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Oncologic safety¹ of colonic stenting as a bridge to surgery in left-sided malignant colonic obstruction: Current evidence and prospects

Pattarajierapan S *et al.* Oncologic safety of colonic stenting

Sukit Pattarajierapan, Nattapanee Sukphol, Karuna Junmitsakul, Supakij Khomvilai

Abstract

Approximately 7%-29% of patients with colorectal cancer present with colonic obstruction.¹ The concept of self-expandable metal stent (SEMS) insertion as a bridge to surgery (BTS) is appealing. However, concerns on colonic stenting possibly impairing oncologic outcomes have been raised. This study aimed to review current evidence on the short- and long-term oncologic outcomes of SEMS insertion as BTS for left-sided malignant colonic obstruction. For short-term outcomes, colonic stenting facilitates a laparoscopic approach, increases the likelihood of primary anastomosis without a stoma, and may decrease postoperative morbidity. However, SEMS-related perforation also increases local recurrence and impairs overall survival. Moreover, colonic stenting may cause negative oncologic outcomes even without perforation. SEMS can induce shear forces on the tumor, leading to increased circulating cancer cells and aggressive pathological characteristics, including perineural and lymphovascular invasion. The conflicting evidence has led to discordant guidelines. Well-designed collaborative studies that integrate both oncologic outcomes and data on basic research (*e.g.*, alteration of circulating tumors) are needed to clarify the actual benefit of colonic stenting as BTS.

Key Words: Bridge to Surgery; Colon cancer; Colorectal surgery; Emergency treatment; Intestinal obstruction; Self-expandable metal stent

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Core Tip: Although the concept⁴ of self-expandable metal stent (SEMS) insertion as a bridge to surgery in patients with left-sided malignant colonic obstruction is promising, there remain concerns of adverse oncologic outcomes. Nowadays, three possible mechanisms of tumor dissemination from SEMS have been proposed: (1) SEMS-related perforation; (2) increased circulating tumor cells; and (3) aggressive pathological features after SEMS placement. However, among these, only SEMS-related perforation clearly influences adverse oncologic outcomes. The other two mechanisms lack consistent clinical evidence for their association with decreased survival. Therefore, further collaborating studies are needed to validate the clinical impact of these hypotheses.

⁷ INTRODUCTION

Colorectal cancer (CRC) is the fourth most common malignant disease worldwide, with more than 1.9 million new cases recorded in 2020^[1]. Patients with CRC are presented with bowel obstruction for 7%-29%^[2]. The outcomes of emergency surgery (ES) for patients with obstructed CRC are worse than those of elective surgery for patients without obstruction. Patients with obstructed CRC also have a higher mortality rate than those without obstruction (17% vs 6%, respectively)^[3]. The causes of the high morbidity and mortality of ES are advanced-stage cancer, malnutrition, electrolyte abnormalities, colonic mucosa injury from¹ distention, and fecal loading of the obstructed colon^[4]. The self-expandable metal stent (SEMS) insertion as a bridge to surgery (BTS) concept, which converts an emergency condition to an elective one, is

fascinating. Colonic decompression by SEMS gives time to stabilize medical conditions that distinctly benefit high-risk patients.

The benefits of SEMS as BTS for right-sided malignant colonic obstruction (RMCO, defined as an obstructed tumor located between the cecum and distal transverse colon) are limited. Currently, right colectomy with primary anastomosis is the recommended treatment for RMCO^[5]. Ileocolic anastomosis is associated with the lowest incidence of leaks, ranging from 1% to 3%, and can be performed in cases with obstructive situation^[6,7]. Therefore, the World Society of ES (WSES) guideline does not recommend SEMS as BTS for RMCO except in high-risk patients^[5]. In contrast, SEMS insertion as BTS in left-sided malignant colonic obstruction (LMCO, defined as an obstructed tumor located between the splenic flexure and rectosigmoid junction) is very beneficial. In addition to the feasibility of laparoscopic resection, SEMS insertion allows the feasibility of elective single-stage colonic resection with a lower risk of permanent stoma creation^[8].

However, the long-term oncologic outcomes are a matter of concern. SEMS induces shear force to the tumor and may lead to cancer cell dissemination into the peritoneal cavity, lymphatic fluid, and bloodstream^[9,10]. A few studies suggested that SEMS insertion was associated with worse oncologic outcomes than ES, especially in patients with SEMS-related perforation^[11,12]. Nevertheless, recent studies with low complication rates reported good oncologic outcomes with SEMS placement with BTS^[13-19]. As a result, current guidelines are dynamic and discordant because of the conflicting evidence^[20-24].

As such, this study aimed to perform a comprehensive review of the current evidence on the short- and long-term oncologic outcomes of SEMS insertion as BTS for LMCO.

TREATMENT OPTIONS FOR LMCO

ES

Emergent procedures for LMCO include various procedures such as Hartmann's procedure, segmental colectomy with/without on-table lavage, and subtotal/total

colectomy. These procedures result in high morbidity and mortality because of the limited time to stabilize the patient's condition before surgery^[4]. Among these, Hartmann's procedure remains one of the most common emergency procedures for the left colon because of the short operative time and avoidance of anastomotic leakage^[25]. However, the rate of reversal of Hartmann's procedure is less than 50% because this operation is associated with high morbidity and possible mortality^[26,27]. As a result, most of them turn to permanent stomas that severely affect the patient's quality of life. Laparoscopic approach for ES of LMCO has limited application because of technical difficulties during surgery. The WSES guideline does not recommend its use except in select cases in specialist centers^[5].

Colonic stenting as a BTS

Dohmoto *et al*^[28] was the first to report the idea of using plastic tubes as colonic stenting for palliation of obstructed rectal cancer in 1991. One year later, Spinelli *et al*^[29] started using SEMS insertion as a palliative modality with good results. After the success of palliative SEMS placement, the BTS concept was introduced by Tejero *et al*^[30] in 1994. They described 3 phases of SEMS as BTS: (1) relieving obstruction by SEMS; (2) recovering the patient's condition and mechanically preparing the colon; and (3) definitive elective surgery. It has been 30 years since the introduction of colonic stenting. Palliative SEMS placement is established as a preferred option in incurable malignant colonic obstruction because it confers superior quality of life by avoiding stoma and is associated with shorter time to initiation of chemotherapy than palliative surgery^[21]. In contrast, the role of SEMS as BTS is still controversial, with concerns of adverse oncologic outcomes after SEMS insertion limiting its application as BTS.

Stent materials and technical considerations

There are different types of SEMS materials including stainless steel, elgiloy, and nitinol^[31]. Endoscopists should be aware of the characteristics of each stent. Stainless steel stents are relatively stiff and interfere with magnetic resonance imaging (MRI)

examination. Meanwhile, elgiloy stents have better elasticity and flexibility and do not interfere with MRI assessment. Nitinol stents are made of nickel-titanium and have poorer fluoroscopic visualization compared with elgiloy stents. Therefore, radiopaque markers, such as gold or silver markers, are added to both ends of these stents. Nitinol stents have superior flexibility and better memory to hold the original shape than stainless steel and elgiloy stents; consequently, nitinol stents are popular worldwide.

SEMS is classified as covered or uncovered. Covered SEMS has a silicone membrane on bare wires, preventing tumor ingrowth. For obstructed CRC, uncovered SEMS is recommended for both curative and palliative settings^[21]. A recent meta-analysis, including one randomized controlled trial (RCT) and nine observational studies, compared covered and uncovered SEMS in curative and palliative settings. The study found that uncovered SEMS was associated with fewer complications (relative risk [RR]: 0.57; 95% CI: 0.44-0.74; $P < 0.001$), tumor ingrowth (RR: 0.29; 95% CI: 0.09-0.93; $P = 0.040$), and SEMS migration (RR: 0.29; 95% CI: 0.17-0.48; $P < 0.001$)^[32]. Meanwhile, there was limited evidence regarding the optimal SEMS diameter^[21]. Previous studies showed no association between SEMS diameter and success or perforation rate^[33,34]. However, a few studies suggested an association between SEMS diameter < 24 mm and adverse events, especially migration^[35-37]. Regarding SEMS length, it is recommended that the SEMS should be long enough to extend at least 1.5-2 cm on each side of the lesion, and the degree of SEMS shortening after deployment must be considered^[21].

Colonic stenting can be performed endoscopically (through-the-scope technique) or fluoroscopically (over-the-wire technique). Several studies showed comparable technical success rate between endoscopic and fluoroscopic methods, but a combined endoscopic-fluoroscopic method showed the highest success rate^[38-41]. Therefore, the European Society of Gastrointestinal Endoscopy (ESGE) guideline recommends that colonic stenting should be performed with the combined use of endoscopy and fluoroscopy^[21]. For the combined technique, a soft-tipped hydrophilic guidewire is passed through the strictured lumen. Contrast injection helps to delineate the stenosis and to confirm guidewire placement under fluoroscopy. The SEMS is then passed over

the guidewire and deployed under endoscopic visualization and fluoroscopic guidance^[42] (Figure 1). Stricture dilation should not be performed either before or after colonic stenting as it increases the risk of perforation^[21,43]. The recommended interval to curative resection after BTS stenting is approximately 2 wk^[21].

Benefit of colonic stenting as a BTS for LMCO

Owing to the high morbidity (45%-50%) and mortality (15%-20%) of ES for obstructed CRC, the BTS concept of avoiding an emergent situation is appealing^[44]. After relieving the obstruction by SEMS placement, the clinicians can have time to stabilize the patients, improve their nutrition, correct electrolyte imbalance, and mechanically prepare the colon before definite resection. In addition, it is crucial that surgeons gain the ability to perform laparoscopic resection after BTS stenting (Figure 2). Compared with open resection, laparoscopic resection is associated with lower postoperative pain, earlier recovery of bowel function, and shorter hospital stay^[45].

Nine RCTs have investigated the short-term outcomes of SEMS placement as BTS in comparison with those of ES for LMCO (Table 1). Notably, perforation after SEMS insertion and the success rate influenced postoperative outcomes. Four RCTs without perforation showed that SEMS insertion as BTS had a lower morbidity rate than ES^[46-49]. Meanwhile, 1 RCT with a low stent success rate (70%) and 3 RCTs with 6.6%-12% perforation rate showed no difference in morbidity between SEMS insertion as BTS and ES^[15,50-52]. Additionally, RCTs with low perforation rate also showed a significantly lower rate of postoperative stoma^[15,46,53]. Stoma is well recognized to adversely affect quality of life. We conducted meta-analyses that included these nine RCTs. Of these, seven, nine, and seven studies reported the stoma rates, postoperative morbidity, and mortality rates, respectively. In the SEMS group, the stoma rate (RR: 0.68; 95%CI: 0.55-0.85, $I^2 = 19\%$) and postoperative morbidity (RR: 0.67; 95%CI: 0.48-0.94, $I^2 = 65\%$) were significantly lower than those in the ES group (Figures 3 and 4). There were no differences in mortality rates between the SEMS and ES groups (RR: 0.95; 95%CI: 0.53-1.70, $I^2 = 0\%$) (Figure 5).

In 2021, Cirocchi *et al*^[54] conducted a systematic review and meta-analysis of RCTs and found that compared with ES, SEMS placement as BTS had a higher rate of successful primary anastomosis (RR: 1.26; 95%CI: 1.01-1.57), lower stoma rate (RR: 0.62; 95%CI: 0.45-0.85), and lower postoperative complication (RR: 0.61; 95%CI: 0.45-0.85). The mortality rate was comparable between the two modalities. To conclude, SEMS placement as BTS clearly has short-term benefits of higher primary anastomosis, lower stoma rate, and lower morbidity than ES. In this context, low perforation and high stenting success rates are needed to benefit from SEMS.

ONCOLOGIC OUTCOMES AFTER COLONIC STENTING IN CURABLE DISEASE

Despite the impressive short-term results of SEMS placement as BTS, its application has been debated due to concerns about adverse long-term oncologic outcomes. Theoretically, shear forces created by SEMS might lead to cancer cell dissemination through the following three possible mechanisms (Figure 6): (1) SEMS-related perforation; (2) increased circulating tumor cells; and (3) aggressive pathological features after SEMS placement.

SEMS-related perforation

In obstructed CRC, manipulation of the ulcerated and necrotic tissue through SEMS may cause tumor perforation, which is the most feared complication of SEMS insertion. Perforation causes tumor dissemination into the peritoneal cavity and increases locoregional recurrence and peritoneal carcinomatosis, which affects long-term outcomes^[55]. Perforation can be classified into clinical and silent perforation. Interestingly, some studies showed that silent perforation in SEMS as BTS can occur in up to 6%-27% of patients^[43,51,52,56]. Further, this rate may still be underestimated because silent perforation can be diagnosed only from pathological assessment of the surgical specimen. Given that there have been sparse reports of silent perforation in the literature, its impact on oncologic outcomes is difficult to verify; however, it should not be disregarded.

¹ In the Dutch Stent-In 2 trial, Sloothaak *et al*^[57] found that 83% of patients with SEMS-related perforation have recurrence. Moreover, Gorissen *et al*^[11] suggested that local recurrence was higher in patients who underwent SEMS placement as BTS than in those who underwent ES (32% *vs* 8%, $P = 0.04$). In this study, all patients with perforation had recurrence. Sabbagh *et al*^[58] found that SEMS-related perforation was an independent risk factor for poor overall survival. ¹ Sensitivity analyses revealed that 3-year overall survival was better in studies with < 8% SEMS-related perforation rate than in those with $\geq 8\%$ ^[59]. Balciscueta *et al*^[55] recently conducted a systematic review and meta-analysis of 13 studies (1 RCT, 4 prospective studies, 8 retrospective studies) with long-term oncologic outcomes. The ³ overall rate of SEMS-related perforation was 8.9%. The locoregional recurrence rate was higher in patients with perforation than in those without perforation (26.6% *vs* 12.5%; OR: 2.41; 95%CI: 1.33-4.34; $P = 0.04$), while the systemic recurrence rate was comparable.

In summary, SEMS-related perforation influences the occurrence of adverse oncologic outcomes; therefore, an endoscopist's experience and expertise are crucial with respect to deciding between SEMS placement as BTS or ES. The ESGE guideline recommends a shared decision-making discussion with the patient that should include the availability of stenting expertise and the risk of perforation in the endoscopy unit^[21].

Increased circulating tumor cells

¹ SEMS placement could impair oncologic outcomes despite the absence of perforation. SEMS exerts shear forces on the tumor and makes tumor cells disseminate throughout the body^[60]. ¹ Maruthachalam *et al*^[9] found a more significant rise in cytokeratin 20 messenger RNA expression in peripheral circulation after SEMS placement than after conventional colonoscopy. The presence of messenger RNA coding for epithelial markers indicates the presence of tumor cells or shed debris in the circulation. Furthermore, Yamashita *et al*^[10] found that SEMS placement induces tumor cell dissemination into the peripheral circulation. Using circulating cell-free DNA (cfDNA) and circulating tumor DNA (ctDNA) as indicators, Takahashi *et al*^[61] recently found

that SEMS insertion may cause massive cellular and tumor damage. The patients who underwent SEMS placement had higher postoperative plasma levels of both cfDNA and ctDNA than did those who underwent transanal tube decompression. On the contrary, Ishibashi *et al*^[62] found that the increase of circulating tumor cells after SEMS insertion may be temporary, as in most cases, the number of circulating tumor cells decreased 4 d after SEMS placement. Although evidence of tumor cell dissemination after SEMS placement exists, there is inadequate clinical evidence of its negative effects on survival and prognosis.

Aggressive pathological features after SEMS placement

SEMS insertion leads to a sudden increase in interstitial pressure inside the tumor mass, possibly causing detachment of cells and tumor embolization towards the lymphatic systems and resulting in lymphatic invasion^[63]. Hayashi *et al*^[64] noted that the tumor pressure is important, not only for the number of tumor cells shed, but also for the size of emboli shedding into lymphatics around the tumor. Several studies revealed that SEMS insertion might promote perineural invasion found in surgical specimens, although these studies failed to translate higher perineural invasion into poorer oncologic outcomes^[18,65-67]. Meanwhile, various studies found that SEMS had no significant effect on the incidence of perineural invasion compared with ES^[8,68-70]. Conflicting findings with respect to other adverse pathological features such as lymphovascular and vascular invasion have also been reported^[13,18,19,65,67,70-72]; therefore, cumulative data are needed. Balciscueta *et al*^[73] recently conducted a meta-analysis of 1273 patients from 10 retrospective cohort studies and found higher perineural invasion (OR: 1.98; 95%CI: 1.22-3.21; $P = 0.006$) and lymphatic invasion (OR: 1.45; 95%CI: 1.10-1.90; $P = 0.008$) after SEMS insertion than after ES. Therefore, the use of SEMS as BTS should be carefully considered due to an increase in adverse pathological characteristics, although the long-term adverse oncological effects have not been demonstrated.

Oncologic outcomes of colonic stenting as a BTS from RCTs

Six RCTs have reported long-term oncologic outcomes after SEMS placement as BTS compared with those of ES (Table 2). For the studies without SEMS-related perforation, the recurrence and survival outcomes are not significantly different between the two modalities^[47,48,74]. In contrast, the Dutch Stent-In 2 trial, which had a high perforation rate of 23%, reported poorer disease-free survival in patients who underwent SEMS insertion as BTS than in those who underwent ES^[57]. This study underlined the strong association between SEM-related perforation and adverse oncologic outcomes. The long-term follow-up outcomes of the ESCO and CReST trials have been recently published. The ESCO trial reported comparable oncologic outcomes between the two modalities, with an 8.9% rate of SEMS-related perforation rate^[75]. Similarly, the CReST trial found a comparable 3-year recurrence rate and overall survival between SEMS as BTS and ES, with a low SEMS-related perforation rate of 3.3%^[53]. The latest systematic review and meta-analysis of these RCTs by Cirocchi *et al*^[54] revealed comparable recurrence rates and oncologic outcomes between SEMS placement as BTS and ES. We conducted a meta-analysis of these six RCTs that reported the recurrence rate. There was no significant difference in recurrence rates between the SEMS and ES groups (RR: 1.45; 95% CI: 0.96-2.17, $I^2 = 45\%$) (Figure 7).

These clinical studies show that among the three proposed mechanisms of cancer cell dissemination by SEMS, only SEMS-related perforation clearly influences adverse oncologic outcomes. Sensitivity analyses showed that a < 8% perforation rate is the oncologically safe cut-off point for SEMS insertion^[59]. Therefore, endoscopy units that aim to perform SEMS as BTS should audit and improve their SEMS-related perforation rate to be lower than 8%. Two other mechanisms, including increased circulating tumor cells and aggressive pathological features, failed to produce consistent clinical evidence in decreased overall and disease-free survival in the SEMS group. Therefore, further studies are needed to validate the clinical impact of these hypotheses.

CHEMOTHERAPY IN PATIENTS WITH COLONIC STENTS

Neoadjuvant chemotherapy in locally advanced colon cancer

The mainstay treatment of the potentially curable colon cancer is complete oncologic resection. However, one of the challenges is the risk of local and distant recurrence, which is estimated at 20%-30% in locally advanced colon cancer (defined as: T3 tumors with ≥ 5 mm invasion beyond the muscularis propria; T4; or extensive regional lymph node involvement without distant metastases)^[76]. Recently, there was increasing evidence to support the use of neoadjuvant chemotherapy in locally advanced colon cancer^[77-81]. The theoretical advantages include the early treatment of micrometastases, increased likelihood of clear resection (R0) margin, and ability to evaluate the chemosensitivity of the tumor^[76]. Gosavi *et al*^[76] conducted a meta-analysis of two RCTs and reported that neoadjuvant chemotherapy increased the likelihood of R0 resection in locally advanced colon cancer (RR 0.47; 95%CI: 0.47-0.96) without an increase in complications (anastomotic leak, wound infection, or re-operation). However, the safety of neoadjuvant chemotherapy after SEMS placement in obstructive colon cancer is also a concern.

There were a few studies using neoadjuvant chemotherapy after SEMS placement in obstructive colon cancer. The FOxTROT trial showed a significant decrease in R1 resection rate in patients who received neoadjuvant chemotherapy for locally advanced colon cancer. However, only a few patients in this trial underwent SEMS placement as BTS; therefore, a conclusion about SEMS safety could not be drawn^[79]. Recently, Han *et al*^[82] conducted a comparative study investigating the safety of neoadjuvant chemotherapy after SEMS placement. They found that the adverse events of preoperative chemotherapy were well-tolerated, and the neoadjuvant chemotherapy did not increase SEMS-related complications ($P = 0.13$). Moreover, this study revealed that patients who received neoadjuvant chemotherapy had better OS than those who received postoperative chemotherapy (mean OS, 53 vs 47 mo, respectively, $P = 0.02$). However, well-designed RCTs with larger sample size and long-term follow-up are needed to confirm the safety and potential survival benefit of neoadjuvant chemotherapy after SEMS placement.

Chemotherapy in patients with incurable stage IV colon cancer

Patients with incurable stage IV colon cancer benefit from SEMS placement by avoiding palliative surgery and early initiation of chemotherapy. However, there is a concern that chemotherapy during SEM placement might induce complications. For palliative SEMS placement, many studies (including patients with and without chemotherapy) reported perforation rates of 7%-13%^[83-88]. Therefore, the decision to perform SEM insertion in patients with incurable stage IV colon cancer must consider the risks of long-term SEMS-related complications weighted against SEMS benefits^[89].

The administration of antiangiogenic agents (*e.g.*, bevacizumab) in patients who underwent SEMS placement was found to increase the risk of SEMS-related perforation. A retrospective study reported 3-fold higher perforation rate in patients who received bevacizumab after SEMS placement than in those who did not receive bevacizumab^[90]. In a large retrospective study of 1008 patients who received bevacizumab for incurable colon cancer, Bong *et al*^[91] found that SEMS placement is a significant risk factor for complications requiring surgery in patients who received bevacizumab (HR 5.69, 95%CI 2.37-13.64, $P < 0.001$). In contrast, a retrospective study reported no significant difference in perforation rate in patients who received chemotherapy with and without bevacizumab (7.3% *vs* 7.0%, respectively, $P = 0.925$)^[92]. The updated 2020 ESGE guideline recommends chemotherapy as a safe treatment in patients who have undergone palliative SEMS insertion. However, SEMS placement should not be performed while patients are receiving antiangiogenic therapy^[21].

FUTURE DIRECTION

Although many RCTs and prospective and retrospective studies have investigated the role of SEMS placement as BTS in comparison with that of ES in LMCO, current evidence is still conflicting, and the international guidelines are also dynamic and discordant^[20,21]. In 2014, the ESGE guideline did not recommend using SEMS insertion as BTS based on previous studies with low success and high perforation rates^[20].

Nevertheless, many comparative studies and one RCT published thereafter^[13-19,93] reported impressive short- and long-term oncologic outcomes. As such, the updated ESGE guideline released in 2020 considers SEMS placement as BTS a valid treatment option in patients with LMCO. The guideline emphasized that the medical team has to discuss the risks and benefits of SEMS with patients and ¹SEMS insertion should be performed or directly supervised by a competent endoscopist^[21].

The proficiency of the endoscopist is crucial when SEMS as BTS is considered. Previous RCTs with low perforation rate showed appreciable short-term outcomes of SEMS, including lower stoma rate, higher primary anastomosis, lower morbidity, and comparable oncologic outcomes to ES^[15,46-49,74,75]. Moreover, current evidence clearly demonstrates the association between SEMS-related perforation and negative oncologic outcomes. Therefore, SEMS placement as BTS is a valid option for competent endoscopists.

Impaired oncological outcomes after SEMS placement that result from increased circulating tumor and adverse pathological characteristics remain a concern. However, current evidence could not demonstrate adverse long-term oncological effects. Further well-designed collaborative studies are needed to investigate the association among the alteration of circulating tumors, adverse pathological characteristics, and oncologic outcomes.

CONCLUSION

Colonic obstruction is a common presentation of CRC that needs emergency intervention. SEMS placement as BTS, converting an emergency situation to an elective one, improves short-term outcomes in LMCO, including higher primary anastomosis, lower stoma rate, and lower postoperative morbidity, compared with ES. However, there remain concerns on adverse oncologic outcomes from shear forces induced by SEMS. There are three possible mechanisms of tumor dissemination from SEMS: (1) SEMS-related perforation; (2) increased circulating tumor cells; and (3) aggressive pathological features after SEMS placement. However, among these, only SEM-related

perforation clearly influences adverse oncologic outcomes. Consistent clinical evidence supporting the association of the other two mechanisms with decreased overall and disease-free survival is lacking. Therefore, further well-designed collaborative studies are needed to validate the clinical impact of these mechanisms. Current guidelines consider SEMS placement as BTS a valid treatment option in patients with LMCO, but it should be performed by competent endoscopists.

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