

A new classification of gastric submucosal tumors under EUS based on blood flow signals

Huikai Li, Yujie Feng, Xiuxue Feng, Fei Gao, Enqiang Linghu*

Abstract

Background and Objectives: Once gastrointestinal stromal tumor is suspected to have a malignant possibility, prompt medical intervention should be initiated. Neovascularization plays a significant role in the initiation and progressing of tumors. This study aims to investigate the morphology and distribution of blood vessels in submucosal tumors (SMTs), thereby providing theoretical support for vascular-targeted therapies.

Methods: This study enrolled patients who underwent EUS at the First Medical Center of PLA General Hospital and stored images in the medical system, which were considered as SMTs with a definitive pathological diagnosis. The proportion of various blood flow signal under EUS was counted, and the correlation between blood flow signal and tumor pathology, ultrasonic features, location, and other factors was analyzed.

Results: The overall occurrence rate of blood flow signal in SMTs was 69.4%. Appearance of blood flow signal of intratumor was 38.8%. Among them, spot-like, stripe-like, and patches-like were 26.5%, 10.2%, and 2.0%, respectively. As for peritumoral, the occurrence rate was 46.9% and was 36.7%, 6.1%, and 4.1% of the above 3 blood flow signals. The appearance of blood flow signals showed a significant correlation with the long diameter of the tumor ($P = 0.042$; odds ratio, 1.142; 95% confidence interval, 1.005–1.297), whereas no apparent correlations were observed between tumor types, presence of anechoic area, boundary, origin layer, and growth patterns.

Conclusions: We propose a new EUS classification of gastric SMTs based on blood flow morphology, revealing a significantly high occurrence rate of blood flow signals in these tumors.

Key words: Blood flow signal; Color Doppler flow imaging (CDFI) mode; Endoscopy ultrasound; GIST; SMT; super-minimally invasive surgery (SMIS); Vascular therapy

Introduction

Gastric submucosal tumors (SMTs) mainly include gastrointestinal stromal tumor (GIST), leiomyoma, schwannoma, and many other tumors.^[1,2] Once it is found that GISTs have a high malignant potential or are at risk of metastasis, medical intervention should be actively pursued.^[1,3–7] The first-line treatment is surgery or endoscopic submucosal dissection. For patients with unresectable tumors or advanced metastasis, targeted drugs (imatinib) are recommended.^[1,8] However, imatinib has multiple systemic adverse reactions such as intratumoral bleeding, diarrhea, anemia, and gastrointestinal disturbances.^[8] Long-term use of imatinib can lead to acquired resistance, which can occur in 50% to 70% patients within 2 or 3 years.^[8–11] However, second-line drugs such as sunitinib have only been recommended for the treatment of drug-resistant patients in certain countries or regions, and research on these treatments remains relatively limited.^[8,9,12–17] In conclusion, there are currently

few treatment options for advanced or relapsed GISTs, and it is necessary to develop some new therapeutic regimen.

Neovascularization plays an important role in tumor development, invasion, and metastasis.^[3] Embolization or chemical ablation of the vessels may suppress tumor growth.^[1,18–20] Vascular treatment of GISTs mainly concentrates on the hemostasis of GISTs' bleeding nowadays.^[20] There are a few systematic studies on the way to inhibit tumor growth by targeting tumor blood vessels.^[21] This study aims to investigate the vascular distribution within and around the SMT, which may provide theoretical support for further exploration of vascular therapy.

Patients and Methods

Patients

Cases were retrospectively collected in the First Medical Center of PLA General Hospital from January 1, 2018, to December 31, 2023. Linear or radial EUS was performed, and SMTs were found. Then, patients underwent surgery or endoscopic submucosal dissection, and pathological results were diagnosed by 2 pathologists in our hospital. Patients with color Doppler flow imaging (CDFI) images who were pathologically diagnosed as GISTs, leiomyomas, or schwannomas were included in our study.

Pathologically diagnosed as adenocarcinoma, squamous cell carcinoma, signet ring cell carcinoma, metastatic tumor, and neuroendocrine tumor were excluded. Cases of ectopic pancreas and lipoma diagnosed by

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Endoscopic Ultrasound (2025) 14:4

Received: 24 January 2025; **Accepted:** 24 July 2025.

Published online: 5 September 2025

<http://dx.doi.org/10.1097/eus.0000000000000142>

EUS, cases that underwent only EUS without CDFI or images, and cases without complete case data were excluded. Forty-nine patients were included in the study eventually.

This study received approval from the Ethics Institution of the First Medical Center of the PLA General Hospital (approval no. S2024-780-01). Informed consent was not required owing to the retrospective nature of the study.

EUS examination

Linear (GF-UCT260; Olympus, Tokyo, Japan) or radial (GF-UE260; Olympus) EUS was used for the examination. The frequency was determined by the operator based on the requirements; whether anesthesia was administered or not was also acceptable.

Images were exported from the hospital's database, and the one with the largest tumor cross-section was selected for evaluating tumor size, boundary, echo, etc. CDFI mode was used to evaluate the intratumor and peritumor blood vessels.

Statistical analysis

All statistical analyses were performed by using SPSS version 25.0 (IBM SPSS Statistics; IBM Corporation, Armonk, NY, USA). Continuous data are expressed as the mean $\pm$ SD or quartile, and categorical data are displayed as frequency (no.) and percentage (%). Correlations involving

continuous data were evaluated using the Student *t* test. Discontinuous data were evaluated using χ^2 test or Fisher exact test. Further analysis was conducted to evaluate whether there was a correlation between the blood flow signals in and around the tumor and other related factors. $P < 0.05$ was considered statistically significant.

Definition

The study used EUS CDFI mode to visualize blood flow signals within and surrounding the tumor. Blood flow signals were categorized into 3 types: spot-like, stripe-like, and patches-like, based on the endoscopic morphology. Accordingly, we have proposed a classification system for gastric SMTs based on the observed distribution of blood flow signals during EUS. This categorization scheme classifies SMTs into 4 types: type 0, type I, type II, and type III (Figures 1–3).

Type 0 was defined as the absence of blood flow signals within and/or around the tumor in the CDFI mode of EUS. Type I is characterized by a spotted distribution of blood flow signals within and/or around the tumor in CDFI mode of EUS, whereas type II exhibits a striped distribution pattern. Lastly, type III displays a patchy distribution pattern.

Results

The general clinical characteristics of the patients involved in this study are summarized in Table 1. The age of enrolled patients

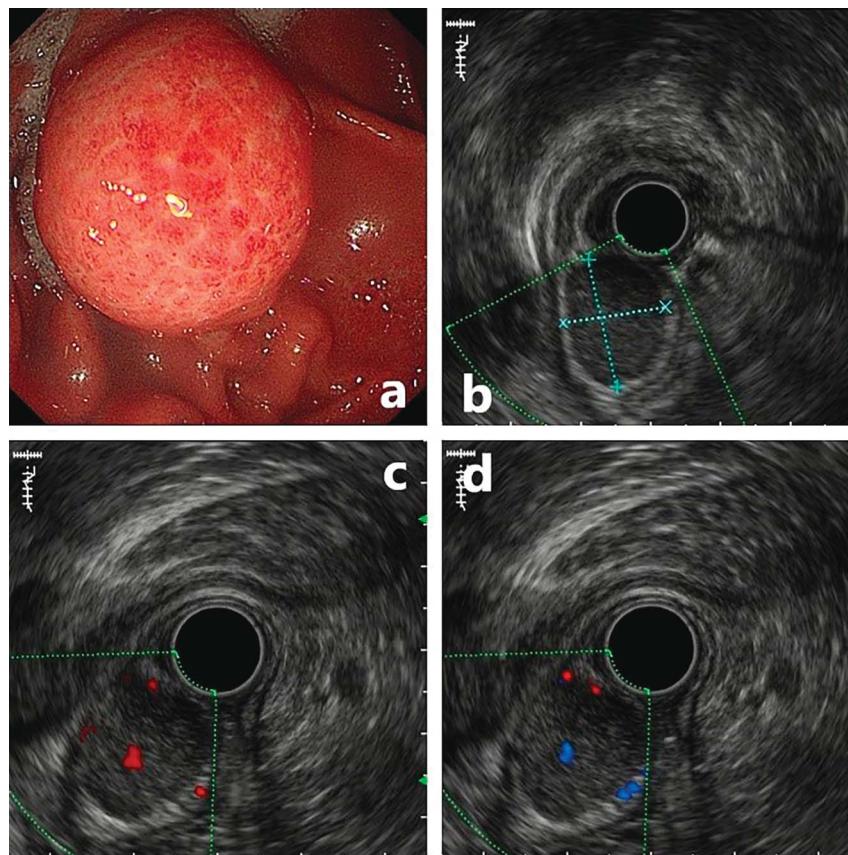


Figure 1. Spot-like (type I). A, A submucosal mass was observed in the anterior wall of the stomach body, and the surface mucosa was hyperemic and erythematous. B, Linear ultrasound showed that the lesion was hypoechoic, with irregular anechoic areas, clear boundaries, and regular geometric shape and originated from the muscularis propria layer, and the size was about 18 mm $\times$ 14 mm. C and D, Spots-like blood flow signals could be seen in and around the tumor under CDFI. After moving the ultrasound probe, the 2 blood flow signals still existed in the corresponding parts of the tumor.

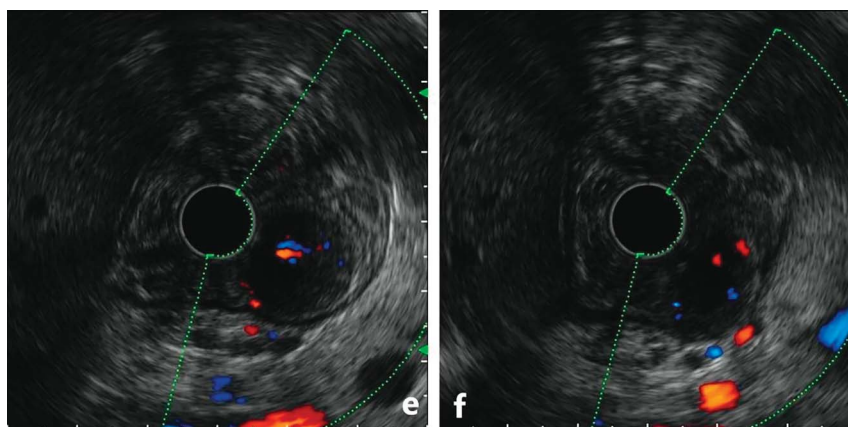


Figure 2. Stripe-like (type II). E, CDFI showed stripe-like blood flow signals in the tumor, and spot-like blood flow signals around the tumor. F, CDFI showed stripe-like blood flow signals around the tumor.

was 54.82 ± 10.41 years, and the body mass index was $25.09 \pm 3.01 \text{ kg/m}^2$. There were slightly more female patients than male patients, and the majority of patients (65.3%) were discovered during routine examinations with no obvious clinical symptoms. Ten patients (20.4%) had diabetes mellitus, 19 patients (38.8%) had hypertension, and 10 patients had 2 or more diseases simultaneously. Among the patients included in this study, tumors were most common in the fundus and body of the stomach, and 1 patient had undergone subtotal gastrectomy for gastric cancer. Most tumors originate from the muscularis propria of the gastric wall with a clear boundary, and half of the tumors have no regular geometry. The mainly growth pattern observed was endoluminal (42.9%), whereas the surface mucosa appeared mostly normal, with only a portion of the mucosa (6 [12.2%]) covered with ulceration and some areas showing red spots or swelling (3 [6.1%]). The intratumoral echoes mainly presented as homogenous hypoecho, whereas some displayed heterogeneous features characterized by the presence of hyperechoic regions, moderate echo regions, hypoechoic regions, and various mixed echo regions. Finally, after pathological diagnosis, 32 cases were definitely diagnosed as GISTs, whereas 16 cases were identified as leiomyomas, and 1 case was schwannoma. When comparing the baseline and endoscopic characteristics of GISTs

and leiomyomas, no statistically significant differences were observed between the 2 groups (Table 2).

The overall occurrence rate of blood flow signal in SMT was 69.4% (Table 3). The presence of intratumoral blood flow signal was observed in 38.8%, with spot-like, stripe-like, and patches-like patterns accounting for 26.5%, 10.2%, and 2.0% respectively. Regarding peritumoral blood flow signals, the occurrence rate was found to be 46.9%, with proportions of 36.7%, 6.1%, and 4.1% for the aforementioned 3 patterns.

The Doppler signals of blood vessels within or around the tumor reviewed by CDFI mode should partially reflect distribution of the vessels in the counterpart of the tumor. When CDFI mode showed blood flow signal within or around the tumor, we could always find blood vessels in the corresponding part of the tumor. For example, our findings revealed the presence of spots-like blood flow signals surrounding the tumor; during Endoscopic Submucosal Dissection resection, corresponding blood vessels were observed in the peritumoral region. There was a clear correlation between these 2 observations (Figure 4).

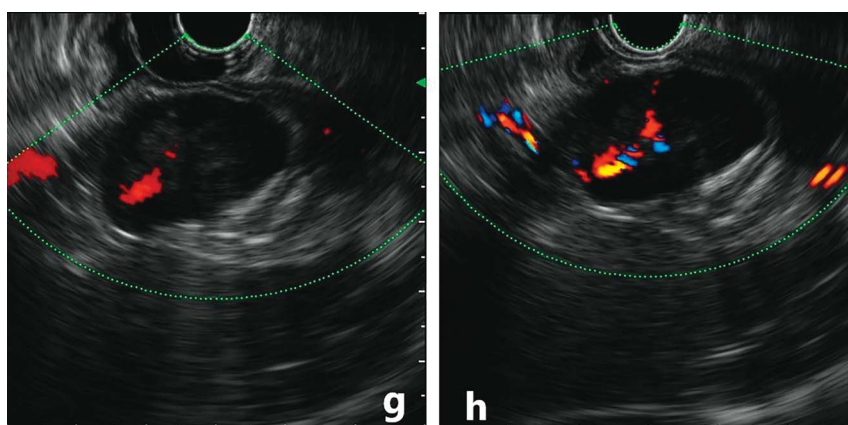


Figure 3. Patches-like (type III). G and H, A patches-like blood flow signal intratumor could be seen using CDFI mode, and the presence of this blood flow signal persisted even after repositioning the probe.

Table 1**Clinical and EUS characteristics of the 49 patients.**

Age, yr	54.82 ± 10.41
Body mass index, kg/m ²	25.09 ± 3.01
	No. (%)
Gender	
Male	23 (46.9)
Female	26 (53.1)
Chief complaint	
No clinical symptom	32 (65.3)
Abdominal discomfort	11 (22.4)
Abdominal pain	3 (6.1)
Gastrointestinal bleeding	2 (4.1)
Obstruction	1 (2.0)
Location	
Fundus	21 (42.9)
Cardia	7 (14.3)
Body	15 (30.6)
Antrum	5 (10.2)
Remnant stomach	1 (2.0)
Layer	
Muscularis propria	43 (87.8)
Submucosa	6 (12.2)
Ulcer	9 (18.3)
Growth patterns	
Intra-luminal	21 (42.9)
Extra-luminal	17 (34.7)
Duplex	11 (22.4)
Long diameters	19.7 [13.4, 28.8]
Anechoic areas	2 (4.1)
Echogenicity	
Homogenous	26 (53.1)
Heterogeneous	
Hyperechoic region	8 (16.3)
Isoechoic region	2 (4.1)
Hypoechoic region	9 (18.4)
Mixed echo region	4 (8.2)
Clear boundary	44 (89.8)
Regular boundary	25 (51.0)
Final diagnosis	
Endoscopic resection	37 (75.5)
Surgery	12 (24.5)
Pathological	
GIST	32 (65.3)
Leiomyoma	16 (32.7)
Schwannoma	1 (2.0)

Further χ^2 testing revealed no statistically significant difference between the pathological types of SMTs and the occurrence rate of blood flow signal under the CDFI mode ($P = 0.186$). There was no statistically significant difference in the types of blood flow signals within the tumor ($P = 0.29$) or peritumoral region ($P = 0.475$) across different pathological types. The overall occurrence rate of blood flow signal in GIST was 75%. Specifically, the incidence rates of spot-like and stripe-like within the tumor were 31.3% and 9.4%, respectively. In the peritumoral region, the incidence rates of spot-like, stripe-like, and patches-like were 40.6%, 9.4%, and 3.1%, respectively.

Further analysis showed that the presence of blood flow signals under EUS was only related to the long diameter of the tumor. Specifically,

Table 2**Comparison of baseline and EUS features between GIST and leiomyoma.**

Case	GIST (<i>n</i> = 32)	Leiomyoma (<i>n</i> = 16)	<i>P</i>
Age, yr	57 [49, 63]	49 [43, 58]	0.072
Gender			0.413
Male	16	10	
Female	16	6	
Location			0.003
Fundus	13	8	
Cardia	1	6	
Body	13	2	
Antrum	4	—	
Remnant stomach	1	—	
Layer			0.355
Muscularis propria	27	15	
Submucosa	5	1	
Ulcer	6	2	0.584
Growth patterns			0.106
Endoluminal	11	10	
Extraluminal	12	5	
Duplex	9	1	
Long diameters	19.5 [13.3, 28]	20.1 [13, 32.3]	0.928
Anechoic areas	1	1	0.610
Echogenicity			0.413
Homogenous	16	10	
Heterogeneous	16	6	
Clear boundary	29	14	0.738
Regular boundary	20	5	0.041
Mitotic index	3 [2, 5]	—	—

when the long diameter of the tumor was more than 23 mm (Figure 5), the occurrence rate of blood flow signals would be markedly increased (area under the curve = 0.750, cutoff = 23 mm). There was no significant correlation between the presence of blood flow signals and the tumor location, original layer, pathological classification, growth pattern, tumor boundary, tumor echogenicity, or anechoic areas (Table 4).

The mitotic index is a critical pathological factor in the evaluation of the malignant potential of GIST. No significant correlation was observed between the mitotic index and blood flow signal in GIST, as determined by the Spearman rank correlation test ($r = 0.028$, $P = 0.88$). Surface ulceration demonstrates a certain degree of significance in assessing the malignant potential of GIST. Although

Table 3**Appearance of blood flow signals of intratumor and peritumor.**

Intratumoral	<i>n</i> = 19 (38.8%)
Spot-like	13
Stripe-like	5
Patches-like	1
Peritumoral	<i>n</i> = 23 (46.9%)
Spot-like	18
Stripe-like	3
Patches-like	2
Total	34 (69.4%)*

*When the blood flow signals are visible under CDFI, the case is calculated.

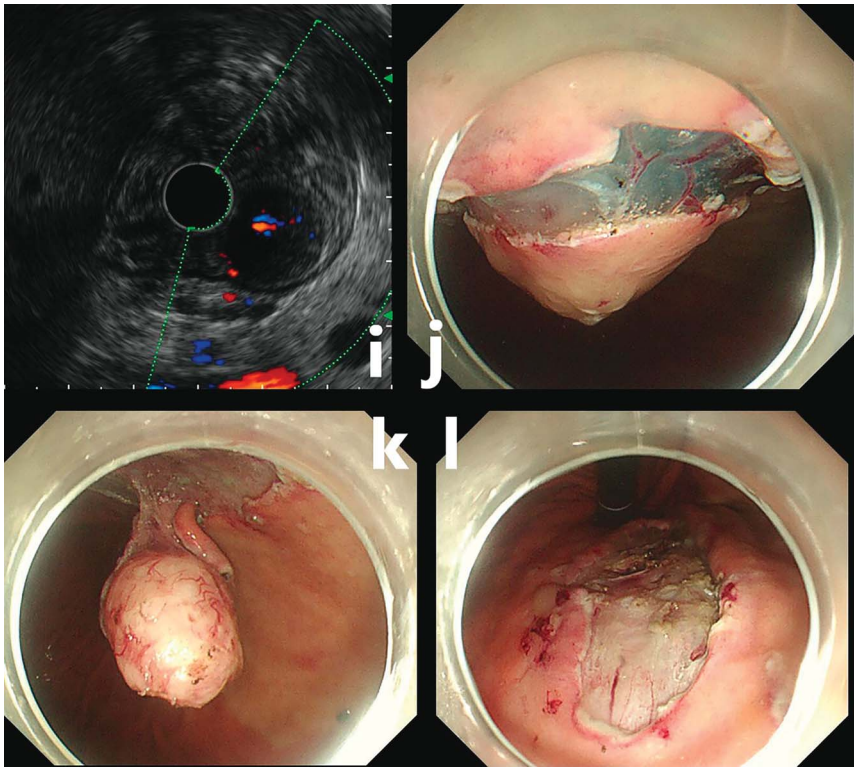


Figure 4. I, Radial EUS revealed multiple spots-like blood flow signals around the tumor and stripe-like blood flow signals within the tumor. J, The ESD processing found multiple blood vessels surrounding the tumor. K, A tumor completed resected by ESD. L, The wound surface after dissection of the tumor.

univariate analysis revealed a statistically significant association between blood flow signal and surface ulceration ($P = 0.027$), this correlation was no longer observed in multivariate analysis.

Further subgroup analysis based on the morphology of blood flow signals revealed that there was no significant correlation between the presence of 3 types of blood flow signals within the tumor and either the long diameter of the tumor or the pathological classification. This suggests that although the probability of blood vessel appearance increases with tumor volume, the morphology of blood flow does not vary significantly with increasing tumor size. This may be attributed to the complex pathways of tumor neovascularization and the irregular shapes of these vessels.

Discussion

The findings of this study showed a high occurrence rate of blood flow signals both within and surrounding GIST during EUS examination. Based on the types of blood flow, we proposed a new EUS classification system for gastric SMT. Additionally, our results indicated that the presence of blood flow signals was correlated solely with tumor diameter, whereas no significant associations were observed with the types of blood flow signals, the layer of origin, or the endoscopic features identified by EUS.

Previous studies have confirmed a significant correlation between tumor volume and malignant potential.^[22–25] Specifically, as the diameter of stromal tumors increases, their malignant potential also rises. This study found that both intratumoral and peritumoral vascular occurrences increase with larger tumor diameters, concurrently enhancing the

malignant potential of GISTs. These findings provide valuable clinical evidences for further medical interventions. Current guidelines recommend that patients with GISTs >2 cm should undergo further medical intervention.^[1] Our study found that when the long diameter of the tumor was

Table 4
Univariate and multivariate analysis of the factors and the occurrence of blood flow signal.

	Univariate analysis	Multivariate analysis	
	<i>P</i>	<i>P</i>	Odds ratio (95% confidence interval)
Gender	0.980	—	—
Age	0.615	—	—
Body mass index	0.654	—	—
Location	0.433	—	—
Long diameter	0.010	0.042	1.142 (1.005–1.297)
Layer	0.429	0.744	0.642 (0.045–9.186)
Ulcer	0.027	0.998	—
Growth patterns	0.143	0.671	—
Intraluminal	—	0.777	1.305 (0.206–8.254)
Duplex	—	0.372	3.427 (0.229–51.265)
Anechoic areas	0.338	0.999	—
Echogenicity	0.980	—	—
Clear boundary	0.631	0.058	0.031 (0.001–1.130)
Regular boundary	0.146	0.183	5.441 (0.450–65.778)
Pathological	0.330	0.224	—
GIST	—	0.084	—
Schwannoma	—	1.000	—

Boldface indicates $P < 0.05$.

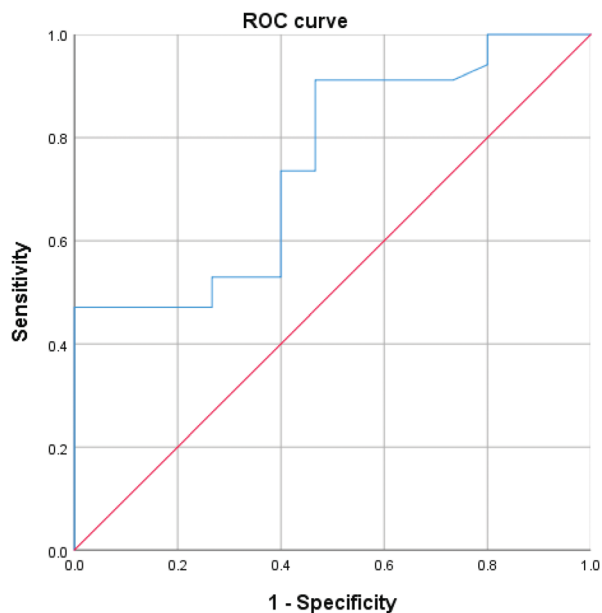


Figure 5. Receiver operating characteristic curve of long diameter and blood signals.

larger than 23 mm, the occurrence rate of blood vessels was significantly higher. The findings of this study are consistent with existing guidelines, supporting the feasibility and necessity of further vascular treatment.

Currently, surgical or endoscopic resection is considered the primary treatment for resectable GISTs.^[22,26] However, in clinical practice, a significant number of patients are either ineligible for surgery or refuse to surgery due to severe cardiac conditions or other systemic diseases. For these patients, while targeted drugs such as imatinib are available, they often present with numerous systemic and multiorgan adverse reactions, leading many patients to discontinue treatment due to intolerable side effects.^[22,26,27] Patients who have been on long-term imatinib therapy often develop acquired resistance, and certain GISTs with specific genotypes exhibit innate immunity to imatinib.^[9,11,16,22,28] Some studies have reported that combining immune checkpoint inhibitors (such as HPS90 or PD-1/PD-L1) with imatinib or other TKIs (like sunitinib) for the treatment of advanced or relapsed GIST that are resistant to drugs can yield promising results.^[16,17,29] However, there is significant variability in efficacy among patients, and adverse reactions are also common.^[15–17,28,29] Therefore, it is imperative to explore new therapeutic strategies for these patients mentioned above.

Neovascularization plays a crucial role in the growth and progression of malignant tumors.^[3,15] Research has demonstrated that the presence of irregular blood vessels in GIST frequently signifies a higher malignant potential.^[7,25,30,31] EUS-guided vascular embolization is an effective treatment for active bleeding from GIST, irrespective of lesion size. The absence of vascular Doppler ultrasound signal following endoscopic intervention is indicative of a decreased risk of tumor rebleeding.^[18,21] EUS-guided chemical ablation or tumor radioablation has also been reported.^[19,20,32,33] These studies show that, despite the presence of neovascularization and irregular blood vessels in GIST, the vascular supply is not intricate, with the tumor likely being supplied by one or several pre-dominant arteries.

Once the vascular distribution about the tumor is clearly identified, we can proceed to analyze the primary blood supply of the tumor.^[18,21,30,34] This will enable us to use further measures such as interventional embolization, alcohol injection, and radiation-induced ablation to effectively cut off the blood supply, thereby inhibiting tumor growth to a certain extent and potentially inducing tumor apoptosis. We think that GISTs, when exhibiting appropriate blood flow signal under CDFI mode, may consider further vascular intervention. Following treatment, the absence of blood flow signal detected by CDFI could indicate successful obstruction of blood flow, suggesting technical success in angiotherapy and potentially leading to a more favorable prognosis.

Recent studies have reported that there is no significant difference in the postoperative recurrence rate between R1 and R0 resections of GISTs.^[10,35] For patients with advanced tumors, local surgery might also provide a certain benefit.^[10,36,37] Additionally, a large-scale, long-term follow-up study demonstrated that recurrence or metastasis of GIST is rare, suggesting that local resection or tumor excision alone may be sufficient for curative intent.^[35,38] Therefore, it is necessary to conduct a thorough evaluation of the risks and benefits of surgery.^[10,18,31,37] In cases where the risks surpass the potential benefits, vascular treatment may be considered as an alternative therapy and may be regarded as comparably effective to local resection to a certain extent. Furthermore, the detection rate, diagnostic sensitivity, and specificity of gastric stromal tumors have significantly improved due to advancements in EUS technology, enhanced puncture techniques, improved equipment, and the use of contrast-enhanced endoscopy ultrasound, EUS-elastography, and other imaging techniques.^[25,30,31,39–43] As early as 2009, a study indicated that more than 60% of endoscopists were able to diagnose GIST based on endoscopic findings when the results of pathological examination were insufficient for an accurate diagnosis.^[44] This suggests that complete resection and subsequent pathological analysis may not always be necessary. For patients with unresectable or recurrent stromal tumors, as well as those at high surgical risk who decline surgery, vascular therapy provides a new clinical treatment option. We tentatively propose that vascular therapy may be used for metastatic or recurrent GISTs with appropriate blood flow signal under EUS. Further resection may be considered if a reduction in tumor size is observed after vascular therapy. Super-minimally invasive surgery may have more advantages than traditional surgery for the resection of GIST in these patients.^[45–49] We believed that vascular therapy would perhaps offer patients the opportunity to undergo further super-minimally invasive surgery resection.

However, vascular therapy for GIST remains in the clinical trial phase, necessitating meticulous patient selection and comprehensive preoperative evaluation. When EUS evaluation indicates sparse blood flow signals, vascular therapy should be considered with caution. This approach can address the needs of a subset of patients who are ineligible for or decline surgery but require active medical intervention. This study is a single-center, descriptive, retrospective study, without standardized surgical protocols, and the sample size is relatively small. To validate the reliability and accuracy of these findings, further multicenter studies, prospective cohort studies, or randomized controlled trials (RCTs) are warranted. Additionally, it is particularly difficult to avoid inherent biases such as selection bias and recall bias, which are common in retrospective studies.

The findings of this study revealed that the overall occurrence rate of blood flow signal in GIST under EUS was 69.4%. Specifically,

the occurrence rate of intratumoral blood flow signals was 38.8%, whereas the occurrence rate of peritumoral blood flow signals was 46.9%. The presence of blood flow signal was found to be related solely with the long diameter of the tumor. Vascular therapy represents a viable treatment option for GIST, offering a new clinical therapy for patients experiencing recurrence, metastasis, or unresectable GIST, as well as those who have failed standard targeted drug therapies or are unable to tolerate the associated side effects.

Conclusions

In this study, we introduce a new EUS-based classification system for gastric SMTs based on blood flow signal. This may facilitate future research on vascular therapy, embolization, or chemical ablation techniques aimed at inhibiting tumor growth.

Author Contributions

Huikai Li and Yujie Feng contributed equally to this paper. Huikai Li and Yujie Feng designed the research and were primarily completed the manuscript. Xiuxue Feng and Fei Gao conducted the research. Yujie Feng and Fei Gao analyzed data and performed statistical analysis. Enqiang Linghu reviewed the manuscript meticulously and approved the final version for publication. All authors reviewed and approved the final manuscript for submission.

Ethical Approval

This study was approved by the Ethics Institution of the First Medical Center of the PLA General Hospital (approval no. S2024-780-01).

Informed Consent

Informed consent was not required owing to the retrospective nature of the study.

Conflict of interest

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Source of Funding

This study was supported by the National Key Research and Development Program of China (2022YFC2503604).

Data Availability Statement

Not applicable.

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