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CONTRAST-ENHANCED CHEST ULTRASOUND – MODERN ACHIEVEMENTS OF PULMONOLOGY IN BULGARIA

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Abstract

Contrast-enhanced ultrasound (CEUS) is an innovative imaging method in pulmonology based on the intravenous administration of a contrast medium in the form of microspheres, and the subsequent detailed representation of the perfusion characteristics of the target tissues. The method allows the distinction between malignant and benign origin of a given pathological lesion. The purpose of the current article is to introduce to the scientific society the modern achievements of contrast-enhanced ultrasound of the thorax in pulmonology in Bulgaria. We present twenty-seven clinical cases from the period 2017–2020, in which CEUS was applied at different stages of the diagnostic process. The results are compared with a previous survey conducted in Bulgaria in 2011.

Key words: contrast-enhanced ultrasound, contrast medium, time to enhancement, thoracic lesions

Introduction. Contrast-enhanced ultrasound (CEUS) is based on the principle of amplification of an ultrasound signal as a result of its interaction with a contrast agent in the form of microspheres (2–6 μm), applied strictly intravascularly. In this way, a distinction is made between the signal that comes from the blood vessels and is created by the vibration of the microspheres in response to the impact of the ultrasonic waves, from that one reflected by the surrounding

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tissues [1, 2]. CEUS may be particularly useful for assessing tissue perfusion in thoracic organs and structures with vessels < 2 mm in diameter, where Colour and Power Doppler modes are of a low sensitivity. The application of CEUS can successfully distinguish pulmonary arterial from bronchial arterial blood supply. Respectively, the malignant or benign nature of a given pulmonary lesion can be assumed according to its perfusion characteristics and especially through the demonstrated "time to enhancement" (TE) [3, 4].

In 2008 the first published guidelines and recommendations for non-hepatic application of CEUS appear [5, 6], and the last guidelines from 2011 and 2017 also pay attention to the use of CEUS in the diagnosis of lung lesions [6, 7]. The first Bulgarian publication on the use of CEUS in pulmonology is by Petkov et al. [8], where the application of contrast material in 30 clinical cases is analyzed in detail.

The aim of the present study is to determine to what extent thoracic ultrasound in CEUS conditions supports the stages of the diagnostic process in various diseases with intrathoracic localization and what is its effect on the precise control of the performance of transthoracic needle interventional manipulations. The new achievements of the application of the method in Bulgaria are considered and the acquired knowledge is summarized, with an emphasis on the optimization of minimally invasive biopsy interventions and reduction of possible errors in their implementation.

Materials and methods. The current study was conducted in the period 2017–2020. We present twenty-seven own clinical cases of CEUS application in malignant and benign thoracic lesions. In 23 cases the patients received the contrast agent sulphur hexafluoride (SonoVue), in the amount of the agent 2.4–4.8 ml i.v., followed by a bolus of 20 ml NaCl 0.9% i.v. In two of the cases, an agitated solution of Gelofusine 4% (high molecular weight succinylated gelatin), mixed in a ratio of 2:1 or 3:1 with 0.9% NaCl and with added 1.5 ml of air, was used as a contrast agent. In another two cases, both contrast agents, Gelofusine 4% and sulphur hexafluoride, were administered sequentially.

An ultrasound machine PHILIPS was used, equipped with sector, linear and convex transducers, as well as with a special software for visualization and image processing of ultrasound examination with the application of a contrast medium. The working mechanical index was low (< 0.7), and the observation and recording time of the target lesion lasted at least 60 s. Particular attention was paid to the accurate measurement of TE, in order to avoid possible errors in specifying the perfusion characteristics of the target lesion and the differentiation of pulmonary arterial from bronchial arterial blood supply, respectively, making possible detection of structures with neoangiogenesis. In some cases, software capabilities for image processing were used – mapping through the ROI (region of interest) function, which allowed to refine the perfusion in different areas of a lesion with "mosaic" characteristics.

Results. The survey published by Petkov et al. [8] included 30 patients, representing many of the possible pathologies in pulmonology in order to analyze the images obtained by contrasting them with the contrast agent sulphur hexafluoride. Subsequently, the pathological lesions were verified histologically by transthoracic cutting type needle biopsy, and the CEUS images were compared with the histological results. It was noted that pathological lesions showed a short time of the contrast enhancement (TE) when the case was a benign process such as pneumonia or compression atelectasis. In the above discussed pathologies pulmonary arterial and venous blood flow were preserved and the contrast entered early, with a TE < 7 s. Disease processes such as pulmonary thromboembolism and pneumosclerosis gave no contrast enhancement. In the presence of necrosis the contrast medium also did not enter the area of liquefaction. All patients with malignant lesions (histologically proven with a transthoracic tru-cut biopsy in this study) demonstrated a delayed TE > 7 s at CEUS. Compared with the Mann–Whitney rank test in [8], a statistically significant difference in TE was found in benign and malignant pulmonary lesions – 4.1 ± 1.1 s and 14.3 ± 5.8 s, respectively. The histological results of the study are shown in Fig. 1.

The current study from the period April 2017 – December 2020 covered the application of CEUS in total of 27 patients – 7 women and 20 men. The average

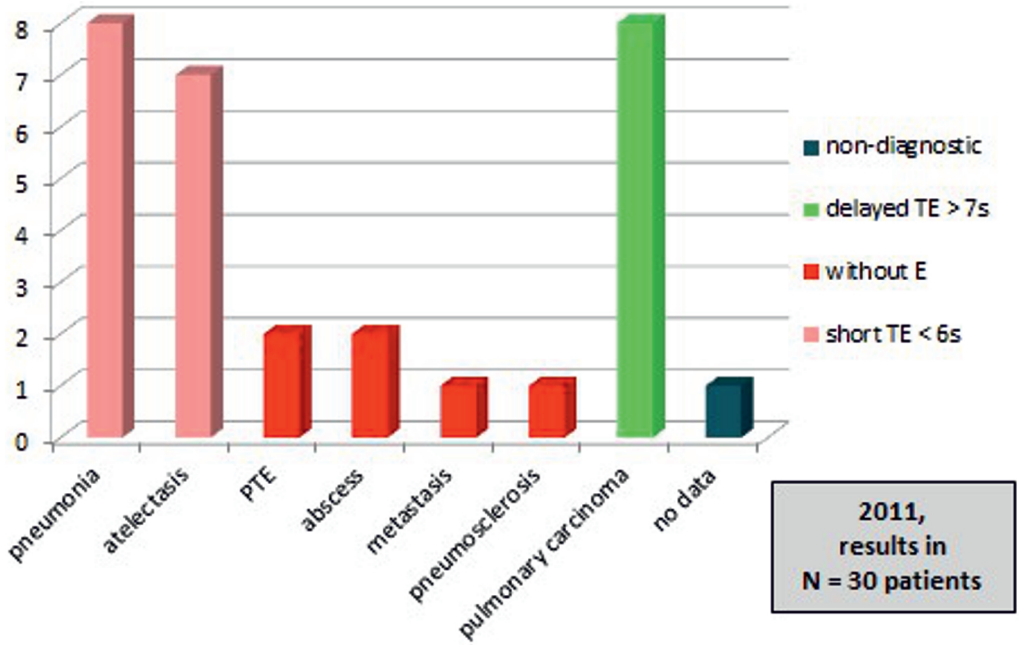


Fig. 1. Histological results from the patients included in the study of Petkov et al. [8] with the application of CEUS in peripheral pulmonary lesions. The method of histological verification is ultrasound-controlled tru-cut needle biopsy. Abbreviations: TE – time to enhancement, E – enhancement, PTE – pulmonary thromboembolism

age of the women was 59 years (36–76 years), and of the men – 64 years (51–83 years). The study was conducted in UMHATPD "St. Sophia", Sofia city. Patient survival was monitored at the time interval of the study and 6 months after the hospital discharge of the last participants in chronological order. A total of 18 patients survived this period and 9 died.

In all of these 27 patients, a transthoracic contrast-enhanced ultrasound examination was realized after the consideration of the native one as insufficiently informative. CEUS was used as a next step in the diagnostic process, contributing to more information regarding the preliminary diagnosis and supporting a more precise choice of location for the biopsy intervention. Necrotic areas with a hypocontrasted imaging representation due to no entering of the contrast agent were accurately visualized. This helped the clinician to avoid them during the achievement of the transthoracic biopsy. CEUS was found to be useful for interventions in parenchyma with "mosaic characteristics" – with the presence of both fields with normal lung parenchymal features and fields with neoplasm growth, as neoplastic zones showed a slower entry of the contrast (correspondingly, delayed TE) and remained longer contrasted due to the predominant neoangiogenesis from the bronchial arteries (Fig. 2). During the observations in our study, Gelofusine 4% approached the characteristics of SonoVue after intravenous injection only in the pulmonary arterial phase, as the agent did not pass through the pulmonary capillary vessels and did not enter the left atrium for being subsequently pushed into the systemic blood circulation. Accordingly, this medium could not provide information about the characteristics of the blood supply from the bronchial arteries. Its advantage was mainly in the contrasting of the pleural cavity, where it better delineated nodular lesions on the pleura, especially in cases when the distinguishing from deposited fibrin was difficult, but this was undertaken only in two patients. In our opinion, it is necessary to study this type of contrast enhancement in a larger cohort of patients in order to accurately analyze its advantages and disadvantages.

In all 27 patients, a total number of 56 ultrasound-controlled transthoracic cutting-type needle biopsies were performed (average 2.07 biopsies per patient), of which 47 were implemented under CEUS conditions (average 1.74 biopsies per patient). The biopsy needles used for ultrasound-controlled biopsies were cutting type (tru-cut) needles, with the possibility of obtaining a sample for histological examination, semi-automatic, allowing two steps of cutting, with a lumen thickness of 16 or 18 G (for intervention on the lung, ribs, mediastinum) and 14 G used for pleural biopsy). In three patients the decision was made to refer them for fibre-bronchoscopy, taking into account the results from the CEUS image. Respectively, in these patients an ultrasound picture of atelectasis was visualized, with a probable endobronchial origin of the same process, a too great depth of intervention through a transthoracic access and a high risk of possible iatrogenic complications if passing through the atelectatic lung parenchyma in an attempt

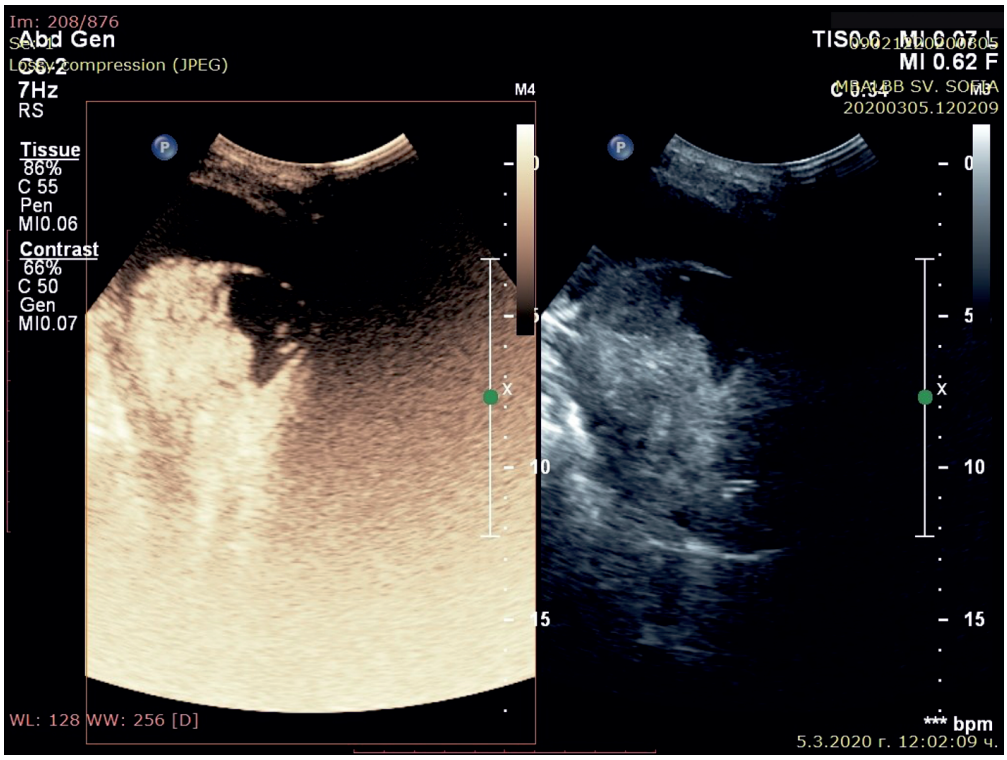


Fig. 2. Thoracic ultrasound examination in the conditions of CEUS with the visualization of a compression atelectasis and a zone with a delayed TE – hypocontrasted area, with signs of neoangiogenesis. Ultrasound-controlled transthoracic tru-cut biopsy with a 18 G/20 mm needle from the hypocontrasted area verified histologically a squamous cell carcinoma

to reach the localized destination. In two of the patients, no peripheral pathological perfusion areas were detected by the function ROI, which could be biopsied with a cutting type needle, and a bronchological examination was preferred in the same cases. From the ultrasound examination performed with the administration of CEUS, sixteen patients were identified as patients with "malignancy", four with "benignity" and in seven it was absolutely necessary to refer them to biopsy verification of the disease in order to reach the definitive diagnosis, as the ultrasound examination was not able to predetermine with absolute accuracy the nature of the process, but it could define a benign or malignant character as "more probable" (Fig. 3). The histological results of the samples of the patients who participated in the study are demonstrated in Fig. 4.

The application of CEUS in the current study demonstrated the following parameters of the methodology: sensitivity Se = 100%, specificity Sp = 57%; positive predictive value PPV = 87%; negative predictive value NPV = 100%; accuracy Acc = 88.9%. No false negative images were observed, i.e. images which could mislead the operator clinician that there is no neoplasm, with a thereafter

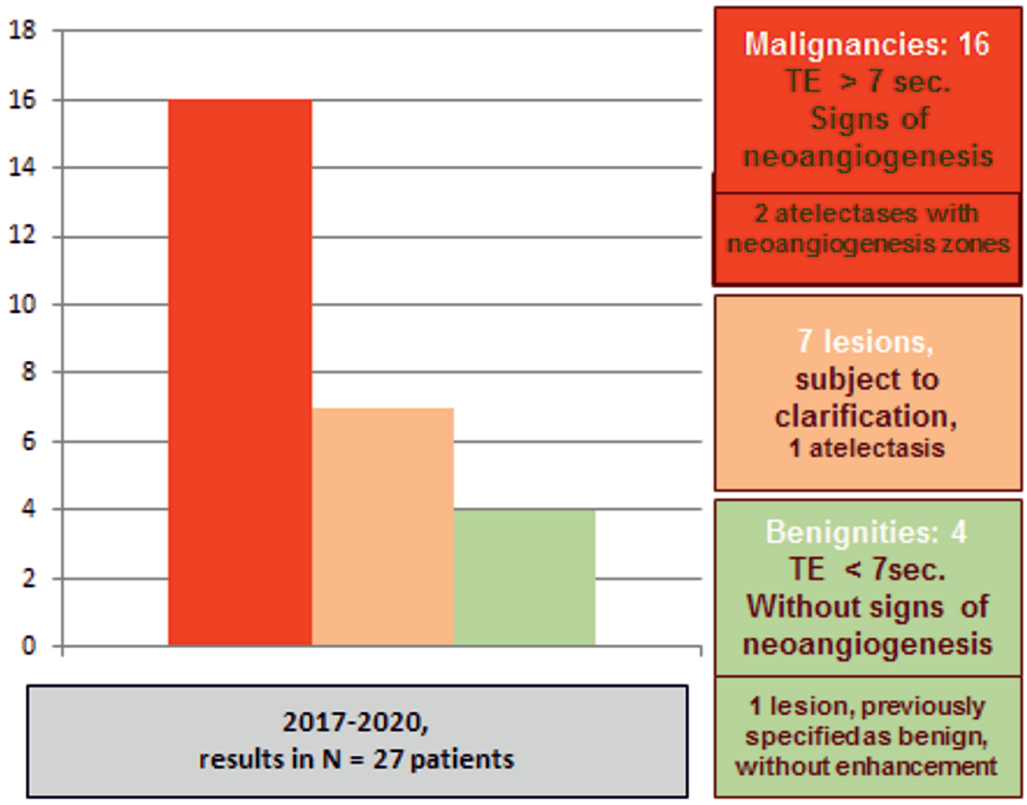
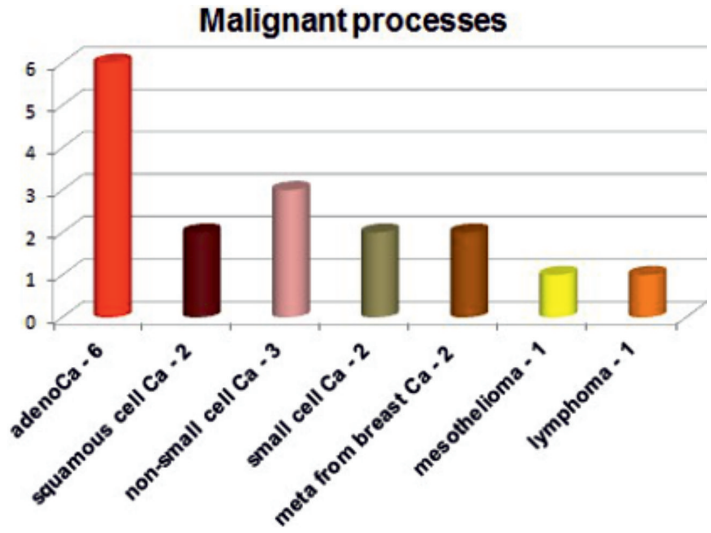


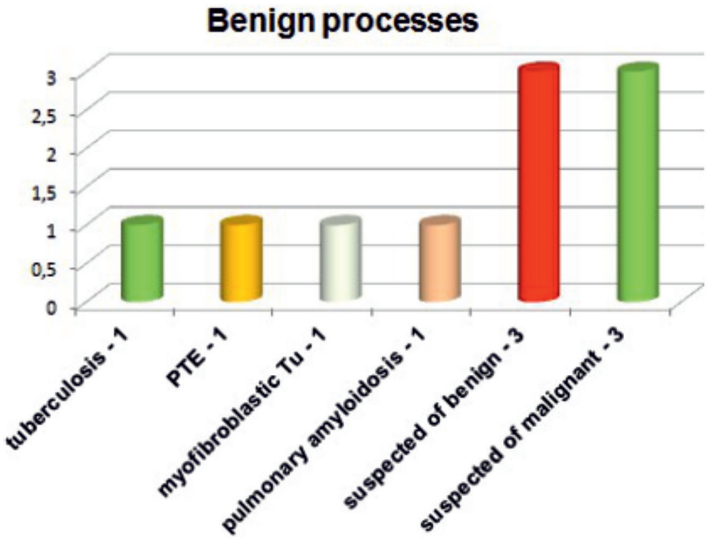
Fig. 3. Results of the thoracic ultrasound examination with administration of CEUS in the patients from the study for the period 2017–2020

histologically detected malignancy in the subsequent biopsy. CEUS also showed permanent benefits in the studies of the Bulgarian teams, especially regarding the accurate visualization of target biopsy lesions, and orienting in advance for the possible diagnosis with a great accuracy. CEUS was even able not only to assist the clinician in selecting the optimal location for intervention, but also to help in deciding whether the manipulation should be undertaken for the particular patient.

Conclusion. The ultrasound examination of the thorax, combined with an intravenous application of a contrast agent, contributes significantly to distinguishing benign from malignant intrathoracic lesions. The images obtained from CEUS guide the clinician about the nature of the target lesion by accurately depicting its perfusion characteristics [9]. The TE parameter is the most informative for the pulmonologist – the delayed amplification time in the arterial phase shows sensitivity Se = 94.32%, specificity Sp = 95.2%, positive predictive value PPV = 96.2% and negative predictive value NPV = 93% in the identification of neoplastic lesions [10]. CEUS is also particularly useful in lesions with large



A



B

Fig. 4. A) Histological results in patients with ultrasound images of neoplastic diseases after CEUS application. B) Histological results of patients in whom after application of a contrast medium a benign nature of the process is suspected or a malignant one is probable and cannot be definitely ruled out only by the ultrasound examination. N.B.: In the suspected for "more likely benign" processes, three patients were followed, two were completely cured by conservative antibacterial therapy, and the third one had an anatomical malformation of the lung verified by right upper lobectomy. The ultrasound examination suggests a greater probability of benignity, but cannot definitely rule out a malignant process. In the suspected for "more likely malignant" processes, one patient died before subsequent biopsy, and in the other two a malignant process was verified again by ultrasound-controlled transthoracic tru-cut needle biopsy. The image in all three abovementioned patients was in favour of the malignant nature of the disease

necrotic areas, where non-diagnostic biopsies can reach between 9–26% [11, 12]. CEUS not only visualizes the available necrotic areas and helps determining the exact location of the biopsy, but also plays a key role in the decision making process for the choice of the type of the minimally invasive interventional biopsy and whether to do it at all. CEUS is very well tolerated by the patient, and in the two studies performed so far in Bulgaria no side effects from the used contrast agents were observed. No complications were observed from the subsequent ultrasound-controlled interventional manipulations, and therefore we believe that the method significantly contributes to their refinement, facilitates the choice of the clinician regarding the diagnostic approach for the particular patient and results in accurate ultrasound and subsequent histological diagnosis.

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