Gastrointestinal Stromal Tumors: How to Increase the Preoperative Endoscopic Ultrasonography Diagnostic Rate

CME Credits

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A subepithelial tumor (SET) was accidentally found at the gastric cardia in a 27-year-old man, who underwent a health examination [Figure 1]. Endoscopic ultrasonography (EUS) discovered a homogeneous hypoechoic gastrointestinal stromal tumor (GIST) approximately 3.8 cm in size growing from muscularis propria [Figure 2]. Since there was no apparent metastasis, and guidelines call for the surgical removal of GISTs over 2 cm in size,[1] the patient received endoscopic submucosal dissection (ESD) last year. A 6 cm tumor was discovered during ESD, but the postoperative pathology report not as an GIST, but as a gastric leiomyoma.

GISTs are the most common SETs in the stomach. About 10%–30% of GISTs have malignant potential and require surgical removal.[2] As a consequence, preoperative prediction and diagnosis are especially important. For instance, the present case underwent ESD; if such a case had been discovered in the past, the patient would not have received this type of microsurgery and would likely have lost most of his stomach at the age of 27 years.

However, can gastric stromal tumors actually be diagnosed before surgery? Conventional EUS relies on tumor size, shape, location, blood vessel distribution, and the echogenicity for diagnosis [Table 1], but it is still extremely difficult to distinguish benign from malignant tumors, and especially difficult to distinguish GISTs from leiomyomas.

Under EUS examination, most GISTs appear as hypoechoic tumors with irregular borders growing from the muscularis propria, while leiomyomas are benign hypoechoic tumors with irregular borders growing from the muscularis mucosa or muscularis propria. A retrospective study of 226 patients with gastric SET found that as many as 48.3% of leiomyomas are located on the muscularis propria, and 9.1% of GISTs are located on the muscularis mucosa.[3] Among gastric SETs removed via ESD in our hospital last year, less than one-half of the final pathology diagnoses of GIST were consistent with the preoperative EUS diagnoses. Further, EUS diagnosis had indicated that more than one-half of leiomyomas were located on the muscularis propria. These findings indicated a lower than expected level of accuracy of the preoperative diagnoses. However, preoperatively distinguishing GISTs from leiomyomas is extremely difficult, and even biopsies cannot achieve an excellent diagnostic accuracy.[4]

Many studies have sought to analyze the ultrasound characteristics of each type of SET in an effort to avoid unnecessary surgeries by accurately distinguishing GISTs with possibly malignant tendencies from benign tumors. A study analyzing the EUS characteristics of gastric SETs in 53 patients found that the following were relatively indicative of GISTs: Heterogeneous, hyperenhancement, hyperechoic spots within tumors and marginal halos around tumors. When two of these four types of characteristics are present, the sensitivity and specificity of GIST diagnosis reached 89.1% and 85.7%, respectively.[4] In addition, scholars have also designed a scoring system based on SET location, echogenicity, shape, and the layer of the gastric wall in which the tumor is located. While this scoring system has a diagnostic sensitivity and specificity for GIST of only 75.8% and 85.4%, respectively, it is a useful reference indicator.[3]

Even when we know the most common characteristics of GISTs under EUS examination, interpreting EUS results still depends on the operator's subjective judgment. Scholars have therefore sought to use digital image analysis software to objectively assess tumor features under EUS. After the standardization of EUS images, this software can analyze the brightness of image features, including overall mean tumor brightness (T_{mean}) and

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Table 1: Characteristics of commonly seen digestive tract subepithelial tumors

	Common locations	Typical distribution under EUS examination	Typical presentation under EUS examination
GIST	Stomach body, fundus, gastric cardia, duodenum, small intestine, large intestine, etc.	Muscularis propria	Homogeneous, hypoechoic, clear margin
Leiomyoma	Esophagus, gastric cardia	Muscularis propria Submucosa Muscularis mucosa	Homogeneous hypoechoic, clear margin
Lipoma	Antrum, duodenum	Submucosa	Homogeneous, hyperechoic, smooth margin
Carcinoid tumor	Stomach, rectum, duodenum	Muscularis mucosa Submucosa	Homogeneous, hypoechoic, smooth margin
Ectopic pancreas	Antrum	Muscularis mucosa Submucosa Muscularis propria	Heterogeneous, hypoechoic, unclear margin
Cysts	All locations	Submucosa	No echo, round or oval
Varices	Esophagus, stomach, duodenum, rectum	Muscularis mucosa Submucosa	No echo

GST: Gastrointestinal stromal tumor, EUS: Endoscopic ultrasonography

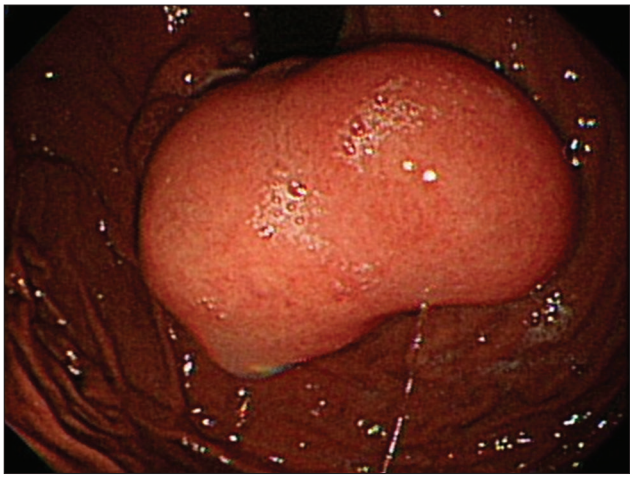

Figure 1: A subepithelial tumor approximately 3 cm in size growing on the gastric cardia

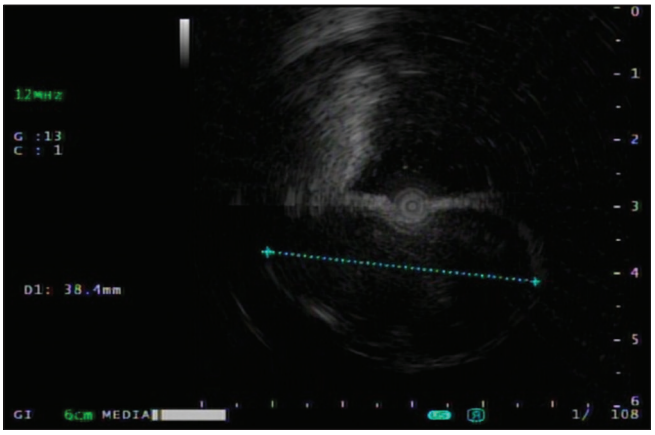

Figure 2: A homogeneous low-echo subepithelial tumor approximately 3.8 cm in size growing from the muscularis propria; diagnosed as a gastrointestinal stromal tumor under endoscopic ultrasonography examination

the variation in brightness within a tumor (T_{SD}) [Figure 3].[4] Analysis of 65 patients revealed that GISTs have a relatively high T_{mean} and T_{SD} compared with other benign tumors, and if T_{mean} is set at 65 and T_{SD} is set at 75, a diagnostic sensitivity and specificity of 94% and 80%, respectively, a positive prediction rate of 94%, a negative prediction rate of 80%, and a diagnostic accuracy of 90.8% can be achieved.[5]

Ultrasound elastography, which is commonly used for examination of the liver, can also be used to assess SETs. A prospective assessment of 25 patients conducted by Japanese scholars used the Giovannini classification method to assess tumor elasticity, and then compared these results with the final biopsy pathology reports. These scholars discovered that the GISTs of nine patients uniformly had higher assessment scores than other SETs, which suggests that GISTs have greater hardness than other types of SETs.[6] However, a German study issued the following year failed to support this conclusion, finding that leiomyomas appeared to have high hardness under ultrasound elastography examination, which led to the conclusion that this method cannot be used to distinguish leiomyomas and GISTs.[7]

Another tool that can be used to boost the SET diagnostic rate is contrast-enhanced EUS (CE-EUS). In CE-EUS, tiny bubbles are first injected into the bloodstream; after the microbubbles have reached the target tissue, the increased ultrasound reflection from the bubble interface enhances the echo signal.[8] Compared with conventional ultrasound, CE-EUS offers dynamic, real-time, and more detailed imaging. In addition, the contrast agent used has fewer side effects and less hepatorenal toxicity than conventional computed tomography contrast agents. While relatively extensive clinical experience has been accumulated and many research reports issued concerning the application of CE-EUS in diseases of the digestive tract and liver, in Europe this method is widely applied to diagnose and assess diseases of the pancreas, biliary system, and gastrointestinal tract.

GISTs typically appear as hyperenhanced tumors under CEEUS; approximately 90% of GISTs have rapid enhancement and approximately 80% have rapid washout characteristic.[9] A study involving 62 patients claimed that CEEUS can correctly distinguish GISTs [Figure 4][7] and leiomyomas [Figure 5]; if tumors appear hyperenhanced under CEEUS examination, the sensitivity and specificity of GIST diagnosis can reach 98% and 100%, respectively, (leiomyomas typically take the form of hypoenhanced images under CEEUS), and diagnostic accuracy can reach 98% [Table 2]. Furthermore, among these patients, 88% of the GIST contained avascular areas.[7] Other researchers have also used CE-EUS to assess GIST malignancy. One retrospective study of 29 patients who received GIST removal found that CE-EUS achieved a diagnostic accuracy of 83%, which was comparable to the 81% diagnostic accuracy of EUS-guided fine-needle aspiration biopsy.[10] Furthermore, researchers using software to analyze the degree to which tumors absorb contrast agents have employed CE-EUS to assess the effect of the drug imatinibon metastatic c-*kit* positive GISTs. They found that a decrease in the absorption of contrast agent during the 1st and 2nd weeks of treatment can serve as an indicator of the effectiveness of imatinib.[11]

Conclusions

Most SETs have no symptoms and are discovered accidentally. As a consequence, EUS is required to gain a further understanding of tumor characteristics and to forecast tumor morphology.

GISTs are the most common gastric SETs, and 10%–30% of GISTs have malignant tendencies and require active surgical removal. Accurate preoperative diagnosis is, therefore, essential to avoid unnecessary surgery and anesthesia, reduce patient stress, and lessen doctor–patient conflict. However, even with the use of advanced medical technology, including plentiful EUS experience and biopsy methods, gastroenterologist still cannot always obtain an accurate preoperative diagnosis of GISTs. In spite of this present limitation, we expect that progress in digital image technologies such as digital image analysis systems and the development of new technologies (such as CE-EUS and ultrasound elastography, among others) will continue to

Table 2: Comparison of gastrointestinal stromal tumors and leiomyomas under contrast-enhanced endoscopic ultrasound examination

	Leiomyoma	GIST		
		Benign	→	Malignant
Enhancement	Hypoenhacement	Hyperenhancement		
Echotexture	Homogeneous	Homogeneous	→	Heterogeneous
Blood vessel		Regular	→	Irregular

GIST: Gastrointestinal stromal tumor, CE-EUS: Contrast-enhanced endoscopic ultrasound, →: To

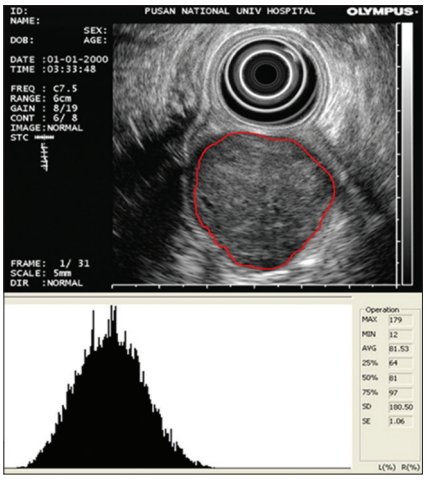

Figure 3: The scope of the tumor is indicated by the red outline in the upper endoscopic ultrasonography image.[4] A digital image analysis system was then used to calculate T_{mean} and T_{SD} in order to determine whether the tumor constituted a gastrointestinal stromal tumor

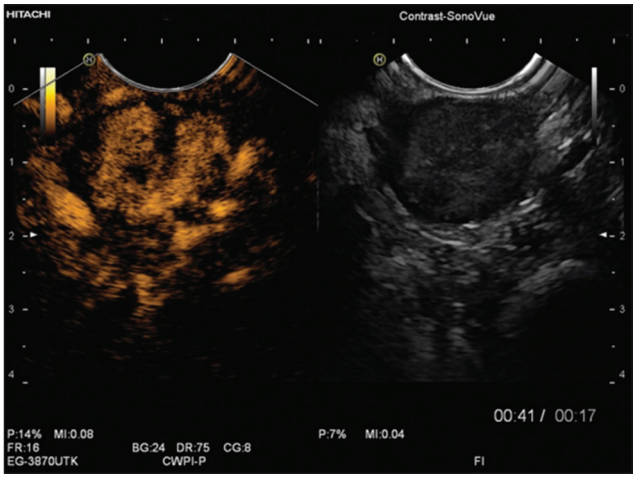

Figure 4: A hyperenhanced gastrointestinal stromal tumor under contrast-enhanced endoscopic ultrasound.[7] An avascular area is located in the center

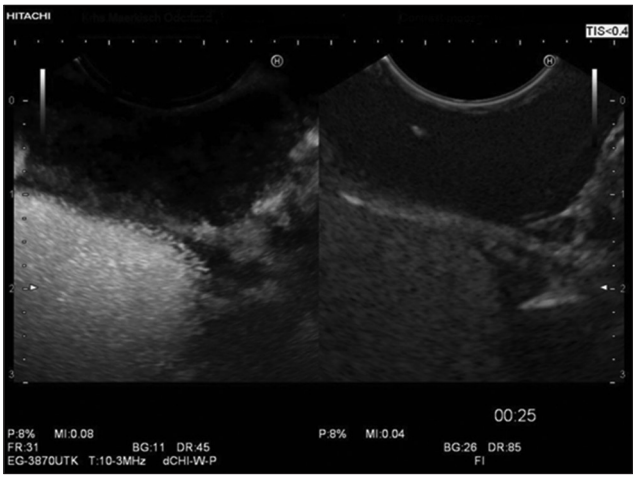

Figure 5: Under contrast-enhanced endoscopic ultrasound, leiomyomas typically present as hypoenhanced tumors

improve the EUS preoperative gastrointestinal SET diagnostic rate.

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Conflicts of interest

There are no conflicts of interest.

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