A Comparison of Outcomes of Endoscopic Submucosal Dissection (ESD) For Early Gastric Neoplasms Between High-Volume and Low-Volume Centers: Multi-Center Retrospective Questionnaire Study Conducted by the Nagano ESD Study Group

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Abstract

Objective Outcomes of endoscopic submucosal dissection (ESD) for early gastric neoplasms at low-volume centers have been unknown, because all previous reports have studied in advanced single centers. The aim of this study was to compare ESD outcomes between high- and low-volume centers.

Methods A retrospective questionnaire survey was conducted and 30 centers (96.8%) responded. The complete en-bloc resection rate (CERR) and the incidence of complications were analyzed. Early gastric cancer (EGC) was divided into three categories on the basis of pathological diagnosis-standard indication (SI), expanded indication (EI) and out-of-indication (OI).

Results A total of 703 early gastric neoplasms (586 EGCs, 117 gastric adenomas) were treated with ESD from January to December 2005. The institutions that treated more than 30 cases a year were classified as high-volume centers, and those with less than 30 cases, low-volume centers. In SI, the CERRs at high- and low-volume centers were 92.1% and 91.1%, in EI, CERRs were 86.2% and 82.6% and in OI, CERRs were 80.3% and 88.0%. The perforation rates at high- and low-volume centers were 3.6% and 4.7%. The intraoperative bleeding rates at high- and low-volume centers were 0.26% and 0%, while the delayed bleeding rates were 0% and 0.63%.

Conclusion There were no significant difference in the outcomes of ESD for early gastric neoplasms between high- and low volume centers.

Key words: gastric cancer, gastric neoplasm, endoscopic resection, endoscopic mucosal resection, endoscopic submucosal dissection

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Introduction

Gastric cancer is the second commonest cancer in the world (1). The areas with the highest incidence rates are East Asia (e.g. Japan and Korea), the Andean region of South America, and Eastern Europe (2). Endoscopic mucosal resection (EMR) is a widely accepted treatment for early gastric cancers (EGCs) with a negligible risk of lymph node metastases (3). Gotoda et al reported on early gastric
cancers with no lymph-node metastases extracted from a large database, involving more than 5,000 patients who underwent gastrectomy with lymph node dissection (4). The guideline for the indication of endoscopic resection for early gastric cancers, determined by the Japanese Gastric Cancer Association (JGCA) (5), served as the basis for the present report.

Conventional EMR techniques [e.g. strip biopsy, endoscopic mucosal resection with cap (EMRC), endoscopic mucosal resection with ligation device (EMRL), endoscopic aspiration mucosectomy (EAM)] had disadvantages, such as the limited lesion size which can be resected en-bloc, and a high incidence of local recurrence (3). Endoscopic submucosal dissection (ESD) was developed in the late 90’s in Japan for large en-bloc resection and precise pathological diagnosis. Some endo-knives, such as the IT knife (6), Hook knife (7) and Flex knife (8) used for ESD, were developed for mucosal incision and submucosal dissection. Moreover, some fluids, such as glycerol (9) and sodium hyaluronate (10-12), are used for submucosal injection to prevent perforations.

Some advanced institutions in Japan report excellent outcomes and tolerable complications with the use of ESD for EGCs (13-17). However, ESD is considered an advanced skill and difficult to learn. Therefore, how to disseminate the ESD technique is considered an important task. The outcomes of ESD at institutions that adopted this technique later and have had a small number of cases yearly have not been investigated. The present study was designed to compare outcomes of early gastric neoplasms between high-volume and low-volume ESD centers on the basis of a retrospective questionnaire survey. This study included the majority of ESD cases in one prefecture in Japan during a 12-month period.

**Patients and Methods**

Thirty-one institutions in Nagano prefecture in Japan were requested by the Nagano ESD Study Group to conduct a questionnaire survey on ESD for early gastric neoplasms. Replies came from 30 institutions (96.8%). The questionnaire included questions about procedures, outcomes and complications for all early gastric neoplasms treated with ESD (see below). The early gastric neoplasms were divided into EGCs and gastric adenomas (GAs). A total of 703 early gastric neoplasms (586 EGCs and 117 GAs) were treated with ESD at those institutions from January to December 2005.

For this study, the institutions that dealt with more than 30 cases a year were classified as high-volume centers and those which dealt with less than 30 cases were classified as low-volume centers. Six institutions were classified as high-volume centers, and 24 as low-volume centers.

Moreover, the EGCs were divided into three categories on the basis of pathological diagnosis after ESD in accordance with the gastric cancer treatment guidelines of the JGCA (5): standard indication (SI), which includes differentiated adenocarcinoma, intramucosal cancer ≤20 mm in size, expanded indication (EI) which includes differentiated adenocarcinoma, intramucosal cancer regardless of tumor size without ulcer findings, intramucosal cancer ≤30 mm in size with ulcer findings, minute submucosal cancer (≤500 μm) ≤30 mm in size; out-of-indication (OI) which includes all but the above.

The findings of the present study were analyzed by distinguishing high-volume centers from low-volume centers. The analysis involved complete en-bloc resection rate (CERR) and reasons for incomplete resection as outcomes of ESD. Complete en-bloc resection was defined as en-bloc and the horizontal/vertical margin was histologically free from tumor. Incomplete resection was defined as piecemeal, or vertical, or lateral margin positive. The rates of perforation, intra-operative bleeding, delayed bleeding and emergent surgery were analyzed as complications. Intra-operative and delayed bleeding was defined as those cases which required blood cell transfusion or surgical intervention. Emergent surgery was defined as an operation within 24 hours following the ESD procedure. All study participants provided written informed consent at each institution.

**Contents of the questionnaire**

Q1: How many cases of early gastric neoplasms (EGCs and TAs) did you treat during the period of January to December 2005? Q2: What is the ratio of ESD in endoscopic resection for early gastric neoplasms? Q3: What device did you mainly use for mucosal incision (multiple answers permitted)? Q4: What device did you mainly use for submucosal dissection (multiple answers permitted)? Q5: What solutions did you mainly use for injection (multiple answers permitted)? Q6: How many were CERRs and the actual numbers in SI, EI and OI, and reasons for incomplete resections? Q7: What were the rates and actual numbers of perforation, intra-operative bleeding, delayed bleeding and emergent surgery?

**Participating institutions**

The institutions participating were the following: Department of Gastroenterology, Saku Central Hospital; Department of Endoscopy, Shinshu University Hospital; Department of Gastroenterology, Nagano Municipal Hospital; Department of Gastroenterology, Marunouchi Hospital; Department of Gastroenterology, Nagano Chuo Hospital; Department of Gastroenterology, Matsumoto Medical Center, Chushin-Matsumoto Hospital; Department of Gastroenterology, Matsumoto Medical Center, Matsumoto Hospital; Department of Internal Medicine, Matsumoto Kyoritsu Hospital; Department of Gastroenterology, Fujimi-kogen Hospital; Department of Gastroenterology, Aizawa Hospital; Department of Gastroenterology, Hotaka Hospital; Department of Gastroenterology Nagano Red Cross Hospital; Department of Surgery, Shimamichi Hospital; Department of Surgery, Higashiguchi Hospital; Department of Gastroenterology, Kiso
Table 1. Numbers of Endoscopic Submucosal Dissection Cases at All Institutions from January to December 2005

<table>
<thead>
<tr>
<th></th>
<th>High-volume centers (6 centers)</th>
<th>Low-volume centers (24 centers)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric cancers</td>
<td>335</td>
<td>251</td>
<td>586</td>
</tr>
<tr>
<td>Gastric adenomas</td>
<td>50</td>
<td>67</td>
<td>117</td>
</tr>
<tr>
<td></td>
<td>385</td>
<td>318</td>
<td>703</td>
</tr>
</tbody>
</table>

**Figure 1. Rates of endoscopic submucosal dissection in endoscopic resection for early gastric neoplasms.**

Hospital; Department of Gastroenterology, Iiyama Red Cross Hospital; Department of Internal Medicine, Chikuma Central Hospital; Department of Gastroenterology, Iida Municipal Hospital; Department of Gastroenterology, Showa Inan General Hospital; Department of Internal Medicine, Iida City Hospital; Department of Gastroenterology, Ina Central Hospital; Department of Gastroenterology, Suwa Red Cross Hospital; Department of Gastroenterology, Okaya City Hospital; Department of Internal Medicine, Fujimori Hospital; Department of Gastroenterology, Nagano National Hospital; Department of Gastroenterology, Suwa Central Hospital; Department of Gastroenterology, Hokushin General Hospital; Department of Gastroenterology, Komoro Kosei General Hospital; Department of Gastroenterology, Yodakubo Hospital; Department of Internal Medicine, Karuizawa Municipal Hospital.

**Statistical analysis**

CERRs and the rates of complications were compared between high- and low-volume centers with a chi-square test. All statistical analyses were performed with Stat Mate Ver.3 for Windows (ATMS Co., Tokyo, Japan). The calculated p values <0.05 were considered statistically significant.

**Results**

The numbers of early gastric neoplasms treated at high- and low-volume centers were 385 (335 EGCs and 50 GAs) and 318 (251 EGCs and 67 GAs) (Table 1). The ratio of ESD used in endoscopic resection for early gastric neoplasms was 67.1%. The ratio of ESD at high-volume centers was significantly higher than at low-volume centers (p<0.001) (Fig. 1). The distribution of each category (SI, EI and OI) at high- and low-volume centers is schematized in Fig. 2. The ratio of SI at low-volume centers was significantly higher than at high-volume centers (p<0.01).

The selection of endo-knives is listed in Table 2. The usage of each device was even in the high-volume centers. However, the use of hook knives was dominant at low-volume centers for both mucosal incision and submucosal dissection. The selection of injection fluids is listed in Table 3. The use of glycerol was dominant, followed by sodium hyaluronate solutions.

Category-specific CERRs for EGCs are schematized in Fig. 3. In SI, CERRs at high- and low-volume centers were 92.1% (152/165) and 91.1% (143/157) (chi-square: p=0.74).
Figure 2. Category-specific distribution of the Japanese Gastric Cancer Association’s guideline for early gastric cancers.

Table 2. Selection of Endo-knives

<table>
<thead>
<tr>
<th>Endo-knives</th>
<th>Mucosal incision</th>
<th>Submucosal dissection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High-volume</td>
<td>Low-volume</td>
</tr>
<tr>
<td>IT knife</td>
<td>33%(2/6)</td>
<td>42%(10/24)</td>
</tr>
<tr>
<td>Hook knife</td>
<td>33%(2/6)</td>
<td>71%(17/24)</td>
</tr>
<tr>
<td>Flex knife</td>
<td>33%(2/6)</td>
<td>33%(8/24)</td>
</tr>
<tr>
<td>Needle knife</td>
<td>33%(2/6)</td>
<td>42%(10/24)</td>
</tr>
</tbody>
</table>

Table 3. Selection of Injection Fluids

<table>
<thead>
<tr>
<th>Injection fluids</th>
<th>High-volume centers</th>
<th>Low-volume centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal saline</td>
<td>17%(1/6)</td>
<td>17%(4/24)</td>
</tr>
<tr>
<td>Glycerol</td>
<td>83%(5/6)</td>
<td>92%(22/24)</td>
</tr>
<tr>
<td>Sodium hyaluronate</td>
<td>33%(2/6)</td>
<td>29%(7/24)</td>
</tr>
</tbody>
</table>

In EI, CERRs at high-volume and low-volume centers were 86.2% (94/109) and 82.6% (57/69) (chi-square: p=0.51). In OI, CERR at high- and low-volume centers were 80.3% (49/61) and 88.0% (22/25) (chi-square: p=0.39). Reasons for incomplete resection of EGCs by category are shown in Fig. 4. The major reasons for the incomplete resection in SI, EI and OI were positive lateral margin, piecemeal resection and positive vertical margin, respectively. The category-specific distribution was not significant between high- and low-volume centers.

Complications in the total number of ESD cases (EGCs and GAs) are listed in Table 4. The perforation rate, when all cases were taken into consideration, was 4.13% (29/703). The perforation rates at high- and low-volume centers were 3.6% (14/385) and 4.7% (15/318) (chi-square: p=0.47). The intra-operative bleeding rate, when all cases were taken into account, was 0.14% (1/703). The intra-operative bleeding rates at high- and low-volume centers were 0.26% (1/385) and 0% (0/318) (chi-square: p=0.92). The delayed bleeding rate, when all cases were taken into consideration, was 0.28% (2/703). The delayed bleeding rates at high- and low-volume centers were 0% (0/385) and 0.63% (2/318) (chi-
Figure 3. Complete en-bloc resection rates of endoscopic submucosal dissection for early gastric cancers.

Figure 4. Reasons for incomplete resection of endoscopic submucosal dissection for early gastric cancers.

Table 4. Rates of Complications in Endoscopic Submucosal Dissection for Early Gastric Neoplasms

<table>
<thead>
<tr>
<th></th>
<th>High-volume centers</th>
<th>Low-volume centers</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perforation</td>
<td>3.6% (14/385)</td>
<td>4.7% (15/318)</td>
<td>4.13% (29/703)</td>
</tr>
<tr>
<td>Intra-operative bleeding</td>
<td>0.26% (1/385)</td>
<td>0% (0/318)</td>
<td>0.14% (1/703)</td>
</tr>
<tr>
<td>Delayed bleeding</td>
<td>0% (0/385)</td>
<td>0.63% (2/318)</td>
<td>0.28% (2/703)</td>
</tr>
<tr>
<td>Emergent surgery</td>
<td>0% (0/385)</td>
<td>0% (0/318)</td>
<td>0% (0/703)</td>
</tr>
</tbody>
</table>

Emergent surgery was not required for any case. Nor was there any treatment associated death.
Discussion

The previous multicenter prospective studies of endoscopic treatment of EGCs in Japan demonstrated outcomes of conventional EMR (18). CERR of EGCs ≤ 20 mm and 21-40 mm were 71.9% and 46.2%. A precise pathological diagnosis of the positive margin is difficult to determine for specimens obtained after piecemeal resection, and the indications for additional treatment are indistinct after incomplete EMR. Conversely, en-bloc resection could be allowed for an accurate histological diagnosis and could reduce the non-assessable resection rate (3).

ESD was developed for large and precise en-bloc resection to improve CERR. The largest single-center study from the National Cancer Center Hospital in Tokyo, including over 1,000 cases of ESD with the IT knife, demonstrated an excellent outcome (13). CERR was 93% for all cases and over 1,000 cases of ESD with the IT knife, demonstrated an excellent outcome equal to those of the high-volume centers (1-3).

What about techniques and outcomes of ESD at low-volume centers, which began performing the procedure more recently? There has been no report on the outcomes of ESD, including those of low-volume centers. The present study includes almost all institutions - both high- and low-volume centers that performed ESD for EGCs in one prefecture in Japan. The results at the low-volume centers of our study demonstrated excellent outcomes equal to those of the high-volume centers.

The major complications associated with endoscopic resection methods were bleeding and perforation. Previous comparative studies suggested that the perforation rate was higher for the ESD group than for the EMR group (14, 19). It was reported that the rates of perforation by ESD for EGCs were 3.6-9.7% (13-17, 19). The rates of bleeding were not significantly different between the EMR and the ESD groups (14, 19). Our present study shows that the perforation rate was about 4%, and there was no significant difference between high- and low-volume centers. Moreover, the rates of both intra-operative and delayed bleeding were very low both at high- and low-volume centers. This report is the first of its kind on the excellent outcomes of ESD for early gastric neoplasms including those of low-volume centers. However, ESD seems to be one of the most skillful endoscopic procedures and it has the possibility of incurring life-threatening complications. Therefore, beginners of ESD must learn the technique of this procedure directly from expert endoscopists or by live demonstration events.

The present study is limited in terms of the retrospective, questionnaire-based design. No detailed data on each case is available, and the therapeutic methods used at each institution varied. Moreover, there was no long-term follow-up data.

The most important matter to disseminate the ESD technique concerns the training system. We began ESD live demonstration seminars with Japanese ESD experts in 2003. At this meeting, trainees can watch and learn the ESD procedure with comments given by experts. Moreover, we organized the Nagano ESD Study Group to improve ESD skills and techniques in 2004. Video presentations on the ESD procedure and experts’ lectures are part of the seminar. A few learning curve studies suggested that experiences with the ESD procedure has improved the outcomes and shortened the procedure time (20, 21). Learning curves of our participating institutions were unclear in this study design. However, our efforts for regional training of ESD might be related to this excellent outcome in the present study. Meanwhile, cases with larger size, ulcer scar or lesion in the greater curvature seem to be difficult for beginners, and thus such cases should be treated in high-volume institutions.

In conclusion, based on a multi-center, retrospective questionnaire study, outcomes of ESD for early gastric neoplasms at low-volume centers were as good as those at high-volume centers.

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References


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