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CEUS in the diagnosis of renal masses

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ABSTRACT

Introduction and purpose

Contrast enhanced ultrasound (CEUS) is a modern diagnostic method that uses ultrasound waves in combination with intravenous administration of a contrast agent. It enables obtaining high resolution and assessing microcirculation in real time, thanks to which the researcher is able to analyze the enhancement and its features, which may help in diagnosing a specific pathology. Contrast agents, similar to CT and MRI, show specific phases of enhancement after administration - arterial, venous, delayed. Their additional advantage is safety, especially for patients with impaired kidney and thyroid function, and causing fewer allergic reactions. The aim of this review is to present the CEUS examination technique and the latest reports in the field of diagnosis of renal lesions.

Material and methods

This review was prepared based on the literature available from recent years
in the PubMed and Google Scholar scientific databases using the keywords: ultrasonography, contrast enhanced ultrasonography, kidney, renal masses.

Results

Studies show that CEUS can be an effective method for imaging both cystic and solid lesions in the kidney. When using a contrast agent, the lesions show characteristic features that can guide the investigator to the diagnosis. Moreover, in comparative analyses, CEUS achieved comparable or better results than other diagnostic imaging methods.

Conclusions

CEUS is a modern and promising diagnostic method that can successfully compete with CT and MRI. Moreover, the metabolism and pharmacokinetics of contrast agents and their safety mean that CEUS can be used for the diagnosis of unclear pathologies in elderly patients, as well as for the control and supervision of changes that require frequent imaging.

Keywords: ultrasonography, contrast enhanced ultrasonography, kidneys, renal masses

Introduction and purpose

Speed, easy availability and lack of radiation make ultrasound one of the most common and universal tests used in diagnostic imaging. Contrast-enhanced ultrasound (CEUS) is a modern diagnostic method that uses ultrasound waves in combination with contrast administered intravenously in a bolus, enabling high spatial and temporal resolution, as well as dynamic assessment of microcirculation [1]. The contrast agents used in this method, similar to MRI and CT, show post-contrast enhancement after a certain period of time: the arterial phase up to 25 seconds after injection, the venous phase 25-45 seconds after injection and the delayed phase up to 2 minutes after injection [2]. Thanks to this, the researcher is able to assess in real time the organ and its strengthening, wash in and wash out kinetics, which may be characteristic and may indicate a specific pathology [1]. CEUS is considered a safer method than other imaging methods because it does not use X-ray radiation, which may be harmful to neighboring organs. Moreover, the contrast agent is safe for patients with impaired thyroid or kidney function and is less likely to cause allergic reactions [3,4]. It may cause mild side effects such as headache, nausea, and chest pain [5]. Moreover, initial studies demonstrated the relative safety of these agents for pregnant women and the fetus [6]. This method can be used to evaluate parenchymal organs and searching for pathology in them. The aim of this review is to present the CEUS examination technique and the latest reports in the field of diagnosis of renal lesions.

Material and methods

This review was prepared based on the literature available from recent years in the PubMed and Google Scholar scientific databases using the keywords: ultrasonography, contrast enhanced ultrasonography, kidney, renal masses.

A few words about contrast agents

Contrast agents used in CEUS consist of microbubbles of minimally diffusible gas in a phospholipid envelope or coating. The coating slows down the diffusion of the substance, making the contrast stable for some time, enabling accurate imaging. Due to their small size (bubbles are smaller than red blood cells), after intravenous administration, microbubbles pass through the lung capillaries into the bloodstream, reaching, among others, the liver or kidneys [7]. The most commonly used in clinical practice are agents with a diameter of 2-6μm containing a gas core, such as sulfur hexafluoride. Fluorination of these compounds increases their density, which makes it difficult for them to pass through the phospholipid envelope and reduces their solubility in the blood. This makes them more stable for a longer period of time [8]. These agents act as acoustic substances. They are diluted using ultrasonic waves, creating a signal that stands out against the background of surrounding tissues. This enables the generation of an image specific to the contrast agent in real time. The metabolism of the contrast agent, as already mentioned, is safe for patients because the gaseous component is removed by the lungs, while the phospholipid coating is metabolized in the liver [4,9]. When performing a CEUS examination of the kidneys, specific post-contrast phases can be observed, such as: the corticospinal phase (enhancement of the renal cortex, with the medulla still not enhanced) lasting from 15 to 30 seconds after the injection and the nephrographic phase (homogeneous enhancement of the cortex and medulla) lasting from 30 to 70 seconds after the injection. It is worth emphasizing that there is no urographic phase because the contrast is not removed by the kidneys [10]. The most commonly used contrast agent for imaging changes in the kidneys is sulfur hexafluoride.

Imaging of cystic lesions

Renal changes are a common clinical problem. Their detection is increasing due to better availability of highly specialized tests such as CT or MRI. Cysts are the most common incidentally detected renal masses. A simple cyst is a fluid lesion with a thin and well-defined wall without partitions or changes in soft tissues. It is anechoic in ultrasound and does not enhance after contrast administration in CT and MRI. Cystic lesions with other features require careful diagnosis because up to 10% of renal cell carcinomas may develop on the basis of cystic lesions [11]. The Bośniak score was originally created to classify cystic lesions detected on CT by determining their malignant potential. According to it, class I and II cysts are characterized as benign lesions, class III as indeterminate with a tendency to malignancy, and class IV as mostly malignant lesions. Category IIF is intended to differentiate lesions that are ambiguous for categories II and III [12]. The latest update includes MRI examination in the classification and also includes a greater number of renal lesions encountered in clinical practice [13]. The studies show that the malignancy rate of surgically removed cysts of class III and IV according to Bosniak is 79.3% and 84.8%, respectively, and class IIF is 60%. However, the progression rate of IIF cysts is relatively low at 4.6%. [14,15]. In another study focusing only on class IIF lesions, the progression rate over a period of approximately 13 months was 7.1% [16]. Class III may contain a significant number of malignant lesions but requires more detailed examination and clarification of factors indicating malignancy, which

is why ultrasound examination may help solve this problem. Additionally, the constantly growing importance of CEUS meant that in 2020, a classification of cystic lesions adapted to this examination was also proposed. It is not intended to replace the scale used in CT, but to complement it and improve accuracy in the assessment of potential malignancies. According to CEUS-Bosniak, class I means changes
with thin walls without irregularities, not enhancing post-contrast or single microbubbles running in the vessels in the wall. Class II are lesions with thin walls
and septa without irregularities, non-enhancing post-contrast or single microbubbles running in the vessels in the wall and septa. Class IIF means lesions with
multiple septa, thin or minimally thickened (2–3 mm), there may be thin septa without irregularities, showing no enhancement or individual microbubbles running in tiny vessels. Class III are changes with smooth, thick walls (>4 mm) and partitions or having irregular walls and partitions (>3 mm), no visible soft tissue nodules. Class IV includes lesions with smooth, thick walls (>4 mm) and partitions or irregular walls and partitions (>3 mm), and additionally visible soft tissue protrusions or nodules [17].

In the study by Herms et al., lesions in the kidneys were assessed using the CEUS-Bosniak scale, and then compared with the results of histopathological examination. All CEUS-Bosniak IIF lesions were shown to be benign. However, in CEUS-Bosniak class III and IV, 60% and 92% of malignant lesions were detected, respectively. It was shown that the CEUS classification was consistent with CT/MR in 58%, which was considered good agreement in this study [18]. Another study analyzed lesions rated as CEUS-Bosniak III. The percentage of malignant lesions in this group was 66% [19]. Another aspect worth mentioning is the reproducibility of the CEUS-Bosniak scale proposed in 2020. To check this, 6 specialists with various levels of advancement assessed 84 CEUS examinations. The unanimous opinion of 2 experts was considered the standard to which the rest of the researchers were compared. Variability among researchers showed almost perfect agreement (lowest kappa 0.74, highest 0.94) - the best results were achieved by experts compared to the standard (kappa 0.95), lower results were achieved by intermediate and beginners, but despite this they were consistent in their groups (lowest kappa 0.59). The most reliable assessment concerned changes in the CEUS-Bosniak I and IV scale, while the lowest was for classes IIF and III. The study shows that the proposed scale has good reproducibility, and training and improving the skills of the examiner increases the diagnostic quality [20]. Another study also found that class IIF and III cystic lesions were the most difficult to evaluate. In this case, the diagnostic performance of

CEUS and CT was similar, but the former examination in the hands of an experienced investigator may be safer and more appropriate for follow-up and repeated testing [21].

Imaging of solid lesions

In the case of solid lesions, it is crucial to diagnose renal cell carcinoma, which is the most common solid lesion in the kidney and accounts for approximately 90% of all kidney cancers [22]. The most common types are clear cell carcinoma (ccRCC), papillary cell carcinoma (pRCC), and chromophobe carcinoma (chRCC). Other solid lesions include renal pelvis urothelial tumor (RPUC), which accounts for 10-15% of renal malignancies, and angiomyolipoma (RAML), which is the most common benign tumor. When comparing benign and malignant lesions in CEUS examination, significant differences were found regarding echogenicity, wash out, perfusion defect (the area where contrast did not reach due to necrosis) and peripheral enhancement of the focal lesion (PRE). 79% of RAML tumors showed slow wash out, while 78% of ccRCC tumors, 74% of pRCC tumors, 71% of chRCC tumors showed fast wash out. The incidence of perfusion defect was significantly higher in ccRCC -48%, pRCC -53%, compared to RAML -14%. Peripheral enhancement occurred in 15% of ccRCC, 26% of pRCC, 24% of chRCC, and only 9% of RAML [23]. In another study, among the CEUS parameters most associated with the occurrence of a malignant lesion was the pseudocapsule sign - peripheral enhancement of the lesion. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) in this case were 85%, 86%, 94%, 71%, respectively, and the diagnostic value was 86%. More importantly, the recorded CEUS images were used to create a time/intensity curve (TIC), thanks to which various parameters were calculated, 2 of which - peak signal intensity (PI) and area under the curve (AUC) were particularly related to the occurrence of a malignant lesion. Sensitivity, specificity, PPV, NPV for PI were 94%, 92%, 96%, 87% and for AUC 99%, 92%, 97%, 97%. The diagnostic value was 93% and 95%, respectively. Moreover, when both parameters were combined, the values of 93%, 100%, 100%, 83% and a diagnostic value of 93% were achieved [24]. In the study by Najafi et al., 215 solid lesions were analyzed using CEUS, of which 155 were correctly classified as benign lesions, 43 as malignant lesions, 16 false positive lesions and 1 false negative, which gives a sensitivity of 97.7%, specificity of 90, 6%, PPV 72.9%, NPV 99.4% [25]. When assessing lesions smaller than 4 cm, CEUS achieved 94% sensitivity, 78% specificity, PPV 95%, NPV 73% [26]. However, the above studies did not focus on the size of the masses as a factor influencing the diagnosis. Another study shows that this parameter may be important in the final diagnosis. In the study by Zhu et al., 156 kidney tumors were divided into 3 groups depending on their size, i.e. group I (up to 2 cm), group II (2.1 cm-4 cm), group 3 (4.1 cm-7 cm). The percentage of histologically confirmed malignant lesions in the groups was as follows: in group I (62.9%), in group II (80.6%), in group III (79.6%). Then, the CEUS image was analyzed using such features as: wash out, degree of contrast enhancement, homogeneity of contrast enhancement and the presence of the pseudocapsule sign. In group I, the homogeneity of enhancement and the pseudocapsule sign were factors differentiating benign lesions and malicious. Malignant lesions more often presented the pseudocapsule symptom and enhanced heterogeneously after contrast administration. In group II, the only feature distinguishing benign from malignant lesions was the degree of contrast enhancement - excessive enhancement in the arterial phase was associated with the occurrence of a malignant lesion. Iso-enhacment was associated with the occurrence of a benign lesion. In group III, cancer lesions differed significantly in terms of wash out and the degree of enhancement. Fast wash out and excessive enhancement more often involved malignant lesions [27]. The results show that CEUS may be a promising tool for minimally invasive diagnosis, but the size of the solid lesion should be taken into account when analyzing image features.

Comparison with other imaging methods

An interesting aspect of CEUS analysis may be its comparison with conventional ultrasound in the detection of solid lesions in the kidneys. In one study, conventional abdominal ultrasound did not reveal 16 lesions that were visible on CEUS, and histopathological examination turned out to be clear cell carcinoma in 10 cases and urothelial tumor originating from the renal pelvis in 6 cases [28], which shows that that in certain specific clinical situations, CEUS is more effective than conventional ultrasound. It seems necessary to check how CEUS compares directly to other imaging tests such as CT and MRI. In one of the analyses, the effectiveness of CEUS described using parameters such as sensitivity, specificity, PPV and NPV was 99.1%, 80.5%, 96.4%, 94.3%, respectively. For CT, these values were 97.1%, 47.4%, 87.0%, 81.8%; for MR 96.4%, 75.0%, 93.1%, 85.7%. Additionally, using CEUS 10 lesions were classified incorrectly - 8 false positives and 2 false negatives, using CT 12 lesions - 10 false positives and 2 false negatives, using MRI 3 lesions - 2 false positives and 1 false negative [29]. Moreover, reports collected in the meta-analysis by Furrer et al. in which the effectiveness of CEUS, contrast-enhanced computed tomography (CECT) and contrast-enhanced magnetic resonance imaging (CEMR) was compared, show that the diagnostic accuracy of CEUS was higher than that of CECT and CEMR. Negative predictive value in the case of CEUS was higher compared to CEMR. The clinical studies collected in this analysis indicate that the qualitative diagnostic effectiveness of CEUS may be higher than the above-mentioned imaging tests [30].

Economic analysis

Finally, an aspect that is not the most important, but may be important for managers of medical facilities, as well as for some patients, i.e. the financial issue and assessment of the effectiveness of CEUS from an economic point of view. In a study taking into account solid lesions, which compared three main imaging methods, the costs of performed tests were analyzed and translated into effectiveness expressed as a QALY indicator.

In the case of CT, the cost was USD 10,285.58 and the effectiveness was 11.95 QALY, in the case of MR it was USD 7,407.70 and 12.25 QALY and USD 5,539.78 and 12.44 QALY in the case of CEUS, which allows us to consider this study as a cost-effective strategy imaging for initial diagnosis and assessment of solid renal masses [31]. In the case of cystic lesions, the values were as follows: USD 9,654.43 and 8.06 QALY for CEUS and USD 9,675.03 and 8.06 QALY for MRI, which shows that both methods can be used alternatively in economic terms [32]. Moreover, especially considering low-class cystic lesions on the Bosniak scale, where repeat examinations are necessary for active surveillance, CEUS was the most cost-effective strategy [33].

Discussion

The aim of this review was to present the CEUS examination and discuss the latest reports on the diagnosis of renal lesions using this diagnostic method. Contrast agents used in this study are metabolized by the liver (envelope) and removed by the lungs (gaseous component) [4,9], which makes them safer for patients with impaired thyroid or kidney function and causes less allergic reactions [3,4]. Moreover, early studies report the safety of these substances in relation to pregnant women and fetus [6]. Taking into account renal masses, cystic lesions are the most frequently detected renal masses. The importance of CEUS led to the creation of the CEUS-Bosniak scale [17], based on the Bosniak scale used in CT, which is adapted to this study. Undoubted analyzes [18,19] have shown that it was correctly constructed taking into account the features of CEUS images associated with an increased risk of malignancy of the lesion. Furthermore, the reproducibility of this scale among CEUS investigators has been found to be good, even when considering beginners or less experienced individuals [20,21]. Continuously improving your skills can raise diagnostic quality to an even higher level. In the case of solid lesions, the most serious diagnosis is renal cell carcinoma. Analyzes show that using CEUS it is possible to create an image with features more indicative of a malignant lesion. This includes rapid wash-out of the contrast agent and perfusion defect [23], as well as peripheral enhancement of the lesion (pseudocapsule sign) [23,24].

The analyzed studies [23,24,25,26] demonstrated high effectiveness of the test
in determining the nature of the renal lesion. However, it is worth noting that the size of the mentioned mass may affect some image features, making diagnosis difficult [27]. In direct comparison with CT and MRI, the qualitative diagnostic effectiveness of CEUS may be higher [29,30], and it can also detect lesions not initially visible in conventional ultrasound [28]. From an economic perspective, CEUS was associated with lower total costs and higher effectiveness in detecting solid lesions [31] and similar to MRI in the case of cystic lesions [32]. However, it should be taken into account that in lesions with a low malignant potential, active surveillance and more tests are necessary, which supports CEUS [33].

Conclusions

CEUS is a modern and promising diagnostic method that can successfully compete with CT and MRI. Moreover, the metabolism and pharmacokinetics of contrast agents and their safety mean that CEUS can be used for the diagnosis of unclear pathologies in elderly patients, as well as for the control and supervision of changes that require frequent imaging.

Author's contribution

Conceptualization: Łukasz Ochyra, Anna Łopuszyńska; methodology: Łukasz Ochyra, Anna Łopuszyńska; software: Łukasz Ochyra, Anna Łopuszyńska, check: Łukasz Ochyra, Anna Łopuszyńska; formal analysis: Łukasz Ochyra, Anna Łopuszyńska; investigation: Łukasz Ochyra, Anna Łopuszyńska; resources: Łukasz Ochyra, Anna Łopuszyńska; data curation: Łukasz Ochyra, Anna Łopuszyńska; writing- rough preparation: Łukasz Ochyra, Anna Łopuszyńska; writing- review and editing: Łukasz Ochyra, Anna Łopuszyńska; visualization: Łukasz Ochyra, Anna Łopuszyńska; supervision: Łukasz Ochyra, Anna Łopuszyńska; project administration: Łukasz Ochyra, Anna Łopuszyńska; receiving funding: Łukasz Ochyra, Anna Łopuszyńska.

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