Comparison of clinical outcomes between colorectal EMR and ESD

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Abstract

Background
Colorectal endoscopic submucosal dissection (ESD) for early colorectal cancer is now covered by national health insurance in Japan.

Aim
To compare the clinical outcomes between endoscopic mucosal resection (EMR) and ESD in early colorectal cancers or adenomas with maximum diameter of 20 mm or more.

Patients and Methods
Total of 552 lesions 20 mm or larger were treated by EMR (350) or ESD (202). Short-term outcomes were compared between EMR and ESD. Tumor recurrence rates were investigated in patients undergoing follow-up for 3 months or longer.

Results
In EMR group, mean tumor diameter was 25.4 mm and en bloc resection rate 65.1%. Adverse events comprised postoperative bleeding in 1.7% and perforation in 0.3%. Mean procedure time was 13 minutes. Histopathological diagnosis was adenoma in 70% and cancer in 30%. Tumor recurrence was seen in 4.7%.

In ESD group, mean tumor diameter was 30.5 mm and complete en bloc resection rate 91.6%. Adverse events were bleeding in 1.0% and perforation in 2.5%. Mean procedure time was 108 minutes. Histopathological diagnosis of adenoma and cancer was made in 16.8% and 83.2%, respectively. Tumor recurrence was seen in 2.2%.

Conclusion
The results suggest that both EMR and ESD are appropriate treatment in large colon tumors of 20 mm or more. Appropriate therapy should be chosen by making a careful preoperative diagnosis.

Introduction
Endoscopic mucosal resection (EMR) is considered standard in the treatment of colorectal tumors such as adenomas and cancers(1-4). However, complete en bloc resection of tumors of greater than 20 mm is generally difficult. Endoscopic piecemeal mucosal resection (EPMR) is often performed for colorectal tumors larger than 20 mm(5-6). However, this entails the risk of residual or local recurrence and inadequate pathological staging if the lesion is any larger(6-8). Endoscopic submucosal dissection (ESD) was originally developed for early gastric cancer, and allows en bloc resection of large superficial tumors(9-12). The primary purpose of ESD is to reduce the risk of local cancer and enable an accurate histopathological diagnosis.

Endoscopic submucosal dissection has recently been reported to be useful in the treatment of superficial...
colorectal tumors\textsuperscript{13-20}. However, ESD has yet to be universally recognized as a standardized therapeutic procedure for early colorectal tumors because it is difficult and time-consuming to perform, and is regarded as inferior to EMR in terms of clinical outcomes, especially risk of adverse events such as perforation and bleeding\textsuperscript{6,21}. However, a number of studies have investigated indications for colorectal EMR and ESD.

In April 2012, colorectal ESD became available under national health insurance coverage in Japan in the treatment of “...colorectal tumors diagnosed as early colorectal cancer prior to treatment with a diameter of 20 to 50 mm”. The aim of this study was to evaluate the validity of the indications for endoscopic treatment by comparing clinical outcomes between EMR and ESD in the treatment of early colorectal cancers or adenomas with a diameter greater than or equal to 20 mm.

**Patients and Methods**

Between June 2007 and August 2012, 552 lesions greater than or equal to 20 mm were treated by EMR (350) or ESD (202) at Tokyo Medical University Hospital. Patient age, tumor macroscopic type, diameter, location, and short-term outcomes were compared between EMR and ESD in terms of rate of en bloc resection, procedure time, and adverse events. Preoperative endoscopy was performed and the lesions examined by magnifying chromoendoscopy to establish depth of invasion. To qualify for EMR or ESD, a lesion must be confirmed as being non-invasive\textsuperscript{22}. Recurrence rates were compared between 256 EMR- and 135 ESD-treated lesions in cases where follow-up was 3 months or longer (Fig. 1). Table 1 shows the types of lesion in which ESD was indicated in accordance with the Working Group of ESD Standardization for Colorectal Tumors in Japan. The first follow-up colonoscopy was performed at between 3 and 6 months after initial resection in patients undergoing EPMR and in those with tumors showing a histologically positive horizontal margin. If a recurrent or residual tumor was detected at the first follow-up colonoscopy, a second round of surveillance colonoscopy was performed 6 months later, with additional endoscopic treatment; if histologically curative resection was observed, however, follow-up colonoscopy was performed at 1 year postoperatively. All procedures were performed by experienced colonoscopists (5 staff physicians), each of whom performed more than 1,000 colonoscopies annually.

**Pit pattern diagnosis**

When a lesion was detected by conventional colonoscopy, its surface was washed with proteinase to remove excess mucus. Magnification was concentrated on those portions of the lesion where invasion appeared to have permeated the deepest, such as depressed areas and large

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{Lesions Treated. Clinical flow-chart. Among 552 colorectal tumors, 350 were treated by EMR and 202 by ESD. Of these, 391 tumors, including 256 treated by EMR and 135 by ESD, were followed for recurrent and/or residual lesions.}
\end{figure}
nodules. The pit pattern of each lesion was initially assessed by magnification chromoendoscopy performed using 0.4% indigo-carmine (IC) dye. If this proved inadequate to determine the surface structure for pit pattern analysis, 0.05% crystal violet was applied instead. The visible pit pattern was then assessed during the course of the examination by the endoscopist conducting the procedure. This pit pattern evaluation method relied on the Kudo classification and the clinical classification system proposed by Fujii et al.22,23.

Procedure

EMR

Endoscopic mucosal resection was performed with a single channel high-definition (HD) colonoscope (Olympus Medical Systems Co., Ltd., Tokyo, Japan) and a high-frequency generator with an automatic control system (ICC200, ERBE, Germany). It was performed using a snare after injecting glycerol containing a small amount of indigo carmine into the submucosal layer with a 23-gauge needle to lift the mucosa. A spiral snare, the Snare Master (Olympus Medical Systems Co., Ltd.) or the Captivator II snare (Boston Scientific Co., Tokyo, Japan) was used for mucosal resection. The snare was selected in reference to the lesion size, location, or situation. If only one piece of tissue was resected, the procedure was classified as EMR, whereas if multiple pieces were resected, it was considered as EPMR. If the lesion was found to be an adenoma, EPMR was performed, regardless of size. If the lesion is a carcinoma classified as a laterally spreading tumor - granular type (LST - G) >20 mm and <40 mm, it is usually treated by EPMR. In such cases, the area including the large nodule suspected of being a carcinoma is resected first, followed by the remaining tumor suspected of being an adenoma. Chromo-magnification colonoscopy was used to determine whether there was any residual tumor tissue following EMR or EPMR. A hot biopsy was also performed for ablative purposes where necessary. Where EPMR was used, all the pieces of the lesion were collected with net-type forceps.

ESD

Endoscopic submucosal dissection was performed with a single-channel HD colonoscope (Olympus Medical Systems Co., Ltd.). When the lesion was located in the rectum or proximal colon, a Q260J endoscope (Olympus Optical, Tokyo, Japan) was the most frequently used. A PCF-Q260JI endoscope (Olympus Optical) was used for lesions located in the distal colon. Endoscopic submucosal dissection was performed using a high-frequency generator with the same automatic control system as used with EMR. An attachment hood was used in all procedures. The injection solutions were glycerol and hyaluronic acid (MucoUp®; Johnson & Johnson, New Brunswick, NJ, USA) with a small amount of indigo carmine. After saline injection, circumferential incision and dissection were performed. A Ball-tip B knife (Zeon Medical Inc., Tokyo, Japan), bipolar knife or Dual Knife (Olympus Medical Systems Co., Ltd.), or monopolar knife for circumferential incision and dissection were used. A carbon dioxide (CO₂) insufflation system was used in all patients, which was essential for reducing abdominal discomfort.

Sedation

The sedative agents flunitrazepam or midazolam were used in all patients undergoing ESD. These agents were intravenously administered initially at the generally recommended doses: 0.006 mg/kg for flunitrazepam, and 0.05 mg/kg for midazolam. An additional 1 or 2 mg was given repeatedly as needed based on the endoscopist’s judgment. No sedation was usually given in patients undergoing EMR.

Histological assessment

All the resected specimens were cut into 2-mm slices and examined microscopically for histological type, depth of invasion, and lateral and vertical resection margins. En bloc resection was defined as one-piece resection of an entire lesion as observed endoscopically. A curative resection was achieved when both the lateral and vertical margins of the specimen were free of cancer and there was no submucosal invasion deeper than 1,000 μm from the muscularis mucosae, no lymphatic invasion, or
vascular involvement, no budding, or no poorly differentiated component. Histological diagnoses were based on the Japanese classification of cancer of the colon and rectum. Lesions were thus classified as adenoma, intramucosal carcinoma, carcinoma with slight submucosal invasion (less than 1,000 μm; SM-s), or carcinoma with deep submucosal invasion (greater than 1,000 μm; SM-d).

**Statistical analysis**
All values are reported as the mean ± standard deviation where applicable. The t test for continuous variables and χ² test for dichotomous variables were used to compare the baseline characteristics between the two groups. All statistical analyses were performed using SPSS version 15.0 (SPSS Inc.). The P-values were 2-sided; a P-value of less than 0.05 indicated a statistically significant difference.

**Results**
**Clinicopathological features of patients and colorectal lesions (Table 2)**
The clinical characteristics of the patients in each group are shown in Table 2. No statistically significant difference was observed between the two groups in terms of mean age or follow-up period. Tumor size was significantly larger in the ESD than in the EMR group. In terms of macroscopic type, the proportion of lateral spreading non-granular (LST-NG) type tumors was significantly higher in the ESD group. The VI pit pattern was significantly higher in the ESD group.

**En bloc and curative resection rates (Table 3)**
En bloc resection was performed in 228 out of 350 lesions (65.1%) in the EMR group, and in 185 out of 202 lesions (91.6%) in the ESD group. The en bloc resection rate was significantly higher in the ESD group.
Curative resection was performed in 196 out of 348 lesions (56.6%) in the EMR group and in 165 out of 202 lesions (81.7%) in the ESD group. The curative resection rate was significantly higher in the ESD group.

**Procedure time (Table 3)**
The median procedure time was in the ESD group (108 min) was significantly longer than that in the EMR group (13 min) (P < 0.001).

**Adverse events (Table 3)**
Perforation occurred in 1 case (0.3%) in the EMR group and in 5 cases (2.6%) in the ESD group. It was significantly higher in the ESD group. However, these cases could be managed with conservative therapy.
Minor delayed bleeding occurred in 2 cases (1.0%) in the ESD group and 6 (1.7%) cases in the EMR group (P

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**Table 2** Clinical characteristics of patients and tumors

<table>
<thead>
<tr>
<th></th>
<th>EMR (n = 350)</th>
<th>ESD (n = 202)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD (year)</td>
<td>68.1 ± 12.3</td>
<td>69.3 ± 10.4</td>
<td>NS</td>
</tr>
<tr>
<td>Tumor size ± SD (mm)</td>
<td>25.4 ± 7.8</td>
<td>30.5 ± 12.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>20-50 mm : 347</td>
<td>20-50 mm : 169</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 : 3</td>
<td>&lt;50 : 23</td>
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<td></td>
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<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right colon</td>
<td>165 (47.2%)</td>
<td>101 (50.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Left colon</td>
<td>89 (25.4%)</td>
<td>38 (18.8%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Rectum</td>
<td>96 (27.4%)</td>
<td>63 (31.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Median follow-up (month)</td>
<td>38.2 ± 15.4</td>
<td>40.6 ± 7.0</td>
<td>NS</td>
</tr>
<tr>
<td>Macroscopic type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is/Isp</td>
<td>98 (28.0%)</td>
<td>13 (6.4%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IIc</td>
<td>1 (0.3%)</td>
<td>2 (1.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>LST-NG</td>
<td>51 (14.6%)</td>
<td>90 (44.6%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LST-G</td>
<td>199 (56.8%)</td>
<td>95 (47.0%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Residual lesion</td>
<td>1 (0.3%)</td>
<td>2 (1.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Pit pattern</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>8 (2.3%)</td>
<td>0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>I/II</td>
<td>289 (82.6%)</td>
<td>90 (44.6%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>II/II</td>
<td>25 (7.1%)</td>
<td>44 (21.8%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IV</td>
<td>212 (3.4%)</td>
<td>20 (9.9%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>VI</td>
<td>16 (4.6%)</td>
<td>48 (2.7%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

EMR : endoscopic mucosal resection, ESD : endoscopic submucosal dissection
LST-NG : laterally-spreading tumor-non-granular type, LST-G : laterally-spreading tumor-granular type
However, all cases were successfully managed conservatively using endoclips, with no blood transfusions or additional procedures necessary.

**Histopathological diagnosis** (Table 4)

Histopathological diagnoses were adenoma in 70.0% of the EMR group and cancer in 83.2% of the ESD group. A significantly higher rate of SM invasion was observed in the ESD group (P < 0.05). No statistically significant difference was observed in lymphovascular invasion between the two groups.

**Residual/recurrent lesions** (Table 5)

There were 12 cases (4.7%) of local recurrence in the EMR group during a mean endoscopic follow-up period of 40.6 ± 7.0 months. In comparison, local recurrence occurred in 3 cases (2.2%) in the ESD group during a mean endoscopic follow-up period of 38.2 ± 15.4 months.

The macroscopic types of residual/recurrent lesions were Is and LST-G in the EMR group. There were 3 residual LST-NG lesions in the ESD group. All local recurrent lesions were treated by piecemeal resection. Tumor size prior to treatment was 42.5 ± 9.8 mm in the EMR group and 41.8 ± 8.6 mm in the ESD group. The number of resected specimens was greater than 5 in both groups. Curative resection was achieved in all residual or recurrent lesions after 1 additional endoscopic treatment.

**Discussion**

The purpose of this study was to assess the validity of indications for endoscopic treatment by comparing clinical outcomes between EMR and ESD for tumors larger than 20 mm. The final pathological diagnosis revealed many adenomas in the EMR group and many cancer lesions in the ESD group. Preoperative magnification endoscopy was used in evaluating the lesions. We believe that using preoperative magnification endoscopy allowed us to choose the most appropriate therapeutic option.
tem30), which allows histological grade and invasion depth to be determined. In this system, a type II pit pattern indicates a hyperplastic polyp or superficial-type serrated adenoma and sessile serrated adenoma or polyp (SSA/P); type III_L primarily indicates an adenoma with mild-to-moderate atypia; type III_S is characteristic of a depressed lesion and primarily indicates a tubular adenoma; type IV is observed in large, protruded, nodule-aggregated type lesions, and represents a tubulovillous adenoma and mucosal carcinoma in many cases. The type V pit pattern is further classified into type V_I, tumors, characterized by an irregular glandular structure, and type V_N, tumors, which have a clear amorphous area. Type V_I is most likely to be an adenoma with severe atypia or submucosal invasive carcinoma, while type V_N is an index for carcinoma with deep submucosal invasion30). In the present study, the V_I pit pattern was significantly higher in the ESD group. The lesions described in Table 1 were likely to be cancerous, indicating ESD. Therefore, we believe that the appropriate preoperative diagnoses were made.

Endoscopic mucosal resection is indicated in the treatment of superficial, early-stage colorectal cancer as it is minimally invasive and offers excellent results in terms of clinical outcome31). However, conventional EMR techniques for resection of LSTs3132) are inadequate for en bloc resection of flat lesions larger or equal to 20 mm, as there is the risk of incomplete removal and problems with local recurrence31). Conventional EMR usually results in EPMR, particularly for large LSTs ≥20 mm, with reports of local recurrence rates ranging from 7.4% to 17%73534). Most of these recurrences, however, receive repeated endoscopic treatment with excellent results regarding preservation of the colorectum. However, only a few cases required surgery after EPMR in a long-term follow-up study35). Those cases may have originally involved either submucosal or lymphatic invasion not diagnosed histologically due to the increased difficulty involved in assessing piecemeal resection.

No recurrence of invasive (submucosal) cancer was observed in the present study. However, some recurrence of adenoma or intramucosal cancer was observed in the EMR and ESD groups when piecemeal resection (5 or more pieces) was performed in lesions of 40 mm or larger. Tumors of 40 mm or larger can often completely cover a haustrum, and occasionally exceed half the lumen of the colon. Such tumors are very difficult to treat endoscopically. In an earlier study, removal of 5 or more pieces was found to constitute an independent risk factor for local recurrence after EPMR35). This suggests that even though piecemeal resection of LST-G tumors of 40 mm or more is possible, it should only be selected when the location of the lesion allows sufficient maneuverability to keep the number of pieces to a minimum.

The primary advantage of ESD over EMR is a higher en bloc resection rate in large colonic tumors, those in which fibrosis has led to a positive result for the non-lifting sign, or those that have already undergone surgical procedures. Additional surgical resection is sometimes required after endoscopic resection for SM invasive cancer. However, after the introduction of ESD, additional surgery for adenomas or intramucosal and SM-s cancers has only been required in 1% of such cases, which is a significantly lower figure than the 20% rate for such sur-

### Table 5 Residual/recurrent lesions after endoscopic resection

<table>
<thead>
<tr>
<th></th>
<th>EMR : 12 (4.7%)</th>
<th>ESD : 3 (2.2%)</th>
</tr>
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<tbody>
<tr>
<td><strong>Macroscopic type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is</td>
<td>2</td>
<td>LST-NG : 3</td>
</tr>
<tr>
<td>LST-G</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right colon</td>
<td>3 (1.8%)</td>
<td>1 (1.0%)</td>
</tr>
<tr>
<td>Left colon</td>
<td>8 (8.9%)</td>
<td>2 (16.5%)</td>
</tr>
<tr>
<td>Rectum</td>
<td>1 (1.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Tumor size prior to treatment ± SD (mm)</strong></td>
<td>42.5 ± 9.8</td>
<td>41.8 ± 8.6</td>
</tr>
<tr>
<td><strong>Number of resected specimens</strong></td>
<td>&lt;5 : 12</td>
<td>&lt;5 : 3</td>
</tr>
<tr>
<td><strong>Tumor size of residual/recurrent lesion ± SD (mm)</strong></td>
<td>7.5 ± 3.3</td>
<td>8.2 ± 6.0</td>
</tr>
<tr>
<td><strong>Additional treatment time</strong></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Additional treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMR : 4</td>
<td></td>
<td>ESD : 2</td>
</tr>
<tr>
<td>Hot biopsy : 8</td>
<td></td>
<td>Hot biopsy : 1</td>
</tr>
<tr>
<td><strong>Histopathology of residual/recurrent lesion</strong></td>
<td>Adenoma : 12</td>
<td>Adenoma : 1</td>
</tr>
<tr>
<td>Carcinoma : 2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EMR: endoscopic mucosal resection, ESD: endoscopic submucosal dissection.
geries before the introduction of ESD. However, surgery time is longer and the incidence of complications is significantly higher than with EMR. It is better to select ESD according to the results of a careful preoperative diagnosis.

It is crucial to establish depth of invasion preoperatively. In the present study, this was done by using magnifying chromoendoscopy. However, one study found that diagnostic performance with this approach was inferior in protruded-type lesions compared with the flat or depressed type. Therefore, large lesions showing the potential for submucosal invasion at preoperative examination should be resected using the appropriate endoscopic procedures, with the aim of en bloc removal or fractionation into only a few pieces. If the aforementioned endoscopic techniques should prove unfeasible, surgical laparoscopy would be an appropriate alternative treatment strategy.

One limitation of this study was that it was not a randomized controlled trial. It is necessary, therefore, to prospectively compare clinical outcomes between ESD and EMR in large colorectal tumors in future study. Another limitation of this study was that 30% of the total EMR and EPMR cases had to be excluded from the analysis as follow-up colonoscopy was either performed elsewhere or further data regarding such results were unavailable.

In conclusion, the present results suggest that both EMR and ESD are appropriate treatment in large colon tumors of 20 mm or more. Good clinical outcomes were obtained by selectively using witch treatment. It may be possible to distinguish EMR and ESD by careful preoperative diagnosis.

To this end, appropriate therapy should be chosen by making a careful preoperative morphological diagnosis and by thoroughly assessing the degree of malignancy as well as invasion depth using the pit pattern-based diagnostic procedure.

References

34) Uraoka T, Fujii T, Saito Y: Effectiveness of glycerol as a submucosal injection for EMR. Gastrointest Endosc 61: 736–740, 2005
大腸 ESD と EMR の治療成績の比較検討

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【要旨】背景】大腸の「最大径が 2 cm から 5 cm の早期癌又は腺腫」に対して内視鏡的粘膜下層剥離術 (ESD) が保険適応となった。しかし ESD は、その難易度の高さから手技の標準化されておらず、多くの研究で EMR と ESD の比較検討が行われている。
【目的】2 cm 以上 5 cm 以下の早期癌又は腺腫に対して行われた大腸 EMR/ESD の治療成績を比較検討する。
【対象と方法】2007 年 6 月から 2012 年 8 月までに 2 cm 以上の大腸腫瘍性病変に対して内視鏡切除（EMR/ESD）を行った 552 病変（EMR：350 病変，ESD：202 病変）の短期治療成績を比較検討した。また 3 ケ月以上経過観察が可能だった病変を対象とし、遺残再発率について検討した。
【結果】EMR
平均腫瘍径は 25.4±7.8 mm、一括切除率は 65.1% であり、偶発症は後出血 6 例（1.7%）、穿孔は 1 例（0.3%）だった。平均治療時間は 13 分だった。組織診断は腺腫：70%、癌：30% だった。遺残再発は 12 例（4.7%）であった。
ESD
平均腫瘍径は 30.5±12.3 mm、一括切除率は 91.6% であり、偶発症は後出血 2 例（1.0%）、穿孔は 5 例（2.5%）であった。平均治療時間は平均 108 分だった。組織診断は腺腫：16.8%、癌：83.2% だった。遺残再発は 3 例（2.2%）であった。
【結論】EMR、ESD とも 20 mm 以上の大腸腫瘍に対する加療として適切な方法であり、両加療法を使い分けることにより良好な加療結果が期待できる。大腸腫瘍に対する内視鏡的治療は、慎重な術前診断を行った上で適切な術式を選択することが望ましいと思われた。

（キーワード） 内視鏡的粘膜切除術、内視鏡的粘膜下層剥離術、拡大内視鏡