

## Original Article

# Miniprobe-endoscopic ultrasound in the diagnosis of esophageal submucosal tumors and the effect of tumor diameters on its diagnostic performance

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**Abstract:** Objective: To study the value of miniprobe-endoscopic ultrasound (EUS) for diagnosing esophageal submucosal tumors with different diameters. Methods: One hundred and seventeen patients with esophageal submucosal tumors were selected to be examined and diagnosed using miniprobe EUS and computed tomography (CT). These patients' tumors were confirmed through the pathological examination of their lesions obtained from their endoscopic surgeries. The diagnostic accordance rates of the two methods were compared with the pathological gold standard, and the diagnostic accordance rates of the tumors with diameters <1 cm, 1-2 cm, and >2 cm were also compared between the two methods. Results: The postoperative pathological diagnoses confirmed esophageal stromal tumors (n=47), esophageal leiomyoma (n=39), esophageal lipoma (n=15), malignant esophageal stromal tumors (n=10), and granulose cell tumors (n=6). The accordance rates of the miniprobe EUS compared to the pathological examinations were significantly higher than the rates using CT (94.87% vs. 73.50%, P<0.001). The accordance rates of the miniprobe EUS compared to the pathological examinations were significantly higher than the rates using CT in the cases with a tumor diameter <1 cm (96.15% vs. 63.46%; P<0.05) and diameters 1-2 cm (97.44% vs. 74.36%; P<0.05). In the tumors (n=26) with a diameter >2 cm, the accordance rates of the miniprobe EUS and CT compared to the pathological diagnosis were 88.46% and 92.31%, separately, but the differences were not statistically significant (P>0.05). Conclusion: Miniprobe EUS has a high diagnostic value for esophageal submucosal tumors, especially for small-diameter tumors. With an increase in tumor volume, the diagnostic accuracy of miniprobe EUS is decreased.

**Keywords:** Miniprobe endoscopic ultrasound, tumor diameters, esophageal submucosal tumors, diagnostic value

## Introduction

Esophageal submucosal tumors are protrusion lesions that occur in the submucosal tissue of the esophagus. They are often caused by space-occupying lesions near the mucous layer, extramural tissue, or organ compression and include leiomyoma, stromal tumors, lipomas, granular cell tumors, and so on. The first two types are the most common [1]. Studies have reported that esophageal submucosal tumors often occur in young adult men [2]. Their shapes are mostly round, oval or horse-shoe, coated by a complete capsule with a tough texture and a gray color, and their diameters are usually less than 5 cm, but they can also grow more than 10 cm in diameter. Patients with smaller esophageal submucosal

tumors often have no obvious symptoms; however, when the tumor diameter exceeds 3 cm, the patients may show symptoms of retrosternal discomfort and dysphagia, etc. and even compression on the surrounding organs, causing dyspnea and other symptoms that seriously affect life and health. At present, esophageal diseases are mostly diagnosed through conventional endoscopy and biopsy. However, as the surface of the esophageal submucosal tumor is smooth and only protuberant changes can be seen, biopsy tissue sampling is difficult to perform. The diagnosis process is more tedious and difficult to popularize widely in the clinical setting [3]. Multi-slice spiral CT is an effective imaging method that can significantly improve the scanning speed and reduce the artifact interference caused by abdominal

movement. It can identify the lesion and determine the extent of the involvement at the same time [4]. Endoscopic ultrasound (EUS) is a diagnostic method of ultrasonic scanning with the aid of endoscopic biopsy. It can be divided into mini-probe, large probe, and sector scanning types, etc. It integrates both the advantages of ultrasound and endoscopic diagnosis, greatly improves the local spatial resolution, and clearly observes the lesions' sizes, shapes, hierarchies, boundary relationships, and invasions [5]. Thus, it can improve the accuracy of the qualitative diagnosis, simplify the processes, and ease pain. Miniprobe EUS is a common diagnostic method for esophageal submucosal tumors [6]. At present, there is no systematic study on the advantages and disadvantages of CT and miniprobe EUS in the diagnosis of esophageal submucosal tumors. By comparing the results of CT, miniprobe EUS, and pathological biopsy, this study aims to provide guidance for the selection of the best diagnostic method for esophageal submucosal tumors.

## Materials and methods

### General materials

This study was approved by the Ethics Committee of the General Hospital of Huainan Eastern Hospital Group. A total of 117 patients with esophageal submucosal tumors diagnosed using endoscopic surgery and pathology examinations at the General Hospital of Huainan Eastern Hospital Group from June 2018 to February 2020 were selected for this study. The study cohort included 71 males and 46 females ranging in age from 21 to 82 years old, with an average age of  $(49.8 \pm 11.7)$  years.

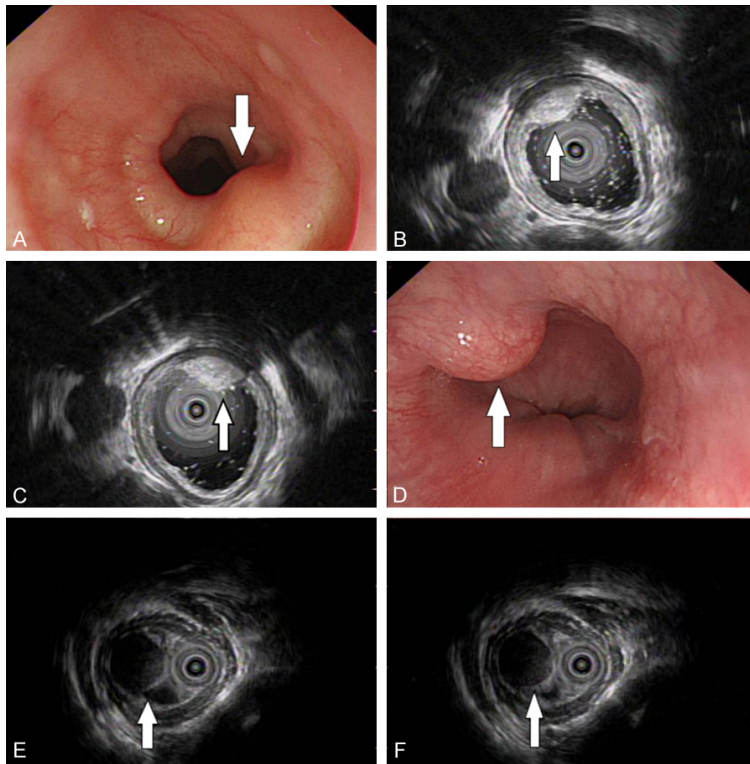
Inclusion criteria: 1) Patients who were treated with endoscopic mucosal resection and endoscopic submucosal dissection or surgery and diagnosed with esophageal submucosal tumors using a postoperative pathological biopsy. 2) Patients who met the examination indications of endoscopic ultrasound and CT. 3) Patients who voluntarily participated in this study and signed an informed consent.

Exclusion criteria: 1) Patients with complications including esophagitis, gastroesophageal reflux disease, esophageal polyps, or other esophageal diseases. 2) Patients with complications including serious blood, immunity, or nervous system diseases. 3) Patients with poor coordination or without a complete medical examination.

### Methods

*Miniprobe EUS:* The patients lay in a left recumbent position with a slight flexion of both lower limbs. After fasting for 8 hours before the examination and emptying the air in the stomach at the same time, each patient received a sublingual administration of lidocaine mucilage (Shanghai Yubo Biotechnology Co., Ltd.) for local anesthesia and lubrication. The SU-9000 endoscopic ultrasound system (Fuji Film (China) Investment Co., Ltd.) was used for the endoscopic ultrasonography, in which the ultrasonic frequency of the miniprobe was controlled at 7-12 MHz. The scanning examination was performed using the water-filled balloon method combined with the no-air water-filling method. First, the gastric cavity was filled with de-aerated water, and then the water-filled balloon contacted and scanned the lesion to minimize the loss of ultrasonic reflection. The location and involved range of the lesion were preliminarily determined, and the location, shape, volume, hierarchy, boundary relationship and the characteristics of the ultrasonic echo including the high, low, and mixed levels of the echoes of the intraluminal tumors were evaluated. However, for the extracavitary tumors, an accurate evaluation should be performed after ruling out other lesions and the compression of normal organs. All the operations and observation records were completed by the same experienced ultrasound doctor. Leiomyoma and benign stromal tumors presented homogeneous or inhomogeneous hypoechoic masses. The echo originated from the muscularis mucosa or lamina propria, and the boundary was clear without peripheral invasion. Except for the contact site of the stomach and the esophageal wall, the other wall structure was clear. Malignant stromal tumors showed a significant peripheral invasion and an unclear boundary. Lipoma showed a medium-high echogenic mass, which originated from the submucosa with a mound-shaped eminence and a clear boundary. The volumes of the granular cell tumors were usually small, showing hypoechoic masses, which originated from the muscularis mucosae.

*Multi-slice spiral CT examination:* The chest or upper abdomen was scanned using the Mx8000 multi-slice spiral CT (Philips (China) Investment Co., Ltd.). The supine position was taken and the patients were fasted for 8 hours before the examination. A liter of lukewarm water was orally administered 30 min before the examination. A raceanisodamine hydrochloride



**Figure 1.** Examination results of miniprobe EUS. A: A lipoma showed a mound-like protuberance with a smooth surface under the endoscope; B and C: The lipoma originated from the submucosa and appeared dense and slightly hyperechoic with a clear boundary under the miniprobe EUS; D: Leiomyoma showed a hemispherical shape with a clear boundary; E and F: The leiomyoma showed uniform hypoechoes and continued with the low-level echoes of the muscular layer, which originated from the muscularis mucosa. EUS: endoscopic ultrasound.

ride injection (Jiangsu Dahongying-Hengshun Pharmaceutical Co., Ltd.) was injected intravenously 15 minutes before the examination. The contrast agent ioversol (Jiangsu Hengrui Pharmaceutical Co., Ltd.) was injected intravenously before the enhancement scanning, with a speed of 3.5-4.0 mL/s and a dose of 1.5 mL/kg. Arterial enhancement scanning was performed 30 seconds after the injection, and vein enhancement scanning was performed 60 seconds later. All the data were transferred to the background processor for the reconstruction analysis, and the parameters such as tumor size, location, origin level, boundary condition, etc. were observed. Finally, the diagnosis of the esophageal submucosal tumor and the determination whether it was benign or malignant were completed by a senior imaging physician. Most of the benign tumors had regular shapes, round or oval, uniform densities, solid mass, homogeneous enhancement, and clear boundaries. However, in the malignant tumors, there was necrosis, cyst walls, etc. with hetero-

geneous internal enhancement, peripheral invasion, and unclear boundaries. For the leiomyoma tumors, the benign stromal tumors, and lipoma, the CT manifestations showed homogeneous density and enhancement, clear and regular boundaries, but the malignant stromal tumors showed inhomogeneous densities, heterogeneous enhancement, and unclear boundaries.

#### Outcome measures

Main outcomes: 1) A performance analysis of the miniprobe EUS examination results. 2) A comparison of the accordance rates between the miniprobe EUS, CT diagnosis, and pathological examination results.

Secondary outcomes: A comparison of the accordance rates between the miniprobe EUS and pathological examination results for esophageal submucosal tumors with diameters <1 cm, 1-2 cm, and >2 cm.

#### Statistical methods

All the data were analyzed using SPSS 21.0, and the measurement data were expressed as the mean  $\pm$  standard deviation, and *t*-tests of independent samples were used for the inter-group comparisons. All the count data were expressed as cases (percentages), and  $\chi^2$  tests were used for the inter-group comparisons.  $P < 0.05$  indicated that a difference was significant.

#### Results

##### A performance analysis of the miniprobe EUS examination results

Mound-like protuberances of lipoma could be seen under the miniprobe EUS (Figure 1A), originating from the submucosa. They were dense and slightly hyperechoic with well-defined, clear boundaries (Figure 1B and 1C). The leiomyoma had long spindle and hemispherical shapes

## The diagnostic performance of the EUS miniprobe for esophageal submucosal tumors

**Table 1.** A comparison of the accordance rate between the results of miniprobe EUS and CT diagnosis in relation to pathological examinations (n, %)

Pathological results	Pathological diagnosis	CT	Miniprobe EUS	$\chi^2$	P
Stromal tumors	47	35/47 (74.47)	45/47 (95.74)		
Leiomyomas	39	30/39 (76.92)	36/39 (92.31)		
Lipomas	15	11/15 (73.33)	15/15 (100.00)		
Malignant stromal tumors	10	7/10 (70.00)	9/10 (90.00)		
Granulosa cell tumors	6	3/6 (50.00)	6/6 (100.00)		
Totals	117	86/117 (73.50)	111/117 (94.87)	17.372	<0.001

Note: EUS: endoscopic ultrasound.

**Table 2.** A comparison of the diagnostic accordance rate between miniprobe EUS and CT in relation to the pathological findings in tumors with diameter <1 cm (n, %)

Pathological results (diameters <1 cm)	n	Miniprobe EUS		CT	
		Accordance	Discrepancy	Accordance	Discrepancy
Stromal tumors	22	21 (95.45)	1 (4.55)	14 (63.64)	8 (36.36)
Leiomyomas	17	16 (94.12)	1 (5.88)	11 (64.71)	6 (35.29)
Lipomas	6	6 (100.00)	0 (0.00)	4 (66.67)	2 (33.33)
Malignant stromal tumors	5	5 (100.00)	0 (0.00)	3 (60.00)	2 (40.00)
Granulosa cell tumors	2	2 (100.00)	0 (0.00)	1 (50.00)	1 (50.00)
Totals	52	50 (96.15)###	2 (3.85)###	33 (63.46)	19 (36.54)

Note: ###is indicated that when compared with CT, the  $P < 0.001$ . EUS: endoscopic ultrasound.

with clear boundaries when viewed with the miniprobe EUS (**Figure 1D**). They originated from the muscularis mucosa or lamina propria with uniform hypoechoes and continued with the hypoecho of the muscular layer (**Figure 1E** and **1F**).

*A comparison of the accordance rates between the miniprobe EUS and the CT diagnosis results in the pathological examination*

The postoperative pathological diagnoses of the 117 patients showed esophageal stromal tumors (n=47), esophageal leiomyoma (n=39), esophageal lipoma (n=15), malignant esophageal stromal tumors (n=10), and granulosa cell tumors (n=6). The accordance rates of the miniprobe EUS diagnoses compared with the pathological examinations was significantly higher than the accordance rate when compared with CT (94.87% vs. 73.50%,  $P < 0.001$ ), and the details are shown in **Table 1**.

*A comparison of the diagnostic accordance rates between the miniprobe EUS and CT for the pathological findings in tumors with diameters <1 cm*

In tumors with diameters <1 cm, the diagnostic accordance rate of the miniprobe EUS com-

pared to the pathological examinations was significantly higher than the accordance rate when compared with CT (96.15% vs. 63.46%  $P < 0.001$ ), and the details are shown in **Table 2**.

*A comparison of the diagnostic accordance rate between the miniprobe EUS and CT for the pathological findings in tumors with diameters of 1-2 cm*

In tumors with diameters between 1 and 2 cm, the diagnostic accordance rate of the miniprobe EUS compared to the pathological examination was significantly higher than the accordance rate when compared with CT (97.44% vs. 74.36%,  $P < 0.005$ ), and the details are shown in **Table 3**.

*A comparison of the diagnostic accordance rate between the miniprobe EUS and CT in tumors with diameters >2 cm*

In tumors with diameters >2 cm, the diagnostic accordance rate of the miniprobe EUS and CT compared to the pathological examination was 88.46% and 92.31%, separately, but the difference was not statistically significant ( $P > 0.05$ ). The details are shown in **Table 4**.



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**Table 3.** A comparison of the diagnostic accordance rate between miniprobe EUS and CT in relation to the pathological findings in tumors with diameters of 1-2 cm (n, %)

Pathological results (diameters: 1-2 cm)	n	Miniprobe EUS		CT	
		Accordance	Discrepancy	Accordance	Discrepancy
Stromal tumors	16	16 (100.00)	0 (0.00)	12 (75.00)	4 (25.00)
Leiomyomas	12	11 (91.67)	1 (8.33)	10 (83.33)	2 (16.67)
Lipomas	6	6 (100.00)	0 (0.00)	4 (66.67)	2 (33.33)
Malignant stromal tumors	3	3 (100.00)	0 (0.00)	2 (66.67)	1 (33.33)
Granulosa cell tumors	2	2 (100.00)	0 (0.00)	1 (50.00)	1 (50.00)
Totals	39	38 (97.44) <sup>#</sup>	1 (2.56) <sup>#</sup>	29 (74.36)	10 (25.64)

Note: <sup>#</sup>is indicated that when compared with CT, the P<0.05. EUS: endoscopic ultrasound.

**Table 4.** A comparison of the diagnostic accordance rate between miniprobe EUS and CT in relation to the pathological findings in tumors with diameters >2 cm (n, %)

Pathological results (diameters >2 cm)	n	Miniprobe EUS		CT	
		Accordance	Discrepancy	Accordance	Discrepancy
Stromal tumors	9	8 (88.89)	1 (11.11)	9 (100.00)	0 (0.00)
Leiomyomas	10	9 (90.00)	1 (10.00)	9 (90.00)	1 (10.00)
Lipomas	3	3 (100.00)	0 (0.00)	3 (100.00)	0 (0.00)
Malignant stromal tumors	2	1 (50.00)	1 (50.00)	2 (100.00)	0 (0.00)
Granulosa cell tumors	2	2 (100.00)	0 (0.00)	1 (50.00)	1 (50.00)
Totals	26	23 (88.46)	3 (11.54)	24 (92.31)	2 (7.69)

Note: EUS: endoscopic ultrasound.

### Discussion

Esophageal submucosal tumors are non-epithelial tumors originating from the submucosal mesenchymal tissue, including the submucosa, muscularis mucosae, and muscularis propria, a few of which can invade into the mucous membrane. They are often benign or borderline tumors including leiomyoma, interstitialomas, lipomas, granulosa cell tumors, and hemangiomas, among which the former two are the most common, accounting for about 90.0% of cases [7]. In our study we found 117 esophageal submucosal tumor cases, including 96 cases (82.05%) of interstitialomas and leiomyomas, and 16 cases (13.68%) of malignant tumors, which was basically consistent with the previous epidemiological results [8]. It has been reported that the key to early diagnosis, treatment, and prognosis improvement is the precise determination of the nature and esophageal origin of the esophageal submucosal tumors [9]. At present, routine endoscopy and biopsy are often used in their diagnosis. Although it often only appears as a protruding lesion with a smooth surface which can occur

due to a variety of causes, including non-neoplastic lesions such as cysts, and tuberculosis, and extra-esophageal lesions; therefore, the identification and diagnosis are relatively difficult with conventional endoscopy. Meanwhile, it's difficult to obtain tissue samples for submucosal biopsies, so determining how to improve the diagnostic accuracy has also become a key research topic.

With the rapid progress of microelectronics and computer technology in recent years, CT technology has been improved and updated. Multi-slice spiral CT is a kind of imaging system which can obtain simultaneous, multi-slice image data. With its more complete image information, combined with two-dimensional reconstruction and virtual endoscopes, multi-slice spiral CT can observe the lesions clearly after post-processing. It also has a higher accuracy for the early detection of small lesions, and can observe the origination, morphology, structure, and boundary relationships of esophageal submucosal tumors [10]. Currently, it is believed that, multi-slice spiral CT combined with pathological biopsy results can provide CT-related

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criteria for the diagnosis of esophageal submucosal tumors, but the accuracy of the diagnostic of originality of each tumor is still not high enough, an accuracy generally reported in the literature to be only about 60.0%, while the diagnostic accordance rate in this study was 73.50%, which may be related to the higher seniority of doctors and the improvement of diagnostic instruments, and the lack of cases may also contribute to the differences in the results [11].

EUS is a digestive tract examination method that combines ultrasound and endoscopy, making up for the shortcomings of ultrasound and endoscopy, and integrating their respective advantages. It can observe the lesion site more closely, enhance the ultrasound frequency and image resolution, and obtain data such as the hierarchical structure of the digestive tract tissue and images of the surrounding organ tissue more easily. It is especially sensitive to superficial and minute lesions that were often used to evaluate the origin, nature, invasion and possibility of surgical treatment for gastrointestinal submucosal tumors, and in addition, it can accurately identify and diagnose the compression of extracavitary lesions [12].

Clinical studies have confirmed that EUS can clearly reflect the anatomical structure of the esophageal wall according to the characteristics of the ultrasonic echo, which include the mucous layer, the mucous muscle layer, the submucosa, the proper muscle layer, the serous layer, and the subserous adipose tissue, from inside to outside, corresponding to high, low, high, low and high echoes respectively [13, 14]. It provides a reliable theoretical basis for the diagnosis of esophageal submucosal tumors and accurately locates the anatomical level of the tumor origin. And combined with the internal echo intensity, uniform or not, the surrounding boundary relationship, it can finally achieve an accurate and differentiated diagnosis. Zhao et al. reported that the accordance rate of the diagnosis of upper gastrointestinal submucosal lesions between EUS and pathological examinations was 91.0%, and the calculated diameters of the diagnostic lesions was almost the same as in the pathological results, which can accurately diagnose its origin. However, there was a certain misdiagnosis rate for hypotonic lesions of the third and fourth layers

of mucosa, which requires special attention [15]. EUS can be divided into mini-probes, large probes, and sector scanning, among which, miniprobe EUS is the first choice for the diagnosis of esophageal submucosal tumors since it can accurately display small lesions, infiltration, and metastasis, and has the advantages of convenient operation, accurate location, less pain, and low cost [16]. Current studies have shown that stromal tumors and leiomyomas often originate in the muscularis mucosa and muscularis propria, and most of the lesions show the characteristics of internal and external hyperechoic capsules, while granulosa cell tumors are mostly benign and originate from submucosa, and the boundary is clear and smooth, with the occurrence of metastasis and recurrence [17]. As the ultrasonic echo is hypoechoic, which is similar to leiomyoma, a pathological biopsy is needed for the differential diagnosis. Lipomas mostly originate in the mucous membrane and submucosa, showing high level and dense echoes, and attenuation occurs when the lesion is large [18]. The performance of the miniprobe EUS on esophageal submucosal tumors in this study was basically consistent with the previous research. The accordance rates of miniprobe EUS and pathological examination was significantly higher than the rate with CT (94.87% vs. 73.50%,  $P < 0.001$ ). This suggests that the accuracy of miniprobe EUS in the diagnosis of esophageal submucosal tumors is significantly higher than CT.

Studies have proved that the results of miniprobe EUS are greatly affected by tumor volume [19]. Clear images can be obtained for tumors with diameters  $\leq 2$  cm, and the diagnostic accordance rate is generally higher than 90.0%. With increasing tumor diameters, the ultrasound image will be affected by ultrasound failure, so the full picture of the lesion can't be displayed. And the organs and lymph nodes around the lesion are difficult to develop into an image, so it is necessary to choose a large probe EUS to show the whole picture of the tumor, which is beneficial to the tumor diagnosis and the differential diagnosis [20]. Teruko et al. reported that the diagnostic accordance rate of miniprobe EUS decreases significantly with an increase of the tumor volume of the digestive tract mucosa, and the diagnostic accordance rate of tumors with diameter  $> 2$  cm

was only 86.6% [21]. This study compared the diagnostic accordance rates of tumors with different diameters. The results showed that the diagnostic accordance rates of small probe EUS for tumors with diameters <1 cm and 1-2 cm were 96.15% and 97.44%, respectively, which were significantly higher than the CT rates. For tumors with diameters >2 cm, the accordance rate was only 88.46%, and the CT rate was 92.31%, suggesting that an increase of tumor volume reduces the diagnostic accuracy of small probe EUS. Thus, the appropriate probe should be selected in clinics according to the actual volume of the tumor, which is basically consistent with recently published studies [22, 23]. With an increase in tumor volume, the advantage of the high spatial resolution of CT can be brought into full play, so the diagnostic accuracy is significantly improved.

However, the cohort selected for this study was small, and the types of diseases studied were few, so the inclusion criteria need to be improved, and some localized lesions in the esophageal wall diagnosed by microprobe were not included, and the results of endoscopic ultrasonography are greatly influenced by clinical skill and the doctors' operation levels, so there was a certain bias in the results. Therefore, it is necessary to increase the sample size and to standardize the diagnostic procedures in future studies.

To sum up, miniprobe EUS has a high diagnostic value for esophageal submucosal tumors, especially for small diameter tumors, and it has a high diagnostic accuracy and an important guiding value for early diagnosis and treatment. With increasing tumor volumes, the diagnostic accuracy of miniprobe EUS may be affected. Therefore, the appropriate probe should be selected for the clinical diagnosis according to the actual volume of the tumor.

## Disclosure of conflict of interest

None.

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