

Safety, efficacy, and long-term outcomes for endoscopic submucosal dissection of early esophagogastric junction cancer

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Abstract

Background Early esophagogastric junction (EGJ) cancer is currently being treated in the same way as early gastric cancer, by endoscopic submucosal dissection (ESD), but long-term outcomes are still unknown. Our aim was to retrospectively evaluate the safety and efficacy of ESD in treating early EGJ cancer and compare risk factors in curative and non-curative resection cases.

Methods Forty-four cases of early EGJ cancer, defined as a Siewert's type II tumor, in 44 patients with a mean age of 70.0 years and a male/female ratio of 90.9:9.1 % were treated by ESD between January 2004 and June 2010. There were 30 standard indication cases; the remaining 14 cases were expanded indication cases.

Results Mean resected specimen and tumor sizes were 35 and 17 mm, respectively, and median procedure time was 121 min, with no bleeding or perforation complications. All cases were resected en bloc with an 84.1 % curative resection rate (37/44). The curative resection rates in the standard and expanded indication cases were 90.0 % (27/30) and 71.4 % (10/14), respectively. There were no significant differences in tumor location, tumor morphology, tumor size, histology of biopsy specimens, or standard versus expanded indication cases with regard to risk factors for curative and non-curative resections. However, submucosal invasion, positive tumor margins, lymphovascular invasion, and some components of poorly differentiated

adenocarcinomas in just the submucosal layer were significantly more common in the non-curative resection cases.

Conclusions ESD was a safe, effective, and minimally invasive treatment for early EGJ cancer. For tumors without any submucosal invasion findings, therefore, ESD is an acceptable treatment option, in addition to also being suitable for diagnostic purposes in evaluating the need for surgery.

Keywords Endoscopic submucosal dissection · Early esophagogastric junction cancer · Long-term outcomes

Introduction

The incidence of esophagogastric junction (EGJ) adenocarcinoma has increased considerably in the United States and other Western countries recently [1–4] and there is a good possibility of the incidence of such EGJ cancer increasing in Japan in the foreseeable future [5]. In Japan, early EGJ cancer is currently being treated by endoscopic submucosal dissection (ESD), in the same way as early gastric cancer [6–8], but long-term outcomes are still unknown. Our aim was to retrospectively evaluate the safety and efficacy of ESD in treating early EGJ cancer.

Patients and methods

A total of 44 early EGJ cancers in 44 patients with a mean age of 70.0 years (range, 42–84) and a male/female ratio of 40:4 (90.9:9.1 %) were treated by ESD between January 2004 and June 2010 at the Cancer Institute Hospital in Tokyo, Japan. EGJ cancer was defined as a type II tumor

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according to Siewert's classification, with the tumor center located within an area 1 cm above and 2 cm below the EGJ [9]. In an effort to clarify the clinical effectiveness of ESD for early EGJ cancer, we retrospectively investigated the clinical characteristics of the 44 patients and 44 early EGJ cancers, the ESD procedures that were performed, and the pathological features of the early EGJ cancers. We then assessed the complication, en-bloc resection, curative resection, local recurrence, and distant metastasis rates and compared risk factors in curative and non-curative resection cases to determine the long-term outcomes.

Indications for ESD

The indications for ESD were defined by the criteria of the Japan Gastric Cancer Association (JGCA) [10].

Standard guideline criteria for endoscopic resection

Differentiated adenocarcinoma or intramucosal cancer ≤ 20 mm in size without an ulcer finding.

Expanded indication criteria for endoscopic submucosal dissection

Differentiated adenocarcinoma regardless of tumor size with no apparent submucosal invasion finding and without an ulcer finding, or ≤ 30 mm in size with an ulcer finding.

Chromoendoscopy using indigo-carmin dye, magnification endoscopy with narrow-band imaging (ME-NBI), and circumferential lesion biopsies were used for determining lateral tumor margins, and endoscopic ultrasonography (EUS) was performed for establishing invasion depth.

ESD procedures

The ESDs were performed by expert endoscopists certified by the Japan Society of Gastrointestinal Endoscopy. The procedures were performed using an insulation-tipped knife (IT knife) (KD-610L; Olympus Optical, Tokyo, Japan) or an IT knife 2 (KD-611L; Olympus) and a single-channel upper gastrointestinal endoscope (GIF-Q260J, GIF-H260; Olympus) with a transparent hood (D-201-11804; Olympus) attached to the tip of the endoscope. An electrosurgical current was applied using a standard electrosurgical generator (VIO300D; ERBE, Tübingen, Germany, or ESG100; Olympus). All procedures were conducted in patients who received intravenous anesthesia using midazolam and pethidine hydrochloride. Tumor identification was followed by circumferential marking around the tumor, using argon plasma coagulation based on previous biopsy scarring (Fig. 1a, b). Glyceol[®] (10 % glycerol and 5 % fructose in a

normal saline solution; Chugai Pharmaceutical, Tokyo, Japan) or hyaluronic acid (MucoUp[®]; Johnson & Johnson Japan, Tokyo, Japan) was then injected into the submucosal layer to lift the mucosa at the oral side of the tumor, using the retroflex view, because controlling the scope was difficult with the forward endoscopic view owing to the narrow lumen of the EGJ. An initial cut, referred to as a pre-cut incision, was made with a standard needle-knife on the oral side of the tumor, followed by a circumferential mucosa incision around the tumor, using the IT knife or IT knife 2 (Fig. 1c–e). The tumor was then completely removed by submucosal dissection, using the IT knife or IT knife 2, performed from the anal side of the tumor, using the retroflex view (Fig. 1f).

Pathological assessment of resected specimens

Early EGJ cancers were categorized according to location, i.e., the anterior wall (AW), greater curvature, posterior wall (PW), and lesser curvature (LC). The Paris endoscopic classification of superficial neoplastic lesions was used to characterize the surface morphology of the tumors [11]. Resected specimens were mounted on boards with pins and fixed in 10 % formalin for 24 h. After fixation, all resected specimens were cut into longitudinal slices 2 mm in width and then embedded in paraffin and stained with hematoxylin–eosin. Pathological assessments, including tumor size, depth of invasion, and the presence of lymphovascular invasion, were performed microscopically. Based on these assessments, a curative resection was regarded as an en-bloc resection with the lateral margin free of neoplasia, with no lymphatic or vascular invasion, and depth of invasion of ≤ 500 μ m from the muscularis mucosa. A tumor was also considered to be curatively resected when some components of a poorly differentiated adenocarcinoma or signet-ring cell carcinoma were found during the pathological examination. The ESD procedure time was defined as the time interval between endoscope insertion and removal.

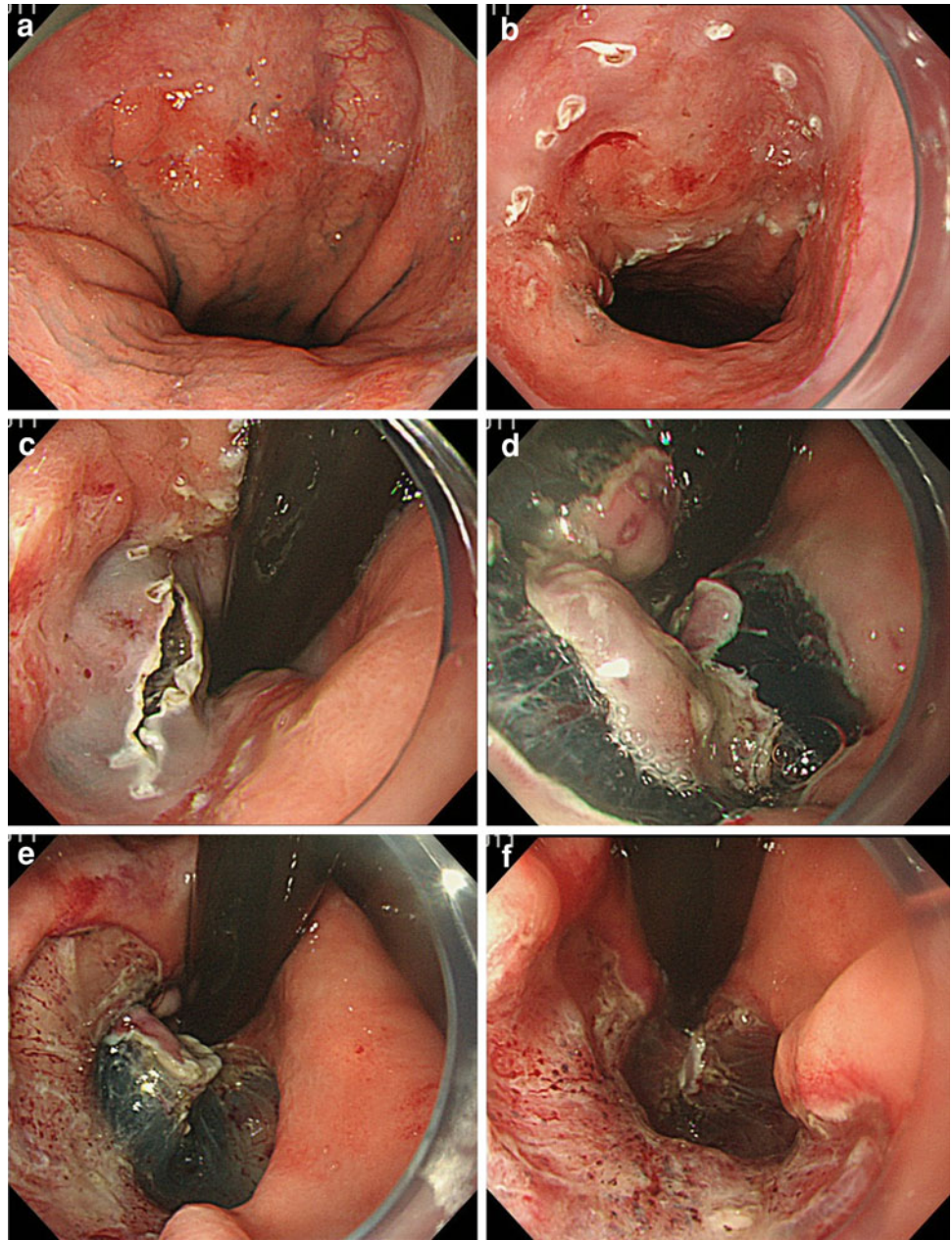
Ethics

The study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by the medical ethics committee of our hospital. The risks and benefits of ESD were explained beforehand and written informed consent was obtained from all 44 patients.

Results

All data on patient characteristics and pathological features are summarized in Table 1. Of the 44 patients with early

Fig. 1 Endoscopic submucosal dissection procedure. **a** Reddish elevated tumor located at the esophagogastric junction (EGJ). **b** Circumferential marking performed around the tumor, using argon plasma coagulation based on previous biopsy scarring. **c** Hyaluronic acid injected into the submucosal layer to lift the mucosa at the oral side of the tumor, using retroflex view. Pre-cut incision made with standard needle-knife on the oral side of the tumor. **d** Circumferential mucosa incision around the tumor made using an insulation-tipped knife (IT knife; KD-610L; Olympus Optical) or an IT knife 2 (KD-611L; Olympus). **e** Submucosal dissection using IT knife or IT knife 2 performed from the anal side of the tumor using retroflex view. **f** Completely resected tumor



EGJ cancer, only four (9.1 %) were females. The mean age of the cohort was 70.0 years (range, 42–84). Twenty-four (54.5 %) tumors were located on the LC of the EGJ, 11 (25.0 %), on the PW, and nine (20.5 %) on the AW. Twenty-three tumors (52.3 %) were elevated and 10 (22.7 %) of these tumors also had a central depression. Twenty (45.5 %) of the other 21 tumors were depressed, but only one (2.3 %) of these tumors had an elevated mucosa (which was reddish in color and located in the center of the depression). The one (2.3 %) remaining tumor was a protruded lesion. Biopsy specimens in all 44 cases revealed differentiated adenocarcinoma, but only three cases included some components of poorly differentiated

adenocarcinoma. There were 30 standard indication cases; the remaining 14 cases were expanded indication cases. All cases were planned for curative treatment. The mean resected specimen and tumor sizes were 35 mm (range, 15–58) and 17 mm (range, 5–47), respectively. The median procedure time was 121 min (range, 49–272), and 13 tumors (29.5 %) were pathologically suspected of having developed from short-segment Barrett's esophagus. All 44 tumors were primarily differentiated adenocarcinomas, although five tumors (11.4 %) included some components of a poorly differentiated adenocarcinoma in either just the submucosal layer (two tumors, 4.5 %) or just the mucosal layer (three tumors, 6.8 %). Biopsy specimens from two of

Table 1 Patient characteristics and pathological features

Gender, male/female (%)	40:4 (90.9:9.1)
Mean age, years (range)	70.0 (42–84)
Location (%)	
Lesser curvature	24 (54.5)
Posterior wall	11 (25.0)
Anterior wall	9 (20.5)
Greater curvature	0 (0)
Tumor morphology (%)	
I	1 (2.3)
IIa	13 (29.5)
IIa + IIc	10 (22.7)
IIc	19 (43.2)
IIc + IIa	1 (2.3)
Biopsy specimen (%)	
Differentiated adenocarcinoma	44 (100)
Some components of poorly differentiated adenocarcinoma	3 (6.8)
Indication (%)	
Standard indication	30 (68.2)
Expanded indication	14 (31.8)
Mean resected specimen size, mm (range)	35 (15–58)
Mean resected tumor size, mm (range)	17 (5–47)
Median procedure time, min (range)	121 (49–272)
Pathology (%)	
Primarily differentiated adenocarcinoma	44 (100)
Complications (%)	0 (0)
En-bloc resection (%)	44 (100)
Curative resection (%)	37 (84.1)
Standard indication	27 (90.0)
Expanded indication	10 (71.4)
Tumor invasion depth (%)	
p-T1 m, mucosal	36 (81.8)
p-T1sm, slight submucosal <500 μ m	3 (6.8)
p-T1sm, deep submucosal \geq 500 μ m	5 (11.4)

these five tumors indicated differentiated adenocarcinomas prior to ESD, but pathological examinations of the two tumors revealed some poorly differentiated adenocarcinoma components in just the submucosal layer of each tumor. There were no complications such as bleeding or perforation and all cases were successfully resected en bloc, with a curative resection rate of 84.1 % (37/44). The curative resection rates of the standard and expanded indication cases were 90.0 % (27/30) and 71.4 % (10/14), respectively. There were no instances of stenosis in any case after ESD. No recurrent or distant metastatic carcinomas were detected during a mean follow-up period of 33 months (range, 6–64) and only two patients, both of whom had undergone curative resections for intramucosal tumors, died (from other cancer-related causes).

The details of the seven non-curative cases are summarized in Table 2. One non-curative resection case was pathologically revealed to be oral lateral margin-positive (case 1, Fig. 2a–d), but the patient declined surgery. Another non-curative resection case (case 2) involved both slight submucosal invasion <500 μ m (SM1) and venous invasion, but this patient also declined subsequent gastrectomy. The tumor in this case, in fact, included some components of a poorly differentiated adenocarcinoma located in just the submucosal layer. The remaining five non-curative resection cases all had deep submucosal invasion \geq 500 μ m (SM2) (cases 3–7) with two of these cases also involving lymphatic invasion (cases 3 and 4) and one of them being vertical margin-positive as well (case 3). The other SM2 case with lymphatic invasion involved some components of a poorly differentiated adenocarcinoma located in just the submucosal layer (case 4, Fig. 3a–d). Another SM2 case was also oral lateral margin-positive (case 5), while the remaining two SM2 cases involved only submucosal deep invasion (cases 6 and 7). All five SM2 non-curative resection patients underwent laparoscopic gastrectomy, with no residual tumors or lymph node metastases revealed pathologically. In conclusion, there were no significant differences in tumor location, tumor morphology, tumor size, histology of biopsy specimens, or standard versus expanded indication cases with regard to risk factors for curative and non-curative resection. However, submucosal invasion, positive tumor margins, lymphovascular invasion, and some components of poorly differentiated adenocarcinomas in just the submucosal layer were significantly more common in non-curative resection cases (Table 3).

Discussion

An increasing number of EGJ cancers have recently been diagnosed in Western countries. For many years, total gastrectomy with a transhiatal resection of the distal esophagus was regarded as the gold standard treatment for all EGJ cancer patients [12]. Such surgery entails the risk of overtreatment and reduces postoperative patient quality of life, however, so the necessity for performing such an extensive resection has been questioned in patients with early EGJ cancers.

In contrast, remarkable progress has recently been made in Japan in the development of various methods of endoscopic resection [13–15]. In particular, the introduction of ESD has made possible the en-bloc resection of larger tumors, as well as tumors in difficult locations such as the EGJ [16, 17]. The en-bloc resection rate has risen to nearly 90 % with the maturation of this procedure in major Japanese medical facilities regularly performing ESDs [18].

Table 2 Pathological findings and short-term outcomes of seven non-curative resection cases

Case number	Gender	Age (years)	Tumor morphology	Ulcerative scar	Resected specimen size, mm	Tumor size, mm
1	M	50	Ic	–	25	9
2	M	81	Ic	–	50	40
3	M	63	Ia + Ic	+	58	38
4	F	68	Ic	–	40	27
5	M	69	Ic	–	23	7
6	M	79	Ia + Ic	–	35	22
7	M	75	Ia + Ic	–	46	19
Some poorly differentiated adenocarcinoma components		Depth of invasion	Lymphatic invasion	Venous invasion	Oral lateral margin	Vertical margin
Case #1		p-T1m, mucosal	–	–	+	–
Case #2		p-T1sm, slight submucosal	–	+	–	–
+ Some poorly differentiated adenocarcinoma in just the submucosa						
Case #3		p-T1sm, deep submucosal	+	–	–	+
Case #4		p-T1sm, deep submucosal	+	–	–	–
+ Some poorly differentiated adenocarcinoma in just the submucosa						
Case #5		p-T1sm, deep submucosal	–	–	+	–
Case #6		p-T1sm, deep submucosal	–	–	–	–
Case #7		p-T1sm, deep submucosal	–	–	–	–
Additional treatment	Residual tumor or lymph node metastasis		Follow-up period, months	Local recurrence or distant metastasis		
Case #1, patient declined	No		54	No		
Case #2, patient declined	No		14	No		
Case #3, laparoscopic gastrectomy	No		31	No		
Case #4, laparoscopic gastrectomy	No		7	No		
Case #5, laparoscopic gastrectomy	No		40	No		
Case #6, laparoscopic gastrectomy	No		18	No		
Case #7, laparoscopic gastrectomy	No		14	No		

Consequently, we believe that ESD is an indispensable treatment method because it is possible to pathologically evaluate the risks of recurrence and metastasis more accurately. ESD does, however, have several limitations, including being a time-consuming procedure with a relatively high complication rate owing to bleeding and perforations. The risk of complications is even higher in more difficult cases such as those involving EGJ tumors,

although our ESD technique using the IT knife 2 with the retroflex view is not usually affected by respiratory movement. Injecting hyaluronic acid into the submucosal layer also usually lifts the mucosa enough so that the muscularis propria and the vessels running through it can be identified more easily and the submucosal layer can be dissected without cutting any of these vessels. As a result, ESD has been demonstrated to be a safe and effective

Fig. 2 Non-curative resection case 1 involved the development of adenocarcinoma below the squamous epithelium. **a** Conventional endoscopy revealed reddish depressed mucosa at the EGJ. **b** Chromoendoscopic view of tumor with indigo-carmin dye. **c** Histological mapping of the resected specimens, with *red lines* indicating cancerous tumor. *AW* anal wedge, *OW* oral wedge. **d** Pathological examination revealed adenocarcinoma that had developed approximately 330 μ m below the squamous epithelium. H&E, $\times 40$

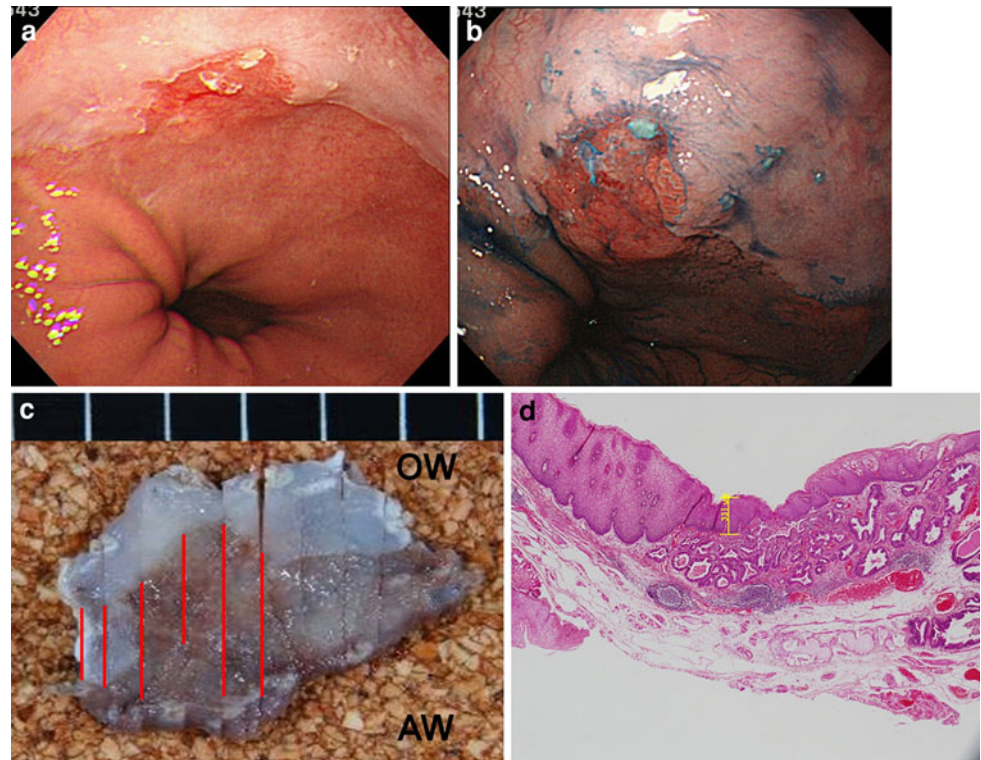
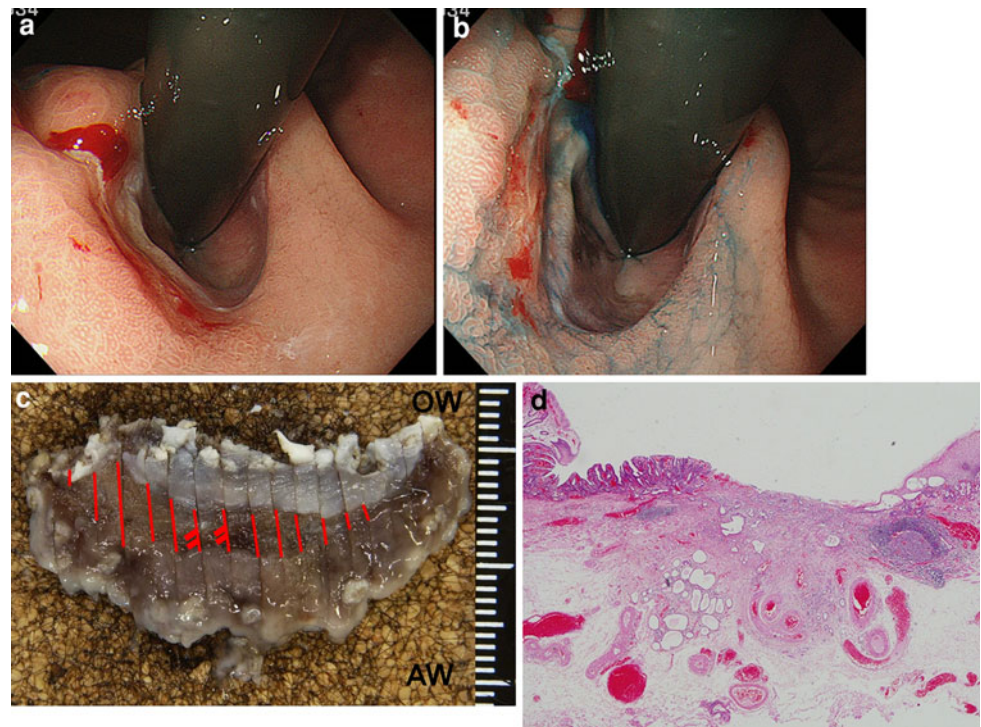


Fig. 3 Non-curative resection case 4 included some poorly differentiated adenocarcinoma components located in just the submucosal layer. **a** Conventional endoscopy revealed reddish depressed mucosa at the EGJ. **b** Chromoendoscopic view of tumor with indigo-carmin dye. **c** Histological mapping of the resected specimens, with *red lines* indicating the cancerous tumor and the *shaded portion* indicating the submucosal invasion lesion. *AW* anal wedge, *OW* oral wedge. **d** Pathological examination revealed mixed primarily differentiated adenocarcinoma with some poorly differentiated components located in just the submucosal layer. H&E, $\times 100$



treatment method despite a somewhat higher risk of complications, such as bleeding and perforation, particularly in more technically difficult locations.

We compared risk factors between curative and non-curative resection cases. Before the ESDs, there were no

significant differences in any risk factors, including tumor location, tumor morphology, tumor size, histology of biopsy specimens, or standard versus expanded indications. However, the tumors were larger, the histology of biopsy specimens included some components of poorly differentiated

Table 3 Risk factors in curative and non-curative resection cases

	Curative resection cases	Non-curative resection cases	<i>P</i> value
Location			0.336
Lesser curvature	19	5	
Anterior wall	9	0	
Posterior wall	9	2	
Tumor morphology			0.748
0-I	1	0	
0-IIa	20	3	
0-IIc	16	4	
Tumor size, mm, mean \pm SD	15.35 \pm 9.23	23.14 \pm 12.90	0.122
Histology of biopsy specimen			0.173
Only differentiated adenocarcinoma	34	5	
Included poorly differentiated adenocarcinoma	3	2	
Indication			0.131
Standard indication	27	3	
Expanded indication	10	4	
Tumor depth			<0.01
Mucosal invasion	37	0	
Submucosal invasion	2	5	
Tumor horizontal margin			<0.01
Negative	37	5	
Positive	0	2	
Tumor vertical margin			<0.05
Negative	37	6	
Positive	0	1	
Lymphovascular invasion			<0.01
No invasion	37	6	
Invasion	0	1	
Poorly differentiated adenocarcinoma			<0.01
None	34	5	
Mucosal layer	3	0	
Submucosal layer	0	2	

adenocarcinomas, and expanded indication cases were more common in the non-curative cases. We believe the reason there were no statistically significant differences in these risk factors was that we did not have a large number of patients with EGJ cancer who underwent ESDs in our hospital. After the ESDs, significant differences between the curative and non-curative cases were shown in tumor depth, tumor margin, lymphovascular invasion, and some components of poorly differentiated adenocarcinomas in just the submucosal layer. Although it is possible to

accurately predict some components of differentiated and undifferentiated adenocarcinomas in the mucosal layer using ME-NBI [19, 20], it is impossible to use this method to diagnose the existence of adenocarcinomas in just the submucosal layer, because ME-NBI microvascular pattern findings apply only to the superficial mucosal layer [21]. Transhiatal esophagectomy for adenocarcinoma of the distal esophagus and cardia may be more invasive treatment in node-negative cancer. We should therefore plan to perform ESDs first to evaluate the pathology of the tumor to avoid unnecessary treatment if we do not suspect deep submucosal invasion of the tumor.

In conclusion, ESD was shown to be a safe, effective, and minimally invasive treatment for early EGJ cancer. For tumors without any submucosal invasion findings, therefore, ESD is an acceptable treatment option, in addition to also being suitable for diagnostic purposes in evaluating the need for surgery.

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