

# Application value of contrast-enhanced ultrasound in the diagnosis of peripheral pulmonary focal lesions

Zina Bai, MD<sup>a</sup>, Tong Liu, MD<sup>b</sup>, Wei Liu<sup>c</sup>, Zhensheng Li, MD<sup>a</sup>, Hao Zheng, MD<sup>b</sup>, Xingbin Li, MD<sup>a,\*</sup>

## Abstract

**Introduction:** Peripheral pulmonary lesions are encountered frequently in clinical practice. Accurate diagnosis of these lesions is of great importance for clinicians. Ultrasound-guided lung tissue puncture is a reliable method for diagnosing these lesions.

**Objectives:** To investigate the application value of contrast-enhanced ultrasound (CEUS) combined with rapid on-site evaluation (ROSE) in the diagnosis of peripheral pulmonary focal lesions.

**Methods:** Eighty patients enrolled from July 2020 to June 2021 were divided into two groups: a conventional ultrasound group and a CEUS group. Both groups underwent diagnostic procedures guided by ROSE to improve the success rate of puncture sampling. The success rates and complications in both groups were compared. The results for lesion enhancement, time taken for the contrast agent to reach the lesions (AT) and lung tissues (L-AT), and the difference between these times ( $\Delta$ AT) were compared in the CEUS group.

**Results:** The success rate of biopsy in the CEUS group was 97.62%, which was significantly higher than that in the conventional ultrasound group (84%;  $P < .05$ ). Puncture complications did not occur in the CEUS group and occurred in 5.26% of the cases in the conventional ultrasound group, but the difference was not statistically significant ( $P > .05$ ). A comparison of enhancement of benign lesions and malignant lesions in the CEUS group showed a statistically significant difference ( $P < .05$ ). The difference between the AT and  $\Delta$ AT of benign and malignant lesions was statistically significant ( $P < .05$ ). The optimal threshold of  $\Delta$ AT was 2.05 s.

**Conclusion:** CEUS combined with ROSE is a very important approach for biopsy in the diagnosis of peripheral pulmonary focal lesions. CEUS has definite clinical value in the diagnosis of benign and malignant lung lesions.

**Abbreviations:** CEUS = contrast-enhanced ultrasound, ROSE = with rapid on-site evaluation, AT = agent reaching lesions, L-AT = lung tissues,  $\Delta$ AT = time difference of lesions and lung tissues.

**Keywords:** biopsy, contrast-enhanced ultrasound, peripheral pulmonary focal lesions, rapid on-site evaluation

## 1. Introduction

Peripheral pulmonary lesions are pulmonary lesions that occur below segmental bronchial openings and are often detected by chest imaging. These lesions are common disease entities, and their incidence has been increasing in people aged over 40 years in China. The lesions can be malignant or benign, and tumors and pneumonia account for more than 60% of the cases, seriously endangering the health of the population. Early and accurate diagnosis can help improve the curative effect, prognosis, and pain profile in patients. The gold standard for diagnosis of peripheral pulmonary disease is pathological

examination. At present, puncture biopsy methods for peripheral lung lesions include bronchoscopy, endobronchial ultrasound-guided transbronchial lung biopsy (EBUS-GS), CT- or ultrasonography-guided lung puncture, and other methods.<sup>[1-4]</sup> However, lesion tissue is difficult to obtain using bronchoscopy, and the positivity rate is low. EBUS-GS can improve the diagnosis rate of peripheral lung lesions by biopsy, but some peripheral pleural lesions still cannot be diagnosed, necessitating prolonged operations, substantial pain, and high treatment costs.<sup>[3,5]</sup> CT-guided lung puncture biopsy<sup>[6,7]</sup> is associated with certain hazards, such as high radiation exposure, high cost, and inconvenient appointments, and real-time guidance

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

The authors have no conflicts of interest to disclose.

The work described was original research that has not been published previously and is not under consideration for publication elsewhere, in whole or in part. The authors have declared that no competing interests exist.

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<sup>a</sup> Second Department of Pulmonary and Critical Care Medicine, <sup>b</sup> Department of Function, <sup>c</sup> First Department of Pulmonary and Critical Care Medicine, Hebei Chest Hospital, Shijiazhuang, Hebei, P.R. China.

\*Correspondence: Xingbin Li, Second Department of Pulmonary and Critical Care Medicine, Hebei Chest Hospital, Shijiazhuang 050000, China (e-mail: DoctorLi002021@163.com).

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cannot be performed throughout the entire process. However, ultrasound-guided lung tissue puncture is a relatively simple procedure that offers real-time guided puncture, safety, lower costs, and fewer complications. Ultrasound-guided lung puncture<sup>[8,9]</sup> has become an important tool for clinicians to identify peripheral lung lesions. Contrast-enhanced ultrasound (CEUS)<sup>[10]</sup> can improve the accuracy of lung puncture and can be used to differentiate benign and malignant peripheral lung tumors. This technique<sup>[8,10]</sup> can clearly show the necrotic area in the mass and the size of the surrounding large vessels and improve the sampling satisfaction and puncture success rates. Thus, the objective of this study was to discuss the value of CEUS-guided puncture in combination with field cytology in the biopsy of peripheral lung lesions. Rapid on-site evaluation (ROSE)<sup>[11,12]</sup> was used to determine whether biopsy sampling was successful.

## 2. Materials and Methods

### 2.1. Ethics

In this study, all methods were performed in accordance with the relevant guidelines and regulations. This retrospective observational study was approved by the ethics review committee of the hospital (No: 2020046). Informed consent was obtained from the patients or their next of kin.

### 2.2. Study participants

A total of 80 patients with peripheral lung lesions diagnosed by CT at our hospital between June 2020 and June 2021 were selected. These patients required ultrasound-guided lung biopsy to confirm the diagnosis. Informed consent was provided by the patient or an authorized representative before the operation. These patients included 45 males and 35 females aged 16 to 81 years (mean age,  $53.18 \pm 1.88$  years). Patients were divided into a conventional ultrasound-guided group (38 patients) and a CEUS-guided group (42 patients) according to the ultrasound method used for diagnosis. We included patients with peripheral lung lesions that were confirmed by CT scan at our hospital and required lung puncture biopsy to confirm the diagnosis. The lesions in these patients were close to the pleura and could be detected by ultrasound examination. The patients and their family members provided informed consent for the procedure. We excluded patients (1) who could not tolerate or cooperate with the operation; (2) showed severe cardiovascular diseases, myocardial infarction, acute myocardial ischemia, and circulatory failure; (3) showed severe respiratory diseases, pneumothorax, hemoptysis, and respiratory failure; (4) showed coagulation dysfunction or severe bleeding tendency; (5) had serious mental illness

### 2.3. Instruments and methods

The instruments used in this study included a HITACHI 850 ultrasound machine manufactured in Japan, Primo Star with an iLED biological microscope manufactured in Germany, CITOGLAS pathology-grade microscope slides, and Diff-Quick stain (R1/R2/R3).

### 2.4. Routine ultrasound examination

A Hitachi 850 ultrasound machine was used for the ultrasound evaluations. An abdominal probe was used to carefully examine the lung lesions. During the procedure, the patient's hands were raised in an upward posture to widen the intercostal space. On the basis of the lesion location indicated by CT, the operator carefully scanned the peripheral lesion of the lung. After identification of the lesion, information regarding the lesion size,

location, shape, presence of blood supply, presence of blood supply, presence of large vessels around the tumor, and presence of necrosis in the lesion and the size of necrotic area was recorded. On the basis of the lesion location and characteristics, the operator selected the best position, puncture point, puncture direction, and puncture depth for lung puncture. Each operation and recording were performed by the same senior attending physician (T.L.).

### 2.5. Contrast-enhanced ultrasound examination

Sulfur hexafluoride powder (Italian Bracco Company) was dissolved in 5 mL of 0.9% sodium chloride and immediately and fully shaken to form a suspension, which was used as an ultrasonic contrast agent. For the CEUS process, 2.0 mL of the suspension was obtained and quickly pushed into the median cubital vein, followed by an injection of 5 mL of 0.9% sodium chloride. CEUS was performed for 1–3 minutes each time. We recorded the enhancement morphology, the time at which the contrast agent reached the lesion tissue (AT), the time at which the contrast agent reached the lung tissue (L-AT), and the difference between these two-time values ( $\Delta$ AT). Each operation and recording was performed by the same senior attending physician (T.L.).

### 2.6. Rapid on-site evaluation

Puncture tissue was collected with a 5 mL syringe needle and rolled over slides to form smears of cells. Diff-Quick staining was then performed.<sup>[13]</sup> After drying, the prepared smears were placed into Diff-Quick stain R1 for 10 seconds to fix them. Next, the slides were placed in Diff-Quick stain R2 and shaken up and down for 10 seconds to evenly distribute the dye. Finally, the slides were placed in Diff-Quick stain R3 and again shaken up and down for 10 seconds to evenly distribute the dye. The residual liquid was rinsed with clean water, dried naturally, and examined under a microscope. ROSE of direct smears under a microscope was performed by an associate chief respiratory physician trained in cytopathology for 3 months.<sup>[14,15]</sup> If the punctured tissue was a nondiagnostic material or the number of cells was relatively small, the puncture site was adjusted for ROSE analysis. The total number of needle punctures in each patient was 4.

### 2.7. Ultrasound-guided puncture

Conventional ultrasound examination or CEUS was performed to determine the optimal puncture site, puncture area, needle entry point, and needle entry path. The local skin was disinfected with iodine volt and covered with sterile drapes. Local skin and pleura were anesthetized layers by layer with 2% lidocaine. The ultrasound probe guided the puncture needle to the lesion in real-time. The patient was asked to hold his or her breath and pull the trigger of the automatic biopsy needle to remove the tissue. After the puncture, all tissues were evaluated by ROSE to decide whether to repeat the puncture. If the puncture tissues qualified the ROSE, the operation was stopped. If not, the needle angle and route were adjusted appropriately, and the puncture was repeated. Biopsies were repeated up to four times. The tissue was fixed with 4% formalin and sent to the pathology department for diagnosis. The same puncture method and puncture needle-type were used in both groups. Ultrasound examination, CEUS, and lung biopsy were performed by the same senior attending physician in all cases.

### 2.8. Statistical analysis

Statistical analysis was performed using the SPSS version 24.0. Measurement data were expressed as  $\bar{x} \pm s$ , and a *t*-test was used for comparisons. Counting data were expressed as frequencies

using the  $\chi^2$  test. When the frequency was lower than 1, using Fisher’s exact probability method,  $P < .05$  indicated that the difference was statistically significant. A receiver operating characteristics (ROC) curve was constructed. The optimal cut-off point for  $\Delta AT$  was calculated according to the Youden index.

### 3. Results

#### 3.1. Characteristics of the included patients

A total of 80 patients were enrolled from July 2020 to June 2021. The conventional ultrasound group included 38 patients (28 males and 10 females; age, 19–80 years; mean age,  $50.42 \pm 17.45$  years) with a mean lesion size of  $5.36 \pm 1.56$  cm. The CEUS group included 42 patients (26 males and 16 females; age, 16–81 years; mean age,  $55.67 \pm 16.15$  years) with a mean lesion size of  $5.57 \pm 1.73$  cm. The two groups showed no significant differences in sex, age, and lesion size ( $P > .05$ ) (Table 1).

#### 3.2. Puncture positivity rate

The conventional ultrasound group included 38 cases (benign lesions, 10 cases; malignant lesions, 28 cases; puncture positivity, 32 cases; puncture negativity, 6 cases; puncture positivity rate, 84%). The CEUS group included 42 cases (benign lesions, 12 cases; malignant lesions, 30 cases; puncture positivity, 41 cases; puncture negativity, 1 case; puncture positivity rate, 97.6%). The puncture positivity rate in the CEUS group was higher than that in the conventional ultrasound group, and the difference between the two groups was statistically significant ( $\chi^2 = 4.492$ ,  $P = .034$ ) (Table 1).

#### 3.3. Incidence of puncture complications in the two groups

No serious complications such as pneumothorax, severe hypoxemia, and arrhythmia were found in this study. Minor bleeding complications occurred in two patients in the conventional ultrasound-guided lung puncture group. These patients did not receive clinical treatment and recovered under close observation. No complications occurred in the CEUS group, and Fisher’s exact test showed no statistically significant difference in the incidence of complications between the two groups ( $P = .222$ ) (Table 1).

#### 3.4. Types of lesions enhanced by CEUS

Enhancement patterns on CEUS can be divided into three types: uniformly enhanced, nonuniformly enhanced, and non-enhanced. In this study, 42 patients in the CEUS group showed

different degrees of enhancement. These included 12 benign lesions, of which five showed uniform enhancement and seven showed uneven enhancement. Among the 30 cases of malignant lesions, six showed homogeneous enhancement and 24 showed inhomogeneous enhancement. The  $\chi^2$  test showed that the difference between the two groups was statistically significant ( $\chi^2 = 5.893$ ,  $P = 0.015$ ) (Table 2).

#### 3.5. Comparison of quantitative parameters in the CEUS group

A contrast-time intensity curve (TIC) curve was constructed using the CEUS findings. The results showed that AT ( $9.84 \pm 2.50$  s) in the benign lesion group was earlier than that in the malignant lesion group ( $12.59 \pm 2.35$  s), and the difference between the two groups was statistically significant ( $P < .05$ ). L-AT in the benign lesion group ( $8.03 \pm 2.29$  s) was lower than that in the malignant lesion group ( $9.63 \pm 2.46$  s), but the two groups did not show a statistically significant difference in L-AT ( $P > .05$ ).  $\Delta AT$  in the benign lesion group ( $1.80 \pm 0.49$  s) was significantly lower than that in the malignant lesion group ( $2.96 \pm 0.69$  s), and the difference was statistically significant ( $P < .05$ ). The ROC curve was plotted, and the maximum area under the  $\Delta AT$  curve (AUC) was 0.914, with a minimum  $P$ -value ( $P < .01$ ). According to the Youden index, when  $\Delta AT = 2.05$  s, the sensitivity and specificity were 93.3% and 75%, respectively, demonstrating the highest value in the differential diagnosis of peripheral benign and malignant lesions (Table 3; Figures 1 and 2).

#### 3.6. Typical features of CEUS distinguish benign and malignant lesions

There are some typical differences between benign and malignant lesions by CEUS (Table 4). Two typical cases were listed, including one malignant lesion and one benign lesion. The female patient was diagnosed with lung squamous cell carcinoma (Figure 3). The other patient, a male, was diagnosed with chronic pulmonary inflammatory disease (Figure 4).

### 4. Discussion

Ultrasound can display lung lesions attached to the chest wall. Thus, ultrasound-guided lung tissue puncture shows the advantages of real-time guidance, convenience, safety, economy, and no radiation, and has attracted increasing attention as a result. Ultrasound-guided puncture of the peripheral lung tissue has been widely used in clinical practice. Studies have shown<sup>[16]</sup> that the success rate of conventional ultrasound-guided puncture

**Table 1**  
Results of both groups [n(%)].

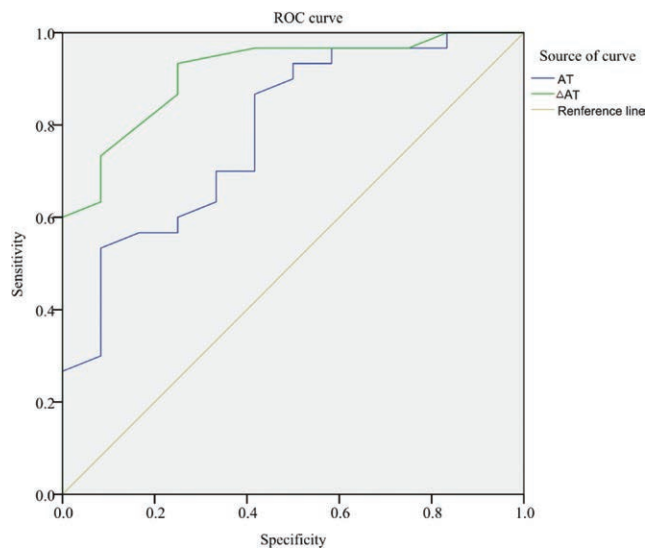
	Conventional ultrasound group (n = 38)	CEUS group (n = 42)	$\chi^2$	P value
Age	50.42 ± 17.45	55.67 ± 16.15	(t)1.396	.167
Sex			1.262	.261
Male	28 (73.68%)	26 (61.90%)		
Female	10 (26.32%)	16 (38.10%)		
Lesion size	5.36 ± 1.56	5.57 ± 1.73	0.558	.457
Pathological diagnosis			0.051	.821
Benign	10 (26.32%)	12 (28.57%)		
Malignant	28 (73.68%)	30 (71.43%)		
Puncture success rate			4.492	.034
Successful	32 (84.21%)	41 (97.62%)		
Failure	6 (15.79%)	1 (2.38%)		
Puncture complications	2 (5.26%)	0 (0)	–	.222

**Table 2**  
Types of lesions enhanced by CEUS [n (%)].

	n	Uniformly enhanced	Nonuniformly enhanced	$\chi^2$	P value
Benign	12	5 (41.67)	7 (58.33)	5.893	.015
Malignant	30	6 (20.00)	24 (80.00)		

**Table 3**  
Comparison of quantitative parameters in CEUS group.

	Benign (n= 12)	Malignant (n = 30)	t	P value
AT	9.84 ± 2.50	12.59 ± 2.35	3.362	.002
L-AT	8.03 ± 2.29	9.63 ± 2.46	1.932	.060
$\Delta AT$	1.80 ± 0.49	2.96 ± 0.69	5.278	.000



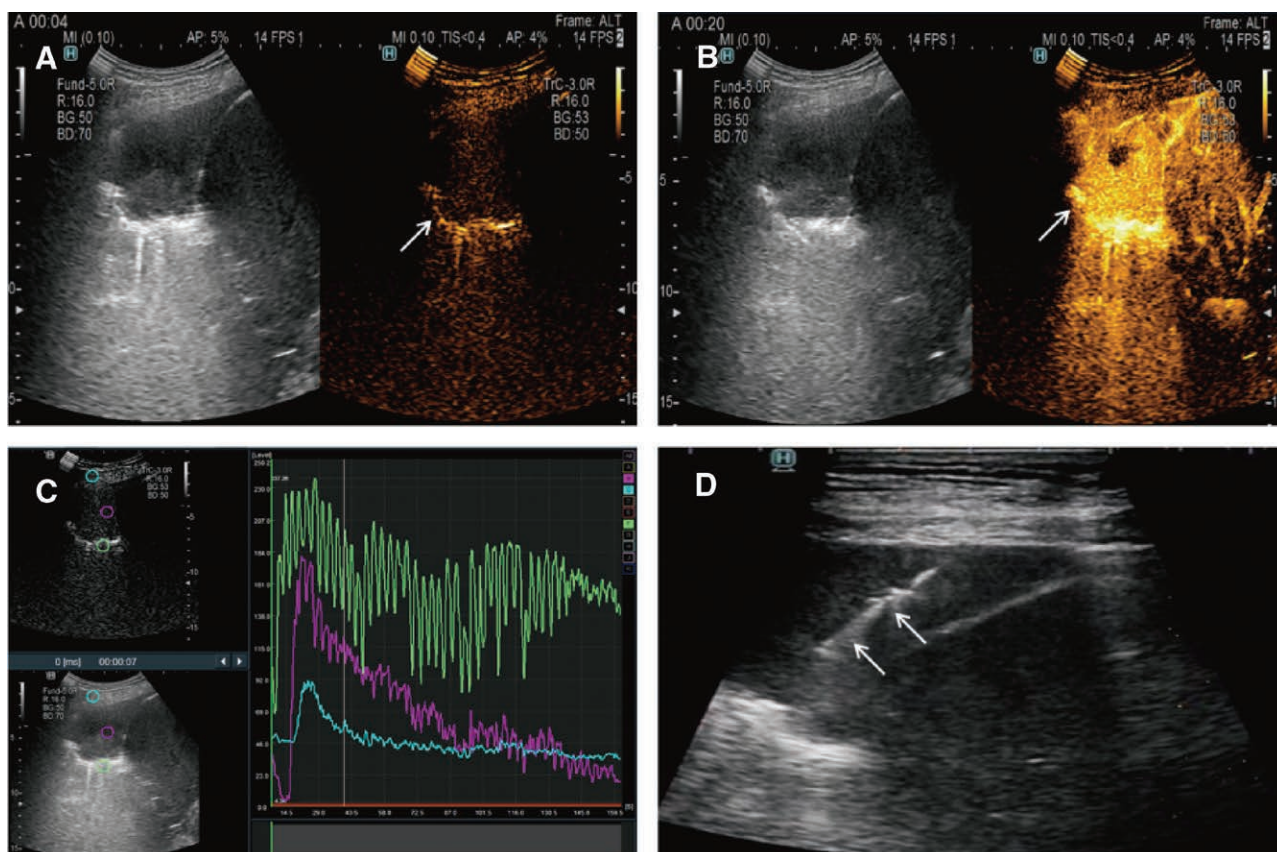
**Figure 1.** The ROC curve and the AUCs of AT and  $\Delta$ AT were 0.785 and 0.914, respectively.  $\Delta$ AT = time difference of lesions and lung tissues, AT = agent reaching lesions; AUCs =  $\Delta$ AT curve, ROC = receiver operating characteristics.

for peripheral lung lesions can be more than 80%. However, conventional ultrasound cannot distinguish the necrotic areas in lung masses, and the adjacent relationships with the surrounding large vessels cannot be clearly distinguished, resulting in certain false-negative results and sampling failure.<sup>[17]</sup> CEUS provides accurate ultrasonic signals for peripheral lung lesions,

differentiates benign and malignant lesions, and provides real-time dynamic guidance for the needle biopsy process, showing the advantages of no nephrotoxicity and high safety. It also reduces the possibility of puncture failure due to tissue scarcity or excessive necrotic tissue.<sup>[18]</sup> In this study, the appropriate needle entry angle and route were selected after CEUS to effectively avoid necrotic areas. ROSE was performed immediately after lung tissue puncture to determine whether the sample was available, effectively avoiding a blind operation, improving puncture positivity, and reducing the number of invasive examinations.

Systematic studies and meta-analyses of modern field cytology techniques began in the year 1993. A meta-analysis by Austin and Cohen<sup>[19]</sup> showed that participation in ROSE greatly improved the effectiveness of diagnosis, and the positive rate of ROSE-guided puncture was 100%, which was significantly higher than the positive rate of no ROSE-guided puncture (80%). Simultaneously, the study confirmed that participation in ROSE could improve the positive rate of surgery and eliminate unnecessary operations. Chandra<sup>[20]</sup> found that the diagnostic rate of cytopathology in the ROSE group was 96.5%, which could mean better sampling and prediction, less trauma, fewer complications, and a simple and easier operation. ROSE plays an important role in respiratory interventions, such as bronchoscopic biopsy, CT, or ultrasound-guided puncture.<sup>[21-23]</sup> In this study, the positive rate of guided puncture combined with field cytological puncture in the CEUS group was high, and there were no complications.

In this study, the success rate of CEUS-guided puncture was 97.6% (41/42), which was significantly higher than that -in the conventional ultrasound group. Wang et al.<sup>[17]</sup> showed that the diagnostic success rate was 96.3% in the CEUS group and 80%



**Figure 2.** CEUS process and guided puncture in the same patient. (A) contrast agent reaching lung tissues. (B) contrast agent reaching lesions tissues. (C) TIC (purple represents the focal tissue, green represents the surrounding lung tissue, blue represents chest wall tissue). (D) ultrasound-guided puncture. CEUS = contrast-enhanced ultrasound, TIC = time-intensity curve.

**Table 4**  
**Typical features of CEUS distinguish benign and malignant lesions.**

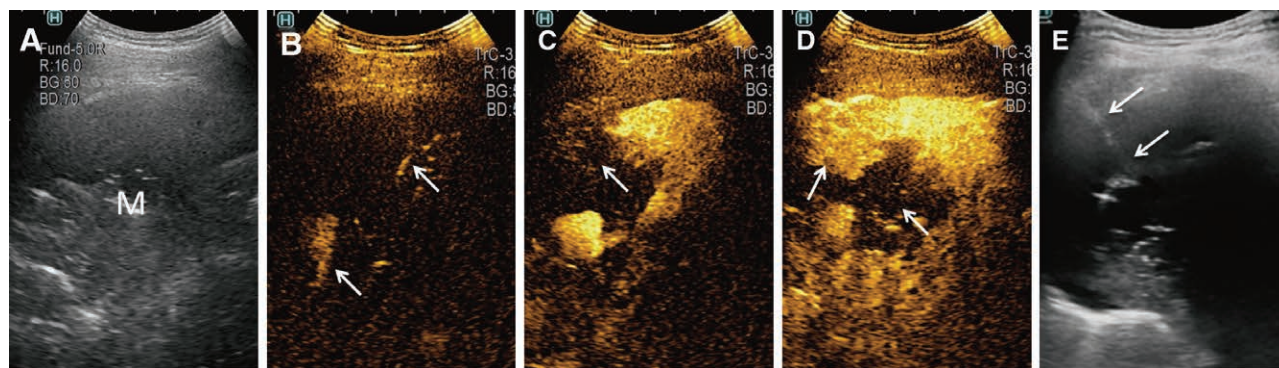
Typical features	Benign	Malignant
Enhancement mode	Dendritic	Centripetal
Internal form of enhancement	Uniformly	Nonuniformly
Enhancement time	Early	Advanced
ΔAT	<2.5 s	> or =2.5 s

in the US group, with statistically significant differences, and there were no significant differences in puncture complications between the two groups. Fu et al.<sup>[24]</sup> showed that 58 patients with unilateral subpleural lesions underwent guided puncture after CEUS, and the diagnostic rate after biopsy was 98.3%. These results are consistent with those of the present study, suggesting that CEUS-guided puncture can improve the puncture success rate.

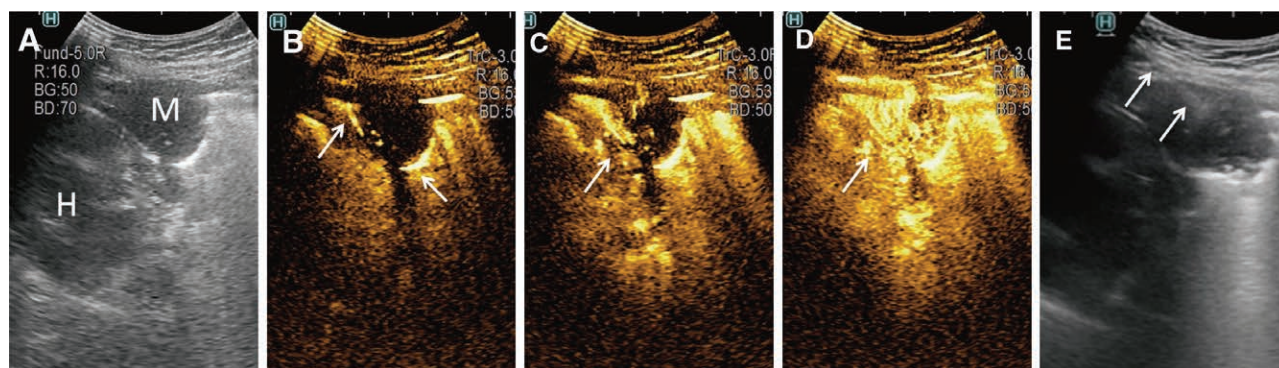
In this study, the results for the CEUS group showed that benign lesions mostly showed uniform enhancement, while malignant lesions showed uneven enhancement. The two groups showed a statistically significant difference. The benign and malignant tendencies of lesions were preliminarily judged according to morphology after ultrasound enhancement. The findings of this study are consistent with the results reported by Wang S,<sup>[25]</sup> Kong J,<sup>[26]</sup> and Gansevoort RT.<sup>[27]</sup> This can be attributed to the following reasons: malignant lesions required

a large number of immature new microvessels without a basement membrane for growth, and these vessels showed a large number of anastomotic branches and lateral branches, which were tortuous and unevenly distributed. Necrosis and non-enhanced areas are often observed. However, the blood supply in benign lesions was mostly from the pulmonary artery and its branches, which usually entered the mass through a single vessel. As a result, the shape of the vessels was relatively smooth, and there are few necrotic areas, so they are mostly uniformly enhanced.

CEUS is very important for differentiating benign and malignant peripheral lung lesions. Before its use for guiding lung puncture, CEUS can be used for preliminary differentiation between benign and malignant tumors, and the required examination items can be prepared in advance. Cases involving infectious disease may require tissue culture and second-generation sequencing for identification of the etiological factor, while those involving malignant disease may require testing for gene or immune receptors to identify therapeutic targets. Simultaneously, this procedure can also increase the confidence of the puncture procedure and guide the puncture. Studies have shown<sup>[10,28]</sup> that pulmonary benign lesions are mainly supplied by the pulmonary artery, while pulmonary malignant lesions are mainly supplied by the bronchial artery, so the enhancement time of benign lesions is earlier than that of malignant tumors. In the CEUS group in this experimental study, the AT of the benign lesion group ( $9.84 \pm 2.50$  s) was earlier than that of the malignant lesion group ( $12.59 \pm 2.35$  s). This significant difference between



**Figure 3.** CEUS and guided puncture process in a patient with lung squamous cell carcinoma. (A) conventional ultrasound showed a mass lesion (M). (B) contrast agent reaching lung tissues, L-AT=4 s. C contrast agent reaching lesions tissues, AT=10 s, ΔAT=6 s(>2.5 s), advanced enhancement. (D) the mass was completely enhanced. the enhancement mode is centripetal, nonuniformly. (E) ultrasound-guided puncture. ΔAT = time difference of lesions and lung tissues, AT = agent reaching lesions, CEUS = contrast-enhanced ultrasound, L-AT = lung tissues.



**Figure 4.** CEUS and guided puncture process in a patient with chronic pulmonary inflammatory disease. (A) Conventional ultrasound showed a mass lesion (M) and heart (H). (B) Contrast agent reaching lung tissues, L-AT=4 s. (C) Contrast agent reaching lesions tissues, AT=6 s, ΔAT=2 s (<2.5 s), early enhancement. (D) The mass was completely enhanced. the enhancement mode is dendritic, uniformly. (E) Ultrasound-guided puncture. ΔAT = time difference of lesions and lung tissues, AT = agent reaching lesions, CEUS = contrast-enhanced ultrasound, L-AT = lung tissues.

the two groups was consistent with the findings reported by Zhang et al.,<sup>[29]</sup> Zhang,<sup>[10]</sup> and Tang.<sup>[30]</sup> The time required for the contrast agent to reach the lung lesion and adjacent lung tissue is affected by many factors, including heart function, lung disease, contrast agent injection speed, and other individual differences. The use of  $\Delta AT$  as an observation index for the differential diagnosis of benign and malignant lung lesions can eliminate the influence of these factors and reduce the minor individual differences. Some studies<sup>[30–32]</sup> found that real-time comparative observations can be used to reduce the influence of individual differences, and the time difference between lesion and lung tissue enhancement ( $\Delta AT$ ) can be used as an observation index for the differential diagnosis of benign and malignant lung lesions.  $\Delta AT < 2.5$  seconds indicates benign lesions with early enhancement, while  $\Delta AT > 2.5$  seconds indicates malignant lesions with late enhancement. The accuracy rate can reach more than 90%. The results of this study were lower, with a value of 2.05 seconds. This may be attributed to the fact that the study participants had many chronic inflammatory diseases, such as mechanized pneumonia and tuberculosis, which may have led to atypical manifestations as a result of the gradual compensatory participation of the bronchial arteries in the blood supply.<sup>[1]</sup>

This study had some limitations. First, the patients were not randomly assigned to the two groups compared in this study. Data for case samples from July 2020 to June 2021 were collected retrospectively and grouped according to the use of CEUS. Second, the number of cases in this study was small, which needs to be further confirmed by increasing the number of cases.

## 5. Conclusion

CEUS-guided puncture combined with ROSE shows great application value for biopsy of peripheral lung lesions and can improve the success rate of puncture. It also shows clinical significance for the differential diagnosis of benign and malignant lesions.  $\Delta AT = 2.05$  seconds showed the highest value in the differential diagnosis of peripheral benign and malignant lesions. All relevant data are within the paper and its Supplemental Digital Content, <http://links.lww.com/MD/G953>.

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## Author contributions

Conceptualization: Zina Bai, Hao Zheng, Xingbin Li.

Data curation: Zina Bai, Tong Liu, Wei Liu, Hao Zheng.

Formal analysis: Zina Bai, Wei Liu.

Methodology: Zina Bai, Tong Liu, Xingbin Li.

Software: Zina Bai.

Supervision: Xingbin Li.

Visualization: Hao Zheng, Xingbin Li.

Writing – original draft: Zina Bai, Tong Liu, Wei Liu.

Writing – review & editing: Zina Bai, Zhensheng Li, Hao Zheng, Xingbin Li.

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