



Predictive factors suggesting an underestimation of gastric lesions initially diagnosed as adenomas by forceps biopsy

STOMACH

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ABSTRACT

Background/Aims: The endoscopic forceps biopsy of gastric lesion may provide inadequate specimens for a correct diagnosis of the entire lesion. Therefore, a histologic discrepancy may exist between specimens obtained by forceps biopsy and by endoscopic resection. The aim of this study was to evaluate the endoscopic characteristics of an underestimation in gastric carcinomas initially diagnosed as adenomas by forceps biopsy.

Materials and Methods: We retrospectively reviewed 431 lesions diagnosed as gastric adenomas by forceps biopsy and resected by endoscopic submucosal dissection (ESD) between January 2008 and December 2011. The endoscopic findings were reviewed for location, size, gross appearance, ulceration, and surface color. We compared these variables between the adenoma group and the carcinoma group, as defined by the post-resection pathological findings.

Results: The mean patient age was 65.63 ± 9.30 years in the adenoma group and 64.75 ± 10.30 years in the carcinoma group. The mean size of the lesion was 21.04 ± 8.65 mm in the adenoma group and 22.06 ± 7.46 mm in the carcinoma group. In the multivariate analysis, high-grade dysplasia from endoscopic forceps biopsy and red discoloration were significant variables associated with carcinoma in post-resection histology.

Conclusion: Gastric adenomatous lesions with endoscopic characteristics of surface redness and high-grade dysplasia on forceps biopsy should be resected completely by ESD because of the high possibility of an underestimation after ESD.

Keywords: Stomach neoplasms, adenoma, carcinoma, gastroscopy

INTRODUCTION

Gastric adenomas are benign epithelial neoplastic tumors with a glandular organization that is characterized by the localized proliferation of adenomatous epithelium with tubular or papillary structures (1,2). Noninvasive carcinomas occasionally coexist within gastric adenomas and can demonstrate neoplastic progression to invasive carcinomas (3,4). The reported incidence of gastric adenoma associated with synchronous gastric cancer varies from 3.6% to 8.7% (3,5,6). The prevalence of carcinomatous transformation in adenomas is reported to be from 2.1% to 21.2% (4,7-10).

The histological results from endoscopic forceps biopsy samples, which include information from only a small

portion of the lesion, are currently the most reliable information available for the diagnosis of gastric tumors before resection (11). Sometimes, the use of pre-treatment forceps biopsy samples in gastric carcinoma leads to inadequate treatment of gastric lesions because foci with malignant changes are not identified (12). Gastric superficial tumors can be misdiagnosed when only the histology of the forceps biopsy samples is used for diagnosis. Therefore, it is necessary to remove the entire adenomatous lesion to establish an accurate diagnosis (13).

In recent years, most gastric adenomas in Korea have been removed using an endoscopic submucosal dissection (ESD) technique. However, ESD is associated with a long procedure time, a high rate of complica-

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Received: August 13, 2015 **Accepted:** January 25, 2016

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tions, and a high cost of care. Therefore, if we can identify predictive factors for lesions including carcinoma, ESD could be performed only in properly selected cases. The aim of this study was to evaluate the predictive endoscopic characteristics that suggest an underestimation of gastric lesions that were diagnosed as gastric adenomas by forceps biopsy.

MATERIALS AND METHODS

We retrospectively reviewed 638 patients with early gastric cancer (EGC) or adenoma who were treated by ESD between January 2008 and December 2011 in a tertiary hospital. The following lesions were excluded from the study: (1) non-adenomatous lesions (gastric subepithelial tumor (SET), EGC, or chronic gastritis) diagnosed on initial forceps biopsy (n=179), (2) tumor tissue not found in the resected specimen (n=1), and (3) unknown dysplastic degrees of adenoma whether it was low-grade dysplasia (LGD) or high-grade dysplasia (HGD) before ESD because the forceps biopsy was performed at a private clinic (n=27). After applying these criteria, our study included 431 lesions (Figure 1).

Gastric adenomas with HGD or LGD were diagnosed in all lesions and confirmed as either adenoma or carcinoma after gastric ESD. The cases were divided into an adenoma group and a carcinoma group according to their final diagnosis, as confirmed by analysis of the post-ESD specimen. The adenoma group included lesions diagnosed as adenoma with LGD and HGD, and the carcinoma group included those diagnosed as adenocarcinomas in adenomas and adenocarcinomas. Characteristics (e.g., patient sex, age) and endoscopic findings (e.g., tumor size, location, color) were analyzed.

The lesions were divided into depressed and non-depressed gross types based on their endoscopic appearance, according to the Paris classification (14). The depressed type was defined as a lesion that had a clear pooling of indigo carmine and was depressed relative to the surrounding mucosa. Flat elevated lesions with a central depression were included in the depressed type. The location of the lesions was classified as the lower (antrum), middle (angulus to middle corpus), or upper (upper corpus to fornix) portions. The diameter of the lesions was measured on

the post-resected specimen. The institutional review board approved the study for ethical research (IRB No. 2015-03-009). This study was exempted from informed consent because it was a retrospective study using data and images.

ESD procedure

Pharyngeal anesthesia was induced with lidocaine, and sedation was induced with midazolam. The gastric lesions were demarcated using white-light endoscopy and chromoendoscopy with indigo carmine dye. The surrounding mucosa of the lesion was marked with electrocautery using a snare tip. Hypertonic saline mixed with 0.1% epinephrine was injected into the submucosal layer to create a submucosal cushion. The lesion was dissected with an IT knife (KD-611L; Olympus, Tokyo, Japan), a hook knife (KD-620LR; Olympus, Tokyo, Japan), or a needle knife (KD-1L-1; Olympus, Tokyo, Japan). Resected specimens were mounted on a board with small pins and fixed in a 10% formaldehyde solution.

Evaluation of the histologic diagnosis

Two pathologists reviewed the specimens obtained by forceps biopsy and endoscopic resection. The diagnosis was determined using the Vienna classification of gastric epithelial neoplasia (15). The specimens fixed in 10% buffered formalin were cut serially into 2-mm slices, embedded in paraffin blocks, then cut into 4- μ m sections and stained with hematoxylin and eosin. When an entire resected adenomatous lesion was histologically diagnosed as a low-grade adenoma/dysplasia, it was defined as LGD. If even part of a resected lesion was diagnosed as a high-grade adenoma/dysplasia, then that lesion was defined as a HGD. When part of a resected specimen was histologically diagnosed as a noninvasive carcinoma or an intramucosal carcinoma, the lesion was defined as an adenocarcinoma in adenoma. When the entire resected specimens were histologically diagnosed as a noninvasive carcinoma or an intramucosal carcinoma, it was defined as an adenocarcinoma (Figures 2, 3).

Statistics

Differences in categorical variables between the two groups were analyzed using univariate analysis with a the χ^2 test, Fisher exact test, or Mann-Whitney U test. Variables with p values <0.05 in univariate analysis were included in a multiple logistic regression model to identify the independent risk factors for the underestimation of gastric neoplasm. P values < 0.05 were regarded as statistically significant. All the data analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 12.0 for Windows (SPSS; Chicago, IL, USA).

RESULTS

Patient characteristics

Data from 431 patients were reviewed (mean age 65.51 ± 9.42 years; 268 men, 163 women). The lower part of the stomach was the most common location for lesions. Fifty-one of the 431 (11.83%) of the adenomas cases diagnosed by forceps

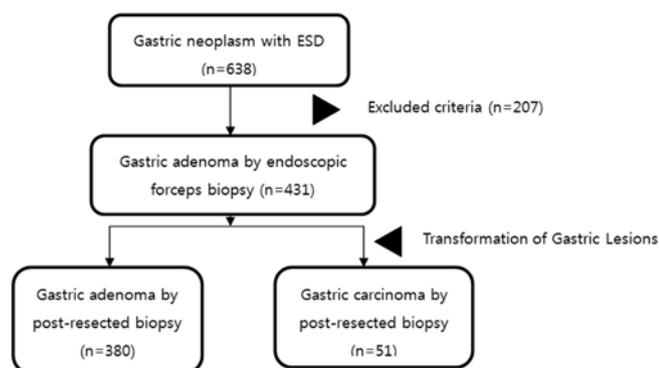


Figure 1. Flow chart of enrolled patients.

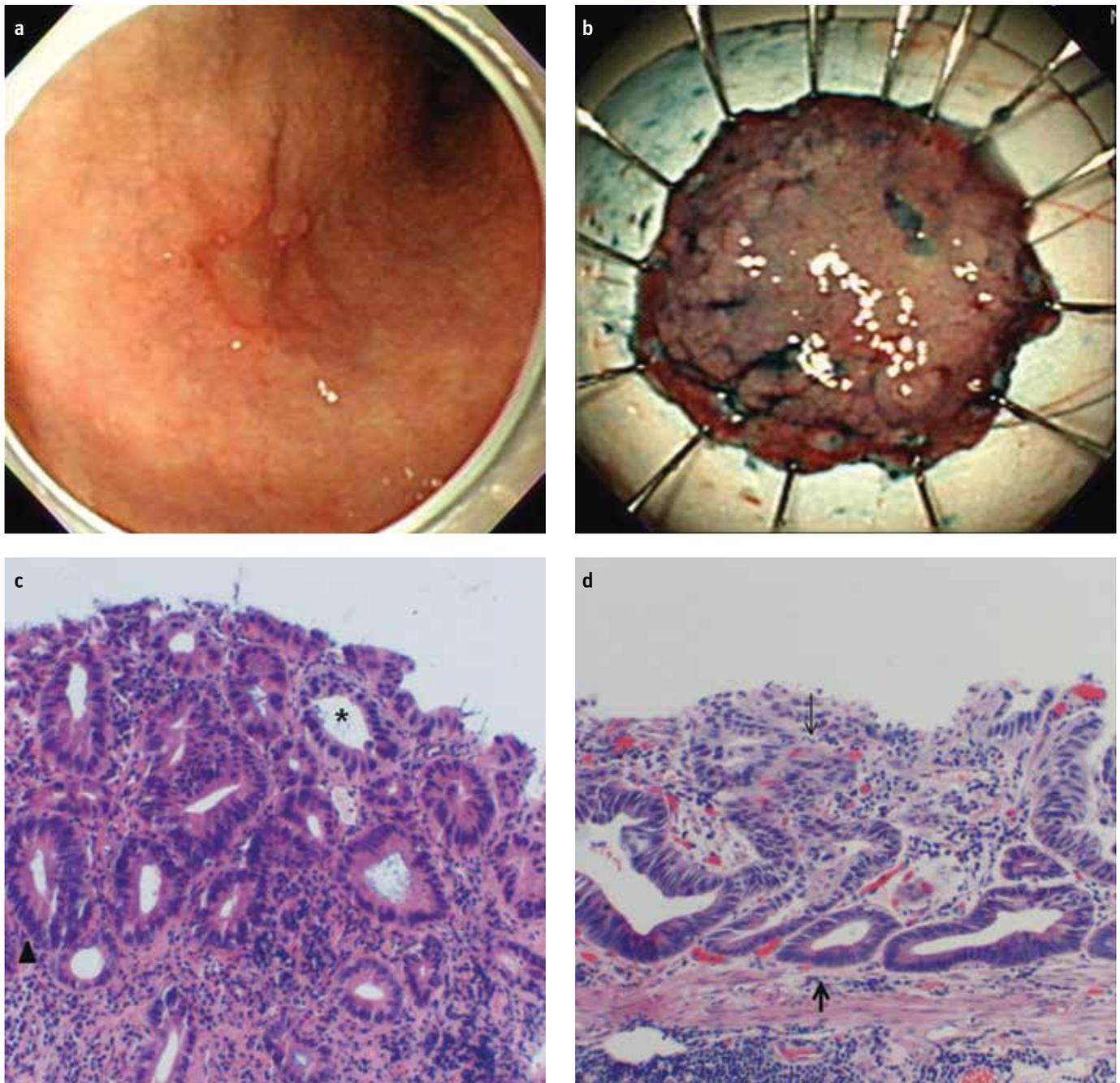


Figure 2. a-d. Endoscopic and pathologic findings of patients with adeocarcinoma in tubular adenoma. (a) 24×28 mm, type 0-IIc lesion observed in the lesser curvature aspect of the body; (b) 38×32 mm, resected specimen obtained; (c) Forceps biopsy showed adenoma with low-grade dysplasia (arrowhead) and high-grade dysplasia (asterisk); (d) The pathologic findings in the ESD specimen showed an adenocarcinoma (thin arrow) with tubular adenoma (thick arrow). The glands had a similar shape with a "picket-fence" arrangement of nuclei, and the nuclei were basally oriented ((c) H & E stain ×100; (d) H & E stain ×100).

biopsy were diagnosed as carcinomas after the procedure. Among the carcinoma group, 25 of 51 (49%) adenocarcinoma cases were with tubular adenoma and 26 cases (51%) were adenocarcinomas without adenoma. We compared the baseline characteristics and endoscopic features in the adenoma group to those in the carcinoma group. The mean age was 65.63 ± 9.30 years in the adenoma group and 64.75 ± 10.30 years in the carcinoma group. The mean size of the lesion was 21.04 ± 8.65 mm in the adenoma group and 22.06 ± 7.46 mm in the carcinoma group.

Factors associated with histological discrepancy

Adenomas larger than 1 cm in diameter were more frequently diagnosed as carcinoma after endoscopic resection, but there was no statistically significant correlation. The depressed type adenoma was more frequently diagnosed as carcinoma (21/103, 20.4%) than the non-depressed type (30/328, 9.1%) after endoscopic resection ($p=0.002$). In addition, adenomas with surface redness (19/90, 21.1%, $p=0.002$), ulceration (8/27, 29.6%, $p=0.008$), and HGD (37/273, 17.4%, $p=0.001$) were more frequently diagnosed as carcinoma than adenomas without these features. Other baseline

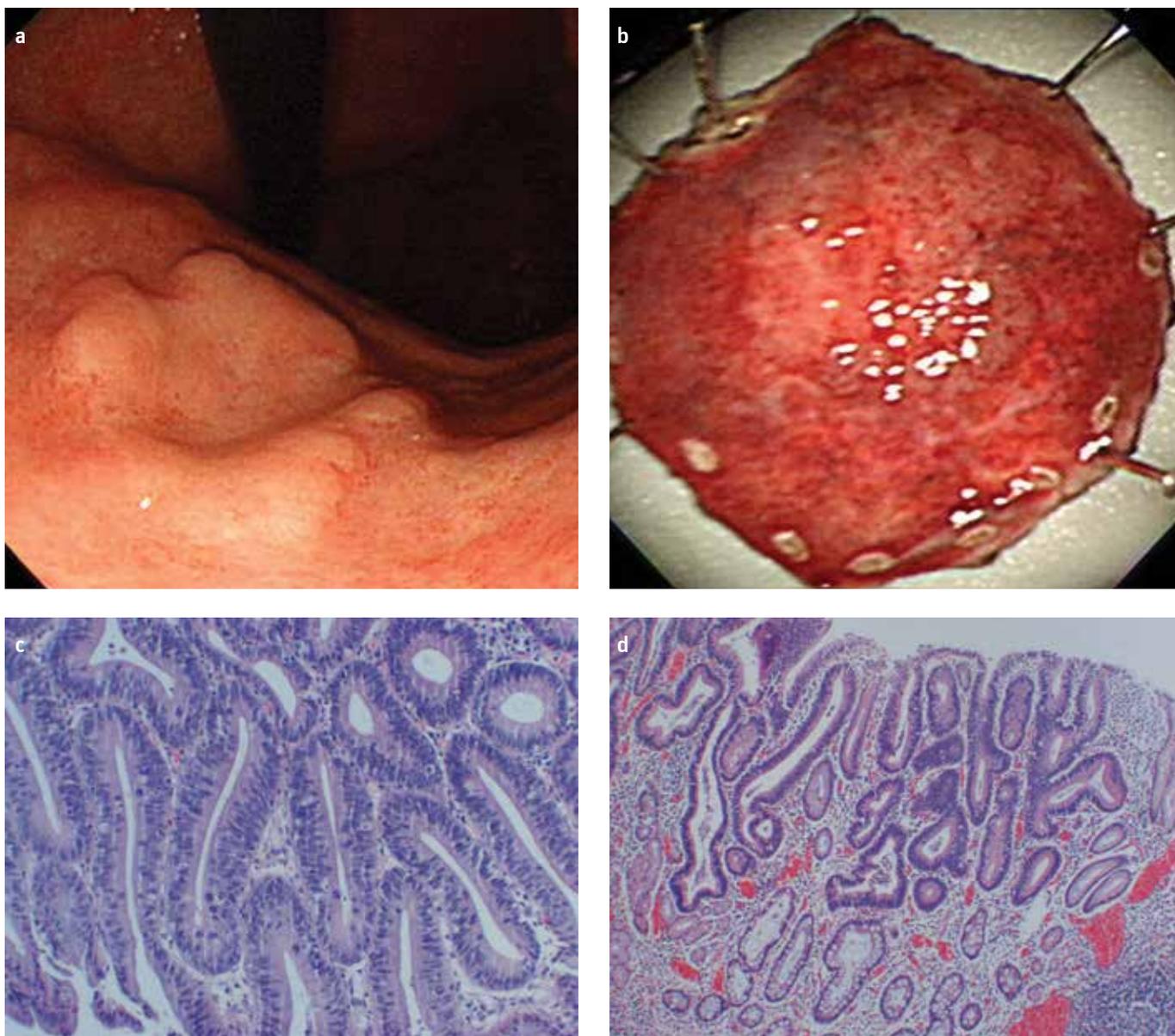


Figure 3. a-d. Endoscopic and pathologic findings of tubular adenoma. (a) 28×25 mm, type 0-IIa lesion observed in the posterior aspect of the body. This lesion had a smooth surface without red color change and mucosal ulceration; (b) 50×45 mm, resected specimen obtained; (c) Forceps biopsy showed adenoma with low-grade dysplasia; (d) The pathologic findings in the ESD specimen showed a tubular adenoma with low-grade dysplasia. The glands had a similar shape and were slightly crowded with a regular arrangement, and the nuclei were basally oriented ((c) H & E stain ×100; (d): H & E stain ×40).

characteristics were not significantly different between the adenoma group and the carcinoma group (Table 1). In the multivariate analysis, surface redness (odds ratio [OR], 2.1; 95% confidence interval [CI], 1.039–4.279) and HGD diagnosed on forceps biopsy (OR, 2.8; 95% CI, 1.444–5.489) were significant risk factors suggesting carcinoma (Table 2). When we investigated the interrelation between the presence of surface redness and the grade of dysplasia from a forceps biopsy, we discovered that lesions having an endoscopic finding of surface redness and HGD from a forceps biopsy were more likely to be carcinoma (34.8% vs. 6.3%; Table 3).

DISCUSSION

Endoscopic submucosal dissection and endoscopic mucosal resection (EMR) are performed worldwide and are accepted as treat-

ment options for mucosal lesions of the stomach and esophagus (16). Because of the long procedure times and high complication risks, these procedures should be performed by well-trained endoscopists (17-19). ESD/EMR has to be performed selectively while considering the clinical and endoscopic characteristics.

Pathological findings from forceps biopsy samples are reliable for the diagnosis of gastric lesions before complete resection. However, some of the adenomatous lesions may be misdiagnosed before treatment. The discrepancy rates between forceps biopsy samples and post-resected specimens ranged from 20% to 40% in previous reports (20-23). Discrepancies occur because the amount of tissue obtained by forceps biopsy is too small to represent the histology of the entire tumor le-

Table 1. Baseline characteristics and endoscopic features in the adenoma and carcinoma groups

	Adenoma group* (n=380)	Carcinoma group* (n=51)	p value
Mean age (years)	65.63±9.30	65.63±9.30	0.809
Sex (Male:Female)	233:147	35:16	0.312
Location			0.657
Upper	14 (3.7%)	1 (2.0%)	
Middle	123 (32.4%)	20 (39.2%)	
Lower	243 (63.9%)	30 (58.8%)	
Size (mm), mean±SD	21.04±8.65	22.06±7.46	0.195
≤10	33 (8.7%)	2 (3.9%)	
>10, ≤20	183 (48.2%)	24 (47.1%)	0.445
>20	164 (43.2%)	25 (49.0%)	
Gross appearance			0.002
Depressed	82 (21.6%)	21 (41.2%)	
Non-depressed	298 (78.4%)	30 (58.8%)	
Ulceration			0.008
Presence	19 (5.0%)	8 (15.7%)	
Absence	361 (95.0%)	43 (84.3%)	
Surface redness			0.002
Presence	71 (18.7%)	19 (37.3%)	
Absence	309 (81.3%)	32 (62.7%)	
Degree of dysplasia			<0.001
LGD	204 (53.7%)	14 (27.5%)	
HGD	176 (46.3%)	37 (72.5%)	

*Lesion diagnosed as adenoma by post-resected biopsy
 *Lesion diagnosed as adenocarcinoma by post-resected biopsy
 LGD: low-grade dysplasia; HGD: high-grade dysplasia

Table 2. Multivariate analysis of associated risk factors for noninvasive carcinoma in post-resection histology

Variables	β	SE	p value	OR	95% CI
HGD from EFB	1.035	0.341	0.002	2.815	1.444–5.489
Gross type (depressed vs. non-depressed)	0.546	0.365	0.135	1.726	0.843–3.532
Presence of ulcer	0.355	0.540	0.511	1.426	0.494–4.114
Surface redness	0.746	0.361	0.039	2.108	1.039–4.279

β: correlation coefficient; SE: standard error; OR: odds ratio; CI: confidence interval; HGD: high-grade dysplasia; EFB: endoscopic forceps biopsy.

sion. Some lesions show a change of histologic diagnosis from adenoma to carcinoma or from carcinoma to adenoma after ESD. Other lesions with carcinoma change their histologic differentiation from “well differentiated” to “poorly differentiated”

Table 3. Comparing LGD and HGD groups from forceps biopsy in the carcinoma group as surface redness

Post-resected biopsy		Carcinoma (n=51)	
Endoscopic forceps biopsy		LGD (n=218)	HGD (n=213)
Surface redness	(-)	11/174 (6.3%)	21/167 (12.6%)
	(+)	3/44 (6.8%)	16/46 (34.8%)

(%): percentages of carcinoma on post-resected biopsy
 LGD: low-grade dysplasia; HGD: high-grade dysplasia

after ESD. In our study, the concordance rate between forceps biopsy samples and post-resected specimens was 60.1%.

Both underestimation and overestimation of dysplasia occur with a diagnosis based on forceps biopsy samples. In lesions progressing from adenoma to carcinoma, pathological findings differ according to the site within the tumor, which is the cause of the underestimation. Overestimation may occur when the area of carcinoma or HGD is removed completely during the forceps biopsy; therefore, the specimen obtained after ESD is diagnosed as having progressive finding (11,23-25). The rate of underestimation and overestimation were 29.9% and 10.0%, respectively, in this study.

Endoscopic findings suggesting noninvasive carcinoma are variable and include features such as fold convergence, moth eaten appearance, and clubbing. However, data of the endoscopic features of the lesion suggesting an underestimation of adenoma on forceps biopsy are limited. Song et al. (26) found that endoscopic findings, such as a lesion size of 15 mm or greater, a depressed appearance, central concavity, and a nodular surface, were predictive factors of an underestimation in forceps biopsy and that HGD proven by forceps biopsy was also a predictive factor on multivariate analysis. Kim et al. (27) reported that significant discrepancies in the pathological findings before and after EMR/ESD were found in the groups of depression and HGD proven by forceps biopsy. Factors such as location and the presence of ulceration were not predictive factors of histological discrepancies across all the studies (26,27).

Kasuga et al. (28) reviewed 231 gastric adenomas initially diagnosed as LGD by forceps biopsy. After endoscopic resection, 43 lesions were diagnosed as adenocarcinoma in adenoma and 23 lesions were de novo adenocarcinoma. Lesion sizes larger than 20 mm and a central-depressed appearance were significant independent factors for cancer. Among protruding lesions, adenocarcinoma was found in 61.0% of the lesions size exceeding 20 mm but in only 5.7% of the lesions of 10 mm or less.

In our results, more carcinomas were found among the lesions sized 10 mm or more, but no statistically significant difference was noted. In addition, the rate of histological discrepancies was higher for depressed or ulcerative lesions in univariable analysis, but not in multivariable analysis. Our results also

showed that HGD from forceps biopsy and the presence of surface redness were independent predictive factors of existing noninvasive carcinoma in the multivariate analysis, and lesions having both factors were more likely to be carcinoma.

Therefore, gastric adenoma with these features should be considered for complete endoscopic resection for accurate diagnosis and proper management.

Some limitations were present in this study. First, the possibility of selection biases may be present because this study was performed retrospectively and patients resected with EMR or surgery were not included. Second, there may be a bias in the pathological and endoscopic findings. We did not perform a central review of the pathological diagnoses and the concordance rate of endoscopic findings between observers was not investigated. Thus, we cannot eliminate inter-observer variations. To overcome these limitations, inter-observer variations between endoscopists and pathologists should be minimized and large-scale multicenter prospective studies are necessary to confirm the findings.

In conclusion, the results of this study demonstrate that surface redness and HGD from a forceps biopsy most reliably suggest the presence of carcinomatous foci in a gastric adenoma. Therefore, gastric adenomas with these predictive factors should be resected completely on ESD because of the possibility of an underestimated malignancy after ESD.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Presbyterian Medical Center. (IRB No. 2015-03-009).

Informed Consent: This study was exempted from informed consent because of retrospective study using data and image.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - J.W.C.; Design - J.W.C.; Supervision - J.W.C.; Funding - J.W.C.; Materials - S.J.K.; Data Collection and/or Processing - S.J.K., M.S.P., S.H.H., S.H.Y.; Analysis and/or Interpretation - S.J.K., M.A.Y., J.W.C.; Literature Review - S.J.K., M.A.Y., J.W.C.; Writer - S.J.K.; Critical Review - J.W.C.

Acknowledgements: The authors want to thank all the members of gastroenterologic division and endoscopy team in Presbyterian Medical Center.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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