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Clinical Implication and Risk Factors for Malignancy of Atypical Gastric Gland during Forceps Biopsy

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Background/Aims: Although forceps biopsy is performed for suspicious gastric tumors during endoscopy, it is difficult to determine treatment strategies for atypical gastric glands due to uncertainty of the diagnosis. The aim of this study was to investigate clinical implications and risk factors for predicting malignancy in atypical gastric glands during forceps biopsy. **Methods:** We retrospectively reviewed medical records of 252 patients with a diagnosis of atypical gastric gland during forceps biopsy. Predictors of malignancy were analyzed using initial endoscopic findings and clinical data. **Results:** The final diagnosis for 252 consecutive patients was gastric cancer in 189 (75%), adenoma in 26 (10.3%), and gastritis in 37 (14.7%). In the multivariate analysis, lesion sizes of more than 10 mm (odds ratio [OR], 3.021; 95% confidence interval [CI], 1.480 to 6.165; p=0.002), depressed morphology (OR, 3.181; 95% CI, 1.579 to 6.406, p=0.001), and surface nodularity (OR, 3.432; 95% CI, 1.667 to 7.064, p=0.001) were significant risk factors for malignancy. **Conclusions:** Further evaluation and treatment should be considered for atypical gastric gland during forceps biopsy if there is a large-sized (>10 mm) lesion, depressed morphology, or surface nodularity. **(Gut Liver 2018;12:523-529)**

Key Words: Atypical gland; Forcep biopsy; Stomach neoplasms; Adenoma; Gastritis

INTRODUCTION

Gastric cancer is the most common gastrointestinal malignancy in East Asia.[1] The National Cancer Screening Program for gastric cancer in Korea has been conducted for adults over 40 years of age due to high prevalence of gastric cancer in this population.[2] With increasing screening endoscopy, early detection of gastric cancer and precancerous lesions has also increased. Pathologic results of forceps biopsy for suspicious malignant lesions can be interpreted as atypical glands that are indeterminate results between malignancy and benign disease. Atypical gland is usually diagnosed when it is difficult to interpret between epithelial neoplasia and inflammatory change with histological morphology of abnormal epithelium and gland formation.[3] Moreover, while endoscopic forceps biopsy is an initial favorable modality for the diagnosis of gastric tumor, the tissue may not be sufficient for definite diagnosis.[4,5]

Previous studies have attempted to determine clinical factors suggesting cancer for pathologic results of indefinite neoplasia in Vienna classification.[6-8] Indefinite neoplasia could be further subcategorized into atypical gland/cellular atypia and reactive/regenerative atypia. Atypical gland usually maintains a glandular structure to some extent that is more likely to be dysplasia while regenerative atypism/atypia is more likely to be an inflammatory change rather than tumor, though there is no clear boundary between them.[9]

Endoscopic re-biopsy is usually recommended according to the guideline if the pathology of initial biopsy results is atypical gland.[10,11] However, if endoscopic findings are strongly suspected to be gastric cancer or high-grade adenoma, endoscopic resection may be a better option for definitive diagnosis and treatment than repeated biopsy.[12] Recently, endoscopic submucosal dissection (ESD) has enabled definitive diagnosis and treatment by *en-bloc* resection of suspicious gastric tumor. It has replaced surgical treatment of early gastric cancer (EGC) in indicated cases and gastric adenoma as precancerous lesion.[13,14]

At present, there have been no studies merely analyzing clinical features of "atypical gland" excluding "regenerative atypia."

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The aim of this study was to determine the clinical implication of atypical gland at initial forceps biopsy and factors for predicting gastric cancer in endoscopic findings.

MATERIALS AND METHODS

1. Patients

Between March 2006 and February 2016, patients who were pathologically diagnosed as atypical gland at forceps biopsy for suspicious gastric tumor at Seoul National University Hospital were enrolled in this study. For patients who were referred from other clinics with diagnosis of atypical gland in pathology, the diagnosis was confirmed by pathologic review of the slide.

Atypical gland was considered when there were pathologic characteristics of dysplasia (cellular atypia, abnormal differentiation, disorganized mucosal architecture) with too good differentiation; Dysplasia appeared in extremely fine part of the regenerative atypia was excluded because of its pathologic features of benign lesion like gastritis with distribution of surrounding inflammatory cells (Fig. 1).[9]

The present study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. H-1704-124-848). It was conducted in accordance with the Declaration of Helsinki. The informed consent was waived with the retrospective nature.

2. Clinical outcomes and histopathological evaluation

Medical records of patients were collected and evaluated for basic clinical and endoscopic findings. Each endoscopic image and report were reviewed for the description of diameter and gross features of the lesion. Endoscopic photographs were taken using the following two versions of endoscope (GIF-H260/H290; Olympus Optical Co., Ltd., Tokyo, Japan). Gross type (elevated, flat, depressed), surface redness, nodularity, presence of ulcer, location of the lesion, endoscopic presence of intestinal metaplasia in background mucosa, and status of *Helicobacter pylori* infection were collected. The status of *H. pylori* infection was classified into four stages (negative to 3 positive) according to the density of *H. pylori* based on the result of pathologic examination of the specimen. Surface redness was defined as a red discoloration on the mucosal surface. Nodularity was defined as the presence of irregular elevation or nodular mucosa.[15] Location of the lesion was divided into three identical sections: upper, middle, and lower.[16]

For cases who had undergone ESD or surgical resection, serial sections with thickness of 2 mm were made in the case of ESD and 4 mm sections were made in case of surgical resection for histological mapping. Gastric cancer was classified according to World Health Organization (WHO) classification method and Japanese Gastroenterological classification according to the degree of differentiation.[16,17]

3. Statistical analyses

For comparison between malignant and benign diseases, we divided patients into two subgroups. Chi-square test, Fisher exact test, and Student t-test were used to analyze the relationship among variables suggestive malignancy with univariate analysis. Multiple logistic regression analyses were used to examine independent risk factors for multivariate analysis with a p-value of less than 0.05 in univariate analysis. SPSS Statistics for Windows version 23.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. Null hypotheses of no difference were rejected if p-values were less than 0.05.

RESULTS

1. Baseline characteristics

During the study period, 859 patients were diagnosed or referred from outside clinic as atypical gland, in which 587 patients were excluded due to coincidental adenoma/adenocarcinoma or no atypical gland at slide review. In addition, 20 patients were excluded because of follow-up loss or other diagno-

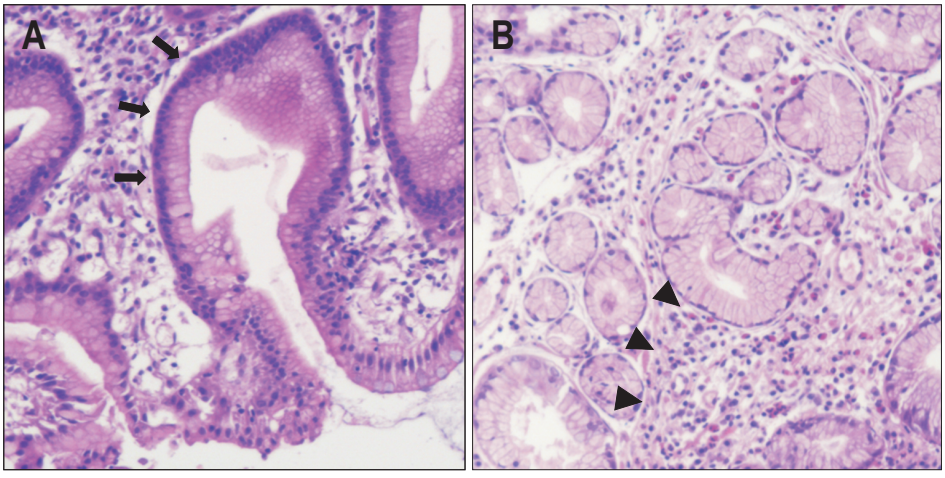

Fig. 1. Typical pathology photograph of an atypical gland and regenerative atypia in indefinite neoplasia. (A) Atypical gland similar to dysplasia with good differentiation (arrows). (B) Regenerative atypia with numerous inflammatory cells (triangles).

sis (fibroelastoma, gastrointestinal stromal tumors). Finally, 252 patients were analyzed for the diagnosis of atypical gland (Fig 2). The malignant group consisted of 141 men and 48 women with a mean age of 61.5 years while the benign group consisted of 49 men and 14 women with a median age of 64.6 years. Of these, initial endoscopic resection or surgical resection was performed for definitive treatment in 48 and 23 patients, respectively. Additional endoscopic biopsy was performed in 181 patients, of which 32 patients remained to have the diagnosis of atypical gland at secondary biopsy, seven patients remained at tertiary biopsy, and two patients remained in the fourth biopsy (Fig. 3). Final diagnoses of consecutive 252 patients were gastric cancer (n=189, 75%), adenoma (n=26, 10.3%), and gastritis (n=37, 14.7%).

2. Risk factors for malignancy in atypical gland

The mean age was 62.24±10.79 years. The proportion of males was 74.6% in the group with gastric cancer, which was not significantly different among groups with different final diagnoses. The mean size of atypical gland in the gastric cancer group (20.4 mm) was larger than that of the adenoma group (8.8 mm) or the gastritis group (9.2 mm) (both $p<0.001$ by one-way analysis of variance). Depressed type and surface nodularity were significantly predominant in the group with gastric cancer than those in the group with adenoma or gastritis. Underlying mucosal atrophy/intestinal metaplasia and the status of *H. pylo-*

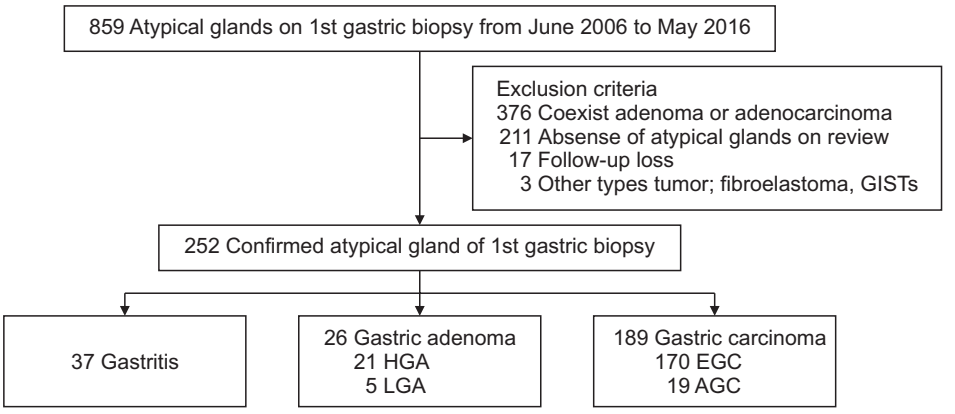

Fig. 2. Study flowchart and enrollment in this study.
GIST, gastrointestinal stromal tumor; HGA, high-grade adenoma; LGA, low-grade adenoma; EGC, early gastric cancer; AGC, advanced gastric cancer.

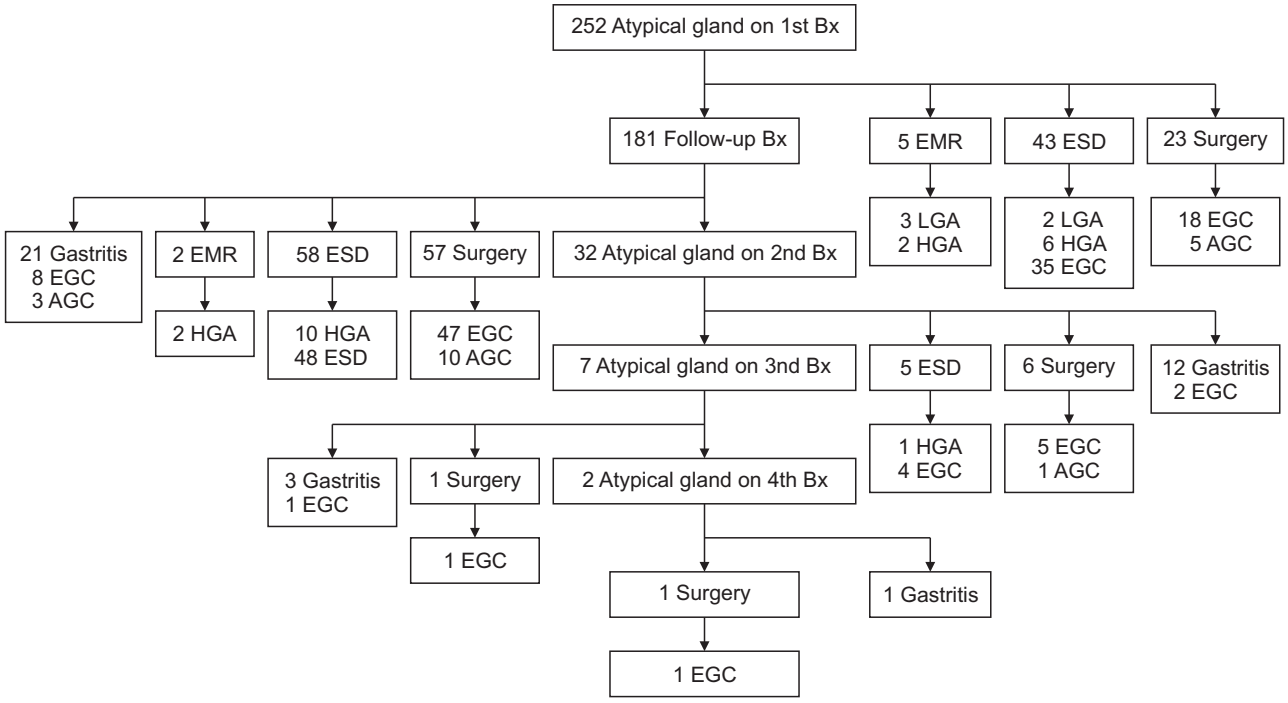

Fig. 3. Assessment and final diagnosis of atypical gland during initial biopsy.
Bx, biopsy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; LGA, low-grade adenoma; HGA, high-grade adenoma; EGC, early gastric cancer; AGC, advanced gastric cancer.

ri infection were not significantly different among these groups (Table 1).

In addition, the malignant group and the benign group (including adenoma and gastritis) were compared and analyzed for clinical and endoscopic factors related to gastric cancer. The proportion of male was 74.6% in the malignant group and 77.8% in the benign group. The mean age of patients was 61.5 years in the malignant group and 64.6 years in the benign group. Differences in these were not statistically significant between the two groups.

Univariate analysis of clinicopathologic factors revealed that lesion size greater than 10 mm, surface nodularity, and surface depression were significant risk factors for malignancy (Table 2). In multivariate analysis, lesion size more than 10 mm (p=0.002; odds ratio [OR], 3.021; 95% confidence interval [CI], 1.480 to 6.165), depressed morphology (p=0.001; OR, 3.181 95% CI, 1.579 to 6.406), and surface nodularity (p=0.001; OR, 3.432; 95% CI, 1.667 to 7.064) remained significant risk factors for malignancy (Table 3).

DISCUSSION

Endoscopic biopsy is usually performed initially for the diagnosis of suspicious gastric lesion during endoscopy.[10,11] However, the diagnosis with forceps biopsy is not always definite. It is often inconsistent with the final pathology due to heterogeneity of the tissue itself as well as the sampling process affected by the location, depth, and the number of biopsies.[14] In addition, biopsy specimens diagnosed as dysplasia/adenoma may be evaluated differently from pathological viewpoints. Atypical gland is a broad concept used in all cases where it is difficult to distinguish between benign reactive lesion and dysplasia or

Table 2. Risk Factors for Gastric Cancer with Atypical Glands

	Malignancy (n=189)	Benign (n=63)	p-value
Age, yr	61.5±11.0	64.6±10.4	0.055
Male sex	141 (74.6)	49 (77.8)	0.736
Lesion size (>10 mm)	148 (78.3)	29 (46.0)	<0.001
Gross type			<0.001
Elevated	18 (9.5)	22 (34.9)	
Flat	37 (19.6)	15 (23.8)	
Depressed	134 (70.9)	26 (41.3)	
Surface nodularity	145 (76.7)	28 (44.4)	<0.001
Surface redness	114 (60.3)	33 (52.4)	0.303
Location of stomach anatomy			0.111
Lower	129 (68.3)	51 (81.0)	
Middle	26 (13.8)	7 (11.1)	
Upper	34 (18.0)	5 (7.9)	
Ulcer	45 (23.8)	14 (22.2)	0.865
Gastric atrophy	142 (75.1)	40 (63.5)	0.104
Intestinal metaplasia	106 (56.1)	36 (57.1)	1
Helicobacter pylori positive	62 (50.4)	31 (50.8)	1

Data are presented as mean±SD or number (%).

Table 1. Baseline Characteristics of Patients with Atypical Glands on the First Biopsy

Characteristic	Adenocarcinoma (n=189)	Adenoma (n=26)	Gastritis (n=37)	p-value
Age, yr	62.2±10.8	63.7±12.4	67.8±5.5	0.695
Male sex	141 (74.6)	18 (69.2)	31 (83.8)	0.368
Lesion size, mm	20.4±15.4	8.8±4.8	9.2±5.3	<0.001
Gross type				<0.001
Elevated	18 (9.5)	14 (53.8)	8 (21.6)	
Flat	37 (19.6)	5 (19.2)	10 (27.0)	
Depressed	134 (70.9)	7 (26.9)	19 (51.4)	
Surface nodularity	145 (76.7)	16 (61.5)	12 (32.4)	<0.001
Surface redness	114 (60.3)	12 (46.2)	21 (56.8)	0.381
Location of stomach anatomy				0.240
Lower	129 (68.3)	21 (80.8)	30 (81.1)	
Middle	26 (13.8)	4 (15.4)	3 (8.1)	
Upper	34 (18.0)	1 (3.8)	4 (10.8)	
Ulcer	45 (23.8)	3 (11.5)	11 (29.7)	0.236
Gastric atrophy	142 (75.1)	16 (61.5)	24 (64.9)	0.266
Intestinal metaplasia	106 (56.1)	18 (69.2)	18 (48.6)	1
Helicobacter pylori positive	62 (50.4)	13 (52.0)	18 (50.0)	0.987

Data are presented as mean±SD or number (%).

carcinoma.[10,20] For lesion with severe inflammation and regeneration of gland, it may be difficult to differentiate between benign and malignant lesion by cellular and glandular atypism, especially for small amount of tissue in forceps biopsy.[18] In this study, 75% of patients who were initially diagnosed as atypical gland in forceps biopsy was finally identified as gastric cancer. In a previous study, 21.8% (26/119) of indefinite neoplasia (category 2) were also confirmed to be gastric cancer.[7] Therefore, atypical gland can be a diagnosis of broad spectrum from benign inflammatory lesion to cancer.

Few studies have dealt with clinical significance of indefinite neoplasia (category 2), including atypical gland.[3,7,8] Precise diagnosis and grading of dysplasia are important in determining the treatment strategy. Although several studies have recommended further evaluation such as big size re-biopsy for strongly suspicious lesion of malignancy,[8,13,19] endoscopic resection can be a modality for definite diagnosis and treatment of atypical gland. However, ESD may be an over-treatment for all cases of atypical gland.

In previous studies about dysplasia, endoscopic findings with lesion size greater than 2 cm,[7] presence of ulcer, depressed morphology,[19] and hemorrhagic tendency[13] have strongly suggested high-grade adenoma or gastric cancer.[20] In revised Vienna classification category 2, lesion greater than 1 cm in diameter and surface discoloration were risk factors for carcinoma.[7] However, previous studies have focused on general endoscopic findings of patients with dysplasia or inflammatory lesions such as regenerative atypism/atypia, instead of focusing on atypical glands only. In this study, only patients with atypical glands from initial gastric biopsy were included. Lesion size greater than 1 cm, surface

Table 3. Significant Risk Factors for Gastric Cancer with Atypical Glands by Univariate Analysis & Multivariate Analysis

Risk factors	Univariate analysis		Multivariate analysis	
	p-value	OR (95% CI)	p-value	OR (95% CI)
Lesion size (>10 mm)	<0.001	4.23 (2.31–7.74)	0.002	3.02 (1.48–6.17)
Mucosal depression	<0.001	3.06 (1.68–5.55)	0.001	3.18 (1.58–6.41)
Surface nodularity	<0.001	4.12 (2.26–7.51)	0.001	3.43 (1.67–7.06)

OR, odds ratio; CI, confidence interval.

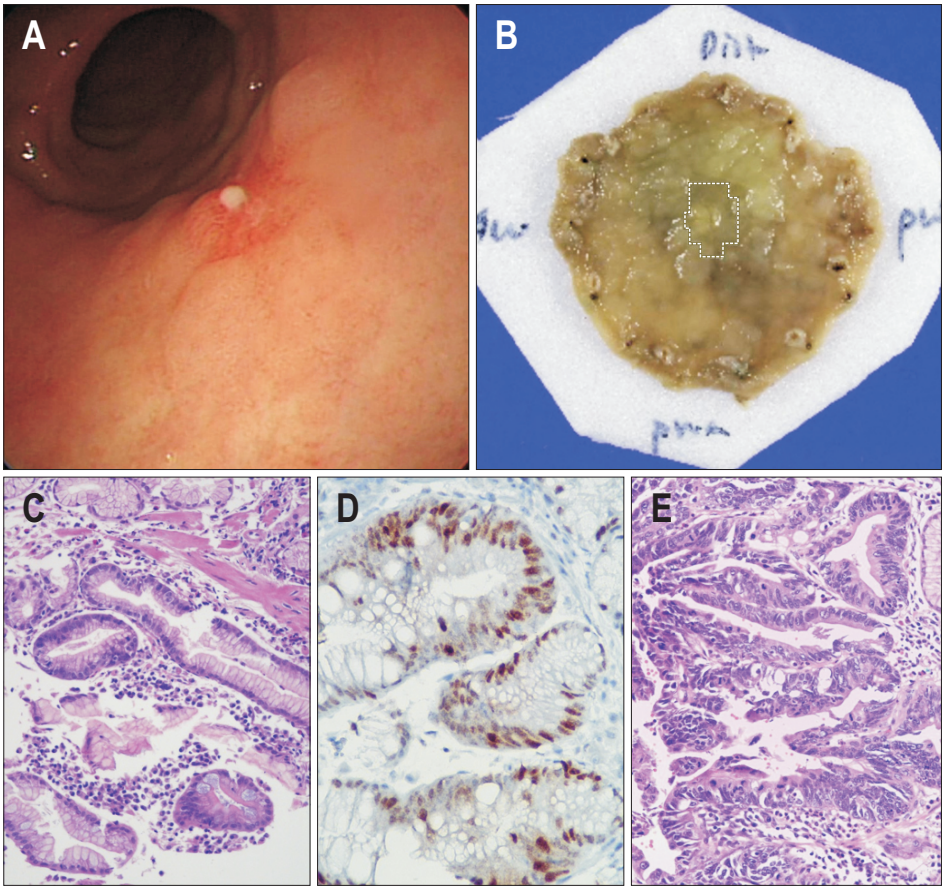

Fig. 4. A case of definite diagnosis after endoscopic submucosal dissection (ESD) in atypical glands during initial biopsy. (A) Hyperemic depressed mucosal nodularity on the antrum posterior wall. (B) Post-ESD histopathological specimen fixed with formalin (white dashed line on the borderline of an adenocarcinoma by pathologic mapping). (C) Histological finding of atypical glands during initial biopsy (H&E, ×200). (D) Positive immunochemical staining during the initial biopsy (p53, ×400). (E) Well-differentiated adenocarcinoma on post-ESD pathology (H&E, ×200).

depression, and surface nodularity were found to be significant risk factors for malignancy. When only EGC and benign lesions were compared, lesion greater than 10 mm and surface nodularity were also risk factors for EGC (Supplementary Tables 1 and 2). Undifferentiated pathology is known to be a reasonable treatment for surgery. We also performed subgroup analysis for undifferentiated and differentiated carcinoma in gastric cancer. Lesions size of more than 2 cm and surface depression were also found to be significant risk factors for undifferentiated type (Supplementary Table 3).

In some cases of atypical glands on biopsy, immunohistochemical staining performed using p53 before ESD or surgery might be helpful for the prediction of malignancy. This stainingcan be a useful tool for the prediction of malignancy in cases with atypical glands (Fig. 4).[21]

This study had several limitations. The interpretation of atypical gland could be influenced by intra- and inter-observer variation.[22-24] In this study, all slides were reviewed by two pathologists to minimize the inter-observer variation. Second, there could be a selection bias due to its retrospective nature. Third, only conventional endoscopic findings were included in the analysis without additional information such as narrowband imaging,[25] chromoendoscopic imaging,[26] or concomitant medication.[27] Finally, we did not evaluate features of atypical gland that were suggestive of benign lesion. In the management of gastric atypical gland, it is important to exclude benign lesions that do not require an invasive diagnostic approach. Therefore, it is necessary to analyze predictors suggesting benign lesion. Further investigation is warranted.

In conclusion, atypical gland can contain malignancy, especially when there is large sized (>10 mm) lesion, depressed morphology, or surface nodularity. Accurate diagnosis by re-biopsy or definitive treatment is mandatory by endoscopic or surgical resection in the suspicion of malignancy. Simple endoscopic follow-up with re-biopsy might be insufficient. It might delay the diagnosis and miss the appropriate treatment period. Repeated examinations can also lead to cost and psychological/social stress. If the above suspicious malignant findings are present, aggressive methods can be applied simultaneously with diagnosis. Treatment such as ESD can be considered.

CONFLICTS OF INTEREST

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

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