Complications after endoscopic submucosal dissection for early colorectal cancer (Review)

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Abstract. Colorectal cancer (CRC) is a gastrointestinal malignancy that seriously threatens human life and health, resulting in a heavy disease burden. Endoscopic submucosal dissection (ESD) is widely used in clinical practice and is an effective treatment for early CRC (ECC). Colorectal ESD is a challenging operation, and the incidence of postoperative complications is relatively high because of the thin intestinal wall and limited space for endoscopic operations. Systematic reports on the postoperative complications of colorectal ESD, such as fever, bleeding and perforation, from both China and elsewhere are lacking. In the present review, progress in research on postoperative complications after ESD for ECC is summarized.

Contents

1. Introduction

Colorectal cancer (CRC) occurs in the colon or rectum, and has the third highest incidence and second highest mortality rate among types of cancer worldwide (1-3), thus it is associated with a heavy disease burden. According to the 2019 China Cancer Center report, China ranked second in CRC incidence and fourth in CRC mortality in 2015 (4). Early CRC (ECC) refers to CRC confined to the mucosal and submucosal layers, with or without lymph node metastasis (5,6). The 5-year survival rates of patients with ECC are ≥90% (7), whereas the 5-year survival rate of patients with progressive CRC is markedly lower, at <10% (8,9). Previous studies have reported that colonoscopy and lesion resection can reduce CRC incidence by 76-90% and mortality by 53% (10,11). The presence of colonic adenomas, particularly progressive adenomas, is associated with significantly increased CRC incidence and mortality, and resection of adenomas significantly reduces CRC incidence [standardized incidence ratio (SIR), 0.24-0.65] and mortality (SIR, 0.26-0.80) (12). Early detection and treatment of cancer are critical to patient prognosis. Current treatments for ECC are primarily surgery, endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR) (13). The advantages and disadvantages of ESD and EMR in different parts of the GI tract are presented in Table I. Surgery was once considered the standard method for treating early-stage gastrointestinal cancer; however, although surgery can completely remove a lesion, it has a number of disadvantages, including the associated trauma, slow recovery and high complication rates. Compared with traditional surgery, ESD preserves normal bowel function, and results in less trauma and faster postoperative recovery (14). Moreover, patients who undergo ESD for the treatment of ECC and precancerous lesions have a higher overall survival rate, with a long-term prognosis similar to that of conventional surgery (15). Compared with EMR, ESD has a relatively higher risk of complications, due to its greater surgical difficulty and longer operative time (16), but can be used to treat larger lesions, reduce the postoperative residual and recurrence rates, and yields a more accurate pathological histology report; therefore, ESD is gradually becoming the main treatment modality for early gastrointestinal cancer and precancerous lesions (17-20) (Fig. 1). Although ESD can achieve relatively good efficacy in the treatment of ECC, the incidence of post-ESD complications, including fever, bleeding, perforation, electrocoagulation syndrome and stricture, is relatively high. The relatively high complication rate

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is due to the limits of endoscopic operation and anatomical factors, such as the rich vascularity of the colorectal mucosa, the thin intestinal wall and the substantial curvature of the intestine. Therefore, understanding and controlling the occurrence of common complications after colorectal ESD surgery, related risk factors, and their prevention and control measures, are important topics for clinicians. The present review provides an overview of the occurrence of common postoperative complications after colorectal ESD, related risk factors, and prevention and control measures, to serve as a reference for clinical treatment.

2. Fever

Risk factors for fever. Fever is common after colorectal ESD, occurring in 46.7-58.3% of cases (21); however, study of fever after colorectal ESD has been somewhat neglected, with investigations focusing primarily on bleeding, perforation or electrocoagulation syndrome (22,23). Tu (24) defined fever as a temperature ≥38.0˚C, whereas Izumi *et al* (21) defined it as >37.0˚C, which indicates that postoperative fever lacks a unified standard definition. Postoperative fever is related to the release of inflammatory factors (21). ESD is a low-risk surgical operation for infection and, even if perforation occurs, the rate of bacteremia is low and transient (25); therefore, prophylactic antibiotics can generally be dispensed with. Nevertheless, certain studies have reported that prophylactic antibiotics can reduce clinical adverse events, including abdominal pain, diarrhea and fever (26,27). Therefore, prophylactic use of antibiotics after ESD remains controversial.

Risk factors for fever after ESD include age, lesion size, postoperative bleeding or perforation, and surgery duration. Advanced age is often associated with numerous underlying diseases and immune deficiency, which, together with longer ESD surgery duration, increase the risk of postoperative infection (28). Nakanishi *et al* (29) also reported that age was a risk factor for fever in patients following colorectal ESD, as was lesion size (21). Usually ESD resection depth is limited to the mucosal and submucosal layers, but sometimes it penetrates the muscular layer or all layers (30). Deeply infiltrated ulcers can form soon after ESD and the inflammatory response during their healing is another cause of fever (31). Furthermore, deep/large ulcers after ESD are associated with postoperative bleeding and perforation and, if postoperative bleeding requiring re-electrocoagulation occurs, burns to the intestinal wall can cause an inflammatory response in the plasma membrane (32). Complete intraoperative clamping of the wound in ESD can reduce perforation and various adverse events, particularly fever (33), supported by the fact that mucosal defect closure accelerates wound healing (34). Postoperative perforation combined with fever and elevated infection indicators, such as white blood cells, may indicate secondary infection (35), and surgical intervention may be required in severe cases of secondary infection (36,37).

Fever control measures. The consensus among Chinese experts is that postoperative antimicrobials should be used for patients with advanced age, extensive underlying disease, large resection area, long operative time, and postoperative bleeding or perforation (38,39). Routine use of antibiotics after ESD for possible postoperative free abdominal, mediastinal, retroperitoneal or systemic infection is recommended (40). Since post-ESD bleeding or perforation can cause fever, preoperative anticoagulation and antiplatelet drugs should be avoided. Submucosal injection of epinephrine-saline and hemostatic clips can achieve intraoperative hemostasis; to prevent perforation, adequate submucosal injection should be ensured. Cooling treatment should be given for postoperative absorption fever, while for electrocoagulation syndrome, cooling, analgesia and antibiotics are recommended For intraoperative perforation, timely clamping and antibiotics should be used. In patients with large lesion diameters and long postoperative fasting time, clinicians must be alert for postoperative fever (41). Shortening operation time and reducing serious postoperative complications, such as bleeding and perforation, are important for fever prevention after ESD.

3. Bleeding

Risk factors for bleeding. Bleeding is a common complication after ESD, and some bleeding associated with the procedure is almost unavoidable, including intraoperative and late postoperative bleeding (Fig. 2). Intraoperative bleeding is defined as active bleeding during ESD. Postoperative delayed bleeding refers to bleeding occurring >6 h after ESD, mainly manifesting as obvious blood in the stool or a decrease in hemoglobin of >20 g/l relative to the preoperative period (42-44), and is an indication for emergency endoscopic hemostasis (45). Bleeding occurs after 0-11.11% of colorectal ESD procedures (42,46-49). Li *et al* (50) reported that most late bleeding after colorectal ESD occurred within 5 days following surgery. Furthermore, the incidence of immediate and delayed postoperative bleeding has been reported to be 0.39% (95% CI, 0.11-1.3%) and 1.8% (95% CI, 1.4-2.4%) in Asian countries, and 3.3% (95% CI, 1.4-7.6%) and 3.9% (95% CI, 2.5-5.8%) in European and North American countries, respectively. Bleeding rates post-ESD are lower in Asia than in Europe (51), which may be related to the fact that ESD was performed relatively earlier and with more advanced techniques in Asian countries.

Risk factors affecting post-ESD bleeding include duration of surgery, lesion size and location, histological type, intraoperative mucosal lift, and preoperative administration of antiplatelet or anticoagulant medications. Yamamoto *et al* (52) reported that operative time, lesion location and histological type were independent risk factors for postoperative bleeding in ESD. Furthermore, the risk of delayed bleeding is higher in cecum lesions than those at other sites (53). Chiba *et al* (54) reported an increased risk of delayed bleeding after ESD when lesions were in the rectum and ≥40 mm. Inadequate submucosal injection volume and high fibrosis at the lesion site are risk factors for delayed bleeding after colorectal ESD (50,55), as well as a major cause of poor separation of the mucosal layer from the mucosal muscle layer. Therefore, more caution is needed for poorly elevated colorectal lesions. A higher risk of postoperative bleeding has been reported in hypertensive patients treated with ESD (56-58); however, other studies reported no correlation between hypertension and postoperative bleeding after ESD (50,59). A previous study reported that the effect of lesion size on delayed bleeding

Table I. Advantages and disadvantages of ESD and EMR at esophagus, stomach and colorectal sites.

A, ESD

Advantages or disadvantages	Site			
	All	Esophagus	Gastric	Colorectal
Advantages	1. High rate of whole resection and radical. resection 2. Low local recurrence rate.	First-line therapy for early-stage esophageal cancer.	1. Preferred for early gastric cancer. 2. Enables accurate pathological assessment and curative resection.	1. The primary treatment option for early colorectal cancer. 2. Enables accurate pathological assessment and curative resection.
Disadvantages	1. High operational requirements. 2. High surgical difficulty. 3. High surgical trauma. 4. High cost.	1. A small operating space. 2. High risk of postoperative complications, including bleeding, perforation and stenosis.	High risk of postoperative bleeding and perforation.	1. Anatomical factors, such as the thin intestinal wall, the relatively free part of the intestinal segment and the small operating space of the intestinal cavity determine that the operation is more difficult than that of the upper gastrointestinal tract. 2. There is a marked risk of postoperative bleeding, perforation and stricture. 3. Only routinely performed by a few large centers.

B, EMR

Advantages or disadvantages	Site			
	All	Esophagus	Gastric	Colorectal
Advantages	1. Simple surgical operation. 2. Low surgical trauma. 3. Lower cost.	1. Lesion diameter ≤10 mm, superficial gastric tumor, choice of whole block resection. 2. Low incidence of postoperative bleeding, perforation and stenosis.	1. UL0 cT1a, differentiated carcinoma, lesion diameter ≤20 mm, able to be resected in its entirety. 2. Low incidence of postoperative bleeding and perforation.	1. Superficial intestinal tumor, ≤20 mm in length and diameter, can be removed whole. 2. Low incidence of postoperative bleeding, perforation and stricture.
Disadvantages	Local residual, high risk of recurrence	1. Early esophageal adenocarcinomas after EMR resection, ablation therapy is recommended after resection. 2. Partial, incomplete resection, making assessing the radical effect difficult	Partial incomplete excision of local residuals or EPMR, which interferes with accurate pathological assessment.	Partial incomplete excision of local residuals or EPMR, which interferes with accurate pathological assessment.

UL0, no ulcer and ulcer scar; cT1a, intramucosal carcinoma; EPMR, endoscopy piecemeal mucosal resection; ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection.

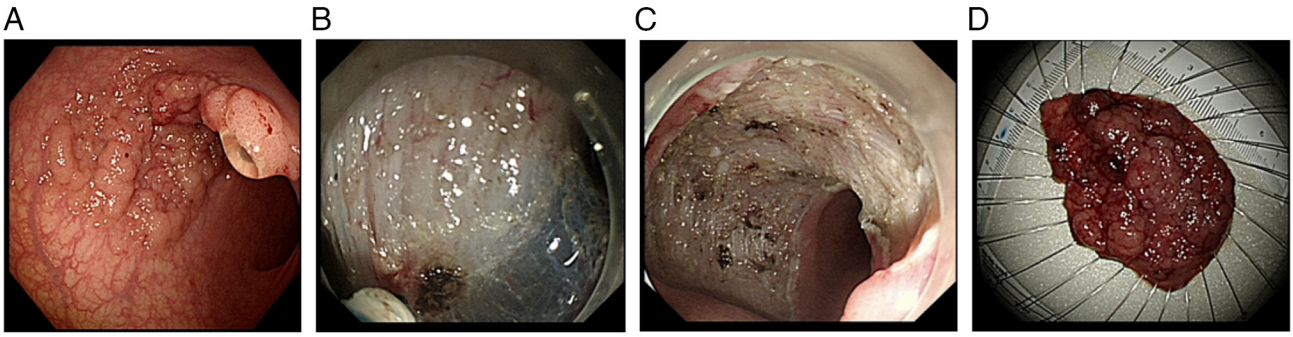

Figure 1. Patient 1. Images were obtained from the Gastrointestinal Endoscopy Center of The First Affiliated Hospital of Kunming Medical University (Kunming, China). Endoscopic submucosal dissection. (A) Laterally spreading tumors located in the rectum. (B) Dissection procedure: Peeling of submucosa and lesions. (C) Post-dissection trauma. (D) A dissected lesion.

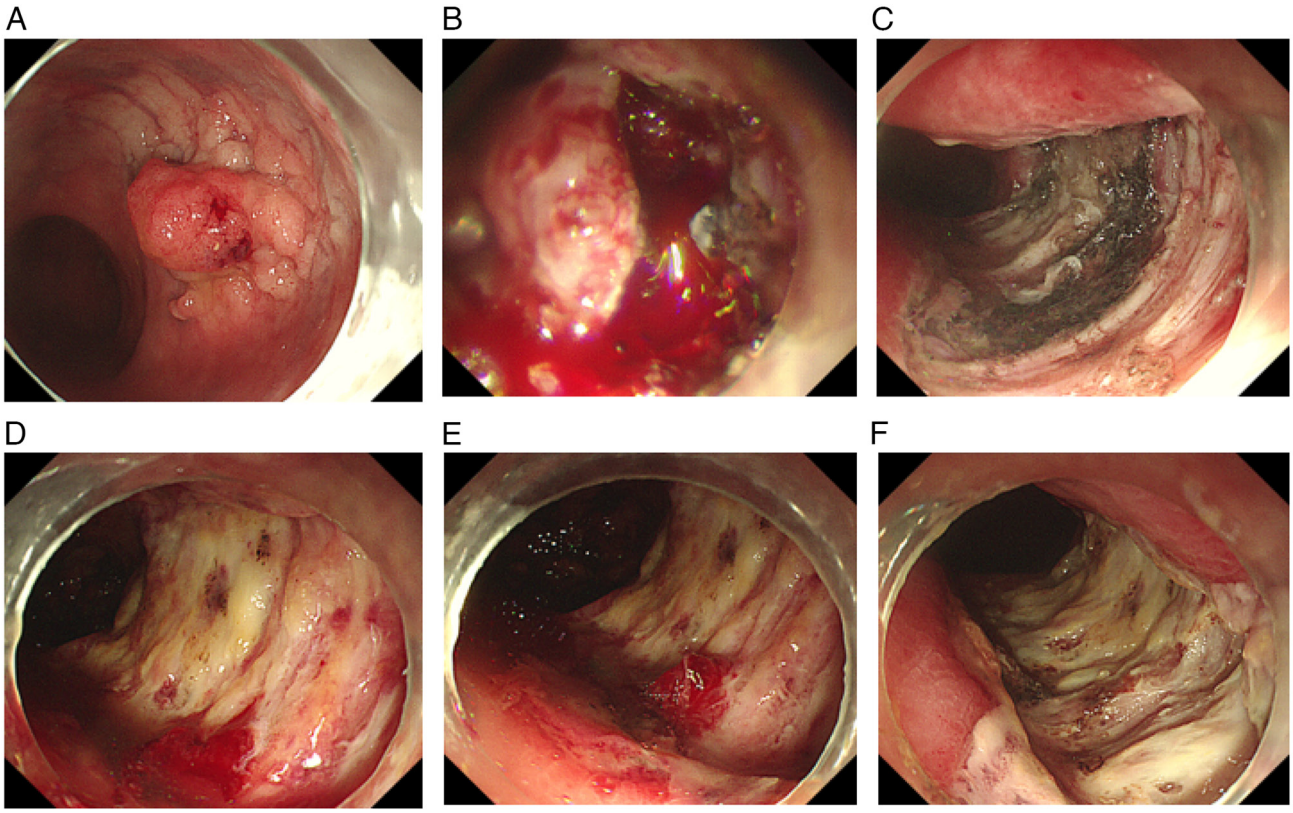

Figure 2. Patient 2. Images were obtained from the Gastrointestinal Endoscopy Center of The First Affiliated Hospital of Kunming Medical University (Kunming, China). Complicated bleeding after endoscopic mucosal dissection. (A) Laterally spreading tumors located in the rectum with (B) bleeding during dissection. (C) Trauma after dissection. (D) Complicated bleeding 1 week after endoscopic submucosal dissection. (E) Postoperative bleeding and (F) following repeated endoscopic hemostasis.

was not statistically significant (60); however, some scholars take the opposite view (59). Previous reports stated that antiplatelet agents should be discontinued before ESD treatment (56,61,62), unless patients are at high risk of combined thromboembolism; however, certain studies disagree (47,59). Therefore, risk factors for postoperative bleeding after ESD to date are controversial, and further research is needed.

Measures to prevent and treat bleeding. Most bleeding from small vessels after ESD can be stopped by electrocoagulation (14). Bleeding from larger vessels requires hemostasis by metal clip closure combined with electrocoagulation (14). During ESD, effective identification of submucosal vessels, timely electrocoagulation and careful treatment of trauma are essential. Furthermore, local cleaning with ice-cold saline containing norepinephrine and hemostatic drugs, such as hemagglutinin, can achieve a hemostatic effect and effectively reduce postoperative bleeding risk (63), while prophylactic clamping of trauma reduces delayed bleeding risk after colorectal ESD (64) by reducing irritation from intestinal contents and accelerating incision healing. Therefore, for larger colorectal lesions, clamping of trauma is beneficial to promote incisional healing and prevent delayed bleeding. Emergency management measures related to postoperative

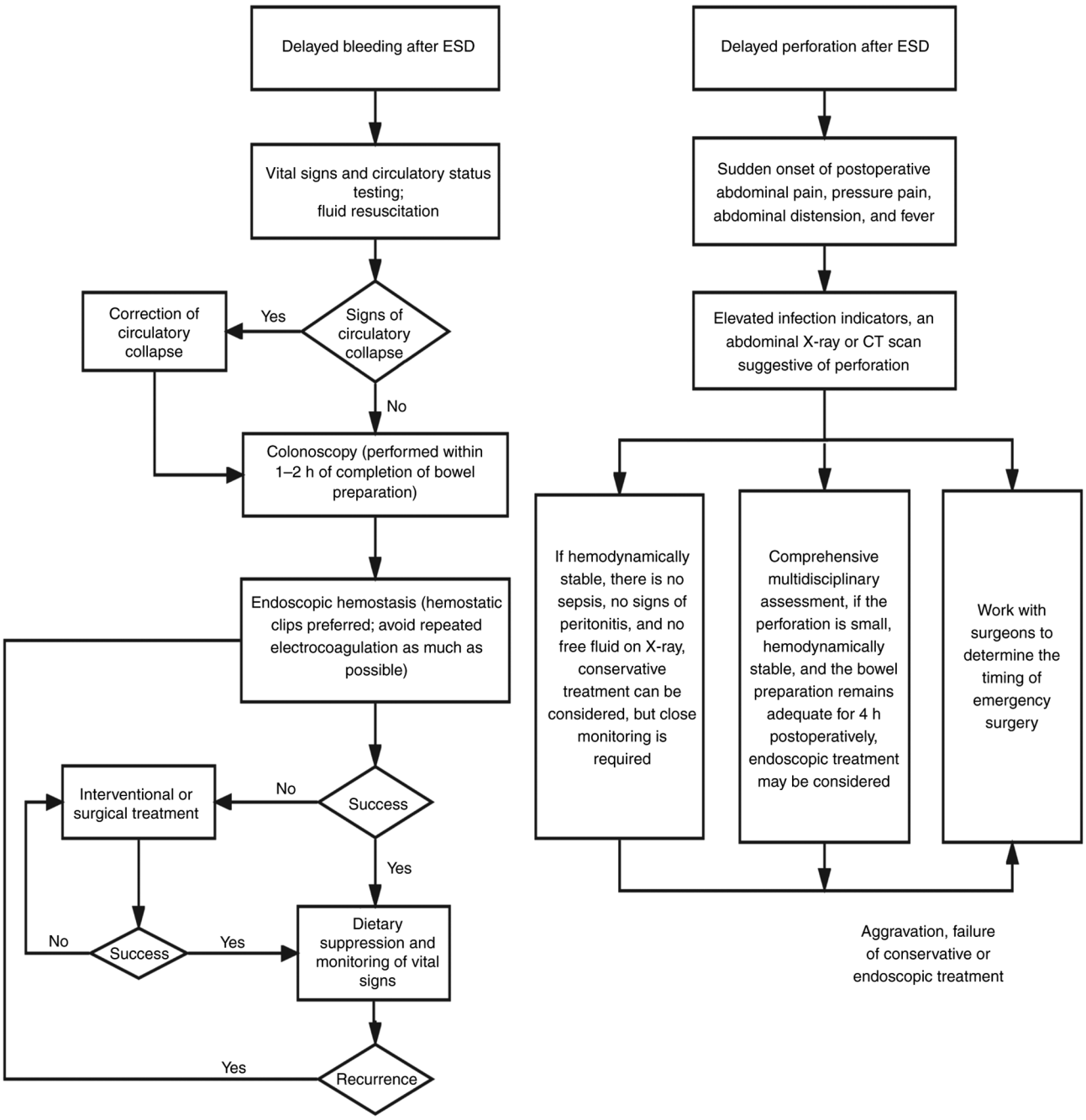

Figure 3. Flowchart for emergency treatment of bleeding or perforation after ESD. ESD, endoscopic submucosal dissection.

bleeding in ESD are shown in Fig. 3. Huang *et al* (65) reported that patients with colorectal lesions who received traction ring-assisted ESD experienced significantly less intraoperative bleeding than those who did not .

4. Perforation

Risk factors for perforation. The risk of perforation is elevated after colorectal ESD because the muscular layer of the intestinal wall is thinner than that in the gastric wall (51,66). The main goal of ESD treatment is complete resection without perforation (67) and reported perforation rates after colorectal ESD are 0-10.7% (44,68). Perforations include intraoperative and delayed perforations. Intraoperative perforation (69) is defined as an intraoperative, endoscopically confirmed bowel wall defect, most of which can be successfully clamped endoscopically. Delayed perforation (70) is defined as perforation occurring after ESD, with postoperative peritonitis, and can be confirmed by abdominal X-ray or computed tomography (CT) (Fig. 4). Most delayed perforations occur within 14 h of surgery (44) and, although incidence is very low, when it occurs, spillage of bowel contents causes severe peritonitis, which often requires surgery (71,72), indirectly illustrating the importance of preoperative bowel cleansing. Similar to postoperative bleeding, immediate and delayed perforation rates were reported to be 3.8% (95% CI, 3.1-4.6%) and 0.18% (95% CI, 0.08-0.42%) in Asian countries, and 6.6% (95% CI, 4.6-9.4%) and 1.2% (95% CI, 0.29-4.6%) in European

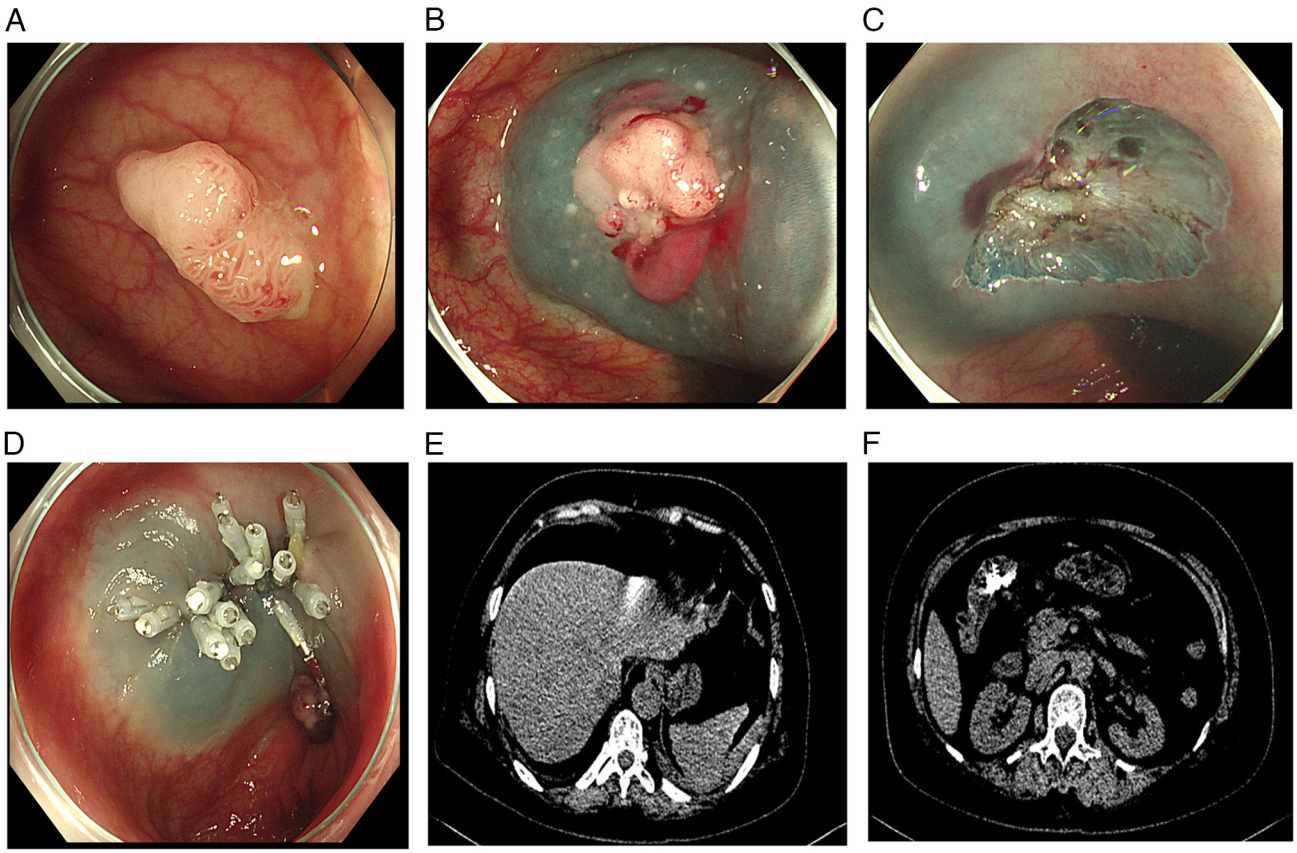

Figure 4. Patient 3. Images were obtained from the Gastrointestinal Endoscopy Center of The First Affiliated Hospital of Kunming Medical University (Kunming, China). Complicated perforation after endoscopic mucosal dissection. (A) A polyp located in the hepatic flexure of the transverse colon. (B) Submucosal injection. (C) Trauma after dissection and (D) closure of the trauma with titanium clips. (E) Abdominal computed tomography scan 12 h after surgery which suggested perforation and (F) a large volume of free gas was seen in the abdominal cavity and under the diaphragm.

and North American countries, respectively. These findings indicated that the incidence of postoperative colorectal ESD perforation is lower in Asia than in Europe (51).

Risk factors influencing perforation after colorectal ESD include duration of surgery, lesion size, lesion location and submucosal fibrosis. Su *et al* (73) reported that the perforation rate in patients with colorectal lesions >4 cm in diameter (7.04%) was higher than that in patients with lesion diameter <4 cm (5.2%), there was a significant difference between the two groups. Hong *et al* (74) reported that lesion size, submucosal fibrosis and duration of surgery were associated with postoperative perforation after colorectal ESD. Another study reported tumor size, site, submucosal fibrosis and operator experience as potential risk factors for postoperative perforation (75). Furthermore, a Japanese study reported that longer operative times were more likely to result in postoperative perforation of the colorectal ESD (52). Prolonged operative time is related to various factors, such as operator experience and the difficulty of the ESD procedure. Another study reported a higher incidence of perforation following left hemicolectomy (73). Further studies are needed in the future regarding the relationship between the lesion site and postoperative perforation of colorectal ESD.

Preventive measures for perforation. Perforation post-colorectal ESD is a serious complication that can cause extensive peritonitis, infectious shock and even be life-threatening. Adequate preoperative preparation, such as water fasting and bowel cleansing, is necessary. The colorectal wall is relatively weak and thermal damage from excessive electrocoagulation may lead to perforation; therefore, avoiding excessive intraoperative electrocoagulation can reduce postoperative perforation incidence (72,76). Adequate submucosal injection reduces perforation due to disruption of the muscularis during dissection caused by electrocoagulation. Furthermore, timely perforation closure is closely related to prognosis and can reduce peritonitis occurrence (77). If intraoperative perforation occurs, it can generally be detected and smaller perforations can be closed with metal clips. For larger perforations, metal clips combined with nylon rope wrap, alongside fasting and gastrointestinal decompression, the use of intravenous antibiotics and other means, may be required; generally, the treatment is effective (78). Surgical laparoscopic exploration and repair are preferable in cases of delayed perforation that cannot be completely closed endoscopically or for cases in which conservative treatment is ineffective (14) (Fig. 3).

5. Post-ESD electrocoagulation syndrome (PEECS)

Risk factors for PEECS. PEECS refers to a group of inflammatory response syndromes, including limited peritonitis, which can are caused by electrocoagulation damage to the intestinal wall during ESD (72,79). The reported incidence of PEECS is 4.8-14.2% (22,80-83). Typical clinical manifestations of

PEECS include abdominal pain, limited peritoneal irritation, fever and chills, among others. Laboratory tests show elevated leukocytes and C-reactive protein, and abdominal X-ray or computed tomography scans reveal no signs of perforation. PEECS does not usually require surgical treatment, but can result in delayed perforation in severe cases (84). Based on analysis of relevant domestic and international literature, the mechanism underlying PEECS remains unclear.

Research on risk factors associated with PEECS has gradually increased in recent years. Age, lesion diameter, combined malignancy and lesion location have been reported as independent risk factors for PEECS development (80). Female sex, lesion site, lesion size and submucosal fibrosis have also been reported to be associated with PEECS occurrence (22,85,86). Sun *et al* (81) reported a higher incidence of PEECS after colonic ESD than rectal ESD, and that larger lesions were associated with a higher incidence of PEECS. Notably, Yamasaki *et al* (87) reported that line-assisted complete clip closure was effective in reducing PEECS incidence. This subject warrants further study in the future.

Prevention and control measures for PEECS. Compared to bleeding and perforation, PEECS are less severe and have a better prognosis, but there remains a risk of delayed perforation. Once diagnosed, immediate treatment, such as fasting, keeping the bowels open and intravenous administration of broad-spectrum antibiotics, can alleviate symptoms; however, in rare cases where conservative treatment is ineffective or the condition worsens, the possibility of delayed perforation should be considered. If intestinal perforation is confirmed, immediate surgical repair is required. Li *et al* (84) reported that placement of anal canal drainage and decompression after ESD reduced the incidence of postoperative PEECS, possibly because of a reduced risk of infection, and delayed perforation, due to reduced exposure of the surgical wound to intestinal bacteria and fecal matter. A study in the United States reported that prophylactic antibiotics reduced the risk of PEECS and effectively relieved abdominal pain (88). Furthermore, prolonging mucosal augmentation time at the lesion may reduce the risk of intestinal wall damage caused by electrocoagulation, thus reducing the risk of PEECS (89).

6. Other complications

Stenosis. Stenosis is a less frequent complication after colorectal ESD, generally defined as the inability of a normal endoscope to pass successfully through the postoperative bowel lumen. A study by Hayashi *et al* (90) reported that the incidence of colorectal stenosis was 0.49% (4/822 cases) and that of postoperative stenosis was 11% (2/18) for 90-100% circumferential lesions. Another study (91) reported that the stenosis rate after rectal ESD was 19.7% (12/61), with that of stenosis after total circumferential resection 71.4% (5/7), and that of stenosis after circumferential >90% lesion resection 43.8% (7/16). The results of these studies suggested that circumferential resection of large lesions is a risk factor for postoperative stenosis. General endoscopic balloon dilatation treatment may improve postoperative stenosis to a certain extent, while local hydrocortisone enemas may also help to prevent postoperative stenosis (92).

Fulminant necrotizing fasciitis (Fournier's syndrome). Due to its anatomical location, perforation of the lower rectum after surgery can easily cause mediastinal or subcutaneous emphysema, and it is challenging to confine the infected lesion to a single location. Therefore, such lesions can easily spread along the loose tissue to the buttocks and abdomen, causing multiple muscle necrosis and inflammation of the surrounding fascia. Such fulminant necrotizing fasciitis (Fournier's syndrome) is rare clinically, and has few reports to date. Once present, the condition can easily cause sepsis and diffuse intravascular coagulation with serious consequences. Fournier's syndrome is exceptionally aggressive, with reports of mortality rates as high as 20-40%. Therefore, prompt treatment with broad-spectrum antibiotics and surgery should be used following detection (44).

7. Summary

In summary, ESD has both advantages and disadvantages for the treatment of ECC, and reducing the occurrence of postoperative complications is an important safeguard for the successful implementation of colorectal ESD surgery. Therefore, endoscopists should strictly grasp the indications for ESD surgery, understand the relevant risk factors affecting postoperative complications, and take immediate and effective measures to intervene once they occur, which will effectively improve the safety of colorectal ESD treatment. Furthermore, the clinical application of colorectal ESD could be further expanded, so that more patients with early-stage colorectal cancer can benefit from ESD technology in the future.

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Availability of data and materials

Not applicable.

Authors' contributions

JS was responsible for research design, conceptualization and writing the first draft. XX, DZ and XH were responsible for conceptualization, organization, investigation and research design. YL and GY were responsible for supervision, conceptualization and revision of the manuscript. QN was responsible for research supervision and revision of the manuscript. Data authentication is not applicable. All authors contributed to the article, and read and approved the final manuscript.

Ethics approval and consent to participate

The publication of the images in the figures was approved by the Ethics Committee of The First Affiliated Hospital of Kunming Medical University (Kunming, China).

Patient consent for publication

Written informed consent for publication of the images in the figures was obtained from the patients.

Competing interests

The authors declare that they have no competing interests.

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