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Diagnostic group classifications of gastric neoplasms by endoscopic resection criteria before and after treatment: real-world experience

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Abstract

Background and study aims There are often discrepancies between the pretreatment evaluation of gastric neoplasms by endoscopy with biopsy and the final diagnosis of resected specimen in terms of pathology and depth of invasion. We evaluated the spectrum of discrepancies between pretreatment and posttreatment diagnosis which may deliver significant differences on clinical practice.

Patients and methods A total of 2041 patients with gastric dysplasia or cancer who underwent curative endoscopic resections or surgeries in 2012 were enrolled. Patients were classified into five different diagnostic groups: low-grade dysplasia (LGD), high-grade dysplasia (HGD), absolute indication early gastric cancer (AI-EGC), beyond absolute indication early gastric cancer (BAI-EGC), and advanced gastric cancer (AGC). The choice of initial treatment and final pathologic diagnosis was analyzed.

Results The study patients belonged to the following pretreatment diagnostic groups: LGDs in 162, HGDs in 164, AI-EGCs in 396, BAI-EGCs in 824, and AGCs in 495 cases. Posttreatment diagnostic groups were LGDs in 140, HGDs in 121, AI-EGCs in 322, BAI-EGCs in 947, AGCs in 505, and no residual tumor in 6 cases. In general, 6.9 % (141/2041) of cases were downgraded and 15.9 % (324/2041) were upgraded. Thirty-four percent of pretreatment HGDs (56/164) were changed to cancers after endoscopic resection. Thirty-three percent of pretreatment AI-EGCs (131/396) were regrouped as posttreatment BAI-EGCs. The additional surgery rate in each pretreatment group was 0.6 % in LGD, 4.3 % in HGD, 15.7 % in AI-EGC, 23.6 % in BAI-EGC among the patients with initial endoscopic resection ($p < 0.01$).

Conclusions Twenty-three percent of gastric neoplasms changed in their final diagnostic group after endoscopic resection or surgery. This discrepancy should be considered when the initial treatment strategy is being selected.

Keywords Stomach neoplasms · Diagnosis · Endoscopic submucosal dissection

Gastric cancer is the second leading cause of global cancer death and the most common malignancy in Korea [1]. Early gastric cancer (EGC) is defined as a gastric cancer that invades no more deeply than the submucosa, irrespective of lymph node metastasis. The proportion of EGC among all gastric cancers is increasing due to technical advances and the introduction of the mass screening program. Endoscopic submucosal dissection (ESD), one of the most advanced endoscopic resection techniques, has become the standard treatment for EGCs meeting the absolute indications [2–4].

In the era of endoscopic treatment of EGC, a precise pretreatment evaluation of gastric neoplasm is important for the choice of treatment method. Despite the development of advanced diagnostic techniques such as endoscopic ultrasonography [5], magnifying endoscopy [6], and chromoendoscopy [7], there remains a considerable discrepancy between the pretreatment and posttreatment

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diagnosis of gastric neoplasm. First, there is a remarkable histological discrepancy between forceps biopsy-based and endoscopic resection specimen-based diagnosis. For example, the final histological diagnosis of 32–53 % of high-grade dysplasia is changed to gastric cancer after endoscopic resection [8, 9]. Second, the lesion size measured before and after endoscopic resection may differ considerably [10]. Third, estimation of the depth of invasion before the treatment is not reliable, even after endoscopic ultrasonography [5]. These discrepancies should be considered during the selection of initial treatment, because they may influence the overall outcome.

Previous studies about the clinical outcome of endoscopic treatment of EGCs have been based on posttreatment pathologic diagnosis [3, 11–18]. Data about treatment outcomes based on pretreatment evaluation are rare [19]. In real clinical practice, however, the choice for initial treatment modality relies on incomplete information such as endoscopic findings, biopsy results, and lymph node status in computerized tomography (CT).

In the present study, we analyzed the real-world discrepancy between pretreatment and posttreatment diagnosis of gastric neoplasms in terms of ESD indications. All cases with gastric dysplasia and cancers were included regardless of their initial treatment options (endoscopic resection or surgery). Because the analysis was based on pretreatment evaluation results, data from the present study can give valuable information to the doctors and the patients while selecting initial treatment options.

Patients and methods

Patients

A total of 2041 patients with gastric dysplasia or cancer who underwent endoscopic or surgical resection at Samsung Medical Center from January 2012 to December 2012 were included. Patients receiving palliative surgery for advanced gastric cancer (AGC) were not included.

Definition of diagnostic groups

We classified the cases into five diagnostic groups based on the histology (dysplasia or cancer), absolute indications for endoscopic resection [20, 21] (within or beyond indications), and depth of invasion (EGC or AGC). We grouped the cases before and after treatment to analyze grouping discrepancies. The five diagnostic groups are (1) low-grade dysplasia (LGD), (2) high-grade dysplasia (HGD), (3) absolute indication EGC (AI-EGC) satisfying absolute indications for endoscopic treatment, (4) beyond absolute indication EGC (BAI-EGC) not satisfying absolute indications for endoscopic treatment, and (5) AGC. Pretreatment groupings were made on the basis of endoscopy results, lymph node status by abdominal CT, and the pathologic report of forceps biopsies. Conventional endoscopy was done mostly with indigo carmine spray, but without magnification. Posttreatment groupings were made on the basis of pathologic findings of ESD or surgical specimens. Absolute indication for endoscopic treatment was defined as a differentiated-type adenocarcinoma without ulcerative findings, where the depth of invasion was confined to the mucosa and the diameter was 2 cm or less [20, 21]. When there was evidence of endolymphatic or vascular invasion in the resected specimen, the lesion was considered as beyond absolute indication.

As a secondary analysis, we applied the concept of expanded indications to group 4 (BAI-EGC) cases. Expanded indications [2, 20, 21] in the present study were defined as (1) differentiated mucosal cancers without ulcer irrespective of size, (2) differentiated mucosal cancer with ulcer $\leq$3 cm, (3) differentiated submucosal cancer with $\leq$500 μm depth of invasion (sm1) $\leq$3 cm in size without angiolymphatic invasion, and (4) undifferentiated mucosal cancer $\leq$2 cm.

Treatments

Each case was initially treated by ESD or surgical resection. The ESDs were performed by three experienced endoscopists (J. H. L., B. H. M, and J. J. K.) in our institution. Surgery was performed when an endoscopically treated gastric cancer showed submucosal invasion more than 500 μm, evidence of endolymphatic emboli, and undifferentiated-type histology with submucosal invasion. Subtotal gastrectomy or total gastrectomy with standard D2 lymph node dissection was done for surgical patients. After endoscopic or surgical resection, the neoplastic lesions were cut into serial sections with the surrounding non-neoplastic mucosa. The size of the lesion was measured with the formalin-fixed specimen. Cell type, depth of invasion (lamina propria, muscularis mucosa, submucosa, proper muscle, or serosa), and presence of microinvasion (lymphatic, venous, or perineural invasion) were analyzed. All specimens were examined by one gastrointestinal pathologist (K. M. K.). Final treatment for gastric neoplasms based on the initial diagnosis was classified into four categories: (1) ESD, when the treatment was finished with initial ESD only; (2) ESD plus second ESD, when additional ESD was performed after initial ESD; (3) ESD plus additional surgery, when additional surgery was done after initial ESD; and (4) surgery, when surgery was initially chosen for the treatment of gastric neoplasms.

Statistical analysis

Statistical analyses were performed with commercially available statistical software, SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). We used the Chi-square test, Fisher's exact test, and Cochran–Armitage test. A p value of <0.05 was considered significant.

Results

Changes in pretreatment and posttreatment groups

Table 1 shows the distribution and the pattern of changes in the diagnostic groups in patients with gastric dysplasia or cancer. Among 2041 patients, pretreatment diagnostic group classification was LGD in 162, HGD in 164, AI-EGC in 396, BAI-EGC in 824, and AGC in 495 patients. Posttreatment diagnostic group classification was LGD in 140, HGD in 122, AI-EGC in 322, BAI-EGC in 947, AGC in 505, and no residual tumor in 6 patients. As a whole, 77.2 % (1576/2041) of gastric neoplasms belonged to the same diagnostic group before and after treatment. However, 6.9 % (141/2041) of cases were downgraded and 15.9 % (324/2041) were upgraded.

Among 326 cases with dysplasia in endoscopic biopsy, 20.2 % (66/326) were changed to gastric cancer based on the final histology of the resected specimen. The rate was 6.1 % for LGDs (10/162) and 34.2 % for HGDs (56/164), which was a significant difference ($p < 0.01$).

Among 396 cases in the pretreatment AI-EGC group, 33.3 % (131/396) were changed to the posttreatment BAI-EGC group. The most common reason for this discrepancy was the tumor size bigger than the pretreatment estimation (53.4 %), followed by submucosal invasion (49.6 %), lymphovascular invasion (19.6 %), and change in the histological differentiation (6.9 %). In contrast, only 2.7 % (22/824) of pretreatment BAI-EGCs were changed to posttreatment AI-EGCs. The reason for this discrepancy included tumor size smaller than the pretreatment estimation (86.4 %) and change in histological differentiation (13.6 %). The discrimination between EGC and AGC was not perfect. As can be seen in Table 1, 6.7 % (82/1220) of pretreatment EGCs were reclassified as posttreatment AGCs and 14.7 % (73/495) of pretreatment AGCs were reclassified as posttreatment EGCs.

Treatment modalities by pretreatment diagnostic groups

Table 2 shows what kind of treatment modalities was used in each pretreatment diagnostic group. Cases with dysplasia were initially treated endoscopically except for one patient with repeated (three times) recurrence of high-grade dysplasia. Among pretreatment AI-EGCs, 89.6 % (355/396) were initially treated by ESD and 10.4 % (41/396) by surgery (Fig. 1). The most common reason for selection of the initial surgery for pretreatment AI-EGCs was suspicious lymphadenopathy on CT scan ($n = 18$), followed by surgeon preference (n=10), multiple lesions (n=6), patient wishes ($n = 3$), difficult location ($n = 2$), and suspicious submucosal invasion on endoscopic ultrasonography ($n = 2$). Among the 355 pretreatment AI-EGCs initially treated by ESD, 120 were BAI-EGCs and 1 was AGC (Fig. 1). Pretreatment BAI-EGCs were initially treated surgically in 93.3 % (769/824) and endoscopically in 6.7 % (55/824) of cases (Table 2).

Table 1 Pretreatment and posttreatment diagnostic group classification for gastric dysplasias or cancers

Posttreatment diagnostic group	Pretreatment diagnostic group (%)				
	LGD (n=162)	HGD (n=164)	AI-EGC (n=396)	BAI-EGC (n=824)	AGC (n=495)
No residual	2 (1.2)	4 (2.4)	0	0	0
LGD	105 (64.8)	33 (20.1)	2 (0.5)	0	0
HGD	45 (27.8)	71 (43.3)	4 (1.0)	1 (0.1)	0
AI-EGC	5 (3.1)	36 (22.0)	258 (64.9)	22 (2.7)	1 (0.3)
BAI-EGC	5 (3.1)	19 (11.6)	131 (33.3)	720 (87.4)	72 (14.5)
AGC	0	1 (0.6)	1 (0.3)	81 (9.8)	422 (85.3)
Downgraded (%)	1.2	23.7	1.5	2.8	14.7
No change (%)	64.8	43.3	64.9	87.4	85.3
Upgraded (%)	34.0	34.1	33.6	9.8	0

LGD low-grade dysplasia, *HGD* high-grade dysplasia, *AI-EGC* absolute indication early gastric cancer, *BAI-EGC* beyond absolute indication early gastric cancer

Table 2 Treatment modalities by the pretreatment diagnostic group

Treatment modality	Pretreatment diagnostic group (%)				
	LGD (*n*=162)	HGD (*n*=164)	AI-EGC (*n*=396)	BAI-EGC (*n*=824)	AGC (*n*=495)
ESD	160 (95.8)	156 (95.1)	297 (75.0)	42 (5.1)	0
ESD + second ESD	1 (0.6)	0	2 (0.5)	0	0
ESD + surgery	1 (0.6)	7 (4.3)	56 (14.1)	13 (1.6)	0
Surgery	0	1 (0.6)	41 (10.4)	769 (93.3)	495 (100)

LGD low-grade dysplasia, *HGD* high-grade dysplasia, *AI-EGC* absolute indication early gastric cancer, *BAI-EGC* beyond absolute indication early gastric cancer, *ESD* endoscopic submucosal dissection

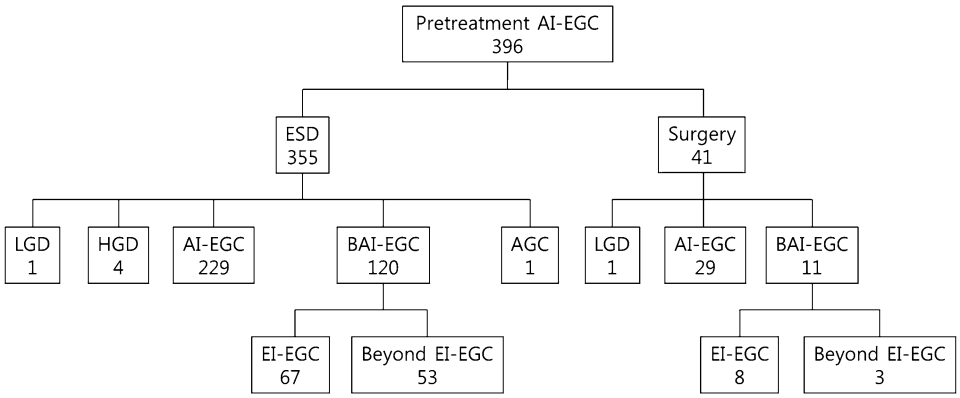

Fig. 1 Real-world treatment algorithm of pretreatment absolute indication early gastric cancers. *AI-EGC* absolute indication early gastric cancer, *BAI-EGC* beyond absolute indication early gastric cancer, *EI-EGC* expanded indication early gastric cancer, *LGD* low-grade dysplasia, *HGD* high-grade dysplasia, *ESD* endoscopic submucosal dissection

Rate of additional surgery after ESD

Among patients with initial endoscopic treatment, the rate of additional surgery was 0.6 % (1/162) in LGDs, 4.3 % (7/164) in HGDs, 15.7 % (56/355) in AI-EGCs, and 23.6 % (13/55) in BAI-EGCs (Table 3). There was a trend of increasing rate of surgery as malignancy potential increased ($p < 0.01$, Cochran–Armitage test). In pretreatment AI-EGCs initially treated by ESD, the most common reason for additional surgery was SM invasion more than 500 μm ($n = 41$), followed by lymphovascular involvement ($n = 20$) and resection margin involvement ($n = 17$), with some characteristics overlapping (Table 3).

Comparison between pretreatment and posttreatment EI-EGCs

Cancers in the BAI-EGC group can be divided into expanded indication EGCs (EI-EGCs) and beyond EI-EGCs (BEI-EGCs). Table 4 shows the comparison between pretreatment and posttreatment EI-EGCs among patients initially treated by ESD. Although we usually choose ESD candidates by absolute indications in our institution, 54 cases with pretreatment EI-EGC were initially treated by ESD. Those patients were not included in the AI-EGC group because of tumor size larger than 2 cm ($n = 52$), undifferentiated-type histology ($n = 1$), and

Table 3 Rate and reasons for additional surgery among patients with initial endoscopic treatment in each pretreatment diagnostic group

	Cases with initial endoscopic treatment in each pretreatment diagnostic group				
	LGD (*n*=162)	HGD (*n*=164)	AI-EGC (*n*=355)	BAI-EGC (*n*=55)	AGC (*n*=0)
Additional surgery (%)	1 (0.6)	7 (4.3)	56 (15.7)	13 (23.6)	0
Reason					
SM invasion more than 500 μm	1	5	41	9	0
RM positive	0	3	17	3	0
LV invasion	0	1	20	6	0

LGD low-grade dysplasia, *HGD* high-grade dysplasia, *AI-EGC* absolute indication early gastric cancer, *BAI-EGC* beyond absolute indication early gastric cancer, *ESD* endoscopic submucosal dissection, *SM* submucosal, *RM* resection margin, *LV* lymphovascular

Table 4 Comparison of pretreatment and posttreatment expanded indication early gastric cancers among patients with initial endoscopic treatment

	Pretreatment EI-EGC (%) (n=54)	Posttreatment EI-EGC (%) (n=111)	p value
Pretreatment			
LGD	0	1 (0.9)	
HGD	0	12 (10.8)	
AI-EGC	0	67 (60.4)	
EI-EGC	54 (100)	31 (27.9)	
Posttreatment			
AI-EGC	10 (18.5)	0	
EI-EGC	31 (57.4)	111 (100)	
BEI-EGC	13 (24.1)	0	
ESD outcome			
Complete resection	46 (85.2)	102 (94.4)	0.185
En bloc resection	51 (94.4)	108 (97.3)	0.360
ESD complication			
Bleeding	5 (9.2)	6 (5.4)	0.353
Perforation	2 (3.7)	1 (0.9)	0.206
Final treatment			0.395
ESD only	41 (75.9)	92 (82.9)	
ESD + second ESD	0	2 (1.8)	
ESD + surgery	13 (24.1)	15 (15.3)	

LGD low-grade dysplasia, *HGD* high-grade dysplasia, *AI-EGC* absolute indication early gastric cancer, *EI-EGC* expanded indication early gastric cancer, *BEI-EGC* beyond expanded indication early gastric cancer, *ESD* endoscopic submucosal dissection

ulcerative findings ($n = 1$). In some cases, there were another factors behind choosing ESD for pretreatment EI-EGCs, such as comorbidities ($n = 12$), age older than 75 ($n = 10$), and patient wishes ($n = 2$). After ESD for 54 pretreatment EI-EGCs, 57.4 % (31/54) were reclassified as EI-EGCs, 24.1 % (13/54) as BEI-EGCs, and 18.5 % (10/54) as AI-EGCs.

There were 111 cases of posttreatment EI-EGCs. However, 74.8 % (83/111) of them were originally considered as LGD ($n = 1$), HGDs ($n = 12$), or AI-EGCs ($n = 67$), so they represent cases upgraded after ESD. The rate of complete resection was slightly lower in pretreatment EI-EGCs than posttreatment EI-EGCs (85.2 vs 94.4 %, $p = 0.185$). Accordingly, the rate of additional surgery was slightly higher in pretreatment EI-EGCs compared to posttreatment EI-EGCs (24.1 vs 15.3 %, $p = 0.155$).

Discussion

Gastric ESD is indicated for most cases with gastric dysplasia and selected cases of EGC, but most of the previous studies have focused on cancers in the posttreatment diagnosis [3, 11, 13]. The present study is very comprehensive. All cases of gastric dysplasia, EGC, and AGC were included, and both pretreatment and posttreatment diagnoses were analyzed. Histological diagnosis may change in a resected specimen. However, the diagnostic group classification based on both histology and clinical staging may change in a greater proportion of patients after treatment. We found that the rate of discrepancy between pretreatment and posttreatment diagnostic groups of gastric neoplasms was considerable. As a whole, the diagnostic group changed for 23.3 % (478/2056)—upgraded in 16.2 % and downgraded in 7.1 %. The treatment algorithm influenced by the pretreatment diagnostic group was also shown in the real-world evaluation. This discrepancy should be considered when the initial treatment strategy is selected.

There were two major types of regrouping: (1) upgrading of dysplasia into cancer and (2) changes among ESD indication groups. The most important factor is histological discrepancy between forceps biopsies and resected specimens. Some cases of pretreatment dysplasia were reclassified as cancers based on the endoscopically resected specimen: 6.2 % (10/162) for LGD and 34.1 (56/164) for HGD. This rate was similar to our previous report more than 10 years ago [8], which suggests the quality of the histological diagnosis of gastric forceps biopsy is quite stable in our institution. In a similar report in Korea [9], the risk of cancer in biopsy-proven HGD is as high as 53 %. One important point of the present study is that surgery was required in eight cases (12.5 %) among 64 cancers diagnosed after endoscopic resection of pretreatment dysplasia. Although selected cases of gastric LGDs can be managed by ablation treatment [22], gastric HGDs should be treated by endoscopic resection due to high risk of cancer.

Changes among ESD indication groups before and after the treatment may make a big clinical problem, because different treatment modalities are recommended for each ESD indication group. Differential diagnosis between EGCs and AGCs was correct in 91.0 % of the time, which is similar to previous studies [23, 24]. One-third of pretreatment AI-EGCs (33.1 %, 131/396) were upgraded to posttreatment BAI-EGCs. Among them, posttreatment EI-EGCs may be carefully followed up without additional treatment, but posttreatment cases classified as BEI-EGCs should be treated by surgery. The downgrade in the diagnostic grouping is also worrisome, because overestimation may lead to overtreatment. For example, 2.8 % (23/824) of pretreatment BAI-EGCs were either dysplasia or AI-EGCs, which can be curatively treated by ESD.

In the present study, the reasons for changes among ESD indication groups included size discrepancy, incorrect estimation of invasion depth, and change in histological differentiation. In a recent evaluation of the endoscopic and the pathologic size, the median difference was 5 mm and the risk

factors for size underestimation were larger lesion, flat/depressed type, and undifferentiated-type histology [10]. Determination of horizontal extent of the lesion is difficult for intestinal-type EGC in lesions with a flat component, large size, and moderately differentiated adenocarcinoma [25]. In cases with extremely well-differentiated adenocarcinoma or histological heterogeneity, the size discrepancy may be larger [17]. In addition, human errors during the ESD specimen fixation may influence the size measurement [26].

In selecting ESD candidate, estimation of invasion depth is based on gross endoscopic findings. Differentiation of mucosal cancers from submucosal cancers using endoscopic ultrasonography has been evaluated in many groups, but the results have not been satisfactory [5, 27, 28]. A comparative study of EUS versus endoscopic evaluation for selecting ESD candidates favored endoscopy due to the risk of overstaging by EUS [5]. A recent study [29] also showed that EUS may not be necessary before ESD, because EUS did not increase the likelihood of selecting the appropriate treatment in differentiated-type EGC. One recent meta-analysis also concluded that EUS may be not indispensable in the staging of EGCs [30]. Pit patterns observed by magnifying chromoendoscopy can be used to predict invasion in colonic lesions [31]. However, the usefulness of magnifying chromoendoscopy for EGCs has not been established yet. Recently, it has been suggested that magnifying endoscopy with NBI may be helpful for better delineation of EGC [32]. However, its meaning is still unclear because depth of invasion is the most common reason of surgery after ESD (Table 3).

Cancers with differentiated-type histology can be changed to cancers with undifferentiated-type histology [16, 33]. One less frequently mentioned factor is the possibility of no residual tumor in the resected specimen. Kim et al. [34] reported that there was no residual tumor in 3.2 % (20/633) of endoscopically resected gastric dysplasia or EGC. No residual tumor after ESD can be due to complete removal of the lesion at biopsy, pathology overestimation, and incorrect localization [35]. In the present study, there were six cases of no residual tumor in the resected specimen. Two were LGD, and four of them were HGD in forceps biopsy.

All of these factors make the treatment algorithm in actual clinical practice very complex. In pretreatment AI-EGCs, for example, ESD was done for the majority of patients, but surgery was done either initially or after ESD in about 25 % (Fig. 1). Overall, the possibility of an incoherent result and the necessity for additional treatment in some cases should be considered and explained to the patient before the final decision is made about initial treatment.

Controversy remains about the definition of expanded indications for endoscopic resection for gastric cancer [4]. There is a consensus about expanded indications for differentiated-type EGCs, but the inclusion of undifferentiated-type EGCs with expanded indications is under debate. An original proposal of expanded indications [36] and guidelines from Japan [20] and Korea [21] include undifferentiated-type EGCs. On the other hand, the literature on expanded indications is heterogeneous; some reports include undifferentiated-type EGCs [15], and others do not [12, 13, 37]. In the present study, we considered small (2 cm or less) mucosal cancer with undifferentiated-type histology as part of expanded indications. In patients initially treated by ESD, there were 54 pretreatment EI-EGCs. Among them, 24.1 % (13/54) were posttreatment BEI-EGCs. Cases of this kind of posttreatment BEI-EGCs are sometimes excluded in clinical studies of expanded indications [13, 18]. In addition, 74.8 % (83/111) of our posttreatment EI-EGCs were considered as LGD, HGD, or AI-EGCs before ESD. When reviewing publications about expanded indications, readers should pay attention to whether undifferentiated-type EGCs are included or not and when the cases were classified—before treatment or after treatment. In the present study, we included undifferentiated-type cancers in EI-EGCs and the group classification was done twice—before and after treatment.

There are some limitations to the present study. First, it was a retrospective study about how cases with gastric dysplasia and cancer were treated in a real clinical setting. Most were treated following standard guidelines, but many factors were considered when selecting the initial treatment modality. In the standard guidelines [20, 21], the recommended treatment of AI-EGC is ESD. In our real-world experience, 10.4 % of AI-EGCs were initially treated by surgery. Second, advanced endoscopic techniques, such as EUS and magnifying endoscopy, were not routinely used. In addition, long-term data were not available, because we focused on immediate outcomes of recent cases. Finally, some cases of LGD were either just followed up or treated by endoscopic ablation in real clinical practice. Those cases were not included in the present study.

In conclusion, diagnostic group classification changes in about a quarter of gastric neoplasms after endoscopic resection or surgery. This discrepancy should be considered when the initial treatment strategy is being selected.

Compliance with ethical standards

Disclosures Jun Hee Lee, Yang Won Min, Jun Haeng Lee, Eun Ran Kim, Hyuk Lee, Byung-Hoon Min, Jae J. Kim, Kee-Taek Jang, Kyoung-Mee Kim, and Cheol Keun Park have no conflicts of interest or financial ties to disclose.

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