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Endoscopic submucosal dissection vs laparoscopic colorectal resection for early colorectal epithelial neoplasia

Sophie SF Hon, Simon SM Ng, Tiffany CL Wong, Philip WY Chiu, Tony WC Mak, WW Leung, Janet FY Lee

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Author contributions: Hon SSF designed the study and drafted the manuscript; Ng SSM, Wong TCL and Chiu PWY designed study and data interpretation; Leung WW analysed data; Mak TWC and Lee JFY contributed to critical revision of the manuscript.

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Abstract

AIM: To compare the short term outcome of endoscopic submucosal dissection (ESD) with that of laparoscopic colorectal resection (LC) for the treatment of early colorectal epithelial neoplasms that are not amenable to conventional endoscopic removal.

METHODS: This was a retrospective cohort study. The clinical data of all consecutive patients who underwent ESD for endoscopically assessed benign lesions that were larger than 2 cm in diameter from 2009 to 2013 were collected. These patients were compared with a cohort of controls who underwent LC from 2005 to 2013. Lesions that were proven to be malignant by initial endoscopic biopsies were excluded. Mid and lower rectal lesions were not included because total mesorectal excision, which bears a more complicated postoperative course, is not indicated for lesions without histological proof of malignancy. Both ESD and LC were performed by the same surgical unit with a standardized technique. The patients were managed according to a standard protocol, and they were closely monitored for complications after the procedures. All hospital records were reviewed, and the following data were compared between the ESD and LC groups: patient demographics, size and location of the lesions, procedure time, short-term clinical outcomes and pathology results.

RESULTS: From 2005 to 2013, 65 patients who underwent ESD and 55 patients who underwent LC were included in this study. The two groups were similar in terms of sex (P = 0.41) and American Society of Anesthesiologist class (P = 0.58), although patients in the ESD group were slightly older (68.6 ± 9.4 vs 64.6 ± 9.9, P = 0.03). ESD could be accomplished with a shorter procedure time (113 ± 66 min vs 153 ± 43 min, P < 0.01) for lesions of comparable size (3.0 ± 1.2 cm vs 3.4 ± 1.4 cm, P = 0.22) and location (colon/rectum:}
59/6 vs colon/rectum: 52/3, \( P = 0.43 \)). ESD appeared to be associated with a lower short-term complication rate, but the difference did not reach statistical significance (10.8% vs 23.6%, \( P = 0.06 \)). In the LC arm, a total of 22 complications occurred in 13 patients. A total of 7 complications occurred in the ESD arm, including 5 perforations and 2 episodes of bleeding. All perforations were observed during the procedure and were successfully managed by endoscopic clipping without emergency surgical intervention. Patients in the ESD arm had a faster recovery than patients in the LC arm, which included shorter time to resume normal diet (2 d vs 4 d, \( P = 0.01 \)) and a shorter hospital stay (3 d vs 6 d, \( P < 0.01 \)).

CONCLUSION: ESD showed better short-term clinical outcomes in this study. Further prospective randomized studies will be required to evaluate the efficacy and superiority of colorectal ESD over LC.

Key words: Early colorectal neoplasia; Laparoscopic colectomy; Endoscopic submucosal dissection

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Core tip: This is the first study that compares endoscopic submucosal dissection (ESD) vs laparoscopic colorectal resection (LC) for endoscopically benign lesions that could not be adequately removed by conventional polypectomy. Case inclusion was based purely on the pre-operative/pre-procedure endoscopic findings. Although the difference in morbidities did not reach statistical significance, the absolute number of complications and the number of patients involved were much higher in the LC arm. The current study provided evidence that surgeons are capable of performing high-quality colorectal ESD procedures. We expect that the participation of the surgeons as well as the close collaboration with gastroenterologists will play a pivotal role in the formulation of a management plan for patients with early colorectal neoplasms.


INTRODUCTION

Laparoscopic colorectal resection (LC) is currently a widely accepted treatment for colorectal neoplasms that are deemed not amenable to endoscopic removal\(^\text{[4-7]}\). However, LC carries an inherent complication rate of over 15%\(^\text{[5-7]}\). Therefore, one could argue that surgery may be too invasive or aggressive as a treatment for early colorectal neoplasms. The potential risks of laparoscopic resection may outweigh the estimated risk of lymph node metastasis if the neoplasms are not resected\(^\text{[5-7]}\). On the contrary, endoscopic piecemeal removal of large sessile or flat polyps by conventional polypectomy or by endoscopic mucosal resection (EMR), although it is less invasive, is known to be associated with a high local recurrence rate of 14%-19.5%\(^\text{[8,9]}\). Endoscopic submucosal dissection (ESD) is a novel technique that was originally developed in Japan more than 10 years ago. ESD was developed to achieve an en bloc mucosal resection with wider margins\(^\text{[10-12]}\). Currently, an increased number of endoscopists throughout the world have acquired this skill and have published promising outcomes of ESD\(^\text{[14-19]}\). The recent retrospective analysis reported by Kiriyama et al\(^\text{[20]}\) that compared ESD for colorectal intramucosal or slightly submucosal invasive cancers vs LC for T1 cancer demonstrated a lower complication rate in the ESD group. Another similar prospective study also compared ESD for adenoma or T1 cancer with less than SM-s (superficial submucosal invasion) vs LC for SM-d (deep submucosal invasion)\(^\text{[21]}\).

Until now, no worldwide consensus has been adopted as to whether the treatment of benign colorectal neoplasms with advanced endoscopic techniques (i.e., ESD) is superior to surgical approaches\(^\text{[22]}\). From the very beginning of the development of colorectal ESD, the procedure was performed primarily by gastroenterologists. No published data exists on the comparison of the clinical outcomes of ESD vs those of LC when both procedures were performed by the same group of surgeons. Surgeons who can perform both procedures may be in an advantageous position in that they can balance the risks and benefits of the endoscopic approach vs the surgical approach. Therefore, we performed a retrospective cohort study that aimed to compare ESD vs LC for endoscopically benign lesions that could not be adequately removed by conventional polypectomy. This is the first comparative study of a similar topic, and this is also the first series where both procedures were performed by the same group of surgeons.

MATERIALS AND METHODS

This was a retrospective cohort study conducted at Prince of Wales Hospital at, The Chinese University of Hong Kong. Since 2005, LC has been the gold standard surgical treatment for all colorectal lesions that are not amenable to endoscopic removal. Colorectal ESD was first established at our centre in 2008, and since that time, it has enriched the armamentarium of endoscopic interventions. Consecutive patients who underwent ESD or LC for early colorectal neoplasms (endoscopically benign lesions larger than 2 cm in diameter) from 2005 to 2013 were included.

Lesions were excluded when endoscopic signs of massive submucosal invasion were present as evidenced by the existence of excavated/depressed morphology or
Kudo’s pit pattern type V. Lesions proven to be malignant by initial endoscopic biopsies were also excluded. Mid and lower rectal lesions were not included because total mesorectal excision, which intrinsically bears a more complicated post-operative course and has a negative impact on gastrointestinal function, would not be offered to patients who were diagnosed with benign lesions by endoscopy. Nevertheless, the input of the patients would also influence the selection between ESD and LC because ESD was a relatively new procedure at that time.

Patients were instructed to eat a low residue diet two days before ESD or laparoscopic colectomy. They received four litres of polyethylene glycol solution as a mechanical bowel preparation on the day of ESD or one day before LC. Both ESD and LC were performed by surgeons who were capable of executing these procedures independently.

All hospital records were reviewed, and the following data were compared between the ESD and LC groups: patient demographics, size and location of the lesions, procedure time, short-term clinical outcomes and pathology result.

The ESD procedure and postoperative care

Our techniques for colorectal ESD have been previously reported[21]. In short, all ESDs were performed when the patients were under conscious sedation after intravenous administration of midazolam and pethidine. Intravenous Buscopan was used if significant colonic spasms were encountered during the ESD procedure. All procedures were performed with a water-jet gastroscope or with a paediatric colonoscope with a transparent cap attached to the tip. Carbon dioxide insufflation was routinely used to reduce patient discomfort. The margins of the lesions were determined by either dye (0.4% indigo carmine spray) or digital (narrow band imaging) chromoendoscopy. Submucosal cushions were created by a mixture of normal saline, adrenaline, indigo-carmine and sodium hyaluronate. Circumferential mucosal incision and submucosal dissection were performed by dual knife or insulated tip knife (Olympus Medical System, Tokyo, Japan), depending on the location of the lesion and the preference of the endoscopists. Haemostasis after ESD was achieved by Coagrasper (Olympus Co. Ltd., Tokyo, Japan).

When perforations were encountered during the ESD procedure, they were immediately closed by endoscopic clips; otherwise, salvage surgery was arranged. For optimal procedures without significant bleeding, a diet would be resumed on the following day. Stable patients who managed to tolerate a full diet were discharged. For those patients with perforations that were managed by endoscopic clipping, they were kept nil per oral and monitored closely for signs of sepsis including fever, tachycardia, leukocytosis and peritonism. Depending on the clinical parameters, parenteral antibiotics were given and diet was gradually introduced. Salvage surgery was offered in cases of persistent or deteriorating sepsis.

All patients were encouraged to maintain mobility, and a diet was introduced gradually as tolerated. Patients were discharged when they could tolerate a full diet without signs of sepsis and the absence of rectal bleeding.

The LC procedure and postoperative care

All LCs were performed under general anaesthesia by the same group of colorectal surgeons, as described in our previous study[24]. In short, the colon or rectum was mobilized laparoscopically from the lateral to the medial area. The isolated lymphovascular pedicles were then transected with either laparoscopic linear staplers or with self-locking plastic clips. One of the working ports was later extended for specimen retrieval. Extracorporeal anastomosis was fashioned for a right-sided resection, while intracorporeal stapled anastomosis was performed for a left-sided resection.

After surgery, the patients were allowed to ingest oral fluid on day one. Diet was resumed gradually during the days following the surgery and depended on the progression of the patients. All patients received regular physiotherapy and were mobilized as soon as possible after surgery. Pain control was achieved by either regular analgesics or by patient-controlled analgesia. Ambulatory patients were discharged if they could tolerate a full diet with no signs of sepsis.

Histological assessment

All ESD specimens were mounted on a foam board for pathological examination by a designated pathologist. Deep and peripheral margins, cellular differentiation as well as the depth of submucosal invasion were recorded. R0 resection was defined as a complete en bloc resection with deep and circumferential margins that were free of adenomatous proliferation or dysplasia. Colectomy specimens were evaluated after fixation in 10% formalin and after staining with haematoxylin and eosin. Macroscopic and microscopic examinations for histological type, depth of invasion, lymph node status and resection margins were performed. Malignant lesions were classified according to the AJCC Cancer Staging Manual, 7th Edition (2010)[25].

Outcomes measurement

In regards to the short-term clinical outcomes, we studied the procedure time, the time to resume diet, the time to full ambulation, the duration of the total hospital stay and the complication rate. Lesions that were located in the colon and at the rectosigmoid junction were defined as “colon”, while lesions in the upper rectum were defined as “rectum”.

Complications were defined as any event that required re-intervention, re-operation, re-admission or a prolonged hospital stay (namely, Clavien-Dindo Grade II or above). Bleeding from the ESD procedure was defined as any bleeding episodes after ESD that warranted surgical intervention.
re-intervention, readmissation, or a blood transfusion. ESD-related perforations were either detected during the procedure or were diagnosed radiologically by the presence of intra-peritoneal free gas.

**Statistical analysis**
Categorical data were analysed using χ² or Fisher’s exact test, while continuous variables were analysed by t test, as appropriate. P values < 0.05 were considered statistically significant. All calculations were conducted with SPSS statistical software package (SPSS version 15.0, Chicago, IL, USA). Data analysis was based on the intention to treat principle.

**RESULTS**
From 2005 to 2013, 55 patients who underwent LC and 65 patients who underwent ESD were included in this study. The mean age of the patients in the ESD group was slightly higher than that of the patients in the LC group. The two groups shared comparable sex and ASA class distributions (Table 1).

No statistically significant differences were observed in terms of lesion size or location, yet ESD could be accomplished with a significantly shorter procedure time (113 ± 66 min vs 153 ± 43 min, P < 0.01) and a faster recovery course, as illustrated by earlier resumption of a full diet (2 d vs 4 d, P = 0.01) and a shorter hospital stay (3 d vs 6 d, P < 0.01) (Table 2).

The overall short-term complication rate for ESD and LC was 10.8% and 23.6%, respectively. Although we could not demonstrate a significant difference between the two groups (P = 0.06), the ESD group exhibited a trend towards a lower short-term complication rate. In the LC arm, a total of 22 complications occurred in 13 patients (Table 3). These included 1 anastomotic leak, which necessitated a laparotomy and stoma formation, 1 mechanical small bowel obstruction, which required re-operation, 6 wound infections, 1 chest infection, 4 urinary tract infections, 1 acute urine retention, 6 cases of prolonged ileus, 1 deep vein thrombosis and 1 mental confusion. A total of 7 complications occurred in the ESD arm, including 5 perforations and 2 bleeding episodes. The remainder of the patients in the ESD arm experienced a smooth intra- and post-procedure course without complications. All of the perforations were observed during the procedure and were successfully managed by endoscopic clipping. Therefore, no emergency surgical intervention was needed. One of the bleeding episodes was successfully stopped during the procedure, and blood transfusion was required. Unfortunately, the other incident was encountered during the removal of a caecal lateral spreading tumour (LST). As a result of malfunction in the water-jet, a clear endoscopic view could not be achieved for safe haemostasis and dissection. Hence, the procedure was abandoned and was followed by emergency LC. The patient was discharged home 4 d after surgery. No delayed perforation, bleeding or other post-procedure complications were recorded in the ESD arm (Table 4).

*En bloc* resection was achieved in 81.5% (53/65) of the ESD procedures. For the remaining 12 lesions, 6 were completely removed by piecemeal EMR. Endoscopic removal had to be abandoned for the other six lesions due to instrumental failure in one case and the presence of dense adhesions in five cases. Amongst the 5 lesions that harboured these dense adhesions, 3 were confirmed T1 adenocarcinomas.

In this study, histological analysis revealed the presence of T1 adenocarcinomas in 25 lesions (LC: 16 and ESD: 9). The proportion of invasive neoplasms was significantly higher in the LC arm (29.1% vs 15.3%, P = 0.04). *En bloc* ESD resection was successfully achieved in 4 of 9 malignant lesions, and all four of these patients were subsequently managed according to the level of submucosal (sm) invasion and other associated histological features. Although salvage surgery was offered to the two patients with sm2 lesions, they both rejected this procedure. On the contrary, one patient with an sm3 lesion agreed to undergo LC, and the pathology of the resected specimen showed no residual primary tumour; however, one metastatic lymph node was identified. The remaining patient with an sm1 lesion was put under close surveillance in light of an adequate resection margin and the absence of lymphovascular permeation. ESD was abandoned in 3 of 9 malignant lesions due to dense submucosal adhesion, of which 2 were salvaged by LC and 1 by TEO (transanal endoscopic operation).
Piecemeal resection was performed in the other 2 of 9 lesions, of which one refused salvage surgery and the other one accepted salvage LC.

**DISCUSSION**

Since the development of colorectal ESD, its feasibility, safety and oncological outcome have been reported in numerous contemporary studies[14-20]. Currently, nearly 3000 colorectal ESDs are performed each year in Japan[26]. The Japanese healthcare insurance system has also approved a reimbursement scheme for colorectal ESD[20]. On the contrary, the adoption rate of ESD is variable in the rest of the world, especially among surgical societies. To explain this, two potential hurdles have been identified. First, the technique of LC had already been widely practised and supported by a high level of evidence at the time when colorectal ESD was introduced outside of Japan. Second, the volume of cases did not justify a large number of endoscopists having to learn and master the technique of ESD. Moreover, current literature that directly compares LC vs ESD for early colonic neoplasms is not available. Two recent studies compared ESD for mucosal or slight submucosal invasive lesions vs LC for T1/deep submucosal invasive lesions[20,21], but the pathological nature of the two comparative groups was different.

This is a retrospective cohort study that compared ESD vs LC for endoscopically confirmed benign lesions that could not be adequately removed by conventional polypectomy. Case inclusion was based purely on the pre-operative/pre-procedure endoscopic findings, and no crossover of abandoned ESD to LC occurred. The results of this study suggested that ESD was superior to LC with respect to short-term outcomes and that ESD leads to a faster recovery. Despite the fact that perforation and bleeding did occur in the ESD arm, all but one of these events could be managed endoscopically. The post-operative course of the only patient who underwent salvage surgery for complications was also uneventful. Although the difference in morbidities did not reach statistical significance, the absolute number of complications and the number of patients involved are much higher in the LC arm.

Moreover, all ESD procedures were performed when the patients were under conscious sedation without general anaesthesia. This definitely avoided the risks of general anaesthesia and post-operative wound pain. Almost immediate mobilization was feasible once the sedative effect subsided. Therefore, we believe that ESD might be more reasonable and acceptable for patients with early colorectal neoplasia or LSTs.

The ESD perforation rate in this study was 7.7%, which was comparable to quoted figures in the literature. In a recent meta-analysis, the highest reported perforation rate was 12%[18], and most of the reported rates in published series were well below 10%[27]. Although these perforation rates might be considered higher than those at some of the high-volume Japanese centres[14,28,29], they were comparable with large series that have been conducted outside of Japan[28,31]. This cohort study only reflected the early phase of our learning curve, and we expect a further reduction in morbidity in the future. Due to the increasing popularity of screening colonoscopy and image-enhanced endoscopy, a greater number of early colorectal lesions might be detected. Therefore, we expect a higher ESD throughput and an improved performance at our centre.

In reality, whether an endoscopically assessed benign lesion is subjected to ESD or colectomy depends to a large extent on who detects the lesion. For instance, if a gastroenterologist who is capable of performing ESD detects an LST, then an ESD procedure might be attempted. Likewise, if the same lesion is detected by a surgeon who does not possess the skills to perform ESD, then colectomy would be offered instead. In our locality, it is rather unique that surgeons actively participate in advanced diagnostic and therapeutic endoscopies. At our centre, we have a group of surgeons who have acquired the skills to perform both LC and colorectal ESD, and who can confidently counsel patients and offer them both options (ESD vs LC). One can also comprehensively balance the risks and benefits between conservative management vs salvage surgery for histologically confirmed malignant lesions that are removed by ESD. The current study provided evidence that surgeons are capable of performing high-quality colorectal ESD. We expect that the participation of the surgeons as well as the close collaboration with gastroenterologists will pay a pivotal role in the formulation of a management plan for

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**Table 3 Complications of laparoscopic colectomy (22 events in 13 patients)**

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<tr>
<th>Complication</th>
<th>Number of complications</th>
<th>Surgical intervention required</th>
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<tbody>
<tr>
<td>Anastomotic leak</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mechanical small bowel obstruction</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Wound infection</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Chest infection</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ileus</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Confusion</td>
<td>1</td>
<td>0</td>
</tr>
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**Table 4 Performance indicators of endoscopic submucosal dissection**

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<thead>
<tr>
<th>Procedure</th>
<th>n</th>
<th>(%)</th>
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</thead>
<tbody>
<tr>
<td>Ext Blu resection</td>
<td>53</td>
<td>81.5</td>
</tr>
<tr>
<td>R0 resection</td>
<td>47</td>
<td>72.3</td>
</tr>
<tr>
<td>Perforation</td>
<td>5</td>
<td>7.7</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2</td>
<td>3.1</td>
</tr>
</tbody>
</table>

No other complication apart from perforation and bleeding were observed.
patients with early colorectal neoplasms.

The major limitation of the current study was its retrospective nature that extended through a period of eight years, during which time major advances in both laparoscopic and endoscopic technology occurred. Most of the LC cases were recruited prior to the availability of image-enhanced endoscopy (2005-2008), when endoscopic diagnoses were less accurate. This explained why patients in the LC arm had more malignant lesions, which was also a major bias of the current study. During the past few years, we have introduced enhanced recovery protocols in our unit, and thus the same LC group may experience a faster recovery and potentially fewer morbidities. To address these biases, a randomized controlled trial is necessary to provide a higher level of evidence to compare these two intervention modalities. We are currently awaiting the results of our randomized controlled trial.

In conclusion, by a comparison of LC and ESD performed by the same group of surgeons for the treatment of early colorectal neoplasms, ESD produced better short-term clinical outcomes with respect to a shorter procedure time and an earlier recovery. Therefore, ESD may be superior to LC for the treatment of this specific type of colorectal lesion.

COMMENTS

Background

Before the development of colonic endoscopic submucosal dissection (ESD), colorectal lesions that were not deemed to be suitable for conventional endoscopic removal were classically treated by colorectal resection. Currently, although minimally invasive surgery can often be performed, the risks associated with surgery should be considered especially for the treatment of benign lesions. While colorectal ESD has become popular in Japan, its adoption rate and its performance quality are still variable in all other areas of the world. It is unknown whether ESD leads to a better short-term outcome for the treatment of early colorectal epithelial neoplasms.

Research frontiers

Results from this study may help surgeons to appreciate the potential benefits of ESD, which has not yet been widely adopted by surgical societies outside of Japan for the treatment of early colorectal epithelial neoplasms.

Innovations and breakthroughs

To date, no worldwide consensus has been adopted as to whether the treatment of benign colorectal neoplasms with ESD is superior to the use of colorectal resection. Moreover, there is no published study on the clinical outcomes of ESD vs laparoscopic colorectal resection (LC), where both procedures were performed by the same group of clinicians. In this retrospective study, the authors compared the short-term outcomes between ESD and LC and focused on the immediate recovery course and the complications.

Applications

This retrospective cohort study suggested that ESD produced better short-term clinical outcomes. The results from future randomized controlled trials would be expected to provide a higher level of evidence in regards to the potential superiority of ESD.

Terminology

In this study, early colorectal epithelial neoplasms referred to lesions without endoscopic signs of massive submucosal invasion, as evidenced by the absence of an excavated/depressed morphology or Kudo’s pit pattern type V.

Peer-review

The authors evaluated one hundred and twenty patients (ESD: 65, LC: 55) who underwent treatment for early colorectal epithelial neoplasms. ESD could be accomplished in a shorter time, and patients experienced a faster recovery. Although the difference in the occurrence of morbidities did not reach statistical significance, the absolute number of complications and the number of patients involved were much higher in the LC arm. Therefore, the option of ESD should be seriously considered in the contemporary management of early colorectal epithelial neoplasms.

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Hon SS et al. Endoscopic submucosal dissection vs laparoscopic colectomy.