Evaluation of Surgeon-Performed Ultrasonography With or Without Contrast Enhancement vs Scintigraphy in Patients With Primary Hyperparathyroidism

Michaelsen, Sanne Høxbroe; Bay, Mette; Gerke, Oke; Vestergaard, Sys; Graumann, Ole; Nielsen, Viveque Egsgaard; Madsen, Anders Rørbæk; Bonnema, Steen Joop; Godballe, Christian

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TITLE PAGE

Surgeon-performed ultrasound with or without contrast enhancement versus scintigraphy in primary hyperparathyroidism: a non-inferiority study

Authors (Orcid ID)

1. Sanne Høxbroe Michaelsen, MD (0000-0002-2771-6127) [A, B]
2. Mette Bay, MD (0000-0001-7992-8490) [A]
3. Oke Gerke, MSc, PhD (0000-0001-6335-3303) [B, C]
4. Sys Vestergaard, MD (0000-0002-1907-8743) [C]
5. Ole Graumann, MD, PhD (0000-0002-9663-8361) [D, B]
6. Viveque Egsgaard Nielsen, MD, PhD (0000-0001-8078-1908) [A, B]
7. Anders Rørbæk Madsen, MD (0000-0001-6231-138X) [A]
8. Steen Joop Bonnema, MD, PhD, DMSc (0000-0002-6898-1752) [E, B]
9. Christian Godballe, MD, PhD (0000-0001-7639-6337) [A, B]

Affiliations

A) Research Unit for ORL – Head & Neck Surgery and Audiology, Odense University Hospital, Odense, Denmark
B) Department of Clinical Research, University of Southern Denmark, Odense, Denmark
C) Department of Nuclear Medicine, Odense University Hospital, Odense, Denmark
D) Department of Radiology, Odense University Hospital, Odense, Denmark
E) Department of Endocrinology, Odense University Hospital, Odense, Denmark

Corresponding author: Sanne Høxbroe Michaelsen, MD, Department of Otorhinolaryngology, Head & Neck Surgery, and Audiology, Odense University Hospital, J. B. Winsløws Vej 4, 5000 Odense C, Denmark
sanne.hoxbroe.michaelsen@rsyd.dk; phone +45 42370703

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Key points

Question

Is surgeon-performed ultrasound, with or without contrast enhancement, non-inferior to scintigraphy for localizing pathological parathyroid glands in primary hyperparathyroidism?

Findings

In this prospective, paired, non-inferiority cohort study, a total of 172 consecutive patients with primary hyperparathyroidism underwent scintigraphy followed by ultrasound and contrast-enhanced ultrasound by a blinded surgeon-sonographer. The study found that ultrasound, both with and without contrast enhancement, was non-inferior to scintigraphy.

Meaning

Conventional ultrasound by an experienced parathyroid surgeon-sonographer is a valid first-line imaging modality for patients with primary hyperparathyroidism, with further imaging reserved for cases that are equivocal or non-localizing on ultrasound.

Abstract

Importance

Scintigraphy and ultrasound are common imaging modalities for the pre-operative localization of enlarged parathyroid glands in primary hyperparathyroidism. When comparing the two modalities, the benefits of ultrasound in terms of convenience, patient comfort, duration, cost, and lack of radiation should be taken into account.

Objective

The aim of the study was to investigate whether surgeon-performed ultrasound, with or without contrast-enhanced ultrasound (CEUS), was non-inferior to scintigraphy for localizing pathological parathyroid glands in patients with primary hyperparathyroidism.

Design

Prospective, paired, non-inferiority cohort study with blinded examiners and a six month follow-up. Inclusion lasted from September 2019 until February 2021. Follow-up ended in December 2021.

Setting

The study took place at a high-volume tertiary referral center for parathyroidectomy.

Participants

Adults (≥18 years) referred for parathyroidectomy due to primary hyperparathyroidism. Of 207 eligible patients, 35 were excluded, leaving 172 enrolled in the study.

Interventions/exposures

^{99m}Technetium-Pertechnetate/^{99m}Technetium-sestamibi subtraction scintigraphy with ^{99m}Technetium-sestamibi SPECT/CT, followed by surgeon-performed ultrasound and CEUS.

Main outcome and measure

The sensitivity of each imaging modality in localizing pathological parathyroid glands, calculated on a per quadrant and a per patient basis, respectively. The a priori non-inferiority margin was a lower 95% confidence limit for the difference in sensitivity not falling below -10%.

Results

Out of 172 participants, 139 (80.8%) were women, the median (min-max) age was 65 (24-87) years, and the median (interquartile range) follow-up was 200.5 (181-280.25) days. Quadrant sensitivity (95% CI) was 70.9% (63.2%-78.5%) for ultrasound, 68.4% (60.4%-76.5%) for ultrasound+CEUS, and 67.0% (60.0%-74.0%) for scintigraphy. The sensitivity difference (95% CI) compared to scintigraphy was 3.9% (-4.1%-11.8%) for ultrasound and 1.5% (-6.4%-9.3%) for ultrasound+CEUS, establishing non-inferiority for both modalities. Per patient sensitivity was 81.4% (74.8%-86.9%) for ultrasound and 79.1% (72.2%-84.9%) for both scintigraphy and ultrasound+CEUS. The sensitivity difference compared to scintigraphy was 2.3% (-6.8%-11.4%) for ultrasound and 0.0% (-9.1%-9.1%) for ultrasound+CEUS, establishing non-inferiority for both modalities.

Conclusions and relevance

Conventional ultrasound by an experienced parathyroid surgeon-sonographer is non-inferior to scintigraphy and constitutes a valid first-line imaging modality in primary hyperparathyroidism,

even without the addition of CEUS. Further imaging should be reserved for cases that are equivocal or non-localizing on ultrasound.

1. Introduction

Primary hyperparathyroidism (PHPT) is characterized by an excessive or inappropriately normal parathyroid hormone production in the presence of hypercalcemia. The diagnosis is strictly biochemical.[1] The definite cure for PHPT is surgical excision of all hyperfunctioning parathyroid glands, and imaging is only indicated when surgery is being considered.[1,2] The majority of patients with primary hyperparathyroidism (PHPT) suffer from a single adenoma (89%) and can be cured by a minimally invasive parathyroidectomy that targets only one side or quadrant of the neck.[3-5] A targeted approach is facilitated by preoperative localization imaging along with intraoperative, post-excision parathyroid hormone monitoring (ioPTH) that indicates whether all hyperfunctioning tissue has been removed.[1,6,7] No consensus exists regarding the optimal preoperative imaging regimen in PHPT, but the most established first-line modalities are ultrasound (US) and ^{99m}Technetium-sestamibi scintigraphy (SM) with single-photon emission computerized tomography (SPECT) or SPECT/CT.[6,8-11] For patients with PHPT, meta-analyses have estimated the pooled sensitivity of SM SPECT/CT as 90% on a per-patient basis (95% CI 86-95%) and the sensitivity of US as 76.1% for localizing adenomas to the correct side of the neck or identifying multiglandular disease (95% CI 70.4-81.4%).[9,12] Studies on surgeon-performed US from high-volume centers, however, have reported sensitivities as high as 87% for localizing pathological parathyroid glands to the correct quadrant of the neck, and have even suggested adopting US as the primary first-line modality, reserving further imaging for non-localizing or equivocal cases.[13-18]

A less investigated modality is contrast-enhanced US (CEUS). This technique is performed as an add-on to the conventional ultrasound examination and uses an exogenous contrast agent to visualize the micro-vasculature of potential parathyroid adenomas.[19] Publications on parathyroid CEUS are sparse, but sensitivities as high as 89-100% have been reported for this technique in localizing pathological parathyroid glands to the correct side or quadrant of the neck prior to surgery.[19-24]

In the Region of Southern Denmark, all patients referred for parathyroidectomy initially undergo dual tracer ^{99m}Technetium-Pertechnetate/^{99m}Technetium-sestamibi subtraction scintigraphy with ^{99m}Technetium-sestamibi SPECT/CT (dtSM SPECT/CT), followed by an in-office conventional cervical US examination by a parathyroid surgeon. With recent publications suggesting that ultrasound be the initial examination, the aim of this study was to investigate whether surgeon-performed ultrasound, with or without the addition of CEUS, was non-inferior to dtSM SPECT/CT for localizing pathological parathyroid adenomas to the correct quadrant of the neck.[2,25] The non-inferiority approach was chosen to reflect the advantages of US and CEUS compared to radiation-based techniques: they are convenient for the patient, can be performed and interpreted in-office, take only minutes to complete, involve no exposure to ionizing radiation, and are relatively inexpensive.[14,20,25] A non-inferiority margin of 10% was chosen to reflect the greatest margin that US and CEUS could perform worse than dtSM SPECT/CT and still be accepted by the involved clinicians as the first-line imaging modality before surgery.

2. Method

This prospective, paired, non-inferiority cohort study was approved by the Regional Committees on Health Research Ethics for Southern Denmark with project ID S-20190077 and registered at https://clinicaltrials.gov/ with identifier NCT04305561. All patients referred for parathyroidectomy to the Department of Otorhinolaryngology, Head & Neck Surgery, and Audiology at Odense University Hospital, Denmark between September 5, 2019 and February 25, 2021 were considered for enrolment. Participants formed a consecutive series and signed an informed consent document.

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[26]

2.1 Study participants

Adult patients (≥18 years) referred for parathyroidectomy due to PHPT were eligible for inclusion. Danish guidelines for referral for parathyroidectomy are plasma ionized calcium >5.8 mg/dL, or mild hypercalcemia combined with either age < 50, or symptoms/co-morbidity that can be attributed to hypercalcemia.[27] The definition of PHPT was an ionized calcium level above the upper reference level combined with a parathyroid hormone (PTH) level in or above the upper third of the reference interval and no competing causes for the hyperparathyroid hypercalcemia. The study excluded patients who did not have a dtSM SPECT/CT performed in the Region of Southern Denmark; could not read or speak Danish; were not legally competent; had prior thyroid or parathyroid surgery; were pregnant or nursing; suffered from an ongoing malignancy; had contraindications to the CEUS contrast agent; were not booked for surgery; or did not complete the CEUS examination.

2.2 Setup, blinding and unblinding

The description of the dtSM SPECT/CT was blinded by a project nurse and was not made available to the sonographer until both US and CEUS had been performed and the results documented (2.2.1). After unblinding, the patient was scheduled for either a targeted surgery or a bilateral neck exploration, based on an evaluation of all imaging modalities. However, if the surgeon estimated that the risk of surgery/anesthesia outweighed the potential benefits of cure, the patient was not offered surgery. In the case of discordant preoperative imaging results, the operating surgeon made an autonomous decision regarding which quadrant to initially target, guided by imaging confidence scores.

2.2.1 Scoring of US and CEUS

The examiner drew in any potential pathological parathyroid glands on a coronal illustration of the thyroid gland, which had been simultaneously divided into a) quadrants and b) a ten-parted classification (right/left: 1. cranial to the gland, 2. upper third of the gland, 3. middle third of the gland, 4. lower third of the gland, 5. caudal to the gland). A confidence score based on a five-point Likert-type scale was then assigned to each pre-defined position. Low scores of 1 or 2 were considered imaging-negative and high scores of 4 or 5 were considered imaging-positive. A neutral score of 3 assigned to all positions identified the examination as non-localizing.

2.2.2. Scoring of dtSM SPECT/CT

The written description of the dtSM SPECT/CT was transferred to the same illustration and Likert-type scale as in 2.2.1. Descriptions that did not mention a specific quadrant, e.g. "parathyroid adenoma behind the right thyroid lobe", were accepted as having correctly located the lesion if a pathological parathyroid gland was located anywhere behind the mentioned lobe.

2.2.3 Surgeon-performed cervical US

US examinations were performed in a systematic fashion by one of three experienced parathyroid surgeon-sonographers on a Canon Aplio a450 version 1.3 US machine (Canon Medical Systems, Japan) with a PLT-1005BT (14L5) linear transducer. Parathyroid adenomas were expected to be hypoechoic and oval with a polar feeding vessel and a peripheral vascular arc.[28] The result of the US examination was documented before CEUS was conducted.

All US examinations were recorded and retrospectively evaluated for quality by a radiologist together with an experienced parathyroid surgeon-sonographer. One point was awarded for each fulfilled criterion, for a total of 7 possible points: 1. Depth adjusted, 2. Frequency optimized, 3. Scan directed from the upper towards the lower thyroid pole, 4. Subclavian artery visualized, 5. Transverse plane scanned, 6. Longitudinal plane scanned, 7. Potential lesions evaluated with Advanced Dynamic Flow and Superb Microvascular Imaging.

2.2.4 Surgeon-performed contrast-enhanced US

CEUS was performed as an add-on examination by one of two surgeon-sonographers in direct continuation of the US scan and according to current recommendations.[29] A PLT-705BT (11L3) vascular linear transducer was employed. After a bolus injection of 1.2 ml stabilized sulfur hexafluoride microbubbles (Sonovue®, Bracco, Milan, Italy), parathyroid adenomas were expected to show an enhancement pattern going from the periphery towards the center, followed by a central wash-out.[21,24] The probe remained stationary on a lesion until maximum enhancement had been reached, followed by intermittent scanning until wash-out was detected or two minutes had passed.[22,24] For the first 60 patients (pilot study), an initial contrast injection was used for continuous alternate screening of the parathyroid regions for wash-in/wash-out before any solitary lesions were examined.[22] A planned evaluation hereafter allowed for an abandonment of the screening phase if it unveiled no additional lesions compared to US.

All CEUS examinations were recorded and retrospectively evaluated for quality by a radiologist with 16 years' expertise in CEUS. One point was awarded for each fulfilled criterion, for a total of 9 possible points: 1. Parallel imaging of CEUS and B-mode, 2. Depth adjusted, 3. Focus set directly under the lesion, 4. Gain set slightly above the noise floor, 5. Lesion clear and measurable, 6. Entire wash-in phase recorded, 7. No unnecessary movement, 8. Recording lasts two minutes or until wash-out, 9. Overall imaging quality is suitable for clinical evaluation.

2.2.5 DtSM SPECT/CT

A ^{99m}Technetium-pertechnetate thyroid scintigraphy was conducted, followed by an intravenous administration of ^{99m}Technetium-sestamibi and sodium perchlorate. After 15 minutes, a dual-phase ^{99m}Technetium-sestamibi scintigraphy of the neck and a ^{99m}Technetium-sestamibi SPECT/CT of the neck and thorax was performed.

2.2.6 Surgery

Surgeries were performed by experienced parathyroid surgeons guided by ioPTH according to the Miami criterion.[30] The surgeon documented the position of excised glands according to the localization specifications in 2.2.1, combined with the Perrier classification.[31] All excised tissue was histopathologically evaluated.

2.2.7 Follow-up

To ensure that no pathological glands had been overlooked intraoperatively, blood tests continued for a minimum of six months after surgery, either at the local department of endocrinology (89%) or with a general practitioner (11%). The aforementioned 11% were normocalcemic during checks at the hospital for a median of 122 days before finalizing follow-up with their general practitioner.

Continued normocalcemia for patients in this group was assumed if they had not been referred to the local department of endocrinology by the end date of the study, i.e. December 31, 2021.

2.3 Outcome measures

The primary outcome was the sensitivity of each modality in localizing pathological parathyroid glands to the correct quadrant of the neck. The reference standard was: surgical localization, histopathology (adenoma or hyperplasia), and long-term cure. Patients who remained normocalcemic six months after surgery were considered cured, whereas patients with residual disease were conservatively regarded as having had four-gland disease at the time of surgery, with one pathological gland in each quadrant.

If a parathyroid lesion had been assigned to the middle of the thyroid gland, i.e. in-between two quadrants, the ten-parted classification (TPC) was used as a reference. Because of the medial traction and rotation of the thyroid lobe during surgery, pathological parathyroid glands in this location were accepted as true positives if removed from TPC position 2-3 for the upper quadrant and TPC position 3-4 for the lower quadrant.

A true positive imaging result suggested the presence of disease in a quadrant from which a hyperplastic or adenomatous parathyroid gland was removed during surgery. A false positive imaging result suggested the presence of disease in a quadrant from which no pathological gland was removed during surgery - in patients without residual disease at follow-up. A true negative imaging result suggested the absence of disease in a quadrant from which no pathological gland was removed during surgery - in patients without residual disease at follow-up. A false negative imaging result suggested the absence of a disease in a location from which a pathological gland was removed (or assumed in residual disease). For 2x2 contingency tables, see Figure 1.

Pre-specified secondary outcomes were a) the in-hospital cost and procedure time of each modality, including the time required for the diagnostic analysis, b) a re-calculation of the primary outcomes solely for localizing scans, c) the quality of the US and CEUS examinations, and d) an evaluation of the 60 patient CEUS screening phase (pilot study).

Exploratory analyses consisted of a multivariable logistic regression analysis on a per patient basis as well as in single gland disease.

2.4 Sample size

The sample size was based on assumed equal true sensitivities of 90% for both US+CEUS and dtSM SPECT/CT.[21,32,33] With a conservative assumption of a correlation of zero between the diagnostic regimens in a paired design, a significance level of 5%, a power of 80%, and a non-inferiority margin of 10%, a total of 112 patients were required. To account for a potential learning curve of 60 patients for CEUS,[34] and to ensure sufficient statistical power in the eventuality of a lower true sensitivity for US+CEUS than 90%, the main study was preceded by a pilot study with 60 patients, resulting in a total of 172 patients to be enrolled.

2.5 Statistical analysis

Results were calculated on a per quadrant basis and a per patient basis (≥1 true positive quadrant per patient). Since all patients suffered from PHPT, calculating patient-based specificity was not meaningful. Patients were assumed to have between 1 and 4 pathological glands, and non-localizing examinations were counted as having 4 imaging negative quadrants. Non-inferiority of ultrasound modalities compared to dtSM SPECT/CT was established if the lower limit of the 95% CI for the difference in sensitivity (e.g. US+CEUS minus dtSM SPECT/CT) exceeded -0.1 (i.e. -10%). Patient-based sensitivity was assessed with McNemar's test. Quadrant-based analyses were done regressing the binary outcome (e.g. true positives vs. false negatives for sensitivity) on modality, using cluster-robust standard errors to account for intra-patient correlation (four quadrants within each patient).[35]

Study data were collected and managed using REDCap® (Vanderbilt University, Nashville, Tennessee, USA) electronic data capture tools hosted at Odense University Hospital, Denmark.[36,37] Statistical calculations were performed with STATA/MP 17 (StataCorp, College Station, TX 77845, USA) and Microsoft Excel 2016, with two-sided *p*-values <0.05 designating statistical significance.

3. Results

In the study period, 362 patients were referred to Odense University Hospital for parathyroidectomy. Of these, 207 patients were eligible for inclusion and wished to participate. Thirty-five patients had to be excluded, leaving 172 enrolled in the study (Figure 1). All patients fulfilled the criteria for PHPT upon diagnosis.

The majority of patients were female (80.8%). Two patients (1.2%) had residual disease at follow-up, despite the excision of at least one confirmed pathological gland in each case. The remaining 170 patients (98.8%) were cured. Patient characteristics are listed in Table 1.

3.1 Primary Outcomes

Primary outcomes are listed in Table 2. On a per quadrant basis, the sensitivity difference (95% CI) of ultrasound modalities compared to dtSM SPECT/CT was 3.9% (-4.1% to 11.8%) for US and

1.5% (-6.4% to 9.3%) for US+CEUS, establishing non-inferiority for both modalities. On a per patient basis, both ultrasound modalities remained non-inferior to dtSM SPECT/CT with a sensitivity difference of 2.3% (-6.8% to 11.4%) for US and 0.0% (-9.1% to 9.1%) for US+CEUS.

3.2 Secondary outcomes

a) The price and time requirements were lowest for US and highest for dtSM SPECT/CT (Table 2).

b) Considering only the localizing scans, the per quadrant sensitivity difference of US modalities to dtSM SPECT/CT (95% CI) was 1.8% (-4.6% to 8.2%) for US and 2.6% (-4.4% to 9.6%) for US+CEUS, establishing non-inferiority for both modalities. The per patient sensitivity difference, however, was -4.0% (-9.9% to 1.9%) for US and -4.3% (-10.5% to 2.0%) for US+CEUS, establishing non-inferiority for US alone, but not for US+CEUS (Table 2).

c) The average scan quality scores were high for both US (score 6.86/7, 98.0%) and CEUS (score 8.85/9, 98.3%), with 100% representing the optimal examination.

d) The CEUS screening phase (n=60 patients) did not identify any additional lesions compared to US alone.

3.3 Exploratory analyses

On the patient-level, the multivariable regression analysis showed a significantly lower odds ratio (OR) for detection by US (OR=0.29; 95%CI 0.12-0.74) and US+CEUS (OR=0.36; 95%CI 0.15-0.88) in male vs. female patients, while the OR for detection by dtSM SPECT/CT increased significantly with higher pre-operative ionized calcium values (OR=2458; 95%CI 6.98-866322) (Table 3).

In single-gland disease, the OR for detection by US (OR=0.31; 95%CI 0.12-0.83) and US+CEUS (OR=0.36; 95%CI 0.14-0.93) remained significantly lower in male vs. female patients, and the OR of detection by dtSM SPECT/CT was found to increase significantly with higher gland weight (OR=1.004; 95%CI 1.002-1.006), but only by 0.4% per mg (Table 4).

3.4 Adverse events and surgical complications

No adverse events occurred during the US+CEUS examinations. One patient had permanent hypoparathyroidism after a combined total thyroidectomy and subtotal parathyroidectomy, and two patients (1.2%) sustained a persisting unilateral laryngeal nerve palsy.

Discussion

In designing this study, we expected CEUS to be a necessary addition to US if non-inferiority was to be achieved. In our experience, however, CEUS was only feasible in lesions that had already been visualized on US. This observation is in contrast to some of the earliest studies on US vs. CEUS,[20,22,23,38] but in line with a recent study showing no significant difference in sensitivity between color Doppler US and CEUS.[39] An explaining factor for these conflicting results could be technical improvements in US with regard to image resolution, combined with the availability of advanced Doppler flow modes that now enable the visualization of small vessels without the need for an exogenous contrast agent.[40,41] Another imaging modality which uses a contrast agent to evaluate hyperfunctioning parathyroid glands is the four-dimensional CT (4D-CT). This technique is more common than CEUS and has gone from being a problem-solving second-line modality to being the first-line test at some institutions.[42,43] The effectiveness of 4D-CT compared to other imaging modalities is still an area of some debate, but at centers with the required experience, it is considered a cost-effective alternative to scintigraphy.[25,44,45]

The sensitivity of US in our cohort was comparable to the reported sensitivity in previous reviews,[5,9] whereas the sensitivity per patient of dtSM SPECT/CT was lower (i.e. 79.1% in our study vs. 90% for SM SPECT/CT in a meta-analysis by Wong et al).[12] Possible reasons for this discrepancy include that patients in historical cohorts potentially had larger pathological glands due to being diagnosed at a later stage in their disease.[46] Furthermore, our cohort may have contained more non-localizing scans than in studies from centers where the decision to operate relies more heavily on a positive imaging result.[12,47] Lastly, different levels of experience among the large, heterogeneous group of examiners describing the dtSM SPECT/CT scans in our study could have affected the sensitivity.

Several studies on surgeon-performed US have questioned the common practice of acquiring US and SM scans in parallel prior to parathyroid surgery, arguing instead for a sequential approach with surgeon-performed US as the first-line modality.[13-17,48-51] The rationale behind the parallel imaging practice is to pre-operatively rule out the presence of multiple gland disease.[52,53] However, multiglandular disease only occurs in approximately 10% of patients, and neither discordant nor concordant imaging results can predict its presence or absence with certainty.[5,54,55] The employment of ioPTH, furthermore, means that the consequence of unanticipated multiglandular disease is not operative failure, but simply the necessary conversion from a targeted approach to a bilateral neck exploration.[56] In view of these circumstances, the request for bimodal imaging on a routine basis for every patient with PHPT seems disproportionate.[48]

Surgeon-performed ultrasound is not yet standard practice. When deciding for or against a sequential approach to parathyroid preoperative imaging, factors related to both the patient, the institution, and the surgeon must be considered. For centers that employ ultrasound in combination with either scintigraphy or 4D-CT, a proposed algorithm in a recent review can be used as a decision aid.[2] In the present study, localizing US scans had a per patient sensitivity of 89.2%, and dtSM SPECT/CT proved a valuable complementary procedure in the remaining non-localizing cases. In fact, an algorithm applying conventional ultrasound as the primary imaging modality, complemented by dtSM SPECT/CT only in case of a non-localizing US examination, would have resulted in a per-patient sensitivity of 89.5% while reducing imaging costs by 73% and markedly reducing the strain on nuclear medicine resources (91% fewer requested dtSM SPECT/CT scans in our example).

Limitations

A few limitations should be addressed: First, ultrasound is known to be very operator-dependent. Accordingly, the generalizability of this single center study could be limited to other high-volume tertiary referral centers with experienced parathyroid sonographers.[57] Second, for ethical reasons, the surgeon was not blinded to the results of the pre-operative imaging, but any effect hereof on the outcome of the study should be minimized by the use of ioPTH. Third, the cure rate could theoretically be over-estimated for patients whose follow-up was finalized by their general practitioner, if patients were not referred back to the hospital despite signs of residual disease. Fourth, because blood tests were often taken at the referring hospital, results from five different PTH assays were included in the exploratory analysis. However, the dichotomization of PTH values (≥/<median) should limit any effect hereof. Finally, although the paired design should minimize

confounding, our results could be influenced by individual patient factors like age, sex, body weight, severity of disease, etc. We have tried to estimate the influence of potential effect modifiers with the regression analysis.

Conclusion

In this prospective cohort study, both US and US+CEUS were non-inferior to dtSM SPECT/CT in localizing pathological parathyroid glands to the correct quadrant. Given the invasive nature of the CEUS procedure, as well as the added cost and time requirement compared to US alone, the routine addition of CEUS to US does not seem justified. Compared to dtSM SPECT/CT, conventional US involves no exposure to ionizing radiation or intravenous contrast agents, it is convenient for the patient, takes only minutes to complete, and is cost-effective for the health system. With ioPTH safeguarding that no pathological glands are overlooked, US by an experienced parathyroid sonographer constitutes a valid primary pre-operative imaging modality for patients with PHPT, with further imaging reserved for cases that are equivocal or non-localizing on US.

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Conflicts of Interest

Dr. Michaelsen reports a grant from Doctor Sofus Carl Emil Friis and Wife Olga Doris Friis' Grant (a non-profit organization) to update the ultrasound software licenses and ultrasound probes on two of the department's ultrasound machines. The grant was received before the onset of the study. The grant provider had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

Non-Author Contributions

None.

Access to Data and Data Analysis

Dr. Michaelsen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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TABLES AND FIGURES

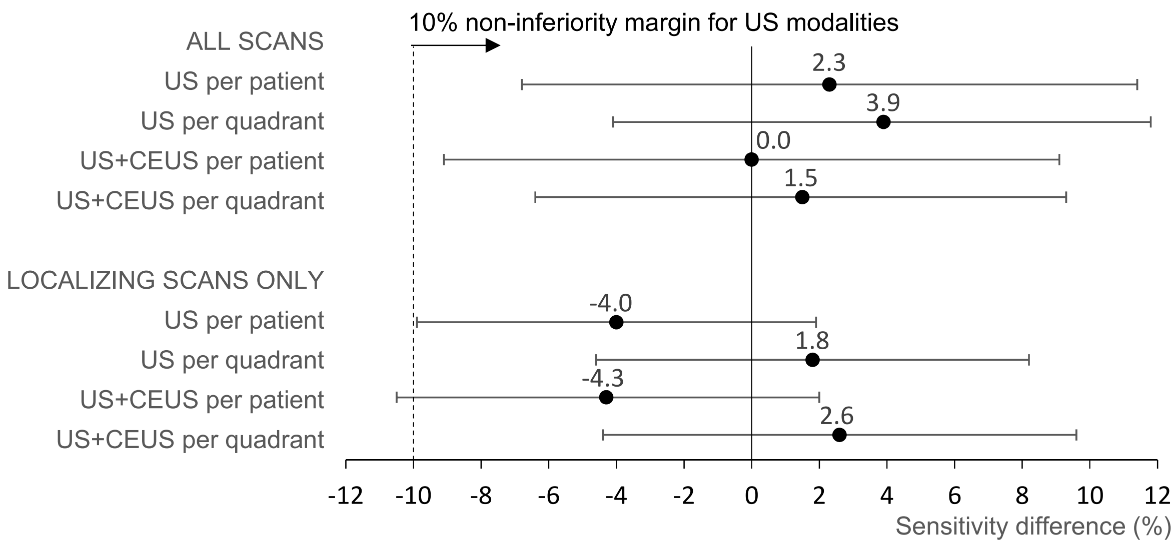
Table 1: Characteristics of 172 patients with primary hyperparathyroidism	
Characteristic	**value**
Age in years, mean (SD)	63.3 (11.6)
Gender (female/male), n (%)	139 (80.8%)/33 (19.2%)
BMI in kg/m^2, median (min-max)	26.3 (14.9-42.8)
Follow-up in days,[a] median (min-max); Q1-Q3	200.5 (7-555); 181-280.25
1-gland disease, n patients (%)	154 (89.5%)
2-gland disease, n patients (%)	10 (5.8%)
4-gland disease, n patients (%)	8 (4.7%)
Thyroid pathology	**n (%)**
Normal thyroid on US	103 (59.9%)
Multinodular goiter	49 (28.5%)
Partly intrathoracic	12 (7.0%)
Solitary adenoma	8 (4.7%)
Diffuse goiter	2 (1.2%)
Other	4 (2.3%)
Preoperative plasma ionized calcium[b]	**median (min-max)**
Reference range 4.73-5.29 mg/dL at pH 7.4	5.73; (5.25-7.18)
Preoperative plasma parathyroid hormone[c,d]	**median (min-max)**
Ref. range 15.1-56.6 pg/mL (n=105)	81.1 (28.3-188.6)
Ref. range 10.4-65.1 pg/mL (n=9)	103.7 (66.0-162.2)
Ref. range 15.1-65.1 pg/mL (n=34)	103.7 (46.2-367.8)
Ref. range 16.0-86.8 pg/mL (n=23)	112.2 (43.4-189.5)
Ref. range 11.3-78.3 pg/mL (n=1)	171.6 (171.6)
Pathological parathyroid glands (n=206)	**value**
Gland weight in mg, median (min-max)	435 (41-8305)
Missing weight,[e] n glands (%)	16 (7.8%)
Ultrasound true positive glands (n=146)	
Largest diameter in mm, median (min-max)	11 (3-50)
Missing size, n glands (%)	3 (2.1%)

[a]Refers to the latest available blood test before a patient is referred to their general practitioner.
[b]To convert ionized calcium from mg/dL to mmol/L, divide by 4.01
[c]Because most patients had blood tests taken at the referring (local) hospital, 5 different parathyroid hormone assays were used.
[d]To convert parathyroid hormone from pg/mL to pmol/L, divide by 9.43
[e]Five presumed pathological glands in patients that were not cured, 6 hyperplastic glands left in situ in patients who had 3 or 3½ hyperplastic glands removed, 1 intrathyroidal gland, 4 excised pathological glands with no recorded weight.

Table 2: Comparison of imaging modalities

All scans (localizing and non-localizing)						
	US		US+CEUS		dtSM SPECT/CT	
Estimated time requirement	10 minutes		20 minutes		140 min	
Cost in USD (EUR)	252 USD (253 EUR)		268-329 USD (269-330 EUR)		980 USD (984 EUR)	
Patients (n)	172		172		172	
	Value	95% CI	Value	95% CI	Value	95% CI
Sensitivity per patient (≥1 true positive quadrant per patient)	81.4%	74.8-86.9	79.1%	72.2-84.9	79.1%	72.2-84.9
Sensitivity per quadrant	70.9%	63.2-78.5	68.4%	60.4-76.5	67.0%	60.0-74.0
Specificity per quadrant	91.3%	88.6-93.9	93.4%	91.0-95.7	93.8%	91.4-96.1
PPV per quadrant	77.7%	71.9-83.5	81.5%	75.7-87.3	82.1%	76.3-88.0
NPV per quadrant	88.0%	84.2-91.8	87.4%	83.5-91.3	86.9%	83.4-90.4
Localizing scans only						
	US		US+CEUS		dtSM SPECT/CT	
n patients	157		153		146	
	Value	95% CI	Value	95% CI	Value	95% CI
Sensitivity per patient (≥1 true positive quadrant per patient)	89.2%	83.2-93.6	88.9%	82.8-93.4	93.2%	87.8-96.7
Sensitivity per quadrant	79.3%	72.3-86.4	80.1%	72.8-87.4	77.5%	69.9-85.1
Specificity per quadrant	90.5%	87.7-93.4	92.7%	90.1-95.2	92.6%	89.9-95.3
PPV per quadrant	77.7%	71.9-83.5	81.5%	75.7-87.3	82.1%	76.3-88.0
NPV per quadrant	91.4%	87.9-94.9	92.0%	88.6-95.4	90.4%	86.3-94.4

Forest plot of difference in sensitivity (95% CI) for US modalities minus dtSM SPECT/CT[a]



[a]*Error bars show the 2-sided 95% confidence intervals. The dashed line at x = -10% indicates the non-inferiority margin. If the entire 95% CI lies to the right of the non-inferiority margin, the given ultrasound modality is non-inferior to dtSM SPECT/CT.*

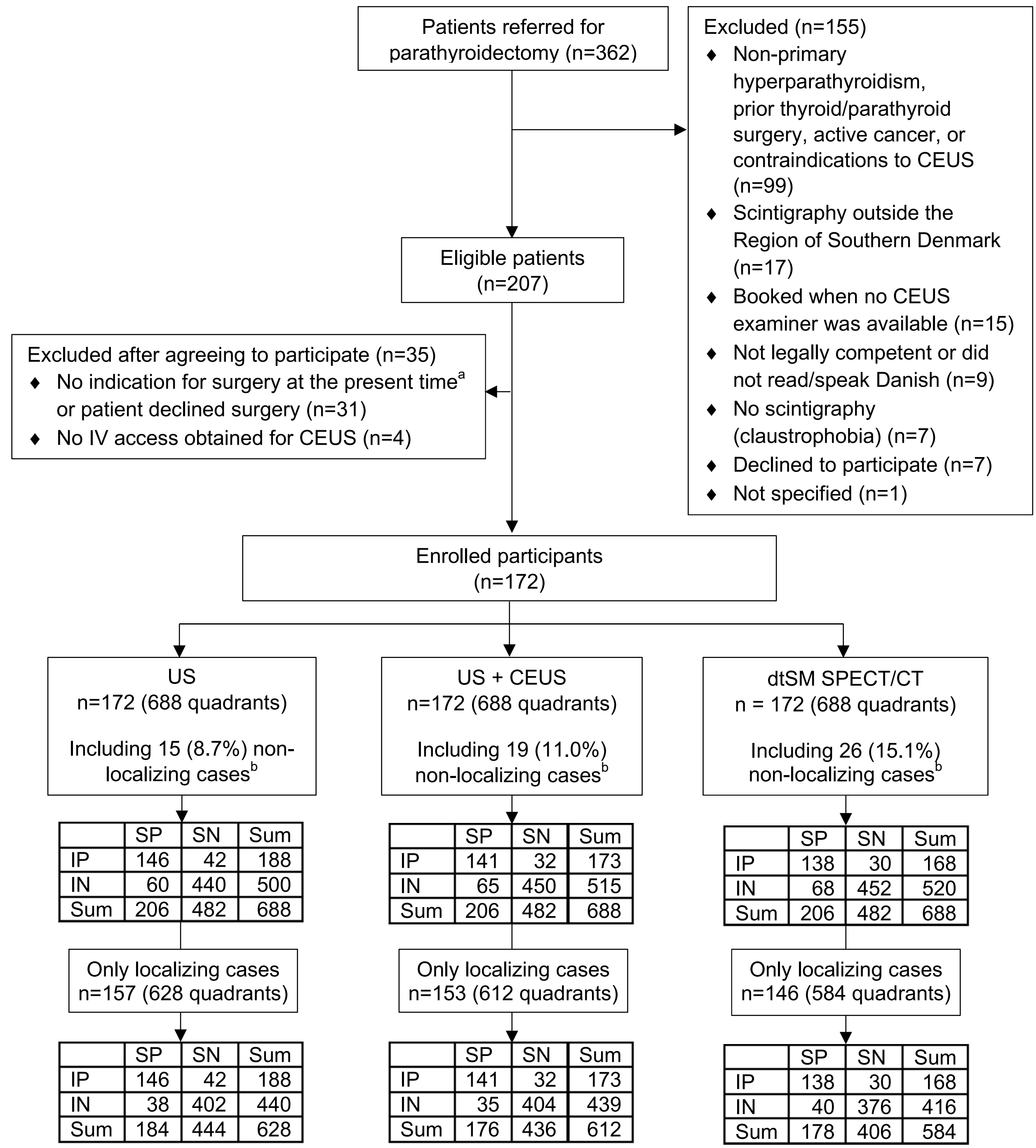
Table 3: Odds ratios (95% CI) of multivariable logistic regression analysis on a per patient basis[a]								
Sensitivity per patient (n=172)[b]	Age (years)	Male sex	BMI (kg/m^2)	Thyroid pathology (yes/no)	Multiple gland disease (yes/no)	Pre-operative ionized calcium (mmol/l)	Pre-operative PTH (≥/< median)[c]	Time between dtSM SPECT/CT and US (days)
US	*1.0 (0.96-1.03)*	*0.29 (**0.12-0.74**)*	*1.02 (0.94-1.11)*	*0.87 (0.37-2.04)*	*1.05 (0.27-4.01)*	*16.4 (0.09-2870)*	*1.37 (0.60-3.13)*	–
US +CEUS	*0.99 (0.96-1.03)*	*0.36 (**0.15-0.88**)*	*1.01 (0.93-1.10)*	*1.03 (0.46-2.31)*	*0.61 (0.19-1.89)*	*6.83 (0.05-878)*	*1.29 (0.59-2.83)*	–
dtSM SPECT/CT	*1.01 (0.97-1.05)*	*2.0 (0.61-6.54)*	*1.06 (0.98-1.15)*	*1.01 (0.44-2.32)*	*2.33 (0.48-11.26)*	*2458 (**6.98-866322**)*	*0.75 (0.33-1.72)*	*1.0 (0.995-1.001)*

[a]The OR refers to an increase by one unit or the presence (yes) of the variable.
[b]The dependent variable is the presence (yes/no) of ≥1 true positive quadrant per patient.
[c]Refers to the median value of each individual assay.

Table 4: Odds ratios (95% CI) of multivariable logistic regression in single gland disease,[a] n=150[b]								
Sensitivity per patient (n=150)	Gland weight (mg)	Age (years)	Male sex	BMI (kg/m^2)	Thyroid pathology (yes/no)	Pre-operative ionized calcium (mmol/l)	Pre-operative PTH (≥/< median)[c]	Time between dtSM SPECT/CT and US (days)
US	*1.0 (0.9996-1.0003)*	*1.0 (0.96-1.04)*	*0.31 (**0.12-0.83**)*	*1.04 (0.94-1.14)*	*0.75 (0.30-1.91)*	*128.5 (0.40-41171)*	*1.19 (0.48-2.93)*	–
US +CEUS	*1.0 (0.9997-1.0005)*	*0.99 (0.95-1.03)*	*0.36 (**0.14-0.93**)*	*1.0 (0.91-1.10)*	*1.02 (0.42-2.52)*	*28.8 (0.12-6929)*	*0.90 (0.38-2.15)*	–
dtSM SPECT/CT	*1.004 (**1.002-1.006**)*	*1.01 (0.97-1.05)*	*1.73 (0.44-6.77)*	*0.99 (0.91-1.08)*	*1.17 (0.44-3.11)*	*73.7 (0.09-58060)*	*0.39 (0.15-1.01)*	*1.0 (0.995-1.001)*

[a]The OR refers to an increase by one unit or the presence (yes) of the variable.
[b]154 patients with single gland disease, excluding four patients with missing gland weight.
[c]Refers to the median value of each individual assay.

Fig. 1: Modified STARD 2015 flow diagram with contingency tables



US (n=172, 688 quadrants):

	SP	SN	Sum
IP	146	42	188
IN	60	440	500
Sum	206	482	688

US + CEUS (n=172, 688 quadrants):

	SP	SN	Sum
IP	141	32	173
IN	65	450	515
Sum	206	482	688

dtSM SPECT/CT (n=172, 688 quadrants):

	SP	SN	Sum
IP	138	30	168
IN	68	452	520
Sum	206	482	688

US, only localizing cases (n=157, 628 quadrants):

	SP	SN	Sum
IP	146	42	188
IN	38	402	440
Sum	184	444	628

US + CEUS, only localizing cases (n=153, 612 quadrants):

	SP	SN	Sum
IP	141	32	173
IN	35	404	439
Sum	176	436	612

dtSM SPECT/CT, only localizing cases (n=146, 584 quadrants):

	SP	SN	Sum
IP	138	30	168
IN	40	376	416
Sum	178	406	584

[a] *Asymptomatic with near-normal ionized calcium levels and non-localizing on all modalities.*
[b] *Non-localizing cases are counted as having four imaging negative quadrants.*
US: ultrasound, CEUS: contrast-enhanced ultrasound, dtSM: dual tracer ^{99m}Tc-Pertechnetate/^{99m}Technetium-sestamibi subtraction scintigraphy.
SP: surgically positive quadrant (histopathologically verified adenomatous/hyperplastic gland or assumed pathology in case of residual disease), SN: surgically negative (no pathological gland removed from the quadrant and the patient remains normocalcemic six months after surgery.
IP: imaging positive quadrant, IN: imaging negative quadrant.