Clinical outcomes of colorectal endoscopic submucosal dissection and risk factors associated with piecemeal resection

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ABSTRACT

Background/Aims: We aimed to investigate the factors associated with piecemeal resection of colorectal neoplasia (CRN), in spite of endoscopic submucosal dissection (ESD).

Materials and Methods: We analyzed the retrospective data for colorectal ESD cases from January 2005 to April 2014. We also reviewed the piecemeal endoscopic mucosal resection (EMR) for CRNs ≥20 mm, performed over the same period.

Results: En bloc resection was possible in 648 (85.7%) of 756 lesions in 740 patients. Multivariate analysis showed that hybrid ESD (odds ratio (OR), 29.07; 95% confidence interval (CI), 15.46–54.65; p<0.01) and mild or severe submucosal fibrosis (OR, 3.62; 95% CI, 1.94–6.76; p<0.01) were independently associated with piecemeal ESD. The en bloc ESD group showed higher histologic complete resection rate than the piecemeal ESD group (80.4% vs. 56.5%; p<0.01), and the piecemeal ESD group showed higher recurrence rate than in the en bloc ESD group (5.6% [4/72] vs. 0.7% [3/450]; p<0.01). Overall recurrence rate was 1.3% (7/522).

Conclusion: Hybrid ESD and submucosal fibrosis are independently associated with piecemeal ESD. Piecemeal ESD cases recurred more frequently than en bloc ESD cases.

Keywords: Endoscopic submucosal resection, colorectal neoplasia, piecemeal resection

INTRODUCTION

Endoscopic submucosal dissection (ESD) is a highly specialized technique for the en bloc resection of large colorectal neoplasia (CRN) (1). The higher en bloc resection rate of ESD yields lower recurrence rates after treatment in cases of large CRN, as compared to that with conventional endoscopic mucosal resection (EMR) (2,3). However, colorectal ESD is technically more challenging and requires longer procedure times as compared to EMR or piecemeal EMR (4-7). Hence, en bloc resection may not be completed in all ESD cases and the piecemeal or incomplete resection rate of colorectal ESD ranged from 1% to 16% in the previous studies (4, 8-12). Only a few studies have investigated the factors related to incomplete resection or piecemeal resection. One study suggested that longer procedure time, submucosal fibrosis, and paradoxical colonic movement during ESD might be associated with incomplete resection, whereas another reported that en bloc ESD failure was associated with low-volume institution (<30 ESDs for 3 years), usage of a snare, and poor lifting after submucosal injection (13,14).

Recurrence data of piecemeal EMR are widely available in the literature. The local recurrence rates of piecemeal EMR for CRN ranges from 12.2% to 23.5% (2,15-17). In a western retrospective study on the outcomes of EMR (including 46.2% cases of piecemeal resection) for colorectal lesions with a mean size of 23 mm, 30.4% were found to have recurrent or remnant lesions during follow-up (18). However, the recurrence rate of piecemeal ESD has not been extensively investigated relative to piecemeal EMR. A recent Japanese multicenter prospective study reported that the recurrence rate (13.9%) of piecemeal ESD was similar to that (14.9%) of piecemeal EMR (2). However, that study included a small number of piecemeal ESD cases (n=36), as compared to piecemeal EMR cases (n=378); hence, a relatively large number of cases may be needed to evaluate the local recurrence rates of piecemeal ESD.
Here, we aimed to reveal the factors affecting piecemeal resection of large (≥20 mm) colorectal epithelial neoplasia, despite the application of ESD, and to investigate the long-term outcomes of piecemeal ESD cases relative to en bloc ESD by using data from a single center.

**MATERIALS AND METHODS**

**Study population**

We reviewed the medical records of patients who underwent ESD for CRNs from January 2005 to April 2014 at our center. Cases with subepithelial lesions such as neuroendocrine tumor, leiomyoma, gastrointestinal stromal cell tumor (GIST), and granular cell tumor were excluded. Furthermore, we excluded cases with a final pathologic diagnosis of hyperplastic or inflammatory polyps. During the study period, 4 endoscopists (D.H.Y., J.S.B., B.D.Y., and K.J.K.) performed ESD and removed 756 lesions in 740 patients. The endoscopists were categorized as high-volume endoscopists (>200 ESDs during the study period) and medium-volume endoscopists (100-200 ESDs during the study period). Regarding the experience before starting colorectal ESD, all endoscopists had performed more than 4,000 colonoscopy procedures including EMR, but none had the experience of gastric ESD. All the ESD cases were also categorized as en bloc or piecemeal resection. Moreover, we analyzed the factors associated with the piecemeal resection of CRNs. After excluding patients who required subsequent surgery and/or chemoradiation or patients who were lost to follow-up, we compared the recurrence rates between en bloc ESD and piecemeal ESD cases (Figure 1). Based on the guidelines of the colorectal ESD Standardization Implementation Working Group (19), colorectal ESD is generally indicated for lesions if en bloc resection was considered challenging via EMR technique due to location or fibrosis. All the data related to the patients, tumors, procedures, and adverse events were collected from the ESD database and medical records. All endoscopic procedures in this study including ESD and surveillance endoscopy were conducted after getting informed consent from the patients. Our institutional review board approved the study protocol (No. 2015-0954).

### ESD/hybrid ESD procedure

Details of the ESD technique and devices has been previously published (7,20,21). Transparent cap-attached endoscope was used for ESD. After submucosal injection using sodium hyaluronate solution (Hyal® Shinpoong Co. or Endo-Ease® Unimed Co., Seoul, Korea) mucosal inci-
sion and submucosal dissection were performed using a Fixed Flexible knife (Kachu Technology Co., Seoul, Korea) or a Dual knife (Olympus Co., Tokyo, Japan).

Hybrid ESD is a procedure wherein submucosal dissection is performed circumferentially until approximately ≤1 cm of the tissue is remaining, which is then resected with the snaring method (21).

**Follow-up endoscopy**
All patients underwent periodic follow-up colonoscopies or sigmoidoscopies to assess the local recurrence or remnants. Follow-up endoscopy was performed approximately in 1 year in case of histologic complete resection was achieved. In case of piecemeal resection or a histologically positive lateral resection margin, the first surveillance endoscopy was done within 6 months after endoscopic treatment.

**Data collection and study outcomes**
The lesion locations were categorized as cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum. The colorectal lesions were classified as laterally spreading tumor granular type (LST-G), laterally spreading tumor non-granular type (LST-NG), and sessile type, based on the morphologic characteristics. The sessile type had 0-Is gross appearance in Paris classification, and did not show a transversal mode of growth on endoscopy (22).

The submucosal fibrosis was graded as none, mild, and severe, according to the endoscopic transparency and appearance of the exposed submucosal layer (23). Intraprocedural bleeding was defined as bleeding during endoscopic resection and interrupted procedure that finally required endoscopic hemostasis with hemostatic forceps. Delayed bleeding was defined as clinical evidence of the occurrence of hematochezia/melena after the procedure that required endoscopic hemostasis. Perforation was identified based on endoscopic and/or radiological findings.

All the resected specimens were fixed in 10% formalin and microscopically evaluated. En bloc resection was defined as grossly complete resection of the lesion in a single piece. The greatest dimension of the gross specimen was measured and recorded as the size of the tumor. In cases of piecemeal resection, the greatest dimension of the assembled gross specimen was considered as the size of the lesion if all of resected tumors could be spread and fixed onto a hard Styrofoam. In cases where the pieces of the specimens could not be accurately assembled, the lesion size was endoscopically estimated using open biopsy forceps as a reference.

Histological diagnoses were made according to the Vienna classification (24). The extension of the tumor cells into the resected margin was evaluated. Histologic complete resection was defined as the absence of tumor cells at the lateral and deep resection margins of the specimen. If the pieces of the specimens could not be accurately assembled after the piecemeal resection, it was considered as histologic incomplete resection. Moreover, superficial submucosal cancer was defined as cancer invasion to a depth of <1000 μm from the muscularis mucosa. Curative resection was defined as the clear deep and lateral resection margins, without deep submucosal invasion (>1000 μm from muscularis mucosa) or other unfavorable histologic risk factors (lymphovascular invasion, poor differentiation, or tumor budding) related with lymph node metastasis. Recurrence of CRN after ESD was defined as any histologically identified CRN that recurred at the site of scar of ESD.

**Statistical analysis**
Continuous parameters were analyzed using Student’s t-test or the Mann-Whitney U test, whereas categorical variables were compared using the χ² test and Fisher’s exact test, as appropriate. Values of p<0.05 were considered statistically significant. Risk factors for piecemeal resection were analyzed using univariate method. A logistic regression model was used for the multivariate analysis of significant factors detected by univariate analysis, defined as p<0.05, with backward stepwise selection. Cumulative recurrence rates were calculated by the Kaplan-Meier method and compared between each group using the log-rank test. SPSS version 21 for Windows (IBM Corp.; Armonk, NY, USA) was used for the statistical analysis.

**RESULTS**

**Baseline and clinical characteristics of the en bloc and piecemeal ESD groups**
Among the 756 lesions in 740 patients who underwent ESD for colorectal epithelial neoplasia, en bloc resection was achieved in 648 (85.7%). The baseline characteristics of the en bloc ESD and piecemeal ESD groups are described in Table 1.

**Procedure-related and histologic variables of the en bloc and piecemeal ESD groups**
With regard to the experience of the endoscopists performing colorectal ESD, high-volume endoscopists tended to have a higher en bloc resection rate as
compared to medium-volume endoscopists (76.4% vs. 67.6%, respectively; p = 0.050). Hybrid ESD, submucosal fibrosis, and intraprocedural bleeding were more frequent in the piecemeal ESD group than in the en bloc ESD group. Piecemeal ESD group required longer procedure time than en bloc ESD group. Deep submucosal or more advanced invasion was identified histologically in 66 patients; of these patients, 5 refused subsequent surgery, whereas the remaining 61 underwent rescue surgery and/or chemoradiation therapy. Details of the procedure-related variables and histologic outcomes are summarized in Table 1.

The overall curative resection rate and histologic complete resection rate were 69.7% (527/756) and 77.0% (582/756), respectively. Both histologically complete resection rate and curative resection rate were higher in the en bloc ESD group compared with the piecemeal ESD group (p<0.001). Positive or uncheckable lateral resection margin involvement was more frequently noted in the piecemeal ESD group than in the en bloc ESD group (p<0.001).

### Factors associated with piecemeal ESD

Univariate analysis indicated that piecemeal ESD was associated with the gross LST-NG type, hybrid ESD, tumors located above the rectum, intraprocedural bleeding, submucosal fibrosis, and procedure time ≥60 min. However, multivariate analysis revealed that only hybrid ESD, submucosal fibrosis, and procedure time ≥60 min were independently associated with piecemeal ESD. Details of the analyses of the factors associated with piecemeal ESD are described in Table 2.

### Recurrence in the en bloc and piecemeal ESD groups

A total of 234 cases were eliminated from the analysis of recurrence due to rescue surgery (58 in the en bloc ESD group and 19 in the piecemeal ESD group), rescue chemoradiation (3 rectal cancers in the en bloc ESD group), and absence of follow-up endoscopy (137 in the en bloc ESD group and 17 in the piecemeal ESD group). Accordingly, recurrence was evaluated in 450 cases of en bloc ESD and 72 cases of piecemeal ESD, as shown in Figure 1. The median follow-up period was 15.4 months (inter-quartile range (IQR), 12.3–29.3 months) in the en bloc ESD group.
and 13.7 months (IQR, 6.9-31.0 months) in the piecemeal ESD group. There were 7 cases of recurrence during follow-up period and the overall recurrence rate was 1.3% (7/522). Clinicopathologic characteristics of each case are summarized in Table 3. Compared with the en bloc ESD group, the recurrence rate was significantly higher in the piecemeal ESD group (5.6% vs. 0.7%; p=0.008). The cumulative recurrence rate was significantly higher in the piecemeal ESD group (4.7% at 1 year and 7.7% at 3 years) than in the en bloc ESD group (0% at 1 year and 1.9% at 3 years) (p<0.001, Figure 2).

According to the univariate analysis, piecemeal ESD (odds ratio (OR), 8.77; 95% confidence interval (CI), 1.92-40.02; p=0.005), tumor size ≥35 mm (OR, 11.46; 95% CI, 1.37-95.91; p=0.024), histologically incomplete resection (OR, 21.35; 95% CI, 2.54-179.13; p=0.005), and medium-volume endoscopists (OR, 21.35; 95% CI, 2.54-179.13; p=0.005) were associated with recurrence after ESD.

**DISCUSSION**

In this study, we found that the en bloc resection rate of colorectal ESD was 85.7%, and that the application rate of colorectal ESD was significantly higher in the en bloc group than in the piecemeal group (6.6% vs. 0.7%; p=0.008). The cumulative recurrence rate was significantly higher in the piecemeal ESD group (4.7% at 1 year and 7.7% at 3 years) than in the en bloc ESD group (0% at 1 year and 1.9% at 3 years) (p=0.001).

**Table 3.** Clinicopathologic characteristics of the cases with recurrence

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (years)/ Sex</th>
<th>Tumor location</th>
<th>Tumor type</th>
<th>Gross type</th>
<th>Endoscopist</th>
<th>Hybrid ESD</th>
<th>Resection (number of pieces)</th>
<th>Tumor size, mm</th>
<th>Histology</th>
<th>Histological complete resection</th>
<th>Deep resection margin</th>
<th>Lateral resection margin</th>
<th>Number of endoscopy to recur</th>
<th>Time to recurrence, months</th>
<th>Histology of the tumor that recurred</th>
<th>Treatment of tumor recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55/F</td>
<td>R</td>
<td>Sessile</td>
<td>Moderate</td>
<td>Yes</td>
<td>Piecemeal (5)</td>
<td>50</td>
<td>Adenoma</td>
<td>No</td>
<td>Negative</td>
<td>Uncheckable</td>
<td>1</td>
<td>6.1</td>
<td>Adenoma</td>
<td>Endoscopic treatment (APC)</td>
<td></td>
</tr>
<tr>
<td>2*</td>
<td>50/M</td>
<td>R</td>
<td>LST-NG</td>
<td>Moderate</td>
<td>Yes</td>
<td>En bloc</td>
<td>12</td>
<td>Superficial s.m. cancer</td>
<td>No</td>
<td>Positive</td>
<td>Negative</td>
<td>4</td>
<td>17.4</td>
<td>Adenocarcinoma</td>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>67/F</td>
<td>R</td>
<td>LST-G</td>
<td>Moderate</td>
<td>No</td>
<td>En bloc</td>
<td>56</td>
<td>M cancer</td>
<td>Yes</td>
<td>Negative</td>
<td>Negative</td>
<td>2</td>
<td>17.8</td>
<td>Adenocarcinoma</td>
<td>Chemotherapy due to lung metastasis</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>78/F</td>
<td>S colon</td>
<td>LST-G</td>
<td>Moderate</td>
<td>Yes</td>
<td>Piecemeal (2)</td>
<td>35</td>
<td>M cancer</td>
<td>No</td>
<td>Negative</td>
<td>Positive</td>
<td>2</td>
<td>16.0</td>
<td>Adenocarcinoma</td>
<td>Endoscopic treatment (EMR)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>66/M</td>
<td>A colon</td>
<td>LST-G</td>
<td>Moderate</td>
<td>Yes</td>
<td>Piecemeal (3)</td>
<td>49</td>
<td>Adenoma</td>
<td>No</td>
<td>Negative</td>
<td>Negative</td>
<td>1</td>
<td>3.5</td>
<td>Adenocarcinoma</td>
<td>Endoscopic treatment (EMR)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>58/M</td>
<td>T colon</td>
<td>Sessile</td>
<td>Highly</td>
<td>Yes</td>
<td>Piecemeal (3)</td>
<td>36</td>
<td>Adenoma</td>
<td>No</td>
<td>Negative</td>
<td>Positive</td>
<td>1</td>
<td>6.6</td>
<td>Adenocarcinoma</td>
<td>Endoscopic treatment (EMR)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>63/F</td>
<td>A colon</td>
<td>LST-G</td>
<td>Moderate</td>
<td>No</td>
<td>En bloc</td>
<td>60</td>
<td>M cancer</td>
<td>No</td>
<td>Negative</td>
<td>Positive</td>
<td>2</td>
<td>32.0</td>
<td>Adenocarcinoma</td>
<td>Surgery</td>
<td></td>
</tr>
</tbody>
</table>

ESD: endoscopic submucosal dissection; APC: argon plasma coagulation; EMR: endoscopic mucosal resection; R: rectum; S: sigmoid; A: ascending; T: transverse; LST-NG: non-granular-type laterally spreading tumor; LST-G: granular-type laterally spreading tumor; s.m: submucosal; M: intramucosal

*Patient 2 refused additional surgery despite a diagnosis of submucosal invasive cancer and positive deep resection margin, and was subsequently diagnosed with local recurrence of invasive cancer at 17.4 months after ESD.
or intraprocedural problems in ESD, the associations of piecemeal ESD with hybrid ESD and submucosal fibrosis observed in the present study appear to be consistent with the findings of previous studies; hence, piecemeal ESD should be considered as an undesirable outcome resulting from technical or situational difficulty during ESD.

As expected, piecemeal resection, despite the application of ESD, led to a significantly higher recurrence rate, as compared to that with en bloc ESD cases (5.6% vs. 0.7%). This is consistent with the results of a recent Japanese prospective study, wherein the recurrence rate was found to be 13.9% in piecemeal ESD cases and 0.7% in en bloc ESD cases (2). They showed that local recurrence was associated with rectal lesions, lesions ≥50 mm in diameter, piecemeal resection, trimming after resection, and a positive horizontal margin. In the present study, we noted that larger lesion size, histologic incomplete resection, and ESD performed by medium-volume endoscopists were associated with recurrence risk, based on univariate analysis. However, we only assessed 7 cases of recurrence in the present study; hence, a further statistical assessment, such as multivariate analysis, to identify the relationships between piecemeal resection and other potential covariates or confounding factors could not be performed in our study. Although piecemeal resection is one of the most important predictive factors for recurrence, additional studies on a larger number of cases should be performed to confirm its impact on local recurrence after ESD of early colorectal epithelial neoplasia.

With regard to the number of pieces in the resection, we found that the recurrence rate was 0.7% (3/450) for 1-piece resection, 2.3% (1/44) for 2-piece resection, and 10.7% (3/28) for ≥3-piece resection. Thus, the local recurrence rate tends to increase with the number of pieces in the resection, consistent with the results of a previous study (2).

Of 4 cases of piecemeal ESD, 3 exhibited local recurrence at the first follow-up endoscopy session after ESD; hence, as mentioned in the current postpolypectomy surveillance guidelines, a follow-up interval of 3–6 months after ESD may be essential in cases of piecemeal resection (25–27). Although the exact mechanism of recurrence could not be identified, a few case reports have described metastasis or recurrence from intramucosal colorectal adenocarcinoma (28,29). In our study, we also noted 2 cases of local recurrence as invasive adenocarcinomas with metastasis in the en bloc ESD group (case 3 and 7 in Table 3), which is extremely rare; the original lesions in these cases were well or moderately differentiated adenocarcinomas confined to the laminar propria. One case (case 3) had a focal least differentiated and the other (case 7) showed severe cautery artifacts at the resection margin. Details of these recurrent cases and the potential mechanism of recurrence have been described in our recent case report (30).

Our study had certain limitations of note. First, as our data were based on a retrospective, single center experience,
selection bias related to surveillance and the decision of rescue treatment after piecemeal resection might have influenced the recurrence rate of the piecemeal ESD cases. Second, the surveillance strategy after en bloc and piecemeal ESD was not standardized among the endoscopists, and a considerable proportion of patients were not compliant to surveillance after ESD. Third, because of the relatively short follow-up duration, the recurrence rate might have been underestimated. Despite these limitations, we believe that our study is helpful for understanding the risk of recurrence after piecemeal ESD, relative to en bloc ESD. The establishment of a well-designed, large prospective cohort, and long-term follow-up of that cohort is essential to investigate the risk of recurrence after en bloc and piecemeal ESD, and finally to help develop a surveillance strategy after colorectal ESD.

In conclusion, the hybrid ESD technique and submucosal fibrosis were independent risk factors for piecemeal resection of large colorectal epithelial neoplasia, even in cases where the ESD technique was applied. As piecemeal ESD is associated with a higher risk of recurrence, relative to en bloc ESD, a more meticulous endoscopic surveillance is required.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Institutional Review Board of Ulsan University School of Medicine (No. 2015-0954).

**Informed Consent:** Written informed consent was obtained from all the patients who participated in this study.

**Peer-review:** Externally peer-reviewed.


**Conflict of Interest:** The authors have no conflict of interest to declare.

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**REFERENCES**