Gastrointestinal Tumors

Research Article

Gastrointest Tumors 2022;9:59–68
DOI: 10.1159/000525586

Received: December 22, 2021
Accepted: June 13, 2022
Published online: June 20, 2022

Usefulness of the Japan Esophageal Society Classification of Barrett's Esophagus for Diagnosing the Lateral Extent of Superficial Short-Segment Barrett's Esophageal Cancer

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Keywords
Barrett's esophagus · Esophageal cancer · Endoscopic submucosal dissection · Magnifying endoscopy

Abstract
Introduction: The Japanese guidelines for endoscopic submucosal dissection (ESD) of Barrett's esophageal adenocarcinoma (BEA) recommend image-enhanced magnifying endoscopic examination for diagnosing the lateral extent of superficial esophageal adenocarcinoma. The Japan Esophageal Society Barrett's Esophagus (JES-BE) classification is proposed recently and is useful in terms of diagnostic accuracy. In this study, we retrospectively examined the usefulness of the JES-BE classification for differential diagnosis and determination of the extent of BEA originating in short-segment Barrett's esophagus. ***Methods:*** The study reviewed 51 lesions which underwent ESD for BEA. The circumference of the esophagogastric junction was divided into four parts, and the lesions were divided into those in the right anterior portion (RA group; $n = 33$) and those in other portions (non-RA group; $n = 18$). Clinicopathological characteristics and clinical outcomes were compared between the two groups. ***Results:*** JES-BE classification findings as "dysplasia" were seen in 48 out of 51 (94.1%) BEA lesions retrospectively. There was no significant difference in histological type, tumor depth, lymphovascular invasion, or the proportion of tumors with a positive or unknown horizontal or vertical margin status between the groups. The proportion of tumors with type 0-I morphology was significantly higher in the RA group ($p = 0.023$). The tumor size was significantly greater in the RA group ($p = 0.034$). According to the JES-BE classification, 31 lesions (93.9%) in the RA group and 17 lesions (94.4%) in the non-RA group were diagnosed as dysplasia. There was also no significant difference in the rate of consistency between the endoscopic and histopathological findings on the lateral extent of the lesion (90.9% vs. 83.3%; $p = 0.612$). ***Discussion/Conclusions:*** The JES-BE classification may be useful for determining the extent of BEA.

Introduction

Barrett's esophagus is widely considered to be a precursor of esophageal adenocarcinoma and has an increasing incidence in Japan and Western countries as a result of dietary changes and the increased incidence of reflux

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disease [1–5]. Advances in endoscopy have improved the outcome of resection for early-stage Barrett's esophageal adenocarcinoma (BEA) [6–12]. We have previously reported that the rates of submucosal and lymphovascular invasion are higher in patients with superficial BEA than in those with nonjunctional cancers [13]. It is important to detect superficial BEA as early as possible, given that the risk of lymph node metastases in superficial BEA is in the range of 1–2% [14]. Recent advances in endoscopic instruments and technology allow for early detection of BEA.

However, severe inflammation of the background mucosa of Barrett's esophagus often makes endoscopic diagnosis difficult, resulting in unnecessary widening of the range of excision during endoscopic submucosal dissection (ESD) or a positive horizontal margin. Several studies have demonstrated the utility of narrow-band imaging (NBI) for diagnosis of lesions in Barrett's esophagus [15–22].

The recently proposed Japan Esophageal Society Barrett's Esophagus (JES-BE) classification is useful in terms of diagnostic accuracy and convenience [23–25]. The Japanese guidelines for ESD of esophageal cancer recommend image-enhanced magnifying endoscopic examination for diagnosing the lateral extent of superficial esophageal adenocarcinoma before endoscopic resection [26]. However, there is limited information on the value of the JES-BE classification when used for this purpose. Therefore, in this study, we retrospectively examined the sensitivity of the JES-BE classification for differential diagnosis and its usefulness in determination of the extent of BEA originating in short-segment Barrett's esophagus (SSBE).

We have previously reported that BEA originating in SSBE tends to arise on the right or anterior-side wall of the esophagogastric junction (EGJ), and its morphology depends on location [27]. An additional study was conducted to see if there was a difference in the diagnostic accuracy depending on the location, the size of the lesion, and the morphological type of the lesion. The circumference of the EGJ was divided into four parts (Fig. 1), and the patients were divided into those with lesions in the right anterior portion (RA group) and those with lesions in other portions (non-RA group). Clinicopathological characteristics and clinical outcomes were compared between the two groups.

Materials and Methods

Patients and Study Design

Patients who underwent ESD for BEA at the Toranomon Hospital, Tokyo, Japan, between January 1, 2008, and February 1, 2021, were retrospectively reviewed. Lesions that had not undergone magnifying endoscopic scrutiny in advance were excluded. Lesions arising from long-segment Barrett's esophagus (LSBE) were also excluded because of the difficulty involved in comparing the magnifying endoscopic boundaries and pathological lateral extent of the lesion. LSBE was defined as Barrett's mucosa circumferen-

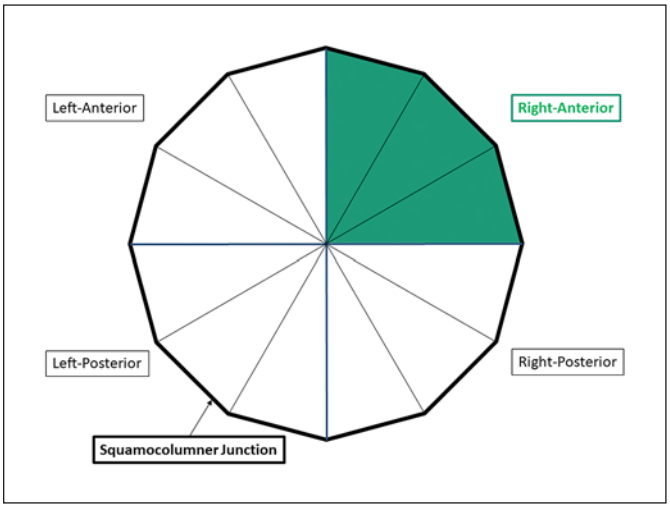

Fig. 1. Circumference of the EGJ was divided into four parts. The patients were divided into those with lesions in the right anterior portion (RA group) and those with lesions in other portions (non-RA group).

Fig. 2. A case in which endoscopic diagnosis of lateral extent and pathological diagnosis are consistent. **a** Red straight bars show the pathological extent of the cancer in the specimen with formalin fixation. Yellow circle shows the extent of the cancer in the submerged specimen (**b**) and magnified narrow-banding images in vivo (**c**, **d**). The depressed lesion showed a visible mucosal pattern that was diagnosed with "irregular non-pit" and a vascular pattern that was diagnosed with "irregular net." The lesion was diagnosed as "dysplasia." On the other hand, the surroundings had the appearance of "regular non-pit" and "regular non-net." The extent of the lesion represented by the red straight bars coincided with the yellow circle. **e**, **f** Histopathological images of the resected specimen. The histological section shows well-differentiated tubular adenocarcinoma in the lamina propria; 0–IIc, 10 × 5 mm, LPM, tub1, ly0, v0, pHM0, pVM0. Hematoxylin and eosin stain; ×100 (**e**), and ×400 of intramucosal carcinoma (**f**). Immunohistochemical analysis of the specimen using immunoperoxidase staining for p53 (**g**), and Ki-67 (**h**). The high expression of both p53 and Ki-67 was seen in the tumor.

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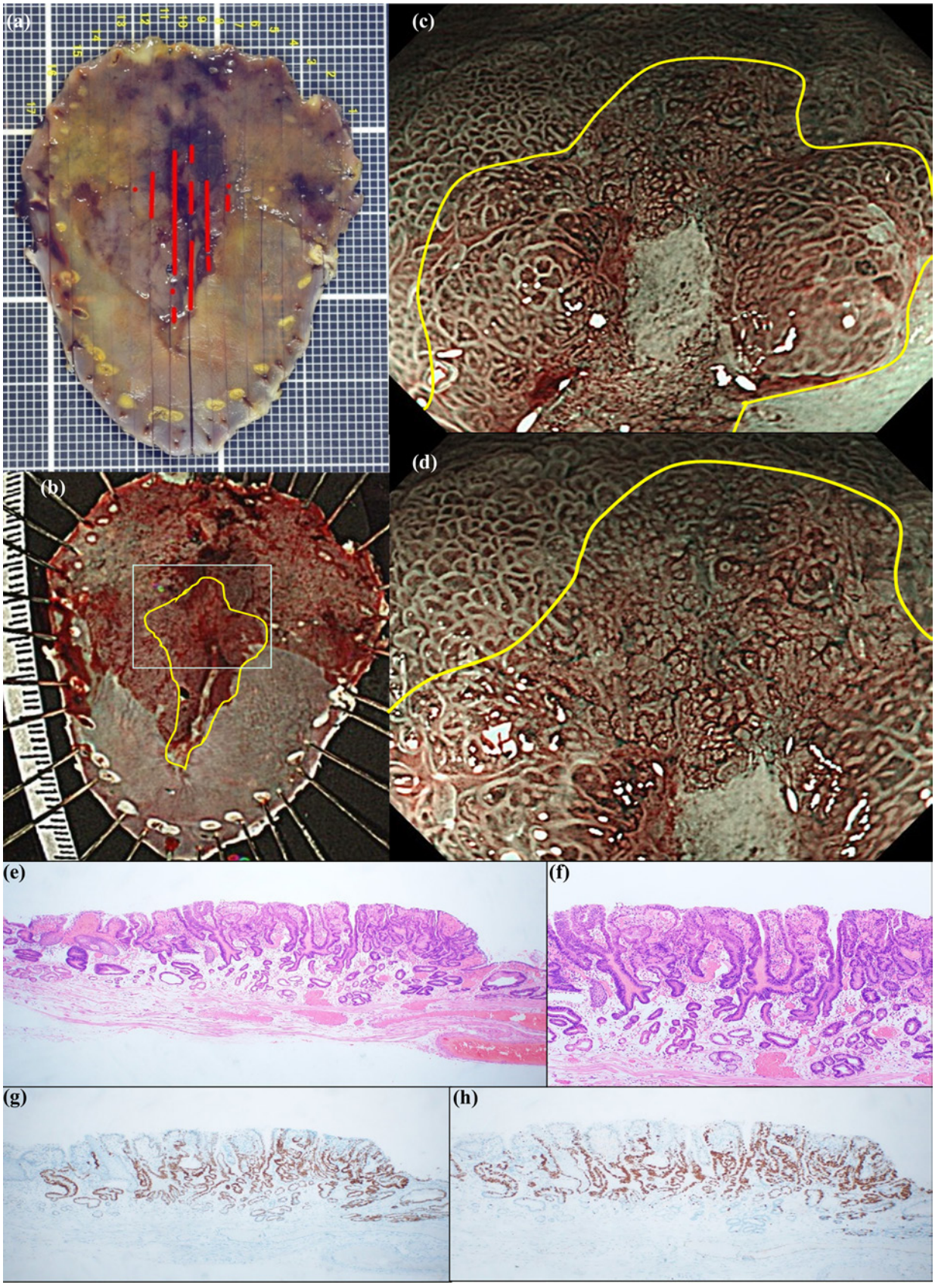

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tially extending for ≥3 cm. Clinicopathological characteristics and clinical outcomes were evaluated.

The primary outcome was the consistency between the magnifying endoscopic and histopathological findings for lateral extent of disease. Secondary outcomes were clinicopathological characteristics and curative and complete resection rates.

The study was approved by the Institutional Review Board of the Toranomon Hospital and performed in accordance with the 1964 Declaration of Helsinki and its later revisions. All patients provided written informed consent to undergo the proposed procedure. Written informed consent for inclusion in the study was not required due to the retrospective observational nature of the research. However, patients were given the opportunity to opt out via the hospital's website.

Indications

The indications for treatment of the lesion were determined based on the preoperative findings on endoscopy, endoscopic ultrasound, and biopsy. Indications for ESD were based on the Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus [28]. Intramucosal BEA was considered an indication for ESD, and a lesion that invaded the superficial submucosa was considered to be a relative indication for endoscopic treatment. If the extent of the lesion was unclear under endoscopic scrutiny before ESD, biopsies were performed on the normal mucosa at approximately 5–10 mm from the tumor margin. Computed tomography was performed to exclude any regional lymph node metastasis or distant metastasis in patients diagnosed to have undifferentiated carcinoma on biopsy or when invasion into the submucosal layer was predicted.

ESD Procedure

The ESD procedure was performed using a Dual Knife (KD650Q; Olympus Medical Systems Corp., Tokyo, Japan). A two-channel scope equipped with multi-bending and water jet functions (GIF-2TQ260M; Olympus Medical Systems Corp.) or a single-channel endoscope (GIF-Q260J; GIF-H290T; Olympus Medical Systems Corp.) was used. A VIO 300D (Erbe Elektromedizin, Tübingen, Germany) system was used as the electrosurgical unit.

Helicobacter pylori *Infection*

Diagnosis of *H. pylori* infection was based on the histologic finding, *H. pylori* antibody (E-plate test; Eiken, Tokyo, Japan), fecal *H. pylori* antigen (Meridian Bioscience, Inc., Cincinnati, OH, USA), or a 13C urea breath test (Otsuka Pharmaceutical Co., Ltd., Tokushima, Japan). Esophageal cancer with current *H. pylori* infection was defined by a positive *H. pylori* test and gastric atrophy on endoscopic or pathological examination, GC with past *H. pylori* infection by a negative *H. pylori* test and gastric atrophy, and *H. pylori*-negative GC by a negative *H. pylori* test without gastric atrophy or a history of *H. pylori* eradication.

Endoscopic Findings

The location, size, and macroscopic features of each lesion were determined using white light endoscopy. Diagnoses were made retrospectively by 3 board-certified fellows of the Japan Gastroenterological Endoscopy Society. The severity of background Barrett's esophagus was evaluated using the Prague C & M Criteria [29], and the severity of reflux disease was graded according to the Los Angeles classification [30]. NBI magnifying endoscopic diagnoses were made retrospectively by the same 3 board-certified fellows of the Japan Gastroenterological Endoscopy Society according to the JES-BE classification, which is based on mucosal pattern and vascular pattern [23]. The mucosal pattern was evaluated at a low magnification and the vascular pattern at a high magnification and was initially classified as "visible" or "invisible." The visible mucosal and vascular patterns were subclassified as "pit" or "non-pit" and as "net" or "non-net," respectively. Each pattern was then classified as "regular" or "irregular," and a comprehensive diagnosis of either "dysplasia" or "non-dysplasia" was made accordingly. The lateral extent of the lesion was determined retrospectively on endoscopy by tracing the boundary of the lesion based on high-definition magnifying NBI scans (Fig. 2, 3). The JES-BE classification was used to determine the boundary between dysplasia and non-dysplasia. The boundary was basically traced on only the columnar epithelial side because tumor invasion under the area of squamous epithelium could not be evaluated by endoscopy. More than 10 images were obtained in each case during endoscopic scrutiny before ESD. In order to compare the endoscopic extent with pathological one, observation during preoperative endoscopic scrutiny was first compared with observation of submerged specimens after ESD to make the endoscopic extent diagnoses. The 3 board-certified fellows of the Japan Gastroenterological Endoscopy Society independently made an extent diagnosis by describing a demarcation line on printed preoperative endoscopic images. The endoscopic extent was decided by majority vote for cases which the 3 board-certified fellows disagreed on. Then the histological mapping of the lesion was compared with observation of submerged specimens, and the consistency between the pathological diagnoses and the endoscopic diagnoses was determined.

A gastrointestinal videoscope (GIF H260Z; Olympus Medical Systems Corp.) was used to evaluate the NBI-magnified endoscopic findings. The endoscopic ultrasonographic images were obtained using a miniature probe (UM2R or UM3R; Olympus Medical Systems Corp.).

Fig. 3. A case in which endoscopic diagnosis of lateral extent and histopathological diagnosis are inconsistent. **a** Red line shows the pathological extent of the cancer in the specimen with formalin fixation. Yellow line shows the extent of the cancer in the submerged specimen (**b**) and magnified narrow-banding images in vivo (**c**, **d**). The flat lesion showed a visible mucosal pattern that was diagnosed with "regular non-pit" and a vascular pattern that was diagnosed with "regular non-net." The lesion was diagnosed as "non-dysplasia" without the demarcation line. It was impossible to determine the extent of the lesion with magnified narrow-banding images. Histopathological images of the resected specimen. The histological section shows very well-differentiated tubular adenocarcinoma; 0–IIb, 4 × 2 mm, SMM, tub1, ly0, v0, pHM0, pVM0. **e** Hematoxylin and eosin stain; ×100 of intramucosal carcinoma. Immunohistochemical analysis of the specimen using immunoperoxidase staining for p53 (**f**), and Ki-67 (**g**). The high expression of both p53 and Ki-67 was seen in the narrow range of the Barrett's esophagus.

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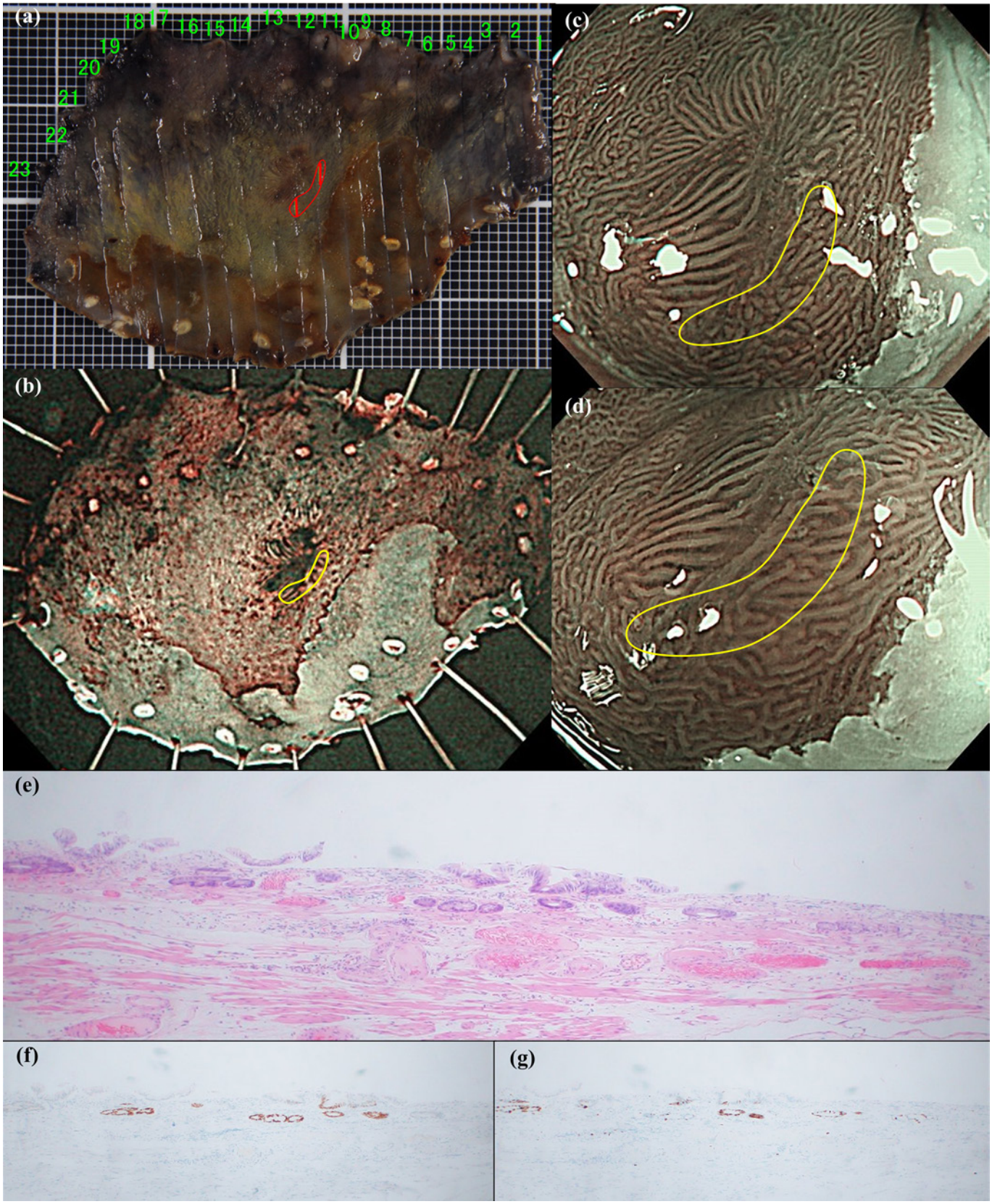

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Table 1. Patients' characteristics

	All patients ($N = 50$)	RA ($N = 33$)	Non-RA ($N = 17$)	RA versus non-RA, p value
Age, years, median (IQR)	61 (57–73)	61 (56–74)	61 (60–68)	0.771
Gender, male:female, %	45:0, 90.0	30:3, 90.9	15:2, 88.2	1.000
BMI, kg/m^2, median (IQR)	22.9 (20.3–24.3)	22.9 (21–24.4)	23 (20.2–23.9)	0.674
Brinkman index, median (IQR)	300 (0–735)	200 (0–740)	480 (40–720)	0.307
Alcohol consumption, g/day, median (IQR)	35.5 (15–54)	30 (10–54)	40.5 (17.5–54)	0.502
H. pylori infection status, *n* (%)				
Negative	36 (72.0)	23 (69.7)	13 (76.5)	0.548
Current	7 (14.0)	5 (15.2)	2 (11.8)	
Past	7 (14.0)	5 (15.2)	2 (11.8)	
Observation period, months, median (IQR)	77.5 (42.5–100.75)	82 (44–113)	65 (37–94)	0.499

IQR, interquartile range; BMI, body mass index; RA, right anterior; *H. pylori*, *Helicobacter pylori*.

Histopathological Assessment of Resected Specimens

All ESD specimens were fixed in 10% formalin, sectioned serially at 2-mm intervals, stained with hematoxylin and eosin, and assessed pathologically based on the Japanese Classification of Esophageal Cancer [31]. Each slice was evaluated for histological type, tumor size, depth of invasion, resection margins, and lymphovascular invasion by specialist pathologists from the Japanese Society of Pathology. Histological types were classified into differentiated type, undifferentiated type, and mixed type.

Dysplasia was defined as the atypical epithelium with irregularity of nuclei such as their placement, elongation, and hyperchromasia, all of which continued to be present in the surface epithelial cells. Evaluation of p53 and Ki-67 by immunohistochemical staining was used as an aid for diagnosis. Immunohistochemical staining using D2-40 and CD31 was performed to confirm the lymphovascular invasion.

Complete (R0) resection was defined as resection in one piece with margins free of tumor but did not include findings for depth of invasion, lymphovascular infiltration, or type of adenocarcinoma. Curative resection was defined as a resected specimen meeting the requirements for R0 resection, without lymphovascular infiltration, and meeting one of the following criteria: (i) mucosal cancer without a poorly differentiated component; (ii) cancer with a submucosal invasion depth ≤500 μm without a poorly differentiated component; and ≤30 mm in diameter. A procedure that did not satisfy the criteria for curative resection was considered noncurative. ESD for synchronous Barrett's esophageal cancer in the same session was classified as noncurative if one of the lesions was diagnosed as noncurative.

Statistical Analysis

Data are presented as the median and interquartile range and were compared using the unpaired t test, χ^2 test, Fisher's exact test, or the Mann-Whitney U test as appropriate. All statistical analyses were performed using SPSS version 25 (SPSS IBM statistics; IBM Corp., Armonk, NY, USA). A p value <0.05 was considered statistically significant.

Results

Clinical Characteristics

Fifty-nine consecutive patients with 66 lesions underwent ESD for BEA during the study period. After exclusion of 7 patients with 13 lesions on a background of LSBE and 2 in whom NBI magnifying endoscopy was not performed, 50 patients with 51 lesions were eligible for enrollment.

Table 1 shows the patient demographics and clinical characteristics. Thirty-three (64.7%) of 51 superficial BEAs were located on the RA-side wall (RA group; 33 patients) and 18 (35.3%) in other areas (non-RA group; 17 patients). Two lesions were resected during the same procedure in 1 patient in the non-RA group.

There was no significant difference in age, sex, body mass index, Brinkman index, or *H. pylori* infection status between the two groups. There was also no significant difference in the median observation period between the RA group and the non-RA group (82 months vs. 65 months).

Endoscopic and Histopathological Findings

The endoscopic and histopathological findings are summarized in Table 2. JES-BE classification findings were seen in 48 out of 51 (94.1%) BEA lesions retrospectively. On the other hand, JES-BE classification findings were not observed in 3 lesions (5.9%) due to the mild irregularity of the mucosal and vascular pattern. Endoscopic and pathological extent diagnoses were consistent with 45 lesions (88.2%). The tumor invasion under the area of squamous epithelium was observed on the oral side of 13 lesions (25.5%), of which 1 had positive oral margin.

Table 2. Endoscopic findings and histopathological results

	All lesions (n = 51)	RA (n = 33)	Non-RA (n = 18)	RA versus non-RA, p value
Prague C and M Criteria				
C, median (IQR)	0.5 (0–1)	1 (0–1)	0 (0–1)	0.150
M, median (IQR)	1 (1–2)	1 (1–2)	1 (1–2)	0.711
Hiatal hernia, *n* (%)	40 (78.4)	28 (84.8)	12 (66.7)	0.164
Reflex diseases, *n* (%)				
Grade N/M/A	22/22/7	17/12/4	5/10/3	0.260
Morphological type, *n* (%)				
0–I	9 (17.6)	9 (27.3)	0 (0)	0.023*
0–IIa	15 (29.4)	8 (24.2)	7 (38.9)	
0–IIb	4 (7.8)	4 (12.1)	0 (0)	
0–IIc	23 (45.1)	12 (36.4)	11 (61.1)	
0–I versus 0–IIa				0.022*
0–I versus 0–IIc				0.013*
JES-BE classification, *n* (%)				
Dysplasia	48 (94.1)	31 (93.9)	17 (94.4)	1.000
Non-dysplasia	3 (5.9)	2 (6.1)	1 (5.6)	
Consistency between endoscopic and pathological extent, *n* (%)	45 (88.2)	30 (90.9)	15 (83.3)	0.652
Tumor size, mm, median (IQR)	15 (10–20.5)	16 (11–21)	10.5 (8.25–16.75)	0.030*
Histological type, *n* (%)				
Differentiated	40 (78.4)	25 (75.8)	15 (83.3)	0.726
Undifferentiated	0 (0)	0 (0)	0 (0)	
Mix	11 (21.6)	8 (24.2)	3 (16.7)	
Depth of invasion, *n* (%)				
LPM-SMM	26 (51.0)	14 (42.4)	12 (66.7)	0.252
DMM-SM1	16 (31.4)	12 (36.4)	4 (22.2)	
SM2	9 (17.6)	7 (21.2)	2 (11.1)	
Lymphovascular invasion, *n* (%)	8 (15.7)	6 (18.2)	2 (11.1)	0.696
Lymphatic invasion, *n* (%)	7 (13.7)	5 (15.2)	2 (11.1)	1.000
Vascular invasion, *n* (%)	4 (7.8)	3 (9.1)	1 (5.6)	1.000
Margin, *n* (%)				
Horizontal margin positive or unknown	1 (2.0)	1 (3.0)	0 (0)	1.000
Vertical margin positive or unknown	3 (5.9)	2 (6.1)	1 (5.6)	1.000
Complete resection, *n* (%)	47 (92.2)	30 (90.9)	17 (94.4)	1.000
Curative resection, *n* (%)	20 (68.6)	20 (60.6)	15 (83.3)	0.122

IQR, interquartile range; JES-BE classification, Japan Esophageal Society of Barrett's Esophagus classification; RA, right anterior. * $p < 0.05$.

No significant difference was noted between the groups in the severity of Barrett's esophagus or reflux disease or in the frequency of hiatal hernia. The proportion of tumors with type 0-I morphology was significantly higher in the RA group.

Examination of the lesions revealed no significant difference in histological type, tumor depth, or lymphovascular invasion between the two groups. Two tumors in the non-RA group had invaded the muscular layer. There was no significant difference between the groups in the proportion of tumors with a positive or unknown horizontal or vertical margin status. However, the tumor size was significantly greater in the RA group (p = 0.034).

The curative and complete resection rates were not significantly different between the groups. Thirteen of 33 patients in the RA group and 3 of 17 in the non-RA group did not meet the curative criteria. According to the JES-BE classification, 31 (93.9%) of 33 lesions in the RA group and 17 (94.4%) of 18 in the non-RA group were diagnosed as "dysplasia"; the difference was not statistically significant (p = 1.000); there was also no significant difference

between the groups in the rate of consistency between the endoscopic and histopathological findings on the lateral extent of the lesion (90.9% vs. 83.3%; $p = 0.612$).

Discussion/Conclusion

According to reports on the treatment outcomes of ESD for superficial BEA or high-grade dysplasia, the R0 resection rate was 74.5% for 524 lesions, and the horizontal margin was positive in 54 lesions (40.3%) with R1 resection [11, 32]. This suggests that endoscopic diagnosis of the extent of the BEA is difficult. Low-grade dysplasia may spread widely around areas of BEA and high-grade dysplasia, making it difficult to assess the extent of a lesion, particularly in LSBE. It has also been reported that when superficial adenocarcinoma of the esophagus extends to the squamous epithelium on the oral side, about half of the lesions invade the subepithelial plane, creating further diagnostic difficulties [33]. To our knowledge, this is the first report on the degree of consistency between the endoscopic diagnosis of the lateral extent of the lesion based on the JES-BE classification and the pathological diagnosis.

In SSBE, BEA tends to arise on the RA-side wall of the EGJ, and its morphology depends on the location [27, 34]. Therefore, to determine the accuracy of JES-BE classification based on magnified NBI, these BEAs should be evaluated according to their location. In the present study, lesions in the RA group were significantly larger than those in the non-RA group and had more proportion of type 0-I morphology. These findings suggest that a lesion that arises in the RA-side wall of the EGJ may be easier to recognize by macroscopic observation with white light endoscopy. However, consistent with previous reports [23, 25], we found that the JES-BE classification was highly accurate for the differential diagnosis regardless of location. Moreover, the consistency between endoscopic diagnosis and histopathological results for lateral extent of the lesion was also highly accurate, with no significant difference between the two groups. These findings suggest that the JES-BE classification is useful for preoperative diagnosis of the lateral extent of BEA originating in SSBE regardless of type of morphology or size of the lesion.

In the current study, the consistency between the endoscopic and histopathological findings on the lateral extent of the lesion was high, but JES-BE classification findings were not observed in 3 lesions (5.9%). These 3 lesions had mild histopathological atypia and were diagnosed as BEA based on the p53 and Ki-67 immunohistochemical staining. The mild histopathological atypia might lead to difficulty in distinguishing between "dysplasia" and "non-dysplasia" by magnifying endoscopy and discrepancy between the endoscopic and histopathological findings.

Accurate preoperative diagnosis is thought to improve the curative resection rate. Magnified observation combined with the acetic acid method and NBI are reported to be useful for diagnosis [23, 25, 35–39]. In this study, the horizontal margin was positive in 1 of the 6 cases in which diagnosis of the lateral extent of the lesion was difficult by magnified NBI observation. Given that there are some cases in which diagnosis of lateral extent is difficult by magnified NBI observation alone, the diagnosis should be made using the acetic acid and/or step biopsy method as necessary.

This study has some limitations. First, it had a retrospective design and included a small sample size from a single center. Second, LSBE was excluded because of the difficulty in comparing the histopathological diagnosis with the endoscopic diagnosis of lateral extent. Third, in some cases, it was difficult to determine the exact boundaries of the lesion because the diagnosis was made retrospectively with reference only to medical records. Therefore, the boundary was determined only in the area for which it could be evaluated. In conclusion, the JES-BE classification may be useful for determining the extent of esophageal cancer in SSBE regardless of the location, size, and morphological type of lesion.

Statement of Ethics

This study protocol was reviewed and approved by Institutional Review Board of the Toranomon Hospital, approval number (2267). Written informed consent for inclusion in the study was not required due to the retrospective observational nature of the research. However, patients were given the opportunity to opt out via the hospital's website. The Institutional Review Board of the Toranomon Hospital made this decision.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study has not received any funding.

Author Contributions

Conceptualization, methodology, writing – original draft, and writing – review and editing: Yugo Suzuki. Investigation and approval of final manuscript: Yugo Suzuki, Takayuki Okamura, Akira Matsui, Junnosuke Hayasaka, Kosuke Nomura, Daisuke Kikuchi, and Shu Hoteya.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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