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# Scoring systems for differentiating gastrointestinal stromal tumors and schwannomas from leiomyomas in the stomach

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**Abstract**

There is no practical predictive model for the diagnosis of gastrointestinal stromal tumors (GISTs). To establish a practical predictive model for the diagnosis of subepithelial lesions in the stomach, we reviewed patients with GISTs (n = 89), schwannomas (n = 7), and leiomyomas (n = 28).

The tumor was more frequently found along the gastric cardia in the leiomyoma group (57.1%) than in the GIST/schwannoma group (2.1%, $P < .01$). Contrast enhancement (57.3% vs 0%, $P < .01$) and intra-tumoral necrosis (34.4% vs 0.0%, $P < .01$) were more frequently observed in the GIST/schwannoma group than in the leiomyoma group. On endoscopic ultrasonography, 58.3% of GISTs/schwannomas showed uneven echogenicity, whereas the echogenicity was uneven in 21.4% of leiomyomas ($P < .01$). There were no differences between the tumor color and the presence or absence of ulcer formation, tumor bleeding, irregularity of the tumor margin, cystic spaces, and hyperechoic spots between the 2 groups. Based on these results, we developed a 2-step diagnostic algorithm for GISTs/schwannomas. The first step comprises 1 endoscopic feature: a cardiac or non-cardiac location. Tumors with a cardiac location were judged as leiomyomas and those with a non-cardiac location were judged as GISTs/schwannomas, with 96.9% sensitivity and 57.1% specificity for GIST/schwannoma diagnosis. The second step comprises a combination of endoscopic (non-cardiac location), radiologic (positive contrast enhancement and intra-tumoral necrosis), and endosonographic (uneven echogenicity) features for a total of 4 points. We assigned 1 point to each feature. Tumors with scores of 2 to 4 were judged as GISTs/schwannomas, with 81.3% sensitivity and 92.9% specificity for GIST/schwannoma diagnosis.

Our predictive model will be a practical guide for the management of gastric subepithelial lesions.

**Abbreviations:** CT = computed tomography, GIMTs = gastrointestinal mesenchymal tumors, GISTs = gastrointestinal stromal tumors.

**Keywords:** gastrointestinal stromal tumors, leiomyomas, schwannomas, tumor location

## 1. Introduction

Various tumors occur as subepithelial lesions in the stomach, including gastrointestinal stromal tumors (GISTs), leiomyomas, lipomas, granular cell tumors, ectopic pancreatic tissue, and neuroendocrine tumors.[1,2] Although these lesions are generally identified during esophagogastroduodenoscopy, prompt diagnosis is challenging because the surface of the tumor is usually covered with intact gastric mucosa and acquisition of the tumor tissue by endoscopic biopsy is difficult. Therefore, imaging findings on computed tomography (CT), endoscopic ultrasonog-

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*The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.*

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raphy, and positron emission tomography are important for gastric subepithelial lesions.[3,4]

In general, subepithelial lesions in the stomach are unexpectedly detected during esophagogastroduodenoscopy for screening purposes or symptoms unrelated to the subepithelial lesion. Thus, a large number of gastric subepithelial lesions are diagnosed in primary healthcare institutions, where CT and/or endoscopic ultrasonography are unavailable. In these settings, physicians must decide based on the endoscopic features alone to refer the patients to secondary or tertiary care centers for further investigation of gastric subepithelial lesions. Although endoscopic features of GISTs and other subepithelial lesions have been investigated, there is no practical predictive model for the diagnosis of GISTs based on endoscopic features alone. The purpose of this study was to develop a 2-step diagnostic algorithm for differentiating GISTs and schwannomas from leiomyomas: a screening method using endoscopic features as the first step and a scoring system combining endoscopic, radiologic, and endosonographic features as the second step.

## 2. Methods

### 2.1. Patients

In this study, we enrolled patients with gastrointestinal mesenchymal tumors (GIMTs) in the stomach that were pathologically diagnosed between August 1994 and September 2021 at Okayama University Hospital. Histological diagnosis was based on morphologic and immunophenotypic analyses of endoscopically biopsied specimens, endoscopic ultrasound-fine needle aspiration specimens, or surgically excised specimens. We excluded patients with a GIMT that was unrecognizable during esophagogastroduodenoscopy or CT performed pre-operatively and those incidentally identified postoperatively because their location and morphologies were not evaluable. Ultimately, 124 patients were included in this study. Clinical data regarding endoscopic, radiological, and biological examinations were obtained from retrospectively reviewed clinical records.

This study was approved by the Ethical Committee of Okayama University Hospital and adhered to the Declaration of Helsinki.

### 2.2. Analysis

Based on the pathological diagnosis, the patients were divided into GIST/schwannoma and leiomyoma groups. To identify factors that differentiate GISTs/schwannomas from leiomyomas, we evaluated patient sex, age at diagnosis, tumor location and color, internal echogenicity, presence or absence of ulceration on the surface, irregular morphology, contrast enhancement, intratumoral necrosis, tumor bleeding, and cystic degeneration.

Location, color, morphology, and presence or absence of ulceration on the surface were evaluated using esophagogastroduodenoscopy images. The location of the GIMT was dichotomized as pericardiac orifice or non-cardial. We defined tumors that adjoined more than one-fourth of the circumference of the cardiac orifice as having a pericardiac orifice location (Fig. 1A and B). Conversely, tumors separated from the cardiac orifice (Fig. 1C) and those adjoining less than one-fourth of the circumference of the cardiac orifice (Fig. 1D) were defined as non-cardial. Internal echogenicity, cross-section margins, and the presence or absence of cystic degeneration were investigated using endoscopic ultrasonography. CT images were used to identify contrast enhancement, intra-tumoral necrosis, tumor bleeding, and irregularity of the tumor margin. We defined positive contrast enhancement as the presence of a clearly enhanced area within the lesion in the arterial phase that contrasted with the normal surrounding structures.

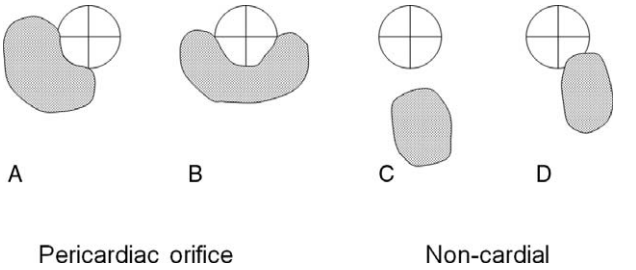


**Figure 1.** Tumors defined as having a pericardiac orifice location were those that adjoined more than one-fourth of the circumference of the cardiac orifice (A and B). Conversely, tumors separated from the cardiac orifice (C) and those adjoining less than one-fourth of the circumference of the cardiac orifice (D) were defined as non-cardial.

### 2.3. Statistical analysis

For comparisons of the 2 groups, statistical analyses including *t* tests, chi-square tests, and F-tests were performed using JMP Pro 14.0.0 software (SAS Institute, Cary, NC). Statistical significance was set at $P < .05$.

## 3. Results

### 3.1. Differences between the GIST/schwannoma and leiomyoma groups

Histologically, 89 patients were diagnosed with GISTs, 7 patients were diagnosed with schwannomas, and 28 patients were diagnosed with leiomyomas. GISTs were diagnosed using endoscopic ultrasound-fine needle aspiration (n = 47), surgical excision (n = 37), or endoscopic biopsy (n = 5). All patients with schwannomas were diagnosed using endoscopic ultrasound-fine needle aspiration (n = 7). Leiomyomas were diagnosed using endoscopic ultrasound-fine needle aspiration (n = 15), surgical excision (n = 10), or endoscopic biopsy (n = 3). Thus, the GIST/schwannoma and leiomyoma groups comprised 96 and 28 patients, respectively. The patients' backgrounds and characteristics are shown in Table 1. There were 41 men and 55 women in the GIST/schwannoma group and 15 men and 13 women in the leiomyoma group ($P = .21$). The age at the time of diagnosis of GISTs/schwannomas was significantly higher than that of leiomyomas (mean, 67.7 vs 51.2 years; $P < .01$).

Representative images of GISTs are shown in Figure 2, and those of leiomyomas are shown in Figure 3. The mean tumor size of GISTs/schwannomas (mean, 34.7 mm; range, 7–140 mm) was significantly larger than that of leiomyomas (mean, 27.0 mm; range, 6–63 mm; $P < .05$). Esophagogastroduodenoscopy was not performed prior to surgical resection in 1 patient with a GIST. Thus, location, color, and ulceration were not evaluated in this patient. The tumor was located around the gastric cardia in 2 patients with a GIST/schwannoma (2.1%) and in 16 patients with a leiomyoma (57.1%, $P < .01$). With respect to the color of

**Table 1**

**Characteristics of patients with GISTs/schwannomas and leiomyomas.**

| | GIST/schwannoma, n (%) | Leiomyoma, n (%) | *P* value |
|---|---|---|---|
| Sex | | | .21 |
| Men | 41 (42.7) | 15 (53.6) | |
| Women | 55 (57.2) | 13 (46.4) | |
| Age (yrs, mean ± SD) | 67.7 ± 12.8 | 51.2 ± 15.9 | <.01 |
| Tumor size (mm, mean ± SD) | 34.7 ± 26.5 | 27.0 ± 13.9 | <.05 |
| Location | | | <.01 |
| Pericardiac orifice | 2 (2.1) | 16 (57.1) | |
| Not around the cardia | 93 (96.9) | 12 (42.9) | |
| Undetermined | 1 (1.0) | 0 (0.0) | |
| Color | | | .47 |
| Reddish | 8 (8.3) | 4 (14.3) | |
| Other than reddish | 84 (87.5) | 24 (85.7) | |
| Undetermined | 4 (4.2) | 0 (0.0) | |
| Ulceration | | | .17 |
| Present | 16 (16.7) | 2 (7.1) | |
| Absent | 76 (79.2) | 25 (89.3) | |
| Undetermined | 4 (4.2) | 1 (3.6) | |
| Vascularity on CT | | | <.01 |
| Hypervascular | 55 (57.3) | 0 (0.0) | |
| Hypovascular | 30 (31.3) | 17 (60.7) | |
| Undetermined | 11 (11.5) | 11 (39.3) | |
| Intra-tumoral necrosis on CT | | | <.01 |
| Present | 33 (34.4) | 0 (0.0) | |
| Absent | 52 (54.2) | 18 (64.3) | |
| Undetermined | 11 (11.5) | 10 (35.7) | |
| Tumor bleeding | | | .34 |
| Present | 8 (8.3) | 0 (0.0) | |
| Absent | 76 (79.2) | 18 (64.3) | |
| Undetermined | 12 (12.5) | 10 (35.7) | |
| Irregularity of the tumor margin | | | .59 |
| Present | 6 (6.3) | 0 (0.0) | |
| Absent | 79 (82.3) | 18 (64.3) | |
| Undetermined | 11 (11.5) | 10 (35.7) | |
| Echogenicity on EUS | | | <.01 |
| Uneven | 56 (58.3) | 6 (21.4) | |
| Even | 10 (10.4) | 13 (46.4) | |
| Undetermined | 30 (31.3) | 9 (32.1) | |
| Cystic space on EUS | | | .51 |
| Present | 14 (14.6) | 2 (7.1) | |
| Absent | 52 (54.2) | 17 (60.7) | |
| Undetermined | 30 (31.3) | 9 (32.1) | |
| Hyperechoic spot on EUS | | | .78 |
| Present | 21 (21.9) | 5 (17.9) | |
| Absent | 45 (46.9) | 14 (50.0) | |
| Undetermined | 30 (31.3) | 9 (32.1) | |

CT = computed tomography, EUS = endoscopic ultrasonography, GIST = gastrointestinal stromal tumor, SD = standard deviation.

the tumor, redness was observed in 8 patients with a GIST/schwannoma (8.3%) and in 4 patients with a leiomyoma (14.3%, $P = .47$). Ulcer formation was observed in 16 patients with a GIST/schwannoma (16.7%) and in 2 patients with a leiomyoma (7.1%, $P = .17$).

CT was performed in 85 patients with GISTs/schwannomas and 18 patients with leiomyomas. Contrast enhancement was positive in 55 patients with GISTs/schwannomas (57.3%), whereas no patients with leiomyomas showed contrast enhancement (0.0%, $P < .01$). Intra-tumoral necrosis was observed in 33 patients with GISTs/schwannomas (34.4%) and in none of the patients with leiomyomas (0.0%, $P < .01$). None of the patients with leiomyomas had tumor bleeding or irregularity of the tumor margin (0.0%). In contrast, tumor bleeding was observed in 8 patients (8.3%, $P = .34$), and the tumor margin was irregular in 6

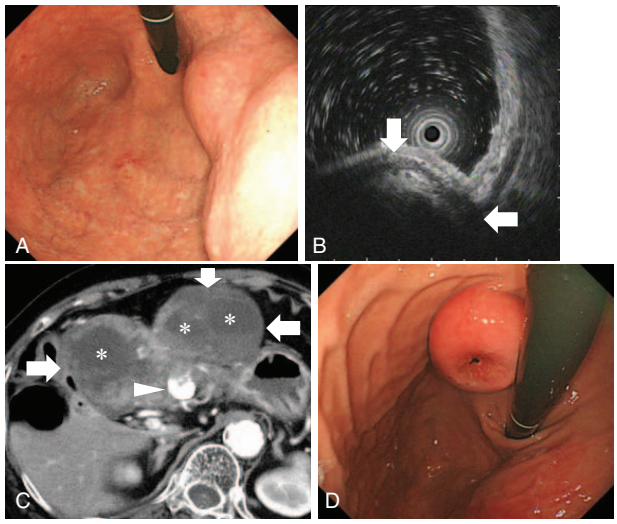


**Figure 2.** Representative images of gastric gastrointestinal stromal tumors. An 88-year-old woman had a large, multinodular subepithelial lesion in the lesser curvature of the body, showing a non-cardial location (A). There was no redness on the tumor surface. Endoscopic ultrasonography showed uneven hyperechogenicity in the tumor, surrounded by a hypoechoic halo (B, arrows). A large tumor, shown on a computed tomography image (C, arrows), was accompanied by avascular, cystic areas with fluid levels of contrast enhancement (asterisks), suggesting intra-tumoral necrosis and bleeding. The tumor also had a calcifying area (arrowhead). A 37-year-old woman had a subepithelial tumor with ulceration in the lesser curvature of the body (D).

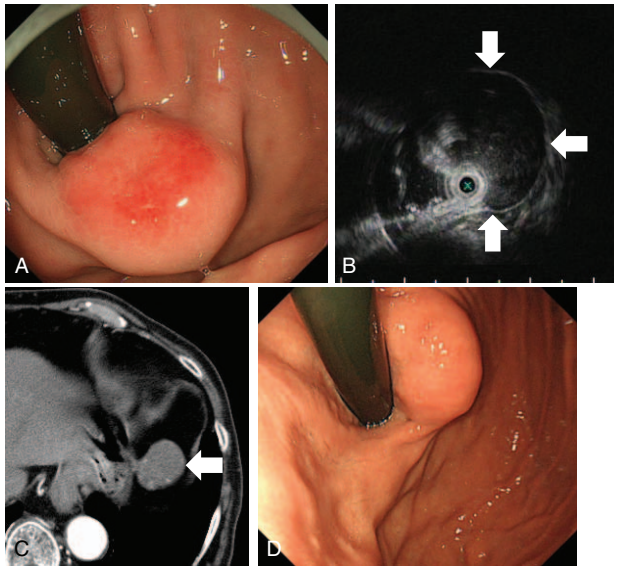


**Figure 3.** Representative images of gastric leiomyomas. A 73-year-old woman had a subepithelial tumor around the cardia, that is, a pericardiac orifice location (A). The mucosa covering the tumor was reddish. On endoscopic ultrasonography, a tumor with low echoic, even echogenicity was observed (B). On contrast-enhanced computed tomography, the tumor was shown to be hypovascular and there was no intra-tumoral necrosis (C). A 73-year-old woman had a gastric leiomyoma, which was located along the gastric cardia (D).

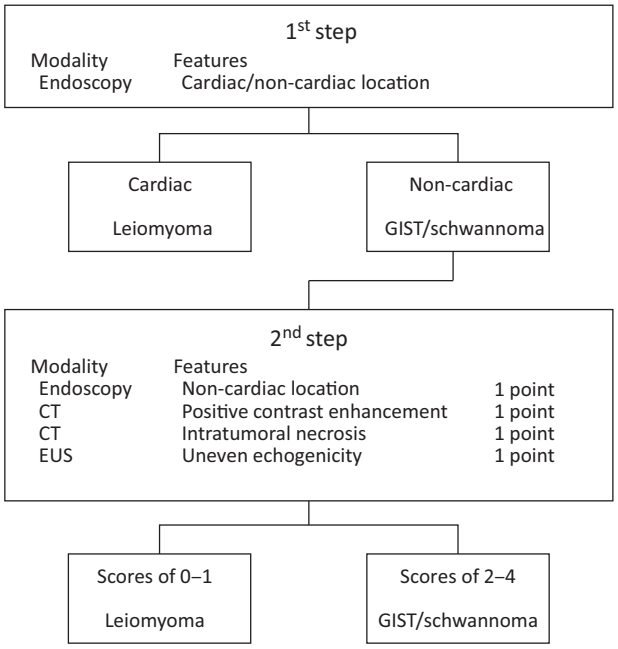


**Figure 4.** A screening method based on an endoscopic feature (first step) and a scoring system based on a combination of endoscopic, radiologic, and endosonographic features (second step). CT = computed tomography, EUS = endoscopic ultrasonography, GIST = gastrointestinal stromal tumor.

patients with GISTs/schwannomas (6.3%, $P = .59$). Statistically, contrast enhancement and intra-tumoral necrosis were more frequently observed on CT in the GIST/schwannoma group than in the leiomyoma group.

Endoscopic ultrasonography was performed in 66 patients with GISTs/schwannomas and 19 patients with leiomyomas. On endoscopic ultrasonography, 56 GISTs/schwannomas showed uneven echogenicity (58.3%), whereas echogenicity was uneven in 6 leiomyomas (21.4%, $P < .01$). In contrast, cystic spaces were observed in 14 patients with GISTs/schwannomas (14.6%) and 2 patients with leiomyomas (7.1%, $P = .51$). There were no differences between the hyperechoic spots in GISTs/schwannomas and leiomyomas (21 vs 5, $P = .78$).

### 3.2. Screening based on an endoscopic feature

As described above, non-cardiac location is the sole significant endoscopic feature that could be suggestive of GISTs/schwannomas. Thus, we used this feature to establish a predictive model to identify patients with GISTs/schwannomas (Fig. 4). Tumors with a non-cardiac location were judged as GISTs/schwannomas, and those with a cardiac location were judged as leiomyomas, with 96.9% sensitivity and 57.1% specificity for GIST/schwannoma diagnosis.

### 3.3. Scoring system based on combination of endoscopic, radiologic, and endosonographic features

In addition to the endoscopic features of non-cardiac location (feature 1), the CT features of positive contrast enhancement (feature 2) and intra-tumoral necrosis (feature 3), as well as endoscopic ultrasonography features of uneven echogenicity (feature 4), were more frequently observed in patients with GISTs. Consequently, we assigned 1 point to each feature. The overall score was calculated based on the number of these 4 features (Fig. 4). Tumors with scores of 0 to 1 were judged as leiomyomas and those with scores of 2 to 4 were judged as GISTs/schwannomas, with 81.3% sensitivity and 92.9% specificity for GIST/schwannoma diagnosis.

In the present study, endoscopic ultrasound-fine needle aspiration was performed in 55 patients with GISTs/schwannomas and 16 patients with leiomyomas. According to the scoring system based on a combination of endoscopic, radiologic, and endosonographic features, 14 of the 16 patients with leiomyomas (87.5%) had a score of 0 to 1, while 53 of the 55 patients with GISTs/schwannomas (96.4%) had a score of 2 to 4. Thus, endoscopic ultrasound-fine needle aspiration might have been deferred in 16 patients, provided that the scoring system was applied, with a 94.4% accuracy for leiomyoma diagnosis.

## 4. Discussion

Among GIMTs, GISTs and leiomyosarcomas essentially require surgical resection owing to their malignant nature. Although gastric schwannomas are slow-growing tumors, some researchers recommend surgical resection as they may become malignant.[5] In contrast, all gastric leiomyomas are virtually benign; thus, they can be followed-up without invasive treatment. Consequently, the differentiation of gastric leiomyomas from other GIMTs is important to ensure appropriate clinical management.[6]

In this study, we developed a 2-step diagnostic algorithm for differentiating gastric GISTs and schwannomas from leiomyomas. The first step comprises an endoscopic feature, and the second step is a scoring system combining endoscopic, radiologic, and endosonographic features. As described above, most gastric subepithelial lesions are unexpectedly identified during esophagogastroduodenoscopy.[7,8] As CT and endoscopic ultrasonography are generally not accessible in primary healthcare institutions, the first step based on an endoscopic feature (cardiac/non-cardiac location) is probably useful in these settings to decide whether patients should referred to a secondary or tertiary care institution for further investigation. Although the specificity for GISTs/schwannoma diagnosis is relatively low (57.1%) in the first step based on an endoscopic feature, it improved to 92.9% when combined with radiologic and endosonographic features. Thus, a scoring system based on a combination of endoscopic, sonographic, and radiologic features (second step) may be useful as a predictive model for the diagnosis of GISTs/schwannomas in secondary or tertiary care institutions.

In actual clinical settings, we noticed that gastric leiomyomas predominantly arise in the esophagogastric junction, whereas gastric GISTs and schwannomas occur in other areas of the stomach. In particular, leiomyomas often "surround" the cardiac orifice. Therefore, in this study, we defined tumors that adjoined more than one-fourth of the circumference of the cardiac orifice as having a pericardiac orifice location (Fig. 1A and B). According to this criterion, 57.1% of leiomyomas but only 2.1% of GISTs/schwannomas occurred in the pericardiac orifice location. Such differences between the location of GISTs and leiomyomas have been reported previously.[9,10] In this context, the first step based on endoscopic features is reasonable for screening leiomyomas from further investigations. Our approach may also be beneficial from an econometric standpoint. In patients who were classified under the leiomyoma group in the first step, CT and endoscopic

ultrasonography can be omitted, and these patients are periodically followed-up by esophagogastroduodenoscopy alone. However, the appropriate interval between follow-up endoscopy examinations should be elucidated. Meanwhile, patients who were classified under the GIST/schwannoma group in the second step should undergo pathological diagnosis, such as endoscopic ultrasound-fine needle aspiration.

In the present study, the mean age at the time of diagnosis of GIST/schwannoma was 67.7 years, which was significantly higher than that of leiomyoma (51.2 years). This observation of older age in patients with a GIST has been reported previously. Liu et al[10] reported that the mean age of patients with a gastric GIST diagnosis was 44.5 years and that of patients with a gastric leiomyoma diagnosis was 40.1 years. The authors proposed a scoring method for the diagnosis of GISTs using 7 clinical and CT features, including older age (>49 years), non-cardiac location, irregular margin, lower attenuation on unenhanced images (≤43 HU), heterogeneous enhancement, necrosis, and absence of enlarged lymph nodes. A cutoff score of ≥4 versus <4 provided a sensitivity of 100% and specificity of 72%. A scoring system for differentiating GISTs from non-GISTs using clinical and CT features has been reported by other authors. For instance, Yin et al[11] proposed 8 features consisting of older age (>46.5 years), tumor long diameter (>4.5 cm), heterogeneous enhancement, high degree of enhancement, mean CT attenuation >69.2 HU, presence of intra-lesional low attenuation and surface ulceration, and absence of calcification. The presence of at least 4 of these 8 features had a sensitivity of 76.7% and specificity of 76.5% for differentiating GISTs from leiomyomas.

Endoscopic ultrasonography is also reportedly useful for GIST diagnosis.[12–14] Kim et al[15] reported that uneven echogenicity, hyperechoic spots, a marginal halo, and higher echogenicity than the surrounding muscle layer were more frequently observed on endoscopic ultrasonography in GISTs than in leiomyomas. Lesions with at least 2 of these features provided a sensitivity of 89.1% and a specificity of 85.7% for predicting GISTs. The round shape and irregular margin of the lesion are also endoscopic ultrasonography features suggestive of GISTs.[16]

In the present study, we incorporated CT features of positive contrast enhancement and intra-tumoral necrosis and an endoscopic ultrasonography feature of uneven echogenicity as items for the scoring system, as statistically significant differences were observed in these features between GISTs and non-GISTs. Although it may be possible to increase the accuracy of our scoring system by adding other features characteristic of GISTs, this concept requires further investigation.

Tumor size is generally important in the management of gastric subepithelial lesions. For example, according to the clinical practice guidelines for GIST in Japan, gastric subepithelial lesions less than 2 cm in size without malignant findings, such as ulceration, irregular margins, and rapid growth in endoscopic examinations can be followed-up by esophagogastroduodenoscopy every other year or every 2 years.[17] In contrast, the representative opinion with respect to the tumor behavior of the GIST is that all GISTs should be considered to have a malignant potential, with the possible exception of very small tumors measuring less than 1 cm.[18] Therefore, we consider that tumors with features suggestive of GISTs should be further investigated by CT and endoscopic ultrasonography, irrespective of tumor size. However, since only 2 patients had GISTs of subcentimeter in the present study, it should be elucidated how to deal with gastric subepithelial lesions less than 1 cm.

Tumor growth is also an important feature suggestive of GISTs. However, we excluded this feature from our scoring systems for the following 2 reasons. First, in the present study, repeat esophagogastroduodenoscopy examinations were performed on 75 lesions (data not shown). Enlargement of the tumor was noted in 16 lesions, all of which were diagnosed as GISTs. Although we incorporated the presence or absence of tumor enlargement in the first step, it did not improve the accuracy of GIST/schwannoma diagnosis, with 96.9% sensitivity and 57.1% specificity. Second, elimination of the features of tumor growth enables simplification of the screening test because it can be applied even in the initial esophagogastroduodenoscopy examination.

Our study has several limitations. First, this was a single-center, retrospective study. Second, the number of enrolled patients was relatively small, particularly those with leiomyomas, owing to the low incidence of these tumors. In particular, because of the missing values in our patient dataset, we could not perform a multivariate analysis reliably. Third, a selection bias existed because we enrolled patients with pathologically diagnosed lesions. In the actual health care setting, the majority of gastric subepithelial lesions are followed-up without histological examinations. Lastly, although we proposed a 2-step diagnostic algorithm for diagnosing GISTs/schwannomas, a validation study was not conducted. Thus, to overcome these issues, validation of our scoring system in a multicenter study with a larger sample size is required.

In conclusion, we developed a 2-step diagnostic algorithm for differentiating gastric GISTs and schwannomas from leiomyomas. Although there are other predictive models for the diagnosis of GIST in the literature, a possible advantage of our 2-step diagnostic algorithm is that our model based on an endoscopic feature (first step) can be used in primary healthcare institutions, since it does not require a CT or an endoscopic ultrasonography. Our report also highlights the non-cardiac location of GISTs and schwannomas. The recognition of which is probably beneficial for gastroenterologists to promptly diagnose gastric subepithelial lesions. Although endoscopists often experience diagnostic difficulties for gastric subepithelial lesions, we hope that our predictive model will be a practical guide for the management of these lesions in different levels of healthcare delivery systems.

## Author contributions

**Conceptualization:** Masaya Iwamuro, Hiroyuki Okada.
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**Supervision:** Hiroyuki Okada.
**Writing – original draft:** Shotaro Okanoue, Masaya Iwamuro.

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