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REVIEW ARTICLE

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The Ability of Contrast-Enhanced Ultrasound, Conventional Ultrasound, and ^{99m}Tc-MIBI Scintigraphy for the Detection of Parathyroid Lesion in Patients with Primary Hyperparathyroidism

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Abstract

The aim of this review was to compare the efficiency of conventional ultrasound (CUS), contrast-enhanced ultrasound (CEUS), and ^{99m}Tc-MIBI scintigraphy in imaging parathyroid gland lesions in patients with primary hyperparathyroidism (PHPT).

In this review, we attempted to present a clear view of the most reliable or precise technique for detecting parathyroid gland (PG) pathology in PHPT. Our study relied on secondary data based on the review of the extant literature on PHPT imaging. The research retrieved articles from the scholarly databases Google Scholar, Web of Science, and PUBMED/MEDLINE that examine the efficiency of CUS, CEUS, and ^{99m}Tc-MIBI scintigraphy in imaging PGs in PHPT patients. The study retrieved secondary data from past research identified using keyword and medical subject heading terms like "Ultrasound," "Contrast-Enhanced Ultrasound," "Sonography in parathyroid," "Primary hyperthyroidism," "Scintigraphy," and "Contrast-enhanced ultrasound in parathyroid disease." This study only relied on original contribution papers presented in English and published between 2011 and 2021. We found that CEUS has a comparable sensitivity to ^{99m}Tc-MIBI scintigraphy so that it can be used in patients who have a contraindication to scintigraphy or in a hospital without nuclear medicine facility. CEUS is able to detect very small size adenomas, whereas the detection using scintigraphy depends on the size of the diseased glands and the cytology.(**International Journal of Biomedicine. 2022;12(1):82-88.**)

Key Words: contrast-enhanced ultrasound • conventional ultrasound • primary hyperparathyroidism • scintigraphy

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Abbreviations

CEUS, contrast-enhanced ultrasound; **CUS**, conventional ultrasound; **CT**, computed tomography; **PTA**, parathyroid adenoma; **PG**, parathyroid gland; **PHPT**, primary hyperparathyroidism; **SA**, single adenoma; **SPECT,** singlephoton emission computed tomography.

Primary hyperparathyroidism (PHPT) is characterized by elevated serum calcium concentration and elevated or inappropriately normal parathyroid hormone levels. Silverberg describes the skeletal hallmark of PHPT as osteitis fibrosa cystica, radiographically characterized by brown tumors of the long bones, subperiosteal bone resorption, distal tapering of the clavicles, and phalanges, and "salt-and-pepper" erosions of the skull. Nephrocalcinosis and nephrolithiasis, as

well as neuromuscular symptoms (proximal muscle weakness, atrophy, hyperreflexia, and gait disturbances), are present in the majority of patients.[1]

PHPT results from excessive secretion of parathyroid hormone from one or more of PGs. The underlying cause of sporadic PHPT is unknown in most cases. Long-term lithium therapy, a history of radioactive iodine therapy for thyroid disease, or external neck radiation are risk factors for sporadic PHPT. Other risk factors recently described are chronically low calcium intake and higher body weight.[2,3]

The most common pathological finding in patients with PHPT is a solitary PTA, occurring in 80% of patients.[4] All 4 PGs are involved in approximately 15% of patients. Golden SH parathyroid carcinoma has been found in <1% of all cases of PHPT.[5]

CUS and ^{99m}Tc-MIBI scintigraphy (^{99m}Tc sestamibi, also known as hexakis 2-methoxyisobutyl isonitrile) are the imaging techniques for the preoperative location of PTAs. Numerous studies comparing these techniques suggest similar sensitivities and specificities for detecting solitary adenoma. Localization accuracy is also improved when both studies are obtained preoperatively. Contrast-enhanced CT and MRI can also effectively locate PTAs but are less commonly used for preoperative location.[6]

Currently, CEUS has been used to help distinguish PTAs from thyroid nodules and lymph nodes. One study revealed CEUS had a sensitivity of 66.7% for detection of SAs compared to 77.8% for ^{99m}Tc-MIBI SPECT scintigraphy and 51.8% for a high-resolution ultrasound.[7] The sensitivity increased to 82.7% when ^{99m}Tc-MIBI scintigraphy and CEUS results were paired together. CEUS may be superior to high-resolution ultrasound because the ultrasound contrast agent allows for amplification of vascular signals in the lesions, providing additional diagnostic value.[7-9] One study showed that the CEUS had a sensitivity of 98.4% and specificity of 98.4% for detecting pathology in PGs.[8] CEUS is a highly sensitive, quick, and cost-efficient method for localization of pathological PGs and is reliable even in the presence of concomitant goiter, after previous neck surgery, and with the multigland disease.[9,10] The CEUS features of the intrathyroidal adenoma include intense, homogeneous, and very early arterial enhancement, which is often apparent as quickly as 4–5 seconds after injection. Further, enhancement tends to persist in the adenoma after the adjacent thyroid has begun to clear the contrast agent. CEUS has localized a PTA in the setting of multiple background thyroid nodules in Hashimoto's disease.[11]

In this review, we attempted to present a clear view of the most reliable or precise technique for detecting PG pathology in PHPT. Our study relied on secondary data based on the review of the extant literature on PHPT imaging. The research retrieved articles from the scholarly databases Google Scholar, Web of Science, and PUBMED/MEDLINE that examine the efficiency of CUS, CEUS, and ^{99m}Tc-MIBI scintigraphy in imaging PGs in PHPT patients. The study retrieved secondary data from past research identified using keyword and medical subject heading terms like "Ultrasound," "Contrast-Enhanced Ultrasound," "Sonography in parathyroid," "Primary hyperthyroidism," "Scintigraphy," and "Contrast-enhanced ultrasound in parathyroid disease." This study only relied on original contribution papers presented in English and published between 2011 and 2021. The study focused on pre-surgical detection and localization of pathologic PGs using CUS, CEUS, and scintigraphy. However, systematic reviews, literature reviews, case reports, and studies undertaken before this period were considered inadequate, or the data was too old, and therefore excluded. The papers provide varying perspectives on PHPT and the treatment approaches. Each of these approaches is individually important towards understanding the collective gains made and existing gaps in the treatment of the disease.

The data needed for the cross-document comparisons included the journal name, date of publication, number of times cited, and the study design. Additional considerations had inclusion and exclusion criteria, population and period, and the accuracy, specificity, and sensitivity of the result. This paper compares and analyzes the efficiency of the 3 discussed techniques (CUS, ^{99m}Tc-MIBI scintigraphy, and CEUS) per the sensitivity, specificity, and ability to detect ectopic glands, thyroid concomitant goiter, and multiglandular disease. The paper considered additional factors influencing efficiencies, including cost, invasiveness, treatment side effects, anatomical resolution, radiology expertise, and availability. These factors are critical to early detection, proper diagnosis, effective treatment of the disease, and potential prevention.

We reviewed a total of 64 articles; 49 studies met exclusion criteria. Results in 15 studies were selected for review: the included studies reported various imaging modalities for pre-surgical localization: CEUS, CUS, and ^{99m}Tc-MIBI scintigraphy. Seven papers compared CEUS with CUS, 2 compared CEUS with ^{99m}Tc-MIBI scintigraphy, and 5 compared ^{99m}Tc-MIBI scintigraphy with CUS. CEUS and ^{99m}Tc-MIBI scintigraphy. Half of the studies included were retrospective studies. All the studies included patients with PHPT, which indicates surgery, diagnosed clinically and by biomedical results. The patients with recurrent, persistent, or secondary hyperparathyroidism or with a history of allergy to contrast media were excluded. The included articles that use CEUS as an imaging modality for localization are summarized in Table 1, and those that use CUS and scintigraphy are summarized in Table 2.

CEUS

Nine articles included had publication periods from 2011 to 2019. All studies used SonoVue (Bracco S.p.A., Milan, Italy) as the contrast agent and were performed by expert operators. The use of CEUS has the advantage of identifying the pathological PGs from the adjacent isoechoic thyroid nodules and the cervical lymphadenopathy, where they may have the same echogenicity. Several studies have demonstrated higher sensitivity of CEUS in detecting single PTA. CEUS alone had a sensitivity of 66.7%-100%. Summarization of 9 published articles can be found in Table 1. Thus, the sensitivity and specificity of CEUS and CUS for detecting SAs are presented. The statistical *P*-value in the sensitivity between the 2 modalities was reported in 7 of the 9 articles included.

Table 1.

Studies that compare the use of CEUS with CUS or/and ^{99m}Tc-MIBI scintigraphy

	STUDY	Imaging Modality	n	SA	MGD/ surgical result	CG	Ectopic	Sensitivity,%	Specificity,%	Sensitivity *P*- value
1	Hornung et al.[12]	CUS CEUS	60 60	22 59	NR NR	8 NR	0/0 0/0	70% 98.3%	NR NR	0.001
2	Uller et al. [8]	CEUS	26	23	2/2	14	0/0	98.4%	98.4%	<0.05
3	Agha et al. [9]	CUS CEUS	30 30	25 29	0/1 1 /1	NR NR	0/0 0/0	80% 100%	NR NR	0.015
4	Karakas et al. [15]	CUS CEUS	25 25	18 18	1/5 1/5	1/1 1/1	0/0 0/0	86% 86%	NR NR	NR
5	Agha et al.[10]	CUS CEUS	75 75	48 68	1/5 5 /5	16 25	NR NR	68.5% 97.1%	NR NR	<0.006
6	Aghaa et al. [24]	Sci CEUS	75 143	45 139	NR NR	NR NR	NR NR	60.8% 97.2%	NR NR	0.019
7	Para Ramírez et al. [7]	CUS Sci CEUS	27 27 27	14 21 18	0/2 0/2 2 /2	NR NR NR	NR NR NR	51.8% 77.8% 66.7%	NR NR NR	NR
8	Da Silva et al. [13]	CUS CEUS	42 42	NR 42	NR NR	NR NR	NR NR	100%	NR NR	0.356
9	Piccin et al. [14]	CUS CEUS	336 198	NR NR	NR NR	99	NR NR	76.2% 72.8%	97.3% 97.3%	0.337

n - number of patients; Sci- ^{99m}Tc-MIBI scintigraphy; SA - single adenoma; MGD - multiglandular disease; CG - concomitant goiter; NR - not reported; Ectopic - ectopic parathyroid gland; 0/0 - none of patients has ectopic glands.

Table 2.

Studies that compare the use of ^{99m}Tc-MIBI scintigraphy (Sci) with CUS

	Study	Imaging modality	n.	SA	MGD	CG	Ectopic	Sensitivity%	Specificity	Sensitivity P- value
10	Elsayed and Ali.[17]	CUS Sci CUS +Sci	45 45 45	NR NR NR	NR NR NR	NR NR NR	NR NR NR	94.4% 97.4% 97.4%	44.4% 71.4% 83.3%	NR
11	Argirò et al.[18]	CUS Sci CUS+ Sci	46 46 46	41 38 43	0 0 0	NR NR NR	0/1 0/1 0/1	89.1% 83.6% 93.4%	97.5% 98.3% 98.3%	NR
12	Scattergood et al.[19]	CUS Sci CUS+ Sci	184 184 184	NR NR/ NR	NR NR NR	NR NR NR	0/0 0/0 00	70% 64% 81%	57% 57% 71%	0.34 <0.001
13	Vitetta et al.[20]	CUS Sci	108 108	NR NR	NR/9	NR NR	14/18 16/18	84% 71%	94% 90%	<0.05 <0.05
14	Ibrahim and Elsadawy [21]	CUS Sci US+ Sci	40 40 40	35 34 37	0 0 (Multidrug)	0/1 NR NR	NR NR NR	87.5% 85% 92.5%	66.6% 100% 100%	NR
15	Akbaba et al.[22]	US Sci US+ Sci	98 98 98	82 66 93	NR/2 NR/2	0/7 NR NR	0/2 2/2 2/2	87.2% 70.2% 94.9%	25% 50% NR	NR

n - number of patients; Sci- ^{99m}Tc-MIBI scintigraphy; SA - single adenoma; MGD - multiglandular disease; CG - concomitant goiter; NR - not reported; Ectopic - ectopic parathyroid gland; 0/0 - none of patients has ectopic glands.

In a study by Agha et al.,[9] which included 30 patients, 3 imaging modalities were used for pre-surgical mapping; the sensitivity of CUS, ^{99m}Tc-MIBI scintigraphy, and CEUS were 80%, 80%, and 100%, respectively. CEUS was superior in detecting PGs in a patient with concomitant thyroid goiter or in the presence of lymphadenopathy, where it is known that the ability of CUS in such cases is limited. However, none of the patients presented with ectopic PG, which is known as one of the CUS limitations that would affect the sensitivity of CEUS.

Hornung et al.[12] concluded that CEUS is a highly sensitive diagnostic tool for localizing pathology in PGs in PHPT patients. Nevertheless, it can only be recommended as a first-line diagnostic procedure in specialized clinical centers with experienced investigators, as its sensitivity is 98.3%, compared to 70% in CUS.

In a study by Silva et al.,[13] a review of 42 patients showed that the sensitivity of CEUS reached 100%. None of the included patients presented with ectopic parathyroid locations. However, that study revealed a new method to quantify the contrast in PGs by using Vuebox Perfusion Analysis software, where the dynamic CEUS analyzed 42 patients with symptoms of PHPT. According to the results, qualitative measurement of contrast perfusion is more accurate than quantitative analysis by Vuebox. However, the latter seems a promising method in the quantification measurement of CEUS, where 25 of 28 cases were successfully diagnosed with PTAs (sensitivity of 89.3%). This result makes the diagnoses more accurate and less expensive but requires slight improvements to the software to prevent potential human-induced errors.

Piccin et al.[14] found that the sensitivity of color Doppler US was significantly higher than SPECT, while the sensitivity of 4D-CT was significantly better than US and SPECT for the preoperative localization of abnormal parathyroid gland/s. The authors concluded that in patients with concomitant thyroid pathology, the combination of US and 4D-CT represents a reliable localization technique.

The sensitivity of CEUS for detecting single adenomas was 97.1%, and double adenomas reached 100% in 70 patients diagnosed with PHPT in a study by Agha et al.[10] Also, CEUS showed the sensitivity of detecting concomitant thyroid goiter as 100%, while that of CUS was 64%. In a study performed by Ramírez et al.,[7] CEUS revealed a sensitivity of 66.7% for detecting SAs, in comparison with 77.8% for ^{99m}Tc-MIBI SPECT scintigraphy and 51.8% for high-resolution US in 29 patients with PHPT. With CEUS, DAs could be detected in both cases.

In a study by Karakas et al.,[15] 25 patients with biochemically proven PHPT underwent preoperative US, MIBI/SPECT, and CEUS. In 17(68%) patients, US and MIBI/SPECT raised suspicion of parathyroid lesions and all suspected lesions were reassessed by CEUS. However, additional information was not obtained about using CEUS compared to results of US and MIBI/SPECT.

The sensitivity of CEUS in detecting small size adenoma (0.5cm -1.5cm) was significantly higher than the CUS. The sensitivity achieved by CEUS and CUS from each study included in this review is represented in a column chart (Fig.1).

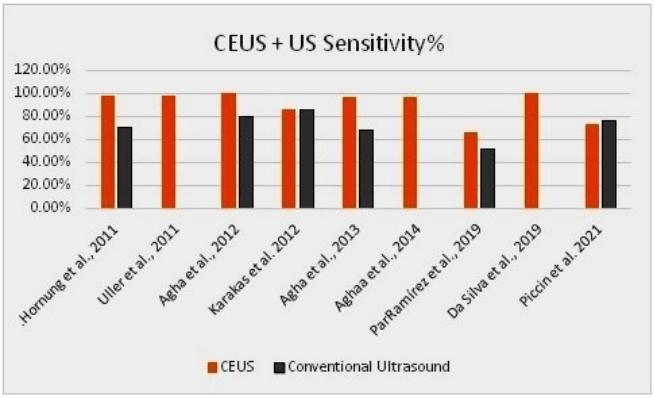

Fig. 1. *The sensitivity achieved by CEUS and CUS.*

CUS and ^{99m}Tc-MIBI Scintigraphy

In a systematic review and meta-analysis, the pooled sensitivity of CUS was reported to reach 80% and scintigraphy 83% among 12 studies. Ruda et al.,[16] analyzing 20,225 cases of PHPT, stated that the sensitivity for ^{99m}Tc-MIBI scintigraphy and CUS were 88.44% and 78.55%, respectively for single adenoma, 44.46% and 34.86% for multiple gland hyperplasia disease, and 29.95% and 16.20% for double adenoma, respectively.

The comparison between 6 studies using CUS and ^{99m}Tc-MIBI scintigraphy and combining the 2 methods is summarized in Table 2. The sensitivity and specificity of each study are included. The numerical values for an single adenoma detected by CUS or ^{99m}Tc-MIBI scintigraphy were not reported in 3 papers, and the *P*-value of the sensitivity between the 2 imaging procedures was calculated only in 2 studies.

Elsayed and Ali [17] compared the efficacy of CUS and ^{99m}Tc-MIBI scintigraphy and a combination of these methods in preoperative detection and localization of PHPT. The study, which included 45 patients, revealed that the sensitivity and specificity for ^{99m}Tc-MIBI scintigraphy were 97.4% and 71.4%, and the values for CUS were 94.4% and 44.4%, respectively. However, the combined approach values were higher, returning 97.4% for sensitivity, 83.3% for specificity, and 95.6% for accuracy. The study recommends a combined approach that uses CUS and ^{99m}Tc-MIBI scintigraphy for PHPT localizing. This approach would result in higher efficiency with a reduced chance of missing parathyroid due to the presence of concomitant thyroid pathology.

Argirò et al.[18] examined the diagnostic accuracy of ^{99m}Tc-MIBI scintigraphy in preoperative localization of PTAs as compared to CUS. The study included 46 PHPT patients who underwent CUS, ^{99m}Tc-MIBI scintigraphy, and MRI. The researchers found that ultrasound was effective, correctly localizing 41 out of the 46 PTA cases. CUS had 89.1% sensitivity and 97.5% specificity. In comparison, ^{99m}Tc-MIBI scintigraphy was accurate for 38 of the 46 cases, with a sensitivity score of 83.6% and a specificity score of 98.3%; the combined method yielded a sensitivity of 93.4% and specificity of 98.3%.

Scattergood et al.[19] analyzed the patients with a histological diagnosis of a PTA. The authors determined that CUS had a higher sensitivity than ^{99m}Tc-MIBI scintigraphy: the sensitivity of CUS was 70%, specificity - 57%, while the sensitivity of ^{99m}Tc-MIBI scintigraphy was 64% and specificity - 57%. There was enhanced sensitivity and specificity when CUS and ^{99m}Tc-MIBI scintigraphy were combined in preoperative localization for PHPT patients - 81% and 71%, respectively.

Vitetta et al.[20] conducted a retrospective comparative study to determine the prospective functions of parathyroid scintigraphy and ultrasonography localization of the neck. The study also measured the intra-operator reliability, and the agreement between the 2 ultrasound sonographers was high.

Ibrahim and Elsadawy[21] stated that the combined use of CUS and ^{99m}Tc-MIBI scintigraphy improved the pre-surgical localization of PTAs.

The study by Akbaba et al.[22] compared various preoperative imaging methods used for PHPT patients. Specifically, the study compared CUS, ^{99m}Tc-MIBI scintigraphy, SPECT, and MRI. The accuracy rates for these preoperative approaches were assessed in 98 patients with known PHPT. Each patient was taken through parathyroidectomy. In that study, a preoperative localization approach was used in 82 cases of patients with abnormal PGs, while ^{99m}Tc-MIBI scintigraphy was done in 66 of the cases. The study determined that CUS has the highest values for sensitivity, specificity, and diagnostic accuracy, compared to other methods. The sensitivity, specificity and diagnostic accuracy values were 87.2%, 25.0%, and 83.0% for CUS, 70.2%, 50.0%, and 69.4% for ^{99m}Tc-MIBI scintigraphy, 75.5%, 50.0%, and 74.5% for SPECT, and 63.8%, 50.0%, and 63.3% for MRI, respectively. Therefore, CUS was found to be the most effective preoperative approach. The combination of CUS with ^{99m}Tc-MIBI scintigraphy yielded more sensitivity, and diagnostic accuracy was 94.9% and 91.1%, respectively.

The sensitivity achieved by ^{99m}Tc-MIBI scintigraphy and CUS from each study included in this review are represented in a column chart (Fig.2).

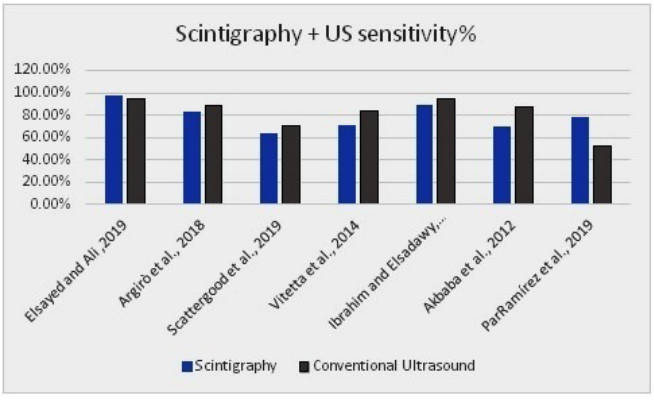

Fig. 2. *The sensitivity achieved by ^{99m}Tc-MIBI scintigraphy and CUS*

It is essential for all patients diagnosed with PHPT to undergo preoperative imaging. Wilhelm et al.[23] recommended that cervical ultrasonography performed by an experienced parathyroid sonographer is the least costly imaging modality and, when combined with ^{99m}Tc-MIBI scintigraphy or 4-dimensional CT, is the most cost-effective strategy. Preoperative, ultrasound-directed, fine-needle aspiration biopsy of parathyroid lesions is highly specific but is rarely necessary and can have undesirable consequences. Cervical ultrasonography is recommended to localize parathyroid disease and assess for concomitant thyroid disease. ^{99m}Tc-MIBI scintigraphy is the dominant radioisotope in parathyroid scintigraphy.

Each sestamibi protocol (dual-phase, iodine 131 subtraction, SPECT) has individual strengths and weaknesses. Combined CUS and ^{99}mTc-MIBI scintigraphy imaging increases localization accuracy and improves sensitivity.[23]

Our review shows that CEUS has a sensitivity of 66.7%-100%, CUS – 51.8%-94.6%, and ^{99m}Tc-MIBI scintigraphy – 61.8%-97.4%. These values place CEUS as one of the imaging procedures that could be selected for pre-surgical mapping. CEUS has a sensitivity slightly higher than CUS and comparable to ^{99m}Tc-MIBI scintigraphy in localization. We found that CEUS does not limit the size of the gland; the ability to detect very small size (6mm) has been proved in 4 studies.

Agha et al.[24] concluded that CEUS represents a high sensitivity method for the localization of PTAs independent of findings in ^{99m}Tc-MIBI scintigraphy, and that in the presence of appropriate expertise in CEUS, no further diagnostic procedures are required. However, Scattergood et al.[19] recommended using CEUS as second-line imaging when the lesions cannot be localized by CUS or ^{99m}Tc-MIBI scintigraphy.

The time required and the cost for the 3 imaging modalities was analyzed by Agha et al.[9] The authors noted that imaging by ^{99m}Tc-MIBI scintigraphy requires the longest time to complete the exam and attracts the highest price. The procedure entails injecting contrast and waiting after the injection until patients leave the exam room. It requires approximately 3h and costs an average of $443. On the other hand, CUS and CEUS need less time and have a lower cost. The differences in the time required and the cost is beneficial for the healthcare provider and the patient's situation. However, the need for sonographers and radiologists to perform the exam limits the prevalent use of CEUS in some countries as this exam is highly operator-dependent, as opposed to scintigraphy, which is less operator-dependent. The early enhancement of the contrast in PTA and early washout (3-5 min after injection) are the imaging characteristics that confirm the presence of PTA. Also, in patients with cervical lymph nodes that are sometimes indistinguishable from parathyroid disease, lymph nodes showed an early enhancement of the contrast at the hilum and a late enhancement of the parenchyma.[9]

Study Limitations

In this literature review, we analyzed only studies that used CEUS and papers that used the first-line methods for pre-surgical localization of parathyroid adenomas. The specificity and accuracy for CEUS could not be achieved in some studies because only non-healthy participants were included in the

analysis. Also, the positive predictive value was not mentioned in most of the papers and the sensitivity confidence intervals were reported in 4 studies only; thererfore, this review cannot achieve a meta-analysis. Difficulties have been found in communications with some affiliation authors, maybe because none used email addresses or for other unknown reasons. Moreover, some studies did not provide the ultrasound grey-scale findings as it was done for all the patients, especially if the patient had concomitant goiter or thyroid nodular, which is known to limit the ultrasound efficiency in detecting parathyroid glands.

Conclusion

CUES represented a safe, cost-efficient, highly sensitive method for detecting the disease in parathyroid glands for PHPT patients, even if the concomitant goiter is present or if patients have multigland disease. CEUS has a comparable sensitivity to ^{99m}Tc-MIBI scintigraphy, so that it can be used in patients who have a contraindication to scintigraphy or in a hospital without nuclear medicine facility. However, further studies are recommended to determine whether CUES can be used as a standard diagnostic procedure for pre-surgical localization. Ultrasound had a higher sensitivity and lower specificity than ^{99m}Tc-MIBI scintigraphy. A combined approach enhances the performance of either method used independently.

Competing Interests

The authors declare that they have no competing interests.

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