European Review for Medical and Pharmacological Sciences 2021; 25: 5781-5789

Assessing value of contrast-enhanced ultrasound *vs.* conventional transthoracic ultrasound in improving diagnostic yield of percutaneous needle biopsy of peripheral lung lesions

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Abstract. – OBJECTIVE: The aim of the present study was to systematically assess the value of contrast-enhanced ultrasound (CEUS) vs. conventional transthoracic ultrasound (TUS) in improving diagnostic accuracy of percutaneous needle biopsy (PTNB) for subpleural lung lesions.

PATIENTS AND METHODS: 232 patients with subpleural lesions were 1:1 randomly assigned to a group were CEUS was performed (n=116, mean age=65.5±5.6, M=69) or not (n=116, mean age=66.0±5.3, M=70). For CEUS study was used an injection of 4.8 mL of SonoVue (Bracco, Italy). For PTNB was employed a Menghini-modified technique with a semi-automatic 18-gauge needle.

RESULTS: The mean diameter of subpleural lesions was 2.85±0.7 cm in the CEUS+ group and 2.95±0.6cm in the CEUS– group. Only 3 lesions, 1 in the CEUS+ group and 2 in the CEUS– group measured >5 cm. CEUS showed no superiority in terms of diagnostic accuracy compared to conventional TUS (p=0.34). Similar results were obtained in the sub-analysis of lesions sized between 1-2 cm (p=1.00) and 2-5 cm (p=0.08). As the lesion size increased, the detection rate of necrosis in lesions increased by CEUS (from 8% to 31%). CEUS showed no superiority in terms of diagnostic accuracy in the sub-analysis of necrotic lesions at CECT (p=0.38). AUC values for both the groups assessed an excellent diagnostic yield for TUS-PTNB (≥0.80).

CONCLUSIONS: CEUS study does not improve the diagnostic accuracy of TUS-guided PTNB for peripheral lung lesions <5 cm of diameter. Further studies evaluating CEUS guidance for larger (>5 cm) and necrotic lesions are needed prior that its potential can be clarified.

Key Words:
Transthoracic ultrasound, Contrast-enhanced ultrasound, Ultrasound contrast agents, Ultrasound-guided percutaneous needle biopsy, Vascular ultrasound.

Introduction

Lung cancer represents the main cancer-related cause of death worldwide. According to international guidelines, the diagnostic and staging process for lung cancer includes several imaging studies, such as chest radiography, chest CT and positron emission tomography (PET) scans[1-4]. The definitive diagnosis is achieved only by biopsy of pathological lung tissue.

Transthoracic ultrasound (TUS) is included in the ERS/ATS[5] and NICE guidelines[6] among the

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possible methods of choice in guiding the biopsy of subpleural lung lesions. The main advantage of TUS-guided biopsy is the possibility to track the needle movements inside the lesion to be biopsied, helping to reduce post-operative complications[3]. Conversely, the main disadvantages include anatomical and technical restrictions linked to lesions location. Indeed, TUS allows to imagine only lesions that are adherent to the parietal pleural surface, when they are not obscured by bone structures of the thoracic cage[7]. Furthermore, it is not always easy to find out detailed information about tissue structure from gray-scale and color Doppler ultrasound, such as whether there is necrosis within lesions[7,8]. In this context, contrast-enhanced ultrasound (CEUS) may find a potential application in guiding the biopsy of peripheral lung lesions, discriminating viable areas to be sampled from non-enhanced areas which are likely to be necrotic.

In Europe, CEUS use is currently approved for several cardiac and/or non-cardiac indications, including echocardiography, assessment of diseases in large vessels (such as aorta, carotid and intracranial vessels, peripheral arteries, renal arteries) and study of the microcirculation of parenchymatous organs (i.e., breast and focal liver lesion)[9]. Despite clinical studies have shown that ultrasound contrast agents could improve accuracy and safety of PTNB of peripheral lung and mediastinal lesions[10,11], CEUS is still used off-label for the study of lung diseases.

The aim of the present intervention study was to compare the diagnostic accuracy of TUS-PTNB for subpleural lung cancers when performed with and without a prior CEUS study. The study hypothesis was that CEUS guidance had a superior effect on lung biopsy diagnostic yield compared with conventional ultrasound alone.

Patients and Methods

This was a single-center prospective 1:1 randomized parallel-group intervention study comparing the diagnostic accuracy of TUS-PTNB for subpleural lung cancers when preceded or not by a CEUS study.

A previous meta-analysis[12] estimated that CEUS-guided PTNB of subpleural lung lesions had a higher success rate compared with conventional ultrasound (95.4% and 80.8%, respectively). At a significant type I error rate of 5%, a power of 90% and a 95% CI, Fleiss' formula with correction for continuity for Fisher's exact test calculated an ideal sample size of 230 patients, with 115 patients in each group (CEUS+ and CEUS–).

In the period between February 2018 and February 2019, a total of 238 patients with subpleural pulmonary lesions scheduled for histological assessment by TUS-PTNB in our Unit of Interventional and Diagnostic Ultrasound of the Research Institute "Casa Sollievo della Sofferenza" (San Giovanni Rotondo, Italy) were assessed for eligibility, using the following inclusion criteria: (1) adults aged > 18 years; (2) presence of subpleural pulmonary lesions confirmed by preoperative contrast-enhanced computed thomography (CECT) and suspected for malignancy. The exclusion criteria included the following: (1) a prolonged prothrombin time (PT-INR>1.5) or a platelet count <30,000; (2) right-to-left shunts; (3) severe pulmonary hypertension (i.e. pulmonary artery pressure >90 mmHg); (4) uncontrolled systemic hypertension (i.e., systolic blood pressure>140 mmHg); (5) massive pleural effusion (i.e. complete or near-complete opacification of the ipsilateral thorax on chest radiograph); (6) adult respiratory distress syndrome (ARDS); (7) pregnancy or breast-feeding. All the patients were asked to sign a written informed consent. 2 patients refused to give their consent and 4 patients were excluded from the study because of peripheral pulmonary lesions not clearly displayed on ultrasound. Finally, 232 patients were enrolled. Recruited patients were consecutively randomized at a 1:1 ratio into CEUS group (CEUS+) or the conventional TUS group (CEUS–), and the corresponding technique was used to assist the biopsy procedure. The CONSORT diagram for this study was shown in Figure 1.

The study followed the amended Declaration of Helsinki, and the Local Institutional Ethical Review Board approved the protocol (TACE-CSS, No. 106/2018).

Pre-Operative CECT

All the patients received a CT scan with contrast within 7-days before the biopsy procedure, according to the current diagnostic and staging protocol for lung cancer[1,2]. Chest CT imaging was performed on a multi-detector CT scanner with 64 channels (Toshiba, Tokyo, Japan) using the following protocol parameters: tube voltage, 120 kVp; standard tube current, 60-120 mAs (using an automatic exposure control system); slice thickness, 0.5 mm; reconstruction interval, 0.5-1.0 mm. Patients in the supine position were asked to

hold their breath during scanning. All the patients received a dose 0,5-2 ml/kg of the nonionic iodine contrast agent Iopamiro 370 mg/ml (Bracco, Milan, Italy) with the use of a power injector *via* an 18 or 20-gauge cannula in an antecubital vein. The enhanced CT scan started 60 seconds after the administration of the contrast medium.

Pre-operative CT scan confirmed the presence of subpleural lesions and was used to record the location and the size of the pulmonary nodules of interest. On the enhanced CT scan, necrosis was defined as a low-attenuation area within a lesion. The degree of tumor necrosis was semi-quantitatively graded in percent, nearest to the 5%, of the total consolidated area of the lesion. Extensive necrosis was defined as >50%.

TUS Examination

TUS was performed with an Esaote MyLab Twice scanner (Genoa, Italy) and a multifrequency dedicated probe (3-8 MHz) provided with a central hole for needle insertion during guided-biopsy. The following pre-setting was used for examination: tissue harmonics on, time gain compensation between 40% and 50%, electronic imaging focus on the pleural line. Bilateral scans were performed in the sitting position through all the ventral, posterior and lateral intercostal spaces. In the CEUS– group, conventional B-mode TUS scan was used to record the ultrasound pattern of the lesion (hypoechoic, anechoic, mixed). Internal tumor necrosis was defined as a focal area of decreased echogenity within the lesion. Although the use of color Doppler ultrasound in the evaluation of lung necrosis may be biased by respiratory movements and heart pulses giving rise to the so-called "flash artifact" (i.e., a spurious flow signal arising due to tissue/transducer motion)[7], the lack of central color Doppler flow within an identified hypo/anecoic area was used to support the diagnosis of necrosis.

Patients in the CEUS+ group received an intravenous injection of 4.8 mL of the new generation ultrasound contrast agent SonoVue (Bracco, Milan, Italy)[13], followed by 10 mL of regular saline. The CEUS scan was performed with a mechanical index of ≤ 0.04 and the chronometer included in the scanner allowed the assessment of temporal characteristics of flow enhancement. The lesion was observed for the necessary time for maximum diagnostic information on lesion vascularity to be obtained. According to EFSUMB guidelines[9], due to the particularity of lung circulation, the bolus of contrast medium will allow to obtain these information after at least 3.5 minutes. CEUS images were recorded and stored as dynamic videoclips and information from CEUS pattern were used to select the sampling site. The enhancement pattern (homogeneous or inhomogeneous) of each lesion was recorded. Active areas were defined as the enhanced regions of the lesion. Tumor necrosis was defined as regions that did not take up contrast agent inside the lesions.

Biopsy Procedure

PTNBs were performed by two interventional radiologists with a 30-year experience using a "modified Menghini" technique[14] in all the patients. Operators were informed about lesion location and size on CT scan, but were blinded regarding their enhancing characteristics on CECT.

Local anesthesia was obtained by applying a solution of lidocaine cloridrate 20 mg/ml. Once the lesion was clearly individuated on B-mode TUS scan, the patient was instructed to suspend

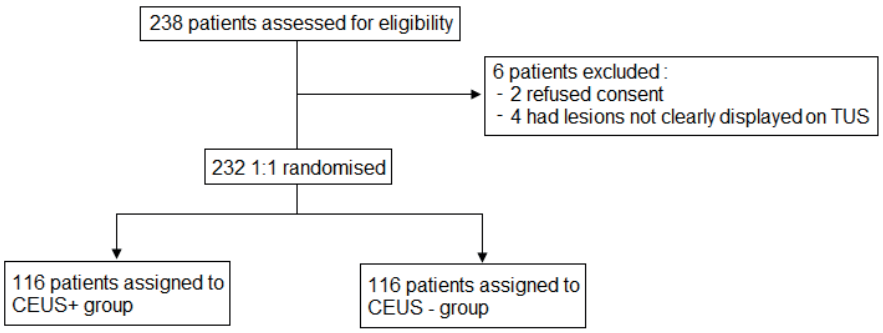

Figure 1. Flow diagram showing randomized trial recruitment.

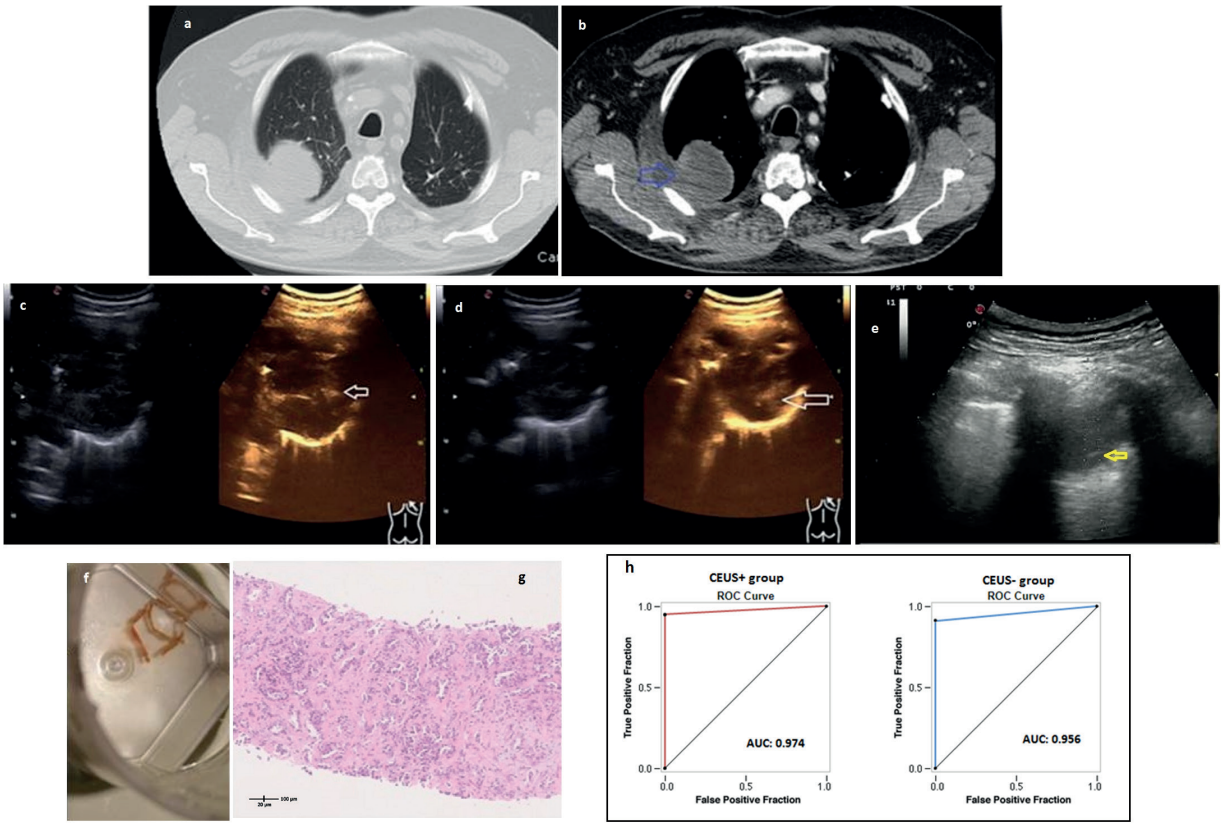

Figure 2. CT, CEUS and histology images of a case of adenocarcinoma. ROC curves for CEUS+ and CEUS– group. **A,** Axial CT scan (lung window), showing lung cancer in the periphery of the posterior segment of the right upper lobe. During the execution of the CEUS study and the biopsy, the patient, in a sitting position, was asked to raise the right arm bringing the right hand on the left shoulder in order to better visualize the lesion (which in the supine position seems to be covered by the shoulder blades). **B,** Mediastinal window of CT scan allows to view that the lesion infiltrates the pleura and contains necrosis (blue arrow) on its right upper posterior part; **(c)** CEUS with SonoVue at 16 seconds: minimum lesion perfusion (white arrow); **(d)** CEUS with SonoVue at 60 seconds: very mild increase of lesion perfusion (white arrow); **(e)** Needle (yellow arrow) directed towards the area of the lesion that was enhanced during the CEUS study. **(f)** Bioptic materials, about 1 cm per whip; **(g)** Lesion histology (10x) whose final diagnosis was adenocarcinoma; **(h)** ROC curves for CEUS+ (red) and CEUS– (blue) group.

respiration and a semi-automatic 18-gauge Menghini-type needle (Biomol, Hospital Service SpA, Aprilia (LT), Italy) was advanced through the tract designed by the dedicated probe and, so, within the lesion under real-time guidance. The syringe plunger was then released, removing the stylet and applying suction. The operator made "a back and forth" movement with the needle in order to facilitate the ascent and sample of pathological material.

A pathologist was not present during the procedure. The repetition of the biopsy in the same session was decided by the operator according to the adequacy of the sample obtained, as judged using visual inspection.

In both the CEUS+ and the CEUS– group the lung lesion biopsy was performed using real-time B-mode TUS image as a guide. The only difference was that in the CEUS + group the recorded US contrast pattern of the lesion was simultaneously shown on a split screen, in order to allow the operator to perform the procedure taking care to avoid non-enhanced areas.

At the end of the biopsy procedure, patients were closely monitored for 3 to 4 hours to exclude complications. A confirmation Chest-X ray was performed to exclude the occurrence of pneumothorax.

Final Diagnosis

Histological diagnosis was performed by two pathologists with expertise in lung cancer that were blinded to the conventional TUS and CEUS findings. Biopsy were considered to be non-diagnostic if the specimens were insufficient or

they did not allow a clear descriptive diagnosis, such as necrosis, fibrotic tissue, chronic inflammation, normal lung. Cases with non-diagnostic results were confirmed to be malignant from other means, such as video-assisted thoracoscopic surgery (VATS) or open surgery.

Statistical Analysis

Numerical results were presented as mean values ± standard deviation (mean±SD) and Student's *t*-test was used to assess differences between CEUS+ and CEUS– group. Categorical variables were presented as number and percentage (n, %) and the differences between CEUS+ and CEUS– group were assessed using Fisher's exact test. Diagnostic accuracy was estimated as the percentage of biopsies allowing a histology diagnosis in both groups. In addition, we made a sub-analysis for different lesion sizes and lesions showing areas of necrosis at CECT by comparing the rate of final diagnosis between the CEUS+ and the CEUS– group, considering significant *p*-values <0.05. TUS-PTNB sensitivity and specificity were calculated with a 95% confident interval (CI) in the CEUS+ and CEUS– groups. The empiric Receiver Operating Characteristic (ROC) curve analysis was used to study the diagnostic accuracy of the procedure in the two groups. Area under the ROC Curve (AUC) values of 0.50-0.59, 0.60-0.69, 0.70-0.79 and ≥0.80 were defined as indicative of none, poor, acceptable and excellent yield, respectively.

Results

Patients in the CEUS+ and the CEUS– group were not different as far as age (65±6.5 *vs.* 66±5.3 years, respectively; p=0.45), number of men/women (69/47 *vs.* 70/46; p=1.00) and percentage of smokers (67% *vs.* 71%; p=0.69). On chest CT, the mean diameter±SD, in cm, of the consolidated areas subjected to biopsy was 2.85±0.7 in the CEUS+ group *vs.* 2.95±0.6 in the CEUS– group (p=0.24). The identified lesions were mostly located at the posterior-basal (99/232, 43% of the total), lateral-basal (62/232, 28%), posterior-medial (31/232, 13%) and lateral-medial (28/232, 12%) portions of the lung. In the remaining 12/232 patients, consolidated areas were localized in the anterior medial (3%) and apical (2%) regions. There was no difference in the topographic distribution of the consolidated areas between the two groups (Table I).

A diagnosis of lung carcinoma or metastasis was reached in 109 out of 166 cases (94.0%) in the CEUS+ group and in 104 out of 116 patients (89.7%) in the CEUS– group, without significant differences (6.0% *vs.* 10.3%, p=0.34) (Table II). 1/22 (4.5%) biopsies were found to be non-diagnostic in the subgroup of lesions measuring between 1-2 cm, 17/107 (15.9%) in that of lesions measuring between 2-5 cm and 1 (33%) among the 3 lesions measuring >5 cm. There were no differences in the diagnostic rate of lesions sized between 1-2 cm (11/12, 91.7% *vs.* 10/10, 100%; p=1.00) and 2-5 cm (98/103, 95.0% *vs.* 92/104, 88.4%; p=0.08) in the two groups. Due to the small number of lesions sized >5 cm, the diagnostic yield of PTNB in such subgroup of lesions was not estimated.

The detection rate of internal necrosis at CECT did not differ between the CEUS+ and the CEUS– group (36/116, 31% *vs.* 39/116, 33.6%, p=0.68). Extensive necrosis at CECT (>50%) was observed in 8/232 lesions sized between 3.75 cm and 6.5 cm, with no difference between the two groups (5/116, 4.3% *vs.* 3/116, 2.6%; p=0.72). As the lesion size increased, the detection rate of necrosis in lesions increased by CEUS. More specifically, CEUS identified not enhancing regions in 1/12 (8%) lesions measuring between 1-2 cm, in 32/103 (31%) lesions measuring 2-5 cm and in 1/1 (100%) lesions measuring >5cm. In the subgroup of lesions showing internal necrosis at CECT, no significant difference was observed in the rate of diagnostic biopsy between the CEUS+ and the CEUS– group (29/36, 80.5% *vs.* 28/39 74.4%, respectively; p=0.38).

On ultrasound, a minimal associated basal pleural effusion was found in 69 lesions (59.5%) in the CEUS– group and in 71 lesions (61.2%) in the CEUS + group, with no differences between the two groups (p=0.76). Anyhow, in no case the effusion was such extent to alter CEUS study or the visualization of the lesion during the guided biopsy procedure.

Causes of non-diagnostic biopsies in both groups were areas of necrosis or fibrotic tissue with necrosis in the samples, causing presence of insufficient amount of viable material for correct and complete diagnosis. In one case the sample showed normal lung. Macroscopically inadequate sampling for which was required the immediate repetition of the biopsy procedure during the same session (i.e., fragmented tissue) occurred in the 3% of cases in both the groups (Table II).

Table I. Demographic characteristics of patients and characteristics of lesions on pre-operative computed tomography (CT) and transthoracic ultrasound (TUS) in the CEUS+ and CEUS– group.

	CEUS+ n=116	CEUS– n=116	*p*-value*
Demographic characteristics			
Age, y (mean ± SD)	65.5±5.6	66.0±5.3	0.48
Women, n (%)	47 (40.5)	46 (39.7)	1.00
Men, n (%)	69 (59.5)	70 (60.3)	
Smokers, n (%)	67 (57.8)	71 (61.2)	0.69
Lesion location on CT, n (%)			
Posterior-basal	51 (44.0)	48 (41.4)	0.79
Posterior-medial	12 (10.3)	19 (16.4)	0.25
Lateral-basal	31 (26.7)	31 (26.7)	1.00
Lateral-medial	15 (13.0)	13 (11.2)	0.84
Anterior-medial	4 (3.4)	3 (2.6)	1.00
Anterior-apical	3 (2.6)	2 (1.7)	1.00
Lesion size on CT, cm (mean ± SD)			
Mean diameter on CT, cm	2.85±0.7	2.95±0.6	0.24
Mean diameter on TUS, cm	2.68±0.6	2.80±0.5	0.22
Distribution of lesions size on CT, n (%):			
1-2 cm	12 (10.3)	10 (8.6)	0.82
2-5 cm	103 (88.8)	104 (89.7)	1.00
>5 cm	1 (0.9)	2 (1.7)	1.00
Internal necrosis on CECT, n (%)	36 (31.0)	39 (33.6)	0.68
Extensive necrosis on CECT, n (%)	5 (4.3)	3 (2.6)	0.72
TUS pattern, n (%)			
Hypoechoic	42 (36.2)	46 (39.7)	0.59
Anechoic, n (%)	14 (12.1)	15 (12.9)	0.84
Mixed (hypo-anechoic), n (%)	55 (47.4)	52 (44.8)	0.69
Mixed (hypo-hyperechoic), n (%)	5 (4.3)	3 (2.6)	0.47
Pleural effusion on TUS, n (%)	71 (61.2)	69 (59.5)	0.76

*Assessed with Student's t-test for numerical data and Fisher's exact test for categorical variables. Abbreviations: CECT, contrast-enhanced computed tomography; TUS, Transthoracic ultrasound; CEUS, contrast-enhanced ultrasound; PTNB, percutaneous needle biopsy.

In the CEUS+ group, 7 lesions had inconclusive diagnoses from US-guided PTB. Among them, 6 lesions were later identified as false-negative for malignant, and 1 lesion was diagnosed as chronic organizing pneumonia after surgical excision (true-negative for malignant). In the CEUS– group 12 lesions showed inconclusive results from US-guided PTB and underwent sur-

Table II. Results of transthoracic ultrasound-guided percutaneous needle biopsy (TUS-PTNB) in the CEUS+ and CEUS– group.

	CEUS + n=116	CEUS – n=116	*p*-value*
Diagnostic biopsy, n (%)	109 (94.0)	104 (89.7)	0.34
Not diagnostic biopsy, n (%)	7 (6.0)	12 (10.3)	
Final diagnosis, n (%)			
Metastasis, n (%)	5 (4.3)	10 (8.6)	0.18
Small cell lung carcinoma, n (%)	10 (8.6)	7 (6.0)	0.45
Squamous carcinoma, n (%)	18 (15.5)	22 (19.0)	0.49
Adenocarcinoma, n (%)	51 (44.0)	41 (35.3)	0.18
Undifferentiated carcinoma, n (%)	25 (21.6)	24 (20.7)	0.87
Necrotic tissue	2 (1.7)	5 (4.3)	0.45
Fibrous tissue with necrosis	5 (4.3)	6 (5.2)	1.00
Normal lung	0 (0.0)	1 (0.9)	1.00
Repeated biopsy in the single session, n (%)	4 (3.0)	4 (3.0)	1.00

*Assessed with Fisher's exact test for categorical variables. Abbreviations: CEUS, contrast-enhanced ultrasound.

gical biopsies for suspected malignancy. From these second biopsy results, 10 lesions were reported as false-negative cases for malignant and 2 lesions showed benign diagnoses including a case of lung abscess and a case of chronic organizing pneumonia. The overall sensitivity and specificity of TUS-PTNB in the CEUS+ group were 94.78% (95% CI: 88.99% to 98.06%) and 100% (95% CI: 2.50% to 100.00%), respectively. The AUC value was 0.974. In the CEUS– group, sensitivity and specificity of TUS-PTNB were 91.23% (95% CI: 84.46% to 95.71%) and 100% (95% CI: 15.81% to 100.00%). The AUC value was 0.956 (Figure 2).

No major complication occurred in both the CEUS+ and CEUS– group. Regarding to minor complication, 1 case in the CEUS+ group and 2 cases in the CEUS– group presented a self-limiting pneumothorax on post-biopsy chest radiograph.

Discussion

This study aimed to systematically assess the value of contrast-enhanced ultrasound (CEUS) in improving the diagnostic yield of PTNB for peripheral lung lesion.

Unlike CT and MR contrast agents that have a molecular size, US contrast micro-bubbles are small enough to cross capillary bed but too large to enter the interstitial space. Therefore, US contrast agents can enhance even vessels as small as 50 μm in size that are well below the detection threshold of power Doppler US, as flow is too slow to be differentiated from the surrounding tissue motion.

Data from other clinical studies[15-17] have showed a remarkable value of CEUS in guiding biopsy of mediastinal and peripheral lung lesions. However, the current literature on CEUS value in guiding biopsy procedures for pleural based lung lesion is too heterogeneous in terms of study design, population selection and lesion location and the risk of bias for meta-analysis is high. In a recent systematic literature review by Jacobsen et al[12] were examined six studies comparing CEUS-guided versus TUS-guided PTNB. All the studies individually reported data favoring CEUS guide, with a mean diagnostic accuracy of 95.4% for CEUS vs. 80.8% for conventional TUS. Despite this, four of the examined studies assessed only mediastinal lesions, one study assessed peripheral pulmonary lesions and one study assessed both mediastinal and peripheral pulmonary lesions.

The strength of this study is to have compared the diagnostic accuracy of PTNB for subpleural lung lesion when guided by conventional TUS or CEUS on a substantially large group of 1:1 randomized patients. According to the study results, CEUS study did not add any substantial advantage to the diagnostic accuracy of PTNB. Otherwise, results confirmed the high efficiency of TUS-PTNB in reaching a histology diagnosis of lung lesions. Indeed, the AUC values for both CEUS+ and CEUS– group assessed an excellent diagnostic yield (i.e., ≥0.80), with a total diagnostic rate for TUS-PTNB of 91.8%.

Main causes of non-diagnostic biopsies in both groups were areas of necrosis or mixed fibrotic and necrotic tissue in the samples. In this study the detection rate of necrosis at CECT did not significantly differ between the CEUS+ and the CEUS– group. Some authors have found an advantage of CEUS during PTNB exclusively for lesions with a diameter greater than 5 cm, where the increase in necrotic tissue could be the main cause of false-negative findings if no contrast agent is used11. According to the literature, the detection rate of internal necrosis by CEUS increased as the lesion size increased (i.e., from 60% in lesions sized 1-2 cm to 85% in lesions sized 2-5%). However, we recorded no difference in the rate of diagnostic biopsy for various lesions size in both groups.

The main limitation of the present study is to have not predisposed a specified subgroup analysis for lesion size. A power analysis to determine the sample size of the study was performed for the overall population, but lesions size was not preselected at the enrollment. Consequently, the number of lesion >5 cm included in this study was too exiguous to effectively prove CEUS guidance effectiveness in improving the diagnostic accuracy of PTNB in bigger lesions.

To this regard, it should be underlined that CEUS study is not free from limitations inherent the sonographic study of the lung. Unlike CT, which allows a spatial resolution study of consolidations, ultrasound is a 2-dimensional imaging method. Therefore, on ultrasound some portions of the consolidation may not be imaged depending on the plane in which it is cut by the US beam. In addition, if a lesion or any part of it is not accessible to US (e.g., it is located behind the bone structures of the thoracic cage or it does not fully adhere to the parietal pleura), it will also be very difficult to see it at CEUS. The CEUS study must be carried out with the patient always in the same position, to avoid bias related to the redistribution

of the circulation when passing from a sitting to supine position. Therefore, all the patients were examined in a sitting position in our study. The compressive effect of a moderate effusion could generate changes in blood flow that may distort the results. Moreover, CEUS will found an area of hypoperfusion both if there is fibrous tissue or necrosis within a lesion. Also a focal vasoconstriction due to an hypoxic stimulus or to inflammation within the heterogeneous environment of a malignant lesion may be imaged as a defect in US contrast enhancement[18].

Conclusions

Results of this study indicate that the routine use of CEUS guidance does not improve the diagnostic accuracy of TUS-PTNB for peripheral lung lesions whose diameter is <5 cm. It remains to be evaluated on large and compared series if, in case of greater lesions (e.g., with a mean diameter >5 cm) CEUS study could really improve the diagnostic accuracy of TUS-PTNB, helping to avoid necrotic areas.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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