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Analysis of endoscopic features for histologic discrepancies between biopsy and endoscopic submucosal dissection in gastric neoplasms: 10-year results

Choong-Kyun Noh[a], Min Wook Jung[a], Sung Jae Shin[a,*], Ju Young Ahn[a], Hyo Jung Cho[a], Min Jae Yang[a], Soon Sun Kim[a], Sun Gyo Lim[a], Dakeun Lee[b], Young Bae Kim[b], Jae Youn Cheong[a], Kee Myung Lee[a], Byung Moo Yoo[a], Kwang Jae Lee[a]

[a] Department of Gastroenterology, Ajou University School of Medicine, Suwon, Republic of Korea
[b] Department of Pathology, Ajou University School of Medicine, Suwon, Republic of Korea

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ABSTRACT

Background and aim: The histologic discrepancies between preoperative endoscopic forceps biopsy (EFB) and endoscopic submucosal dissection (ESD) specimens sometimes confuse the endoscope operator. This study aimed to analyze the limitation of the biopsy-based diagnosis before ESD and to evaluate which factors affect the discordant pathologic results between EFB and ESD.
Methods: A total of 1427 patients, who were diagnosed with gastric adenoma by EFB, were enrolled. Cancer confirmed on EFB was excluded (n = 513). We retrospectively reviewed cases and compared histologic diagnoses in the biopsy sample with the final diagnosis in the endoscopically resected specimen.
Results: The diagnosis was upgraded (from low-grade dysplasia to high-grade dysplasia or adenocarcinoma, or from high-grade dysplasia to adenocarcinoma) in 328 cases (23.0%), concordant in 944 (66.1%), and downgraded (from high-grade dysplasia to low-grade dysplasia or non-neoplasia, or from low-grade dysplasia to non-neoplasia) in 155 (10.9%). Multivariate logistic regression analysis showed that surface ulceration and depressed lesions were associated with significant risk factors for upgrading. Age younger than 60 years and size <1 cm were associated with significant factors for downgrading.
Conclusions: Careful endoscopic observation should consider size, ulceration, and depression to ensure accurate diagnosis when a gastric neoplasm is suspected.

1. Introduction

The incidence of early gastric cancer in Korea is increasing because of widespread use of early endoscopic screening programs and advances in diagnostic tools [1,2]. Endoscopic mucosal resection and endoscopic submucosal dissection (ESD) are the most popular resection methods and are widely used for treatment of these early gastric neoplasms (early gastric cancer, gastric adenoma). In particular, ESD is more useful than endoscopic mucosal resection, because curative en bloc resection and complete histological assessment of specimens are possible [3].

An endoscopic biopsy must be performed to determine the preoperative diagnosis and indication for endoscopic resection (ER). However, the results of biopsy samples do not always correspond to the endoscopic diagnosis (post-ESD pathology). A biopsy-based diagnosis has the limitation of sampling error and can lead to errors in the choice of treatment. Therefore, histologic discrepancies between preoperative endoscopic forceps biopsy (EFB) and ER specimens sometimes confuse the endoscope operator.

Although many previous studies have reported histologic discrepancy rates of 2–49% [4–7], few studies have examined which endoscopic features influence histologic discrepancies, whether downgraded or upgraded. The EFB finding plays a significant role in determining treatment. In particular, additional treatment may be required if the adenoma is upgraded to cancer. Identifying the factors that affect discrepancy may help in the choice of ESD tech-

* Corresponding author at: Department of Gastroenterology, Ajou University School of Medicine, 164, World Cup-ro, Yeongtong-gu, Suwon, 16499, Republic of Korea.
E-mail addresses: cknoh23@gmail.com (C.-K. Noh), shsj9128@ajou.ac.kr (S.J. Shin).

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nique as well as the treatment decision in the diagnosis of adenoma based on EFB.

If cancer was identified on EFB, the treatment strategy did not change. If endoscopic resection was possible, ESD was performed. Therefore, we only analyzed cases in which adenoma was confirmed on EFB. Therefore, the aim of this study was to analyze the endoscopic features of discordant histology in EFB and ER specimens and to compare the 10-year results of the downgraded and upgraded discrepancy groups with the concordant group in all adenoma lesions.

2. Materials and methods

2.1. Patients

Between February 2005 and December 2014, 2096 consecutive patients underwent gastric ESD at Ajou University Hospital (Suwon, Republic of Korea). We reviewed cases of ESD diagnosed with gastric adenoma (low-grade or high-grade dysplasia) by EFB. This study was approved by the institutional review board (approval no. AJIRB-MED-MDB-17-240).

2.2. Pre-ESD protocol

If suspected epithelial dysplasia was found on diagnostic endoscopy, lesion-targeted EFB was performed. Before EFB, the operator used chromoendoscopy with indigo carmine dye spray in all the cases and used narrow-band imaging (NBI) if possible. The size of the lesion was estimated macroscopically using 6-mm circular pieces of punched-out paper [8–10] or using standard biopsy forceps with 6-mm opening diameter (FB-21 K-1; Olympus, Tokyo, Japan). The operator determined the number of biopsy fragments after considering the size and surface features of the lesion. The forceps biopsy was performed at least three times on the lesion, except for the cases where the lesion size was small and could affect the procedure. After the lesions were pathologically confirmed as gastric dysplasia, the patients underwent ESD after admission. The inclusion criteria were: histologic confirmation of dysplasia on EFB performed before ESD by two expert pathologists, and lesion removed by ESD with en bloc resection. The exclusion criteria were: gastric cancer (both intramucosal and submucosal cancer) in pre-ESD biopsy; incomplete resection; and lesions for which the histologic diagnosis by either endoscopy or surgery was not available.

2.3. ESD procedure

ESD was performed using a one-channel or two-channel endoscope (Olympus Q260J, 2TQ260M; Olympus Optical Co., Tokyo, Japan) under sedation with both midazolam and propofol. After observing the lesion, several spots were marked 5 mm outside the tumor margin using argon plasma coagulation or a FlexKnife (Olympus, Tokyo, Japan). Then, the submucosal layer of the tumor was raised by injection of a mixture of normal saline and indigo carmine with diluted epinephrine (1:10,000). The submucosal layer was dissected with an IT-knife (Olympus, Tokyo, Japan) or FlexKnife. The resected specimen was retrieved with a net, fixed in 10% formalin, sectioned serially at 2-mm intervals, and subjected to histological mapping. The histologic type, depth of invasion, lymphatic and vascular invasion, and presence of tumor cells in the resection margin were assessed.

2.4. Endoscopic features

The following endoscopic features were analyzed: size of the tumor (length: long diameter), the location of the tumor (upper: upper third, middle: middle third, lower: lower third), and the gross morphologic features of the tumor (elevated: protruding into the lumen of the stomach, flat: similar to the level of the surrounding mucosa, depressed: lesion lower than the surrounding mucosa, ulcerated: excavated lesion involving more than mucosa).

2.5. Histologic features

Two experienced pathologists (D.L and Y.B.K) determined the histologic diagnoses of the EFB and the ESD specimens. The histologic diagnoses were based on the revised Vienna classification of gastrointestinal neoplasia (Category 1: Negative for neoplasia, Category 2: Indefinite for neoplasia, Category 3: Mucosal low-grade neoplasia, Category 4.1: High-grade adenoma/dysplasia, Category 4.2: Non-invasive carcinoma, Category 4.3: Suspicious for invasive carcinoma, Category 4.4: Intramucosal carcinoma, Category 5: Submucosal invasion by carcinoma) [11,12]. For patients who were referred from other centers with a pathology slide, a pathologist reevaluated the pre-ESD EFB slide. The percentage of change from external histology (other center) to internal histology (by expert pathologists in our center) was as follows; upgrade: 1.24% (n = 9), concordant: 96.29% (n = 701), downgrade: 2.47% (n = 18). When the histologic diagnoses changed after ESD, all slides from the EFB and ESD specimens were reviewed again.

We classified the lesions into three groups according to histologic discrepancies between the EFB and the ESD specimens: a concordant group (when the diagnoses of EFB and ESD specimens were the same), an upgraded group (when the diagnoses of subsequent ESD specimens showed a histology of more malignant potential, e.g., from low-grade dysplasia to high-grade dysplasia or from high-grade dysplasia to adenocarcinoma), or a downgraded group (when the diagnoses of subsequent ESD specimens showed a histology of less malignant potential, e.g., from high-grade dysplasia to low-grade dysplasia or from low-grade dysplasia to non-neoplasia) [9,10].

2.6. Statistical analysis

Continuous variables were expressed as the mean ± standard deviation, and categorical variables were expressed as the total number and percentages. Chi-square test (with the Yates continuity correction as appropriate) was used for comparisons of categorical data. One-way analysis of variance and Kruskal–Wallis test, with post hoc analysis by the Bonferroni method, were used to assess differences in continuous and ordinal variables. Univariate and multivariate logistic regression analyses were conducted to identify significant endoscopic predictors of histologic discrepancy after ESD. Statistical analyses were performed using the SPSS 23.0 software package (SPSS, Inc., Chicago, IL, USA), which calculates the area under the curve and 95% confidence intervals (CIs). A P-value <0.05 was considered significant.

3. Results

3.1. Demographics and clinical characteristics

A total of 2096 patients received gastric ESD, of whom 669 were excluded (523: gastric cancer in the pre-ESD biopsy, 146: incomplete resection). Finally, 1427 patients were included in the study for analysis (Fig. 1). Of the enrolled patients, 1068 (74.8%) were men and the mean age was 62.7 (range: 20–89) years. The mean lesion size was 19.6 ± 10.38 mm, and 833 (58.4%) cases were located in the lower third of the stomach. Only 73 cases (5.1%) had surface ulceration. We classified three types of gross morphology as elevated, flat, and depressed; 560 (39.2%) specimens were elevated, 779 (54.6%) were flat, and 88 (6.2%) were depressed. A total of 1144 (80.2%)

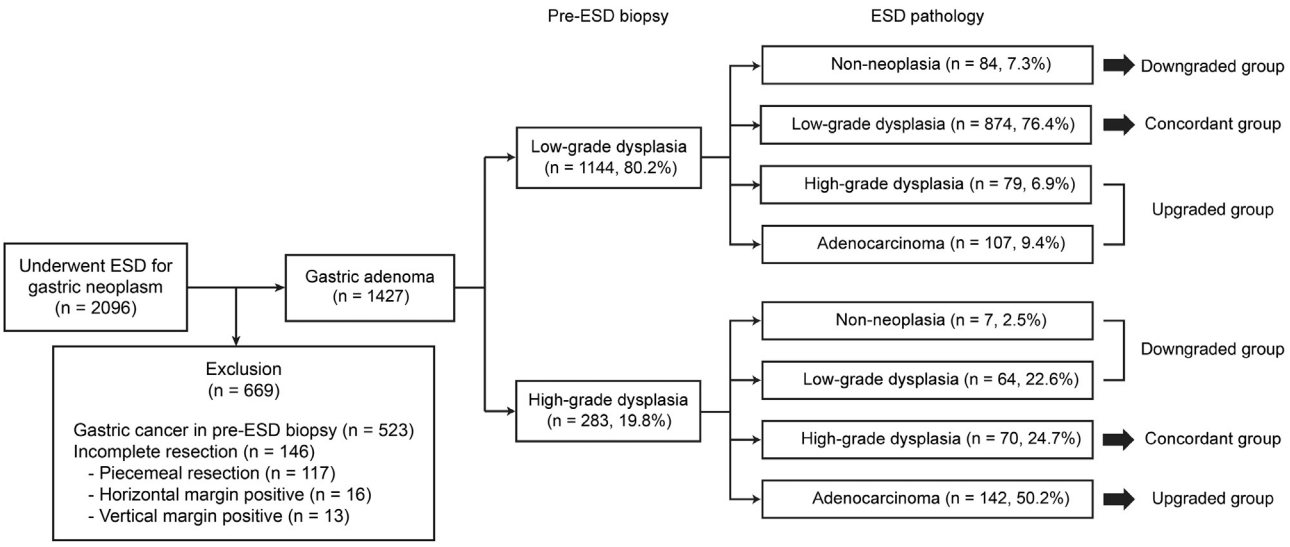

Fig. 1. Flow chart of histologic discrepancy grouping.

Table 1
Clinicopathological characteristics of all patients with gastric dysplasia and comparison of the two groups divided by the referral centers.

Variables	All patients	Referral center		*P*-value[a]
		Local clinic	Our center	
Total cases, n (%)	1427	728 (51.1)	699 (48.9)	
Age, mean, years (range)	62.7 (20–89)	62.1 (20–85)	63.2 (27–89)	0.527
Gender, n (%)				0.024
Male	1068 (74.8)	526 (72.3)	542 (77.5)	
Female	359 (25.2)	202 (27.7)	157 (22.5)	
Location, n (%)				0.101
Upper third	79 (5.5)	31 (4.3)	48 (6.9)	
Middle third	515 (36.1)	266 (36.5)	249 (35.6)	
Lower third	833 (58.4)	431 (59.2)	402 (57.5)	
Lesion diameter, mean, mm	19.6 ± 10.38	19.9 ± 9.60	19.3 ± 9.76	0.281
Gross morphology type[b], n (%)				0.303
Elevated	560 (39.2)	276 (37.9)	284 (40.6)	
Flat	779 (54.6)	416 (57.2)	363 (51.9)	
Depressed	88 (6.2)	36 (4.9)	52 (7.5)	
Ulceration, n (%)	73 (5.1)	34 (4.7)	39 (5.6)	0.472
Number of biopsy, n		No data	3.18 ± 0.70	
Pre-ESD EFB histology, n (%)				0.791
Low-grade dysplasia	1144 (80.2%)	586 (80.5)	558 (79.8)	
High-grade dysplasia	283 (19.8%)	142 (19.5)	141 (20.2)	
Post-ESD diagnosis, n (%)				0.501
Negative for neoplasia	91 (6.4%)	50 (6.9)	41 (5.9)	
Low-grade dysplasia	938 (65.7%)	486 (66.8)	452 (64.7)	
High-grade dysplasia	149 (10.4%)	77 (10.6)	72 (10.3)	
Carcinoma	249 (17.4%)	115 (15.7)	134 (19.1)	
Differentiated	241 (96.8)	110 (95.7)	131 (97.8)	
Undifferentiated	8 (3.2)	5 (4.3)	3 (2.2)	
Discrepancy				0.096
Concordant	944 (66.1)	489 (67.2)	455 (65.1)	
Upgrade	328 (23.0)	152 (20.1)	176 (25.2)	
Downgrade	155 (10.9)	87 (12.0)	68 (9.7)	

n: number; ESD: endoscopic submucosal dissection; EFB: endoscopic forceps biopsy.
[a] Local clinic vs. our center.
[b] According to the Japanese classification of gastric carcinoma [10].

patients were diagnosed with adenoma with low-grade dysplasia and 283 (19.8%) had adenoma with high-grade dysplasia. In the post-ESD diagnosis, 91 (6.4%) were negative, 938 (65.7%) had low-grade dysplasia, 149 (10.4%) had high-grade dysplasia, and 249 (17.4%) had carcinoma (intramucosal vs. submucosal: 226, 90.8% vs. 23, 9.2%). Most of the adenocarcinomas were differentiated cancers (241, 96.8%). The initial endoscopy performed at the local clinic and that performed at our center was 728 (51.1%) and 699 (48.9%), respectively. Additionally, we divided the cases into two groups according to the referral centers. Baseline characteristics of the two groups showed no significant differences except in gender (Table 1).

3.2. Histologic discrepancy between pre-ESD biopsy and post-ESD pathology

In patients with low-grade dysplasia in the pre-ESD biopsy, post-ESD pathologic diagnoses showed that 84 (7.3%) did not have adenoma (defined as non-neoplasia), 874 (76.4%) remained as low-grade dysplasia, and 79 (6.9%) were changed to high-grade dys-

Table 2
Comparison of baseline and endoscopic features between histologic discrepancy groups.

Variables	Concordant group	Upgraded group	Downgraded group	*P*-value
Total, n (%)	944 (66.1)	328 (23.0)	155 (10.9)	
Age, mean, years (range)	62.6 (28–87)	64.0 (31–89)	60.1 (28–86)	0.001[a], 0.029[b], 0.085[c]
Gender, n (%)				0.132
Male	704 (74.6)	256 (78.0)	108 (69.7)	
Female	240 (25.4)	72 (24.0)	47 (30.3)	
Location, n (%)				0.943
Upper third	50 (5.3)	21 (6.4)	8 (5.2)	
Middle third	343 (36.3)	118 (35.0)	54 (34.8)	
Lower third	551 (58.4)	189 (57.6)	93 (60.0)	
Gross morphology type, n (%)				<0.001
Elevated	382 (40.5)	120 (36.6)	58 (37.4)	
Flat	522 (55.3)	172 (52.4)	85 (54.8)	
Depressed	40 (4.2)	36 (11.0)	12 (7.7)	
Ulceration, n (%)	33 (3.5)	36 (11.0)	4 (2.6)	<0.001
Tumor size, mean, mm	19.1 ± 9.59	22.3 ± 10.86	16.9 ± 10.25	<0.001[a,b,c]

n: number.
[a] Upgraded group vs. downgraded group.
[b] Concordant group vs. downgraded group.
[c] Concordant group vs. upgraded group.

Table 3
Logistic regression analysis of risk factors for the upgraded group.

Variables	Crude OR		*P*-value	Adjusted OR		*P*-value
	OR	95% CI		OR	95% CI	
Age ≥60 years	1.232	0.948–1.600	0.119			
Male gender	1.257	0.937–1.686	0.128			
Location			0.734			
Mid third[a]	0.821	0.478–1.408				
Lower third[b]	0.811	0.480–1.370				
Size (long diameter ≥1 cm)	1.721	1.073–2.759	0.024			
Ulceration	3.539	2.197–5.700	<0.001	2.549	1.547–4.199	<0.001
Morphology						
Elevation	0.864	0.670–1.115	0.262			
Flat	0.894	0.698–1.144	0.373			
Depression	2.068	1.608–2.661	<0.001	1.835	1.408–2.392	<0.001

OR: odds ratio; CI: confidence interval.
[a] Mid third lesion compared with upper third lesion.
[b] Lower third lesion compared with upper third lesion.

plasia. The final diagnosis for the remaining 107 (9.4%) patients was confirmed as adenocarcinoma. As defined above, we classified three groups according to changes between pre- and post-ESD pathology: downgraded, concordant, and upgraded. We identified 84 (7.3%) patients in the downgraded group, 874 (76.4%) in the concordant group, and 186 (16.3%) in the upgraded group (Fig. 1).

Of 283 patients with confirmed high-grade dysplasia in the pre-ESD biopsy, no adenoma was found in seven (2.5%) patients on post-ESD pathology. Low-grade dysplasia, high-grade dysplasia, and adenocarcinoma were observed in 64 (22.6%), 70 (24.7%), and 142 (50.2%), patients, respectively. Of note, 50.2% of the high-grade dysplasia (upgraded) group was confirmed to have adenocarcinoma in the final ESD pathology (Fig. 1).

3.3. Comparison of baseline and endoscopic features in histologic discrepancy groups

We compared baseline endoscopic features of the three histologic discrepancy groups defined as above, regardless of pre-ESD biopsy results. The concordant group comprised 944 (66.1%) patients, the upgraded group had 328 (23.0%), and the downgraded group had 155 (10.9%). The tumor locations and the genders in the three groups did not differ significantly. However, there were significant differences in age between the upgraded and downgraded groups ($P = 0.001$), as well as between the concordant and downgraded groups ($P = 0.029$). Additionally, there was a significant difference in the gross morphology among the three groups ($P < 0.001$). In the concordant group, 382 (40.5%) specimens were elevated, 522 (55.3%) were flat, and 40 (4.2%) were depressed. In the upgraded group, 120 (36.6%) were elevated, 172 (52.4%) were flat, and 36 (11.0%) were depressed. The most remarkable aspect of these results was that the proportion of depressed lesions was the highest in the upgraded group (11.0% in the upgraded group, 4.2% in the concordant group, and 7.7% in the downgraded group). In the surface ulceration and tumor size, there were significant differences among the three groups ($P < 0.001$). The mean tumor size was 19.1 ± 9.59 mm in the concordant group, 22.3 ± 10.86 mm in the upgraded group, and 16.9 ± 10.25 mm in the downgraded group ($P < 0.001$). In addition, the proportion of lesions with depression and ulceration was the highest in the upgraded group (Table 2).

3.4. Analysis of factors affecting discrepancy

Univariate analyses based on a binary logistic regression model were performed to investigate predictors of risk factors associated with the upgraded group (Table 3). Among the clinical features, lesion size (maximum diameter ≥1 cm), surface ulceration, and surface depression were significantly associated with risk factors in the upgraded group ($P < 0.05$). In a multivariate regression model, surface ulceration (odds ratio [OR] 2.549, 95% confidence interval [CI] 1.547–4.199, $P < 0.001$) and surface depression (OR 1.835, 95% CI 1.408–2.392, $P < 0.001$) were associated with risk factors (Table 3). On the other hand, age below 60 years (OR 1.477, 95% CI 1.052–2.074, $P = 0.024$) and size <1 cm (OR 2.586, 95% CI

Table 4
Logistic regression analysis of risk factors for the downgraded group.

Variables	Crude OR		*P*-value	Adjusted OR		*P*-value
	OR	95% CI		OR	95% CI	
Age <60 years	1.496	1.068–2.096	0.019	1.477	1.052–2.074	0.024
Male gender	0.747	0.518–1.076	0.117			
Location			0.906			
Mid third[a]	1.040	0.475–2.276				
Lower third[b]	1115	0.521–2.390				
Size (long diameter <1 cm)	2.615	1.686–4.056	<0.001	2.586	1.665–4.018	<0.001
Ulceration	0.462	0.166–1.284	0.139			
Morphology						
Elevation	0.917	0.650–1.294	0.622			
Flat	1.011	0.723–1.414	0.948			
Depression	0.72	0.507–1.057	0.096			

OR: odds ratio; CI: confidence interval.
[a] Mid third lesion compared with upper third lesion.
[b] Lower third lesion compared with upper third lesion.

1.665–4.018, $P<0.001$) were associated with significant factors for the downgraded group in the multivariate regression model (Table 4).

In our study, as many as 50% of the patients with high-grade dysplasia had confirmed adenocarcinoma on post-ESD pathology (Fig. 1). As in the upgraded group of high-grade dysplasia, ulceration (OR 2.144, 95% CI 1.185–3.878, $P=0.012$) and depression (OR 2.121, 95% CI 1.537–3.209, $P<0.001$) were identified as significant risk factors in a multivariate regression model (Table 5).

4. Discussion

This study was the first to analyze discrepancies between upgraded and downgraded groups for all gastric adenomas. Additionally, we also collected and analyzed the results of endoscopic treatment for 10 years. In our study, histologic discrepancies between pre-ESD biopsy and post-ESD pathology were observed. We divided the lesions into three groups according to histologic discrepancies between the EFB and ESD specimens as concordant, upgraded, and downgraded. There were significant differences in gross morphology between the concordant and upgraded groups. The average tumor size in the upgraded group was larger than that in the concordant group. Surface ulceration and depression, in gross morphology, were associated with risk factors for the upgraded group. In the downgraded group, size of lesion <1 cm was associated with significant risk factors in the multivariate regression model. Thus, we demonstrated that tumor morphology and size could be predictive of discrepancy between pre-ESD biopsy and post-ESD pathology.

ER is the treatment of choice for high-grade dysplasia, and early detection is essential. There are three methods for early identification of the exact pathology of the ESD specimen. First, an accurate biopsy is required. The quality of biopsy specimens is sometimes poor because of inadequate sampling or incorrect targeting, which leads to discrepancies. Second, using NBI before the biopsy is helpful. Third, a short follow-up interval after a biopsy that did not confirm adenoma should be considered. Nevertheless, discrepancies between pre-ESD biopsy and post-ESD pathology are still reported and reasons for discrepancies are as follows. First, sampling error can occur, because cancer cells are often focally present in a lesion. Thus, a biopsy may not detect focal cancer cells [13]. Second, some cases of high-grade dysplasia or cancer are not identified by the final pathology, because it is possible that inflammation after forceps biopsy can prevent pathologists from detecting high-grade dysplasia or cancer [13].

Some previous studies reported similar results. Takao et al. [5] reported that an ER diagnosis of gastric cancer was made in 49% (118/241) of lesions diagnosed as borderline from EFB. In our study, 33.8% (483/1427) demonstrated a discrepancy between the forceps biopsy and post-ESD pathology. Notably, 23.0% (328/1427) were upgraded. Previous studies suggested that risk factors associated with malignant dysplastic changes included lesion diameter >1 cm, depressed morphology, erythematous mucosal change, and surface erosion [14–17]. Kim et al. reported through multivariate analysis that the absence of whitish discoloration, which might be related to cell degeneration, was a statistically significant factor influencing histologic discrepancy (OR 5.29, 95% CI 1.95–14.37, $P=0.001$) [14]. Choi et al. observed a significant correlation with lesion size, surface redness, and surface nodularity for an upgraded group [18]. Similar results were observed in our study. Surface ulceration (OR 2.549, 95% CI 1.547–4.199, $P<0.001$) and surface depression (OR 1.835, 95% CI 1.408–2.392, $P<0.001$) were associated with risk factors for our upgraded group.

We distinguished between erosion and ulceration. It was reported that malignancy increases in erythema and surface erosion in a previous study [17]. However, our review concluded that the evaluation of erosion was inappropriate in a retrospective analysis. We speculate that judging the presence of erosion by only using previous (old) photographs and reports is inaccurate. The opinion on erosion was also different among the authors (12 expert endoscopists). Ulceration was defined as an excavated lesion. In other words, ulceration was defined when an excavated lesion in the mucosa and submucosa was involved, not surface erosion. In this case, there was no difference between the endoscopists' opinions when reviewing the photographs of endoscopic examination. Therefore, we focused on ulceration and considered it as a factor affecting discrepancy. As a result, OR 2.549 ($P<0.001$) was confirmed in the upgraded discrepancy.

Efforts to reduce the ratio of upgraded cases are necessary. Therefore, EFB before ER is crucial. In lesions with depression or ulceration, the number of forceps biopsies should be increased and performed at various sites in adenomatous lesions, rather than focusing on only one site [19]. However, increasing the number of forceps biopsies increases the probability of receiving non-neoplastic pathology results after ER. The sampling ratio is defined as the long diameter of the tumor divided by the number of forceps biopsy fragments. In other words, the greater the number of biopsies fragments, the lower the sampling ratio. Yang et al. reported that the likelihood of a non-neoplastic pathology report decreases with an increased sampling ratio (OR 0.52, 95% CI 0.42–0.64, $P<0.001$) [20]. Thus, the greater the number of biopsies, the higher the probability of non-neoplastic pathology reporting when ESD is performed. Therefore, sufficient biopsies are necessary, but multiple biopsies should be performed care-

Table 5
Logistic regression analysis of risk factors for upgrading of high-grade dysplasia.

Variables	Crude OR		*P*-value	Adjusted OR		*P*-value
	OR	95% CI		OR	95% CI	
Age ≥60 years	1.054	0.803–1.384	0.705			
Male gender	1.079	0.796–1.461	0.625			
Location			0.263			
Mid third[a]	0.650	0.373–1.132				
Lower third[b]	0.756	0.443–1.290				
Size (long diameter <1 cm)	1.253	0.791–1.983	0.336			
Ulceration	3.246	1.848–5.702	<0.001	2.144	1.185–3.878	0.012
Morphology						
Elevation	0.981	0.751–1.281	0.886			
Flat	0.816	0.629–1.059	0.126			
Depression	2.019	1.549–2.631	<0.001	2.121	1.537–3.209	<0.001

OR: odds ratio; CI: confidence interval.
[a] Mid third lesion compared with upper third lesion.
[b] Lower third lesion compared with upper third lesion.

fully considering the possibility of non-neoplastic pathology after ESD, especially in small-sized lesions. In these cases, the NBI mode may also be helpful. A magnified NBI mode may show a demarcating line, an irregular microvascular pattern, or a lesion with a white globe appearance; these have a high probability of being cancers or precancerous lesions and should be targeted for histological examination [21,22].

Most discrepancy studies have focused on the upgraded group. On the other hand, our study also analyzed the downgraded group and showed a favorable OR for age below 60 years and lesion size <1 cm. The downgrading discrepancy was thought to increase with smaller adenoma size, the feasibility of lesion removal by forceps biopsy, and the change in results due to different interpretations by pathologists [20]. We speculate that the downgrading of the lesion is also important in terms of operator's technical aspect. Because the cardia, fundus, and prepyloric area are technically difficult locations, and thus, obtaining a sufficient dissection range is challenging. In this case, if there is a favorable factor for the low-grade group, it may help in resolving the technical difficulties.

We focused on the final histopathologic diagnosis of cancer in the 50% of patients identified as having high-grade dysplasia in EFB. We tried to identify the different risk factors that were associated with upgrading in these patients, but unfortunately did not observe any differences between the upgraded and high-grade dysplasia groups. However, it is necessary to pay more attention to the margin when the lesion is removed by ESD in cases of high-grade dysplasia, as confirmed by EFB. In particular, cases of high-grade dysplasia with ulceration or depression should be evaluated and treated in accordance with a diagnosis of cancer.

Takao et al. reported that the discrepancy rate was different between lesions diagnosed as differentiated or undifferentiated cancer in a concordant group (97% vs. 83% respectively) [5]. The heterogeneity of cancer, in which the lesion consists of mixed histology with differentiated and undifferentiated types, was one of the reasons for the discrepancy between EFB and ER. Another explanation was that forceps biopsy can cause tissue damage due to technical problems [5]. As a result, even if the duct formation is actually intact, it can be misinterpreted as undifferentiated cancer due to the damage caused by forceps biopsy [5]. This was not evaluated in our study because we did not focus on cancer lesions. Further research is needed for clarification.

This was a retrospective cohort study and therefore had some limitations. There are other reasons to examine these discrepancies. In Korea, upper endoscopic examinations are popular because of easy accessibility and relatively low cost. As a result, many cases are performed at local clinics before referral to a tertiary medical center or university hospital for final lesion removal. The approach will therefore differ between the primary examiner at the local clinic and the procedural ER operator. In particular, the number of biopsies may vary from center to center. Further studies are needed only for patients who were diagnosed and treated at the same center. Old endoscopic findings and data did not have any results for NBI; hence, we could not analyze it. NBI was used only in some enrolled patients. In addition, NBI interpretation did not have a high degree of agreement with the inter-endoscopist. Therefore, we could not use the NBI results for analysis. The NBI mode is known to be helpful in predicting histologic characteristics of lesions. If we perform a biopsy using the NBI mode, targeting of the lesion will be more accurate and the proportion of the concordant group will increase. Although two expert pathologists reviewed the study and agreed on all cases of discrepancy, there was disagreement in a small number of cases. However, our study was aimed at a larger number of patients than in previous studies and was able to enhance the existing results. In addition, for the first time, we analyzed all upgraded and downgraded adenoma cases simultaneously.

In conclusion, there was a histologic discrepancy between preoperative EFB and ER specimens. If the size is greater than 1 cm and any ulceration or depression is present, there is a high probability of an upgraded pathology after ER. Therefore, the endoscopist should perform ER carefully. In particular, special attention is needed for evaluation and treatment in accordance with a diagnosis of cancer if high-grade dysplasia with ulceration or depression is observed on EFB prior to ER.

Guarantor of the article

Sung Jae Shin, MD, PhD.

Conflict of interest

None declared.

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