Clinical Efficacy of Endoscopic Submucosal Dissection for Adenocarcinomas of the Esophagogastric Junction

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Background and Study Aims
There are a few reports about the efficacy of endoscopic submucosal dissection (ESD) for adenocarcinomas of the esophagogastric junction (EGJ). However, there is no detailed analysis that divides EGJ cancers into Barrett's adenocarcinoma and gastric cardia adenocarcinoma. The aim of this study was to analyze the efficacy of ESD for EGJ cancers, comparing these two adenocarcinomas.

Patients and Methods
This study included 43 patients who underwent ESD for type II EGJ cancers between 2004 and 2011. Pathological examination of resected specimens confirmed 14 cases of Barrett's adenocarcinoma and 29 cases of gastric cardia adenocarcinoma. Cutting margins on the oral side were placed 1 cm from the squamocolumnar junction, or 1 cm away from the slight elevation that is an endoscopic sign of subsquamous carcinoma extension. Clinical outcomes, prevalence and length of subsquamous carcinoma extension, and long-term outcomes were compared between these two types of adenocarcinoma.

Results
No significant differences in clinical outcomes were found between these two types of adenocarcinoma (en bloc, 100% versus 100%; complete, 100% versus 89.7%; curative, 85.7% versus 75.9%). No serious adverse events were encountered. The prevalence of subsquamous carcinoma extension was significantly higher in Barrett’s adenocarcinoma compared with gastric cardia adenocarcinoma. Local and distant recurrence were not observed in any cases with curative resection during the follow-up period (1.6–87.6 months).

Conclusion
ESD for EGJ cancers, including both Barrett’s adenocarcinoma and gastric cardia adenocarcinoma, was efficient and useful. ESD with a 1 cm safety margin may be acceptable for EGJ cancers.

Introduction
Although the incidence of adenocarcinoma of the esophagus and esophagogastric junction (EGJ) is dramatically increasing in Western countries, [1, 2] esophageal adenocarcinoma (Barrett’s adenocarcinoma) is uncommon, accounting for only 1%–4% of the esophageal carcinoma in Eastern countries, including Japan. [3, 4] Since most cases of Barrett’s adenocarcinoma found in Japan arise from short-segment Barrett’s esophagus, [3, 5, 6] it is difficult to distinguish Barrett’s adenocarcinoma preoperatively from gastric cardia adenocarcinoma in patients with type II EGJ cancers (tumors invading the EGJ, in which the center is located between 1 cm above and 2 cm below the EGJ). [5–7]

Endoscopic submucosal dissection (ESD) is potentially a useful, safe, and curative treatment for superficial gastrointestinal cancers including esophageal, gastric, and colonic cancers. [8–10] There are a few reports that examine the efficacy of ESD for EGJ cancers, [5, 11–14] but there has not been a more detailed analysis that subdivides EGJ cancers into Barrett’s adenocarcinoma and gastric cardia adenocarcinoma. Adenocarcinoma of the EGJ often invades underneath the normal esophageal squamous epithelium (subsquamous carcinoma extension). [3, 4] This is clinically problematic in EGJ cancers treated with ESD, because cancer margins (especially on the oral side) cannot be accurately determined when subsquamous carcinoma extension is not visible during the preoperative endoscopy.

The aim of the present study was to analyze EGJ cancers retrospectively and compare the efficacy, adverse events, and long-term outcomes of ESD, as well as disease prevalence and length of subsquamous carcinoma extension, between Barrett’s adenocarcinoma and gastric cardia adenocarcinoma. The classification of the type of adenocarcinoma extension, and long-term outcomes were compared between these two types of adenocarcinoma.

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carcinoma was confirmed by pathological examination of resected specimens.

**Patients and Methods**

**Patients**

Between 2007 and 2011, 1024 cases of superficial gastric and esophageal cancer were treated with ESD by our department. From this group, 43 (4.2%) cases of type II EGJ cancer, identified according to Siewert’s classification, [15] were retrospectively analyzed. ESD is indicated in cases where preoperative endoscopic evaluation and endoscopic biopsy find EGJ cancer that is a differentiated adenocarcinoma with mucosal invasion. EGJ cancers were classified as either Barrett’s adenocarcinoma or gastric cardia adenocarcinoma based on pathological examination after ESD. We compared procedure time, resection rate, adverse event incidence, pathology, and long-term outcomes such as recurrence and survival time between these two groups. The protocol of this study was approved by the Institutional Review Board of the Osaka City University Graduate School of Medicine.

**Determination of the Lateral Margin of the Tumor and Setting of Marking before ESD**

Preoperative endoscopy was performed by using an Evis Lucera Spectrum system (Olympus, Tokyo, Japan) with a magnifying upper gastrointestinal endoscope (GIF-H260Z; Olympus). We delineated the area of the lesion using conventional white light endoscopy (Fig. 1a) and magnifying endoscopy with narrow-band imaging (NBI). We assessed the presence of a demarcation line with the presence of an irregular microvascular pattern or irregular microsurface pattern by performing magnifying endoscopy with NBI according to a systematic but simple classification system based on microvascular pattern and microsurface pattern (the VS classification system) [16,17] (Fig. 1b). An endoscopic sign of subsquamous carcinoma extension is a slight elevation that is similar in appearance to a submucosal tumor located at the esophageal squamous epithelium and continuing from the squamocolumnar junction (Fig. 1c). Marking dots were placed using a bipolar needle knife (B knife; Xemex Co., Tokyo, Japan) or the monopolar needle knife (Flush knife, DK2618JN; Fujifilm Medical, Tokyo, Japan). The marking dots were positioned at least 2 mm outside the margin of the tumor, except on the oral side, where the marking dots were placed 1 cm away from the slight elevation (Fig. 1d), or 1 cm from the squamocolumnar junction in cases with no abnormal endoscopic findings that were suggestive of subsquamous carcinoma extension (Fig. 1e). Fig. 1f demonstrates the histology of subsquamous carcinoma extension.

**ESD Procedure**

Experienced endoscopists conducted all endoscopic procedures. Intravenous midazolam and pethidine hydrochloride were used to place patients under conscious sedation for endoscopic procedures. During ESD procedures, a single-channel upper gastrointestinal endoscope with a water jet system (GIF-Q260J; Olympus) with a transparent hood (D-201 – 11804; Olympus) attached to the tip of the endoscope and a standard electrosurgical generator
Follow-up

For the patients who underwent curative resection, endoscopic examinations were performed 2 and 12 months after ESD, and annual surveillance was performed thereafter. Contrast-enhanced computed tomography was also performed annually to detect lymph node and distant metastasis. For the patients who underwent noncurative resection, additional surgical resection or chemotherapy was recommended, but the choice of additional treatment depended on the case.

Statistical Analysis

Characteristic values of the enrolled patients and clinical outcomes are presented as the median with the range, the mean ± standard deviation (SD), or as a percentage. Differences between the groups were examined by using chi-square tests, one-way ANOVA followed by Fisher’s paired least-significant difference test, or Student’s t-test. P < 0.05 was considered significant. Long-term outcomes were analyzed using the Kaplan–Meier method and log-rank test. Again, P < 0.05 was considered significant. Statistical analyses were performed using SPSS software version 21.0 for Windows (SPSS Inc., Japan).

Results

Clinicopathological Characteristics of the Study Subjects

Of the 43 cases of EGJ cancer, 14 (32.6%) were pathologically diagnosed as Barrett’s adenocarcinoma while 29 (67.4%) were gastric cardia adenocarcinoma. One case of Barrett’s adenocarcinoma arose from long-segment Barrett’s esophagus, while the remaining 13 cases arose from short-segment Barrett’s esophagus. The clinicopathological characteristics of the study subjects are shown in Table 1. There were no significant differences in age, gender, tumor size, macroscopic appearance, or depth of cancer invasion between the Barrett’s adenocarcinoma group and the gastric cardia adenocarcinoma group. However, the incidence of subsquamous carcinoma extension was significantly higher in Barrett’s adenocarcinoma (12/14, 85.7%) than in gastric cardia adenocarcinoma (2/29, 6.9%). The median length of subsquamous carcinoma extension was 3.0 mm, with a range of 0.2 mm to 7.0 mm, showing that subsquamous carcinoma extension measured less than 1 cm in all cases. Among the 14 cases of subsquamous carcinoma extension, 6 (42.9%) were detected by preoperative endoscopy, but 8 (57.1%) were undetected by preoperative endoscopy. There was no significant difference in length

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<tr>
<th>Table 1</th>
<th>Clinicopathological characteristics of the study subjects.</th>
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<tr>
<td></td>
<td>Barrett’s adenocarcinoma</td>
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</tr>
<tr>
<td>n = 14</td>
<td>n = 29</td>
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<tr>
<td>Age, years, mean ± SD</td>
<td>61.4 ± 14.2</td>
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<tr>
<td>Sex, male/female, n</td>
<td>13/1</td>
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<tr>
<td>Tumor size, mm, median (range)</td>
<td>18 (8 – 30)</td>
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<tr>
<td>Macroscopic appearance, elevated/depressed, n</td>
<td>6/8</td>
</tr>
<tr>
<td>Depth of cancer, mucosa/submucosa, n</td>
<td>12/2</td>
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<tr>
<td>Subsquamous carcinoma extension, n (%)</td>
<td>12 (85.7)</td>
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Adverse Events

Perforation was defined as a visual hole in the esophageal or gastric wall that exposed the mediastinal or peritoneal cavity as recognized on endoscopy. Delayed bleeding was defined as bleeding with hematemesis or melena that required endoscopic reinsertion or transfusion after the ESD procedure. Esophageal stricture was defined as diameter reduction with dysphagia that a standard 9.2-mm-diameter endoscope (GIF-Q260; Olympus) failed to pass through.
Clinical outcomes and adverse events are shown in Table 2. Although total procedure times of ESD for Barrett’s adenocarcinoma and gastric cardia adenocarcinoma were not significantly different, the procedure speed of ESD for Barrett’s adenocarcinoma was significantly faster than the speed for gastric cardia adenocarcinoma (P = 0.03). There were no significant differences in en bloc, complete, and curative resection rates between Barrett’s adenocarcinoma and gastric cardia adenocarcinoma. All lesions were resected en bloc by ESD. Pathological examination showed that all Barrett’s adenocarcinoma and gastric cardia adenocarcinoma lesions were resected with a negative lateral margin, but in two cases of gastric cardia adenocarcinoma that had invaded the submucosa a positive vertical margin was revealed. Twelve cases (85.7%) of Barrett’s adenocarcinoma and 22 cases (75.9%) of gastric cardia adenocarcinoma were found to have curative resection. Among curatively resected cases of Barrett’s adenocarcinoma, five had an invasion depth of T1a-SMM (superficial muscularis mucosa), 2 cases T1a-LPM (lamina propria mucosa), and 5 cases T1a-DMM. [18] Among curatively resected cases of gastric cardia adenocarcinoma, 19 had a mucosal invasion depth and 3 cases a submucosal invasion depth (less than 500µm, SM1) [19]. One case of noncuratively resected Barrett’s adenocarcinoma was a tumor with submucosal invasion over 200µm (SM2), while one case was a poorly differentiated adenocarcinoma with submucosal invasion less than 200µm (SM1). [18] On the other hand, all cases of noncuratively resected gastric cardia adenocarcinoma were tumors with submucosal invasion over 500µm (SM2), and 2 cases of these had lymphovascular invasion. [19] There was 1 case (3.4%) of procedure-related perforation among the gastric cardia adenocarcinoma group. Postoperative adverse events were delayed bleeding and esophageal stricture, which were each encountered in 1 case (3.4%) of gastric cardia adenocarcinoma. All patients recovered with endoscopic and conservative treatment such as oral intake restriction and antibiotics. No serious adverse events that required blood transfusion or surgical treatment were encountered.

Additional Treatment and Long-Term Outcomes
Among the 9 patients who underwent noncurative resection, 2 patients with Barrett’s adenocarcinoma and 2 patients with gastric cardia adenocarcinoma underwent salvage surgery, and 2 of these 4 patients died of other causes. Two patients with gastric cardia adenocarcinoma received chemotherapy, and the remaining 3 patients were observed without additional treatment, but no local or distant recurrence was found during the follow-up period (median 41.5 months, range 2–65).

Among the 34 patients who underwent curative resection, there were no local or distant recurrences during a median follow-up period of 42.3 months (range 11.9–77.4) in patients with Barrett’s adenocarcinoma and 41.5 months (range 1.6–87.6) in patients with gastric cardia adenocarcinoma. Two patients with gastric cardia adenocarcinoma died of lung cancer (n = 1) and esophageal squamous cell carcinoma (n = 1). The patient with esophageal cancer was followed for 5 years at our hospital and cancer was discovered at another hospital 79 months after he underwent ESD at our hospital. The 5-year overall survival rate of patients with curative resection was 100% for Barrett’s adenocarcinoma and 88.9% for gastric cardia adenocarcinoma, which shows no statistical difference (log-rank test 0.74). The 5-year cause-specific survival rate for both Barrett’s adenocarcinoma and gastric cardia adenocarcinoma was 100%.

Discussion
The indication for endoscopic resection of superficial EGJ cancers, including Barrett’s adenocarcinoma, has not been established because the incidence of lymph node metastasis of these cancers is not well known. Although several studies have suggested that ESD and its criteria for curative resection may be indicated for
EGJ cancers, based on gastric cancer guidelines, have suggested that EGJ cancers have a higher possibility of lymph node metastasis than gastric cancer. [20] Leers et al. reported that the prevalence of lymph node metastasis in Barrett’s adenocarcinoma was 13% in patients with mucosal cancer and 22% in those with submucosal invasion. [21] A systematic review using data from surgical resections showed that 26 of 1350 patients with mucosal Barrett’s adenocarcinoma who were treated by surgical resection (1.93%) had lymph node metastasis. [22] These reports suggest that curative resection of Barrett’s adenocarcinoma by performing ESD should be defined as resection of cancer limited to the mucosa and not found in the submucosa. This is the reason why we used pathological examination after ESD to divide EGJ cancers into Barrett’s adenocarcinoma and gastric cardia adenocarcinoma and evaluated curative resection of these two cancers on the basis of different criteria. Recently, a large Japanese survey demonstrated that there was no disease-specific death among 111 patients with mucosal Barrett’s adenocarcinoma treated by endoscopic resection, and 1 of 32 patients with submucosal invasion (3.1%) died because of peritoneal dissemination during an observation period that was longer than 2 years. [3] Since our results showed no recurrence or metastasis in any patient with curative resection, the definition of curative resection used in this study may be acceptable. Several studies have reported that en bloc resection rates of ESD for EGJ cancers of 90%–100%. [11–14, 23] Our results also showed a 100% en bloc resection rate. The curative resection rates of EGJ cancers according to the Japanese Classification of Gastric Carcinoma are reported to be 72.0%–84.1%. [11–14] When Hoteya et al. subdivided EGJ cancers into Barrett’s adenocarcinoma and gastric cardia adenocarcinoma, as in our study, they found curative resection rates of 48.0% for Barrett’s adenocarcinoma and 80.6% for gastric cardia adenocarcinoma. [23] The higher rates of curative resection found in our study might be due to differences in rates of positive lateral margins of the resected specimens. In Hoteya’s study, 36% of Barrett’s adenocarcinomas had positive lateral margins due to subsquamous carcinoma extension. [23] However, in our study no cases with positive lateral margins were found because we set 1 cm safety margins not only in cases in which subsquamous carcinoma extension was detected at preoperative endoscopy, but also in those in whom subsquamous extension was not detected at preoperative endoscopy. In most cases with subsquamous carcinoma extension, the extension was reported to be less than 1 cm; [24] in only 1 case has extension greater than 1 cm been reported. [25] Therefore, whether an oral safety margin that is placed 1 cm from the squamocolumnar junction or the slight elevation that is an endoscopic sign of subsquamous carcinoma extension is sufficient or not should be evaluated in the future.

There have been several attempts to detect subsquamous extension of EGJ carcinomas by performing preoperative endoscopy. [4] Goda et al. found that subsquamous carcinoma extension was accurately diagnosed in 97 of 175 Barrett’s adenocarcinomas (55%) by performing conventional white light endoscopy and in 42 of 70 (60%) by performing magnifying endoscopy with NBI, [3] a detection rate similar to that in our study. Recently, Yamagata et al. reported in a small study that magnifying endoscopy with NBI did not provide additional information for the diagnosis of subsquamous carcinoma extension compared with conventional white endoscopy, but acetic acid spraying and magnifying endoscopy with NBI detected 100% of six patients with subsquamous carcinoma extension. [26] A large study is required to establish the utility of acetic acid spraying and magnifying endoscopy with NBI for the diagnosis of subsquamous carcinoma extension in EGJ cancer.

The results of the present study show that the procedure speed of ESD for Barrett’s adenocarcinoma was significantly faster than that of ESD for gastric cardia adenocarcinoma. The exact reasons for this difference are unknown. Tumor location could be a factor, because among type II EGJ cancers gastric cardia adenocarcinoma may extend beyond the cardia, including the angle of His, while Barrett’s adenocarcinoma does not. In such cases, it is technically difficult to complete the ESD procedure: the complicated shapes make it difficult to attach the endoknife to mucosa or submucosa. Surgical resection, including total gastrectomy with transthiatal resection and esophagectomy, has been performed for EGJ cancers. Long-term outcomes for superficial cancers were reported to be favorable. Endoscopic therapy was adapted as an alternative therapy for superficial EGJ cancers, because surgical resection has a high mortality rate that often exceeds 2%, [27,28] with substantial morbidity and no guarantee of curing metastases. Other therapies such as photodynamic therapy, radiofrequency ablation (RFA), endoscopic mucosal resection (EMR), and a combination therapy of EMR and RFA are mainly applied to adenocarcinomas in long-segment Barrett’s esophagus. [2,29,30] Because Barrett’s esophagus has potent malignant potential and the incidence rates of recurrent or metachronous cancers are high, and these therapies enable treatment of both Barrett’s adenocarcinoma and Barrett’s esophagus. Since most Barrett’s adenocarcinoma found in Japan arises from short-segment Barrett’s esophagus and metachronous cancer in the Barrett’s esophagus is rare, we believe that ESD is an acceptable first-line treatment for superficial EGJ cancers including Barrett’s adenocarcinoma.

Our study has some limitations. First, the sample size was small because EGJ cancers are very rare in Japan. The incidence of superficial EGJ cancer in our study was 4.2%, which was comparable to other recent Japanese studies. Second, our study was a retrospective observational analysis, not a randomized clinical trial. A prospective randomized study is required to determine the appropriate positioning of safety margins on the oral side of...
EGJ cancers. Third, this study was a single Japanese expert center experience. The present results may not be applicable to EGJ cancers in Western countries because Barrett’s adenocarcinomas in their patients mainly arise from long-segment Barrett’s esophagus. In addition the technique of ESD for EGJ cancers requires some expertise.

In conclusion, ESD was efficient and useful for the treatment of superficial EGJ cancers including Barrett’s adenocarcinoma and gastric cardia adenocarcinoma. ESD with a 1 cm safety margin may be effective for EGJ cancers with submucosal carcinoma extension.

Competing interests: Yes; Tetsuo Arakawa had advisory committees by Otsuka Pharmaceutical Co. Ltd and Eisai Co. Ltd. Yasuhiro Fujiwara had advisory committees by Eisai Co. Ltd. Kenji Watanabe had advisory committees by Mitsubishi Tanabe Pharma Corporation Co. Ltd, Abbott Japan Co. Other authors declare that they have no conflict of interest.

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