Current status of endoscopic resection strategy for large, early colorectal neoplasia in Japan

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Abstract

Background Conventional endoscopic resection (CER) for early colorectal neoplasia (CRN) is widely accepted as a minimally invasive treatment. Endoscopic submucosal dissection (ESD) was developed in Japan to resect larger lesions, but ESD was not covered by the Japanese national health insurance until April 2012. In addition, treatment strategies vary considerably among medical facilities. To evaluate the current situation in Japan regarding endoscopic treatment of CRNs measuring ≥20 mm, we conducted a prospective multicenter study at 18 medium-volume and high-volume specialized facilities in cooperation with the Japan Society for Cancer of the Colon and Rectum (JSCCR).

Methods The JSCCR conducted a multicenter, observational study of all patients treated by CER and ESD of CRNs measuring ≥20 mm.

Results From October 2007 to December 2010, CERs and ESDs were performed on 1,845 CRNs (CERs 1,029; ESDs 816). Lesions diagnosed as protruded, flat, and depressed totaled 541, 1224, and 48, respectively. En bloc resection rates and mean procedure times for CER/ESD were 56.9 %/94.5 % (P < 0.01) and 18 ± 23 min/96 ± 69 min, respectively. The average ESD procedure time was 129 ± 83 min in the ≥40-mm group. As lesion size increased, the CER en bloc resection rate decreased significantly (trend P < 0.01), but the ESD en bloc resection rate remained over 93 %. Perforation and delayed bleeding rates of CER/ESD were 0.8 %/1.6 % (P < 0.05) and 2 %/2.2 % (P = 0.3), respectively.

This study was reported at the United European Gastroenterology Week held at Stockholm, Sweden, October 24, 2011.

This study was conducted on behalf of the Colorectal Endoscopic Resection Standardization Implementation Working Group, Japanese Society for Cancer of the Colon and Rectum, Tokyo, Japan. The working group that participated in this study are listed in “Appendix”.

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Conclusions The en bloc resection rate for ESD was significantly higher than for CER, although complication rates were fairly low. Despite a longer procedure time, safety of colorectal ESD has improved in various facilities in Japan. However, ESD for lesions measuring ≥40 mm must be performed by experienced endoscopists due to the longer procedure time.

Keywords Endoscopic mucosal resection · Endoscopic submucosal dissection · Colorectal cancer · Colorectal neoplasia

The number of endoscopic submucosal dissections (ESDs) for colorectal neoplasms has been increasing in Japan, and the effectiveness of colorectal ESD has been reported not only in Japan but also in western countries. However, colorectal ESD still has a higher risk of perforation because the colonic wall is thinner and endoscope stabilization is more difficult than in gastric and esophageal ESD. Consequently, treatment strategies for CRN vary considerably among facilities even in Japan.

Colorectal cancer is a major cause of morbidity and mortality in the world [1]. According to the adenoma–carcinoma sequence theory, early detection and resection of colorectal neoplasm (CRN) is essential for improving cancer mortality [2, 3]. CRNs without risk of lymph node metastasis, including adenomas, are good candidates for endoscopic resection (ER) [4]. Conventional endoscopic resection (CER), including polypectomy and endoscopic mucosal resection (EMR), was developed as a minimally invasive treatment for CRN [5, 6] and is widely accepted. However, CER for lesions exceeding 20 mm in diameter sometimes results in piecemeal resection, decreasing the accuracy of pathological diagnosis and resulting in local recurrences [7–9].

ESD is an established therapeutic technique for the treatment of gastrointestinal neoplasms. Because it is typically completed as en bloc resection, this technique provides a complete specimen for precise histopathological evaluation [10–12]. Following widespread use in treatment of gastric ESDs, the number of medical facilities performing colorectal ESDs has been increasing not only in Japan, but also in western countries [13–21]. However, In the guidelines of the Japanese Society for Cancer of the Colon and Rectum (JSCCR), CRN diagnosed as clinical mucosal cancer or superficial submucosal cancer (invasion depth of <1,000 μm), a size of ≥20 mm was initially recommended for surgical resection [22] because of the greater technical difficulty involved and the risk of perforation and resultant peritonitis [19, 23, 24]. Consequently, treatment strategies (and payment arrangements) for CRN vary considerably among facilities. To evaluate the current situation in Japan regarding endoscopic treatment of CRNs measuring ≥20 mm, we conducted a cross-sectional multicenter study in cooperation with JSCCR. We seek to convey the effectiveness and safety of both CER and ESD treatments to the world.

Materials and methods

From October 2007 to December 2010, patients were prospectively and consecutively enrolled at the 18 institutions affiliated with the Colorectal Endoscopic Resection Standardization Implementation Working Group of JSCCR, and all obtained data were sent to a data center. JSCCR has proposed Japanese guidelines and this working group has a responsibility in ER section of the guideline [19, 20]. The study was conducted with the approval of each institution’s ethical review board, and informed written consent was obtained from all patients for each specific colonoscopic treatment. The clinical trial number of this study is UMIN000001642.

We analyzed the following clinicopathological factors: ER method, patient age at the initial ER, sex, tumor size, location, macroscopic type, histological margin, histological grade, depth of submucosal invasion, and lymphatic/venous involvement, determined based on the Japanese classification of cancer of the colon and rectum (JCCCR) [22].

All procedures were performed by experienced colonoscopists, or under their supervision, with a standard videoendoscopic system (EVIS LUCERA system, Olympus Optical, Tokyo, Japan; or Advancia HD/Advancia, Fujifilm, Tokyo, Japan).

Inclusion criteria

ER is indicated to treat intramucosal CRNs and lesions with submucosal invasion limited to less than 1,000 μm, because the risk of lymph node metastasis is very low [4, 25]. Before treatment, only depth of invasion could be estimated endoscopically in combination with conventional endoscopic findings and, if possible, pit pattern analysis with magnifying chromoendoscopy (CF-H260AZI, CF-Q260AZI, or PCF-Q240ZI, Olympus, Tokyo, Japan; and EC590Z series, Fujifilm, Tokyo, Japan) [26–32]. We have indicated the use or nonuse of magnification.

The Colorectal ESD Standardization Implementation Working Group has attempted to standardize colorectal ESD, and guidelines have been proposed by this group.
Based on extensive clinicopathological analyses, the indications for colorectal ESD in this study are the same as those recommended in the guidelines: a tumor for which the use of a snare EMR for en bloc resection is difficult, such as a laterally spreading tumor of the nongranular type (LST-NG) [7, 20, 33, 34], especially the pseudo-depressed type, a tumor with a type V1 pit pattern, a shallow infiltrating submucosal carcinoma, a large depressed tumor, and large elevated, probably malignant lesions (tall nodule-aggregating lesions such as a granular-type LST; LST-G), because these lesions have a high submucosal invasion rate and are difficult to treat even by piecemeal EMR [19, 33, 35]. Other lesions, such as intramuscular tumors accompanied by submucosal fibrosis, which are induced by a biopsy or peristalsis of the lesion, sporadic localized tumors in chronic inflammation, including ulcerative colitis, and local residual early carcinomas after EMR, also are indications for colorectal ESD [19].

Exclusion criteria for ER

Exclusion criteria included findings of submucosal cancer such as VN pit pattern, an invasive pattern as determined by magnification chromoendoscopy [27, 29, 36], and presence of other invasive cancers and circumferential tumors that require surgical treatment because of the increased technical difficulty involved and the anticipated risk of stenosis.

Clinicopathological characteristics

The location of tumors was based on the Japanese classification of cancer of the colon and rectum [22, 37] and included the cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum.

For macroscopic typing, we divided the lesions into five macroscopic groups according to the Paris classification and LST features as follows: (1) protruded type, which is 0-Isp; (2) flat type, which is 0-IIa and 0-IIc with LST features; (3) mixed type, 0-Isp + IIa, most of which have LST character; (4) depressed type, 0-IIc or IIa + IIc in Paris classification without LST features; and (5) recurrent cases.

CER procedures

In this study, CER was defined as snare technique, EMR, or snare polypectomy; endoscopists, including gastroenterologists and digestive surgeons, chose treatment methods according to the size and endoscopic features of the CRN. In EMR, after successful fluid injection of normal saline and/or glycerol [38] and/or 0.4 % hyaluronic acid solution into the submucosal layer, the endoscopist performed resection using the snare [6]. After resection, additional snare resection or coagulation using hot biopsy forceps also was performed if there was a suspicion of small residual tumors in the resection plane.

ESD procedures

Procedures were primarily performed using one or two ESD knives, including a bipolar needle knife (Xeon Medical Co, Tokyo, Japan) [9, 15, 39], flex knife [40], hook knife (Olympus Co, Tokyo, Japan) [41], flush knife (Fujinon Co, Tokyo, Japan) [42], and insulation-tipped knife (Olympus) [10, 13]. Hemostatic forceps (Coagrasper; Olympus) and Hemostat Y (PENTAX Co., Tokyo, Japan) were used for hemostasis. Lesion margins were delineated before ESD using 0.4 % indigo-carmine spray dye. Following injection of Glycerol and/or sodium hyaluronate into the submucosal layer, a circumferential incision was made using the ESD knife [14]. Both partial circumferential incision and subsequent submucosal dissection were performed alternately using ESD knives.

Definition of ESD and CER

Some lesions were treated by a combined CER/ESD technique, using a special ESD knife and resected by snaring. We defined those cases of resection by snaring with only circumferential incision [43] as CER and cases in which the physician performed any submucosal dissection after marginal resection as ESD.

Definition of complication

Perforation during an ESD procedure was defined as immediate, and delayed perforation was defined as any perforation occurring after completion of the procedure. Immediate perforation was defined as a full-thickness defect in the colonic wall. Closure with endoscopic clips was performed or surgical treatment was pursued. Postoperative bleeding was defined as bleeding that required repeat colonoscopy for hemostasis therapy, blood transfusion, or decreased level of hemoglobin ≥ 2 g/dl.

Histological assessment

All specimens were fixed in 10 % formalin, cut into 2-mm sections, and examined microscopically for histological type, depth of invasion, and lateral and vertical resection margins. Resections were considered tumor-free when the lateral and vertical margins of a specimen were both negative for tumor cells, independent of histological features. The submucosal depth was defined as the distance determined by microscopic observation of specimens using an optical micrometer [4]. A curative resection was achieved when both the lateral and vertical margins of the specimen were free of cancer, with none of the following features: submucosal invasion deeper than 1,000 μm, lymphatic invasion, vascular involvement, or poorly differentiated.
components [4]. An adenoma with an unknown lateral margin also was considered to be resected curatively when the neoplasm met all other criteria. Lesions resected in a piecemeal fashion were reconstructed faithfully on the basis of the mirror endoscopic images obtained before treatment and fixed in formalin. Histological diagnoses were based on the Japanese classification of cancer of the colon and rectum [37] and the Vienna classification [44]. The former is a standard pathological classification in Japan, and these results were converted to the latter form for standardization with global classifications.

Statistical analysis

Statistical analysis was performed using SPSS version 20 (SPSS Inc., Chicago, IL). Data are presented as mean ± standard deviation, medians, ranges, and percentages. For analysis of clinicopathological characteristics, we used Student’s t test and χ² and Fisher’s exact tests, as appropriate. All tests were two-tailed, and P < 0.05 was considered significant.

Results

Patient and lesion characteristics

A total of 1,845 CRNs that were ≥20 mm in size were examined in this study. CER was used in 1,029 cases and ESD in 816. Mean lesion sizes in CER and ESD cases were 26.4 ± 8.6 (range 20–120) mm and 39.4 ± 18.2 (range 20–174) mm, respectively. Patient characteristics and distributions of lesions are detailed in Tables 1 and 2. Tumor distribution between the two groups was different (P < 0.01). The frequency of cecum and sigmoid colon lesions were higher in the CER group than in the ESD group. On the other hand, lesions of the rectum were less frequent in the CER group. Submucosal cancer, including both superficial submucosal cancer and deep submucosal invasion cancer, was more common in the ESD group. Thus, the distribution of tumor characteristics differed between CER and ESD. The frequency of use of magnification colonoscopy also differed in the two groups (71.9 % in CER vs. 85.7 % in ESD, P < 0.01).

Differences in endoscopic treatment choice according to tumor size and macroscopic type

We divided the cases into three groups according to lesion size: 20–29, 30–39, and ≥40 mm. Associations between tumor size, macroscopic type, and treatment choice are detailed in Table 3. In the 20–29-mm group, 77 % (729/948) of the lesions were treated by CER. In contrast, as the lesion size increased, lesions were more likely to be treated by ESD. Macroscopic type also influenced treatment choice. In the 20–29-mm group, 93.8 % of the protruded lesions were treated by CER, whereas 37 % of the flat lesions were treated by ESD. In the 30–39-mm group, approximately 70 % of mixed and flat lesions were treated by ESD. In the ≥40-mm group, approximately 80 % of mixed and flat lesions were treated by ESD. All five cases of recurrence were treated by ESD, regardless of lesion size.

Table 1 Patients and tumor location

<table>
<thead>
<tr>
<th>Pathological results</th>
<th>CER</th>
<th>ESD</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of lesions</td>
<td>1,029</td>
<td>816</td>
<td>1,845</td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD (range)</td>
<td>65.2 ± 11.7 (20–89)</td>
<td>66.6 ± 9.9 (23–91)</td>
<td>65.8 ± 10.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sex, male/female (ratio)</td>
<td>0.637/0.392 (1.6)</td>
<td>0.468/0.348 (1.3)</td>
<td>0.1105/0.740</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Use of magnification (%)</td>
<td>0.740 (71.9)</td>
<td>0.700 (85.7)</td>
<td>0.1440 (78)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Table 2 Pathological results, by procedure type and lesion size

<table>
<thead>
<tr>
<th>Range of lesion sizes (mm)</th>
<th>20–29 CER/ESD</th>
<th>30–39 CER/ESD</th>
<th>≥40 CER/ESD</th>
<th>Total CER/ESD</th>
<th>Total CER/ESD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathological results</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoma</td>
<td>380/72</td>
<td>86/95</td>
<td>36/95</td>
<td>502/262</td>
<td>764</td>
</tr>
<tr>
<td>(%)</td>
<td>(84/16)</td>
<td>(48/52)</td>
<td>(27/73)</td>
<td>(66/34)</td>
<td></td>
</tr>
<tr>
<td>Intramucosal cancer</td>
<td>283/95</td>
<td>85/109</td>
<td>65/194</td>
<td>433/398</td>
<td>831</td>
</tr>
<tr>
<td>(%)</td>
<td>(75/25)</td>
<td>(44/56)</td>
<td>(25/75)</td>
<td>(52/48)</td>
<td></td>
</tr>
<tr>
<td>Submucosal cancer</td>
<td>48/52</td>
<td>17/51</td>
<td>5/47</td>
<td>70/150</td>
<td>220</td>
</tr>
<tr>
<td>(%)</td>
<td>(48/52)</td>
<td>(25/75)</td>
<td>(10/90)</td>
<td>(32/68)</td>
<td></td>
</tr>
<tr>
<td>&lt;1,000 μm</td>
<td>18/34</td>
<td>8/31</td>
<td>3/23</td>
<td>29/88</td>
<td>117</td>
</tr>
<tr>
<td>(%</td>
<td>(35/65)</td>
<td>(21/79)</td>
<td>(12/88)</td>
<td>(25/75)</td>
<td></td>
</tr>
<tr>
<td>≥1,000 μm</td>
<td>30/18</td>
<td>9/20</td>
<td>2/24</td>
<td>41/62</td>
<td>103</td>
</tr>
<tr>
<td>(%</td>
<td>(63/38)</td>
<td>(31/69)</td>
<td>(8/92)</td>
<td>(40/60)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0/0</td>
<td>0/1</td>
<td>0/2</td>
<td>0/3</td>
<td>3</td>
</tr>
<tr>
<td>(%)</td>
<td>(0/0)</td>
<td>(0/100)</td>
<td>(0/100)</td>
<td>(0/100)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>18/0</td>
<td>6/2</td>
<td>0/1</td>
<td>24/3</td>
<td>27</td>
</tr>
<tr>
<td>(%)</td>
<td>(100/0)</td>
<td>(75/25)</td>
<td>(0/100)</td>
<td>(89/11)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>729/219</td>
<td>194/258</td>
<td>106/339</td>
<td>1029/816</td>
<td></td>
</tr>
</tbody>
</table>
Treatment results: comparison of CER and ESD

The treatment results for CER and ESD are detailed in Table 4. Operation time for ESD was much longer than for CER, although the en bloc resection rate was significantly higher in the ESD group. We found that procedure time and tumor size were associated, especially in ESD cases. Compared with the CER cases, as lesion size increased, the ESD procedure time increased.

Even in the 20–29-mm group, the en bloc resection rate for CER was only 66.5 %, which is significantly lower than that of the ESD group. As lesion size increased, the en bloc resection rate in the ≥40-mm group was only 12.3 %. In contrast, the en bloc resection rate for ESD was maintained at >93 %, even in the ≥40-mm group.

Complication rate

The number of delayed bleeding cases was 18 (1.7 %) in the CER group and 18 (2.2 %) in ESD (P = 0.3). The number of perforation cases in these groups was 8 (0.8 %) and 16 (2 %; P < 0.05), respectively. The ESD perforation rate was higher than the CER rate, but most ESD and CER perforation cases were successfully treated endoscopically; only three cases (1 CER, 2 ESD) required emergency surgery.

Table 3 Macroscopic type of lesion, by procedure type and lesion size

<table>
<thead>
<tr>
<th>Range of lesion sizes (mm)</th>
<th>20–29 CER/ESD</th>
<th>30–39 CER/ESD</th>
<th>≥40 CER/ESD</th>
<th>Subtotal CER/ESD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion number</td>
<td>729/219</td>
<td>194/258</td>
<td>106/339</td>
<td>1,029/816</td>
<td>1,845</td>
</tr>
<tr>
<td>Macroscopic type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protruded</td>
<td>363/24</td>
<td>87/27</td>
<td>25/17</td>
<td>475/68</td>
<td>543</td>
</tr>
<tr>
<td>Mixed</td>
<td>88/28</td>
<td>39/86</td>
<td>56/220</td>
<td>183/334</td>
<td>517</td>
</tr>
<tr>
<td>Flat</td>
<td>275/164</td>
<td>68/144</td>
<td>25/101</td>
<td>368/409</td>
<td>777</td>
</tr>
<tr>
<td>Depressed</td>
<td>3/0</td>
<td>–/–</td>
<td>–/–</td>
<td>3/0</td>
<td>3</td>
</tr>
<tr>
<td>Recurrence</td>
<td>0/3</td>
<td>0/1</td>
<td>0/1</td>
<td>0/5</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 4 Treatment results by procedure type and lesion size

<table>
<thead>
<tr>
<th>Range of lesion sizes (mm)</th>
<th>CER</th>
<th>ESD</th>
<th>CER</th>
<th>ESD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion number</td>
<td>729</td>
<td>194</td>
<td>106</td>
<td>219</td>
<td>1,029</td>
</tr>
<tr>
<td>Procedure time (min, mean ± SD)</td>
<td>13 ± 13</td>
<td>4 ± 23</td>
<td>42 ± 46</td>
<td>66 ± 4</td>
<td>96 ± 6</td>
</tr>
<tr>
<td>Complication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed bleeding</td>
<td>12</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>(%)</td>
<td>(1.6)</td>
<td>(2.1)</td>
<td>(1.9)</td>
<td>(1.4)</td>
<td>(1.7)</td>
</tr>
<tr>
<td>Perforation</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>(%)</td>
<td>(0.7)</td>
<td>(1.5)</td>
<td>(0)</td>
<td>(1.8)</td>
<td>(0.8)</td>
</tr>
<tr>
<td>Emergency surgical operation</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>(%)</td>
<td>(0.5)</td>
<td>(0.6)</td>
<td>(0.1)</td>
<td>(0.2)</td>
<td>(0.2)</td>
</tr>
<tr>
<td>En bloc resection rate</td>
<td>485</td>
<td>88</td>
<td>13</td>
<td>206</td>
<td>317</td>
</tr>
<tr>
<td>(%)</td>
<td>(66.5)</td>
<td>(45.4)</td>
<td>(12.3)</td>
<td>(94.1)</td>
<td>(96.1)</td>
</tr>
<tr>
<td>Non-curable resection</td>
<td>33</td>
<td>9</td>
<td>2</td>
<td>23</td>
<td>31</td>
</tr>
<tr>
<td>(%)</td>
<td>(4.5)</td>
<td>(4.6)</td>
<td>(1.9)</td>
<td>(10.5)</td>
<td>(9.3)</td>
</tr>
<tr>
<td>Additional surgery</td>
<td>29</td>
<td>9</td>
<td>3</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td>(%)</td>
<td>(4.0)</td>
<td>(4.6)</td>
<td>(2.8)</td>
<td>(7.8)</td>
<td>(8.5)</td>
</tr>
</tbody>
</table>
Pathological results and additional surgery

Histopathological assessment led to the diagnosis of 44 (4.3 %) CER cases and 77 (9.4 %) ESD cases as noncurative resections. Furthermore, 41 CER patients (4 %) and 62 ESD patients (7.6 %) underwent additional surgery.

Discussion

Key findings

In this prospective, multicenter study in Japan, we surveyed the current status of endoscopic treatment for relatively large CRNs (>20 mm). As size increased, Japanese endoscopists were more likely to select ESD, especially for the treatment of flat- and mixed-type CRNs. As a result, the en bloc resection rate for ESD was significantly higher than for CER, although complication rates were very low in both groups. Despite longer procedure time, ESD is becoming safe and is considered a standard procedure in Japan for the treatment of large, superficial CRNs.

Before this study, Saito et al. reported the results of an initial, prospective, multicenter cohort study of ESD [18]. They analyzed the results of all colorectal ESD cases from the time of introduction of the procedure, performed at ten specialized facilities (n = 1,111). By contrast, the present study was planned after approval of ESD with advanced medical care systems, with a strict treatment indication; therefore, both highly advanced medical facilities and general facilities participated, enrolling the cases in a limited research registration period. In our study, the overall perforation rate was only 1.3 % (n = 24), and the rate of emergency surgery was extremely low (0.3 %, n = 3) compared with the previous study [18], suggesting improved safety of colorectal ESD in various facilities.

Japanese guidelines for ER for colorectal cancer and ESD indication

According to the guidelines of the JSCCR, CRNs diagnosed as clinical mucosal cancer or superficial submucosal cancer (<1,000 μm) are indicated for ER. However, 20 mm is the largest size of a tumor that can be easily resected en bloc by polypectomy or snare EMR. If the preoperative diagnosis is adenoma or carcinoma in adenoma, piecemeal resection can be performed. It should be noted, however, that piecemeal resection is associated with a high incomplete resection rate and a high local recurrence rate. Therefore, such lesions were a relative indication for surgical resection [22]. After introduction of the ESD technique for CRN treatment, it became possible to perform en bloc resections for lesions measuring > 20 mm.

Our study shows that Japanese endoscopists selected ESD rather than CER, as tumor size increased, especially for mixed- and flat-type CRNs. Endoscopists make this choice, because they know the pathological character of large CRNs, which incur the risk of noncurative resection contrary to pre-ESD expectations and because they know the indication of colorectal ESD.

Treatment selection and outcome as related to tumor size

In this study, we performed endoscopic treatment according to the guidelines of JSCCR and indication of ESD. As size increased, selection of ESD became more common, perhaps because Japanese endoscopists understand the difficulty of performing en bloc resection for larger CRNs by CER.

However, ESD has a big limitation. As tumor size increased, procedure time increased, compared with CER. Our data showed that the average procedure time for colorectal ESD for lesions measuring ≥40 mm was more than 2 h. It should be noted that such lesions were treated by surgery before ESD became widespread; therefore, it may be more informative to compare ESD procedure time with that of surgical cases instead of EMR cases. ESD for CRNs measuring ≥40 mm is thought to be a difficult and time-consuming treatment, so we recommend that ESD for lesions <40 mm be considered a general procedure but that lesions measuring ≥40 mm should be treated in medical facilities with more experienced staff.

Treatment selection as related to tumor macroscopic type

In the 20–29-mm group, protruded-type CRNs were likely to be treated by CER. However, the proportion of CER for mixed and flat lesions was less than that for protruded type. As the lesion size increased, mixed and flat lesions were more likely to be treated by ESD. As the proportion of the flat component in the CRN groups increased, the proportion of ESD increased.

En bloc resection rate and complication rate

We found that the en bloc resection rate for ESD was significantly higher than for CER, although complication rates in both groups were quite low in these representative Japanese facilities. The ESD technique enabled complete resection even for the large-sized tumors. This may indicate that recent improvements in endoscopic devices and instruments have reduced complications (such as perforation) in ESD. Most perforation cases were managed...
endoscopically; only two ESD cases required emergency surgical treatment. Due to these improvements, the ESD technique is now widely accepted for the management of large CRNs in Japan.

Considering the learning curve for colorectal ESD, in a previous study, we retrospectively reviewed clinical outcomes of colorectal ESD performed by trainees. Under the guidance of experienced specialists, trainee endoscopists are able to perform colorectal ESD without serious complications after preparatory training and experience with ≥30 cases [45]. Saito et al. [18] reported that the complication rate was 17.6% at medical facilities in which the number of ESDs performed was less than 50. Univariate and multivariate analysis revealed that large tumor size (>50 mm) and less experience performing ESDs (<50 cases) were independent risk factors for complications [15]. Tanaka et al. [19] reported that the perforation rate in colorectal ESD decreased annually with experience.

Multicenter studies of ER have been conducted outside Japan. Moss et al. [46] reported outcomes of ER for lesions more than 20 mm, in an important Australian prospective, multicenter, observational study. They concluded that EMR is a safe and effective therapy for large sessile polyps. Some differences between their study and ours include the following: (1) their study reported only EMR results; (2) the percentage of submucosal cancers in their study was relatively low compared with our study (33 cases, 6.9% and 220 cases, 11.9%, respectively). Based on these differences, we assume that the Australian group referred some cases directly for surgical resection, whereas we may perform ESD as the first treatment. Long-term follow-up evaluation was not extensive in both studies.

Saito et al. [9] reported the results of long-term follow-up after EMR and ESD and described one recurrence case as invasive cancer after 2.5 years; the case was histologically diagnosed in the first EPMR as a curative resection. In an evaluation of one leading Japanese hospital, Kobayashi et al. [47] reported that after introduction of colonic ESD, use of ER was widespread and reduced the incidence of repeat surgery for large-size intramucosal cancer.

Moss et al. also concluded that lesions having a high possibility of submucosal deep invasion, such as LST-NG or lesions with advanced pit pattern, should be treated en bloc to achieve accurate pathological assessment. In light of these findings, our study shows that ESD is becoming a standard procedure for en bloc resection in Japan.

Limitations

The major strength of our study is the large sample size; however, our study has some limitations. First, this was a prospectively enrolled, multicenter cohort study, not randomized; thus, eligibility criteria for performing colorectal ESDs were sometimes unclear at some institutions. Until the end of 2011, ESD was performed in more than 180 medical facilities in Japan as a generalized technique; therefore, randomization between CER and ESD was considered too difficult. Second, the recurrence rate of CER and ESD 1 year after initial endoscopic treatment is an important goal of this working group study; therefore, we will analyze those data and report them elsewhere. For the prescription of colorectal ESD by Japanese national health insurance, an additional nationwide survey to assess the clinical outcomes of colorectal ESD is recommended.

Conclusions

The en bloc resection rate for ESD was significantly higher than that for CER regardless of the tumor size; otherwise, submucosal cancer was more common in the ESD group. In addition, there was no significant difference in complications between the two groups. Our study proves that ESD is a feasible treatment for patients with mucosal CRN >20 mm, although long-term outcomes should be evaluated in the future. Such findings were presented at the annual meeting of United European Gastroenterology Week, 2012. For en bloc resection of lesions measuring ≥40 mm, ESD is an essential technique, but the procedure must be performed by experienced endoscopists in well-equipped medical facilities, because the procedure time is long.

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Disclosures

Takeshi Nakajima, Yutaka Saito, Shinji Tanaka, Hiroyasu Iishi, Shin-eti Kudo, Hiroaki Ikematsu, Masahiro Igarashi, Yuusuke Saitoh, Yuji Inoue, Kiyonori Kobayashi, Takashi Hisasbe, Takahisa Matsuda, Hideki Ishikawa, and Ken-ichi Sugihara have no conflict of interests or financial ties to disclose.

Appendix

Facilities that participated the study

The patients were enrolled at the 18 institutions affiliated with the Colorectal Endoscopic Resection Standardization Implementation Working Group of JSCCR as follows: (1) Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan (Takeshi Nakajima, Yutaka Saito, Takahisa Matsuda); (2) Department of Endoscopy, Hiroshima University Hospital, Hiroshima, Japan (Shinji Tanaka); (3)
Department of Gastrointestinal Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan (Hiroyasu Iishi); (4) Diagnostic Disease Center, Showa University Northern Yokohama Hospital, Kanagawa, Japan (Shin-ei Kudo); (5) Department of Gastroenterology & Gastrointestinal Oncology, National Cancer Center Hospital East, Chiba, Japan (Hiroaki Ikematsu); (6) Department of Endoscopy, Cancer Institute Ariake Hospital, Tokyo, Japan (Masahiro Igarashi); (7) Digestive Disease Center, Asahikawa City Hospital, Hokkaido, Japan (Yuusuke Saitho); (8) Institute of Gastroenterology, Tokyo Women’s Medical University, Tokyo, Japan (Yuji Inoue); (9) Department of Gastroenterology, Kitasato University East Hospital, Kanagawa, Japan (Kiyounori Kobayashi); (10) Department of Gastroenterology, Fukuoka University Chikushi Hospital, Fukuoka, Japan (Takashi Hisasbe); (11) Division of Gastroenterology, Department of Medicine, Kure University School of Medicine, Fukuoka, Japan (Osamu Tsuruta); (12) Gastrointestinal Center, Sano Hospital, Hyogo, Japan (Yasushi Sano); (13) Department of Gastroenterology, Akita Red Cross Hospital, Akita, Japan (Hiro-o Yamano); (14) Department of Gastroenterology, JR West Osaka Railway Hospital, Osaka, Japan (Seiji Shimizu); (15) Department of Gastroenterology, Toranomon Hospital, Tokyo, Japan (Naohisa Yahagi); (16) Department of Surgery, Teikyo University Hospital, Tokyo, Japan (Toshiaki Watanabe); (17) Department of Gastroenterology, Chofu Surgical Clinic, Tokyo, Japan (Hisashi Nakamura); (18) Gastroenterology, Takahiro Fujii Clinic, Tokyo, Japan (Takahiro Fujii).

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