar GS, Perez JA, Banga A, Qasba RK, Qasba RK, Hussain M contributed to provision, collection, and assembly of data; Kogilathota Jagirdhar GS, Perez JA, Banga A, Qasba RK, Qasba RK, Hussain M contributed to the review of the literature and drafting the manuscript; Kogilathota Jagirdhar GS, Bains Y, Surani S contributed to revision of key components of the manuscript and final approval of manuscript; Kogilathota Jagirdhar GS, Perez JA, Banga A, Qasba RK are accountable for all aspects of the work.

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Corresponding Author's Membership in Professional Societies: Society of Critical Care Medicine.

S-Editor: Qu XL
L-Editor: A
P-Editor: Cai YX

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