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ORIGINAL ARTICLE

Pre- and post-ESD discrepancies in clinicopathologic criteria in early gastric cancer: the NECA–Korea ESD for Early Gastric Cancer Prospective Study (N-Keep)

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Abstract

Background Discrepancies in the clinicopathologic parameters pre- and post-endoscopic submucosal dissection (ESD) sometimes necessitate additional surgical resection. The aim of this study was to assess such discrepancies in clinicopathologic parameters before and after ESD in the context of reducing the risk of failure of curative ESD.

Methods Data on 712 early gastric cancer patients were prospectively collected from 12 university hospitals nationwide. The inclusion criteria were differentiated carcinoma <3 cm in size, no ulceration, submucosal invasion <500 μm, and no metastasis. Clinicopathologic factors were compared retrospectively.

Results The discrepancy rate was 20.1 % (148/737) and the most common cause of discrepancy was tumor size (64 cases, 8.7 %). Ulceration, undifferentiated histology, and SM2 invasion were found in 34 (4.6 %), 18 (2.4 %), and 51 cases (6.9 %), respectively. Lymphovascular invasion (LVI) was observed in 34 cases (4.6 %). Cases with lesions exceeding 3 cm in size showed more frequent submucosal invasion, an elevated gross morphology, and upper and

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middle locations ($p < 0.05$). In the cases with ulceration, depth of invasion (DOI) was deeper than in the cases without ulceration ($p = 0.005$). Differentiation was correlated with DOI and LVI ($p = 0.021$ and 0.007). DOI was correlated with tumor size, ulceration, differentiation, LVI, gross type, and location. There were statistically significant differences between mucosal cancer cases and submucosal cancer cases in tumor size, differentiation, ulceration, LVI, and location.

Conclusions The overall discrepancy rate was 20.1 %. To reduce this rate, it is necessary to evaluate the DOI very cautiously, because it is correlated with other parameters. In particular, careful checking for SM-invasive cancer is required due to the high incidence of LVI irrespective of the depth of submucosal invasion.

Keywords Endoscopic submucosal dissection · Early gastric cancer · Indication · Preoperative diagnosis · Discrepancy

Introduction

Endoscopic mucosal resection/endoscopic submucosal dissection (EMR/ESD) is accepted as a curative treatment modality for early gastric cancer (EGC) to improve the quality of life of patients [1]. However, the application of ESD should be limited—it should be assigned based on strict inclusion criteria—because of the risk of metastasis. There is still debate regarding the indications for ESD. Current definitive indications for endoscopic resection include differentiated cancer limited to the mucosa, a polypoid lesion <2 cm in size, and an excavated type <1 cm in size without concurrent ulceration [2]. Due to the advances made in ESD, Gotoda et al. [3] expanded the criteria for ESD to include differentiated mucosal cancers without ulcers regardless of lesion size, differentiated mucosal cancers with ulcers ≤3 cm in size, undifferentiated mucosal cancers ≤2 cm in size, and differentiated submucosal cancers ≤3 cm in size and ≤500 μm (SM1) in depth without lymphatic or vascular invasion. To fulfill these criteria, close examinations must be performed prior to the procedures, such as measurements of invasion depth and tumor size as well as evaluations of differentiation and ulceration via endoscopy, ultrasonography, and endoscopic biopsy. Even after meticulous inspection, discrepancies between pre- and post-ESD clinicopathologic parameters can occur, which can necessitate additional curative surgeries in cases presenting deviations from the appropriate parameter ranges. In the work reported in the present paper, the frequency and causes of such discrepancies between pre- and post-ESD parameters were examined with a view to reducing the risk of failure of curative ESD.

Patients and methods

Collection of ESD specimens

The study was conducted with approval from the Institutional Review Board of The National Evidence-based Healthcare Collaborating Agency (NECA). This study involved 12 organizations across the country that have actively implemented ESD (NECA–Korea ESD for Early Gastric Cancer Prospective Study: the N-Keep Study). In each organization, ESD was performed by experienced endoscopists.

From June 2010 to May 2011, each organization performed ESD for adenomas or for EGCs that met all of the following criteria: (1) age 20 years or older, (2) lesion ≤3 cm in length based on endoscopic findings, (3) well or moderately differentiated carcinoma based on histologic examination of endoscopic biopsy tissue, (4) absence of ulceration in the lesion, (5) depth of submucosal invasion ≤500 μm, and (6) no metastasis based on abdominal computed tomography (CT) findings prior to the procedure. The clinical characteristics of each patient, such as their age, gender, endoscopically measured tumor size, location (location 1: upper, middle, and lower; location 2: greater curvature, lesser curvature, anterior wall, and posterior wall), and gross type (I: polypoid, IIa: elevated, IIb: flat, IIc: depressed, others: mixed or unclassified), were evaluated. For ESD, narrow-band imaging and endoscopic ultrasound were routinely used. The number of biopsies was usually 8 (4 inside and 4 outside the lesion), but the number selected was ultimately left at the discretion of the endoscopist rather than being strictly regulated. The tumor invasion depth was judged by the endoscopist based on their experience. Endoscopic findings suggestive of submucosal invasion >500 μm were an irregular mucosal surface, marked marginal elevation, abrupt marginal cutting, and substantial clubbing and fusion of converging folds.

Pathological diagnosis

ESD specimens were fixed immediately on a plate using pins, placed in 10 % neutral formalin for >4 h, and then cut into 2-mm-thick slices and embedded completely in paraffin. Hematoxylin and eosin (H&E) staining was performed according to standard protocol and observed using an optical microscope. For the pathological diagnosis, a team of 16 pathologists experienced in gastrointestinal pathology was organized and met 15 times for consensus meetings. At least ten of the 16 team members attended each meeting and examined the slides using a multiview microscope; diagnoses were made via consensus. The

diagnostic criteria for carcinoma were based on invasion, per Western standards. If more than 6 of the 10 team members present at the meeting agreed with a proposed diagnosis, that diagnosis was considered final. In situations where fewer than seven members agreed on a diagnosis, a re-examination was conducted after a certain time interval and voting was then performed again. In cases in which less than seven of the members agreed on the diagnosis on at least two occasions, the diagnosis that was most popular among the members was considered the final diagnosis. In this study, a total of 737 ESD specimens collected from 712 patients were used, and the final diagnosis of carcinoma was made via the aforementioned process. Tissue type, degree of differentiation, and depth of invasion were also determined by voting and were assigned by the team members in a similar manner.

Tissue type was classified as papillary, well differentiated, moderately differentiated, poorly differentiated, or other. The papillary and tubulopapillary adenocarcinomas and the well and moderately differentiated adenocarcinomas were considered to be of "differentiated type." Poorly differentiated adenocarcinomas and signet ring cell carcinomas were considered to be of "undifferentiated type" by voting. Cases (one each) of clear-cell carcinoma, carcinoma with lymphoid stroma, and neuroendocrine carcinoma were excluded. The degree of differentiation was determined based on the extent of gland formation in the entire tumor. Specifically, the degree of differentiation was considered "well" if the extent of gland formation exceeded 95 %, "moderate" if the extent of gland formation was 50–95 %, and "poorly differentiated" if the extent of gland formation was 0–49 %. The DOI was determined by the deepest invasion of the tumor. Muscularis mucosae (MM) infiltration was based on the clear invasion of the tumor into the muscularis mucosae layer, rather than reactive proliferation. The depth of submucosal invasion was measured as the depth of tumor infiltration from directly under the MM. The depth of submucosal invasion was classified as SM1 ($\leq$500 μm) or SM2 (>500 μm). Ulceration was defined as MM exposure due to loss of gastric mucosa. Cases in which the mucosa was reproduced post ulcer and was subsequently covered with epithelial cells or granulation tissue were not considered to present ulceration—only an active ulcer was considered a pathologic ulcer. LVI was determined based on close visual examination by pathologists from each organization. D2-40 or CD34 was conducted if diagnosis proved difficult based on ordinary H&E staining. Venous invasion (VI), neural invasion (NI), and the resection margin (RM) were also judged by the pathologists in each organization. Statistical analyses included Fisher's exact test, the chi-square test, and Bland–Altman plots.

Results

A total of 737 lesions were finally categorized as carcinoma. The clinicopathologic characteristics of these lesions are summarized in Table 1. These lesions were present in 712 patients (548 men and 164 women) ranging between 27 and 87 years of age (mean age: 62.8 years). ESD was performed in cases of differentiated EGC without ulceration, lesion $\leq$3 cm in size, and submucosal invasion $\leq$500 μm, but 20.1 % (148 cases) of the carcinoma cases did not meet the inclusion criteria on the final pathological evaluation, and 18 cases had two coincidental factors that did not comply with the inclusion criteria. More specifically, 63 cases (8.5 %) had lesions >3 cm in size, 34 cases (4.6 %) had ulceration, and 18 cases (2.4 %) were of the undifferentiated type. In terms of invasion depth, there were 368 cases (49.9 %) with invasion of lamina propria (LP), 250 (33.9 %) with invasion of the MM, and 116 (15.7 %) with invasion of the submucosa (SM). Among the cases with invasion of the SM, SM1 invasion $\leq$500 μm was found in 65 cases (8.8 %) and SM2 invasion >500 μm in 51 cases (6.9 %). The DOI could not be determined in three cases (0.4 %) because there was involvement of the deep RM by the deepest focus of the tumor. Lateral and deep RM involvement was observed in three and 13 cases, respectively. LVI was observed in 31 cases (4.2 %). Results for gross type and location are also summarized in Table 1. The most common type was IIc. There were no cases of gross type III (excavated) because the cases with ulceration were excluded. The lower third and the lesser curvature were most common for locations 1 and 2.

Comparison of endoscopic and pathological tumor sizes

Endoscopic tumor size data were available in 707 cases (Tables 2, 3; Fig. 1). A comparison of the mean endoscopic and pathological tumor sizes is presented in Table 2. Figure 1 shows the associated scatter and Bland–Altman plots. The absolute difference between the average endoscopic and pathological measurements was proportional to tumor size. The mean endoscopic measurement was significantly lower than the mean pathological estimate (1.51 ± 0.66 cm vs. 1.66 ± 1.02 cm, $p < 0.001$). An absolute difference of $\leq$0.5 cm was found in 55.0 % (389/707) of cases. The Bland–Altman plot showed that 93.2 % of cases were within the 95 % limits of agreement. The tumor size had a statistically significant correlation with DOI ($p = 0.028$), gross type, and location 1, but did not have any correlation with ulcer, degree of differentiation, LVI, or location 2 ($p > 0.05$) (Table 3). In an additional χ^2 test, cases showing SM invasion, elevated gross

Table 1 Clinicopathologic characteristics of the 737 endoscopic submucosal dissection cases that were finally diagnosed as carcinoma

Clinicopathologic finding	Classification	Number of specimens (%)
Gender	Male	564 (76.5)
	Female	173 (23.5)
Age (years)	<50	59 (8.0)
	50–59	224 (30.4)
	60–69	283 (38.4)
	≥70	171 (23.2)
Size	≤3 cm	674 (91.5)
	>3 cm	63 (8.5)
Ulcer	Absent	703 (95.4)
	Present	34 (4.6)
Differentiation	Differentiated	719 (97.6)
	Undifferentiated	18 (2.4)
Depth of invasion	Mucosal cancer	
	Lamina propria	368 (49.9)
	Muscularis mucosae	250 (33.9)
	Submucosal cancer	
	Submucosal invasion ≤500 μm	65 (8.8)
	Submucosal invasion >500 μm	51 (6.9)
	Uncertain	3 (0.4)
Resection margin involvement		
Lateral	Absent	734 (99.6)
	Present	3 (0.4)
Deep	Absent	724 (98.2)
	Present	13 (1.8)
Gross type	EGC I	9 (1.2)
	EGC IIa	79 (10.7)
	EGC IIb	111 (15.1)
	EGC IIc	332 (45.1)
	Others	7 (0.9)
	No data	199 (27.0)
Location 1	Upper	85 (11.5)
	Middle	187 (25.4)
	Lower	465 (63.1)
Location 2	Anterior wall	148 (20.1)
	Lesser curvature	282 (38.3)
	Posterior wall	140 (19.0)
	Greater curvature	167 (22.7)
Lymphovascular invasion	Absent	706 (95.8)
	Present	31 (4.2)

morphology (EGC type I vs. IIb or IIc, and IIa vs. IIc), and upper or middle location were associated with tumor size >3 cm ($p < 0.05$). In particular, the proportion of the cases with lesion size >3 cm decreased with type: type I (44.4 %) > IIa (17.7 %) > IIb (9.9 %) > IIc (7.3 %). The largest pathologic tumor was 8.5 cm in size; in this case, the endoscopic tumor size was 2 cm and it was located at the greater curvature of the cardia. Pathologically, the tumor was tubular, well differentiated, and confined to the muscularis mucosae, without ulceration or LVI. Even though there was such a large discrepency between the pathological and endoscopic tumor sizes, the resection margin in this case was free of tumor.

Comparison of endoscopic and pathological ulcers

In 34 cases (4.6 %) with pathological (active) ulcers, the DOI was statistically significantly deeper than in cases

Table 2 Comparison of endoscopic and pathological tumor sizes

	Endoscopic tumor size (*E*)	Pathological tumor size (*P*)
Mean ± SD (cm)	1.51 ± 0.66	1.66 ± 1.02
Range (cm)	0.1–3.0	0.1–8.5
Number (%) of cases: $E < P$	325 (46.0 %)	
Number (%) of cases: $E = P$	81 (11.4 %)	
Number (%) of cases: $E > P$	301 (42.6 %)	
Limits of agreement (reference range for difference)	−1.74 to 2.04	
Mean difference	0.148 (CI 0.077–0.219)	

Table 3 Clinicopathologic analysis according to tumor size

Clinicopathologic factor	Pathological tumor size [number of cases (%)/relative %]		*p* value
	≤3 cm	>3 cm	
Ulcer			0.350
Absent	641 (87.0)/95.1 (641/674)	62 (8.4)/98.4 (62/63)	
Present	33 (4.5)/4.9 (33/674)	1 (0.1)/1.6 (1/63)	
Differentiation			0.194
Differentiated	657 (89.4)/97.8 (657/672)	60 (8.1)/95.2 (60/63)	
Undifferentiated	15 (2.0)/2.2 (15/672)	3 (0.4)/4.8 (3/63)	
Depth of invasion			0.028
Lamina propria	344 (46.9)/51.0 (344/674)	24 (3.3)/38.1 (24/63)	
Muscularis mucosae	229 (31.2)/34.0 (229/674)	21 (2.9)/33.3 (21/63)	
SM1	55 (7.5)/8.2 (55/674)	10 (1.4)/15.9 (10/63)	
SM2	43 (5.9)/6.4 (43/674)	8 (1.1)/12.7 (8/63)	
Uncertain	3 (0.4)/0.4 (3/674)		
Lymphovascular invasion			0.175
Absent	648 (87.9)/96.1 (648/674)	58 (7.9)/92.1 (58/63)	
Present	26 (3.5)/3.9 (26/674)	5 (0.7)/7.9 (5/63)	
Gross type			<0.001
EGC I	5 (0.9)/1.0 (5/492)	4 (0.7)/8.7 (4/46)	
EGC IIa	65 (12.1)/13.2 (65/492)	14 (2.6)/30.4 (14/46)	
EGC IIb	100 (18.6)/20.3 (100/492)	11 (2.0)/23.9 (11/46)	
EGC IIc	315 (58.6)/64.0 (315/492)	17 (3.2)/37.0 (17/46)	
Others	7 (1.3)/1.4 (7/492)	0 (0.0)/0.0 (0/46)	
Location 1			0.004[a]
Upper	72 (9.8)/10.7 (72/674)	13 (1.8)/20.6 (13/63)	
Middle	165 (22.4)/24.5 (165/674)	22 (3.0)/34.9 (22/63)	
Lower	437 (59.3)/64.8 (437/674)	28 (3.8)/44.4 (28/63)	
Location 2			0.944[a]
Anterior wall	135 (18.3)/20.0 (135/674)	13 (1.8)/20.6 (13/63)	
Lesser curvature	256 (34.7)/38.0 (256/674)	26 (3.5)/41.3 (26/63)	
Posterior wall	129 (17.5)/19.1 (129/674)	11 (1.5)/17.5 (11/63)	
Greater curvature	154 (20.9)/22.8 (154/674)	13 (1.8)/20.6 (13/63)	
Total	674 (91.5)	63 (8.5)	

[a] Chi-square test

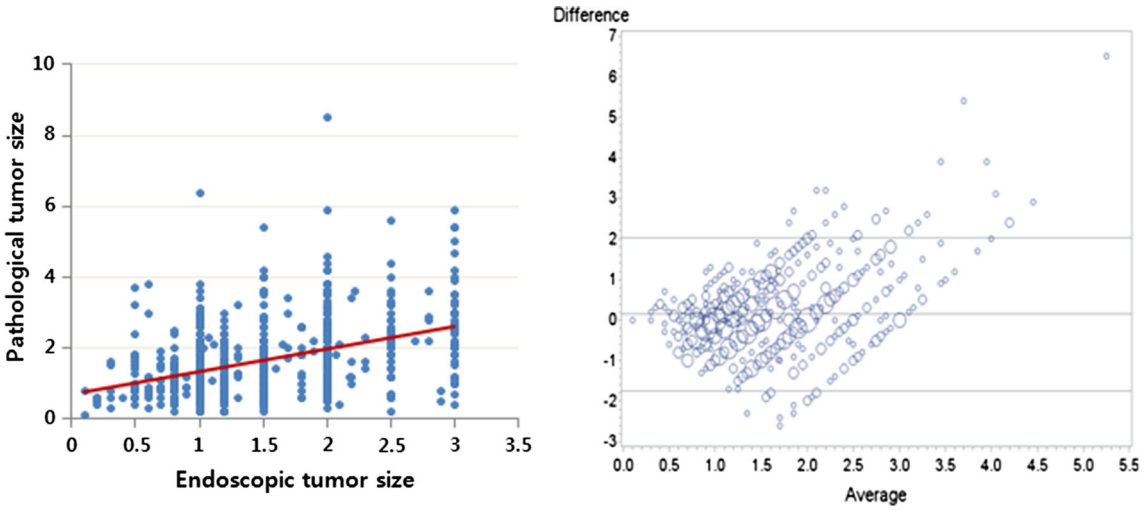

Fig. 1 Scatterplot (*left*) and Bland–Altman plot (*right*) of the endoscopic and pathological tumor sizes

without ulcers ($p = 0.005$). In cases showing SM invasion, ulceration was more frequent ($p = 0.003$). The presence or absence of a pathological ulcer was not correlated statistically with tumor size, degree of differentiation, LVI, gross type, or location ($p > 0.05$). Just one case in the group with lesions >3 cm showed ulceration. Thus, in cases with a large tumor, the endoscopist tended to be stringent when checking for ulceration.

Discrepancy in differentiation pre- and post-ESD

Among the ESD specimens, 18 cases (2.4 %) were categorized as undifferentiated, and the diagnosis for 97.6 % of those patients was consistent with the biopsy diagnosis for tumor differentiation. Unusual histologic types of cancer were excluded from the analysis. Among the undifferentiated cases, submucosal invasion was found in eight cases (44.4 %) and LVI in four cases (22.2 %). On univariate analysis, DOI and LVI were correlated with differentiation ($p = 0.021$, $p = 0.007$, respectively). In an additional χ^2 test, undifferentiated histology was associated with SM invasion (SM1 or SM2) ($p = 0.01$). However, no statistical correlation with tumor size, ulceration, gross type, or location was found.

Discrepancy in DOI pre-and post-ESD

Patients who underwent ESD were assumed to have mucosal or SM1 cancer on preoperative evaluation. However, an invasion depth of SM2 or more was found in 51 cases (6.9 %; see Table 4), representing approximately half (44.0 %) of all cases with submucosa invasion. On multivariate analysis, DOI showed correlations with tumor size, ulceration, differentiation, LVI, gross type, and locations 1 and 2. These results imply that such pathological factors are important for predicting pathological T staging. In an additional χ^2 test and Fisher's exact test, the mucosal cancer group (LP and MM invasion) showed statistically significant differences in tumor size, differentiation, ulceration, LVI, location 1, and location 2 compared to the SM cancer group (SM1 and SM2 invasion). In contrast, cancers associated with the superficial invasion group (LP, MM, and SM1 invasion) showed no significant differences in tumor size, differentiation, and ulceration compared to the deep invasion group (SM2 invasion). Based on these results, excluding SM-invasive cancer would be expected to reduce the rate of discrepancy between the clinicopathologic parameters before and after ESD. However, the risk of LVI differed statistically significantly between groups no matter which of the groups were compared.

Discussion

ESD should only be assigned based on strict criteria in order to avoid lymph node (LN) metastasis. Gotoda et al. [3] reported that LN metastasis was not observed in any case of ulcer-free differentiated mucosal cancer, regardless of the tumor size. However, Kang et al. [4] reported LN metastasis in two (1.4 %) of 146 cases of intestinal-type mucosal cancer of any size without ulcer and with no lymphovascular emboli. Chung et al. [5] also reported LN metastasis in two (0.23 %) of 882 patients with ulcer-free differentiated mucosal cancer regardless of the tumor size. In a study involving 487 EGC cases treated with ESD, Lee et al. [6] suggested that ESD for curative purposes was most feasible in nonulcerative cases and that differentiated EGC was the best option for tumors ≤ cm in size. Thus, in

Table 4 Clinicopathologic analysis according to the depth of invasion

Clinicopathologic factor	DOI [number of cases (%)]					*p* value
	LP	MM	SM1	SM2	Total	
Tumor size						0.028
≤3 cm	344 (46.9)	229 (31.2)	55 (7.5)	43 (5.9)	671 (91.4)	
>3 cm	24 (3.3)	21 (2.9)	10 (1.4)	8 (1.1)	63 (8.6)	
Ulcer						0.005
Absent	357 (48.6)	239 (32.6)	56 (7.6)	48 (6.5)	700 (95.4)	
Present	11 (1.5)	11 (1.5)	9 (1.2)	3 (0.4)	34 (4.6)	
Differentiation						0.021
Differentiated	363 (49.5)	245 (33.4)	60 (8.2)	49 (6.7)	717 (97.7)	
Undifferentiated	5 (0.7)	5 (0.7)	5 (0.7)	2 (0.3)	17 (2.3)	
LVI						<0.001
Absent	367 (50.0)	245 (33.4)	52 (7.1)	37 (5.0)	701 (95.5)	
Present	1 (0.1)	5 (0.7)	13 (1.8)	14 (1.9)	33 (4.5)	
Gross type						<0.001
EGC I	1 (0.2)	6 (1.1)	0 (0.0)	2 (0.4)	9 (1.7)	
EGC IIa	49 (9.1)	16 (3.0)	2 (0.4)	12 (2.2)	79 (14.7)	
EGC IIb	61 (11.4)	35 (6.5)	12 (2.2)	2 (0.2)	110 (20.5)	
EGC IIc	152 (28.4)	124 (23.1)	34 (6.3)	21 (3.9)	331 (61.8)	
Others	4 (0.7)	2 (0.4)	0 (0.0)	1 (0.2)	7 (1.3)	
Location 1						0.008[a]
Upper	35 (4.8)	23 (3.1)	15 (2.0)	11 (1.5)	84 (11.4)	
Middle	95 (12.9)	65 (8.9)	16 (2.2)	9 (1.2)	185 (25.2)	
Lower	238 (32.4)	162 (22.1)	34 (4.6)	31 (4.2)	465 (63.4)	
Loccation 2						0.022[a]
Anterior wall	79 (10.8)	41 (5.6)	16 (2.2)	12 (1.6)	148 (20.2)	
Lesser curvature	142 (19.3)	101 (13.8)	26 (3.5)	11 (1.5)	280 (38.1)	
Posterior wall	57 (7.8)	51 (6.9)	15 (2.0)	17 (2.3)	140 (19.1)	
Greater curvature	90 (12.3)	57 (7.8)	8 (1.1)	11 (1.5)	166 (22.6)	
Total	368 (50.1)	250 (34.1)	65 (8.9)	51 (6.9)		

Fisher's exact test

[a] Chi-square test

the present study, cases with ulcers and tumors >3 cm in size were excluded to decrease the risk of metastasis that could result from the application of the extended criteria.

The definition of gastric carcinoma can vary among pathologists. Japanese pathologists base a diagnosis of cancer on severe cytologic atypia with enlarged vesicular oval nuclei and prominent nucleoli, irrespective of the presence of invasion. On the other hand, Western pathologists believe that evidence of invasion into the LP must be present to make a cancer diagnosis. However, apparent invasion is not easily observed in well-differentiated carcinomas. Therefore, very careful and close microscopic examination is required, along with a pathologist with extensive experience. Histologic findings of high-grade dysplasia/adenoma overlap with those of well-differentiated adenocarcinoma, even if the diagnosis is based on the same criteria, so the diagnosis may differ depending on the pathologist [7, 8]. In this study, the Western viewpoint was applied, and a multicenter study was conducted to minimize evaluation errors arising from differences in diagnostic criteria. Obtaining a diagnostic consensus among 10 pathologists allowed cases of high-grade dysplasia to be excluded. Moreover, a set of criteria were defined, including those for measuring the depth of invasion, to evaluate the degree of differentiation and pathological findings of ulceration.

Discrepancies between endoscopic and pathological tumor sizes result not only from differences in the measurement methods used, such as visual estimations, open biopsy forceps, and linear probes [9], but also from variations in practitioner experience [10]. In addition, tumor location, endoscopic approach to the lesion, and gross and histologic type may affect the accuracy. Choi et al. [10] reported reliable agreement between endoscopic visual

estimation and pathological measurement as well as good interobserver agreement. In our study, 6.8 % of the cases were outside of the 95 % limits of agreement, and such deviations occurred more frequently in cases with larger lesions. The largest discrepancy between endoscopic and pathological tumor size was 6.5 cm. The reason for this large discrepancy was not clear. Based on the free ESD margin in this particular case, the endoscopist may have defined the tumor border as the only discrete area, not including the suspicious portion. According to our study, tumor location in the upper or mid portion and elevated gross morphology were causes of endoscopic size underestimation leading to categorization as <3 cm, but histologic type of tumor was not. In the literature, Asada-Hirayama et al. [11] reported that presence of a flat component, large size, and moderately differentiated histology were significantly related to inaccurate endoscopic evaluation in intestinal-type early gastric cancer. However, their results were not comparable with those from our study because their study focused on whether pretreatment demarcation was accurate or not. In the study of Shim et al. [12], larger size, flat/depressed type, and undifferentiated histology were independent risk factors for endoscopic size underestimation, and smaller size was the only independent predictor for endoscopic overestimation of size. An absolute difference of less than 0.4 cm was found in 47.1 % of cases in their study, similar to the corresponding value obtained in our study (an absolute difference of $\leq$0.5 cm in 55.0 % of cases). According to the current study, elevated gross type was commonly found in cases >3 cm, probably due to somewhat excessive enrollment of patients presenting a discrete elevated gross morphology. DOI was meaningfully deep in the cases with lesions >3 cm ($p = 0.028$); thus, tumor depth should be estimated cautiously in these cases.

An ulcer is a discontinuity of the mucosal layer caused by loss of this layer. The presence or absence of ulceration influences LN metastasis in EGC. The study by Gotoda et al. [3] showed that the incidence of LN metastasis was 3.4 % for mucosal cancer with ulceration and 0.5 % for mucosal cancer without ulceration. According to the meta-analysis of EGC by Kwee et al. [13], there was a high risk of LN metastasis when an ulcer was present, although more than moderate heterogeneity was apparent in the studies investigating this variable. They suggested that the reason for this heterogeneity was interobserver variability in the assessment of tumor ulceration among studies. In the study by Gotoda et al. [3], they defined an ulcer as a lesion with ulceration or scarring from previous ulceration. Nonetheless, accurately distinguishing between an ulcer and erosion by endoscopy is a difficult task because such erosion also involves damage to the mucosal layer. Lee et al. [14] emphasized that the morphology of an ulcer may change over time, considering the life cycle of a malignant ulcer, and that interobserver variation may result when the presence or absence of ulcer is determined endoscopically. In the present study, the main focus was the discrepancy between clinicopathologic variables pre- and post-ESD. Thus, we compared the pre-ESD endoscopic ulceration with the post-ESD pathologic ulceration. We considered it reasonable to define a pathologic ulcer as an active ulcer with no scarring from ulceration. We also excluded lesions that were regenerating post ulcer and were covered with epithelial cells or granulation tissue. Despite the application of strict pathological criteria, accurate endoscopic evaluation of ulcers proved difficult considering that 34 cases (4.6 %) with ulceration were included. However, there was only one case with both ulceration and a differentiated mucosal carcinoma >3 cm in size, which constitutes deviation from the extended criteria, implying that the endoscopists strictly applied the criteria for distinguishing the presence or absence of an ulcer when the tumor was large. In this study, the DOI was significantly deeper in cases with ulceration than in those without ulceration. Therefore, accurate endoscopic determination of the presence or absence of ulceration may be necessary.

The degree of differentiation is a very important factor in candidate selection. In the WHO classification [15], tumor differentiation is determined by the grading of gland formation. According to the Japanese Gastric Cancer Association [16], undifferentiated gastric carcinomas include poorly differentiated adenocarcinomas and signet ring cell carcinomas, while differentiated carcinomas include well and moderately differentiated tubular carcinomas. Interobserver variability is even present when defining differentiation. In this study, the degree of differentiation was determined by a consensus meeting to eliminate this interobserver variability. In cases of undifferentiated intramucosal EGC, curative endoscopic treatment can be conducted only in very limited cases because it has a higher frequency of LN metastasis than intramucosal EGC does (4.2 vs. 0.4 %) [3]. According to the meta-analysis conducted by Kwee [13], more than moderate heterogeneity was identified among studies investigating the variable "main histological tumor type (differentiated vs. undifferentiated)." Pre-ESD biopsy of the tumor sometimes results in a different histology to that seen in the post-ESD specimen, which can be attributed to inter- and intraobserver variability as well as the fact that a gastric cancer can present histological heterogeneity (it can be both differentiated and undifferentiated) [17, 18]. Mita and Shimoda [19] reported that the rate of LN metastasis was significantly higher in differentiated submucosal cancers with histological heterogeneity (i.e., of differentiated type with a poorly differentiated component) than in cancers without such histological heterogeneity (27 vs. 7 %). Lee

et al. [20] compared the histologic differentiation observed using radical gastrectomy with that seen in preoperative gastric biopsy in 1326 patients with gastric mucosal cancer. The results showed that the degree of differentiation was consistent in 1041 patients (78.5 %); 99 patients (7.5 %) showed a differentiated histology on preoperative biopsy but a poorly differentiated histology on postoperative results, whereas the opposite was seen in 58 patients (4.4 %). Matsubara et al. [21] compared the pre- and postoperative differentiation of gastric cancer. The rates of agreement for early and advanced gastric cancer were 82.5 and 72 %, respectively. In the differentiated cases, the rates of agreement were 90.0 and 63.6 % for early and advanced cancers, respectively. Our study targeted cases diagnosed as differentiated on biopsy; among those cases, only 19 were found to be the undifferentiated type, with a consistency rate as high as 97.4 %. Our high consistency rate can be attributed to the application of the strict inclusion criteria applied to ESD, whereas the studies by Lee et al. [20] and Matsubara et al. [21] targeted patients who underwent gastrectomy. Additionally, in our study, the undifferentiated group showed deeper invasion and more frequent LVI than the differentiated group did. This result indicates that tumor heterogeneity is commonly associated with deep invasion and LVI.

Accurate diagnosis of invasion depth prior to the ESD procedure is very important when attempting to identify an appropriate treatment plan. DOI can be determined by conventional endoscopy, a barium study, endoscopic ultrasonography (EUS), virtual endoscopy, or abdominal CT [22]. Mandai et al. [23] measured the invasion depth of EGC using EUS. Among the 280 cases considered to be mucosal/SM1 cancer based on EUS findings, 20 (7.1 %) corresponded to SM2 cancer. This result was similar to our finding of 51 such cases (6.9 %). Mandai et al. [23] stated that the factors leading to misdiagnosis based on DOI measurement include ulceration, tumor size >2 cm, and use of an US endoscope. Yamada et al. [24] described three risk factors for submucosal and lymphovascular invasion in ESD specimens: a dominant histology of moderately differentiated or papillary adenocarcinoma; a non-flat-type gross morphology; and a tumor size ≥1.5 cm. In our study, SM2 invasion correlated with tumor size, ulceration, undifferentiated histology, gross type, and location of the tumor in the multivariate analysis. Among the 117 cases showing submucosal invasion, 52 (44.4 %) demonstrated SM2 invasion. Therefore, in cases suspicious for submucosal invasion, very careful selection of the patients for ESD is mandatory in order to prevent the need for additional surgery. According to the extended criteria for ESD eligibility, SM1 cancer is eligible for ESD, but the mucosal cancer group (LP and MM invasion) showed statistically significant differences in tumor size, differentiation, ulceration, LVI, location 1, and location 2 compared to the SM cancer group (SM1 and SM2 invasion) in our study. In contrast, cancers associated with the superficial invasion group (LP, MM, and SM1 invasion) revealed no significant differences in tumor size, differentiation, and ulceration compared to the deep invasion group (SM2 invasion). Based on these results, excluding SM-invasive cancer would be expected to reduce the rate of discrepancy between the clinicopathologic parameters before and after ESD. However, in our study, the risk of LVI differed statistically significantly between groups regardless of the groups compared.

Conclusions

Among 737 cases of carcinoma in EGC patients, discrepancies in the clinicopathologic parameters pre- and post-ESD occurred in 148 (20.1 %). The most common cause of discrepancy was tumor size >3 cm (63 cases, 8.5 %), but 93.2 % of these cases lay within the 95 % limits of agreement. Ulceration, undifferentiated histology, and SM2 invasion were found in 34 cases (4.6 %), 18 cases (2.4 %), and 51 cases (6.9 %), respectively. Depth of invasion was correlated with other clinicopathologic parameters such as tumor size, ulceration, differentiation, and LVI. DOI should therefore be evaluated very cautiously in order to reduce the discrepancy rate. Among the 116 cases that showed submucosal invasion, 51 cases (44.0 %) demonstrated SM2 invasion. SM-invasive cancer cases showed a high incidence of LVI irrespective of the depth of SM invasion. In cases suspicious for submucosal invasion, cautious selection of patients for ESD is necessary in order to reduce the risk of SM2 invasion and LVI.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki of 1964 and later versions. Informed consent or a substitute for it was obtained from all patients before they were included in the study.

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