

## ORIGINAL ARTICLE

# Efficacy of endoscopic submucosal dissection in treating early colorectal cancer and precancerous lesions

Lianlian Qu<sup>1</sup>, Yifeng Cheng<sup>2</sup>

<sup>1</sup>Department of Critical Care Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. <sup>2</sup>Department of Gastrointestinal Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

## Summary

**Purpose:** To compare the efficacy and safety between endoscopic submucosal dissection (ESD) and conventional surgical treatment in the treatment of colorectal cancer (CRC) and the precancerous lesions.

**Methods:** A retrospective analysis was performed on the clinical data of 65 patients with CRC or precancerous lesions (ESD group) and another 65 patients receiving surgical treatment at the same period (Surgery group). The surgical indicators, incidence of complications, and quality of life score were compared between the two groups, and the survival and tumor progression were followed up and recorded.

**Results:** The rate of en bloc tumor resection was 89.2% (58/65) and 100% (65/65) and the rate of tumor curative resection was 92.3% (60/65) and 100% (65/65) in ESD group and Surgery group. Moreover, ESD group had markedly shorter operation time and mean hospital stay. After treat-

ment, ESD group had higher scores of emotional functioning, fatigue, constipation, and diarrhea symptoms and general quality of life on the European Organization for Research and Treatment of Cancer quality of life questionnaire Core 30 (EORTC QLQ-C30) than Surgery group. The follow-up results showed no statistically significant difference in the 5-year recurrence rate between ESD group and Surgery group (7.7% vs. 0%,  $p=0.208$ ).

**Conclusion:** ESD and surgery have similar long-term clinical efficacy in treating early CRC and precancerous lesions, but ESD is more minimally invasive and safer, and is superior in accelerating postoperative recovery and improving the overall survival of patients.

**Key words:** endoscopic submucosal dissection, colorectal cancer, early stage, precancerous lesions, efficacy

## Introduction

With the increase in the living standards and the change in dietary habits, the incidence rate of colorectal cancer (CRC) has been increasing year by year in China, reaching the 3<sup>rd</sup>-5<sup>th</sup> place among all malignant tumors, and increasingly more early CRC and precancerous lesions are being detected [1-3]. Early CRC refers to the CRC with the lesions limited to the mucosa and submucosa, and the precancerous lesions in the colorectum mean some diseases that may indicate cancer in the colorectal mucosa, such as adenoma, adenomatosis and in-

flammatory bowel disease-related heterogeneous hyperplasia [4].

Specialists in China and beyond clinically treat early CRC and precancerous lesions using mainly endoscopic treatment and surgery. Conventional surgery causes large trauma, increased incidence rate of postoperative complications, and poor prognosis to patients, while endoscopic minimally invasive surgery produces small trauma and fewer postoperative complications, serving as a new option for the treatment of early CRC [5,6].

Corresponding author: Yifeng Cheng, MM. Department of Gastrointestinal Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Ave, Wuhan, Hubei 430022, China.  
Tel: +86 015972911298; Email: 46181279@qq.com  
Received: 21/05/2021; Accepted: 29/07/2021

The present study aimed to compare the efficacy and safety between endoscopic submucosal dissection (ESD) and conventional surgery treatment in the treatment of early CRC and precancerous lesions.

## Methods

### General data

The clinical data were collected from 130 patients with early CRC and precancerous lesions treated in our hospital, among whom, there were 76 males and 54 females aged 27-77 years old (mean 59.34±9.79). Inclusion criteria: 1) patients aged ≥18 years, and 2) those diagnosed with early CRC or precancerous lesions and receiving endoscopic or surgical treatment (the early CRC refers to colorectal epithelial tumor of any size with the invasion depth limited to the mucosa and submucosa regardless of the presence or absence of lymph node metastasis). Exclusion criteria: 1) patients whose postoperative pathology indicated that the tumor invaded beyond the submucosa; 2) those with concomitant severe heart, lung, liver and kidney and other vital organ diseases; or 3) those complicated with severe immune system disease, other malignancies or severe mental diseases. The baseline clinical data of the two groups of patients were not statistically significantly different and were comparable (Table 1). All the subjects were informed of this study and signed the informed consent form in accordance with the *Declaration of Helsinki*. This study was approved by the

ethics committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (17-HB-042-WH-031).

### Treatment methods

ESD: Before operation, colonoscopy and biopsy were performed. The invasion depth and the surrounding lymph node metastasis were assessed by computed tomography (CT), magnetic resonance imaging (MRI) and endoscopic ultrasonography. All the patients were anesthetized with propofol. Argon plasma coagulation was conducted at 0.5 cm from the lateral lesion margin for electrocoagulation marking, and the prepared mixture (5 mL of methylene blue + 1 mL of adrenalin + 100 mL of 0.9% normal saline) was submucosally injected through multi points using a 23 G injection needle until the lesion was fully lifted. The submucosa was then stripped using insulated tip (IT) knife, Flush knife and Hybrid knife when the field of view was confirmed to be clear, until complete removal or a certain degree of stripping, followed by the complete removal by snare. After the removal of the lesion, the bleeding point was treated using thermal biopsy forceps, and the wound was clamped by metal clips. At the end of operation, a tube was indwelled in the anus. Finally, the specimen was taken out and fixed on a foam board, and then sent for pathologic examination after size measurement.

Surgery: All patients underwent general anesthesia after tracheal intubation. An incision was made in supine position or lithotomy position according to the surgical method. The nature and size of the lesion, and whether there were any lesions in the lymph nodes, liver and pel-

**Table 1.** Demographics and general clinical data of all studied patients

Parameters	ESD group (n=65) n (%)	Surgery group (n=65) n (%)	p value
Gender (Male/Female)	40/25	36/29	0.594
Age (years)	58.82±9.59	60.11±9.89	0.452
Tumor location			0.635
Rectum	10 (15.4)	13 (20.0)	
Sigmoid colon	29 (44.6)	26 (40.0)	
Left colon	14 (21.5)	17 (26.2)	
Right colon	12 (18.5)	9 (13.8)	
Histological classification			0.440
Poor	0 (0)	1 (15.4)	
High/ Moderate	51 (78.5)	55 (84.6)	
Precancerous lesion	14 (21.5)	9 (13.8)	
Tumor diameter (cm)	2.41±0.54	2.59±0.67	0.194
Endoscopic classification			0.331
Protrude type	57 (87.7)	53 (81.5)	
Flat / Depressed type	8 (12.3)	12 (18.5)	
Invasion depth			0.266
Mucosal layer	15 (23.1)	10 (15.4)	
Submucosal layer	50 (76.9)	55 (84.6)	

ESD: endoscopic submucosal dissection.

vis were explored intraoperatively. Radical resection was then performed, and the lesion tissues were removed from the upper and lower ends 5-6 cm away from the lesion. If the lesion distance was less than 5 cm from the anal margin, Miles operation was performed. The operation should be fine and the anastomosis should be appropriately tight, so as to avoid damaging other organs and tissues. A drainage tube was retained in the pelvic cavity and drawn out through another hole poked. After checking hemorrhage, the incision was sutured layer by layer. There was little bleeding during the operation, and no blood transfusion was performed. Then, the operation was ended. After the size was measured, the specimen was sent for pathologic examination.

#### Observation indicators

The *en bloc* resection rate, complete resection rate, lymph node metastasis rate, operation time, hospital stay, and incidence rate of complications were analyzed and compared between the two groups of patients.

The postoperative quality of life of patients was evaluated using the European Organization for Research and Treatment of Cancer quality of life questionnaire Core 30 (EORTC QLQ-C30) from two years after the operation. The EORTCQLQ-C30 comprises 4 parts: 1) functional scale, including physical functioning, role functioning, cognitive functioning, emotional functioning, and social functioning; 2) symptom scale, including pain, fatigue, and nausea and vomiting; 3) single-item measurement scale, including 6 items: insomnia, dyspnea, constipation, diarrhea, loss of appetite, and financial difficulties; and 4) overall quality of life scale. The patients with higher scores had higher quality of life.

The first colonoscopy follow-up was completed at 3-6 months after the operation. If there was no abnormality, the colonoscopy and CT were repeated once a

year for 3 consecutive years. If CT showed no enlarged lymph nodes, it was considered that there was no lymph node metastasis. If no abnormality was found, colonoscopy and CT were conducted once every 2-3 years. The patients were followed up until June 2020 and tumor recurrence was recorded.

#### Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were presented as mean  $\pm$  standard deviation and intergroup comparisons were made using pairwise t-test. Enumeration data were expressed as percentage (%), and  $\chi^2$  was performed for intergroup comparisons. Survival curves were plotted using the Kaplan-Meier method, and statistically significant difference in survival was determined by log-rank test.  $P < 0.05$  suggested statistically significant difference.

## Results

#### Comparison of surgical indicators between the two groups of patients

The rate of *en bloc* tumor resection was 89.2% (58/65) and 100% (65/65) and the rate of tumor curative resection was 92.3% (60/65) and 100% (65/65) in the ESD group and Surgery group, respectively, showing no statistically significant differences ( $p=0.069$ ,  $p=0.098$ ). The resection margins were all negative. The pathologic results in the Surgery group showed no lymph node metastasis and neurovascular invasion, while the ESD group had 1 case of positive lymph node metastasis and tumor invading deep into the submucosa. Moreo-

**Table 2.** Comparison of parameters related to surgery

Parameters	ESD group (n=65) n (%)	Surgery group (n=65) n (%)	p value
<i>En bloc</i> tumor resection rate	58 (89.2)	65 (100%)	0.069
Tumor curative resection rate	60 (92.3)	65 (100%)	0.098
Lymph node metastasis positive rate	1 (1.5)	0 (0%)	0.679
Operation time (min)	45.57 $\pm$ 19.46	88.43 $\pm$ 18.48	0.001
Hospital stay time (d)	6.82 $\pm$ 2.60	10.39 $\pm$ 2.95	0.001
Complications			
Incision infection	1 (1.5)	2 (3.1)	0.773
Intraoperative hemorrhage	3 (4.6)	1 (1.5)	0.619
Delayed postoperative hemorrhage	2 (3.1)	0 (0)	0.496
Perforation	1 (1.5)	0 (0)	0.679
Stomal complications	0 (0)	2 (3.1)	0.496
Anastomotic fistula	0 (0)	1 (1.5)	0.679
Anastomotic stenosis	0 (0)	0 (0)	1.000
Abdominal abscess	0 (0)	0 (0)	1.000
Ureteral injury	0 (0)	0 (0)	1.000

ESD: endoscopic submucosal dissection.

ver, the ESD group exhibited markedly shorter operation time and mean hospital stay [(45.57±19.46) min vs. (88.43±18.48) min, and (6.82±2.60) d vs. (10.39±2.95) d] ( $p < 0.001$ ). The two groups of patients had surgical complications, such as incision infection, intraoperative hemorrhage, postoperative delayed hemorrhage, perforation, stomal complications, and anastomotic fistula, without anastomotic stenosis, abdominal abscess, and ureteral complications. The postoperative incision infection rate was 1.5% (1/65) and 3.1% (2/65), the incidence rate of intraoperative hemorrhage was 4.6% (3/65) and 1.5% (1/65), respectively, in the ESD group and Surgery group. The ESD group had 1 case of massive intraoperative hemorrhage that was stopped by endoscopic electrocoagulation. The incidence rate of delayed postoperative hemorrhage was 3.1% (2/65) and 0%, respectively, in the ESD group and Surgery group, and there were 2 cases of postoperative delayed hemorrhage in the ESD group, and the hemostasis was performed by endoscopic electrocoagulation again. The incidence rate of perforation was 1.5% (1/65) and 0%, respectively, in the ESD group and Surgery group, and perforation patients were improved through hemoclipping combined with prolonged postoperative fasting, anti-infection and other conservative treatments. Besides, the incidence rate of stomal complications was 0% and 3.1% (2/65), and the incidence rate of anastomotic fistula was 0% and 1.5% (1/65), re-

spectively, in the ESD group and Surgery group. Anastomotic fistula was relieved after laparotomy and ostomy and treatment with sufficient antibiotics. No statistically significant difference was found between the two groups regarding the incidence rate of surgical complications ( $p > 0.05$ ) (Table 2).

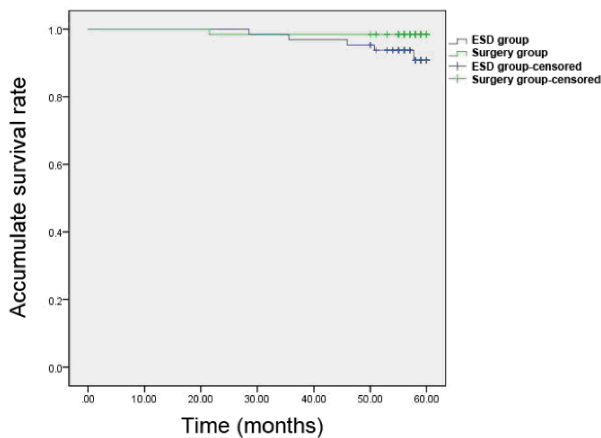
#### Quality of life scores

The quality of life of patients at two years after treatment was followed up and recorded. According to the EORTC-QLQ-C30 scoring, the ESD group had a substantially higher emotional functioning score on the functional scale than the Surgery group after treatment [(87.74±16.76) points vs. (81.77±17.47) points,  $p = 0.049$ ], and there were no statistically significant differences between the two groups in the scores of physical functioning, role functioning, social functioning and cognitive functioning ( $p > 0.05$ ). After treatment, the scores for nausea and vomiting, pain, loss of appetite, dyspnea, sleep disturbance and financial impact on the symptom scale showed no statistically significant differences between the two groups ( $p > 0.05$ ). The scores of fatigue, constipation and diarrhea in the ESD group were notably higher than those in the Surgery group [(23.83±10.98) points vs. (19.70±8.09) points,  $p = 0.016$ , (44.88±9.49) points vs. (41.43±6.93) points,  $p = 0.019$ , and (14.79±4.75) points vs. (12.83±5.73) points,  $p = 0.036$ ]. The ESD group had a markedly higher general quality of life

**Table 3.** Comparison of 2-year postoperative EORTC-QLQ-C30 scale scores of the studied patients in two different groups

Parameters	ESD group (n=65)	Surgery group (n=65)	p value
Functioning scales			
Physical	82.82±16.46	80.03±18.11	0.460
Role	90.29±19.57	89.19±18.08	0.640
Emotional	87.74±16.76	81.77±17.47	0.049
Social	72.71±17.63	69.64±19.50	0.348
Cognitive	80.38±19.07	82.62±18.58	0.499
Symptom scales			
Nausea and vomiting	27.23±6.15	28.22±6.04	0.356
Pain	22.17±7.89	23.69±8.31	0.287
Fatigue	23.83±10.98	19.70±8.09	0.016
Appetite loss	33.38±7.45	32.63±8.44	0.592
Constipation	44.88±9.49	41.43±6.93	0.019
Diarrhea	14.79±4.75	12.83±5.73	0.036
Dyspnea	13.98±4.95	14.68±3.53	0.245
Sleep disturbance	40.65±8.26	42.24±6.02	0.212
Financial impact	32.14±5.47	31.80±5.85	0.633
General quality of life	77.46±20.45	69.52±21.04	0.031

EORTC: European Organization for Research and Treatment of Cancer.



**Figure 1.** Kaplan-Meier survival curves of patients in the ESD group and Surgery group. The difference between progression-free survival rate of patients in the ESD group and Surgery group had no statistical significance ( $p=0.094$ ).

score than the Surgery group [(77.46±20.45) points vs. (69.52±21.04) points,  $p=0.031$ ], suggesting that the quality of life in the ESD group was higher than that in the Surgery group (Table 3).

#### Postoperative follow-up results of patients in the two groups

All the patients were followed up for 21-60 months. The ESD group had 5 (7.7%) cases of local recurrence. Among them, 4 cases received ESD again, and no local recurrence was found any more after a mean follow-up of 33.7 months. Meanwhile, the remaining 1 patient, who was not eligible for endoscopic resection, was operated and no recurrence was found after 48 months of follow-up. There were no cases of local recurrence during follow-up, 1 patient died of liver and lung metastasis (no local recurrence) 2 years after surgery, and 1 another one due to a traffic accident in the Surgery group. The difference in the recurrence rate between the two groups of patients was not statistically significant ( $p=0.208$ ). The survival curves were plotted for the two groups of patients using the Kaplan-Meier method, and Figure 1 showed the progression-free survival (PFS) curves. The log-rank test indicated no statistically significant difference in the PFS between the two groups ( $p=0.094$ ).

## Discussion

Primary colorectal tumors progress to cancers generally through the pattern of “adenomas – precancerous lesions – mucosal cancers (early-stage cancers) – invasive cancers”, and the incidence rate of cancer is 2.00-10.00%. Removing the early-stage colorectal tumor can decrease the incidence rate

of cancer and the death rate by 76-90% and 53%, respectively [7]. Lymph node metastasis rarely occurs when CRC is confined to the inner layer of the mucosa or only invades the superficial layer of the submucosa. Once it invades the submucosa beyond 1,000  $\mu\text{m}$ , the rate of lymph node metastasis can reach 6-12% [8, 9]. In this study, the rate of lymph node metastasis was only 1.5% in 65 cases of early CRC in the ESD group, of which high-level mucosal tumors showed no lymph node metastasis, and the metastasis rate of cancer in the deep layer of the submucosa was 1.5%. None of the 65 patients in the Surgery group had lymph node metastasis. Therefore, the cancers in the inner layer of the mucosa and the superficial layer of the submucosa with a smaller probability of lymph node metastasis (stage SM1 cancer) can basically be cured by endoscopic treatment [10]. At present, the resection can be considered to be curative when the endoscopically completely resected lesion has the invasion depth in the submucosa of less than 1,000  $\mu\text{m}$ , with negative incision margin and no vascular infiltration, and is well differentiated. The rate of lymph node metastasis is less than 1% in such lesions [11]. Surgery will cause relatively large damage to patients with cancer in the inner layer of the mucosa and stage SM1 cancer. In particular, patients with low rectal cancer need to undergo ostomy, and the postoperative urination function and sexual function will be affected in some of them, greatly lowering their quality of life.

In the present study, it was found that the ESD group had slightly lower rates of *en bloc* resection and complete resection than the Surgery group, with no statistically significant differences ( $p>0.05$ ). Moreover, the operation time and hospital stay in the ESD group were substantially shorter than those in the Surgery group ( $p<0.05$ ), and ESD relatively alleviated patients' pain and reduced the medical expense. Tumor recurrence is a critical factor for the decline in survival. A Japanese retrospective study pointed out that the short-term local recurrence rate of CRC is 2% after ESD, but the 5-year recurrence has not been reported. However, early rectal cancer has a relatively low recurrence rate, and its 5-year recurrence rate can reach 16.8% [12,13]. According to a study including 887 cases of lesions, the *in situ* recurrence after surgery is associated with the primary cancer cell colonization and tumor residuals during surgery, while the postoperative recurrence of tumors in the intestine and other sites may be caused by skip lymph node metastasis or intestinal dissemination [14]. Thus, surgery inevitably destroys the normal physiological structure of the intestine, leading to a higher postoperative recurrence rate and decreased qual-

ity of life. A latest Japanese large-sample retrospective analysis showed that the safety and low invasiveness of endoscopic excision increase the quality of life for patients with early CRC, and even less traumatic laparoscopic surgery causes a higher recurrence rate of rectal cancer than ESD and needs more time [15]. This suggests that endoscopic resection is the first option for CRC with no lymph node metastasis. According to the results of the follow-up in the present study, there were no statistically significant differences in the 5-year recurrence rate and PFS rate between two group ( $p>0.05$ ), implying that the two treatment methods have comparable 5-year long-term efficacy in treating early CRC and pre-cancerous lesions.

Hemorrhage and perforation are the major complications of ESD [16]. In this study, 4 patients undergoing ESD suffered from intraoperative hemorrhage, with a small amount of blood loss, which was effectively controlled by endoscopic electrocoagulation hemostasis. Moreover, 2 patients receiving ESD experienced delayed hemorrhage that was found to be blood oozing from the wound surface, the blood oozing site was clipped using metal clips, and the endoscope was withdrawn when no blood oozing was observed. It is relatively difficult to treat the hemorrhage during endoscopic operation. Blind hemostasis easily causes intestinal perforation, and the best way to deal with hemorrhage is to prevent it through fully lifting of the lump, skillful use of Hybrid knife, coagulation and hemostasis at the hemorrhage point, and clamping, externally pulling and electrocoagulation of the relatively thick submucosal vessel [17,18]. The ESD group had 1 case of perforation and large resected lesions, and the perforation was resolved through

hemoclipping combined with prolonged postoperative fasting, anti-infection and other conservative treatments.

In this study, EORTC-QLQ-C30, an internationally recognized core scale for the quality of life, was used to objectively, accurately and comprehensively reflect the overall quality of life and survival of patients [19,20]. The results showed that the ESD group had markedly higher scores of emotional functioning, fatigue, constipation, and overall quality of life than the Surgery group, and no statistically significant differences were found in the scores of the other items. It can be inferred that conventional surgery causes larger destruction of the normal physiological structure of the intestine and psychological trauma to patients than the ESD, and the ESD better improves the patient overall postoperative quality of life.

This retrospective study was limited by the sample size and less comprehensive follow-up contents, so the conclusion of the present study needs further corroborating by multicenter, large-sample prospective clinical studies in the future.

## Conclusions

ESD and surgery have similar long-term clinical efficacy in treating early CRC and precancerous lesions, but ESD is more minimally invasive and safer, and is superior in accelerating postoperative recovery and improving the patient overall quality of life.

## Conflict of interests

The authors declare no conflict of interests.

## References

1. Dzunic M, Petkovic I, Cvetanovic A, Vrbic S, Pejcic I. Current and future targets and therapies in metastatic colorectal cancer. *JBUON* 2019;24:1785-92.
2. The LO. Colorectal cancer: a disease of the young? *Lancet Oncol* 2017;18:413.
3. Jasarovic D, Stojanovic D, Mitrovic N, Stevanovic D. Anastomotic leak after colorectal cancer surgery - risk factors in 21th century. *JBUON* 2020;25:2199-204.
4. Vavra P, Dostalík J, Martinek L et al. Familial adenomatous polyposis as a precancerous of colon cancer. *Bratisl Lek Listy* 2002;103:418-21.
5. Buccafusca G, Proserpio I, Tralongo AC, Rametta GS, Tralongo P. Early colorectal cancer: diagnosis, treatment and survivorship care. *Crit Rev Oncol Hematol* 2019;136:20-30.
6. Dumoulin FL, Hildenbrand R. Endoscopic resection techniques for colorectal neoplasia: Current developments. *World J Gastroenterol* 2019;25:300-7.
7. Zauber AG, Winawer SJ, O'Brien MJ et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012;366:687-96.
8. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 2003;58:S3-43.
9. Morson BC, Whiteway JE, Jones EA, Macrae FA, Williams CB. Histopathology and prognosis of malignant colorectal polyps treated by endoscopic polypectomy. *Gut* 1984;25:437-44.
10. Nakadoi K, Tanaka S, Kanao H et al. Management of

- T1 colorectal carcinoma with special reference to criteria for curative endoscopic resection. *J Gastroenterol Hepatol* 2012;27:1057-62.
11. Heo J, Jeon SW, Jung MK, Kim SK, Kim J, Kim S. Endoscopic resection as the first-line treatment for early colorectal cancer: comparison with surgery. *Surg Endosc* 2014;28:3435-42.
  12. Saito Y, Fukuzawa M, Matsuda T et al. Clinical outcome of endoscopic submucosal dissection versus endoscopic mucosal resection of large colorectal tumors as determined by curative resection. *Surg Endosc* 2010;24:343-52.
  13. Patel SA, Chen YH, Hornick JL et al. Early-stage rectal cancer: clinical and pathologic prognostic markers of time to local recurrence and overall survival after resection. *Dis Colon Rectum* 2014;57:449-59.
  14. Thomson WH, Foy CJ, Longman RJ. The nature of local recurrence after colorectal cancer resection. *Colorectal Dis* 2008;10:69-74.
  15. Saito Y, Yamada M, So E et al. Colorectal endoscopic submucosal dissection: Technical advantages compared to endoscopic mucosal resection and minimally invasive surgery. *Dig Endosc* 2014;26 Suppl 1:52-61.
  16. Sakamoto T, Mori G, Yamada M et al. Endoscopic submucosal dissection for colorectal neoplasms: a review. *World J Gastroenterol* 2014;20:16153-8.
  17. Yamamoto K, Shimoda R, Ogata S et al. Perforation and Postoperative Bleeding Associated with Endoscopic Submucosal Dissection in Colorectal Tumors: An Analysis of 398 Lesions Treated in Saga, Japan. *Intern Med* 2018;57:2115-22.
  18. Odagiri H, Yasunaga H, Matsui H, Fushimi K, Iizuka T, Kaise M. Hospital volume and the occurrence of bleeding and perforation after colorectal endoscopic submucosal dissection: analysis of a national administrative database in Japan. *Dis Colon Rectum* 2015;58:597-603.
  19. Nolte S, Liegl G, Petersen MA et al. General population normative data for the EORTC QLQ-C30 health-related quality of life questionnaire based on 15,386 persons across 13 European countries, Canada and the United States. *Eur J Cancer* 2019;107:153-63.
  20. Ameri H, Yousefi M, Yaseri M, Nahvijou A, Arab M, Akbari SA. Mapping EORTC-QLQ-C30 and QLQ-CR29 onto EQ-5D-5L in Colorectal Cancer Patients. *J Gastrointest Cancer* 2020;51:196-203.