Endoscopic characteristics in predicting prognosis of biopsy-diagnosed gastric low-grade intraepithelial neoplasia

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Abstract

Background: Endoscopic biopsy can underestimate gastric malignancies as low-grade intraepithelial neoplasia (LGIN). Definitively diagnosed LGIN would progress. This study aimed to evaluate predictive factors to identify malignancies misdiagnosed as LGIN by biopsy and LGIN at high risk of progression.

Methods: The clinical records of patients diagnosed with gastric LGIN by endoscopic biopsy who underwent at least two endoscopies during the first year of follow-up between 2007 and 2017 were retrospectively collected. Three endoscopists reviewed photographs of the initial endoscopy, described lesion characteristics, and made endoscopic diagnoses. Logistic regression was used to analyze predictors to identify malignancies underestimated as LGIN. A receiver operating characteristic curve was used to evaluate the diagnostic accuracy of these predictors. Patient clinical outcomes of follow-up >1 year were collected. Kaplan–Meier estimates with log-rank tests and Cox proportional hazards regression were used to analyze predictors of progression.

Results: Overall, 48 of 182 (26.4%) patients were proven to have malignancies. A single lesion, a large lesion size, and marked intestinal metaplasia (IM) were independent predictors of initially misdiagnosed malignancies. The area under the curve of these predictors was 0.871, with a sensitivity of 68.7% and specificity of 92.5%. Twelve of 98 patients (12.2%) progressed during the 33-month median follow-up period. A whitish appearance, irregular margins, marked IM, and histological diagnosis of LGIN more than twice within the first year were predictors for progression.

Conclusions: Lesions diagnosed as LGIN by biopsy with marked IM and other predictors above should be prudently treated for high potential to be malignancies or progress. Endoscopic follow-up with repeated biopsies within the first year is recommended.

Keywords: Diagnostic errors; Disease progression; Endoscopy; Metaplasia; Stomach neoplasms

Introduction

Gastric cancer (GC) has been a major public health problem in China, remaining the third most common reason for new cases and cancer-related deaths.[1] It was demonstrated that survival rate of GC patients can be markedly increased by an early diagnosis.[2] The 5-year survival rate of early gastric cancer (EGC) patients after lesion resection is >90%.[3,4] Early detection of GC relies heavily on endoscopic screening through conventional white light endoscopy (WLE), because patients with EGC always have few symptoms. However, EGC is limited to the mucosa or submucosa layer and has minute morphological change, which make its identification ambiguous for endoscopists.

After the detection of suspected lesions, another challenge for endoscopists is to obtain tissue through endoscopic forceps biopsy (EFB) because histological discrepancies sometimes occur between biopsied and resected specimens due to heterogeneity or sampling errors. According to the Correa cascade, the carcinogenesis of GC results from the sequential progression from atrophic gastritis to intestinal metaplasia (IM), to intraepithelial neoplasia, and ultimately to adenocarcinoma.[5] Low-grade intraepithelial neoplasia (LGIN) is considered a precancerous lesion, but one-

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quarter of EFB-diagnosed LGINs are proven to be more advanced lesions after resection, such as high-grade intraepithelial neoplasia (HGIN) or EGC.[6] It was also reported that the standard incidence of GC in patients with LGIN was nearly 25-fold higher than that in the general population and eight-fold higher than that in patients with unclassified lesions.[7,8] Therefore, appropriate management of lesions diagnosed as LGIN by EFB is important for the prevention and early detection of GC.

Therefore, this study contained mainly two relevant aims. The first aim was to evaluate clinical predictive factors for the recognition of malignancies underestimated as LGIN by EFB initially. Then, the diagnostic accuracy of these predictors was evaluated. The second aim was to study the natural history and long-term progression risk of LGINs after eliminating EFB-underestimated malignancies.

Methods

Ethical approval

This study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee of Peking Union Medical College Hospital (No. S-K1292). As a retrospective study in which data analysis was performed anonymously, this study was exempt from obtaining informed consent from patients.

Patients

Consecutive patients with gastric superficial lesions diagnosed as LGIN based on the index EFB who received at least one more endoscopy with repeated EFB for surveillance or for treatment within the first year after the initial WLE at Peking Union Medical College Hospital (Beijing, China) between January 2007 and December 2017 were enrolled. The exclusion criteria were as follows: (1) patients with a medical history of gastrointestinal tract carcinoma; (2) patients with a remnant stomach; or (3) patients with a medical history of chemical therapy or radiotherapy on the abdomen. The flowchart of patient enrollment in this study is presented in Figure 1.

Endoscopic evaluation

WLE was performed using a GIF-H260 or GIF-Q260 endoscope (Olympus, Tokyo, Japan). All endoscopic photographs of these lesions taken before EFB during actual clinical practice of the initial WLE were selected. The images were independently reassessed by three endoscopists (Guo T, Jiang QW, and Wu X) with >10 years of experience performing gastroscopy without any information about these patients, their endoscopic diagnosis or histologic diagnosis. If the patient had multiple gastric superficial lesions diagnosed as LGIN, only the most severe one was included in the analysis.

Each endoscopist described the endoscopic characteristics and made an endoscopic diagnosis of lesions after reviewing their photographs at the initial WLE. Endoscopic characteristics included the number, location, direction, gross type, size, surface configuration, margin, and background mucosa. The number of lesions was classified as singular or multiple, and multiple lesions were defined as the presence of ≥2 lesions with similar gross types and colors around the same location.[9] The location of lesions was classified as being in the body or antrum of the stomach. The direction was classified as the anterior/posterior wall and lesser/greater curvature. The gross type was categorized according to the Paris classification as elevated (type 0–I or type 0–IIa), flat (type 0–IIb), or depressed (type 0–IIa + c, type 0–IIc, type 0–IIc + a, or type 0–III).[10] The lesion size was estimated using endoscopic forceps. The color, nodularity, erosion, ulcer, and spontaneous bleeding of lesions were described as the surface configuration. The color of lesions was categorized according to the discoloration on the surface compared to the surrounding mucosa as reddish, whitish, or the same. Nodularity was defined as the presence of an irregularly raised nodular mucosa. Erosion was defined as a superficial mucosal defect, and an ulcer was defined as a deeper mucosal defect with discontinuity of the muscularis propria. Spontaneous bleeding was defined as minor bleeding of the friable mucosa resulting from aeration or a weak touch.[9,11] Lesions with clearly delineated margins were defined as having clear margins, and their regularity was further described. The background mucosa of lesions was evaluated for the presence of acute gastritis, marked atrophy, or marked IM. Representative photographs of these endoscopic characteristics are shown in Supplementary Figure 1, http://links.lww.com/CM9/A668. The endoscopic diagnosis was classified as malignant or benign. The level of diagnostic confidence was estimated as high or low. The conclusions were determined based on the agreement of at least two endoscopists.

Histological evaluation

All specimens were evaluated using hematoxylin and eosin staining by highly experienced pathologists. The histological diagnoses were classified into five categories according to the revised Vienna classification.[12] In this study, lesions histologically diagnosed as category 4 (non-invasive high-grade neoplasia, including HGIN and EGC limited in the mucosal layer) or category 5 (submucosal EGC) were considered malignant, and those histologically diagnosed as category 1 (negative for dysplasia), category 2 (indefinite for dysplasia), or category 3 (LGIN) were considered benign.

Follow-up

All patients underwent at least one more endoscopic test in the first year after being initially diagnosed with LGIN by EFB. During endoscopies after the index WLE, targeted EFBs for surveillance or resection for treatment were performed. The most severe histological diagnosis of biopsied or resected specimens within the first year after the initial endoscopy was considered the definite diagnosis of lesions and the gold standard.[7] The time interval between the index endoscopy and the definite diagnosis was recorded. If the lesion was definitively diagnosed as a malignancy, it was considered an initially misdiagnosed malignant lesion by EFB.

Except for those who were misdiagnosed by the initial EFB, patients receiving long-term follow-up were included to analyze the natural history of their lesions. Patients who

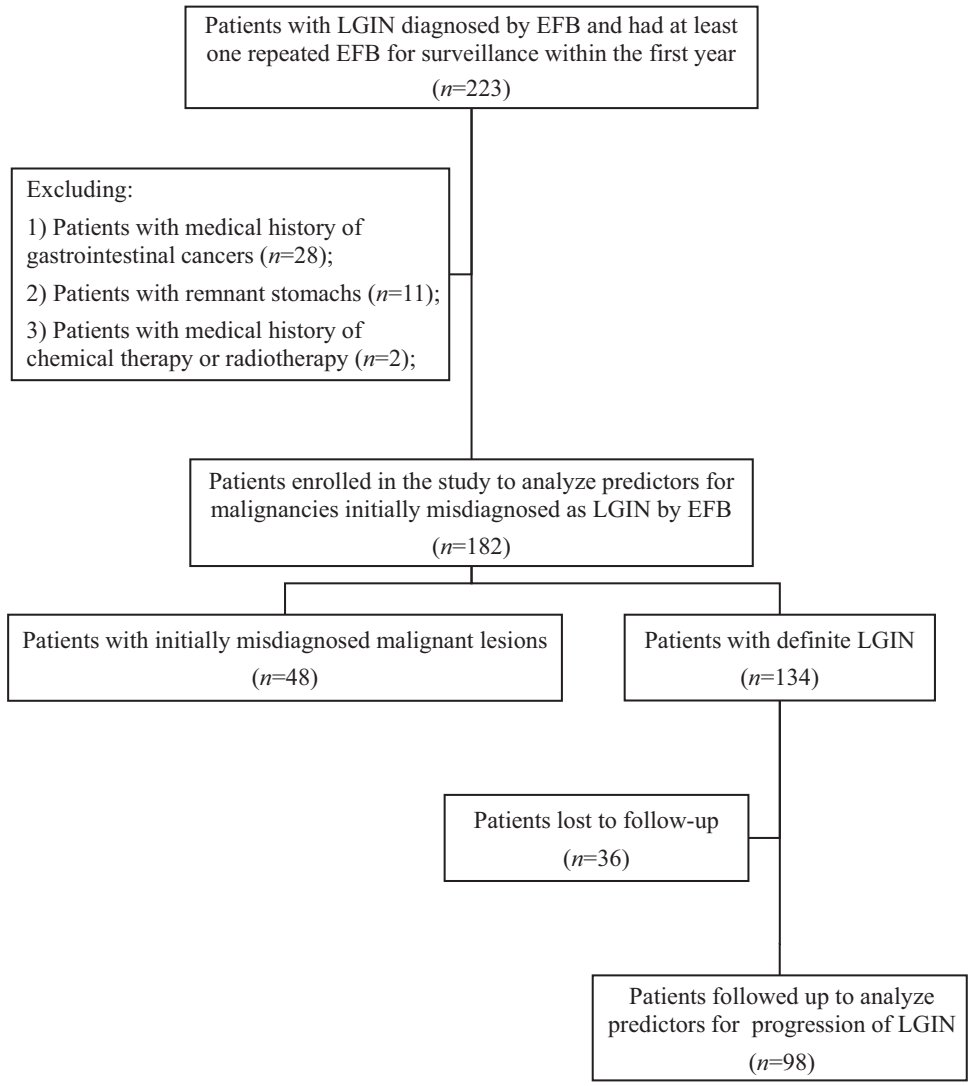

Figure 1: Flowchart of the study participants' enrollment. The patients were diagnosed with gastric LGIN by endoscopic biopsy and underwent at least two endoscopies during the first year of follow-up. EFB: Endoscopic forceps biopsy; LGIN: Low-grade intraepithelial neoplasia.

were followed up for <1 year were considered lost to follow-up. The start points of follow-up were the initial diagnosis dates for LGIN. The endpoints were defined as follows depending on which came first: (1) when the lesion was resected; (2) when the lesion was histologically diagnosed as malignant by EFB specimens; or (3) the last time of endoscopic test with EFB when the lesion was considered non-malignant. If the histological diagnosis at the endpoint was malignant, the outcome of the patient was considered progressed.

Statistical analysis

Continuous variables were presented as mean ± standard deviation or median (interquartile range) and compared with independent *t*-test or Kruskal–Wallis test. Categorical variables were presented as numbers (percentages) and compared with Pearson χ^2 test or Fisher exact test. A multiple logistic regression model was used to evaluate clinical predictive factors for the recognition of malignancies underestimated as LGIN by initial EFB. The diagnostic accuracy of these predictors was evaluated and quantified by area under the receiver operating characteristic curve (AUC), sensitivity, specificity, likelihood ratio, and predictive value.

We used the Kaplan–Meier method to estimate the incidence rate of progression and log-rank test to compare the difference of progression risks among different groups. We used the multiple Cox proportional hazard regression model to test the risk factors of disease progression.

The statistic analyses of diagnostic accuracy were carried out with MedCalc software (version 12.4; MedCalc Software Ltd., Oostende, Belgium), and other analyses were carried out with SPSS software (version 23.0; IBM, Armonk, NY, USA). $P < 0.050$ on a two-tailed test was considered statistically significant.

Results

Predictive factors for initially misdiagnosed malignant lesions by EFB

In total, 182 patients were enrolled [Figure 1]. A total of 48 (26.4%) patients (46 diagnosed by endoscopically resected

Table 1: Baseline characteristics of patients: comparison between benign lesions and initially misdiagnosed malignant lesions.

Characteristics	Total (*n*=182)	Misdiagnosed patients (*n*=48)	Patients with LGIN (*n*=134)	Statistics	OR (95% CI)	*P* value
Age (years), mean ± SD	59.0 ± 10.2	60.5 ± 9.1	58.4 ± 10.5	−1.255*	1.021 (0.988–1.056)	0.211
Sex				0.174		0.677
Male	107 (58.8)	27 (56.3)	80 (59.7)		0.868 (0.446–1.690)	
Female	75 (41.2)	21 (43.8)	54 (40.3)		1.000	
Number of lesions				25.184		<0.001
Single	126 (69.2)	47 (97.9)	79 (59.0)		32.722 (4.383–244.306)	
Multiple	56 (30.8)	1 (2.1)	55 (41.0)		1.000	
Location				0.003		0.959
Body	45 (24.7)	12 (25.0)	33 (24.6)		1.000	
Antrum	137 (75.3)	36 (75.0)	101 (75.4)		0.980 (0.457–2.101)	
Direction				0.089		0.993
Anterior wall	41 (22.5)	11 (22.9)	30 (22.4)		1.000	
Lesser curvature	82 (45.1)	22 (45.8)	60 (44.8)		1.000 (0.429–2.331)	
Posterior wall	30 (16.5)	8 (16.7)	22 (16.4)		0.992 (0.342–2.874)	
Greater curvature	29 (15.9)	7 (14.6)	22 (16.4)		0.868 (0.290–2.596)	
Gross type				23.677		<0.001
Elevated	66 (36.3)	11 (22.9)	55 (41.0)		1.000	
Flat	36 (19.8)	2 (4.2)	34 (25.4)		0.294 (0.061–1.408)	
Depressed	80 (44.0)	35 (72.9)	45 (33.6)		3.889 (1.776–8.515)	
Size				56.110		<0.001
<10 mm	111 (61.0)	9 (18.8)	102 (76.1)		1.000	
10–20 mm	58 (31.9)	28 (58.3)	30 (22.4)		10.578 (4.502–24.854)	
>20 mm	13 (7.1)	11 (22.9)	2 (1.5)		62.333 (11.928–325.744)	
Color				0.547		0.764
Reddish	136 (74.7)	34 (25.0)	102 (76.1)		0.741 (0.308–1.781)	
Whitish	17 (9.3)	5 (10.4)	12 (9.0)		0.926 (0.251–3.420)	
Same	29 (15.9)	9 (18.8)	20 (14.9)		1.000	
Erosion				5.973		0.015
Present	90 (49.5)	31 (64.6)	59 (44.0)		2.318 (1.171–4.588)	
Absent	92 (50.5)	17 (35.4)	75 (56.0)		1.000	
Spontaneous bleeding				N/A		0.016†
Present	12 (6.6)	7 (14.6)	5 (3.7)		4.405 (1.326–14.628)	
Absent	170 (93.4)	41 (85.4)	129 (96.3)		1.000	
Nodularity				51.205		<0.001
Present	42 (23.1)	29 (60.4)	13 (9.7)		14.206 (6.297–32.049)	
Absent	140 (76.9)	19 (39.6)	121 (90.3)		1.000	
Ulcer/ulcer scar				N/A		0.484†
Present	11 (6.0)	4 (8.3)	7 (5.2)		1.649 (0.461–5.905)	
Absent	171 (94.0)	44 (91.7)	127 (94.8)		1.000	
Clear margin				6.739		0.009
Present	153 (84.1)	46 (95.8)	107 (79.9)		5.804 (1.325–25.427)	
Absent	29 (15.9)	2 (4.2)	27 (20.1)		1.000	
Irregular margin				36.024		<0.001
Present	50 (32.7)	31 (67.4)	19 (17.8)		9.572 (4.339–21.114)	
Absent	103 (67.3)	15 (32.6)	88 (82.2)		1.000	
Acute inflammation				1.110		0.292
Present	36 (19.8)	7 (14.6)	29 (21.6)		0.618 (0.251–1.522)	
Absent	146 (80.2)	41 (85.4)	105 (78.4)		1.000	
Marked atrophy				2.928		0.087
Present	31 (17.0)	12 (25.0)	19 (14.2)		2.018 (0.894–4.553)	
Absent	151 (83.0)	36 (75.0)	115 (85.8)		1.000	
Marked IM				7.533		0.006
Present	19 (10.4)	10 (20.8)	9 (6.7)		3.655 (1.384–9.651)	
Absent	163 (89.6)	38 (79.2)	125 (93.3)		1.000	

Values were shown as mean ± SD or *n* (%). *t value was calculated by Student's t test. †Calculated by Fisher exact test without statistics; other statistics were the χ^2 value calculated by the Pearson χ^2 test. CI: Confidence interval; IM: Intestinal metaplasia; LGIN: Low-grade intraepithelial neoplasia; N/A: Not applicable; OR: Odds ratio; SD: Standard deviation.

specimens and two diagnosed by EFB specimens) were considered to be misdiagnosed by EFB initially because they were diagnosed with malignancies in the first year. The interval time between the initial endoscopy and the endoscopy that provided a definite diagnosis had a median of 2 months and an interquartile range of 5 months. They underwent two to four endoscopies (average 2.3 endoscopies) in total until definite diagnoses. Detailed information is listed in Supplementary Table 1, http://links.lww.com/CM9/A668.

The baseline characteristics of the initially misdiagnosed malignant lesions and definitively diagnosed LGINs are listed in Table 1. Initially misdiagnosed malignant lesions were more frequently associated with a singular appearance (97.9%), the depressed gross type (72.9%), a size

Table 2: Logistic regression in the backward model for the multivariate analysis of factors predicting initially misdiagnosed malignant lesions.

Variables	Regression coefficient	*P* value	OR	95% CI
Number of lesions				
Single	3.180	0.009	24.036	2.189–263.870
Multiple			1.000	
Gross type				
Elevated			1.000	
Flat	−1.877	0.077	0.153	0.019–1.223
Depressed	0.017	0.977	1.017	0.333–3.107
Nodularity				
Absent			1.000	
Present	0.814	0.163	2.256	0.719–7.075
Irregular margin				
Absent			1.000	
Present	0.982	0.077	2.670	0.900–7.920
Size				
<10 mm			1.000	
10–20 mm	1.182	0.050	3.260	1.001–10.619
>20 mm	3.371	0.002	29.115	3.313–255.839
Marked IM				
Absent			1.000	
Present	2.046	0.011	7.735	1.594–37.537

CI: Confidence interval; IM: Intestinal metaplasia; OR: Odds ratio.

>10 mm (81.2%), the presence of erosion (64.6%), spontaneous bleeding (14.6%), nodularity (60.4%), clear margins (95.8%), irregular margins (67.4%), and marked IM (20.8%) compared to lesions proven to be definite LGIN, the proportions of which were 59.0% ($\chi^2 = 25.184$, $P < 0.001$), 33.6% ($\chi^2 = 23.677$, $P < 0.001$), 23.9% ($\chi^2 = 56.110$, $P < 0.001$), 44.0% ($\chi^2 = 5.973$, $P = 0.015$), 3.7% ($P = 0.016$ calculated by Fisher exact test), 9.7% ($\chi^2 = 51.205$, $P < 0.001$), 79.9% ($\chi^2 = 6.739$, $P = 0.009$), 17.8% ($\chi^2 = 36.024$, $P < 0.001$), and 6.7% ($\chi^2 = 7.533$, $P = 0.006$), respectively. The multivariate analysis revealed that a single lesion (odds ratio [OR] = 24.036, 95% confidence interval [CI]: 2.189–263.870), a large lesion size (OR = 3.260, 95% CI: 1.001–10.619 for lesions 10–20 mm; OR = 29.115, 95% CI: 3.313–255.839 for lesions >20 mm), and marked IM (OR = 7.735, 95% CI: 1.594–37.537) were independent predictive factors for initially malignant lesions [Table 2].

Diagnostic accuracy of endoscopists or predictive factors for identifying initially misdiagnosed malignant lesions

Endoscopists made a diagnosis of the malignancies based mainly on their experience and subjective opinions. The AUC of the endoscopists' diagnosis for identifying initially misdiagnosed malignant lesions was 0.852 (95% CI: 0.792–0.900), with a sensitivity of 79.2% (95% CI: 65.0%–89.5%) and a specificity of 77.6% (95% CI: 69.6%–84.4%) [Figure 2]. A total of 30 benign lesions (22.4%, 30/134) were overestimated as malignant, and ten malignant lesions (20.8%, 10/48) were underestimated as benign by endoscopists through reviewing photographs of the initial endoscopy.

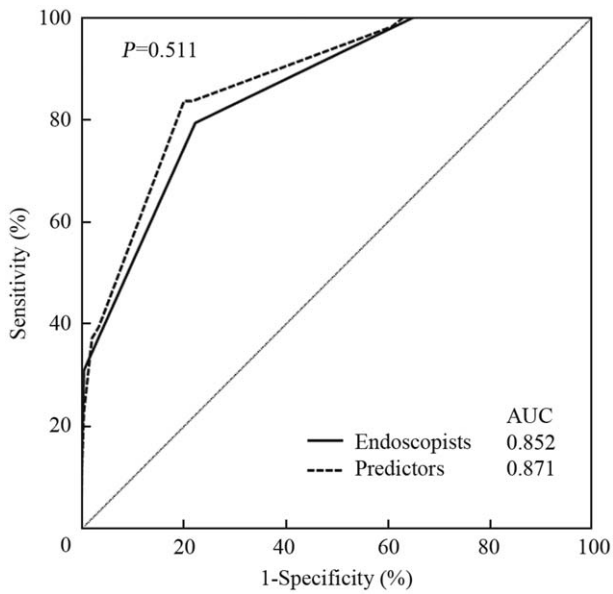

Figure 2: Receiver operating characteristic curve of the endoscopists' diagnosis and predictive variables. AUC: Area under the receiver operating characteristic curve.

If the predictive factors above were combined and weighted by the coefficient of the logistic regression analysis, the AUC for identifying initially misdiagnosed malignancies was 0.871 (95% CI: 0.814–0.916), with a sensitivity of 68.7% (95% CI: 53.7%–81.3%) and a specificity of 92.5% (95% CI: 86.7%–96.4%) [Figure 2]. The AUCs of the endoscopists' diagnoses and these

predictors were not significantly different ($Z = 0.6572$, $P = 0.511$). Among all lesions, 11.4% (8/70) with one predictor, 55.2% (32/58) with two predictors, and 80.0% (8/10) with three predictors were proven to be malignancies initially misdiagnosed by EFB. The diagnostic specificity for identifying initial malignancies was improved as the number of predictors increased, while the diagnostic sensitivity was reduced. Lesions with two predictors had the most accurate diagnosis [Supplementary Table 2, http://links.lww.com/CM9/A668].

Predictors for LGIN progression

Except for patients with initially misdiagnosed malignancies, the clinical outcomes of the remaining 134 patients were analyzed to study the natural history of LGIN and predictors for progression. A total of 36 patients (26.9%) were considered lost to follow-up. The baseline characteristics of patients who were followed up or lost to follow-up are listed in Supplementary Table 3, http://links.lww.com/CM9/A668. In brief, those lost to follow-up showed significantly more clear margins (94.4%) than those were successfully followed up (74.5%; $\chi^2 = 6.516$, $P = 0.011$), and other characteristics were not significantly different.

A total of 98 patients were followed up by repeated EFB. The median follow-up time was 33 months, with an interquartile range of 31 months. Twelve patients (12.2%) were diagnosed with malignancies after a 1-year follow-up and considered to have progressed. The median follow-up time was 39.5 months (40.0 months) for progressed patients and 31.5 months (29.0 months) for non-progressed patients. In total, 311 endoscopies (average 3.2 endoscopies per patient, range 2–8 endoscopies per patient) were performed.

The mean progression interval time of patients with different characteristics are listed in Supplementary Table 4, http://links.lww.com/CM9/A668. The univariate analysis showed that patients with irregular margins [Figure 3B] or marked IM background mucosa [Figure 3C] had a significantly worse prognosis than those without, with P value of 0.002 ($\chi^2 = 9.446$) and 0.001 ($\chi^2 = 11.305$), respectively. After revising the P value by the Bonferroni method, it was found that patients with whitish lesions had a significantly worse prognosis than those with reddish lesions ($P = 0.015$) [Figure 3A]. Patients who were diagnosed with LGIN more than twice during the first year were also at a significantly higher risk of progression than those only diagnosed with LGIN only at the first EFB ($\chi^2 = 17.618$, $P < 0.001$) [Figure 3D]. Patients diagnosed by endoscopists with low confidence had a higher risk of progression than those diagnosed with high confidence ($\chi^2 = 4.921$, $P = 0.027$) [Figure 3E]. There were no significantly different prognoses according to age, sex, lesion number, lesion location, gross type, size, surface configuration, margin clarity, background mucosal inflammation, or atrophy [Supplementary Figure 2, http://links.lww.com/CM9/A668].

The prognostic values of a whitish appearance, irregular margins, background mucosa with marked IM, and a histological diagnosis of LGIN more than twice within 1 year from the initial endoscopy were significantly worse than those of a non-whitish appearance (hazard ratio [HR] = 28.616, 95% CI: 3.260–251.190), non-irregular margins (HR = 15.723, 95% CI: 3.056–80.877), non-marked IM (HR = 66.942, 95% CI: 6.031–743.095), and a histological diagnosis of LGIN only at the initial endoscopy (HR = 16.648, 95% CI: 3.579–77.441) in the Cox regression analysis [Table 3].

Discussion

The malignancies of patients who had underwent endoscopy up to 3 years before the diagnosis of GC were presumed to had been missed.[13-15] However, most malignancies identified in these studies were advanced GC, which need a longer time to grow than HGIN and EGC (analyzed in this study). Guidelines for the treatment of EGC state that EGC discovered during follow-up at intervals of 6 to 12 months from the index endoscopy is considered synchronous lesions.[16] A study also revealed that diagnostic delays of early malignancies <1 year were not associated with a worse prognosis.[9] Therefore, in this study, it was presumed that the most severe histological diagnosis within the first year of follow-up reflected the initial condition, as in other studies.[17,18] Patients diagnosed with malignancies within the first year of follow-up were considered to be initially misdiagnosed by the EFB histology. Those who were considered to have benign lesions during the first year of follow-up but diagnosed with malignant lesions after the first year of follow-up were regarded as patients who progressed.

In this study, 26.4% (48/182) of patients initially diagnosed with LGIN through EFB were considered to be misdiagnosed because they were diagnosed with malignancies during the first year of follow-up. Among them, 95.8% (46/48) obtained a final diagnosis by endoscopically resected specimens. Discrepancies between the EFB diagnosis and the definite diagnosis existed partially because of cancer heterogeneity. EFB-diagnosed LGINs were confirmed to be malignancies after resection at a rate ranging from 10.8% to 33.9%.[11,19-24] A total of 40.8% to 100.0% of lesions showing upgraded histologic discrepancies from biopsy exhibited histological heterogeneity in resected specimens.[19,23] The discrepancy rate reported in this study is within the previously reported range, and 45.6% (21/46) of resected specimens had histological heterogeneity with LGIN. However, in this study, only a small proportion of patients diagnosed with LGIN by EFB who had been regarded as at high risk of an upgrade by endoscopists based on their experience underwent resection. This would greatly overestimate the rate of discrepancy between the EFB diagnosis and the definite diagnosis and the rate of misdiagnosis. Therefore, in this study, patients who had not undergone resection but had undergone several biopsies within the first year of follow-up, by which the sensitivity of the EFB diagnosis can be improved, were enrolled, and the most severe histological diagnosis was used as the definite diagnosis.[25] As a result, 4.2% (2/48) of initially misdiagnosed patients received a definite diagnosis of malignancy by biopsied specimens in this study.

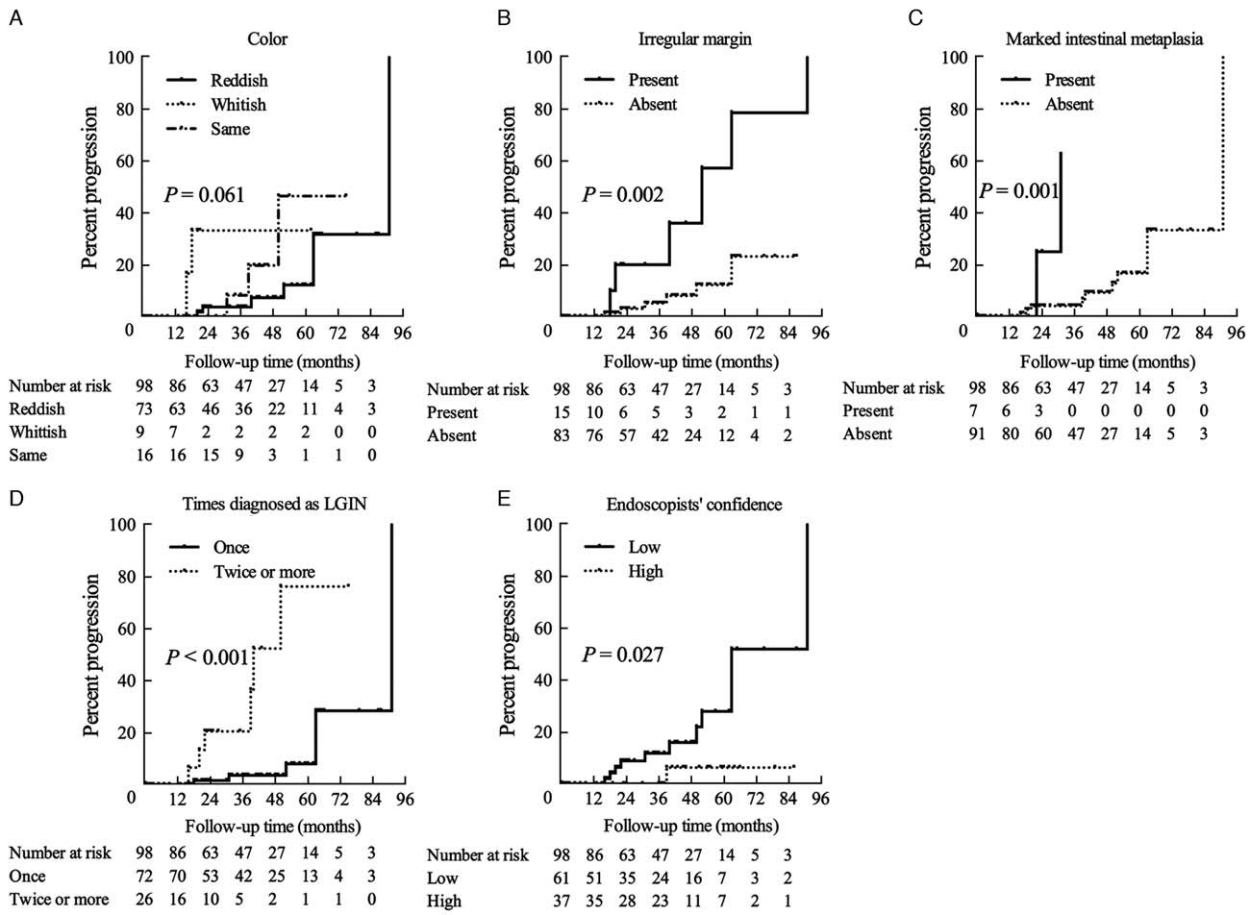

Figure 3: The cumulative progression risk of lesions with different characteristics. Lesions were grouped by color (A), regularity (B), background mucosa with marked IM (C), times diagnosed as LGIN in the first year after initial endoscopy (D), and the diagnostic confidence of the endoscopists (E). IM: Intestinal metaplasia; LGIN: Low-grade intraepithelial neoplasia.

Table 3: Cox proportional hazards regression in the backward model for analyzing factors related to a poor prognosis of LGIN.

Variables	Regression coefficient	*P* value	HR	95% CI
Color				
Non-whitish			1.000	
Whitish	3.354	0.002	28.616	3.260–251.190
Irregular margin				
Absent			1.000	
Present	2.755	0.001	15.723	3.056–80.877
Marked IM				
Absent			1.000	
Present	4.204	0.001	66.942	6.031–743.095
Times diagnosed as LGIN				
Once			1.000	
Twice or more	2.812	<0.001	16.648	3.579–77.441

CI: Confidence interval; HR: Hazard ratio; IM: Intestinal metaplasia; LGIN: Low-grade intraepithelial neoplasia.

Because of the risk for a malignancy to be initially diagnosed as LGIN through EFB, it is of clinical importance to seek predictors to identify patients who were misdiagnosed when encountering LGIN in pathologic reports of superficial gastric lesions. After analyzing the baseline demographic and endoscopic features of patients, a single lesion, a large lesion size, and marked IM were found to be independent predictors of initially malignant lesions. The diagnostic specificity for identifying initially misdiagnosed malignancies was improved as the presence

of these predictors accumulated. The best diagnostic accuracy was achieved when the lesion had two predictors and reached 0.871 when the predictors were weighted by the coefficient of the logistic regression analysis. These predictors could identify misdiagnosed malignancies as accurately as the subjective opinions of experienced endoscopists through more objective criteria.

Several previous studies reported the progression risk in patients with LGIN, while the findings were controversial. A multicenter study in the Netherlands found that none (0/7) of the patients with LGIN progressed.[26] A population-based study in the USA reported that 4.2% (6/141) of patients progressed with a median time of 2.6 years.[7] A study in northeastern Italy prospectively followed up patients with LGIN and observed that 15.4% (14/90) of patients progressed with a mean time of 48 months.[27] A study in South Korea found that 26.9% (7/26) of patients with LGIN progressed with a median follow-up period of 66 months.[28] The contradiction of these results was not merely because of the high incidence rate of GC in Asia. A Japanese study followed up patients with LGIN for 3 to 18 years and found that LGIN patients had a low risk of progression (3%, 1/38), most (84%, 32/38) of whom showed non-notable changes.[29] The researchers stated that the high progression rate of LGIN in other studies was because some malignancies were incorrectly classified as LGIN at the initial EFB.[29] Therefore, in our study, to assess natural history of LGIN, patients who were considered to be initially misdiagnosed were excluded, and the long-term follow-up outcomes of the remainder of patients were collected. This was a retrospective study, and the follow-up plan of patients could not be altered. A total of 26.9% (36/134) patients were lost to follow-up. However, the baseline characteristics of patients with or without long-term follow-up were similar. As a result, 12.2% (12/98) of patients were considered to experience progressing, with a median progression time of 39.5 months. In this study, patients without a repeat EFB were not included, but they are likely to have a low risk of progression. Thus, the progression rate was speculated to be overestimated in this study. Therefore, the progression rate of LGIN is relatively low when misdiagnosed malignancies are excluded, even in a country with a high incidence rate of GC.

This study also tried to identify initial characteristics related to the risk of LGIN progression. Few studies have discussed predictors for LGIN progression. Park *et al*[28] analyzed 26 LGINs but did not reveal any distinguishable features related to progression, possibly because of the lack of statistical power from a small number of cases. Li *et al*[7] analyzed the prognostic value of demographic information and determined that Hispanic patients and patients older than 70 years had a higher risk of progression. This study identified prognostic factors for definite LGIN. Our data indicated that the prognosis of lesions with a whitish appearance, irregular margins, background mucosa with marked IM, and a histological diagnosis of LGIN more than twice within the first year of follow-up was significantly worse than those without these features.

Background mucosa with marked IM was a predictor for an initially misdiagnosed malignancy and the most hazardous predictor for the progression of definite LGIN in this study. In previous studies, IM was an endoscopic finding related to the risk of GC, with an OR of 9.3 (95% CI: 4.5–18.9).[30-32] However, data on the progression rate of LGIN with IM are limited. This study indicated that EFB-diagnosed LGIN with marked IM should be taken seriously, especially lesions with other risk factors above, because of their high potential to be actual malignancies or their high risk of progression.

Predictors for the progression of LGIN in this study were not consistent with predictors for recognizing initially misdiagnosed malignancies, indicating that the baseline characteristics of patients who progressed after the first year of follow-up were not the same as those diagnosed with malignancies within the first year of follow-up. Theoretically, patients with lesions suspected to be malignant endoscopically tended to obtain earlier diagnoses than underestimated patients because of more frequent follow-ups. It is possible that patients considered to have progressed after the first year of follow-up had malignancies initially, but the lesions were not aggressive and appeared different than those diagnosed early, so they were diagnosed later and the diagnostic delay did not affect their prognosis. Thus, predictors of progression in this study should be of considerable value as well.

There were some important limitations to the present study. First, this was a retrospective study in a single center. The follow-up data were not strictly regulated, and patient selection bias existed. Second, endoscopists could only retrospectively review still endoscopic photographs in our study. However, both moving and still images are available for observation and diagnosis during actual clinical practice. Moreover, the quality of the endoscopic images was affected by several factors, such as the degree of air inflation and the skill of the practitioners, which might have affected the diagnostic accuracy by reviewing previously obtained endoscopic photographs. Third, the overall number of participants and follow-up time were limited. This sample size and follow-up time might have restricted the statistical power to detect some important predictors. Therefore, our findings should not be considered conclusive. A continuous follow-up of patients and a prospective multicenter study with a larger sample size are necessary. Nevertheless, this study also had some strengths. It included all LGINs with repeat EFBs instead of resected lesions only to diminish selection and observer biases, which increase the sample size at the same time. Additionally, endoscopists performed blinded evaluations by reviewing the initial endoscopic photographs without being aware of the clinical outcomes, which is also an effective method to diminish observer bias. More importantly, this was a rare study describing clinical characteristics associated with the progression risk of LGIN after excluding initially misdiagnosed malignancies. These findings may enable the identification of high-risk factors for LGIN and the sequential establishment of appropriate therapeutic strategies for LGIN.

In conclusion, this study calculated the misdiagnosis rate and progression rate of EFB-diagnosed LGINs in an area with a high incidence of GC. A proportion of EFB-diagnosed LGINs were proven to be initially misdiagnosed malignancies. Endoscopic characteristics, such as a single lesion and a large lesion size, had fair diagnostic accuracy for identifying these malignancies. After excluding these lesions, definite LGINs had a relatively low risk of progression during the long-term follow-up. A whitish appearance and irregular margins were independent risk factors for progression. Marked IM is a predictor for identifying not only initially misdiagnosed malignancies but also a high progression risk of definite LGIN. If patients have lesions not definitely diagnosed but with marked IM background as well as other predictors described above, they should be treated with caution because of their increased risk of malignancies actually of progression. Otherwise, endoscopic follow-up with repeated EFB within 1 year is recommended. Patients with an additional EFB diagnosis of LGIN within the first year of follow-up should also be treated seriously to avoid worsening long-term outcomes.

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Conflicts of interest

None.

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