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ORIGINAL ARTICLE

Value of quantitative microsurface structure analysis for evaluating the invasion depth of type 0–II early gastric cancer

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Abstract

Background and Aim: The microsurface structure reflects the degree of damage to the glands, which is related to the invasion depth of early gastric cancer. To evaluate the diagnostic value of quantitative microsurface structure analysis for estimating the invasion depth of early gastric cancer.
Methods: White-light imaging and narrow-band imaging (NBI) endoscopy were used to visualize the lesions of the included patients. The area ratio and depth-predicting score (DPS) of each patient were calculated; meanwhile, each lesion was examined by endoscopic ultrasonography (EUS).
Results: Ninety-three patients were included between 2016 and 2019. Microsurface structure is related to the histological differentiation and progression of early gastric cancer. The receiver operating characteristic curve showed that when an area ratio of 80.3% was used as a cut-off value for distinguishing mucosal (M) and submucosal (SM) type 0–II gastric cancers, the sensitivity, specificity, and accuracy were 82.9%, 80.2%, and 91.6%, respectively. The accuracies for distinguishing M/SM differentiated and undifferentiated early gastric cancers were 87.4% and 84.8%, respectively. The accuracy of EUS for distinguishing M/SM early gastric cancer was 74.9%. DPS can only distinguish M-SM1 (SM infiltration <500 μm)/SM (SM infiltration ≥500 μm) with an accuracy of 83.8%. The accuracy of using area ratio for distinguishing 0–II early gastric cancers was better than those of using DPS and EUS ($P < 0.05$).
Conclusion: Quantitative analysis of microsurface structure can be performed to assess M/SM type 0–II gastric cancer and is expected to be effective for judging the invasion depth of gastric cancer.

Introduction

The importance of staging of early gastric cancer has been increasing with the development of endoscopic resection techniques. Gotoda *et al.*[1] found that patients with well-differentiated lesions sized <3 cm, lesions showing a submucosal invasion depth of <500 μm, and undifferentiated lesions sized <2 cm confined to the mucosa were almost entirely free of lymph node metastasis. Such lesions were included in the absolute indications or expanded indications for endoscopic resection.[2–5] The invasion depth of early gastric cancer is currently determined using traditional and ultrasound endoscopy.[6–8] The results of traditional and ultrasound endoscopy did not meet the needs of endoscopic submucosal dissection.[9–11]

The development of magnifying gastroscopes has improved the diagnosis of early gastric cancer. The microsurface is the surface of the gastric mucosa seen on magnification combined with narrow-band imaging (NBI). The microsurface consists of the marginal crypt epithelium (MCE)/white zone and the intervening part between them. The epithelium is visualized as a semitransparent white belt-like structure (the MCE), showing a circular or oval shape, at the center of which lies the crypt opening.[12] Figure 1a shows the map of the microsurface structure

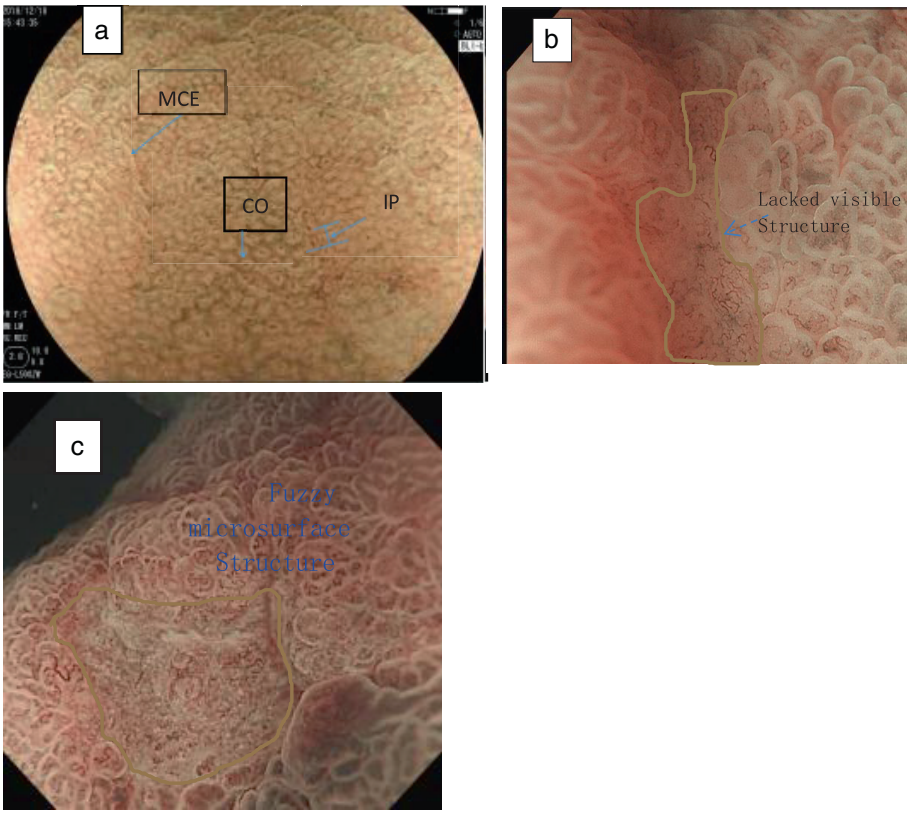

Figure 1 (a) Map of the microsurface structure in the stomach body. (b) Within the black line: lack of microsurface structures in gastric cancer. (c) Within the black line: Fuzzy microsurface structures (CO, crypt opening; IP, intervening part; MCE, marginal crypt epithelium).

and gland structure of the stomach body. When gastric cancer occurs, the microsurface structure changes accordingly.

Early gastric cancer is classified into two types: differentiated and undifferentiated. Differentiated gastric cancer infiltrates the glands of the gastric mucosa after it arises at the bottom of the gland, replacing the normal cells but not destroying the glandular ducts.[12–15] On endoscopy, an irregular microsurface structure is seen. When tumor cells destroy the entire mucosa or the degree of differentiation worsens, the microsurface structures also disappear (lack of a visible structure) or become fuzzy (microsurface structures cannot be seen clearly on endoscopy; they can be observed after acetic acid staining)[12] (Fig. 1b,c). Undifferentiated gastric cancer arises at the neck of the gland and shows horizontally infiltration, but the structure of the bottom and top of the gland remains intact, we call this stage the middle layer type. The tumor infiltrates the top and bottom of the gland. At this stage, destruction of gland structure is seen on histological examination, and the microsurface structures disappear on endoscopy (Fig. 2).[15] The appearance of microsurface structures is associated with the invasion depth of early gastric cancer.

Based on NBI magnifying endoscopy findings, Okada divided lesions into groups according to whether the microsurface structures were damaged and according to the degree of destruction. The results showed differences in the depth of invasion across different groups.[16] However, whether there is a correlation between the area ratio and invasion depth of gastric cancer has not yet been reported.

To develop a more accurate method of assessing the invasion depth of early gastric cancer, this study evaluated the diagnostic value of quantitative microsurface structure analysis for the invasive depth of early gastric cancer.

Methods

Patients. Patients with type 0–II early gastric cancer confirmed by endoscopic submucous dissection (ESD) or examination of surgical specimens at our hospital in 2016–2019 were included prospectively. Lesion size and invasion depth were confirmed by pathological examination. The exclusion criteria were as follows: (i) Lesions diagnosed as obviously advanced cancer (cancer invading the muscularis propria or deeper layers) by endoscopy; (ii) incomplete or blurry imaging data; and (iii) type 0–I or type 0–III gastric cancer (these two types suggest deep invasive carcinoma). A total of 97 cases of early gastric cancer were collected. Four cases involving incomplete imaging data were excluded. Thus, 93 cases were included. This study was approved by the Ethical Review Committee. All patients provided written informed consent for undergoing gastroendoscopy.

Imaging. This study included prospectively patients with type 0–II early stage cancer who met the inclusion criteria. A

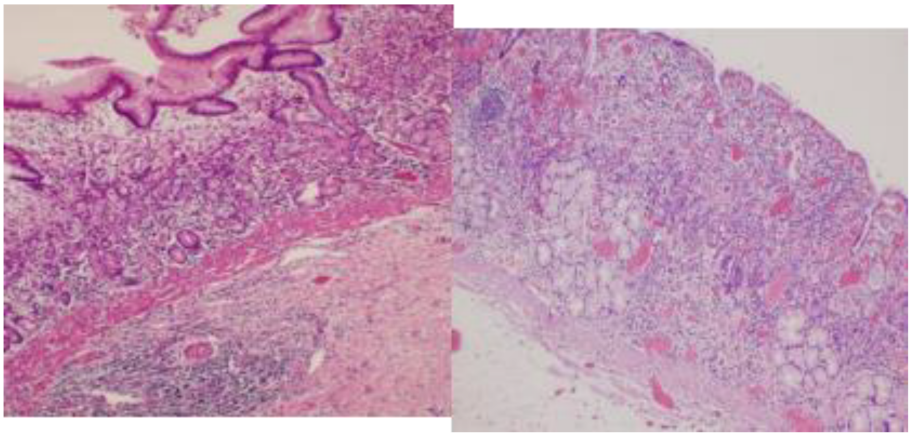

Figure 2 Development pattern of undifferentiated early gastric cancer(stained with hematoxylin and eosin, the magnification is 10 times).

Table 1 Baseline characteristics of patients and early gastric cancer

Characteristics	Total
Age, mean (SD)	57.3 (13.50)
Gender (M/F)	34/59
Location	
Upper	5
Middle	29
Lower	59
Macroscopic type	
O-IIa	23
O-IIb	18
O-IIc	15
IIa + IIc/IIc + IIb	37
Pathological classification	
Differentiated type	58
Undifferentiated type	35
Treatment methods	
ESD	50
Surgical resection	34
ESD + surgical resection	9
Tumor size	
≤2 cm	77
>2 cm, <5 cm	16
Invasion depth	
Differentiated M	46
SM1	6
SM2	6
Undifferentiated M	29
SM	6

ESD, endoscopic submucous dissection; M, mucosal; SM, submucosa.

Table 2 Depth-predicting scores (DPSs) of the patients with differentiated early gastric cancer according to DPS

Depth-predicting score	M-SM1	SM2
<3	73	5
≥3	10	5
Total	83	10

M, mucosal; SM, submucosa.

endoscopist with extensive experience in diagnosing early stage gastric cancer using NBI magnifying endoscopy analyzed the patients' images. White-light images of the lesions were observed. The following characteristics were evaluated: tumor location (upper, middle, lower); tumor size (mm); macroscopic type (according to the Paris classification; Table 1); and five other endoscopic findings that are widely accepted as markers of deeper submucosal invasion among Japanese endoscopists, namely remarkable redness, uneven surface, margin elevation, ulceration, and enlarged folds. We described the five endoscopic features according to Abe's criteria. Remarkable redness was defined as a reddish area similar to the color of regenerative epithelium. Nodulation on the tumor surface was used to define an uneven surface. Margin elevation referred to the finding of a protruding edge surrounding the tumors, including submucosal tumor-like component with a limited amount of air insufflation. Presence of a scar or an ulcerative area within the tumor was identified as ulceration (except for biopsy ulcers or scars). Finally, enlarged folds included any thickened or merged convergent folds.[1,2] Next, the NBI magnifying endoscopy images were analyzed to identify the boundary of the lesion and areas that lacked visible structures or contained fuzzy structures. The area where the microsurface structure or microvessels suddenly changed was defined as boundary and marked with black line on non-magnified white light image. The area where the microsurface structure blurred (the microsurface structure was not clearly displayed under the magnifying endoscope, but it was presented after acetic acid staining, these areas were defined as blurred microsurface structure) or disappeared (including ulcer and scar areas but excluding biopsy related ulcers and scars) was defined as invisible area, marked with a green line (these boundaries were compared with pathological margins, if the consistency was lower than 80%, the reliability of endoscopic judgment of boundaries was low, and the test was terminated). When endoscopy was unable to determine the boundaries, negative biopsy was used to determine them (take a four quadrant biopsy 1 cm outside the visible boundary). Histopathological diagnoses were based on the Japanese Gastric Cancer Association criteria (Table 2).

Computer-aided drafting (CAD) is a classical lightweight and rapid drawing tool. The software has the functions of filling patterns, filling graphics, measuring area, and intelligent recognition of graphical boundaries. The method involves importing the endoscopy images of each case in turn, and the software automatically calculates areas based on different color outlines in each lesion and outputs them into Excel tables.[17] In this study, CAD was used to calculate the total lesion area (area a) and the area lacking visible structures/containing fuzzy structures (area b) to quantitatively analyze the area ratio (area a − area b/area a) (Fig. 3). At the same time, each lesion was scored using the depth-predicting score (DPS), and invasion depth was predicted accordingly. One point was given for remarkable redness and an uneven surface, while 2 points were given for margin elevation and tumor size of >30 mm because the relative magnitude of the b-coefficient was roughly twice as those of other variables. Thus, the range of the resulting DPS was 0–6 points. A total of 3 points was defined as the cut-off to distinguish between M-SM1 and SM2-.[18]

Endoscopy. A GIF-H260Z forward-viewing electronic gastroscope (Olympus, Tokyo, Japan) was used in this study. The principle of NBI involves replacing the traditional broadband filter between the white-light endoscope rotary filter and the herniation light with two filters (wavelengths of 415 and 540 nm). This kind of narrow-band light can protrude from the mucosal capillaries and dendritic vessels under the mucosal myometrium and demonstrate the crypt structure of the mucosa, which can be used to judge the nature and boundary of the early malignancy. Magnifying endoscopy combined with NBI can be used to clearly observe the microsurface structure and lesion microvessels.

Cases of suspicious early gastric cancer in our center were diagnosed as follows: white-light endoscopy was first used to observe and photograph the lesions (observed from far to near). Next, NBI was used to observe from far to near the entire area of the lesion by gradually increasing the magnification.

Patients with early gastric cancer also underwent endoscopic ultrasonography for assessment of the invasion depth. A 20-MHz high-frequency endoscopic ultrasound probe was used (Olympus, Tokyo, Japan). The interval between gastroscopy and endoscopic ultrasonography should not exceed 1 week.

Histology. Surgically or endoscopically resected specimens were systematically examined based on the standard procedure specified in the Japanese Classification of Gastric Carcinoma. Specimens were fixed and stained with hematoxylin and eosin, and based on invasion depth, tumors were classified as intramucosal cancer (M), minute submucosal cancer (SM1; < 500 μm deep), and deeper submucosal cancer (SM2; ≥500 μm deep; Table 2).

Statistical analysis. Using the invasion depth reported by pathology as the gold standard, we used receiver operating characteristic (ROC) curves to calculate the area ratio corresponding to different infiltration depths in cases of type 0–II gastric cancer. We also calculated the specificity, accuracy, and sensitivity of evaluating invasion depth in cases of type 0–II gastric cancer. Correlation analysis was performed to evaluate the correlations of lesion size, endoscopic morphology (based on the Paris classification), pathological type, area ratio, sex, age, and lesion location with the invasion depth of early gastric cancer. Logistic regression analysis was used to identify the factors influencing invasion depth in type 0–II gastric cancer. A chi-square test was used to compare the predictive effectiveness of various methods for estimating the invasion depth of early gastric cancer. A rank-sum test was used for other nonparametric variables.

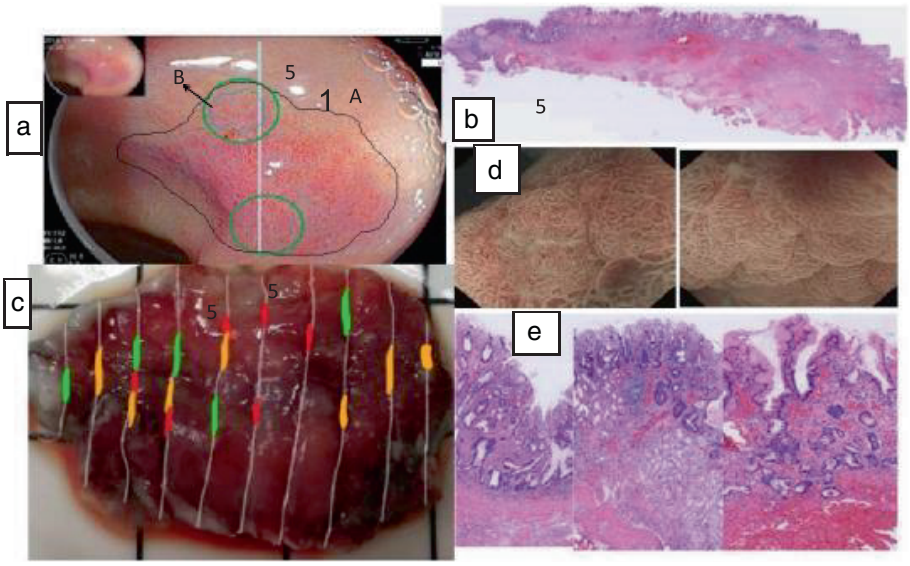

Figure 3 Area ratio = (area A − area B)/area A. (a) Non-magnification imaging, black line outlines the whole lesion A, while blue line outlines the lacked visible structure area B in the lesion; (b) pathological picture of No. 5 tissue strip; (c) pathological restoration map of the lesion; (d) magnification narrow-band imaging of green circle; (e) the original pathology of green circle, stained with hematoxylin and eosin.

Results

Analysis of endoscopic features. A total of 93 cases (34 male, 59 female; mean age, 57.3 years; range, 33–78 years) were included and analyzed. There were 18 cases of ulcers. ESD was performed in 50 cases, and 34 patients underwent surgery, 9 patients underwent ESD + surgical resection (Table 1). The average lesion size was 1.4 ± 1.2 cm (range, 0.5–5.5 cm). The consistency between endoscopic and pathological boundaries was 90%. An irregular microsurface structure was observed in 80% of well-differentiated gastric cancers (TUB1). A fuzzy local microsurface structure was observed in 91.5% of moderately differentiated gastric cancers (TUB2), and the local microsurface structures disappeared in 93.5% of undifferentiated cancers. The DPS of each lesion is shown in Table 2. The correlation analysis showed no correlation of sex, age, gross lesion type, histopathological classification, presence of ulcers, and lesion location with invasion depth, and the corresponding correlation coefficients were 0.065, 0.056, 0.043, 0.094, 0.083, and 0.211, respectively ($P > 0.05$). Lesion size was weakly correlated with invasion depth, with a correlation coefficient of 0.313 ($P < 0.05$). There was a moderate negative correlation between the area ratio of the lesion and invasion depth (correlation coefficient, −0.43; $P < 0.05$). The area ratio of TUB1 cancer was greater than that of TUB2 cancer, and the invasion depth was smaller than that of TUB2 cancer. There was no significant difference in area ratio or invasion depth between differentiated and undifferentiated gastric cancers ($P > 0.05$; Table 3).

The value of area ratio, DSP, and endoscopic ultrasonography in predicting the invasion depth of early gastric cancer.

A logistic regression model showed that area ratio was meaningful in the fitting curve (partial regression coefficient, −9.0; $P < 0.05$), but lesion size, presence of ulcers, and pathological type were meaningless in the fitting curve ($P = 0.21$, 0.69, and 0.19, respectively). The ROC curve showed that when an area ratio of 84.7% was used as a cut-off value for distinguishing between M and SM 0-II differentiated gastric cancers, the sensitivity, specificity, and accuracy were 76.9%, 90.0%, and 87.4%, respectively. When an area ratio of 73.9% was used as a cut-off value for distinguishing between M-SM1 and SM2 0-II differentiated gastric cancers, the sensitivity, specificity, and accuracy were 90.4%, 84.0%, and 93.5%, respectively. The sensitivity, specificity, and accuracy of predicting invasion depth were similar between differentiated and undifferentiated gastric cancers (Table 3). However, as submucosal undifferentiated cancer was not an indication for ESD, there was no need to differentiate between M-SM1 and SM2 cancers. The accuracy of the DPS for distinguishing between M-SM1 and SM2 cancers was 83.8%. The accuracy of endoscopic ultrasonography for the diagnosis of intramucosal cancer was 74.9%, while that for the diagnosis of submucosal cancer was 77.8%. These values were lower than those of the area ratio ($P < 0.05$; Tables 4 and 5).

Table 3 The sensitivity, specificity and accuracy of area ratio in predicting invasion depth of differentiated and undifferentiated early gastric cancer (%)

	Differentiated		Undifferentiated
	M/SM	M-SM1/SM2	M/SM
Cut off value	84.7	73.9	82.5
Sensitivity	76.9	90.5	80.6
Specificity	90.0	84.0	85.7
Accuracy	87.4	93.5	84.8

M, mucosal; SM, submucosa.

Table 4 The sensitivity and specificity of area ratio and endoscopic ultrasonography in predicting M/SM of type 0–II gastric cancer (%)

	Area ratio	Endoscopic ultrasonography
Cut off value	80.3	
Sensitivity	82.9	76.9
Specificity	80.2	70.6
Accuracy	91.6	74.9

M, mucosal; SM, submucosa.

Discussion

Our study found that the area ratio was negatively correlated with the invasion depth of early gastric cancer, and its value in predicting the invasion depth of early gastric cancer was better than DSP and endoscopic ultrasonography.

Many studies have reported that tumor invasion depth is a significant prognostic factor for early gastric cancer.[1,16–21] M tumors are suitable for endoscopic treatment. Studies have shown that the traditional endoscopic assessment of the total invasive depth of early gastric cancer was 55.5–64.8% and 55.5–69% for M and 47–88% for SM.[6,7,22,23] Abe used the DPS system to predict the invasion depth of early gastric cancer; the results showed that the accuracy of DPS assessment was higher than that of the traditional method. In this study, the DPS was used to predict the invasion depth of early gastric cancer, it can distinguish M-SM1/SM2 with an accuracy of 83.8%, and the results were consistent with those of Abe. However, the accuracy of DPS assessment is insufficient to guide clinical practice. In addition, because SM1 undifferentiated early gastric cancer is not suitable for endoscopic treatment, DPS has limited value in predicting undifferentiated early gastric cancer. With the development of ultrasound endoscopy, high-frequency endoscopic ultrasound may be the most effective method for assessing the invasion depth of early gastric cancer. Studies have shown that the overall accuracy of assessing the invasion depth of early gastric cancer

Table 5 The sensitivity and specificity of depth-predicting score (DPS) system and endoscopic ultrasonography in predicting M-SM1/SM2 of differentiated type 0–II gastric cancer (%)

	DPS	Endoscopic ultrasonography
Sensitivity	66.7	71.4
Specificity	85.9	84.2
Accuracy	83.8	77.8

M, mucosal; SM, submucosa.

varies among centers (range, 64.8%–90%). The accuracy was still affected by numerous factors.[24–28] The accuracy of the diagnosis of intramucosal cancer in our center was 74.9%. In comparison, that of the diagnosis of submucosal cancer was 77.8%, similar to the average value reported among centers; however, this value is lower than desired.

According to Grundmann *et al.*[15] the microsurface structures showed different manifestations in different stages of early gastric cancer. Early gastric carcinomas with different levels of differentiation showed different histological characteristics. TUB1 tumors showed columnar cells. TUB2 cells formed glandular structures of different sizes, and some of these were solid structures.[13,29–30] Therefore, it is speculated that the microsurface structure is irregular in TUB1 tumors, whereas the microsurface structure of TUB2 tumors is fuzzy. When the cancer showed infiltration into the deep submucosa, the glandular structure disappeared, the microsurface structure would also disappear.[31] In this study, the microsurface structure of 91.5% of TUB2 tumors was fuzzy. The area ratio of TUB1 tumors was greater than that of TUB2 tumors ($P < 0.05$). Some studies have reported that gastric cancer with a low level of atypia can develop into gastric cancer with a high level of atypia. Other studies have found that only TUB1 tumors and signet ring cell cancer were found in tiny gastric cancer less than 2 mm, TUB2 was only found in patients with gastric cancer larger than 5 mm. The degree of differentiation of tubular cancer worsens with tumor progression. Besides, these studies speculated that TUB1 tumors can transform into TUB2 tumors and poorly differentiated cancer with an intestinal mucosal phenotype and genetic characteristics.[32–34] Therefore, in the course of development, gastric cancer can also infiltrate into the deep mucosa, the changes in and development of microsurface structures are related to the degree of differentiation and invasion depth. This study showed that the invasion depth of TUB1 tumors was less than that of TUB2 tumors ($P < 0.05$). However, there was no significant difference in invasion depth between differentiated and undifferentiated tumors. This lack of difference may be related to the different origins of undifferentiated cancer.[35]

The area ratio reflects the characteristics of surface microstructure. We further discussed the relationship between the area ratio and invasion depth of type 0–II gastric cancer. The correlation analysis showed that the area ratio was moderately correlated with the invasion depth of early gastric cancer. The results of ROC curve showed that when the area ratio was 80.3%, the accuracy of distinguishing M/SM early gastric cancers was 91.6%. The accuracy was higher than those of traditional endoscopy and high-frequency small probe ultrasound, which have been used for assessing invasion depth.[16] The cut-off value of area ratio for differentiating M/SM differentiated and undifferentiated early gastric cancer were 84.7%, 82.5%, respectively, and the accuracy were 87.4%, 84.8%, respectively. These results suggested that the degree of progression and the change of microsurface structure with different differentiated early gastric cancer were similar.

However, in case of severe inflammation, inflammatory mediators caused destruction of the microstructure, which made the infiltration depth appear greater. This study also included the lesions with ulceration, and it was sometimes impossible to determine whether the ulcers were caused by tumor infiltration or inflammation on endoscopy. Therefore, patients with ulcers or severe inflammation may require reexamination after anti-inflammatory therapy, and reassessment of infiltration depth may help improve the diagnostic accuracy of magnified gastroscopy combined with NBI and CAD mapping. However, if endoscopy is performed after anti-inflammatory therapy, the normal mucosa at the edge of the lesion will grow toward the lesion's center, which would affect the judgment of the lesion's boundary and nature. Therefore, it is necessary to identify the optimal timing for performing repeat gastroendoscopy. Some lesions appeared less obvious and the boundaries appeared unclear after anti-inflammation treatment for 1 month, so we asked patients to undergo gastroscopy after treatment for 2 weeks. Considering that the invasion depth of early stage gastric cancer may be affected by many other factors, we performed a correlation analysis, which showed no correlation of sex, age, gross lesion type, histopathological classification, presence of ulcers, and lesion location with invasion depth. Lesion size and invasion depth were slightly correlated. This result was also confirmed by multiple factor analysis. Logistic regression analysis also showed that only area ratio was meaningful in the fitting curve. Biological behavior differs among different pathological types, but in this study, correlation analysis showed that there was no correlation between the invasion depth and pathological type of type 0–II gastric cancers. However, the rank-sum test showed that invasion depth was lower in well-differentiated gastric cancer than in moderately differentiated gastric cancer. ROC curve analysis showed that similar cut-off values of area ratio showed similar accuracies for distinguishing differentiated and undifferentiated intramucosal cancers, which may be related to the fact that most undifferentiated intramucosal cancers had residual mucosa, and its area was included in the area of the whole lesion. Lesion size was an influencing factor for ESD use, but this study also showed a weak correlation between invasion depth and lesion size. This may be related to our choice of patients; In this study, there were only 16 cases with the lesion size larger than 2 cm, and most of these cases were TUB1. For highly differentiated intramucosal early gastric cancer, the size of the lesion does not affect the risk of lymph node metastasis. This study also found no correlation between ulceration and invasion depth. However, the indications for ESD treatment must consider lesion ulceration since those with ulcers have been reported to have a greater likelihood of developing vascular metastasis.

This study was limited by its small sample size; in particular, the number of cases of submucosal infiltrating carcinoma was relatively small, which may have caused the deviation in results. Second, the boundaries of area A and area B were determined before the operation, which may have been affected by the experience of the endoscopist. In addition, the area of ulceration was included in area B, which may have also affected the results. Lastly, the proportions of undifferentiated gastric cancer and women were high in this study, the reason for this situation also needs to be further confirmed.

Conclusion

Our study reported that the area ratio showed high accuracy for evaluation of the invasion depth of type 0–II gastric cancer. The use of the area ratio is an important method for clinical

evaluation and has clinical value. However, confirmation of our findings in future, large-scale, multi-center studies is required.

Data availability statement. The datasets analyzed during the current study available from the corresponding author on reasonable request.

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