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Identification of gastrointestinal stromal tumors from leiomyomas in the esophagogastric junction

A single-center review of 136 cases

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Abstract

To identify significant clinical and CT features for the differentiation of gastrointestinal stromal tumors (GISTs) from leiomyomas in the esophagogastric junction (EGJ).

One hundred thirty six patients with pathologically proven GISTs (n = 87) and leiomyomas (n = 49) in the EGJ were enrolled. And preoperative CT images were available in 73 GISTs cases and 34 leiomyoma cases. Two radiologists reviewed the CT images by consensus with regard to tumor size, shape, growth pattern, surface, enhancement pattern, enhancement degree, attention at each phasic image and the presence of surface ulcer, calcification, and intralesional low attention.

Eight significant clinical and CT features were identified for differentiating GISTs from leiomyomas: older age (>46.5 years), tumor long diameter >4.5 cm, heterogeneous enhancement, high degree enhancement, mean CT attenuation >69.2 HU, presences of intralesional low attenuation and surface ulcer, absences of calcification ($P < .05$). On the receiver operating characteristic curve analysis, an optimal cutoff score of 3.5 was achieved for differentiating GISTs from leiomyomas with an AUC of 0.844 (sensitivity: 76.7%, specificity: 76.5%).

older age (>46.5 years), tumor long diameter >4.5 cm, heterogeneous enhancement, high degree enhancement, mean CT attenuation >69.2 HU, presences of intralesional low attenuation and surface ulcer, absence of calcification are significant features highly suggestive of GISTs in differentiation from leiomyomas in the EGJ.

Abbreviations: CI = confidence interval, EGJ = esophagogastric junction, EUS = endoscopic ultrasound, GISTs = gastrointestinal stromal tumors, IHC = immunohistochemical, LD = long diameter, ROC = receiver operating characteristic, ROI = regions of interests, SD = short diameter, SETs = subepithelial tumors, SMA = smooth muscle actin.

Keywords: CT, gastroesophageal junction, gastrointestinal stromal tumor, leiomyoma

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1. Introduction

Upper gastrointestinal subepithelial tumors (SETs) consist of a group of mesenchymal lesions and include a variety of tumor types, such as leiomyomas, gastrointestinal stromal tumors (GISTs), granular cell tumors, schwannomas, leiomyosarcomas, and aberrant pancreas. SETs located in the esophagogastric junction (EGJ) are extremely rare, leiomyomas and GISTs occupy predominately among these tumors.[1] Resection of tumors in such location remains challenging because of the specific anatomy location. For GISTs with high potential malignancy, curative surgical resection with an adequate margin is required. Partial or wedge resection, even proximal gastrectomy or total gastrectomy, are often applied for GIST located in the EGJ due to the potential risk of stricture and leakage.[2] However, leiomyomas, as benign tumors, can be treated with conservative therapy or enucleation or tumor-everting resection instead of extended resection.[3,4] Hence, to distinguish these 2 tumors in the preoperative stage is important for surgeons to select the optimal therapeutic strategies.

The accurate differentiation between leiomyoma and GIST is quite difficult before surgery, and the final diagnosis is depended on postoperative pathological examination. Endoscopic biopsy or endoscopic ultrasound (EUS)-guided fine needle aspiration biopsy may provide useful information preoperatively, but they often provide inadequate tissue yield and increase the risk of tumor rupture and seeding.[5] Recently, several studies were reported by using CT characteristics to differentiate gastric GISTs from other benign SETs.[6–8] Several characteristic CT features that could differentiate leiomyomas from GISTs in the gastric cardia were identified. However, the reliability of these results was limited by the extremely small-sized study population and lack of important clinical parameters in previous studies, further investigation is warranted.

Therefore, in this retrospective analysis, we analyzed the clinical and CT features of leiomyomas and GISTs in the EGJ in relatively larger population, with the aim of better distinguishing these 2 tumors preoperatively.

2. Methods

2.1. Patient selection

This was a single-center, retrospective study. This study was approved by the Institutional Review Board of the West China Hospital of Sichuan University, and informed consents were obtained from each patient in this cohort. All procedures for this study were carried out in accordance with the approved guidelines and regulations. Subjects for this study were selected from a total of 1943 patients with esophago-gastric GISTs or leiomyomas presenting to West China Hospital of Sichuan University between April 2010 and July 2018 (Fig. 1). The inclusion criteria were as follows:

1. pathologic diagnosis of leiomyomas or GISTs;
2. located in the esophagogastric junction;
3. underwent surgical resection (endoscopic, laparoscopic, or open surgery) at our hospital.

Exclusion criteria were:

1. tiny (<1 cm) incidental GISTs or leiomyomas found in other operations;
2. recurrent tumors receiving reoperation.

First, 49 patients with leiomyomas and 87 patients with GISTs were identified in our study for clinical analysis. Second, analysis of CT images between leiomyoma and GIST was conducted in patients with available preoperative contrast-enhanced CT images. Fifteen patients with leiomyomas and 14 patients with GISTs were excluded because there were no available CT images. Finally, 34 patients with leiomyomas and 73 patients with GISTs were included in our study for CT image analysis.

2.2. Acquisition of CT images

Contrast-enhanced CT scans were performed using a SOMATOM Definition Flash unit (Siemens Healthineers, Erlangen, Germany). To achieve gastric distension, 1000 ml tap water was ingested for each patient before the CT examination. Intravenous

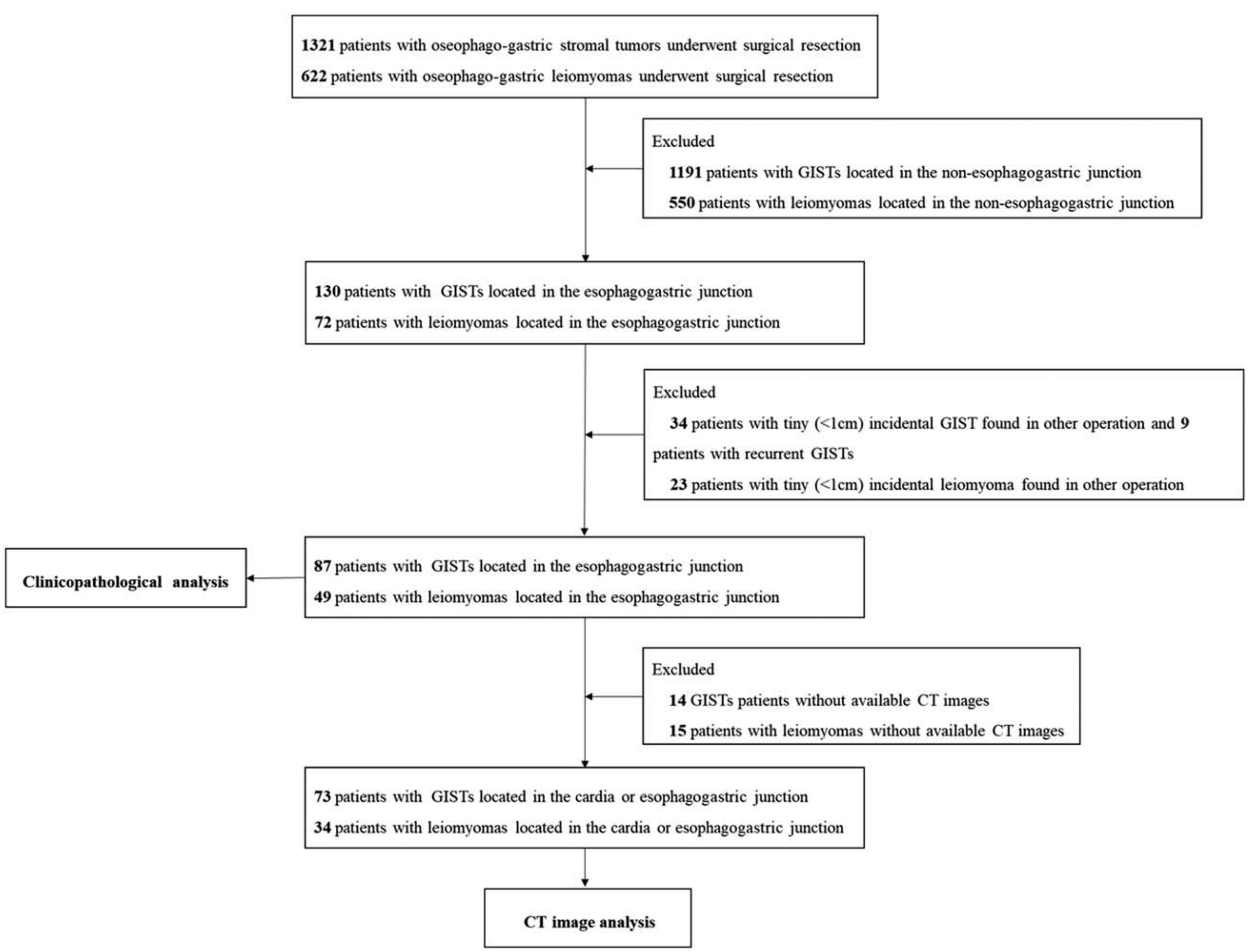

Figure 1. Inclusion process of patients included in the present study.

nonionic contrast agent (2 ml/kg; iopromide, Ultravist, Schering) were injected in an antecubital vein at a flow rate of 3 ml/second. Scan parameters were as follows: 128×0.6 mm collimation, gantry rotation time of 0.28 second, 120 kV and 210 mAs. Contrast-enhanced images were available at 25 to 35 seconds (hepatic arterial phase), 60 to 70 seconds (portal venous phase), and 3 to 5 minutes (delayed phase) after initiation of IV injection of contrast material. All images were reconstructed with slice thickness thinner than 5 mm for statistical analysis.

2.3. Image analysis

Two gastrointestinal radiologists (with 5 and 8 years of experience, respectively) retrospectively and independently reviewed the CT findings, and discrepancies were resolved according to their consensus. The 2 radiologists knew that patients had either leiomyomas or GISTs in the EGJ, but who were blinded to the clinical data and the histopathologic results. The images were reviewed on a vendor-specific postprocessing software (Syngo.Via, Siemens, Germany).

The following CT finding were analyzed: tumor size, tumor shape (round or ovoid, irregular), surface (regular or irregular), growth pattern, enhancement pattern, enhancement degree of the tumor, presence of surface ulcer, presence of calcification, presence of internal low attenuation areas (necrosis, gas, hemorrhage or cystic degeneration). Growth patterns were classified as endoluminal, exophytic, or mixed. Enhancement patterns included homogeneous or heterogeneous enhancement. The enhancement degrees included low, intermediate, and high, which were defined in comparison to the enhancement of back muscles. A CT attenuation value less than 20 HU within the tumor was considered as the presence of internal low attenuation. When measuring the degree of tumor enhancement, CT attenuation values of the tumors were measured in Hounsfield units using 16 to 18 mm^2 circular regions of interests (ROIs). Three ROIs were placed on the most strongly enhanced portion of the tumors in each hepatic arterial, portal venous, and delayed phase. The mean tumor attenuation was measured as the average values of 3 ROI values.

2.4. Pathological evaluation

The final diagnoses of all enrolled patients were determined according to the specific immunohistochemical (IHC) analysis in conjunction with molecular genetic analysis. For IHC analysis, positive expression of c-KIT (CD117) and/or DOG-1 is consistent with GISTs, and positive expression of smooth muscle actin (SMA) and desmin indicates leiomyoma. For c-KIT/DOG-1 double negative tumors that cannot exclude GISTs morphologically, molecular genetic analyses that harbor a KIT or PDGFRA mutation can also be diagnosed as GISTs.

2.5. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for windows (V21.0, IBM corp, NY, USA). Continuous variables were summarized with mean ± standard deviation (SD), dichotomous variables were expressed as frequency and percentages. To analyze difference of CT and clinicopathological findings between GISTs and leiomyomas, the student t test or variance (ANOVA) were performed for continuous variables, whereas the χ^2 test or Fisher exact test were performed for categorical variables. For significant clinical and CT features, the optimal cutoff values for these date for differentiating leiomyomas from GISTs were determined by the receiver operating characteristic (ROC) curves (highest sum of the sensitivity and the specificity). Each patient was given 1 point for each significant feature, and a GIST-risk score was calculated as the sum of significant features. The optimal GIST-risk scoring model was established when the sum of the specificity and the sensitivity was highest, and the optimal cut-off point of the score was calculated for differentiating leiomyomas from GISTs. A P value of $<.05$ was considered statistically significant, and a 95% confidence interval (CI) was reported for each variable.

3. Results

3.1. Clinical characteristics in total participants

A total of 49 and 87 patients with leiomyomas and GISTs were identified in this study. The demographic and clinical features of patients are listed in Table 1. Patients with leiomyomas were younger than those with GISTs (46.82 years vs 55.44 years, $P<.001$). The optimal cutoff value of 46.5 years for the age yielded a sensitivity of 80.5%, a specificity of 57.1%, and an area under the receiver operating characteristic curve (AUC) of 0.681. The mean size of tumor was larger in GISTs group than leiomyomas group significantly (5.19 ± 2.9 cm vs 4.05 ± 2.45 cm, $P=.024$). The finding of surface ulcer ($P=.001$) during operation was more frequently observed in GISTs. In addition, open laparotomy was the predominant surgical strategy for leiomyomas and GISTs, although endoscopic resection was more frequently applied to leiomyomas ($P=.011$). No statistically significant differences were found in gender, symptom, resection range, growth pattern, and tumor shape between the patients with leiomyomas and those with GISTs ($P>.05$).

Table 1

Clinical features of patients with Leiomyomas (n=49) and GISTs (n=87).

Variables	Leiomyoma (n=49)	GISTs (n=87)	*P* value
Age, years (range)	46.82 (24–71)	55.44 (24–75)	<.001
Gender			
Male	22 (44.9)	48 (55.2)	.250
Female	27 (55.1)	39 (44.8)	
Symptom			
Yes	39 (79.6)	79 (90.8)	.064
No	10 (20.4)	8 (9.2)	
Tumor size (cm)	4.05±2.45	5.19±2.97	.024
Surgical procedures			
Open laparotomy	31 (63.3)	70 (80.5)	.011
Laparoscopic resection	2 (4.1)	7 (8.0)	
Endoscopic resection	16 (32.7)	10 (11.5)	
Resection range			
Proximal gastrectomy	24 (49)	45 (51.7)	.759
Local resection	25 (51)	42 (48.3)	
Growth pattern (operation findings)			
Endoluminal	33 (67.3)	46 (52.9)	.101
Exophytic or mixed	16 (32.7)	41 (47.1)	
Tumor shape (operation findings)			
Round or ovoid	29 (59.2)	65 (74.7)	.060
Irregular	20 (40.8)	22 (25.3)	
Surface ulcer (operation findings)			
Yes	11 (22.4)	45 (51.7)	.001
No	38 (77.6)	42 (48.3)	

Table 2

CT findings of leiomyomas (n=34) and GISTs (n=73).

Variables	Leiomyoma (n=34)	GISTs (n=73)	*P* value
Tumor long diameter (LD)	3.69±1.48	4.90±2.40	.002
Tumor short diameter (SD)	2.78±1.24	3.77±1.82	.005
LD/SD ratio	1.38±0.36	1.33±0.30	.468
Tumor shape			
Round or ovoid	21 (61.8)	51 (69.9)	.406
Irregular	13 (38.2)	22 (30.1)	
Growth pattern			
Endoluminal	21 (61.8)	37 (50.7)	.284
Exophytic or mixed	13 (38.2)	36 (49.3)	
Surface			
Regular smooth	29 (85.3)	50 (68.5)	.066
Irregular lobulated	5 (14.7)	23 (31.5)	
Surface ulcer			
Yes	9 (26.5)	39 (53.4)	.009
No	25 (73.5)	34 (46.6)	
Calcification			
Yes	7 (20.6)	4 (5.5)	.035
No	27 (79.4)	69 (94.5)	
Enhancement pattern			
Homogeneous	25 (73.5)	32 (43.8)	.004
Heterogeneous	9 (26.5)	41 (56.2)	
Enhancement degree			
Intermediate or low	33 (97.1)	40 (54.8)	<.001
High	1 (2.9)	33 (45.2)	
Intralesional low attenuation area			
Yes	7 (20.6)	35 (47.9)	.007
No	27 (79.4)	38 (52.1)	
Attenuation value	67.57±11.05	75.60±20.05	.031

3.2. CT features between GISTs and leiomyomas

The CT findings between leiomyomas and GISTs are summarized in Table 2. The tumor long diameter (LD) was significantly larger in GISTs compared to leiomyomas (4.90±2.40 cm vs 3.69±1.48 cm, $P=.002$) with an optimal cutoff value of 4.5 cm (sensitivity: 53.4%, specificity: 76.5%) and an AUC of 0.681. The tumor short diameter (SD) was also significantly larger in GISTs compared to leiomyomas (3.77±1.82 cm versus 2.78±1.24 cm, $P=.005$). The LD/SD ratio, tumor shape, growth pattern, and surface were not significantly different between patients with leiomyomas and those with GISTs ($P>.05$). There was a statistically significant higher rate of surface ulcer (53.4% vs 26.5%, $P=.009$), heterogenous enhancement (56.2% vs 26.5%, $P=.004$), and high degree enhancement (45.2% vs 2.9%, $P<.001$) among GISTs compared to leiomyomas. The rate of intralesional low attenuation was also higher among GIST (47.9% vs 20.16%, $P=.007$). However, the presence of calcification (20.6% vs 5.5%, $P=.035$) was more common in leiomyomas. Mean CT attention value was significantly lower in leiomyomas than that in GISTs (67.57±11.05 HU vs 75.60±20.05 HU, $P=.031$). The cutoff value of for 69.2 HU for the CT attention value yielded a sensitivity of 61.6%, a specificity of 64.7% and an AUC of 0.632.

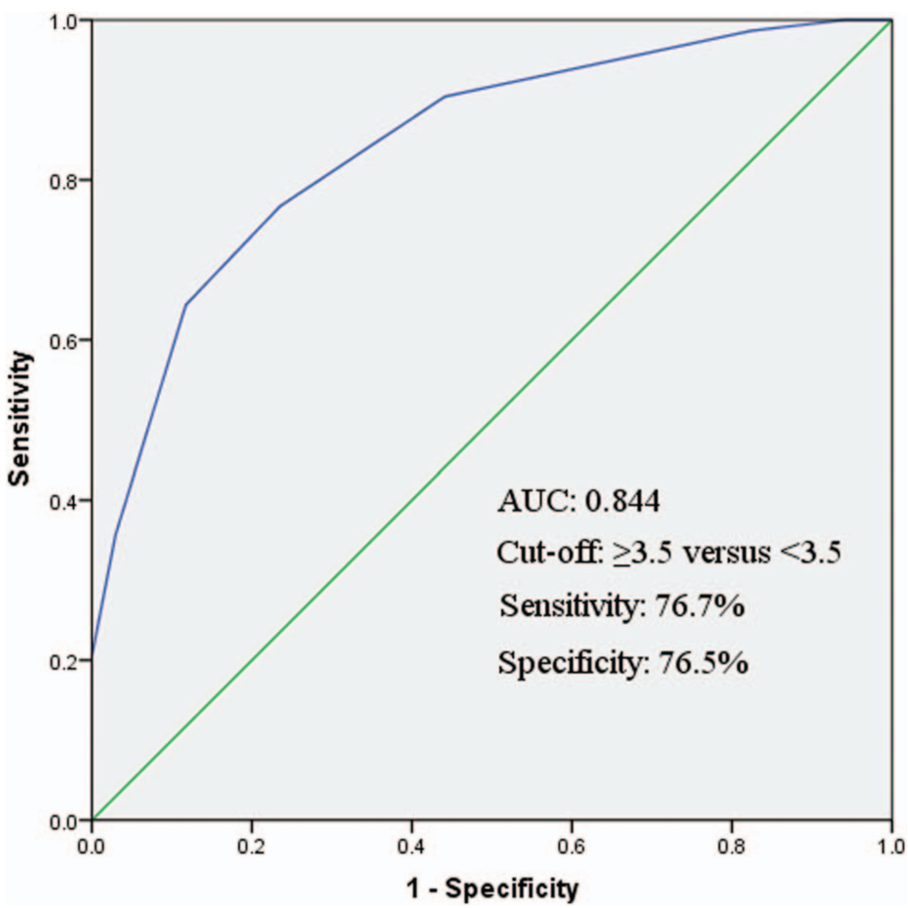

Figure 2. Receiver operating characteristic curve analysis for the differentiation of gastrointestinal stromal tumors from leiomyomas.

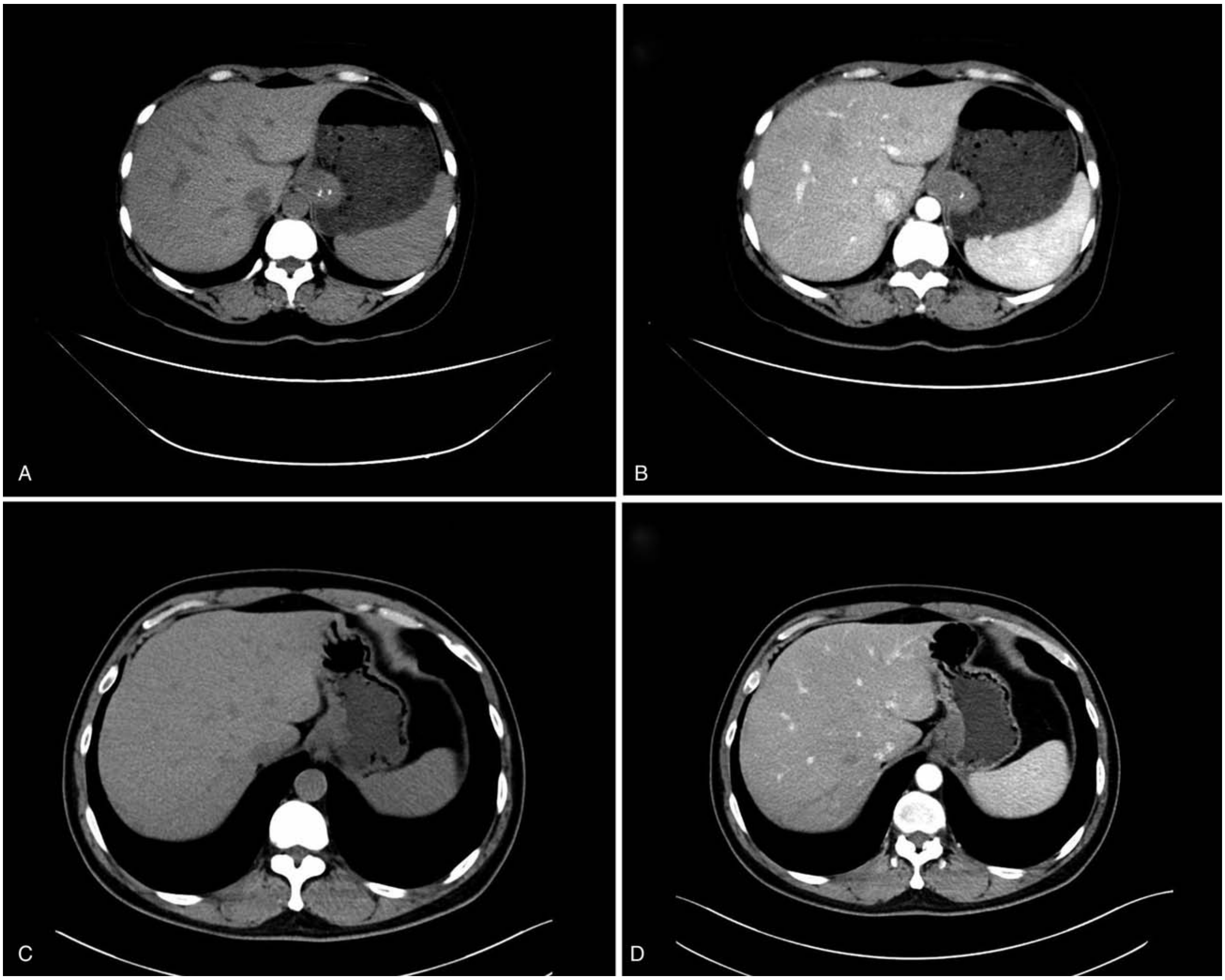

Figure 3. Leiomyoma in the esophagogastric junction. (A, B) 44-year-old woman with a 3.7-cm leiomyoma in the esophagogastric junction. CT images show homogeneous enhancement, low degree enhancement, lower CT attention value (58.1 HU, ≤69.2 HU), presence of calcification, absence of surface ulcer and intralesional low attention. A score of 0 was assigned. (C, D) 42-year-old man with a 3.6-cm leiomyoma in the esophagogastric junction. CT images show homogeneous enhancement, low degree enhancement, lower CT attention value (62.3 HU, ≤69.2 HU), absence of calcification, surface ulcer and intralesional low attention. A score of 1 was assigned.

3.3. Exploration of a novel scoring system for identifying GISTs

Considering the clinical and CT features involved in our study, there were 8 significant characteristics that could differentiate GISTs from leiomyomas: age >46.5 years, tumor long diameter >4.5 cm, heterogeneous enhancement, high degree enhancement, mean CT attenuation > 69.2 HU, presences of intralesional low attenuation and surface ulcer, absences of calcification. Each patient in this study was given 1 point for each significant feature, the total score of each patient was determined based on how many significant features he had. The optimal number of significant features differentiating leiomyomas and GISTs was explored using ROC analysis. We found that when all 8 significant features were used in combination, a highest AUC of 0.844 was achieved with an optimal cutoff value of 3.5 (sensitivity: 76.7%, specificity: 76.5%, Fig. 2). Representative CT images of leiomyomas and GIST are illustrated in Figs. 3 and 4.

4. Discussion

With the widespread use of endoscopic examination, the detection rate of upper gastrointestinal SETs has obviously increased. According to the literature, a majority of SETs are leiomyomas and GISTs confirmed by pathological examination. Leiomyomas are benign fibromuscular tumors originating from the inner circular layer of the muscularis propria and are mostly located in the distal third of the esophagus.[9] GISTs, the most common mesenchymal tumors of gastrointestinal tract, are potential malignancy arising from the intestinal cells of Cajal.[10] For patients with GISTs larger than 2 cm, resection is recommended according to the guidelines of the National Comprehensive Cancer Network.[11] For other benign SETs, tumor size >3 cm or symptomatic require surgical resection, as recommended by current guidelines.[12] The present methods available for these tumors include endoscopic resection, open or laparoscopic wedge resection.[13,14] However, tumors located in the EGJ still remain a stimulating challenge for the surgeon. Proximal or total gastrectomy instead of wedge resection

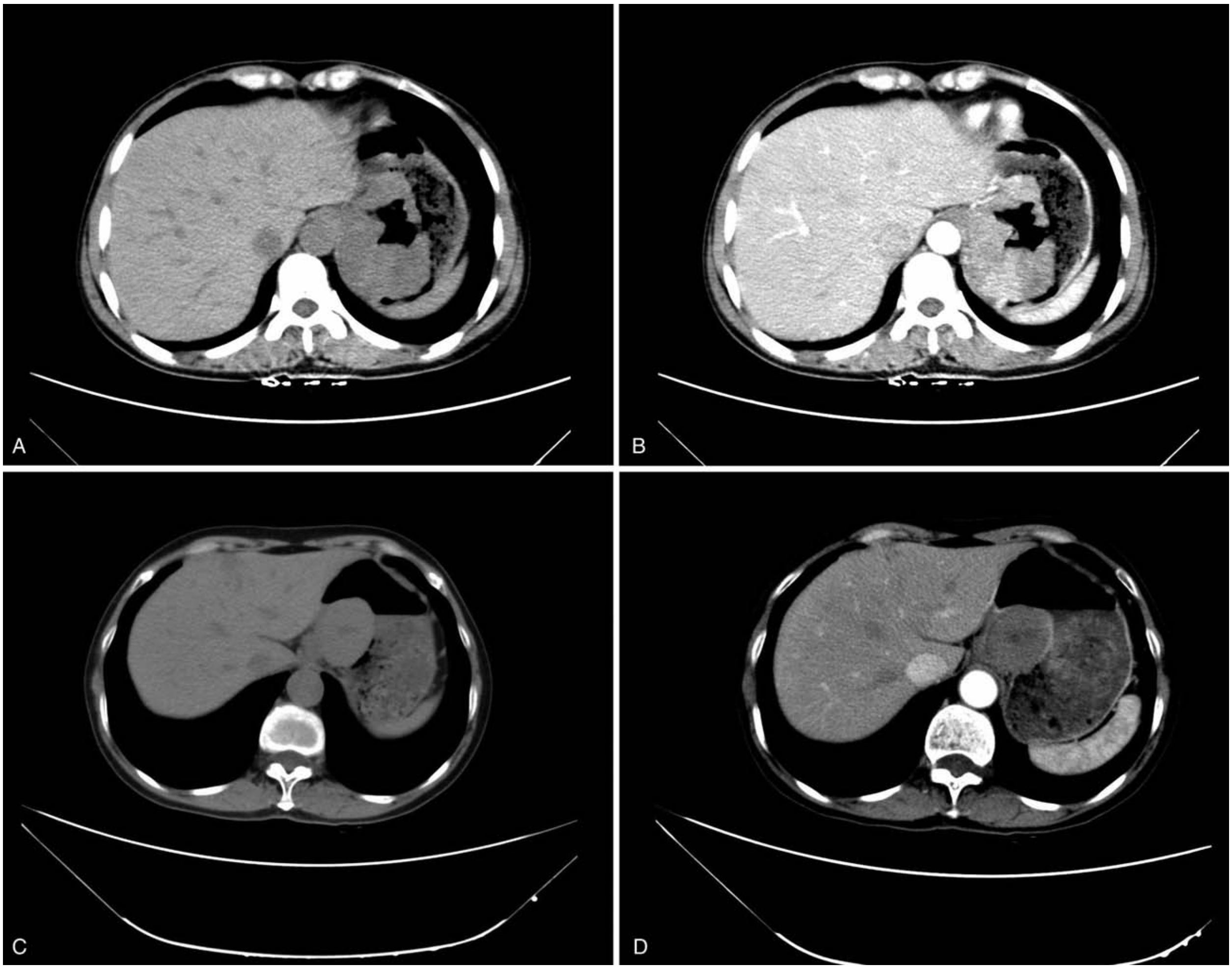

Figure 4. GIST in the esophagogastric junction. (A, B) 47-year-old man with an 8.5-cm GIST in the esophagogastric junction. CT images show heterogeneous enhancement, high degree enhancement, surface ulcer, higher CT attention value (135.7 HU, >69.2 HU), absence of calcification and intralesional low attention. A score of 7 was assigned. (C, D) 59-year-old woman with a 5-cm GIST in the esophagogastric junction. CT images show heterogeneous enhancement, high degree enhancement, intralesional low attention, lower CT attention value (67.8 HU, ≤69.2 HU), absence of calcification and surface ulcer. A score of 6 was assigned.

is typically chosen because of the potential stricture of gastroesophageal junction after surgery. In our study, 49.0% (24/49) of leiomyomas and 51.7% (45/87) of GISTs were treated with proximal gastrectomy. No statistically significant differences were found in resection range between GISTs and leiomyomas, even though leiomyomas are benign tumors. Partial or wedge resection, even proximal gastrectomy, is often chosen for GISTs located in such location, whereas benign leiomyomas can be treated with conservative therapy, enucleation, or tumor-everting resection, which could decrease the possibility of postoperative complications. Hence, exact preoperative differentiation between GISTs and leiomyomas may obviate the overtreatment of leiomyomas.

Our study indicates that 8 clinical and CT findings: older age (>46.5 years), tumor long diameter >4.5 cm, heterogeneous enhancement, high degree enhancement, mean CT attenuation > 69.2 HU, presences of intralesional low attenuation and surface ulcer, absence of calcification are significant features for GISTs in differentiation from leiomyomas. When all 8 significant features were used in combination using a scoring system, GISTs could be differentiated from leiomyomas with a relative high sensitivity (76.7%) and specificity (76.5%). However, there are still a small fraction of tumors could not be distinguished successfully in the preoperative setting. For symptomatic tumors or tumors with large size (>2 cm) in the EGJ, active surgical intervention is recommended in our study.

Our study results demonstrated that older age (>46.5 years) and larger long diameter (>4.5 cm) were more often observed in patients with GISTs than those with leiomyomas, which are concordant with those of previous studies.[7,15] In a single-center review of subepithelial esophagus tumors, the author found that patients with leiomyomas were younger than those with GISTs or leiomyosarcomas, and leiomyomas were smaller at presentation compared with GISTs and leiomyosarcomas.[15] Contrary to the study reported by Yang et al, the LD/SD ratio was not a significant differential CT feature between GISTs and leiomyomas in our study. Most of leiomyomas and GISTs in our study had a round or ovoid shape, which is in line with a previous study.[16]

In our study, the presence of surface ulcerations was more frequently appeared in GISTs compared to leiomyomas. Surface ulcerations were considered as the result of enlarging tumor restricting mucosal circulation, resulting in its ischemic and damage by gastric acidity.[17,18] In previous studies, the presence of surface ulcer was also regarded as a significant feature of GISTs more than of leiomyomas.[19] Contrary to surface ulcerations, the presence of calcification was commonly found in leiomyomas but was hardly seen in GISTs in our study, which has not been reported. This result differs from previous studies, in which the presence of calcification was not a significant differential CT feature between leiomyomas and GISTs.[7,8] However, we have a larger sample sizes compared to previous studies, and further studies are needed for confirmation.

Intralesional low attention and heterogeneous enhancement were more prevalent in GISTs than in leiomyomas in our study. Intralesional low attention was defined as the presence of intratumoral necrosis or degeneration, hemorrhage, or gas. In GISTs with malignant potential, intralesional low attention, and heterogenous enhancement can be explained by the mistuning of neovascularization with quick growth of tumor.[20,21] Conversely, these features rarely appeared in benign tumors, in which tumor growth rate is line with the neovascularization. Our study also demonstrated that high degree enhancement, and mean CT attention >69.2 HU are significant features to differentiate GISTs from leiomyomas. These results are in accordance with those of previous studies.[8,22,23] The high-grade enhancement in GISTs reveals richer blood supplies and vascularity of tumor, which reflects an aggressive tumor biology.[24]

Based on the significant clinical and CT features, a simple scoring method was established in our study. However, the sensitivity (76.7%) and specificity ((76.5%) of the present scoring method is not higher than that of a previous study, in which Liu et al [7] used 7 features to differentiate gastric GISTs from non-GISTs and got very high sensitivity (100%) and specificity (72%). Tumor location limited to the esophagogastric junction in our study may contribute to the condition. In addition, our study drew a relatively conservative conclusion although we incorporated a larger population than previous studies. This result suggests the limited differential ability of conventional CT characteristics, and a deep learning-based radiomics may be a better alterative technique and will be the future direction.

There are several limitations to our study. First, the number of GISTs and leiomyomas included in our study is different and patients who did not underwent tumor excision were excluded, which may lead to a certain selection bias. Second, our study included a small number of patients, although which incorporates a larger number than previous studies.

5. Conclusion

In conclusion, older age (>46.5 years), tumor long diameter >4.5 cm, heterogeneous enhancement, high degree enhancement, mean CT attenuation >69.2 HU, presences of intralesional low attenuation and surface ulcer, and absence of calcification are clinical and CT features highly suggestive of GISTs in differentiation from leiomyomas in the EGJ. When all these clinical and CT features are incorporated in combination using a scoring system, a higher sensitivity and positivity could be achieved for differentiating GISTs from leiomyomas in the EGJ.

Author contributions

Bo Zhang and Dan Cao proposed the idea and conceptualization. Xiaonan Yin and Yuan Yin performed data analysis, experimentation and scientific discussions, and prepared the original draft. Xijiao Liu and Caiwei Yang performed data analysis and scientific discussions. Xin Chen, Chaoyong Shen and Zhixin Chen validated the findings and helped in revision and organization of the paper.

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