Clinical Outcomes of Endoscopic Resection for Low-Grade Dysplasia and High-Grade Dysplasia on Gastric Pretreatment Biopsy: Korea ESD Study Group

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Background/Aims: Some cases of gastric low-grade dysplasia (LGD) and high-grade dysplasia (HGD) on forceps biopsy (FB) are diagnosed as gastric cancer (GC) after endoscopic resection (ER). This study aims to evaluate the clinical outcomes of ER for gastric LGD and HGD on pretreatment FB and to identify the factors that predict pathologic upstaging to GC.

Methods: Patients who underwent ER for LGD and HGD on pretreatment FB from March 2005 to February 2018 in 14 hospitals in South Korea were enrolled, and the patients’ medical records were reviewed retrospectively.

Results: This study included 2,150 cases of LGD and 1,534 cases of HGD diagnosed by pretreatment FB. In total, 589 of 2,150 LGDs (27.4%) were diagnosed as GC after ER. Helicobacter pylori infection, smoking history, tumor location in the lower third of the stomach, tumor size >10 mm, depressed lesion, and ulceration significantly predicted GC. A total of 1,115 out of 1,534 HGDs (72.7%) were diagnosed with GC after ER. Previous history of GC, H. pylori infection, smoking history, tumor location in the lower third of the stomach, tumor size >10 mm, depressed lesion, and ulceration were significantly associated with GC. As the number of risk factors predicting GC increased in both LGD and HGD on pretreatment FB, the rate of upstaging to GC after ER increased.

Conclusions: A substantial proportion of LGDs and HGDs on pretreatment FB were diagnosed as GC after ER. Accurate ER procedures such as endoscopic submucosal dissection should be recommended in cases of LGD and HGD with factors predicting pathologic upstaging to GC.

Key Words: Low-grade dysplasia; High-grade dysplasia; Endoscopic resection; Gastric cancer; Risk factors

INTRODUCTION

In the latest published global cancer statistics, gastric cancer (GC) is ranked as the third most common cause for cancer-related mortality worldwide. Early detection and proper management of GC and precancerous lesions are crucial to improving GC-related mortality. Gastric dysplasia is regarded as a precancerous lesion. The risk of carcinoma generally increases with the histological grade of the dysplasia (low to high grade). According to the revised...
Vienna classification, gastric low-grade dysplasia (LGD) is classified as category 3, and endoscopic resection (ER) or regular follow-up examination is recommended. Category 4 is defined as noninvasive high-grade neoplasia. Category 4 is further divided into category 4.1 defined as high-grade dysplasia (HGD); 4.2, noninvasive carcinoma (carcinoma in situ); 4.3, suspicion of invasive carcinoma based on the degree of structural or cytological atypia of the neoplastic glands; and 4.4, intramucosal carcinoma. It is strongly recommended that gastric HGD, which is highly predictive of carcinoma be treated with ER or surgical resection.

Endoscopic examination is useful in detecting gastric neoplasia in its early stage, and pathological examination of endoscopic forceps biopsy (FB) is the gold standard for an accurate diagnosis. However, cases in which the initial pathological diagnosis on pretreatment FB is corrected after ER are frequently found, due to the difficulty of making solid diagnosis based on small biopsy specimens. For this reason, GC may be underdiagnosed as LGD or HGD on pretreatment FB. Previous studies have reported that 12.1% to 63% of LGD lesions are upgraded to HGD or GC after ER. In addition, gastric HGD has been shown to be GC in about 27% to 80% of cases after ER.

In this study, we aimed to evaluate the clinical outcomes of ER for gastric LGDs and HGDs on pretreatment FB, using the multicenter large-scale endoscopic submucosal dissection (ESD) registry database. In addition, we investigated the factors predicting the pathologic upstage to GC.

1. Study population

We identified and reviewed cases which were treated with ER for LGD and HGD on pretreatment FB and involved in the Korean ESD registry database- an online registry created in 2015. It is a project which collects ESD or endoscopic mucosal resection (EMR) data from multiple centers, each representing its district in South Korea, and is under the control of Korean Society of Gastrointestinal Endoscopy. This registry contains clinical information, endoscopic findings, pathologic results, therapeutic outcomes, and follow-up data related to ER for gastric neoplasms.

This study included patients who had undergone ER for gastric LGD and HGD on pretreatment FB at 14 university hospitals in South Korea from March 2005 to February 2018. Medical records of patients involved in this study were retrospectively reviewed. Patients’ data include age, sex, family history of GC, previous history of GC, the presence of hypertension or diabetes mellitus, aspirin use, smoking history, and Helicobacter pylori infection.

2. Endoscopic and pathologic evaluation

Endoscopic reports of all enrolled lesions were reviewed to determine the features of lesions. The Japanese classification of GC was used to describe the location of lesions. The Paris classification was used to define the gross types of superficial lesions, which were divided into elevated, flat, or depressed. Ulcers which were defined as breaks in the mucosal surface >5 mm in size with depth to the submucosa, were also evaluated.

Pathologic reports of the resected tissues, which were reported by experienced pathologists in hospitals involved in this study, were reviewed. All of the lesions were classified as gastrointestinal epithelial neoplasia following the Vienna classification.

3. Statistical analysis

Univariate analysis with the chi-square test or Fisher exact test for categorical variables and the Student t-test for continuous variables were performed. Multivariate analysis with a multiple logistic regression model was performed.

### Table 1. Baseline Characteristics

| Characteristics                  | LGD on pretreatment FB (n=2,150) | HGD on pretreatment FB (n=1,534) |
|----------------------------------|----------------------------------|----------------------------------|
| Age, yr                          | 63.89±9.36                      | 65.24±9.17                      |
| Male sex                         | 1,493 (69.4)                    | 1,113 (72.6)                     |
| Family history of GC             | 73 (3.4)                        | 60 (3.9)                         |
| Previous history of GC           | 43 (2.0)                        | 70 (4.6)                         |
| Helicobacter pylori infection    | 570 (26.5)                      | 371 (24.2)                       |
| Smoking history                  | 379 (17.6)                      | 527 (34.4)                       |
| Hypertension                     | 748 (34.8)                      | 579 (37.7)                       |
| Diabetes mellitus                | 338 (15.7)                      | 270 (17.6)                       |
| Aspirin use                      | 232 (10.8)                      | 180 (11.7)                       |
| Tumor location                   |                                  |                                  |
| Lower third of stomach           | 1,217 (56.6)                    | 952 (62.1)                       |
| Middle third of stomach          | 789 (36.7)                      | 461 (30.0)                       |
| Upper third of stomach           | 144 (6.7)                       | 121 (7.9)                        |
| Tumor size, mm                   | 13.9±11.28                      | 15.8±11.92                       |
| Gross type                       |                                  |                                  |
| Elevated                         | 1,249 (58.1)                    | 851 (55.5)                       |
| Flat                             | 692 (32.2)                      | 322 (21.0)                       |
| Depressed                        | 209 (9.7)                       | 361 (23.5)                       |
| Ulcer                            | 91 (4.2)                        | 220 (14.3)                       |
| Pathologic concordance           | 1,038 (48.3)                    | 328 (21.4)                       |
| Pathologic downstage             | 131 (6.1)                       | 91 (5.9)                         |
| Pathologic upstage to GC         | 589 (27.4)                      | 1,115 (72.7)                     |
| Endoscopic resection method      |                                  |                                  |
| EMR                              | 996 (46.3)                      | 405 (26.4)                       |
| ESD                              | 1,154 (53.7)                    | 1,129 (73.6)                     |
| En bloc resection                | 2,065 (97.1)                    | 1,486 (96.9)                     |
| Complete resection               | 2,092 (97.4)                    | 1,494 (97.4)                     |

Data are presented as mean±SD or number (%). LGD, low-grade dysplasia; HGD, high-grade dysplasia; FB, forceps biopsy; GC, gastric cancer; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.
to identify risk factors for GC. The p<0.05 was considered statistically significant. Statistical calculations were performed with SPSS version 21.0 for Windows (IBM Corp., Armonk, NY, USA).

4. Ethics statement

This study was conducted according to the principles expressed in the Declaration of Helsinki, and approved by the Institutional Review Board of Chuncheon Sacred Heart Hospital (IRB number: 2016-87).

RESULTS

From March 2005 to February 2018, 2,277 LGD lesions and 1,620 HGD lesions, which were managed by ER, were enrolled in the Korean ESD registry database. Among these, 127 LGD lesions and 86 HGD lesions were excluded because they were incomplete to be used as valid data. Ultimately, the data from 2,150 LGD lesions and 1,534 HGD lesions were analyzed.

Table 1 shows the clinical and endoscopic characteristics of LGD and HGD on pretreatment FB. The patients' mean age was 63.89±9.36 years in LGD group and 65.24±9.17 years in HGD group. There were 1,493 (69.4%) males in the LGD group and 1,113 (72.6%) in HGD group. Forty-three cases (2.0%) in the LGD group and 70 cases (4.6%) in HGD group had a previous history of GC. We identified incidence rate of H. pylori infection as 26.5% (570/2,150) in the LGD group and 24.2% (371/1,534) in the HGD group. The 379 cases (17.6%) in the LGD group and 527 cases (34.4%) in the HGD group had past or current smoking history. Most lesions were elevated in gross type (58.1% in the LGD group and 55.5% in the HGD group) and located in the lower third of stomach (56.6% in the LGD group and 62.1% in the HGD group). Ninety-one cases (4.2%) in the LGD group and 220 cases (14.3%) in the HGD group showed ulceration. The 1,154 cases (53.7%) in the LGD group and 1,129 cases (73.6%) in the HGD group were managed by ESD. The en bloc resection rate was 97.1% in the LGD group and 96.9% in the HGD group. The complete resection rate was 97.4% in both groups.

Pathologic concordance rate was 48.3% (1,038/2,150) in the LGD group and 21.4% (328/1,534) in the HGD group. The 589 of 2,150 cases (27.4%) in the LGD group and 1,115 of 1,534 cases (72.7%) in the HGD group showed pathologic upstage to GC after ER.

Table 2 shows the factors for upgrade diagnosis to GC of LGD in univariate and multivariate analyses. Multivariate analysis revealed that H. pylori infection (absence of H. pylori infection compared with H. pylori infection; odds ratio [OR], 0.686; 95% confidence interval [CI], 0.498 to 0.945; p=0.021), smoking history (OR, 4.928; 95% CI, 3.290 to 7.383; p<0.001), tumor location in the lower third of the stomach (middle third compared with lower third: OR, 0.654; 95% CI, 0.487 to 0.878; p=0.005), tumor size of >10 mm (OR, 3.467; 95% CI, 2.571 to 4.675; p<0.001), depressed lesion (OR, 3.270; 95% CI, 2.067 to 5.171;
p<0.001), and ulceration (absence of ulceration compared with ulceration: OR, 0.203; 95% CI, 0.147 to 0.282; p<0.001) were significant predictive factors of the upstage diagnosis to GC of LGD. Table 3 and Fig. 1 show the effect of the presence of 0–6 risk factors on upstage diagnosis to GC of LGD. An increase in the number of risk factors was significantly associated with an increasing rate of upstage diagnosis to GC of LGD.

Table 4 shows the factors for upgrade diagnosis to GC of HGD in univariate and multivariate analyses. Multivariate analysis revealed that previous history for GC (absence of previous history for GC compared with previous history of GC: OR, 0.459; 95% CI, 0.257 to 0.819; p=0.008), *H. pylori* infection (absence of *H. pylori* infection compared with *H. pylori* infection: OR, 0.585; 95% CI, 0.430 to 0.795; p=0.001), smoking history (OR, 2.527; 95% CI, 1.790 to 3.567; p<0.001), tumor location in lower third of the stomach (upper third compared with lower third: OR, 0.544; 95% CI, 0.332 to 0.890; p=0.015), tumor size of >10 mm (OR, 1.934; 95% CI, 1.438 to 2.600; p<0.001), depressed lesion (OR, 2.551; 95% CI, 1.731 to 3.758; p<0.001), and ul-

### Table 3. The Effect of the Presence of 0–6 Risk Factors upon Upstaging of LGD to GC

| No. of risk factors | LGD or downstage diagnostic group (n=1,169) | GC group (n=589) | Total (n=1,778) |
|---------------------|---------------------------------------------|------------------|------------------|
| 0                   | 0                                           | 3                | 3                |
| 1                   | 65                                          | 1                | 66               |
| 2                   | 394                                         | 39               | 433              |
| 3                   | 462                                         | 162              | 624              |
| 4                   | 222                                         | 234              | 456              |
| 5                   | 23                                          | 134              | 157              |
| 6                   | 0                                           | 19               | 19               |

Date are presented as number. Risk factors: *Helicobacter pylori* infection, smoking history, tumor location in the middle third of the stomach, tumor lesion size >10 mm, depressed lesion, and ulcer.

### Table 4. Factors Associated with Upstaging of HGD to GC in Univariate and Multivariate Analysis

| Factor                          | Univariate analysis | Multivariate analysis |
|---------------------------------|---------------------|-----------------------|
|                                 | OR  | 95% CI | p-value | OR  | 95% CI | p-value |
| Age >65 yr                       | 0.868 | 0.691–1.090 | 0.223 | 0.789 | 0.600–1.039 | 0.092 |
| Male sex                        | 1.307 | 1.020–1.675 | 0.034 | 0.862 | 0.625–1.189 | 0.366 |
| Family history of GC            | 0.714 | 0.365–1.398 | 0.326 |              |          |        |
| Absence of previous history of GC | 0.622 | 0.378–1.023 | 0.061 | 0.459 | 0.257–0.819 | 0.008 |
| Absence of *Helicobacter pylori* infection | 0.655 | 0.197–0.863 | 0.003 | 0.585 | 0.430–0.795 | 0.001 |
| Smoking history                 | 2.399 | 1.844–3.121 | <0.001 | 2.527 | 1.790–3.567 | <0.001 |
| Hypertension                    | 1.016 | 0.806–1.281 | 0.892 |              |          |        |
| Diabetes mellitus               | 1.115 | 0.826–1.506 | 0.475 |              |          |        |
| Aspirin use                     | 0.944 | 0.668–1.334 | 0.744 |              |          |        |
| Tumor location                  | 1.000 |              | 1.000 |              |          |        |
| Lower third of stomach (reference) | 0.866 | 0.660–1.084 | 0.185 | 0.849 | 0.628–1.147 | 0.285 |
| Middle third of stomach         | 0.702 | 0.468–1.053 | 0.087 | 0.544 | 0.332–0.890 | 0.015 |
| Upper third of stomach          | 1.293 | 1.015–1.649 | 0.038 | 1.934 | 1.438–2.600 | <0.001 |
| Tumor size >10 mm               | 1.000 |              | 1.000 |              |          |        |
| Gross type                      | 1.000 |              | 1.000 |              |          |        |
| Elevated (reference)            | 0.874 | 0.661–1.156 | 0.346 | 1.048 | 0.752–1.461 | 0.780 |
| Flat                            | 2.430 | 1.747–3.381 | <0.001 | 2.551 | 1.731–3.758 | <0.001 |
| Absence of ulcer                | 0.627 | 0.484–0.812 | <0.001 | 0.537 | 0.388–0.743 | <0.001 |

HGD, high-grade dysplasia; GC, gastric cancer; OR, odds ratio; CI, confidence interval.
ceration (absence of ulceration compared with ulceration: OR, 0.537; 95% CI, 0.388 to 0.743; p < 0.001) were significant predictive factors for upstage diagnosis to GC of HGD.

Table 5 and Fig. 2 show the effect of the presence of 0–7 risk factors on upstage diagnosis to GC of HGD. An increase in the number of risk factors was significantly associated with an increasing rate of upstage diagnosis to GC of HGD.

| No. of risk factors | HGD or downgrade diagnostic group (n=419) | GC group (n=1,115) | Total (n=1,534) |
|---------------------|------------------------------------------|--------------------|-----------------|
| 0                   | 1                                       | 0                  | 1               |
| 1                   | 9                                       | 3                  | 12              |
| 2                   | 54                                      | 63                 | 117             |
| 3                   | 175                                     | 266                | 441             |
| 4                   | 120                                     | 445                | 565             |
| 5                   | 51                                      | 246                | 297             |
| 6                   | 9                                       | 84                 | 93              |
| 7                   | 0                                       | 8                  | 8               |

Date are presented as number. Risk factors: previous history of GC, Helicobacter pylori infection, smoking history, tumor location in the upper third of the stomach, tumor lesion size >10 mm, depressed lesion, and ulcer.

HGD, high-grade dysplasia; GC, gastric cancer.

**DISCUSSION**

The specimens obtained by endoscopic FB—an essential diagnostic tool for gastric superficial neoplasms, may not be representative of the entire lesion. The possible reasons for this discrepancy may be as follows: (1) FB samples are small in size, and therefore do not represent the entire lesion; (2) cancer is sometimes hidden in other parts of the lesion; or (3) the atypia of adenoma and adenocarcinoma is too subtle to detect in a small biopsy specimen.

In previous studies, it has been reported that 12.1% to 63% of LGD lesions are upgraded to HGD or GC after ER. In 2,150 LGD cases of our study, 981 cases (45.6%) showed diagnostic upgrade to HGD or GC after ER, which is similar to the results of previous studies. Diagnostic upgrades to HGD and GC were 392 cases (18.2%) and 589 cases (27.4%), respectively. Likewise, in the case of HGD, previous studies showed that gastric HGD on pretreatment FB was diagnosed as GC in about 27.6% to 80% of cases after ER. Diagnostic upgrade to GC was found in 72.7% of cases in our study, which is similar to the results of previous studies.

Previous studies reported that several endoscopic findings were associated with the risk of GC. We investigat-ed the risk factors for GC in LGD and HGD, respectively. In addition, we investigated endoscopic findings as well as clinical characteristics when investigating risk factors for GC. In the case of LGD, previous articles examined factors that could predict HGD as well as GC. Although the modified Vienna classification of epithelial neoplasia is used widely, differences exist between the Asian and Western pathologists regarding the histological criteria in grading dysplasia. Moreover, Western gastroenterologists are more interested in GC than HGD or LGD. For these reasons, this study only focused on risk factors for GC.

Kang et al. reported that the rate of diagnostic upstage to HGD or GC of LGD increased as the number of risk factors increased. In the present study, we evaluated the association between the total number of risk factors and the incidence of diagnostic upstage to GC in LGD and HGD respectively. As the number of risk factors increased in both LGD and HGD, the rate of upstage diagnosis to GC also increased.

Our study showed that the location in lower third of LGD and HGD, compared with the location in middle third of LGD and upper third of HGD respectively, was associated with histologic upgrade to GC. We assume that investigators could miss LGD or HGD in blind spots of middle or upper third of stomach before the lesions change to cancer and observed clearly.

When we conducted the study, we used the ESD registry database—an online registry created in 2015. ESD registry involved more than 9,000 cases. Of them, we identified
and reviewed cases which were treated with ER for LGD and HGD on pretreatment FB. We knew that the percent of *H. pylori* infection was low after analysis of data. We assume this is the limitation of retrospective study. Although the percent of *H. pylori* infection was low and the bias was thought to be involved, we think the analysis conducted with data showing bias would be make sense to assure the risk of *H. pylori* for GC.

In recent years, ESD has become an accepted curative treatment modality for the treatment of early GC. Therefore, it is important to completely remove the lesions identified to be LGD or HGD on pretreatment FB, if risk factors predicting upstage diagnosis to GC are identified. Compared to EMR, ESD can effectively remove LGD or HGD lesions without marginal involvement of the lesion. ESD increases the en bloc resection rate for lesions >10 mm, compared with EMR. The Korean National Health Insurance System provides insurance for ESD of LGD and HGD lesions >15 mm. In South Korea, until recently, LGD or HGD lesions between 10 mm and 15 mm were treated with modified EMR involving EMR after precutting or EMR using scope detaching cap in the tip instead of conventional EMR. According to our study, the insurance criteria for the size of the lesion in South Korea may need to be changed. In addition to the size of the lesion, other risk factors involving *H. pylori* infection, smoking history, tumor location, depressed lesion and the presence of ulcer were significantly associated with the upgrade diagnosis to GC. Therefore, it is necessary to expand the coverage of medical insurance for ESD in the cases of LGD and HGD involving risk factors predicting the upgrade diagnosis to GC.

Fourteen hospitals in South Korea participated in this study. The researchers participated in this study of each hospital shared respective definitions for the data that they wanted to collect. They checked the low data of the patients enrolled in their hospitals and filled up the missing data as much as possible. Despite these efforts, this study has limitations. This is retrospective study, so for example the percentage of *H. pylori* infection in individuals involved in this study is low. We could not guarantee that all pathologists of 14 hospitals involved in this study show concordance of pathologic diagnosis. Although the definitions for clinical data have been shared in advance, not all data may be consistent in terms of definitions. The gross size and type for the lesions confirmed by the endoscopic photographs may vary depending on the examiner. ESD registry did not involve the factor for the color change of the lesion, such as reddish color change of mucosa. The presence of an ulcer can also vary from person to person. However, despite these limitations, this study is a multicenter study conducted by the most influential institute in the field of gastrointestinal endoscopy in South Korea. In addition, this study involves many subjects.

In conclusion, a substantial proportion of LGD and HGD on pretreatment FB were diagnosed as GC after ER. As the number of risk factors predicting GC increased in both LGD and HGD on pretreatment FB, the rate of upstage diagnosis to GC after ER also increased. Therefore, accurate ER such as ESD should be recommended in cases of LGD and HGD with factors predicting pathologic upstage to GC.

No potential conflict of interest relevant to this article was reported.

**CONFLICTS OF INTEREST**

**AUTHOR CONTRIBUTIONS**

Study concept and design: J.W.J., G.H.B. Statistical analysis: S.J.K. Study supervision: S.J.H. Data acquisition: J.Y.J., S.M.K., C.H.L., J.M.P., C.G.K., S.W.J., S.H.L., J.K.S. Writing - original draft: J.W.J. Writing - review and editing: G.H.B., J.W.J., S.J.K. Approval of final manuscript: all authors.

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