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Evaluation of endoscopic findings for discriminating between early carcinomas and low-grade adenomas in superficial elevated gastric lesions

STOMACH

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Original Article

ABSTRACT

Background/Aims: This study aimed to determine the useful endoscopic findings in a differential diagnosis between early carcinomas (EC) and low-grade adenomas (LGA) in superficial elevated gastric epithelial neoplasia during conventional endoscopy with white-light imaging (C-WLI).

Materials and Methods: We investigated 270 consecutive cases of superficial elevated gastric epithelial neoplasias, which were removed by endoscopic submucosal dissection. The pathological diagnostic criteria were based on the revised Vienna classification: category 4 (mucosal high-grade neoplasia) or 5 (submucosal invasion by carcinoma) lesions were diagnosed as EC, while category 3 (mucosal low-grade neoplasia) lesions were diagnosed as LGA. The association between the postoperative pathological diagnoses (EC or LGA) and the following endoscopic findings: localized site, lesion size, color (reddish or whitish), shape (smooth, petal, or irregular), and presences of depression, erosion, ulceration, or nodularity on the surface, were evaluated.

Results: Of 270 epithelial neoplasias, 222 (58 LGA and 164 EC) were retrospectively evaluated. Multiple logistic regression analysis revealed that the lesion size [odds ratio (OR), 1.216; $p<0.001$) and reddish color (OR, 5.274; $p<0.001$) were independent findings for EC.

Conclusion: The lesion size and reddish color were useful optical findings for discriminating between EC and LGA.

Keywords: Gastric adenoma, early gastric carcinoma, superficial elevated gastric epithelial neoplasias, conventional endoscopy

INTRODUCTION

Superficial elevated gastric epithelial neoplasias can be broadly divided into early carcinomas (EC) and low-grade adenomas (LGA). Early detection and curative treatment are the best strategies for gastric carcinomas, and the indications of endoscopic treatment for EC have been nearly established by the introduction of endoscopic submucosal dissection (ESD) in Japan (1,2). However, therapeutic strategies for LGA, which was defined as a benign tumor, currently vary among facilities (3-6). In addition, in contrast with depressed gastric epithelial neoplasias, which almost consist in carcinomas, endoscopic differentiation between EC and LGA in superficial elevated epithelial neoplasias is difficult in the clinical settings. Although the biopsy method is considered an essential modality for making a differential diagnosis, we have often experienced that lesions diagnosed as LGA by preoperative biopsies were actually EC after being removed by ESD. Several studies indicate that preoperative biopsy sampling is inadequate for correct diagnosis (7-10). Therefore, it is important for endoscopists to understand the useful optical signs for discriminating between EC and LGA without being only dependent on the biopsy results.

To date, while there are some published reports regarding studies focusing on the differential diagnosis between EC and LGA, most studies have been conducted without distinction of the macroscopic appearance of the lesions as elevated or depressed, and the results are

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controversial. This study was conducted to clarify the useful optical findings for discriminating between EC and LGA in superficial elevated gastric epithelial neoplasias in conventional endoscopy with white-light imaging (C-WLI).

MATERIALS AND METHODS

Subjects and materials

We examined 270 superficial elevated gastric epithelial neoplasias, regardless of whether preoperative diagnosis by biopsy was EC or LGA, which were resected by ESD in 234 consecutive patients during the period from May 2008 through May 2013 at Yokohama City University Hospital.

In this study, superficial elevated lesions were defined as gross appearance with <3 mm elevation on the basis of the Japanese classification of gastric carcinoma (1) and having nodularity, depression, erosion, or ulceration on the surface of superficial elevated lesion. With respect to gross appearances, protruding, completely flat, depressed, or ulcerated lesions without any superficial elevated components and predominant depressed lesions with non-neoplastic elevated borders or a central elevation were not included. Gastric carcinoma invading the muscularis propria (muscular layer) or deeper into the gastric wall were also excluded, even if their endoscopic appearances satisfied the criteria with respect to gross appearance. However, there were no case of gastric carcinomas invading the muscularis propria or deeper in cases of superficial elevated lesions that were resected by ESD. Other exclusion criteria were coexisting advanced gastric carcinomas, coexisting carcinomas of other organs, local recurrent lesions, and past history of surgical resection of the stomach. The exclusion criteria under "other exclusion criteria" were as follows (19 patients were excluded under this criteria): resection of the upper portion by ESD before distal gastrectomy for coexisting advanced gastric carcinoma in the lower part (n=1), coexisting carcinomas of other organs (n=2), local recurrent lesions (n=5), and past history of surgical resection of the stomach (n=11).

Table 1. Revised Vienna classification of gastrointestinal epithelial neoplasias (3)

Category	Diagnosis
1	Negative for neoplasia
2	Indefinite for neoplasia
3	Mucosal low-grade neoplasia
	Low-grade adenoma/dysplasia
4	Mucosal high-grade neoplasia
4.1	High-grade adenoma/dysplasia
4.2	Non-invasive carcinoma (carcinoma in situ)
4.3	Suspicious for invasive carcinoma
4.4	Intramucosal carcinoma
5	Submucosal invasion by carcinoma

Indication for endoscopic submucosal dissection (ESD) at our institution

The indication for ESD in cases of gastric epithelial neoplasias that were diagnosed as EC by preoperative biopsies was in accordance with the recommendations of Gotoda et al. (11). All cases of superficial elevated gastric epithelial neoplasias that were diagnosed as LGA by preoperative biopsies were recommended to undergo ESD with sufficient informed consent. However, whether endoscopic resection or follow-up would be selected was eventually left to the discretion of each patient.

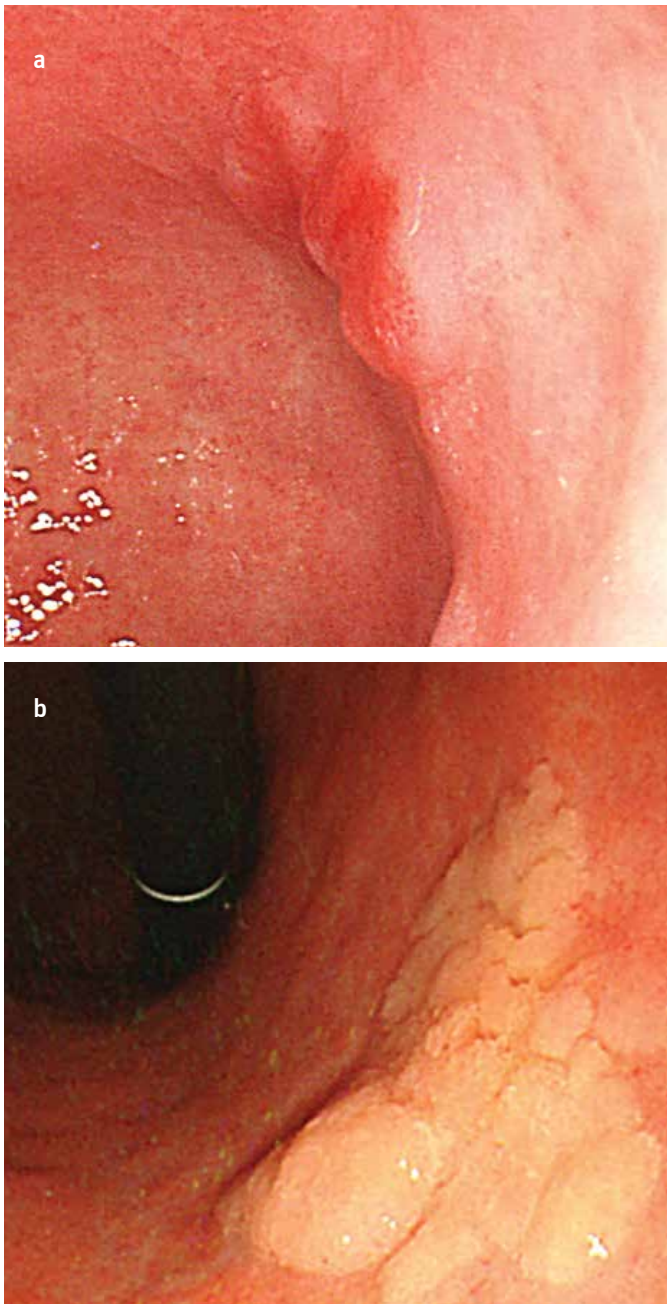

Figure 1. a, b. Reddish (a) and whitish (b) color of the lesion by endoscopic findings.

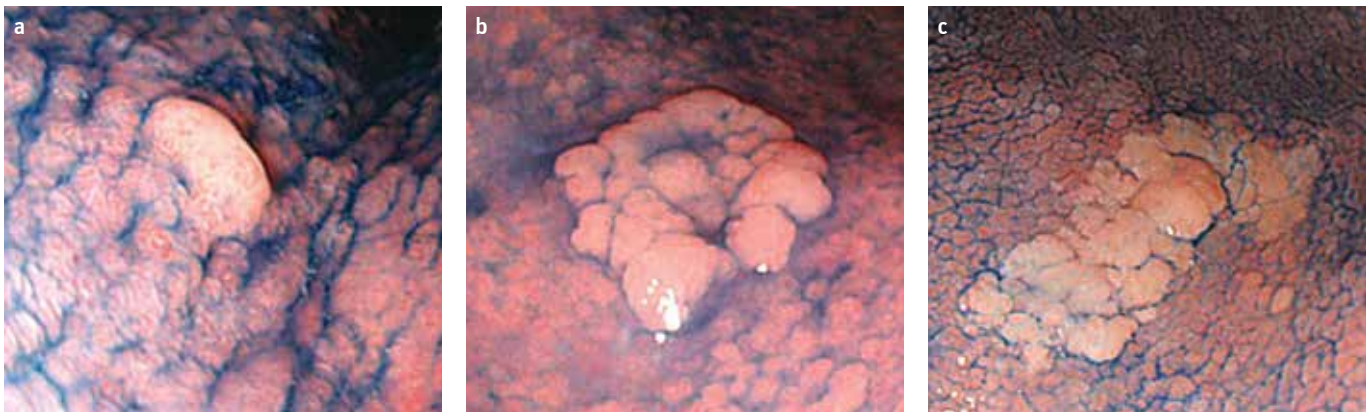

Figure 2. a-c. Smooth (a), petaloid (b), and irregular (c) shape of the lesion by endoscopic findings.

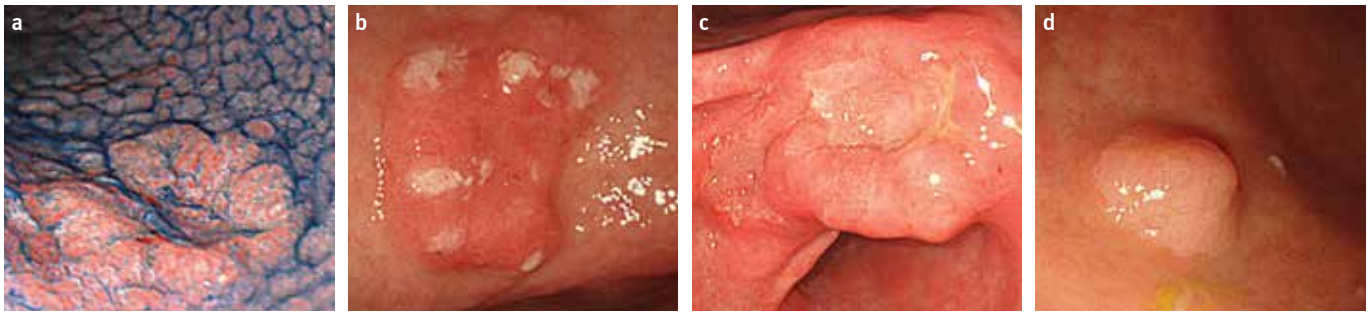

Figure 3. a-d. Depression (a), erosion (b), ulceration (c), and nodularity (d) of the surface of the lesion by endoscopic findings.

Pathological diagnosis

All resected neoplasias were fixed in 10% buffered formalin and segmented at 2 mm intervals. Each section was stained with hematoxylin and eosin and was evaluated by more than two pathologists at our institution. The diagnoses were based on the revised Vienna classification (Table 1) (3). For this study, we re-categorized the revised Vienna classification category 4 (mucosal high-grade neoplasia) or category 5 (submucosal invasion by carcinoma) as EC and category 3 (mucosal low-grade neoplasia) as LGA. Histological gradings of EC were classified into either intestinal-type (differentiated type) carcinoma or diffuse-type (undifferentiated type) carcinoma according to the quantitative predominance (12).

Endoscopic findings and data analysis

Clinical and endoscopic characteristics were retrospectively reviewed from the proprietary database in all cases by three experienced endoscopists who were blinded to any pre- or postoperative histological results. Endoscopic findings were determined by consensus among the three endoscopists.

We assessed patient clinical characteristics that included age and sex, the lesion localized site, the lesion maximal diameter (mm), and the following endoscopic appearances (Figure 1-3): color (reddish or whitish), shape (smooth, petaloid: regular, or irregular), and presence of depression, erosion, ulceration, or nodularity on the surface of superficial elevated lesion.

Localized site was classified as the upper, middle, and lower part by the lines connecting the trisected points on the lesser and greater curvatures according to the Japanese classification of gastric carcinoma (1). Lesion maximal diameter was determined using a measuring resected specimen. Moreover, we also investigated the lesion size, which was divided into ≥20 mm and <20 mm with respect to diameters, on the basis of the median value of the lesion size for each group. The color of the lesion was classified into reddish or whitish in comparison with the surrounding non-neoplastic mucosa. The shape was divided into regular (comprising smooth or petaloid shape) or irregular shape. Petaloid shape of a tumor denotes a shape resembling a flower petal, which suggests the proliferation of a tumor with regularity and symmetry. In contrast, irregular shape means the asymmetry of shape, which suggests the proliferation of a tumor in a disorderly manner. We investigated the relationship between post-ESD histological diagnoses (EC or LGA) and the aforementioned clinical and endoscopic characteristics.

Statistical analysis

We used the Chi-square test and Fisher's exact test for categorical comparison of the data. Differences for continuous data were compared using the Mann–Whitney U test. Regarding the distinctive endoscopic findings for EC in the univariate analyses, multiple logistic regression analysis was performed. The significance level was set at a p value of <0.05. All statistical analyses were performed using the Stat View software (SAS Institute; Cary, NC, USA).

Table 2. Univariate analysis of the clinical characteristics and endoscopic findings in cases with superficially elevated lesions diagnosed as EC and LGA (n=222)

	EC (n=164)	LGA (n=164)	p
Age: median, range (years)	74, 43–87	72.5, 45–88	0.098*
Sex: men/women	119/45	46/12	0.312**
Lesion site: U/M/L	28/65/71	3/25/30	0.076**
Size: median, range (mm)	16, 2–95	8, 2-30	<0.001*
<20 mm/≥20 mm	96/68	56/2	<0.001***
Color: reddish/whitish	101/63	13/45	<0.001**
Shape: regular/irregular	91/73	52/6	<0.001***
Depression: present/absent	49/115	10/48	0.083***
Erosion: present/absent	14/150	2/56	0.250***
Ulceration: present/absent	8/156	0/58	0.115***
Nodularity: present/absent	15/149	1/58	0.076***

EC: early carcinomas; LGA: low-grade adenomas; U: upper part of the stomach; M: middle part of the stomach; L: lower part of the stomach
* Mann–Whitney's U test; ** Chi-square test; ***Fisher's exact test

Ethics

This study was conducted according to the Declaration of Helsinki. Our hospital approved the study protocol, and written informed consent was obtained from all participants not only for the endoscopic treatment but also for the use of the patients' clinical data for research purposes.

RESULTS

Of 270 epithelial neoplasias from 234 cases, 222 neoplasias from 198 cases could be retrospectively analyzed. In all, 48 lesions could not be assessed because of poor endoscopic records or indistinct pathological findings. Of 222 epithelial neoplasias, 58 were diagnosed as LGA (category 3) after ESD. A total of 164 were diagnosed as EC, of which 152 were mucosal high-grade neoplasias (category 4) and 12 submucosal invasive neoplasias (category 5). All were regarded as intestinal-type carcinoma; however, 14 lesions included diffuse-type components in part.

Table 2 shows comparisons of clinical characteristics and C-WLI findings between EC and LGA in the 222 superficial elevated epithelial neoplasias (Table 2). The results of univariate analysis were as follows. Lesion maximal diameter was significantly larger in EC than in LGA (p<0.001). As for the lesion size, when lesions were divided into a group of ≥20 mm and <20 mm, there were significant differences between EC and LGA (p<0.001). Our results revealed there were only two lesions of ≥20 mm diameters in LGA. As for endoscopic appearances, the frequencies of reddish color (p<0.001) and irregular shape (p<0.001) were significant predictive factors for EC. However, there was no significant difference between these two groups with respect to the frequencies of depression, erosion, ulceration, and nodularity of surface appearance.

Table 3. Multiple logistic regression analysis to identify the distinctive findings among the factors identified to be significant by univariate analysis for discriminating between EC and LGA

Factor	Odds ratio (95% confidence interval)	p
Age	1.034 (0.985–1.085)	0.177
Sex	1.271 (0.513–3.150)	0.605
Lesion size	1.216 (1.125–1.15)	<0.001
Reddish color	5.274 (2.324–11.969)	<0.001
Irregular shape	1.712 (0.596–4.921)	0.318

EC: early carcinomas; LGA: low-grade adenomas

Table 4. Diagnostic efficacy of CE-WLI and biopsy for discriminating between EC and LGA

	CE-WLI	Biopsy
Sensitivity	0.787	0.561
(95% CI)	(0.716–0.847)	(0.481–0.638)
Specificity	0.741	0.862
(95% CI)	(0.610–0.847)	(0.746–0.939)
Diagnostic accuracy	0.775	0.640
(95% CI)	(0.714–0.828)	(0.573–0.703)

CE-WLI: conventional endoscopy with white-light imaging; EC: early carcinomas; LGA: low-grade adenomas; CI: confidence interval

Table 3 shows the results of multiple logistic regression analysis of these distinctive findings in the univariate analysis (Table 3). Multivariate analysis confirmed that the lesion size [odds ratio (OR), 1.216; 95% confidence interval (CI), 1.125–1.315; p<0.001] and reddish color (OR, 5.274; 95% CI, 2.324–11.969; p<0.001) were independent predictive findings for discriminating between EC and LGA.

Table 4 shows the diagnostic efficacy of endoscopy and preoperative biopsy for discriminating between EC and LGA in this study. We defined "lesions that were >20 mm in diameter or reddish colored lesions" as EC on the basis of the results of a multivariate analysis in this study. There were 129 lesions that were defined as EC according to this definition in this study. Conversely, there were 35 lesions presenting both <20 mm in diameter and whitish coloration in a total of 164 EC. Furthermore, lesions diagnosed as Group 4 or 5 by preoperative biopsy were defined as EC according to the Group Classification in the Japanese classification of gastric carcinoma (1). According to these diagnostic criteria, Table 4 shows the calculated sensitivity, specificity, and diagnostic accuracy of each of the diagnostic modalities for discriminating between EC and LGA.

DISCUSSION

We focused on the gross appearance of the superficial elevated lesions because of the difficulty in the differential diagnosis between EC and LGA in clinical settings; this is in contrast to the case for depressed gastric epithelial neoplasias, which are

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almost always carcinoma. LGA may also present with a flat or depressed appearance; however, few such cases are encountered in clinical practice, and most LGA present with a superficial elevated appearance. In contrast, superficial elevated gastric epithelial neoplasias include not only cases of LGA but also many cases of EC. From this viewpoint, we investigated the useful optical findings of superficial elevated-type gastric epithelial neoplasias for discriminating between EC and LGA.

This study clarified that the lesion size and reddish color are useful optical signs that can discriminate EC from LGA by univariate and multivariate analyses. Similar studies have been conducted to identify the indicators of malignancy in gastric epithelial neoplasias. Although these studies reported many significant predictive findings, such as localized site, lesion size, reddish color, lack of glossiness, step rise of edge, presence of nodularity, and depression or ulceration on surface appearance, these results have been controversial (13-21). Moreover, the data provided in these past literatures may be difficult to compare with the findings of this study because most of these studies investigated whether gastric epithelial neoplasias that were diagnosed as LGA on the basis of preoperative biopsies were EC or LGA, occasionally without the distinction of macroscopic appearances of whether they were elevated or depressed.

The multivariate logistic regression analysis in this study demonstrated that the reddish color was a strong predictive factor with a larger OR of 5.27. It is known that angiogenesis is an important factor in gastrointestinal carcinogenesis and tumor progression (22). Recently, hypervascularity was reported in differentiated gastric carcinomas using a confocal laser endomicroscopy (23). From these findings, the difference in vascularity between EC and LGA may cause the difference in lesion color in the C-WLI.

This study also revealed that the lesion size was significantly larger in carcinomas than in adenomas using multivariate analysis. Tumor size is generally regarded as a prognostic indicator. In practice, inter-observer variation exists concerning the lesion size among the past literatures. It may account for the discrepancy that majority of past studies focused on gastric neoplasias that were diagnosed as low-grade neoplasia on the basis of initial biopsy, and thus, typical carcinomas with a larger size may be excluded. While, the present study investigated gastric epithelial neoplasias that were diagnosed as not only LGA but also EC by preoperative biopsy. Therefore, this study must have included lots of cases of carcinomas with a larger size. In addition, the differences in the gross appearances of the investigated specimens, inter-examiner variation in pathological diagnoses among pathologists, and sample size may affect the reported tumor size.

In this study, we proposed a 20 mm diameter as a cutoff value on the basis of the median value of the lesion size for each group by considering a more simple and practical value than the exact value calculated from the receiver operating characteristic curve. When the lesion size was divided into ≥20 mm and <20 mm in diameters, there were only two lesions of ≥20 mm in the group diagnosed as LGA after removal. Furthermore, lesion size of ≥20 mm was also statistically significantly predictive in the multivariate analysis with OR of 1.22. Although the lesion size, which was identified as a useful factor for discriminating between EC and LGA, was measured only in the resected specimens in this study, it is practical to determine from endoscopic images whether the detected gastric lesions are ≥20 mm in size. It is also relatively easy for endoscopists to identify tumors that are ≥20 mm in diameter because they often have to determine the indication of ESD for EC in clinical settings. In contrast to the rate in the group diagnosed as LGA, 96 of 164 lesions (58.5%) in the group diagnosed as EC showed less than 20 mm in size. Special attention should be given regarding small superficial elevated epithelial neoplasias that are composed of carcinomas or adenomas.

While deciding the endoscopic treatment, it is important to distinguish intramucosal or minute submucosal gastric cancers, which have an extremely small risk of lymph node metastases, from the deeper submucosal gastric cancers, which have the possibility of lymph node metastasis (11). A previous report has demonstrated that a tumor size of >30 mm, remarkable redness, uneven surface, and margin elevation were significantly associated with deeper submucosal gastric cancers (24). In our retrospective study with 222 superficial elevated gastric lesions, seven cases of deeper submucosal cancers were included, of which four had a tumor size of >30 mm in diameter, six had a reddish color, four had nodularity on the surface of the superficial elevated lesion, and the lesions of all the cases had an irregular shape.

Gastric adenomas are regarded as precancerous lesions but are clinically heterogeneous because some may progress to carcinoma, whereas others are immutable for long periods. Moreover, it is believed that progression to carcinoma in adenomas proportionally increases with its histological grade. To date, various follow-up studies were conducted to evaluate the risk of carcinoma posed by gastric non-invasive neoplasias (4, 5, 25-30). From these results, gastric high-grade neoplasias are accepted to have a high potential for malignancy and should be endoscopically or surgically resected. In contrast, the handling of gastric low-grade neoplaisas remains controversial. In practice, most gastric epithelial neoplasias are resected by ESD, regardless of whether they are EC or LGA, without sufficient consideration. However, endoscopic resection remains an invasive treatment, which can occasionally cause severe complications (31). On the basis of a recent long-term follow-up study of LGA (6), observation without resection is considered as a valid therapeutic strategy for all patients with LGA, which reveals quite a low risk of progressing to invasive carcinomas. The clinical relevance of this study is that CE-WLI can aid in the ac-

curate diagnosis of gastric epithelial lesions, thereby enabling the physician to avoid needless endoscopic resection and provide appropriate treatment for LGA.

Biopsy is essential to differentiate between carcinomas and adenomas; however, we frequently encounter inconsistencies between the histological findings from biopsy and resected specimens. The reasons for imprecise diagnosis of biopsy specimens are because the parts of carcinoma may not be included in sampling or small biopsy samples often do not contain enough tissue for a correct malignancy diagnosis. Several studies indicate that diagnostic precision of biopsy for gastric epithelial neoplasias is insufficient (7-10). Of 222 lesions, 122 were diagnosed as LGA by preoperative biopsy, of which 72 were finally diagnosed as EC after ESD; in contrast, 100 of the 222 lesions were diagnosed as EC by preoperative biopsy and only eight of the 100 EC were finally diagnosed as LGA after ESD in this study. The sensitivity, specificity, and accuracy of CE-WLI versus preoperative biopsy were 0.787 vs. 0.561, 0.741 vs. 0.862, and 0.775 vs. 0.64, respectively. Thus, endoscopic predictors may be more useful than biopsy for discriminating between EC and LGA.

With the recent introduction of advanced technology, including magnifying endoscopy (ME) and narrow-band imaging (NBI), the usefulness of ME-NBI for discriminating between cancerous and non-cancerous lesions in the stomach has been reported (18, 19, 32-35). However, the number of institutes that are capable of performing endoscopy with ME-NBI is not so much, and thus, C-WLI endoscopy remains the standard imaging modality for diagnosing gastric epithelial neoplasias worldwide. In addition, compared with ME-NBI, CE-WLI provides not only a good cost performance but also simplicity for an endoscopic procedure and diagnosis without consuming time. Therefore, it is important to understand the endoscopic findings with CE-WLI for discriminating between EC and LGA.

There are several limitations to this study. First, it was a retrospective study conducted in a single center. Second, selection bias may also have influenced our results. At our institution, whether endoscopic resection or follow-up would be selected for gastric epithelial neoplasia that was diagnosed as LGA by preoperative biopsies is left to the discretion of each patient because of the current inconsistent therapeutic strategies for LGA. Therefore, further investigation should be conducted in a prospective fashion to confirm the usefulness of endoscopic findings for discriminating between EC and LGA.

In conclusion, we have demonstrated that conventional endoscopic findings correlated with the histopathology of superficial elevated gastric lesions and provided useful optical signs for discriminating EC from LGA. With regard to therapeutic strategies, we should consider endoscopic resection for superficial elevated gastric lesions that are ≥2 cm in size and have reddish color as EC, even if biopsy indicates LGA, because pretreatment biopsy may be inadequate for an accurate histological diagnosis.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Yokohama City University Hospital.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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