A B S T R A C T

Introduction: Colorectal endoscopic submucosal dissection is not a widely adopted procedure due to its technical difficulties. This study aimed to share the experience in setting up this novel procedure and to report the learning curve for such a procedure at a low-volume district hospital in Hong Kong.

Methods: This case series comprised 71 colorectal endoscopic submucosal dissections that were performed by a single endoscopist without experience in gastric or colorectal endoscopic submucosal dissection. Lesion characteristics, procedure time per unit area of tumour, en-bloc resection rate, R0 resection rate, complications, and length of stay were recorded prospectively. Results were compared for two consecutive periods to study the learning curve.

Results: Overall, 41 (57.7%) tumours were located in the right colon, 21 (29.6%) in the left colon, and nine (12.7%) in the rectum. The median tumour area was 4 cm² (range, 0.25-16 cm²). The median operating time was 105 (range, 47-342) minutes. The median procedure time per unit area of tumour was 24.9 min/cm². There was one instance of intra-operative bleeding that required conversion to laparoscopic colectomy. There was no postoperative haemorrhage.

Conclusion: Untutored colorectal endoscopic submucosal dissection is feasible with acceptable clinical outcomes at a low-volume district hospital in Hong Kong.

New knowledge added by this study

• Untutored colorectal endoscopic submucosal dissection (ESD) has an acceptable clinical outcome after 35 procedures at a low-volume centre.

Implications for clinical practice or policy

• ESD can be safely performed at a low-volume centre.
• ESD can be started at the colorectum instead of the stomach.

Introduction

For many years, conventional endoscopic mucosal resection (EMR) and surgery were the only options for treating a large (>20 mm) sessile or flat colorectal lesion. Conventional EMR, however, often results in piecemeal removal and there is a significant local recurrence rate ranging from 7.4% to 17%. Full histological evaluation is also difficult.

Endoscopic submucosal dissection (ESD), pioneered in Japan for treating early upper gastrointestinal malignancy, was introduced in the late 1990s by Yamamoto et al and Fujishiro et al to treat colorectal lesions. The technique has an advantage over EMR in that its effectiveness is not limited by size or shape of the lesion. In the past decade, colorectal ESD has been shown to be superior to EMR, in terms of higher en-bloc resection rate and lower recurrence rate. Colorectal ESD can be applied not only to adenoma, but also to intramucosal carcinoma and low-risk submucosal carcinoma, as defined by the Paris classification’ and the Japanese Society for Cancer of the Colon and Rectum. Recently, a large-scale multicentre study has shown that ESD alone is adequate in the management of patients with low-risk submucosal carcinoma and achieves an excellent 5-year recurrence-free survival of 98% and 5-year
overall survival of 94%.3

Despite the growing evidence to support the use of colorectal ESD, it is not established as a standard treatment outside Japan. The drawbacks of colorectal ESD include longer operating time4 and higher complication rates, especially perforation. Although the perforation rate of ESD is much higher than that of EMR, most ESD perforations can be treated conservatively by clip closure during endoscopy.10,11 In a multicentre study of iatrogenic perforations in Japan, the respective EMR and ESD perforation rate was 0.58% and 14% in 15,160 therapeutic colonoscopies.12 Endoscopic clipping failed in 43.5% of ESD perforations and surgical intervention was necessary.12

Perhaps one of the major hurdles to its general application is that it is a technically demanding procedure that is difficult to set up at a low-volume district hospital. We would like to share our experience of applying this novel technique in a district hospital in Hong Kong.

Methods

Case selection

North District Hospital was a district hospital serving 700,000 population with a case volume of 15 to 20 cases of ESD per year. Since the introduction of the ESD technique at the hospital in 2009, all lateral spreading tumours larger than 2 cm or those unable to be resected en bloc by conventional polypectomy were referred to a single endoscopist to determine the appropriateness of ESD. Colonoscopy was repeated by a single endoscopist to determine the location, size, and nature of each tumour by white-light and narrow band imaging (NBI). Benign polyps not amendable to removal by EMR were triaged to ESD. Target biopsy was performed on Sano III lesions that were triaged to conventional colonoscopy. No tumours were excluded based on location.

Preoperative evaluation of the depth of invasion

Evaluation of the depth of invasion is important to determine the treatment strategy. To predict the depth of invasion, we used NBI colonoscopy, based on Sano’s capillary pattern classification. The underlying principle is that angiogenesis is critical for transition of a premalignant lesion to a malignant one and the microcapillary pattern changes in this process. Sano et al13 focused on this microcapillary difference based on their histopathological findings and devised three classifications: types I, II, and III. Type III was further subdivided into IIIA and IIIB.14

The diagnostic accuracy of NBI colonoscopy in differentiating a neoplastic from non-neoplastic lesion is superior to conventional colonoscopy and equivalent to chromoendoscopy using indigo-carmine.15 For estimation of the depth of invasion, the sensitivity, specificity, and diagnostic accuracy of capillary pattern type III for differentiating pM-ca (intramucosal) or pSM1 (superficial) from pSM2-3 (deep) was 84.8%, 88.7% and 87.7%, respectively.14 We preferred NBI colonoscopy because it is fast and easy to use, without the need to spray dye as in chromoendoscopy.

Preparation

The procedure was performed in the operating theatre with the patient under conscious sedation. All patients were assessed by an anaesthetist in a preoperation clinic. Patients were instructed to eat a low-residue diet 2 days before the procedure and a fluid diet on the day before ESD. Bowel preparation with 4 L polyethylene glycol solution was given on the day before ESD. Prophylactic antibiotics were not prescribed.

Setting

All procedures were performed in the operating theatre. This ensured that all equipment was on hand should conversion to an open procedure be required, for example, if there was full-thickness perforation that could not be closed endoscopically.
Endoscopic system

In our hospital, ESD was performed using a single-channel colonoscope (CF-H180AL; Olympus, Tokyo, Japan). This colonoscope was a high-density television compatible with a wide angle of 170°, 3.7-mm instrument channel, and auxiliary water jet. A short transparent hood was fitted to the tip of the endoscope so that the whole ring could be seen in endoscopic view. Carbon dioxide was used for insufflation to decrease patient discomfort. We used a high-frequency electrosurgical generator (ESG-100; Olympus, Tokyo, Japan) with a peristaltic pump (AFU-100; Olympus, Tokyo, Japan). The energy setting used for incision and dissection was “forced coagulation 2” 30W, whereas “soft coagulation” 100W was used for haemostasis.

Cutting devices

In our initial practice, we used the Flex Knife (KD-630L; Olympus, Tokyo, Japan) to perform the procedure. It had a loop-shaped tip that allowed easy control in any direction, as it was soft and flexible. Nonetheless, we found it difficult to adjust the length of the tip and there was frequent accumulation of debris around the tip. We then changed to Dual Knife (KD-650L; Olympus, Tokyo, Japan) with a fixed length (1.5 mm) and hence a more stable knife movement. More recently, we have used Flush Knife BT (DK2618J/B/DK2618J/N; Fujifilm, Saitama, Japan) for dissection. It has a ball tip of fixed length that touches a wider part of tissue and enhances haemostasis. The knife has a water jet channel and achieves two purposes: (1) it can wash away any tissue that accumulates around the tip, thereby maintaining the sharpness of the knife; and (2) submucosal normal saline injection can be performed without the need to change the instrument for further hyaluronate injection.

Injecting agent

We used a mixture of 10% sodium hyaluronate (LG Chemical, South Korea) and 1:200000 adrenaline saline at a ratio of 1:1.5. This solution was chosen for three reasons: the addition of adrenaline can produce a haemostasis effect; dilution of sodium hyaluronate made it less viscous and thus easier to inject; and it reduced the amount used of the relatively more expensive sodium hyaluronate.

Endoscopist

All ESD procedures were performed by a single experienced endoscopist who had performed more than 500 therapeutic colonoscopic procedures and more than 200 laparoscopic colectomies. The ESD procedure was implemented by the endoscopist following completion of training on an animal model in the Second Master Workshop on Novel Endoscopic Technology & Endoscopic Submucosal Dissection in 2009 at Prince of Wales Hospital in Hong Kong, which was organised by the Department of Surgery, The Chinese University of Hong Kong (http://www.surgery.cuhk.edu.hk/events/2009-07-22-ESD.pdf). The workshop included both lecture sessions and hands-on sessions to perform ESD in a pig. The endoscopist had no experience in gastric or colorectal ESD. He received further overseas training in ESD in 2011 at Osaka Medical Center for Cancer and Cardiovascular Diseases in Japan as a clinical observer with hands-on animal model training.

Procedure

With the patient initially lying in the left lateral position, a full colonoscopy was first performed to confirm and locate the site of pathology. Patients were then re-positioned such that the lesion was at an anti-gravitational position in the endoscopic view at 6 o’clock. This could be easily achieved by seeing the injected water pooling opposite to the lesion. In this position, the gravitational force aided in retracting the lesion away from the submucosal plane during dissection. We then injected 1:100 000 adrenaline saline at 1 cm distal to the lesion, aiming at the submucosal layer. This could be ascertained by seeing the formation of a dwell. With the injecting needle still in situ, the solution was then changed to the mixture of adrenaline saline and sodium hyaluronate to provide a precipitous elevation of sufficient height. After elevating the lesion, a mucosal incision was made proximal to the lesion. The mucosal incision was started at the proximal two thirds of the lesion. After mucosal incision, the submucosal plane was dissected with the submucosa dissected away from the muscle layer. Care was taken to manipulate the dissection plan parallel to the intestinal wall to prevent perforation. When a more than 1-mm diameter vessel was detected, it was coagulated using haemostasis forceps (Radial Jaw 4; Boston Scientific, US). When the flap was sufficient for retraction, the mucosal incision was completed. In case of perforation, the defect was closed with endoscopic clipping (EZ Clip; Olympus, Tokyo, Japan). The resected area was not closed as healing usually occurred in a few weeks without complications.16

Histological assessment

All specimens were pinned on a piece of foam and fixed in formalin. Histological type, depth of invasion, as well as lateral and vertical resection margins were recorded. En-bloc resection was defined as one-piece resection of an entire lesion as observed endoscopically. R0 resection was defined as clear lateral and vertical resection margin.

Post–endoscopic submucosal dissection

All patients were allowed to resume a full diet on the
same day. We performed no routine blood tests or imaging and patients were discharged the next day if there were no signs of perforation or haemorrhage. Postoperative haemorrhage was defined as clinical evidence of bleeding manifested by melena or haematochezia that required endoscopic haemostasis within 0 to 14 days of the procedure.11

Follow-up
All patients were followed up in clinic 2 weeks later to review the pathology report. Additional surgery would be offered in case of carcinoma with one of the following criteria: (1) margin involved; (2) >1 mm submucosal invasion; (3) positive lymphovascular permeation; (4) poorly differentiated adenocarcinoma, signet ring cell carcinoma, or mucinous carcinoma; or (5) high-grade tumour budding.17 Surveillance colonoscopy was performed 1 year after ESD.

Statistical analysis
All continuous variables were described as median and range. To study the learning curve, all patients were grouped chronologically into two periods: group 1 with cases 1 to 35; and group 2 with cases 36 to 71. Comparisons between non-parametric data were done with Mann-Whitney U test, while Chi squared test was used for categorical variables. A P value of <0.05 was considered statistically significant.

Results
From March 2009 to December 2013, a total of 71 ESDs were performed. Characteristics of the patients are shown in Table 1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>67 (46-88)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42 (59.2%)</td>
</tr>
<tr>
<td>Female</td>
<td>29 (40.8%)</td>
</tr>
<tr>
<td>Location of tumour</td>
<td></td>
</tr>
<tr>
<td>Right colon</td>
<td>41 (57.7%)</td>
</tr>
<tr>
<td>Left colon</td>
<td>21 (29.6%)</td>
</tr>
<tr>
<td>Rectum</td>
<td>9 (12.7%)</td>
</tr>
<tr>
<td>Tumour area (cm²)*</td>
<td>4 (0.25-16)</td>
</tr>
<tr>
<td>Procedure time (mins)*</td>
<td>105 (47-342)</td>
</tr>
<tr>
<td>Procedure time per unit area (min/cm²)*</td>
<td>24.9</td>
</tr>
<tr>
<td>Postoperative length of stay (days)*</td>
<td>1 (0-11)</td>
</tr>
<tr>
<td>Perforation rate</td>
<td>15.5%</td>
</tr>
<tr>
<td>En-bloc resection rate</td>
<td>81.2%</td>
</tr>
<tr>
<td>Additional snare</td>
<td>27.5%</td>
</tr>
<tr>
<td>R0 resection rate</td>
<td>58.0%</td>
</tr>
</tbody>
</table>

* Median (range) is shown

In these 69 patients, the resection margin was unclear in 15 patients as it was too close to the cauterised edge. These, together with piecemeal resection, were classified as R1 (29 patients in total). R0 resection was achieved in 40 (58.0%) patients. The histopathological diagnosis was tubular adenoma for 26 (36.6%) tumours, tubulovillous adenoma for 28 (39.4%), villous adenoma for two (2.8%), serrated adenoma for six (8.5%), carcinoid for one (1.4%) with involved margin, intramusosal carcinoma for two (2.8%), and carcinoma with submucosal invasion for six (8.5%). The ESD procedure was considered curative for the two patients with intramusosal carcinoma. One patient who had submucosal carcinoma refused further treatment because of a subsequent diagnosis of primary lung cancer. All other patients with submucosal carcinoma had curative interval laparoscopic surgeries. There was no residual tumour and no lymph node involvement found in the surgical specimen for any of these patients. The patient with rectal carcinoid also underwent subsequent interval laparoscopic total mesorectal excision: the pathology was well-differentiated carcinoid with invasion to the muscularis propria. There was one lymph node metastasis out of 11 lymph nodes retrieved.

Recurrence and surveillance colonoscopy
After excluding the six interval surgeries and two conversions to laparoscopic colectomy, the remaining 63 patients were offered colonoscopy surveillance of whom four refused and one defaulted from follow-up. Until August 2014, 51 patients had undergone surveillance colonoscopy and seven
were awaiting colonoscopy. Recurrence of polyp occurred in seven (13.7%) out of 51 patients: three recurrences occurred after piecemeal resection, another three recurrences occurred after additional snare to complete the en-bloc resection. All three cases had uncertain margin due to proximity to the cauterised edge. In one patient, recurrence occurred after successful en-bloc resection by ESD, in which the deep margin was clear but the circumferential margin was not certain.

**Learning curve between the two chronological groups**

All patients were grouped chronologically into two periods: group 1 with cases 1 to 35; and group 2 with cases 36 to 71. The comparison between the two groups is shown in Table 2. The median procedure time per unit area of tumour improved significantly from 31.5 min/cm² to 21.5 min/cm² (P=0.032).

There were three (8.6%) perforations in group 1; one of them required conversion to laparoscopic colectomy. There were eight (22.2%) perforations in group 2; all managed successfully by endoscopic clipping. There was no significant difference in perforation rate (P=0.054). The intra-operative bleeding that required a conversion to laparoscopic colectomy also belonged to group 1.

For the 33 patients in group 1 who completed the endoscopic procedure, en-bloc resection was successful in 26 (78.8%), while 30 (83.3%) out of 36 patients in group 2 had successful en-bloc resection. This trend of improvement, however, did not reach statistical significance (P=0.15). Among these successful en-bloc resections, 15 (57.7%) out of 26 patients in group 1 and four (13.3%) out of 30 patients in group 2 required additional snare to complete the en-bloc resection (P<0.01).

R0 resection rate had improved significantly in group 2 despite a lower rate of snare application: 13 (39.4%) of 33 patients in group 1 had R0 resection, whereas in group 2, 27 (75.0%) of 36 patients had R0 resection (P<0.01).

The median postoperative stay was 1 day in both groups and was not significantly different (P=0.25). The median postoperative stay in patients with perforation in group 1 and group 2 was 1 day (range, 1-7 days) and 2 days (range, 1-11 days), respectively (P=0.73).

**TABLE 2. Comparison between the two chronological groups**

<table>
<thead>
<tr>
<th>Location</th>
<th>Group 1 (case No. 1-35)</th>
<th>Group 2 (case No. 36-71)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right colon</td>
<td>22 (62.9%)</td>
<td>19 (52.8%)</td>
<td>-</td>
</tr>
<tr>
<td>Left colon</td>
<td>10 (28.6%)</td>
<td>11 (30.6%)</td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td>3 (8.6%)</td>
<td>6 (16.7%)</td>
<td></td>
</tr>
<tr>
<td>Tumour area (cm²)*</td>
<td>4 (0.25-16)</td>
<td>4 (1.5-9)</td>
<td>0.23</td>
</tr>
<tr>
<td>Procedure time (mins)*</td>
<td>125 (53-323)</td>
<td>98 (47-342)</td>
<td>0.19</td>
</tr>
<tr>
<td>Procedure time per unit area (min/cm²)*</td>
<td>31.5</td>
<td>21.5</td>
<td>0.032</td>
</tr>
<tr>
<td>Perforation rate</td>
<td>8.6%</td>
<td>22.2%</td>
<td>0.054</td>
</tr>
<tr>
<td>En-bloc resection rate</td>
<td>78.8%</td>
<td>83.3%</td>
<td>0.15</td>
</tr>
<tr>
<td>Additional snare</td>
<td>45.5%</td>
<td>11.1%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>R0 resection rate</td>
<td>39.4%</td>
<td>75.0%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Postoperative stay (days)*</td>
<td>1 (1-7)</td>
<td>1 (1-11)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

* Median (range) is shown.
reported learning curve for untutored colorectal ESD has an acceptable outcome, however. Berr et al. reported a case series of 48 colorectal ESDs with 76% en-bloc resection, 14% perforation, and 4% requirement for surgical intervention. This compared favourably with results in Japan. Another learning curve study of colorectal ESD found procedure time could be significantly shorter after 25 procedures.

With a similar situation in Hong Kong, this study showed that untutored colorectal ESD is safe and feasible. Results demonstrated obvious improvement after 35 procedures, as evidenced by the significant reduction in combined ESD and EMR with snare from 45.5% to 11.1%. Procedure time per unit area of tumour as well as R0 resection rate also significantly improved after 35 cases. Although there were more perforations in group 2, it did not determine adverse outcome. None of the perforations in group 2 required conversion to laparoscopic colectomy. There was no significant impact on hospital stay. The higher perforation rate in group 2 may reflect a second learning curve of anaesthesia—in the first few patients, de novo of procedure—operating theatre was chosen instead of an endoscopic unit to enable conversion to conventional laparoscopic colectomy without the need to change location as well as the ready availability of an anaesthetist to give conscious sedation. Positioning of patients was clumsy particularly when a prone position was needed to perform the procedure. Subsequently conscious sedation by an anaesthetist was used instead. Patients could follow instructions for positioning and deeper sedation could be achieved if necessary. There were no complaints from patients about any discomfort during the procedure.

Choice of injecting agents—albumin 20% (Albumex 20; CSL, Australia) was used as submucosal injecting agent in the first few patients when sodium hyaluronate was not available. Albumin 20% has both a good cushioning effect without any inflammatory effect and the cost was much cheaper at HK$2.7/mL compared with commercially available sodium hyaluronate at HK$68/mL. Yet sodium hyaluronate has the longest lasting cushioning effect among all injecting agents. We recommend its use whenever available. A mixture of adrenaline saline and sodium hyaluronate was favourable for the assistant to inject and a lesser volume of sodium hyaluronate was required. Moreover, there were no instances of postoperative haemorrhage, although it was difficult to conclude whether this was due to the addition of adrenaline saline.

Endoscopic technique—in our initial practice, we performed a full circumferential mucosal incision before submucosal dissection. We noticed it was technically more difficult compared with a two-third circumferential incision, because firstly, the submucosal elevation was lost quickly due to faster leakage of injecting agent, and secondly, it was difficult to retract the lesion at the end of dissection, and we had to complete the en-bloc resection with snare. After changing to two-third circumferential incision in the second period of the study, the need for additional snare to complete the en-bloc resection was significantly decreased (from 57.7% to 13.3%).

Postoperative management—it was feasible and safe to resume diet immediately after the procedure and discharge patients the day following ESD without the need for routine blood taking or imaging. In one study from Japan, abdominal computed tomography was performed on day 1 and blood tests were carried out for 2 consecutive days. Oral intake was gradually stepped up and patients were discharged 5 days after ESD. In contrast, we allowed full diet on the same day after ESD and did not perform computed tomography or blood tests routinely. Our overall median postoperative stay was 1 day. Further...
development of ESD as a day procedure can be explored. There are a number of limitations in this study. First, this was the learning curve of a single endoscopist and 35 procedures may not be a typical number required for such a learning curve. Second, the inclusion criteria for colorectal ESD were less strict than those in Japan. Lesion less than 2 cm that could not be removed en bloc would be subjected to ESD instead of piecemeal resection. These kinds of lesion were expected to be easier with shorter operating time. Third, this was a retrospective comparison of two chronological groups which might not have been directly comparable. Lastly, the 7.9% patient default rate may lead to underestimation of recurrence in this series.

Conclusion

Untutored colorectal ESD at a low-volume centre was an option in the absence of enough experts to supervise the procedure. Training on an animal model and clinical observation of real-time demonstrations was useful to start ESD without supervision. A cut-off at 35 procedures showed an acceptable R0 resection rate at a significantly improved procedure time per unit area. There was a second learning curve to achieve a complete ESD procedure without EMR at a higher perforation rate. Colorectal ESD performed by a colorectal surgeon enables any complications to be managed by the same operator, or any lesion unresectable by ESD to be surgically removed. It was not necessary to first perform gastric ESD as the start of ESD training. When more endoscopists have gained experience in colorectal ESD, a structured training programme with accreditation can be established.

Declaration

All authors have disclosed no conflicts of interest.

References