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Pathologic outcomes of endoscopic submucosal dissection for gastric epithelial neoplasia

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Abstract

Endoscopic submucosal dissection (ESD) has been widely implemented for the treatment of gastric superficial neoplasia. However, the final pathologic diagnosis after ESD may be different from that indicated by the results of endoscopic forceps biopsy. This study identified risk factors for gastric epithelial lesions so that early gastric cancer (EGC) could be diagnosed after ESD.

From December 2008 to January 2017, 1541 lesions (1410 patients) diagnosed as initial adenoma or indefinite for neoplasia by endoscopic forceps biopsy were enrolled. The EGC rate and factors predicting upstaged diagnoses were analyzed retrospectively.

The diagnostic discrepancy rate was 31.1%. Upstaged and downstaged diagnostic rates after ESD were 23.8% and 7.3%, respectively. The upstaged diagnosis rate for EGC was 18.8%. Gross depression (OR, 16.017) and surface redness (OR, 22.136) were significantly associated with EGC and lesions indefinite for neoplasia during the initial endoscopic forceps biopsy. Central depression (OR, 2.959), nodular surface (OR, 6.581), and surface redness (OR, 6.399) were significantly associated with EGC and lesions with low-grade dysplasia during the initial endoscopic forceps biopsy. Central depression (OR, 1.999), nodular surface (OR, 1.733), surface redness (OR 2.283), lesion location (upper third of the stomach) (OR, 3.989), and tumor size ≥10 mm (OR, 2.200) were significantly associated with EGC and lesions with high-grade dysplasia during the initial endoscopic forceps biopsy.

Central depression, nodular surface, surface redness, lesion location, and tumors >10 mm were associated with EGC. Gastric epithelial lesions with these characteristics require attention before ESD.

Abbreviations: CI = confidence interval, EGC = early gastric cancer, ESD = endoscopic submucosal dissection, HGD = high-grade dysplasia, LGD = low-grade dysplasia, OR = odds ratio, SD = standard deviation, SM = submucosa.

Keywords: biopsy, dysplasia, early gastric cancer, endoscopic submucosal dissection

1. Introduction

Gastric cancer is the most common gastrointestinal malignancy in East Asia, including South Korea. In South Korea, the National Cancer Screening Program recommends biennial gastric endoscopic or radiologic contrast examinations and gastric cancer screening for people >40 years.[1] Increasing endoscopic screening for the general population leads to increased detected cases of early gastric cancer (EGC) and premalignant gastric superficial neoplasms such as adenomas (low-grade dysplasia or high-grade dysplasia). The proportion of EGC cases among gastric cancers has increased to 57.6% in South Korea.[2] Endoscopic submucosal dissection (ESD) is useful for the treatment of EGC or gastric adenomas because of the higher en bloc resection rate compared with conventional endoscopic mucosal resection using a snare, regardless of the lesion size.[3] Recently, ESD has been approved as a treatment modality for EGC without the risk of lymph node metastasis.[4,5] Overall survival rates associated with ESD and surgical resection for EGC were similar to those for EGC determined by absolute and expanded indications.[6]

According to the Correa hypothesis, the intestinal type of gastric cancer develops from precursor lesions such as atrophic gastritis, intestinal metaplasia, and adenomas (low-grade dysplasia/high-grade dysplasia).[7] According to the revised Vienna classification, gastric epithelial neoplasia can be divided into 5 groups: category 1, negative for neoplasia; category 2, indefinite for neoplasia; category 3, mucosal low-grade neoplasia; category 4, mucosal high-grade dysplasia; and category 5, invasive carcinoma.[8] Curative resection by endoscopic or surgical maneuvers should be recommended for category 4 or category 5; however, the recommended treatment plans for category 2 and category 3 are ambiguous and include regular follow-up or endoscopic resection. An endoscopic forceps biopsy for suspected EGC or premalignant lesions is a simple diagnostic tool. However, the pathologic results of endoscopic forceps biopsy used for tissues and resected specimens may be different. The reported discrepancy rates were 20% to 76% and were highly associated with pathologic grading of tissues examined by endoscopic forceps biopsy.[9–11]

To treat gastric superficial neoplasia such as gastric adenomas, it is important to know the endoscopic features associated with EGC. The aim of this study was to identify factors associated with

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upstaged diagnoses of EGC after ESD for category 2 to 4 lesions (indefinite for neoplasia, low-grade neoplasia, or high-grade dysplasia) after endoscopic forceps biopsy.

2. Materials and methods

2.1. Patients

From December 2008 to January 2017, the medical records of patients who underwent ESD at the Pusan National University Yangsan Hospital in South Korea were retrospectively reviewed. During the study period, a total of 2011 gastric lesions were removed by ESD. Among these, 443 lesions were diagnosed as gastric cancer before ESD and 27 gastric subepithelial tumors were excluded. Ultimately, the data of 1541 lesions (contributed by 1410 patients) were included in our analysis (Fig. 1).

Written informed consent was obtained from all patients before the procedure. The study was approved by the ethics committee of the Institutional Review Board (Institutional Review Board no. L-2017-255).

2.2. Endoscopic procedure

Diagnostic endoscopy (GIF-H260 or GIF-H290; Olympus Optical Co., Ltd., Tokyo, Japan) and endoscopic forceps biopsies were performed for all patients before ESD. Most patients were referred from other hospitals and underwent an additional biopsy or their referred biopsy specimens were reviewed again. We performed ESD using the technique previously described.[9] After creating marks 1 to 2 mm outside of the lesion, normal saline with an epinephrine and indigo carmine mixture was injected into the submucosal layer to elevate the lesion from the muscularis propria. The mucosa surrounding the lesion was then cut using an electrosurgical generator (ERBE VIO 300D, Endocut I mode, Effect 3, duration 2; Erbe Co, Tubingen, Germany) with a needle or an insulation-tipped electrosurgical knife. Finally, the connective tissue of the submucosa beneath the lesion was dissected with the coagulation current (Swift coagulation 60 W, ERBE VIO 300D). After removal of the lesions, preventive post-ESD coagulation was performed for all visibly exposed vessels (Figs. 2–4).

2.3. Endoscopic and pathologic evaluations

Baseline characteristics and endoscopic findings of all enrolled lesions were assessed. Endoscopic photographs and endoscopic reports were reviewed to determine the features of the lesions. A blind review was performed for all endoscopic photographs and data by 2 endoscopists (D.G. Ryu and S.J. Kim). There was agreement between the 2 regarding most lesions. When there was disagreement regarding the lesions, a diagnosis was made after further discussion. The Paris classification was used to define the gross types of superficial lesions, which were divided into elevated, flat, or depressed.[12] Central depression, surface redness, nodularity, ulceration, and submucosa fibrosis were also evaluated. Central depression was determined when the inner part of the lesion was depressed compared to its surroundings, regardless of gross type (Fig. 5A). Surface redness was determined when there was red discoloration on the mucosal surface of the lesion compared with the surrounding mucosa (Fig. 5B). Surface nodularity was defined as the presence of irregularly raised or nodular mucosa (Fig. 5C). Lesions with ulcerations or scarring from previous ulceration (converging folds or deformity of the muscularis propria or fibrosis in the submucosa) were regarded as ulcerated (Fig. 5D). If submucosa fibrosis was observed during the ESD procedure, then it was recorded with endoscopic pictures (Fig. 5E). The lesion location was described using the Japanese Classification of Gastric Cancer.[13] Using this system, the gastric area is divided into 3 equal sections: the upper third, middle third, and lower third of the stomach.

All of the resected tissue slides were blindly reviewed by 2 pathologists. Doubtful cases were reevaluated under a multi-headed microscope to reach a consensus. The resected specimens were stretched, pinned, and fixed with formalin. Piecemeal-resected specimens were reconstructed as much as possible. Fixed specimens were sectioned at 2-mm intervals. The lengths of the major and minor axes were measured for all lesions. All lesions were classified as gastrointestinal epithelial neoplasia according to the Vienna classification.[8] En bloc resection was defined as resection in a one-piece manner with no residual tumor viewed endoscopically. Complete resection was defined as en bloc resection without any positive resection margins or lymphovascular invasion.

2.4. Statistical analysis

Data were analyzed based on individual lesions because some patients had multiple lesions. Univariate analysis with the chi-square test or Fisher exact test for categorical variables and Student *t* test for continuous variables were performed. Multivariate analysis with a multiple logistic regression model

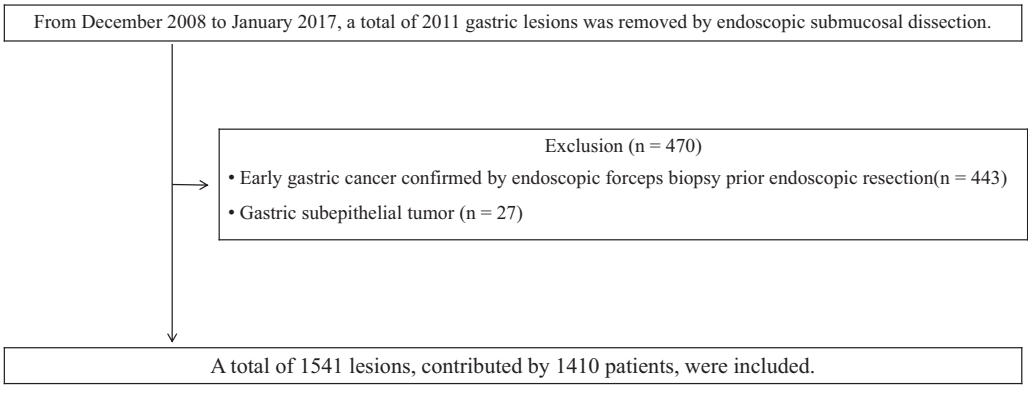

Figure 1. Flow chart of the enrolled lesions in this study. ESD = endoscopic submucosal dissection.

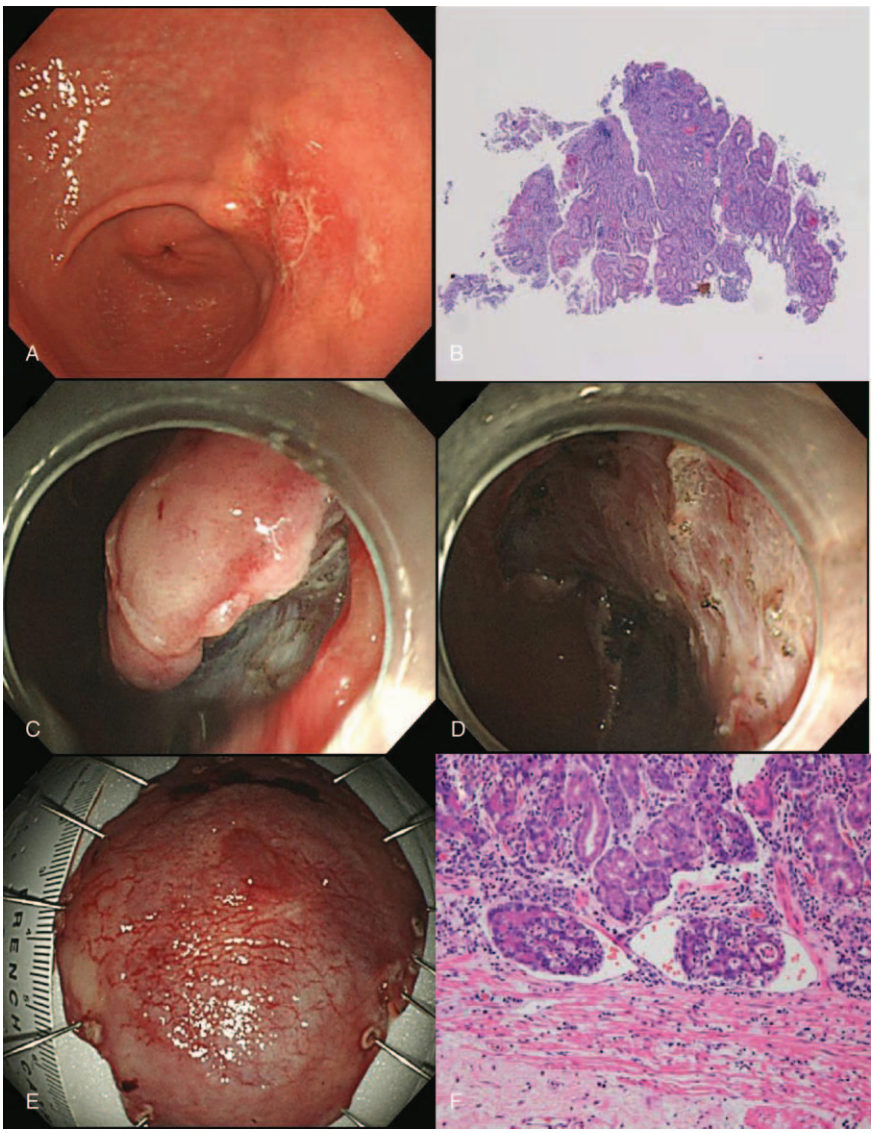

Figure 2. A case of upgrade diagnosis from indefinite for neoplasia to EGC (32-year-old man). (A) Conventional endoscopic image: the lesion located at antrum posterior wall with nodular surface redness. (B) Histology of endoscopic forceps biopsy shows a few atypical glands. (C, D) Endoscopic finding during ESD. (E) En bloc-resected ESD specimen (long diameter 5 cm). (F) Pathologically diagnosed with adenocarcinoma with lymphatic invasion. EGC = early gastric cancer; ESD = endoscopic submucosal dissection.

was performed to identify risk factors for EGC. $P < .05$ was considered statistically significant. Statistical calculations were performed with SPSS version 21.0 for Windows (SPSS Inc., Chicago, IL).

3. Results

During the study periods, a total of 1541 lesions were analyzed. The mean patient age was 63.6 ± 8.9 years. The patient population was predominantly male (71.6%; 1104/1541). The mean lesion size was 12.7 ± 8.6 mm. The main location of the lesions was the lower third of the stomach (77.5%; 1195/1541). The results of endoscopic forceps biopsy were indefinite for neoplasia (5.2%), low-grade dysplasia (71.1%), and high-grade dysplasia (23.8%). En bloc resection and complete resection rates were 97.3% (1500/1541) and 95.5% (1471/1541) (Table 1). The overall diagnostic discrepancy rate was 31.1% (479/1541). The upstaged and downstaged diagnostic rates after endoscopic resections were 23.8% (366/1541) and 7.3% (113/1541), respectively. The upstaged diagnostic rate of EGC was 18.8% (290/1541). The upstaged and downstaged diagnostic rates were 12.2% (134/1095) and 2.3% (25/1095) for the low-grade dysplasia group, 53.7% (197/367) and 12.0% (44/367) for the high-grade dysplasia group, and 43.8% (35/80) and 55.0% (44/80) for the indefinite for neoplasia group. Rates of noncancer upstaged to EGC were 6.0% (66/1094) for the low-grade dysplasia group, 53.7% (197/367) for the high-grade dysplasia group, and 33.8% (27/80) for the indefinite for neoplasia group (Table 2).

Endoscopic characteristics associated with EGC were analyzed. Multivariate analysis revealed that central depression (OR, 2.959; 95% confidence interval [CI], 1.497–5.848), nodular surface (OR, 6.581; 95% CI, 3.731–11.608), and surface redness (OR, 6.399; 95% CI, 3.476–11.780) were significantly associat-

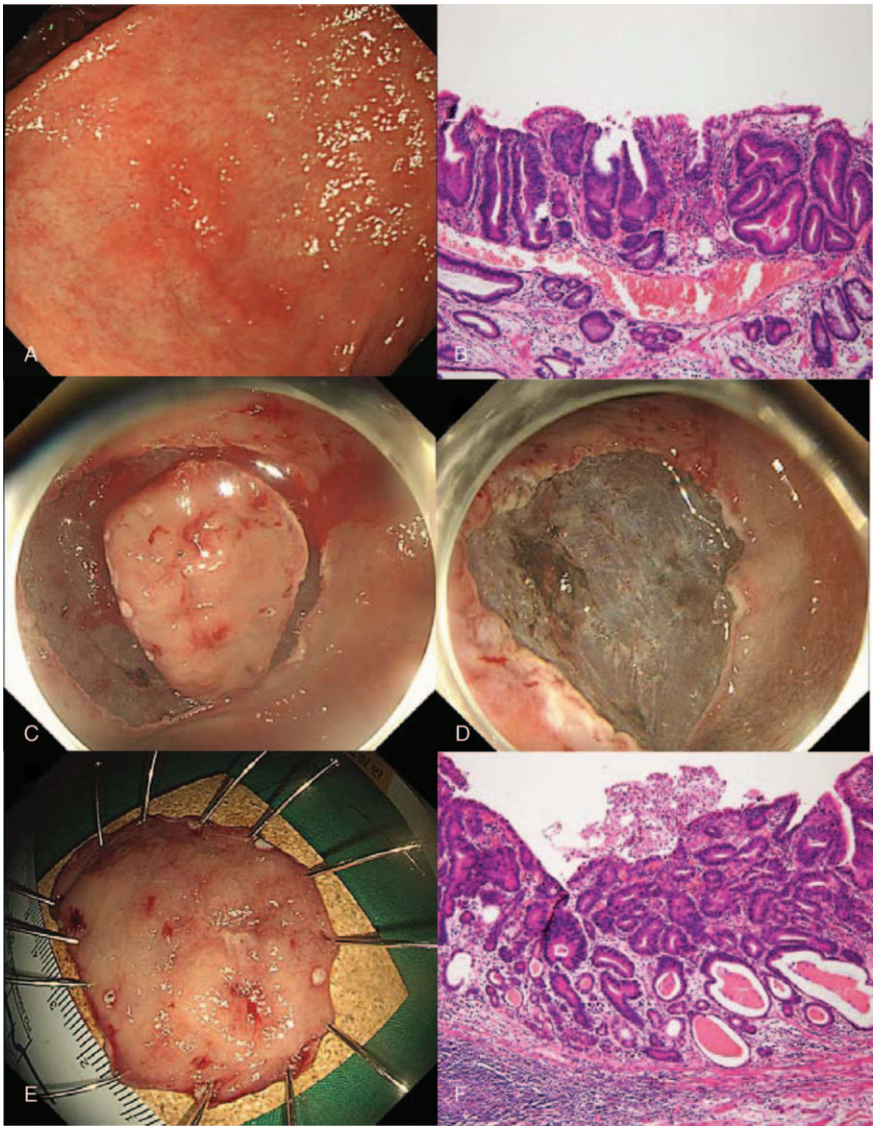

Figure 3. A case of upgrade diagnosis from low-grade dysplasia to EGC (51-year-old man). (A) Conventional endoscopic image: the lesion located at antrum lesser curvature side with nodular surface, central depression and redness. (B) Histology of endoscopic forceps biopsy shows tubular adenoma with low-grade dysplasia. (C, D) Endoscopic finding during ESD. (E) En bloc-resected ESD specimen (long diameter 5 cm). (F) Pathologically diagnosed with adenocarcinoma confined to mucosa. EGC = early gastric cancer; ESD = endoscopic submucosal dissection.

ed with EGC in the low-grade dysplasia group (Table 3 and Fig. 3). Central depression (OR, 1.999; 95% CI, 1.212–3.294), nodular surface (OR, 1.733; 95% CI 1.090–2.756), and surface redness (OR, 2.283; 95% CI, 1.441–3.619) were significantly associated with EGC in the high-grade dysplasia group (Table 4). In addition, lesion location (upper third of the stomach) (OR, 3.989; 95% CI, 1.716–9.274) and larger tumor size (≥10 mm) (OR, 2.200; 95% CI, 1.393–3.474) were significantly associated with EGC in the high-grade dysplasia group (Table 4 and Fig. 4). In the indefinite for neoplasia group, depressed gross morphology (OR, 16.017; 95% CI, 2.496–102.76) and surface redness (OR, 22.136; 95% CI, 5.267–93.029) were significantly associated with EGC (Table 5 and Fig. 2).

4. Discussion

Recently, ESD has been accepted as treatment for EGC without the risk of lymph node metastasis or gastric premalignant superficial neoplasia. After successful endoscopic resection, discrepant diagnoses using endoscopic forceps biopsy and ESD specimens have been clinical concerns. EGC cases with a high risk of lymph node metastasis require additional surgical gastrectomy, and patients diagnosed with EGC after endoscopic resection may be confused about future treatments. In the present study, the overall diagnostic discrepancy rate was 31.1%. The overall rate of upstaged diagnosis to EGC was 18.8%: low-grade dysplasia (6.0%), high-grade dysplasia (53.7%), and indefinite for neoplasia (33.8%). The overall rates of discrepant diagnoses were similar to those of previous studies and ranged from 20% to 40%.[14] There are a few possible reasons for discrepant diagnoses using endoscopic forceps biopsy and resected specimens. First, the adenocarcinoma lesion is too subtle to detect in a small biopsy specimen. Cancerous lesions may exist focally within background dysplastic lesions. Therefore, sampling error during an endoscopic forceps biopsy may be the major cause of diagnostic discrepancy.[9] Second, regeneration of tissue showing

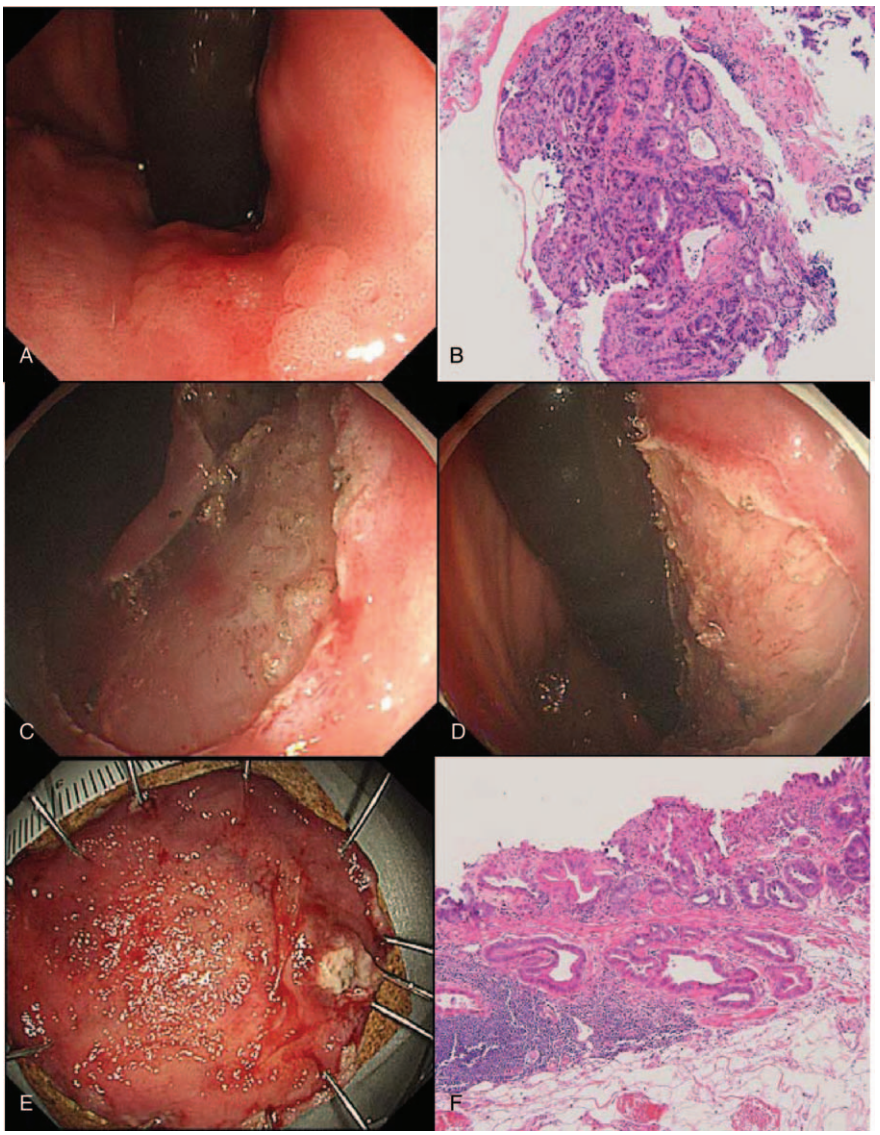

Figure 4. A case of upgrade diagnosis from high-grade dysplasia to EGC (80-year-old man). (A) Conventional endoscopic image: the lesion located at cardia with nodular surface, central depression and redness. (B) Histology of endoscopic forceps biopsy shows tubular adenoma with high-grade dysplasia. (C, D) Endoscopic finding during ESD. (E) En bloc-resected ESD specimen (long diameter 5 cm). (F) Pathologically diagnosed with adenocarcinoma invaded the submucosa. EGC = early gastric cancer; ESD = endoscopic submucosal dissection.

cellular atypia induced by active inflammation induces histologic modification, which may be associated with downstaged diagnoses after endoscopic resection. In the present study, the possible endoscopic features associated with EGC were lesion size (maximal diameter >10 mm), surface appearance (depression lesion, nodular surface, redness), and lesion location (upper third of the stomach). These results were comparable with those of previous studies.[9,11,15]

According to the revised Vienna classification, high-grade dysplasia lesions should be resected because they are definitely premalignant or potentially malignant lesions.[8] The treatment plan is ambiguous for gastric low-grade dysplasia or indefinite for neoplasia after endoscopic forceps biopsy: do nothing if indefinite for neoplasia, endoscopic follow-up, or endoscopic resection for low-grade dysplasia.[8] However, in the present study, 33.8% of lesions indefinite for neoplasia and 6.0% of low-grade dysplasia lesions were confirmed as EGC after ESD. Therefore, it may not be appropriate to recommend regular follow-up for all these lesions. Although the natural course of gastric dysplastic lesions is not clear, reported rates of progression from dysplasia to gastric cancer vary greatly, from 0.6% to 6% per year, according to the grade of dysplasia.[16] In recent years, better en bloc resection for gastric superficial neoplasia regardless of lesion size can be achieved by ESD compared with conventional endoscopic mucosal resection using a snare. In the present study, en bloc resection and complete histologic resection rates for ESD were 97.3% and 95.5%, respectively. Therefore, gastric low-grade dysplasia and lesions indefinite for neoplasia according to endoscopic forceps biopsy that have high-risk endoscopic features of EGC should be considered for endoscopic resection, if possible, rather than regular follow-up or doing nothing.

To decrease the diagnostic discrepancy between endoscopic forceps biopsy and resected specimens, a proper endoscopic biopsy is required. An increasing number of biopsy specimens

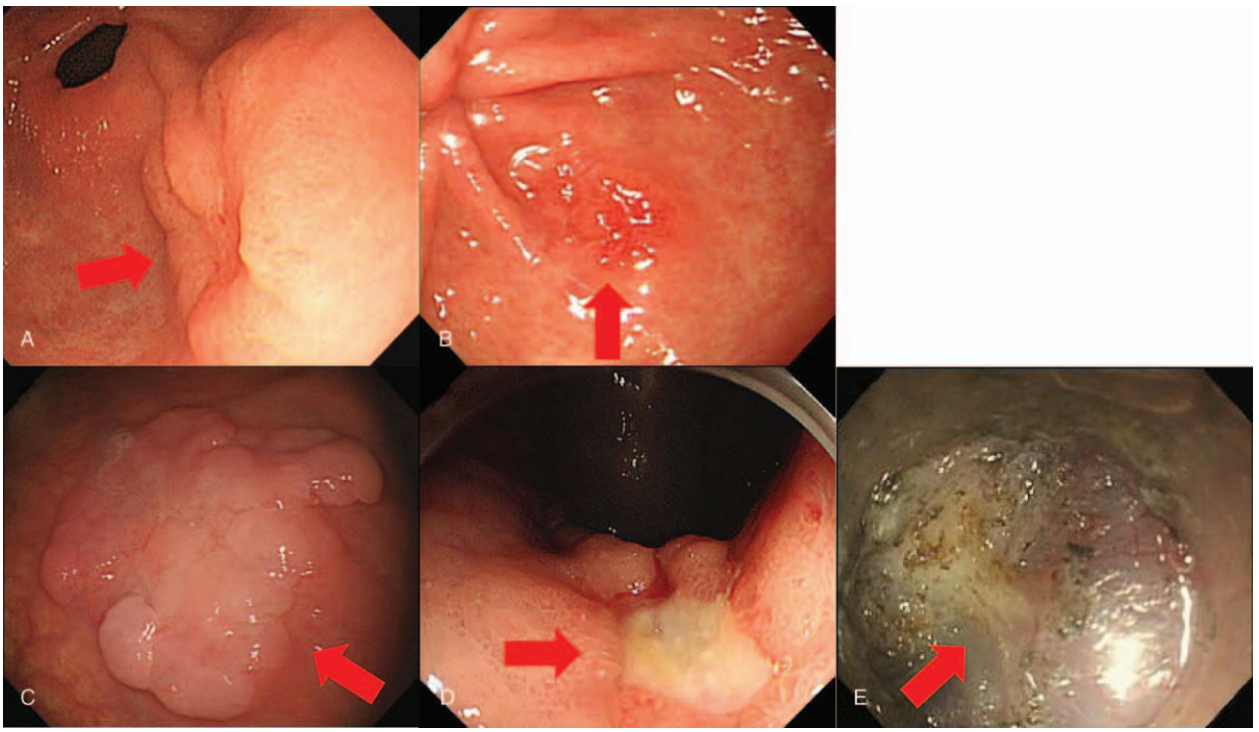

Figure 5. Endoscopic features showing upstage diagnostic lesions. (A) Central depression; (B) surface redness; (C) surface nodularity; (D) ulceration; and (E) submucosal fibrosis.

Table 1

Baseline characteristics in this study.

	Total (n = 1541)
Male, n (%)	1104 (71.6)
Mean age [y (±SD)]	63.6 ± 8.9
Tumor size, n (%)	
≤10 mm	744 (48.3)
>10 mm	797 (51.7)
Mean size [mm (±SD)]	12.7 ± 8.6
Tumor location, n (%)	
Upper third of stomach	136 (8.8)
Middle third of stomach	210 (13.6)
Lower third of stomach	1195 (77.5)
Gross type, n (%)	
Elevated	784 (50.9)
Flat	485 (31.5)
Depressed	272 (17.6)
Central depression	234 (15.2)
Nodular surface	428 (27.8)
Surface redness	319 (20.7)
Ulcer	126 (8.2)
Submucoal fibrosis	201 (13.0)
En bloc resection, n (%)	1500 (97.3)
Complete resection, n (%)	1471 (95.5)
Endoscopic forceps biopsy result, n (%)	
Low-grade dysplasia	1095 (71.1)
High-grade dysplasia	367 (23.8)
Indefinite for neoplasia	80 (5.2)
Endoscopic submucosal dissection result, n (%)	
Low-grade dysplasia	998 (64.8)
High-grade dysplasia	201 (13.0)
Early gastric cancer	290 (18.8)
Negative for neoplasia	52 (3.4)

SD = standard deviation.

may increase the diagnostic rates. In a previous study, if 7 endoscopic forceps biopsy samples were available, then the diagnostic rate was >98% for advanced gastric cancer.[17] For gastric epithelial neoplasia before ESD, diagnostic rates of endoscopic forceps biopsy increased up to 79.1% and 83.1% after 4 endoscopic biopsies (diagnostic yield of 1 endoscopic biopsy was 65.7%–70.8%).[18] However, for gastric superficial neoplasia, especially small lesions, multiple endoscopic biopsies may be an obstacle for endoscopic resection because submucosal fibrosis is induced by endoscopic biopsy. In a previous study, the diagnostic rate of the first endoscopic biopsy was 92.3% for minute gastric cancer, but the diagnostic rates of the second biopsy were <63.6%.[19] Therefore, the first biopsy is important because bleeding in the lesion may cover the entire lesion, which may interfere with adequate tissue acquisition after the first biopsy. Theoretically, larger biopsy specimens may improve the diagnostic accuracy of gastric epithelial neoplasia. However, the diagnostic accuracy rate was not increased significantly by the use of large biopsy forceps.[18] Therefore, it is important to perform a target biopsy for the suspected EGC lesions with depression, nodular surface, and redness.

In clinical practice, proper selection of patients who need ESD is important. Therefore, characteristics of the endoscopic findings predictive of EGC are important. In the present study, risk factors associated with EGC after ESD for low-grade dysplasia were central depression, nodular surface, and surface redness. As lesions progress, structural changes appear. Central depression and nodular surface are associated with lesion progression.[20] Surface redness is associated with the development of vascular structures with disease progression.[21] In addition, larger tumor size (≥10 mm) and lesion location (upper third of the stomach) were significantly associated with upstaged diagnosis of EGC in the high-grade dysplasia group. Size is a commonly known

Table 2

Histologic comparison between endoscopic forceps biopsy and final endoscopic submucosal dissection.

	Endoscopic forceps biopsy			
ESD	**LGD (n = 1094)**	**HGD (n = 367)**	**Indefinite for neoplasia (n = 80)**	**Total (n = 1541)**
Downstaged, n (%)	25 (2.3)	44 (12.0)	44 (55.0)	113 (7.3)
Concordance, n (%)	935 (85.5)	126 (34.3)	1 (1.2)	1062 (68.9)
Upstaged, n (%)	134 (12.2)	197 (53.7)	35 (43.8)	366 (23.8)
Early gastric cancer, n (%)	66 (6.0)	197 (53.7)	27 (33.8)	290 (18.8)

ESD = endoscopic submucosal dissection; LGD = low-grade dysplasia; HGD = high-grade dysplasia.

Table 3

Characteristics and associated risk factors for upgrade diagnosis low-grade dysplasia to EGC in univariate and multivariate analysis (*premalignant epithelial lesion, n = 1028/EGC, n = 66).

			Univariate analysis			Multivariate analysis		
Variables	**Premalignant epithelial lesion, n (%)**	**EGC, n (%)**	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Age > 60	656 (63.8)	45 (68.2)	1.215	0.713–2.071	.474	1.072	0.590–1.947	.819
Mean age [y ± (SD)]	63.6 ± 9.08	63.5 ± 9.07						
Male sex	713 (69.4)	55 (83.3)	2.209	1.141–4.277	.019	1.808	0.888–3.679	.102
Gross type								
Elevated (ref.)	613 (59.6)	26 (39.4)	1.000			1.000		
Flat	321 (31.2)	26 (39.4)	1.910	1.091–3.344	.024	1.624	0.655–4.028	.295
Depressed	94 (9.1)	14 (21.2)	3.512	1.770–6.967	<.001	1.877	1.003–3.513	.049
Central depression	58 (5.6)	19 (28.8)	6.761	3.729–12.259	<.001	2.959	1.497–5.848	.002
Nodular surface	216 (21.0)	43 (65.2)	8.586	5.068–14.548	<.001	6.581	3.731–11.608	<.001
Surface redness	88 (8.6)	29 (43.9)	8.372	4.913–14.266	<.001	6.399	3.476–11.780	<.001
Ulcer	36 (3.5)	11 (16.7)	5.400	2.608–11.181	<.001	2.493	0.993–6.259	.052
SM fibrosis	97 (9.4)	19 (28.8)	3.880	21.89–6.878	<.001	1.825	0.664–5.012	.243
Location								
Lower (ref.)	782 (76.1)	54 (81.8)	1.000			1.000		
Upper	87 (8.5)	4 (6.1)	0.666	0.235–1.883	.443	0.919	0.300–2.814	.882
Middle	159 (15.5)	8 (12.1)	0.729	0.340–1.561	.415	0.639	0.269–1.521	.312
Size > 10mm	507 (49.3)	43 (65.2)	1.921	1.141–3.234	.014	1.056	0.579–1.926	.858
Mean size [mm ± (SD)]	12.6 ± 8.39	13.9 ± 7.58						

* Premalignant epithelial lesion: low-grade dysplasia, high-grade dysplasia, indefinite for neoplasia.
EGC = early gastric cancer; SM = submucosa; SD = standard deviation.

Table 4

Characteristics and associated risk factors for upgrade diagnosis high-grade dysplasia to EGC in univariate and multivariate analysis (*premalignant epithelial lesion, n = 170/EGC, n = 197).

			Univariate analysis			Multivariate analysis		
Variables	**Premalignant epithelial lesion, n (%)**	**EGC, n (%)**	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Age > 60	108 (63.5)	136 (69.0)	1.280	0.829–1.980	.266	0.948	0.584–1.536	.827
Mean age [y ± (SD)]	63.2 ± 8.30	64.6 ± 8.84						
Male sex	135 (79.4)	148 (75.1)	0.783	0.479–1.281	.331	0.810	0.464–1.414	.458
Gross type								
Elevated (ref.)	53 (31.2)	64 (32.5)	1.000			1.000		
Flat	52 (30.6)	61 (31.0)	0.972	0.578–1.632	.913	0.863	0.483–1.543	.619
Depressed	65 (38.2)	72 (36.5)	0.917	0.556–1.504	.733	0.530	0.279–1.005	.052
Central depression	43 (25.3)	86 (43.7)	2.288	1.465–3.571	<.001	1.999	1.212–3.294	.007
Nodular surface	57 (33.5)	97 (49.2)	1.923	1.259–2.937	.003	1.733	1.090–2.756	.020
Surface redness	59 (34.7)	111 (56.3)	2.428	1.591–3.707	<.001	2.283	1.441–3.619	<.001
Ulcer	25 (14.7)	38 (19.3)	1.386	0.800–2.409	.247	1.194	0.617–2.3611	.599
SM fibrosis	23 (13.5)	48 (24.4)	2.059	1.192–3.557	.010	1.597	0.843–3.024	.151
Location								
Lower (ref.)	141 (82.9)	155 (78.7)	1.000			1.000		
Upper	9 (5.3)	28 (14.2)	2.830	1.291–6.204	.009	3.989	1.716–9.274	.001
Middle	20 (11.8)	14 (7.1)	0.637	0.310–1.308	.219	0.822	0.402–1.680	.591
Size > 10 mm	80 (47.1)	132 (67.0)	2.285	1.500–3.488	<.001	2.200	1.393–3.474	.001
Mean size [mm ± (SD)]	12.4 ± 8.87	14.3 ± 8.47						

* Premalignant epithelial lesion: low-grade dysplasia, high-grade dysplasia, indefinite for neoplasia.
EGC = early gastric cancer; SM = submucosa; SD = standard deviation.

Table 5

Characteristics and associated risk factors for upgrade diagnosis indefinite neoplasia to EGC in univariate and multivariate analysis (*premalignant epithelial lesion, n = 53/EGC, n = 27).

Variables	Premalignant epithelial lesion, n (%)	EGC, n (%)	Univariate analysis			Multivariate analysis		
			OR	95% CI	P	OR	95% CI	P
Age > 60	30 (56.6)	13 (48.1)	0.712	0.281–1.804	.474	1.372	0.283–6.663	.695
Mean age [y ± (SD)]	60.9 ± 7.43	61.2 ± 12.12						
Male sex	35 (66.0)	18 (66.7)	1.029	0.385–2.745	.955	2.096	0.381–11.537	.395
Gross type								
Elevated (ref.)	25 (47.2)	3 (11.1)	1.000			1.000		
Flat	18 (34.0)	7 (25.9)	3.241	0.736–14.265	.120	5.267	0.763–36.351	.092
Depressed	10 (18.9)	17 (63.0)	14.167	3.391–59.19	<.001	16.017	2.496–102.76	.003
Central depression	10 (18.9)	18 (66.7)	8.600	2.993–24.71	<.001	2.700	0.363–20.082	.332
Nodular surface	7 (13.2)	8 (29.6)	2.767	0.879–8.709	.082	4.417	0.814–21.12	.087
Surface redness	10 (18.9)	22 (81.5)	18.920	5.755–62.20	<.001	22.136	5.267–93.029	<.001
Ulcer	6 (11.3)	10 (37.0)	4.608	1.453–14.614	.010	1.161	0.133–10.152	.893
SM fibrosis	7 (13.2)	7 (25.9)	2.300	0.713–7.424	.163	1.053	0.146–7.572	.959
Location								
Lower (ref.)	42 (79.2)	21 (77.8)	1.000			1.000		
Upper	4 (7.5)	4 (14.8)	2.000	0.455–8.800	.359	3.833	0.255–57.677	.331
Middle	7 (13.2)	2 (7.4)	0.571	0.109–2.995	.508	1.540	0.158–15.006	.710
Size > 10mm	19 (35.8)	16 (59.3)	2.603	1.006–6.737	.049	2.547	0.551–11.776	.231
Mean size [mm ± (SD)]	9.9 ± 8.12	13.2 ± 6.66						

* Premalignant epithelial lesion: low-grade dysplasia, high-grade dysplasia, indefinite for neoplasia.
EGC = early gastric cancer; SM = submucosa; SD = standard deviation.

feature of malignancy; as the size increases, so does disease progression.[10] However, in this study, size was not significant for the low-grade dysplasia and indefinite for neoplasia groups. In clinical practice, a huge adenoma with low-grade dysplasia is sometimes seen, but the reason is unclear. Furthermore, we do not definitely know why the upper third of the stomach is a significant risk factor associated with EGC for the high-grade dysplasia group. One possible explanation is that EGC located in the lower third of the stomach, especially in the antrum, might be easily detected. To detect EGC in the upper third of the stomach, more practical experience and endoscopic procedures might be required. Therefore, EGC lesions located in the upper third of the stomach might result in delayed or missed diagnoses. Another possible explanation is that targeted biopsy of lesions located in the upper third of the stomach is difficult. Additional studies might be required to clearly explain the reasons for this finding.

There were several limitations to this study. First, it was retrospectively conducted at a single center; therefore, selection biases might be present and it is impossible to generalize the conclusions of this paper. However, we believe that this is a meaningful study because we included a large number of patients compared to other previous studies. Second, we used the conventional endoscopic appearances of lesions for the analysis. If recent diagnostic tools such as image-enhanced endoscopy were used, then more accurate diagnoses may have been made before ESD. Third, there was a possibility of discrepancy caused by performing biopsies once or twice during endoscopic resection. Multiple biopsies may result in excessive fibrosis, which is a serious problem during ESD.

In summary, when high-grade dysplasia is found by endoscopic forceps biopsy, ESD should be considered. Low-grade dysplasia lesions with central depression, nodular surface, and surface redness and lesions that are indefinite for neoplasia with depression and surface redness should also be considered for ESD. Furthermore, lesions with these risk factors should be examined for the possibility of gastric cancer and the possibility for surgery before endoscopic resection.

Author contributions

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