

Clinical value of contrast-enhanced ultrasound in improving diagnostic accuracy rate of transthoracic biopsy of anterior-medial mediastinal lesions

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Abstract

Objective: To evaluate the clinical value of contrast-enhanced ultrasound (CEUS) in transthoracic biopsy of anterior-medial mediastinal lesions.

Methods: A total of 123 patients with anterior or middle mediastinum lesions required ultrasound guided transthoracic biopsy for pathological diagnosis. Among them, 72 patients received CEUS examinations before biopsy. After CEUS, 8 patients were excluded from biopsy and the rest 64 patients underwent biopsy (CEUS group). During the same period, 51 patients received biopsy without CEUS examination (US group). The ultrasonography characteristics, the number of biopsy puncture attempts, diagnostic accuracy rate and the incidence of complications were recorded and compared between the two groups.

Results: A large portion of necrosis area or superficial large vessels was found in 8 patients, so the biopsy was cancelled. The internal necrosis was demonstrated in 43.8% of the lesions in CEUS group and in 11.8% of US group ($P>0.001$). For thymic carcinoma, CEUS increased the detection rate of internal necrosis and pericardial effusion than conventional ultrasound (62.5% vs. 18.8%, $P=0.012$; 56.3% vs. 12.5%, $P=0.023$). The average number of punctures in CEUS group and US group was 2.36 ± 0.70 and 2.21 ± 0.51 times, respectively ($P>0.05$). The diagnostic accuracy rate of biopsy in CEUS group (96.9%, 62/64) was significantly higher than that in US group (84.3%, 43/51) ($P=0.022$). In US group, 2 patients suffered from mediastinal bleeding (3.9%), while no major complications occurred in CEUS group.

Conclusions: CEUS examination provided important information before transthoracic mediastinum biopsy and improved diagnostic accuracy rate in biopsy of anterior and middle mediastinum lesions than conventional ultrasound.

Keywords: Biopsy; contrast-enhanced ultrasound (CEUS); diagnostic accuracy rate; mediastinal

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Introduction

The mediastinum is the central portion of the thoracic cavity, limited by pleural cavities laterally, thoracic inlet superiorly, and the diaphragm inferiorly. Mediastinal lesions are a common type of diseases in thoracic surgery.

Correct pathological diagnosis is of vital importance for determining the proper therapeutic option. In recent years, ultrasound-guided transthoracic biopsy of mediastinal lesions has attracted clinical attention due to its advantages of being economic, convenient, safe, quick, and no radiation (1-3). However, conventional ultrasound (US)

cannot clearly reveal the internal structures of the mediastinal lesions and the detection of superficial vessels or presence of internal necrotic tissue was limited (4). As a consequence, there is a risk of complications, such as bleeding, or false-negative results of biopsy.

Contrast-enhanced ultrasound (CEUS) is now employed widely for the diagnosis of solid tumors. After intravenous injection of contrast agent, SonoVue, ultrasound can provide very useful information for both macrovasculature and microvasculature. CEUS could continuously monitor the dynamic perfusion of the lesions in real time and increase diagnostic accuracy than conventional ultrasound (5-7). Several investigators reported that CEUS also improved the diagnostic accuracy of the biopsy procedure in the liver or other organs (5,8-11), because it can help differentiate viable from necrotic tissues. In this study, we evaluate the clinical value of CEUS in transthoracic biopsy of mediastinal lesions. Lesions in posterior mediastinum are vulnerable to be blocked by the lung and bone. Therefore the lesions in posterior mediastinum are difficult to be shown by ultrasound. The patients who were recommended for ultrasound-guided transthoracic biopsy mainly have anterior and medial mediastinal lesions. We examined 123 patients with anterior-medial mediastinal lesions who intend to receive biopsy for pathological diagnosis, analyzed the perfusion features of the CEUS group and explored the clinical value of CEUS in improving biopsy diagnostic accuracy of anterior-medial mediastinal lesions.

Materials and methods

Patients

From April 2011 to April 2016, 123 patients who were diagnosed with anterior-medial mediastinal lesions by chest computed tomography (CT) and were recommended for ultrasound-guided transthoracic biopsy in the Department of Ultrasound, Peking University Cancer Hospital were enrolled in this study. Among them, 72 patients underwent CEUS before biopsy, of whom 8 cases were found not

suitable for needle biopsy. As a consequence, the rest 64 cases were recruited into the CEUS group, including 32 males and 32 females, aged 18–75 years old (mean: 45.2 ± 15.3 years), with a mean lesion size of 7.8 ± 2.7 cm. At the same period, the other 51 patients who received conventional ultrasound-guided biopsy without CEUS were regarded as the US group. These patients refused CEUS because of economic factors after fully explaining the advantages and risks of CEUS application. There were 24 males and 27 females, aged 18–71 years old (mean: 42.4 ± 16.4 years), with a mean lesion size of 7.5 ± 2.8 cm. *Figure 1* summarizes the patients selected in this study. There was no statistically significant difference in clinical characteristics between the CEUS group and the US group (*Table 1*).

This study was approved by the Research and Ethics Committee of Peking University Cancer Hospital, and written informed consent was obtained from each patient before the CEUS examination and biopsy procedures.

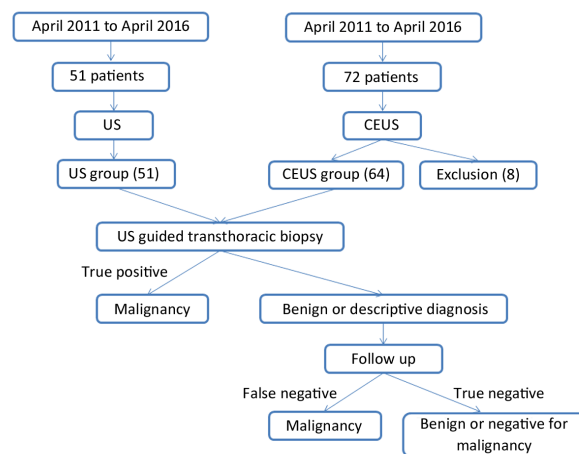


Figure 1 Flow chart summarizes the patients selected in this study.

Contrast agent and sonography procedures

For the CEUS group, patients underwent CEUS examination 30–60 min before the biopsy. SonoVue (Bracco SpA,

Table 1 Patients' demographics between CEUS group and US group

Characteristics	CEUS group (N=64)	US group (N=51)	P
Age [$\bar{x} \pm s$ (range)] (year)	45.2 ± 15.3 (18–75)	42.4 ± 16.4 (18–71)	0.350
Male/Female (n/n)	32/32	24/27	0.754
Lesion size ($\bar{x} \pm s$) (cm)	7.8 ± 2.7	7.5 ± 2.8	0.186
Malignant/benign (n/n)	46/18	34/17	0.546

Milan, Italy) was used as the sonography contrast agent, supplied as a lyophilized powder and reconstituted with 5 mL of saline to form a homogeneous microbubble suspension that contains 8 $\mu\text{L}/\text{mL}$ sulfur hexafluoride stabilized by a phospholipid shell. SonoVue was administered intravenously as 1.5 mL boluses through the antecubital vein in 2–3 s. Logiq E9 sonography system (GE, USA) with real-time gray-scale contrast tuned imaging and a 3.0–5.0 MHz C5-1 probe (GE, USA) were used when CEUS was performed.

Chest CT was performed in all patients before our study. With the reference of chest CT, conventional sonography was performed to investigate the location, texture and size of the lesion. Contrast-enhanced imaging was then initiated, and the acoustic power output was adjusted to about 0.11 to 0.13 mechanical indexes on the basis of the lesion depth and body habitus of the patient. After contrast agent administration, the perfusion and enhancement patterns, necrosis (anechoic) area of the target lesions and nearby structures were observed about 5 min in real time. The conventional ultrasound images were recorded by still images and dynamic images. The CEUS images were recorded by dynamic images with digital imaging and communications in medicine (DICOM) format. CEUS analysis was performed on the basis of review of stored sonographic clips. Patterns of enhancement were evaluated by 2 observers (W.Y. and S.W.), who reached a consensus with emphasis on the presence of necrotic (anechoic) areas.

In both groups, the biopsy puncture plan was established by collecting the information of the location and size of lesions, necrosis area, pericardial effusion and superficial vessels.

Biopsy indication and method

The indications for ultrasound-guided transthoracic biopsy of anterior-medial mediastinal lesions were as follows: 1) accessibility of lesions via a transthoracic approach with ultrasound; 2) a lesion larger than 2 cm in diameter; 3) a lesion with mixture texture has at least 2 cm thickness of solid content; 4) a patient can well control breath; 5) no superficial large vessel in the puncture path; and 6) platelet count was greater than $60 \times 10^9/\text{L}$.

In the US group, conventional ultrasound (including color Doppler imaging) was routinely used for selection of an optimal biopsy path. The sampling site was localized according to the sonographic appearance (solid part of the lesion with the shortest pathway). In the CEUS group,

besides conventional ultrasound, the information from contrast-enhanced sonography was also used to select the biopsy path and sampling site (solid part of the lesion with the shortest pathway).

For the biopsy procedures in this study, sonography system Logiq E9 (GE, USA) with 3.5–5.0 MHz small-sector convex probes accessorized with biopsy was used to provide sonographic guidance. Biopsy was performed using an 18-gauge automatic cutting needle (Bard Magnum, Bard, USA). After careful planning, the skin was sterilized, and local anesthesia was applied using 5 mL of 1% lidocaine (Liduokayin; Yimin Pharmaceutical Co., Ltd, Beijing, China). After the probe was fixed and the guiding needle was inserted into the chest wall, the biopsy needle was inserted for biopsy. It should be noted that the biopsy route should avoid damaging large blood vessels and advance into the target area under real-time visualization. The number of puncture attempts was decided by the quantity and color of the specimen obtained. The puncture attempts were no more than 3 times. The specimens obtained during the biopsy were fixed in 10% formalin.

The patient stayed in the hospital for at least 1 h to monitor whether there was complication after biopsy. The specimens were sent to the Department of Pathology for histologic examinations by two experienced pathologists. The second or third session of biopsy required if the initial biopsy could not get definite diagnosis.

Imaging evaluation

The conventional ultrasound and CEUS features were summarized and compared. It was defined as necrosis in CEUS group if CEUS showed the lesion was complete absence of enhancement during arterial phase and parenchymal phase (12). It was defined as necrosis in US group if conventional ultrasound showed there was anechoic area within lesions, clear boundaries, and color Doppler flow imaging (CDFI) showed no blood flow within the anechoic area. Contrast-enhanced CT was adopted as the diagnosis criterion for the detection rate of necrosis in lesions.

Final diagnosis

The final diagnosis was made as definite diagnosis, descriptive diagnosis, and unable diagnosis based on comprehensive diagnosis of all pathological specimens from two experienced pathologists. Definite diagnosis was considered correct if the pathologic diagnosis confirmed

malignancy. Benign diagnosis and descriptive diagnosis need to be confirmed with other imaging examinations and 6 months of follow-up. If the other imaging examination and follow-up confirm the diagnosis, the diagnosis was considered correct. If no tissues or undeterminable necrotic tissues were described in the descriptive diagnosis, the diagnosis was considered failure.

Statistical analysis

All analyses were performed using IBM SPSS Statistics (Version 21.0; IBM Corp., New York, USA). Numerical data were given as $\bar{x} \pm s$ and were analyzed with independent samples *t*-test or paired *t*-test. Categorical variables were analyzed with Pearson χ^2 and Fisher's exact test. $P < 0.05$ was considered statistically significant.

Results

Biopsy indication selection with CEUS

After the CEUS examination, 8 of the 72 patients were excluded from ultrasound-guided transthoracic biopsy. Of them, 5 patients had the lesions with more than 80% of the necrotic portion (Figure 2), and another 3 patients had superficial large vessels at puncture path which were difficult to avoid (Figure 3). The remaining 64 patients underwent biopsy within 30–60 min.

Features of ultrasound images

The tumor sizes of the CEUS group and the US group

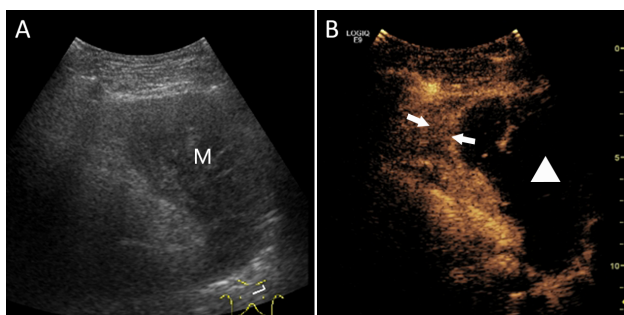


Figure 2 Images from a 37-year-old female with chest pain for 2 months. (A) Conventional ultrasound showed an 8.5×5.3 cm lesion (M) with hypoecho texture in medial mediastinum; (B) CEUS showed >80% area presented enhancement defect in the lesion (Δ). The solid proton was too little to biopsy on the edge of the lesion (\uparrow). It had high risk for the false negative result of the biopsy. So the biopsy was canceled.

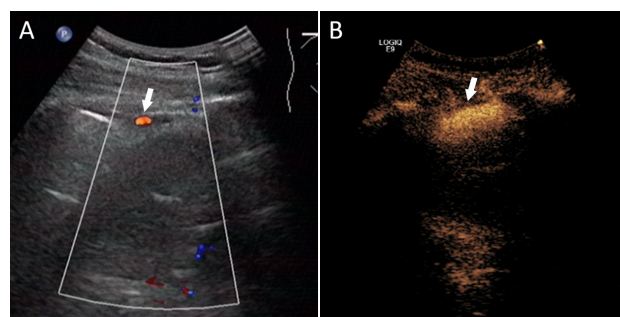


Figure 3 Images from a 45-year-old female with cough for 20 d. (A) Color Doppler ultrasound showed little blood flow signals (\uparrow) at the surface of the lesion; (B) CEUS showed that it was a large blood vessel (\uparrow) at superficial location of the mediastinum lesion. Biopsy was canceled because it was hard to avoid it.

were 7.8 ± 2.7 cm and 7.5 ± 2.8 cm, respectively ($P = 0.186$). The detection rate of internal necrosis in the CEUS group (43.8%, 28/64) was statistically higher than that of the US group (11.8%, 6/51) ($P < 0.001$). Based on the sizes of the lesions, the cases were further subdivided. For lesions ≤ 5 cm in diameter, the necrosis rate was only 14.3% (1/7) in CEUS group and 11.1% (1/9) in US group ($P = 1.000$). For lesions > 5 cm in diameter, the detection rate of necrosis in CEUS group (47.4%, 27/57) was significantly higher than that of US group (11.9%, 5/42) ($P < 0.001$). With the lesion size increased, the detection rate of necrosis in lesions increased by CEUS (Table 2).

Table 2 Detection rate in internal necrosis between CEUS group and US group

Groups	Internal necrosis (%)		P
	CEUS group	US group	
≤ 5 cm	14.3 (1/7)	11.1 (1/9)	1.000
> 5 cm*	47.4 (27/57)	11.9 (5/42)	< 0.001
Total*	43.8 (28/64)	11.8 (6/51)	< 0.001

*, There was a statistically significant difference in necrosis detection rate between the CEUS group and US group ($P < 0.001$), especially for those lesions > 5 cm in diameter ($P < 0.001$).

Based on the final diagnosis, there were 46 cases had malignant lesions and 18 cases had benign lesions in the CEUS group, and 34 cases had malignant lesions and 17 cases had benign lesions in US group (Table 3).

Next we summarized the CEUS features of different histopathology lesions, including lymphoma, thymoma and thymic carcinoma, which are commonly found in anterior-medial mediastinum. Compared with lymphoma and

Table 3 Final diagnosis of CEUS group and US group after biopsy

Characteristics	Case No.	
	CEUS group (N=64)	US group (N=51)
Malignant	46	34
Lymphoma	23	10
Thymic carcinoma	16	12
Malignant thymoma	4	7
Neuroendocrine carcinoma	2	1
Seminoma	1	1
Metastatic carcinoma	0	2
Malignant mesothelioma	0	1
Benign	18	17
Benign thymoma	10	8
Teratoma	3	3
Nodular goiter	3	3
Fibrous mediastinitis	2	3

thymic carcinoma, a majority of thymoma cases had homogenous enhancement patterns in the arterial phase (100% vs. 56.5%, P=0.006; 100% vs. 25.0%, P<0.001). Compared with thymic carcinoma, thymoma had less frequency to be found having the internal necrosis (7.1% vs. 75.0%, P<0.001) (Table 4). In addition, compared with

Table 4 Enhancement patterns and necrosis among lymphoma, thymic carcinoma and thymoma

Pathological types	Cases	Enhancement patterns [% (n)]*		Necrosis [% (n)]**	
		Homogeneous	Inhomogeneous	No	Yes
Lymphoma	23	56.5 (13)	43.5 (10)	60.9 (14)	39.1 (9)
Thymic carcinoma	16	25.0 (4)	75.0 (12)	25.0 (4)	75.0 (12)
Thymoma	14	100 (14)	0 (0)	92.9 (13)	7.1 (1)
P		<0.001		0.001	

*, Compared with lymphoma and thymic carcinoma, a majority of thymoma cases had homogenous enhancement patterns in the arterial phase (Fisher's exact test, 100% vs. 56.5%, P=0.006; 100% vs. 25.0%, P<0.001); **, Compared with thymic carcinoma, thymoma had less frequency of internal necrosis (7.1% vs. 75.0%, P<0.001).

Table 5 Detection rate for internal necrosis and pericardial effusion before CEUS and after CEUS between thymic carcinoma and thymoma

Groups	Internal necrosis [% (n)]		Pericardial effusion [% (n)]	
	Thymic carcinoma (N=16)	Thymoma (N=14)	Thymic carcinoma (N=16)	Thymoma (N=14)
Before CEUS	18.8 (3)	7.1 (1)	12.5 (2)	7.1 (1)
After CEUS	62.5 (10)	7.1 (1)	56.3 (9)	14.3 (2)
P	0.029*	1.000	0.023*	1.000

*, Compared with conventional ultrasound, CEUS increased the detection rate for internal necrosis (62.5% vs. 18.8%, P=0.029) and pericardial effusion (56.3% vs. 12.5%, P=0.023) in thymic carcinoma.

conventional ultrasound, CEUS increased the detection rate for internal necrosis (62.5% vs. 18.8%, P=0.029) and pericardial effusion (56.3% vs. 12.5%, P=0.023) in thymic carcinoma (Table 5).

Number of biopsy puncture attempts and diagnostic accuracy rate

Regarding to the number of biopsy puncture attempts, the CEUS group had a mean of 2.36±0.70 times of puncture attempts, and the US group had 2.21±0.51 times of puncture attempts. The two groups had similar results in the number of puncture attempts (P>0.05, Table 6).

Using the final diagnosis as the criterion, the biopsy diagnostic accuracy rate was 96.9% (62/64) in the CEUS group, which was significantly higher than 84.3% (43/51) in the US group (P=0.022). We also found the close relationship between tumor sizes and biopsy diagnostic accuracy rates. For lesions ≤5 cm in diameter, the accuracy rates of CEUS group (100%) and US group (88.9%) were not significantly different (P=1.000). For lesions >5 cm in diameter, the accuracy rate of the CEUS group (96.5%) was significantly higher than that of the US group (83.3%, P=0.034, Table 6).

Complications

Two cases in the US group suffered mediastinal hemor-

Table 6 Puncture attempts and biopsy diagnostic accuracy in CEUS group and US group

Groups	Puncture attempts ($\bar{x}\pm s$)		Biopsy diagnostic accuracy (%)	
	≤ 5 cm	>5 cm	≤ 5 cm	>5 cm
CEUS group	1.83 \pm 0.75	2.40 \pm 0.71	100 (7/7)	96.5 (55/57)
US group	2.29 \pm 0.49	2.19 \pm 0.52	88.9 (8/9)	83.3 (35/42)
P	0.220	0.120	1.000	0.034*

*, For lesions >5 cm in diameter, there was a statistically significant difference in the biopsy accuracy rate between the CEUS and US group (96.5% vs. 83.3%, $P=0.034$).

rhage after the needle biopsy (Figure 4). Both patients received hemostasis treatment and prolonged hospitalization period. No major complications happened in the CEUS group. Regarding to minor complications, 1 case in the CEUS group and 2 cases in the US group developed slight chest pain after the biopsy and relieved after rest.

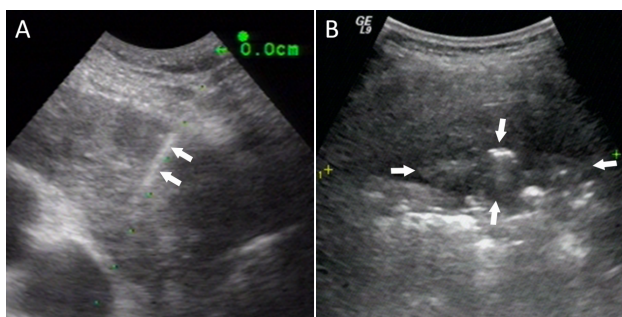


Figure 4 A bleeding complication after biopsy in US group. A 56-year-old male with anterior mediastinum lesion chose US-guided transthoracic biopsy without CEUS. (A) ultrasound guided biopsy (\uparrow) was performed. The patient had chest choke after puncture in 1 h; (B) Four days later, bloody effusion (\uparrow) was detected on ultrasound. The symptom was controlled after hemostatic treatment in hospital. The case discussion showed that conventional ultrasound failed to detect the superficial large vein and caused bleeding in this case.

Discussion

Mediastinal space-occupying lesions are characterized by complex histological types (13-15). Some lesions lack apparent specific features in both clinical and imaging examinations, therefore, it is difficult to generate a qualitative diagnosis for such lesions. Ultrasound scanning through suprasternal fossa and parasternal intercostal space can reveal most anterior-medial mediastinal lesions. In recent years, ultrasound-guided biopsy has been increasingly applied in the diagnosis of peripheral

pulmonary and mediastinal lesions due to its many advantages, such as flexibility, repeatability, non-radiation and real-time monitoring throughout the procedure, compared to chest CT; it can even be performed in general wards (16,17). So the application of ultrasound-guided biopsy technology in mediastinal lesions has attracted increasing attention from clinicians (18).

In general, conventional ultrasound-guided mediastinum biopsy is sufficient to obtain the necessary pathological tissues. However, during the growth process of tumors, tissue liquefaction and necrosis often occur due to inadequate blood supply to the tumors. In addition, most patients lack typical clinical symptoms, which make it difficult to prompt diagnosis, resulting in large lesions. It is relatively difficult to use gray-scale ultrasonography to determine lesion property and whether there is intra-lesion necrosis (19). With the emergence of a new generation of ultrasound contrast agents, such as SonoVue, ultrasound is more convenient than CT scanning to reveal the blood supply inside lesions, because SonoVue is pure blood pool imaging agent (5,20,21). In the present study, we explored the role of CEUS prior to biopsy in mediastinal lesions. CEUS facilitated screening indications for biopsy to avoid zones of liquefied necrosis, thereby achieving a relatively high accuracy rate of biopsy.

CEUS plays a crucial role in the screening of indications for biopsy of solid organs and tissues as well as in guiding biopsy (22-24). Wang *et al.* and Cao *et al.* reported that in comparison with conventional ultrasound, CEUS could help to increase the accuracy rate of biopsy of pulmonary peripheral lesions and mediastinal lesions (24,25). However, the report only recruited about 10 patients with mediastinal lesions, which made it difficult for further analyses. Here, we recruited a relatively large sample size of patients undergoing mediastinal biopsy to compare CEUS and conventional ultrasound. We investigated not only the number of needle biopsies, accuracy rate of biopsy, and complications, but also the perfusion feature and neighboring structures of the lesions.

In this study, we performed CEUS-based assessment before biopsy and revealed that 3 cases had large superficial blood vessels in the puncture path, which were difficult to avoid; in addition, another 5 cases had internal necrotic zone being more than 80% of the lesion. Biopsy was therefore not performed for these patients to reduce the false negative rate as well as the risk of complications such as hemorrhage. Biopsy is an invasive diagnostic method and causes pain and complication risk for patients. At this point, CEUS could help to exclude the potential failure cases to avoid unnecessary invasive procedure, which is one of advantage of CEUS application before biopsy.

Ultrasound imaging analysis revealed that compared with the US group, CEUS generated a significantly higher detection rate of internal necrosis as well as a higher accuracy rate of pathological diagnosis for biopsy, which was consistent with the results of Wang *et al.* (24). Wang *et al.* performed biopsy of peripheral lung masses and revealed that CEUS improved necrosis detection rate and success rate of biopsy as the lesion size increased compared with conventional ultrasound. Similar to Wang's study, our findings showed that CEUS achieved a statistically significant difference in the display rate of internal necrosis mediastinal lesions, especially the lesions >5 cm in diameter. Hence, using CEUS prior to biopsy for anterior-medial mediastinal lesions could effectively bypass necrotic zones, and select optimal sites of tissue sample. In conventional ultrasound examination, color Doppler was performed to evaluate the vascularity. However, the display of vascularity by color Doppler is not sensitive as CEUS. CEUS could also accurately differentiate the viable regions from necrotic tissues in a lesion. As a consequence, CEUS had super role in screening indications for biopsy and choosing a proper puncture path, compared to color Doppler.

In addition, we also summarized the CEUS feature of lymphoma, thymoma and thymic carcinoma, which commonly occur in anterior-medial mediastinum. The results revealed that lymphoma and thymoma displayed significant differences in enhancement patterns during the arterial phase and thymoma typically manifested homogeneous enhancement. Compared with thymic carcinoma, thymoma had less frequency for internal necrosis. In addition, thymic carcinoma was associated with a significantly higher necrosis rate than that of lymphoma. Comparison of the necrosis rate and pericardial effusion between thymoma and thymic carcinoma before and after CEUS revealed that thymic carcinoma had high accident

for internal necrosis and pericardial effusion. This finding could be related with tumor biology that thymic carcinomas are more likely to develop intra-tumor necrosis and pericardium infiltration (26). As a consequence, it provides useful information to distinguish a benign tumor from a malignant tumor.

Moreover, the two groups had no difference in the total number of biopsy attempts. Comparison of the complications revealed that 2 cases in the US group developed mediastinal hemorrhage and prolonged hospitalization period for hemostasis treatment. No patients in the CEUS group developed any severe complications. In both groups, no patients developed other complications, such as pneumothorax, breathing difficulties, or pinhole metastasis (27). This low rate of complication results for biopsy could be explained by our strict screening of indications.

There were some limitations in our study. First, the two groups classified in this study were not randomized. Patients refused CEUS examination mainly because of economic factors. Second, compared to enhanced CT, CEUS has limitation for visualization of mediastinal lesion due to gas or rib. Also CEUS or ultrasound had difficulty to show some small lesions behind the sternum. CEUS-guided biopsy cannot be performed in such cases. Last, although CEUS improved the accuracy rate of biopsy compared to conventional ultrasound, there was high risk for biopsy in lesions close to heart or large vessels. So cautions should be paid in mediastinal biopsy.

Conclusions

In summary, CEUS technique could reliably differentiate the viable regions from necrotic tissues in a lesion and identify large superficial blood vessels in anterior medial mediastinal lesions. As a consequence, this technique may provide valuable information for screening indications for biopsy and choosing a proper puncture path, thereby addressing the shortcomings of conventional ultrasound-guided biopsy. CEUS prior to biopsy could improve the accuracy rate of biopsy, reduce the risk of complications, and thus become clinically important for mediastinal biopsy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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