Comparison of the Clinicopathological Characteristics and Results of Endoscopic Submucosal Dissection for Esophagogastric Junction and Non-Junctional Cancers

Shu Hoteya Akira Matsui Toshiro Iizuka Daisuke Kikuchi Akihiro Yamada
Satoshi Yamashita Tsukaka Furuhashi Kaoru Domon Masanori Nakamura
Toshifumi Mitani Osamu Ogawa Mitsuru Kasie

Department of Gastroenterology, Toranomon Hospital, Tokyo, Japan

Key Words

Endoscopic submucosal dissection • Barrett's adenocarcinoma • Esophagogastric junctional cancer • Submucosal invasion • Lymphovascular invasion • Subepithelial invasion

Abstract

Background: Esophagogastric junction (EGJ) cancers are not only located in regions anatomically difficult for endoscopic submucosal dissection (ESD), but they also have higher clinicopathological malignant potential than non-junctional gastric cancers (NJC). Despite this, no ESD-based comparative studies of junctional cancer (JC) and NJC have been conducted to date. The aims of this study were to clarify the clinicopathological characteristics of EGJ cancers and the short- and long-term outcomes after ESD. **Methods:** Between April 2005 and December 2010, ESD was performed on 1,463 lesions that were divided into the following three groups: Barrett's adenocarcinoma (BA; n = 25); JC (n = 103), and NJC (n = 1,335). They were assessed for short-term outcomes, clinicopathological malignancy and long-term outcomes. **Results:** Rates of complete and curative resection were significantly lower for BA than for JC and NJC (64.0 vs.

96.1 and 96.0%; and 48.0 vs. 80.6 and 85.8%, respectively). The perforation rate was significantly higher for BA than for JC and NJC (20.0 vs. 2.9 and 2.7%). Clinicopathologically, submucosal invasion rates were higher in BA and JC than in NJC (32.0 and 30.1 vs. 13.6%), and positive rates of lymphatic and/or vascular invasion were remarkably higher in BA and JC versus NJC (24.0 vs. 9.7 vs. 4.8%, respectively). The 5-year survival rate in all patients with curative resection was 100%. **Conclusion:** This study confirmed the technical and theoretical validity of ESD for EGJ as a diagnostic treatment. However, we have to pay attention to the high rates of submucosal and lymphovascular invasive malignant potential of these cancers.

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Introduction

With the development and widespread use of endoscopic submucosal dissection (ESD) [1–4], endoscopic therapy now provides similar radical treatment for early-stage cancer as is possible through surgery, even for lesions conventionally difficult to resect, such as those with a large size, irregular shape, coexisting ulcers and diffi-

cult location. Several previous reports have investigated the advantages of ESD using specialized devices compared with conventional endoscopic resection [5–8]. Further, using the curability criteria proposed by Gotoda et al. [9], the indications for ESD of cancers that have a low risk of lymph node metastasis have expanded to include submucosally invasive cancers [9, 10].

However, pretreatment endoscopic diagnosis of the existence of lymphovascular cancer involvement or minute submucosal invasion, which is the most important prerequisite for establishing the absence of nodal metastasis, is inadequate. Therefore, en bloc resection is necessary for estimation of curability based on a perfect specimen, according to the expanded criteria.

Esophagogastric junction (EGJ) cancers, including Barrett's adenocarcinoma (BA) and cardiac gastric cancer, the so-called junctional cancer (JC), are not only located in regions anatomically difficult for ESD, they also have higher clinicopathological malignancy than non-junctional gastric cancers (NJC). Despite this, no ESD-based comparative studies of JC and NJC have been conducted to date. The aims of this study were to clarify the clinicopathological characteristics of EGJ cancers and the status and issues related to short- and long-term outcomes after ESD.

Patients and Methods

Patients

A total of 1,463 lesions in 1,224 patients who underwent ESD at Toranomon Hospital, including for diagnostic purposes, between April 2005 and December 2010 were divided into the following three groups: BA (n = 25); JC (gastric cardia cancer, type-2 cancer according to Siewert's classification [11]; n = 103), and NJC (n = 1,335). Lesions in a remnant stomach after gastrectomy or esophagectomy and palliative treatment were excluded from the study.

ESD Indications

Because preoperative diagnosis could not confirm minimum submucosal invasion or lymphatic-vascular invasion accurately, pretreatment indications of JC/NJC for ESD were lesions which were suspected by endoscopic findings and biopsy with the possibility of according to the curability criteria based on the Gastric Cancer Treatment Guidelines as follows: (1) intramucosal cancer without ulceration showing differentiated type, irrespective of tumor size; (2) intramucosal cancer with ulceration showing differentiated type, <3 cm in diameter, and (3) minimally invasive submucosal cancer (invasion <500 μ m from the muscularis mucosa) <3 cm in diameter showing differentiated type.

ESD Technique

The ESD procedure was performed using both the hook knife (KD-620LR; Olympus Optical, Tokyo, Japan) and the flex knife

(KD-630L; Olympus Optical) through a two-channel scope equipped with multi-bending and water jet functions (GIF-2TQ260M; Olympus Optical), as previously reported [3]. Briefly, a soft transparent hood (D-201-13404; Olympus Optical) was attached to the tip of the endoscope to obtain good, direct endoscopic views of the submucosal layer. Marking dots were placed on the normal mucosa approximately 5 mm from the tumor margin to provide safety margins. After submucosal injection of glycerol (10% glycerol and 5% fructose; Chugai Pharmaceutical, Tokyo, Japan), which contained a small amount of indigo carmine and epinephrine, a mucosal incision was made outside the marking dots. Hyaluronic acid solution was added to the injection solution when mucosal elevation was insufficient due to ulceration of the lesion or massive fibrosis of the submucosal layer [12]. After mucosal incision, direct dissection of the submucosal layer was performed to obtain the perfect specimen, and complete en bloc resection was performed. Hemostatic forceps (HDB2422W; Pentax, Tokyo, Japan) were used to control bleeding during the procedure. ESD was usually performed under conscious sedation using diazepam (5–10 mg/body) and pethidine hydrochloride (35–70 mg/body). However, when the procedure was expected to exceed 2 h, patients were given general anesthesia.

Postoperative bleeding was defined as hematemesis or melena requiring an endoscopic hemostatic procedure after ESD. Perforation during the procedure was confirmed by detection of free air on plain radiography and was sutured by clipping.

Histological Assessment

The resected specimen was cut into 2-mm slices after fixation in formalin. Histological type, size, depth of invasion, lateral and vertical margins and lymphovascular invasion were evaluated in each slice according to the Japanese Classification of Gastric Carcinoma [10]. 'Complete resection' meant that complete physical regional resection was proved histologically. 'Curative resection' meant that the lesion was completely resected, and furthermore, the resected specimen met the curability criteria described above (1–3) with no lymphovascular invasion.

BA in Japan is not accurately diagnosed preoperatively because most of them arise from short-segment Barrett's esophagus. Therefore, if the cancer was proved to be arising from Barrett's epithelium histologically after ESD, it was defined as BA. In this study, an invasion depth of T1a-DMM (deep muscularis mucosa) with no lymphovascular invasion and negative resection margins was defined as the curability criteria for BA.

Evaluations

Comparative investigations were conducted regarding: (1) short-term outcomes, including resection size, rate of local complete en bloc resection, curative resection rate and complications (postoperative bleeding, perforation); (2) clinicopathological malignancy, including submucosal invasion rate and rate of lymphovascular invasion, and (3) long-term outcomes, including local recurrence rate, distant metastasis rate and overall survival rate.

Statistical Analysis

The data are presented as means $\pm$ standard deviation. Statistical analysis was performed using the χ^2 test, Fisher's exact test and Student's t test, with p values <0.05 considered statistically significant. The Kaplan-Meier method was used for analysis of long-term outcomes.

Table 1. Clinicopathological characteristics and short-term outcomes of 1,463 tumors resected by ESD in 1,224 patients

	BA	JC	NJC
Patients, n	25	101	1,098
Mean age $\pm$ SD, years	63.5 $\pm$ 12.5	68.8 $\pm$ 9.3	68.5 $\pm$ 9.4
Sex (male/female)	22/3	85/16*	828/270
Lesions, n	25	103	1,335
Mean size $\pm$ SD, mm	20.2 $\pm$ 17.6	21.8 $\pm$ 15.8	20.6 $\pm$ 17.8
Endoscopic macroscopic type, n			
Polypoid type (0-I)	5	6	42
Non-polypoid type (0-IIa, 0-IIb, 0-IIc)	20 (10/0/10)	91 (33/2/56)	1,192 (42/56/694)
Mixed type	0	6	101
Mean surgical time $\pm$ SD, min	84.9 $\pm$ 52.3	107.0 $\pm$ 64.4*	87.3 $\pm$ 54.7
Complete resection rate, n ¹	16/25 (64.0)*	99/103 (96.1)	1,279/1,335 (95.8)
Curative resection rate, n ²	12/25 (48.0)*	83/103 (80.6)	1,144/1,335 (85.7)
Postoperative bleeding rate, n	0/25 (0)	1/103 (1.0)	67/1,335 (5.0)
Perforation rate, n	1/25 (4.0)	3/103 (2.9)	35/1,335 (2.6)

Values in parentheses are percentages. * $p < 0.05$, compared with NJC.

¹ En bloc resection with lateral and vertical margins free of tumor. ² Complete resection meeting the curability criteria.

Table 2. Submucosal invasion rates of tumors according to tumor size

Tumor size	BA (n = 25)	JC (n = 103)	NJC (n = 1,335)
1–10 mm	1/10 (10)	3/20 (18)	20/373 (5.4)
11–20 mm	3/8 (37.5)*	9/40 (22.5)	58/465 (12.5)
21–30 mm	3/4 (75.0)*	8/26 (30.8)	52/269 (19.3)
31–40 mm	1/2 (50.0)	7/8 (87.5)*	20/106 (18.9)
41+ mm	0/1 (0)	4/9 (44.4)	28/122 (23.0)
Total	8/25 (32.0)*	31/103 (30.1)*	178/1,335 (13.3)

Values in parentheses are percentages. * $p < 0.05$, submucosal invasion rates compared with NJC.

Results

The clinicopathological characteristics of the lesions and short-term outcomes are shown in table 1. Mean age of patients with BA, JC and NJC were 64.4, 68.8 and 69.3 years, and male to female ratios were 22:3, 16:87 and 319:1021, respectively. No significant difference was observed in mean tumor size (20.2, 21.8 and 20.5 mm, respectively), but rates of complete local and curative resection were significantly lower for BA than for JC and NJC (64.0 vs. 96.1 and 95.8%; and 48.0 vs. 80.6 and 85.7%, respectively).

All cases of incomplete resection for BA were due to positive lateral margins caused by proximal sub-epithelial progression of the tumor (fig. 1). Postoperative bleeding (0, 1.0 and 5.0%) and perforation rates (4.0 vs. 2.9 and 2.6%) for BA, JC and NJC were similar.

Clinicopathologically, total submucosal invasion rates were higher in BA and JC than in NJC (32.0 and 30.1 vs. 13.6%). Furthermore, as shown in table 2, the submucosal invasion rate according to tumor size was also higher in BA and JC than NJC at each size, respectively. As indicated in table 3, positive rates of lymph duct and venous invasion were higher in BA than in JC and NJC (16.0 vs. 3.9 and 3.6%; and 12.0 vs. 8.7 and 3.6%, respectively). Further, positive rates of lymph duct invasion and/or venous invasion were remarkably higher with BA and JC than in NJC (24.0 vs. 9.7 vs. 4.8%).

In terms of patient-based long-term analysis during a median follow-up of 34 months (range 2–96), no differences in local recurrence rates (0.0, 0.0 and 0.3%) were observed between the different types of cancer, and the 5-year disease-specific survival rate for patients determined to have been curatively resected was 100% in all

Table 3. Comparison of rates of lymphovascular invasion with early BA and early esophagogastric junctional cancer comparison versus early NJC

	BA (n = 25)	JC (n = 103)	NJC (n = 1,335)
Ly positive, n	4/25 (16.0)*	4/103 (3.9)	48/1,335 (3.6)
V positive, n	3/25 (12.0)*	9/103 (8.7)*	48/1,335 (3.6)
Ly and/or V positive, n	6/25 (24.0)*	10/103 (9.7)*	64/1,335 (4.8)

Values in parentheses are percentages. * $p < 0.05$, positive lymphovascular invasion compared with NJC. Ly = Lymphatic invasion; V = vascular invasion.

patients. Three patients of BA, 3 of JC and 45 of NJC died during the follow-up period. Of them, 1 patient with BA and 1 with NJC who underwent non-curative resection died due to distant metastasis after additional surgery or chemotherapy. Another 49 patients died due to diseases other than gastric cancer. Overall, the 5-year survival rates of BA, JC and NJC were 74.3, 94.3 and 93.6%, respectively, which were not significantly different ($p = 0.078$).

Discussion

Although ESD requires skillful endoscopic procedures, it not only averts surgical risk, but also improves patient quality of life by preserving the gastrointestinal tract, unlike surgical resection of EGJ cancers, which involves total or proximal gastrectomy. Successful conduct of ESD requires understanding of the merits and demerits of this technique.

While discussing the short-term outcomes of ESD, two previous studies [13, 14] reported the technical feasibility of ESD for EGJ cancers, although they had relatively few case samples and analyzed BA and JC together, without comparisons. In this study, we divided a large number of cancers treated by ESD into three groups and analyzed the outcomes in detail. As shown in table 1, the short-term outcomes after ESD were equally favorable for both JC and NJC. These data strongly suggest that ESD is technically valid and provides safe resectability for EGJ cancers. The complete and curative resection rates of BA, on the other hand, were significantly lower than those of the other two groups. Our data revealed that the cause of incomplete resection for BA in all cases was positive lateral margins caused by sub-epithelial progression of the tumor proxi-

mally, which was hard to recognize before treatment. Considering the high rate of sub-epithelial invasion, accurately diagnosing the proximal tumor margin preoperatively is an issue that must be addressed in the future.

A few studies [15, 16], each describing a small series, have reported the histopathological malignancy of EGJ cancers using surgically resected specimens. Regarding the pathogenesis of cancer metastasis, as reported by Fidler [17], the initial step of the metastatic process is regional lymphovascular invasion. In this study, based on evaluation of perfect and more detailed specimen samples obtained by ESD, we analyzed lymphovascular and submucosal invasion as risk factors for lymph node metastasis. As indicated in tables 2 and 3, BA and JC had a high submucosal invasion rate irrespective of size compared with NJC. Furthermore, positive rates of lymph duct invasion and/or venous invasion were remarkably higher in BA and JC. Our data demonstrates that esophagogastric JCs have high malignant potential, indicating the need for caution during ESD. However, since these factors are impossible to accurately diagnose preoperatively, detailed pathological investigation is required of the specimen obtained by definitive en bloc resection via ESD.

In our study, the long-term prognosis of patients declared to have undergone curative resection was favorable. Hirasawa et al. [18] analyzed the long-term prognosis of 57 JC patients and 1 BA patient together and reported no local or distant recurrences. In this study, with detailed analysis of a much larger study population, we demonstrated a favorable prognosis of both BA and JC compared with NJC, which is similar to previous findings. In addition, our study suggested the utility of the criteria for curative resection by endoscopic therapy for BA, i.e. an invasion depth of T1a-DMM with negative lymphovascular invasion and negative resection margins, although with the limitation of a small sample series. In conclusion, the present study confirmed the technical and theoretical validity of ESD for EGJ cancers as a diagnostic treatment. We also revealed the high rates of submucosal and lymphovascular invasive malignant potential of EGJ cancers, which require much attention.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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