

Review Article

Current Status and Prospects of Endoscopic Resection Technique for Colorectal Tumors

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Abstract

Currently, endoscopic submucosal dissection (ESD) is a well-established and common treatment for intramucosal colorectal cancer in Japan. However, colorectal ESD is technically more difficult to perform than esophageal and gastric ESD, and some lesions, such as fibrotic lesions, are difficult to dissect by endoscopy. Several techniques, such as the pocket-creation method and laparoscopically assisted endoscopic polypectomy, have been utilized for challenging targets. In recent years, endoscopic full-thickness resection (EFTR) using full-thickness resection devices have mainly been performed in Western countries. We have used laparoscopy and endoscopy cooperative surgery for colorectal tumors (LECS-CR) since 2011 for the challenging treatment of colorectal ESD. Improvements in ESD techniques have resulted in an increase in the literature on EFTR, and LECS-CR may be considered an effective endoscopic technique for colorectal ESD in the future.

Keywords

endoscopic submucosal dissection, laparoscopy and endoscopy cooperative surgery, combined of endoscopic and laparoscopic surgery, endoscopic full-thickness resection

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Introduction

Colorectal cancer (CRC) is the second most common cause of mortality due to cancer in Japan[1]. Moreover, more than one million patients are diagnosed annually with CRC worldwide, with more than 600,000 deaths reported globally[2]. Meanwhile, most cases of CRC are sporadic and develop slowly over several years through the adenoma-carcinoma sequence[2]. Therefore, regular endoscopic screening every few years is useful, and resection at the adenoma or intramucosal cancer stage has a very good five-year survival rate with little risk of metastasis.

In Japan, endoscopic treatment is recommended for intra-

mucosal carcinoma or carcinoma with slight submucosal invasion. Moreover, endoscopic submucosal dissection (ESD) is performed on lesions >2 cm in size[3]. Currently, colorectal ESD is a common procedure that is performed along with endoscopic mucosal resection and has become widely used since it was approved for under the national health insurance for early stage colorectal neoplasia in 2012. However, lesions with severe fibrosis, such as the presence of residual or local recurrent lesions after endoscopic treatment, or tumors involving the diverticulum or appendix, are challenging targets within the digestive tract. Endoscopic resection has scarcely been utilized in the treatment of these colorectal tumors due to technical difficulties and the possibil-

ity of perforation and failure associated with en bloc resection[4-7].

Although there are reports regarding the utility of traction devices or the performance of pocket-creation methods for challenging targets[8-10], the technical challenges and risks of perforation still persist. In contrast, although more invasive than endoscopic treatment and particularly used for elderly patients or patients with poor general condition, surgical resection is the treatment of choice for patients undergoing procedures other than endoscopic treatment.

To overcome these problems, EFTR and other laparoscopically assisted endoscopic treatments have been widely reported. In 2011, we developed a full-thickness resection method for colorectal tumors using laparoscopy and endoscopy, which we called laparoscopy and endoscopy cooperative surgery for colorectal tumors (LECS-CR), which has been previously reported[11,12].

LECS-CR was developed based on a novel procedure for gastric submucosal tumors (SMTs) called laparoscopy and endoscopy cooperative surgery (LECS), which was reported in 2008 by Hiki et al.[13]. LECS was approved for implementation under national health insurance for gastric SMT in 2014 and is now performed at several healthcare centers. In addition to the classical LECS procedure, several LECS procedures have been developed, such as the combination of laparoscopic and endoscopic approaches for neoplasia with nonexposure technique, nonexposed endoscopic wall-inversion surgery, and closed LECS[14-16].

LECS-CR achieves good results in the form of high en bloc resection rates and improved short-term outcomes[11,12]; LECS-CR differs from other EFTRs in that the resection line is endoscopically confirmed, and full-thickness resection along with the previously made resection line is performed both laparoscopically and endoscopically. This article presents the methods and treatment outcomes of LECS-CR and reviews the current situation of other methods.

Patients and Methods

In total, 22 lesions were treated with LECS-CR at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research from November 2011 to August 2020. LECS-CR was indicated in the following cases: (1) adenoma or intramucosal cancer with severe fibrosis; (2) adenoma or intramucosal cancer involving the diverticulum or appendix; and (3) SMT.

In all cases, the lesion was evaluated by magnified image-enhanced endoscopy prior to surgery, and for lesions suspected to have deep invasion into the submucosal layer, LECS-CR was not indicated owing to the risk of lymph node metastasis. If the lesion involving the appendix could be resected with a sufficient safety margin using a linear sta-

pler alone and ileocecal valve preservation was possible, we did not perform LECS-CR; instead, we performed laparoscopic sleeve resection-assisted endoscopically and combined endoscopic and laparoscopic surgery (CELS). Whenever a surgeon approximated a laparoscopic linear stapler to the cecum, an endoscopist would ensure the appropriate margin from the lesion via the endoscopic direct vision. This approach can also be categorized as CELS[17,18].

The methods of LECS-CR at our hospital are described below. Figure 1 shows a simple graphical illustration of the technique.

This procedure is performed under general anesthesia in the operating room, and the patient assumes a modified lithotomy position. Typically, a main operator and an assistant surgeon stand on the left side of the patient, with another assistant surgeon standing on the right side of the patient; however, when approaching the cecum, all surgeons are positioned on the left side of the patient (Figure 2a). An endoscopist stands between the patient's legs and operates the endoscope, while the assistant operates the treatment device from behind the endoscopist.

First, five trocars are placed on the abdomen, starting with 8 mmHg CO₂ pneumoperitoneum. Following confirmation of the tumor location by endoscopy and laparoscopy, the colon wall at the site of the lesion is exposed. Subsequently, an endoscopist performs an intraluminal wash out around the lesion with approximately 1,000 ml of saline solution and takes the last 10 mL of the irrigated saline solution as a sample for urgent cytology examination. After confirming absence of malignant cells in the sample, circumferential markings surrounding the lesion were made using a needle knife or a Dual Knife J[®] (Olympus Medical, Tokyo, Japan).

The mucosal incision and submucosal dissection were performed endoscopically with an appropriate safety margin. To prevent the leaking of intraintestinal fluid in the abdominal cavity, full-thickness resection was performed using the crown method reported by Nunobe et al.[19] in the treatment of gastric LECS. Complete full-thickness dissection and excision is performed by combining the endoscopic and laparoscopic procedures.

The specimen is retrieved in the intraluminal route via the anus and confirmed by macroscopic en bloc resection with a safety margin. After the resection, the colon wall was sequentially closed using laparoscopic linear staplers.

All endoscopic procedures were performed using a single-channel endoscope with a water-jet system (PCF-Q260J, Olympus Optical Co., Ltd., Tokyo, Japan) with a large opening end attachment (D-201-11804; Olympus Medical, Tokyo, Japan).

A mixture of concentrate glyceride with small amounts of indigo carmine and epinephrine was used as a submucosal injection solution.

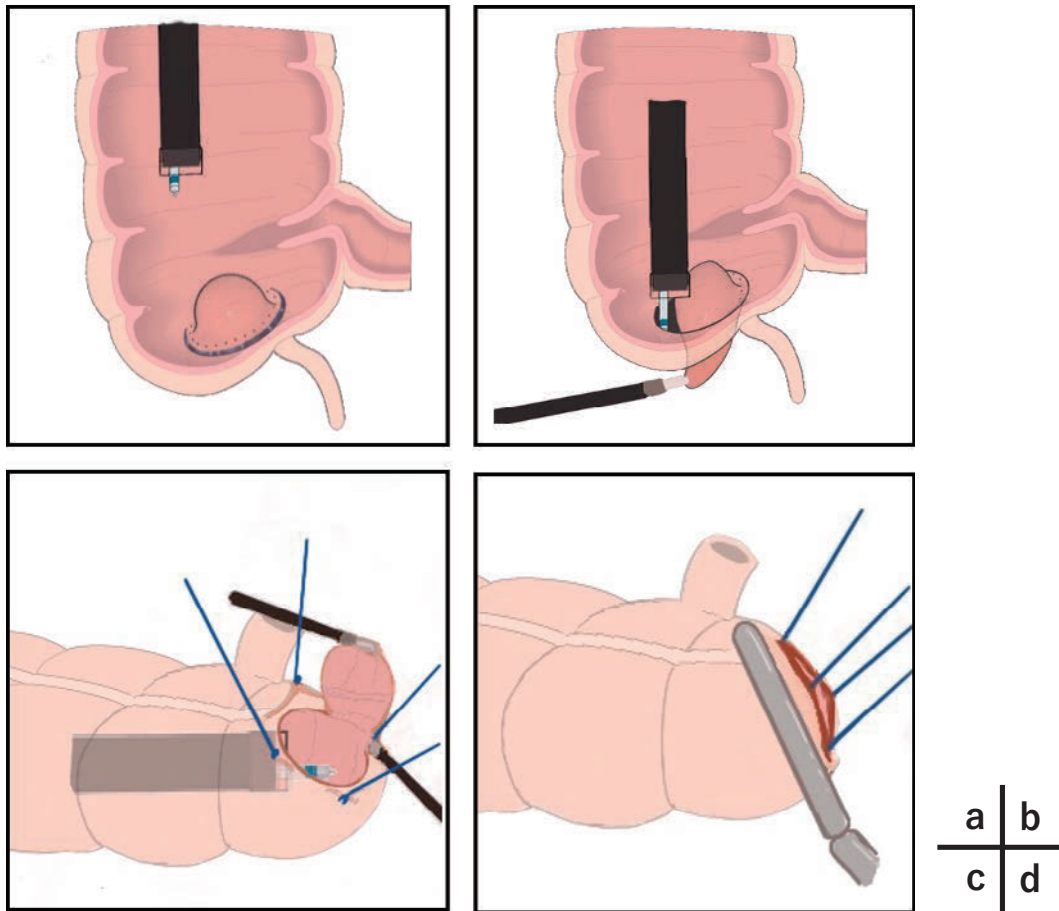


Figure 1. The procedure of laparoscopy and endoscopy cooperative surgery for colorectal tumors.
 a: The marking surrounds the lesion and mucosal incision with the endoscopic technique.
 b: The submucosal dissection and seromuscular layer resection.
 c: The lesion is lifted by the “crown method.” Laparoscopic ultrasound-activating scissors are also used for seromuscular layer resection and for the endoscopic collection of lesions.
 d: Finally, the colon is closed with a laparoscopic linear stapler.

The mucosal incision was performed with a needle knife or a Dual Knife J[®], and seromuscular layer resection was performed with a Hook knife (Olympus Medical, Tokyo, Japan), ITknife 2[®] (Olympus Medical, Tokyo, Japan), or Dual Knife[®]. In normal colorectal ESD, ITknife2[®] is significantly easier to use than ITknife nano[®] (Olympus Medical, Tokyo, Japan).

As an electrosurgical unit for the endoscopic procedure, we used VIO 300 D (ERBE Elektromedizin GmbH, Tübingen, Germany) under the following settings: EndoCut I mode (effect: 2, duration: 2, interval: 2) for the mucosal incision and resection of most of the seromuscular layer and SWIFT coagulation mode (effect: 3, 45 W) for numerous blood vessels. As a laparoscopic linear stapler, Endo GIA (Covidien, Dublin, Ireland) or Powered ECHELON (Ethicon Inc., Bridgewater Township, New Jersey, United States) was used.

Results

The number of lesions resected using the LECS-CR was 22. Patient demographics and lesion characteristics are shown in Table 1. With the most common histological diagnosis being adenoma, followed by adenocarcinoma, in which all cases presented with invasion of the intramucosal layer, most of the lesions treated using LECS-CR were observed in the cecum and involved the appendix.

In the two histologically diagnosed cases of sessile serrated lesion (SSL), both cases presented with invasion that extended into the appendiceal orifice. These two cases had been previously diagnosed endoscopically as SSL without dysplasia. Therefore, we suggested a follow-up observation; however, both were resected based on the patient’s request.

There were three cases of SMTs, one of which was pathologically diagnosed as a neuroendocrine tumor (NET) having initially been suspected as GIST by ultrasound endo-

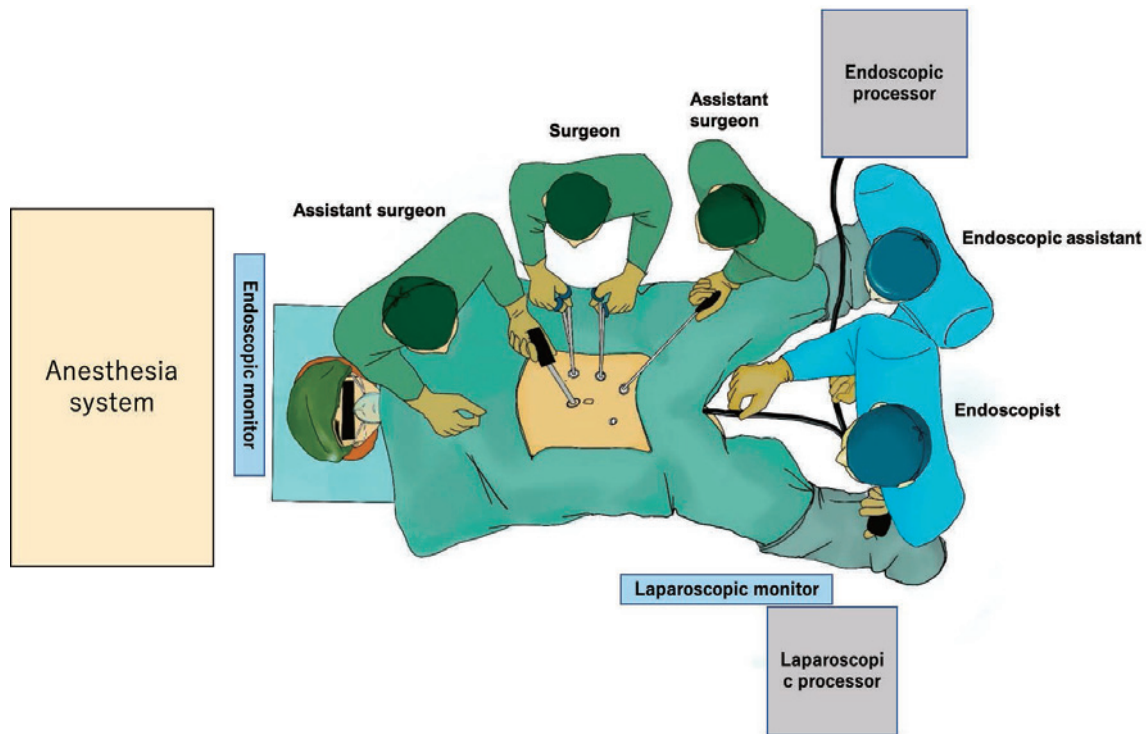


Figure 2a. Suggested endoscope and laparoscope placement for cecal lesions.



Figure 2b. The image of LECS-CR.

scopy. Although total mesorectal excision with lymph node dissection is generally recommended for rectal NETs >2 cm in diameter, this patient declined additional surgical intervention despite providing all disease-related information.

The intraoperative and postoperative data are shown in Table 2. Both the complete one-piece resection rate and R0 resection rate were 100%. While there were no cases of conversion to open surgery, one patient conversely underwent laparoscopic ileocecal resection due to intraoperative injury of the terminal ileum. We speculated that the reason for the injury was the strong adhesion between the terminal ileum and the appendix due to previous asymptomatic appendicitis. Postoperative complications of grade III or higher according to the Clavien-Dindo classification were not ob-

served in this series. All 17 patients who were followed up for at least one year were free of recurrence and metastasis.

Procedures and Current Status of Other Techniques

Combined endoscopic and laparoscopic surgery (CELS)

CELS is widely used as a common term for a collaborative technique of laparoscopy and endoscopy, and several methods have been reported. Since Beck et al.[20] reported a laparoscopically assisted snaring technique for the colon in 1993, several studies have been published, mainly in Western countries. CELS for colorectal lesions can be divided into the following subcategories. One category is laparoscopy-assisted endoscopic resection (LAER), which is defined as a technique involving endoscopic polypectomy with visualization using laparoscopy; another category includes endoscope-assisted laparoscopic resection (EALR), which is characterized by the resection of a lesion using laparoscopic techniques, while the lesion is visualized by endoscopy. Several papers on EALR reported the technical benefits of this method, especially relating to the colon[20-26]. The technique reported by Beck et al. is called laparoscopic-assisted polypectomy, which is a type of LAER and is the most widely adapted technique among the currently performed colorectal CELS procedures.

While combined laparoscopic endoscopic resection, could

Table 1. Baseline Characteristics of the Patients and Lesions Treated with Laparoscopy and Endoscopy Cooperative Surgery for Colorectal Tumors.

Sex (Male/Female), n	15/7
Median age (years) [range]	66 [50-81]
Size (mm) [range]	20 [9-50]
Macroscopic Type	
Superficial	15
Polypoid	4
Submucosal tumor	3
Location, n	
Terminal ileum	1
Cecum	11
Ascending	5
Transverse	3
Descending	1
Sigmoid	0
Rectum	1
Pathology, n	
Adenoma	10
Intramucosal cancer	6
Sessile serrated lesion	2
Hamartoma	1
Neuroendocrine tumor (NET-G1)	1
Schwannoma	1
Lipoma	1

be considered as a type of CELS, although few resections have been reported to be used in the colon, colonic EALR is mainly performed using laparoscopic wedge resection under endoscopic observation, which is performed with a linear stapler along the long axis of the intestinal tract[27,28].

According to the literature, in each procedure, patients are operated in the lithotomy position under general anesthesia, similar to the LECS-CR. After trocar insertion via the peritoneum, carbon dioxide insufflation is applied followed by laparoscopy. Endoscopy is sequentially performed for assistance in the laparoscopic procedures. These series of flows are similar to our LECS-CR. CELS can be converted to laparoscopic surgery when adverse events, such as perforation, are observed.

Other endoscopic full-thickness resection (EFTR) procedures

Although there are few institutions that perform the laparoscopic combined procedure in the treatment of colorectal lesions as frequently as in the upper GI tract, in the upper GI tract, LECS and several other combination techniques of EFTR with laparoscopy are widely used. Meanwhile, the incidence of EFTR without laparoscopy has gradually increased in the treatment of colorectal lesions in recent years. Particularly in the past couple of years, an increased number of studies on EFTR using FTRD[®] (Ovesco

Table 2. Intraoperative and Postoperative Data.

Hemorrhage (ml)	5
Median procedure time (min)	174
En bloc resection (%)	100
R0 resection (%)	100
Intraoperative adverse event, n (%)	1 (4.5)
Conversion to other surgery, n (%)	1 (4.5)
Postoperative adverse event (CD Grade III or more), n (%)	0 (0)
Postoperative days (days)	6

AG, Tübingen, Germany), which is an all-layer ablation device based on the Over-The-Scope Clip system, have been reported. Table 3 shows some of the most recent studies on this subject.

A principal method of EFTR using FTRD is as follows: the attachment with a large suture clip is placed on the tip of the endoscope, then the colonoscope reaches the lesion, and the lesion is grasped and pulled enough into the attachment. The clip was then deployed, and the tissue above the clip was immediately resected with a snare. The lesions were collected via the perianal route.

This new technique is of interest to endoscopists in Western countries because it is easier to perform than ESD procedure.

Discussion

Colonic partial resection is generally considered a challenging target of ESD. However, in recent years, despite the efforts of laparoscopic and function-preserving surgeries having been attempted to achieve less invasive resections while ensuring radical cure, there is still a large difference in the degree of invasiveness between these techniques and endoscopic treatment. Although the technique of closing all layers, including the seromuscular layer, is still in its infancy and has not yet been standardized as a treatment method, in terms of invasiveness, endoscopy alone (pure EFTR) is the goal of endoscopists. To date, sufficient suturing techniques and instruments have been developed in the field of laparoscopic surgery, and considering the current situation, where pure EFTR is not widely used, LECS-CR is a type of EFTR that can be performed at any institution.

Before the introduction of LECS-CR, conventional laparoscopic colorectal resection was performed for challenging targets in ESD at our institution. Laparoscopic colorectal resection is superior to open colon resection since it is less invasive and is associated with faster recovery of bowel function[29]. In 2019, Suzuki et al.[12] reported that LECS-CR for challenging lesions in ESD resulted in a significantly shorter hospital stay compared with conventional laparoscopic surgery for the same types of lesions. These results suggest that LECS-CR surgery should be preferred in these

Table 3. Literature of Colorectal EFTR.

Author	Literature	Publish Year	Method	Case (n)	R0 resection (%)	hospital stay (days)	Adverse events (%)	Conversion to LAC/open surgery (n)	Residual/ Recurrence (n)
Fähndrich M [31]	Endoscopy	2015	EFTR	17 (colorectal 14)	100	-	0	0	-
Richter-Schrag HJ [32]	Chirurg	2016	EFTR	20	80	8.5	5.0	17	5.0
Schmidt A [33]	Gut	2017	EFTR	181	77	4	9.9	-	12.3
Andrisani G [34]	Digestive and liver disease	2018	EFTR	114	90	-	11	1	6.3
Valli PV [35]	Surg Endosc	2018	EFTR	60	79	-	7	-	0
Aepil P [36]	United European Gastroenterol J	2018	EFTR	33	87.9	3.1	12.9	-	6.1
Zwager LW [37]	Endoscopy	2019	EFTR	401	82.4	1.0	9.3	13	-
Mão de-Ferro S [38]	GE Port J Gastroenterol	2019	EFTR	9	100	1.4	0	0	0
Kuellmer A [39]	GastroIntestinal Endosc	2020	EFTR	156	71.8	-	14.1	0	5.8
Ichkhanian Y [40]	Surgical Endosc	2020	EFTR	95	82.7	-	5.3	2	10
Albrecht H [41]	Tech Coloproctol	2019	EFTR	70	90.8	-	14.9	0	
Our case	-	2019	LECS	22	100	6	4.5	1	0

EFTR, endoscopic full-thickness resection; LAC, laparoscopic colectomy; LECS, laparoscopy and endoscopy cooperative surgery

cases owing to the degree of invasiveness of the method compared with conventional laparoscopic surgery.

CELS, EFTR with FTRD, and LECS-CR are still considered minimally invasive treatment options that can be currently performed. CELS could be considered a useful treatment because it has been developed for a relatively long time, and several studies have proven its utility; however, although LECS-CR is sometimes considered a part of CELS, we have emphasized on it as a different method. Its long-term results are also good, with only one case of local recurrence in a systematic review by Nakajima et al.[30]. The treatment outcomes of LECS-CR have been shown to be superior to those of CELS, especially in terms of the R0 resection rate, which is higher than that of CELS[12]. LAER has a limitation in the size of tumors that can be resected en bloc owing to the snare size. It is considered that en bloc resection would have better oncological results, such as lower local recurrence rate, than piecemeal resection, indicating the technical superiority of the LECS-CR over the LAER.

Recently, there have been an increasing number of reports on EFTR using FTRD. The number of multicenter studies is also increasing, and a prospective nonrandomized clinical trial (the WALL-RESECT study) was conducted at nine centers in Germany and reported by Schmidt et al.[33]. EFTR with FTRD was not technically complex, and the success rate of all procedures was relatively good. However, the R0 resection rate varied among different reports, as shown in Table 3. Kuellmer et al.[39] reviewed 156 cases accumulated at a German multicenter and reported an R0 resection rate of 60.9%. Andrisani et al. reported results from 12 centers

in Italy and found that the R0 resection rate was similar to that reported by Ischkanian et al. regarding the treatment outcome at 12 centers in the USA, which was 82.7%[34]. A meta-analysis of nine studies showed a total of 469 patients with an R0 resection rate of 84.9%[42]. In the literature, the R0 resection rate of EFTR with FTRD was only 90% at best reported within two years of the accumulation of cases, in which the curative potential of EFTR with FTRD can be assured.

Where the EFTR with FTRD has shown better results in that it requires a shorter procedure time and can be completed by endoscopy alone, the LECS-CR has an R0 resection rate of 100% and is considered superior to CELS and EFTR with FTRD in terms of cure rate. However, EFTR with FTRD tends to have a lower R0 resection rate in cases of large tumors due to the characteristics of the device[40], which is one of the difficulties of EFTR with FTRD. Additionally, the postoperative residuals rate is high[33].

It is remarkable that EFTR with FTRD has a higher incidence of adverse events than LECS-CR. The WALL-RESECT study shows a high complication rate, with a procedure-related adverse events rate of 9.9%[33]. Furthermore, there have been several reports of acute appendicitis after EFTR with FTRD for lesions involving the appendix, which required an appendectomy[33]. While it has been considered that cases involving the appendix may be better candidates for LECS-CR, appendix resection in LECS-CR is performed in cases involving the appendix, which can prevent the subsequent development of appendicitis and unnecessary surgical intervention. Other adverse events in FTRD

procedures include fistula formation, perforation, and bleeding[33].

The indication for LECS-CR is limited to intramucosal lesions from the viewpoint of curative properties. Furthermore, we have discussed the further adaptation for LECS-CR including the following: (1) deep submucosal invasive cancer after rapid intraoperative lymph node evaluation using sentinel biopsy or one-step nucleic acid amplification; (2) treatment for metachronous cancer in patients with previously operated CRC with a substantially shortened colon; and (3) treatment in elderly patients who may not be able to choose between routine surgery or no surgery at all.

Although colorectal ESD has been widely performed in Japan, it is not considered a popular technique in Western countries similar to other endoscopic procedures, with another problem with LECS-CR being the technical difficulty associated with the procedure. LECS-CR is based on ESD technology; therefore, it is more difficult than EFTR and CELS for endoscopists unfamiliar with ESD.

In LECS-CR, the crown method is used to prevent colonic content leakage; however, this method does carry the possible risk of peritoneal dissemination. Closed LECS-CR was attempted to be performed previously; nevertheless, we converted it to the conventional method due to technical difficulties.

If it will be considered an indication for invasive cancers in the future, closed LECS should be adopted for use in gastric SMT[14-16]. At present, it is necessary to have a long-term follow-up to determine whether peritoneal dissemination or multiple organ metastases occur.

Although this method has been mainly performed at our institution, there have been case reports from other institutions in recent years, and additional cases are expected to be reported in the future[43,44].

Conclusion

Minimally invasive treatments for colorectal tumors have merited attention and various techniques have been developed, but to date their curability and safety have never been sufficient. In contrast, LECS-CR will be promised for a feasible treatment as a full-thickness resection near the future.

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Conflicts of Interest

There are no conflicts of interest.

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