The American Journal of Surgery 217 (2019) 108–113

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

# Value of $^{123}I/^{99m}Tc$-sestamibi parathyroid scintigraphy with subtraction SPECT/CT in primary hyperparathyroidism for directing minimally invasive parathyroidectomy

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ARTICLE INFO

*Article history:*
Received 13 May 2018
Received in revised form
18 June 2018
Accepted 26 June 2018

*Keywords:*
Hyperparathyroidism
Radionuclide imaging
Mini-invasive surgery

ABSTRACT

*Background:* Primary hyperparathyroidism/(PHPT) is one of the most common endocrinological conditions. Surgery remains the only curative option. We have evaluated the performance of double isotope $^{123}I/^{99m}Tc$-sestamibi parathyroid scintigraphy/(PS) with subtraction SPECT/CT in PHP for identifying uniglandular disease.

*Methods:* Ninety PHPT patients undergoing parathyroidectomy (December 2015–August 2016) were included. All patients were evaluated with neck ultrasound/(US), PS and SPECT/CT with a new protocol. Outcomes from imaging modalities were reported as: uniglandular disease/(UGD), multiglandular disease/(MGD), or negative, and were compared to post-operative diagnoses.

*Results:* Post-operatively, 72 and 18 patients had true UGD and MGD, respectively. Sensitivities and specificities of US, pinhole scintigraphy with subtraction, pinhole and SPECT/CT with subtraction, and all modalities combined were 91.7%/38.9%, 88.9%/72.2%, 93%/66.7% and 84.72%/77.78%, respectively: specificity of US + PS superior to US alone, $p = 0.074$. SPECT/CT enables reclassification of doubtful uptake foci.

*Conclusions:* Combination of neck US and PS with subtraction SPECT/CT offers a higher specificity for guiding towards minimally invasive parathyroidectomy.



## Introduction

Primary hyperparathyroidism (PHPT) is the commonest cause of hypercalcemia. It results from hyperproduction of intact PTH by a single or multiple parathyroid glands that could be located in eutopic or ectopic positions.[1] Parathyroidectomy remains the only curative treatment with different strategies that can be tailored to varying clinical situations. Although bilateral cervical exploration has a 98% success rate and low morbidity, it is no longer the preferred option for patients with single parathyroid adenomas, also called uniglandular disease (UGD). Focused approaches have been developed for parathyroidectomy (i.e., minimally invasive parathyroidectomy, MIP) with several potential benefits and similar outcomes to the conventional approach. Selection of best candidates for MIP requires a highly sensitive and specific imaging modality.[2,3] Until present, parathyroid scintigraphy (PS) and cervical ultrasonography (US) are the most common first-line imaging tools. US has several advantages over PS: it is inexpensive, widely available and does not require exposure to ionizing radiation. US also provides information about the thyroid gland. Finally, US can also be performed by surgeons.[4,5]

However, mediastinal or posterior glands could be missed by US. PS has several advantages over US: it can detect major parathyroid ectopias, is more specific, and enables fusion of scintigraphic

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https://doi.org/10.1016/j.amjsurg.2018.06.027
0002-9610/

images with computed tomography (CT) for better resolution and localization.[6] In the recent years, PET imaging using $^{18}$F-fluorocholine has gained an increasing role in parathyroid imaging. However, its use in the preoperative imaging work-up of patients with primary hyperparathyroidism is currently limited to situations with doubtful or discordant imaging findings.[7–9] It is therefore of major importance to evaluate hyperparathyroid patients with an optimal parathyroid scintigraphy protocol. Based on the literature and our longstanding experience in parathyroid imaging, the combination of $^{123}$I/$^{99m}$Tc-sestamibi pinhole acquisition with subtraction and SPECT/CT offers the optimal information for guiding surgeons towards the most suitable surgical approach.[10–16]

The aim of the present study was to evaluate the performance of $^{123}$I/$^{99m}$Tc-sestamibi parathyroid scintigraphy with subtraction SPECT/CT in primary hyperparathyroidism for identifying UGD.

## Materials and methods

### *Patient population*

Between December 2015 and august 2016, 371 patients underwent $^{123}$I/$^{99m}$Tc-sestamibi subtraction pinhole and SPECT/CT in the department of Nuclear Medicine department of La Timone University Hospital for hyperparathyroidism. Only those who fulfilled the following criteria were included[1]: PHPT,[2] preoperative cervical US performed in our institution by a radiologist with over 30-yrs of experience in thyroid US (JVL),[3] parathyroidectomy performed in our institution,[4] follow-up for at least 6-months after parathyroidectomy.

According to the results of the preoperative imaging workup, patients underwent surgery via a focused approach or a transverse cervicotomy approach. In patients who underwent a focused approach, intra-operative PTH dosing (IOPTH) was performed to ensure operative success.

### *Neck ultrasound*

Neck US was performed for all patients using a Philips IU22 with a 12-MHz linear transducer. The area examined extended from the angle of the mandibule to the superior part of the anterior mediastinum (examined by including the transducer toward the retrosternal region).

### *Parathyroid scintigraphy*

All patients underwent dual isotope ($^{123}$I/$^{99m}$Tc-sestamibi) static planar pinhole imaging (pinhole collimator) followed by dual isotope ($^{123}$I/$^{99m}$Tc-sestamibi) SPECT/CT (parallel-hole collimators) on the same day. The same camera (Siemens ECAM, Siemens Medical Systems, Erlangen, Germany) was used for both image acquisitions. The patients first received 12MBq of intravenous $^{123}$I. Two hours later, 740 MBq of $^{99m}$Tc-sestamibi was injected. Pinhole acquisition was started 3min after the Tc99m-sestamibi injection; static anteriorcervical views were obtained during 20 min with two photopeaks of 7% energy windows, centered, respectively, over the 140 keV (Tc99 m) and 159 keV (I123) photopeaks (128 × 128 matrix, zoom of 2.67). Interactive software was used for image normalization and subtraction. The tomographic study was then started with parallel-hole collimators LEHR (Low Energy High Resolution) (at 30–45 min after $^{99m}$Tc-sestamibi injection), on a double detector SPECT/CT camera, Symbia Intevo® T6 (Siemens®), in a double isotope mode, $^{99m}$Tc-sestamibi and $^{123}$I (140 keV (14%) and 159 keV (14%)), with the following parameters: 128 × 128 matrix, zoom of 2, 30s per projection at each of 64 angular steps, providing two perfectly superimposable volumes after reconstruction. The reconstruction was performed with a 3D OSEM (6 iterations and 8 subsets) with a Gaussian filter and the attenuation correction was based on the CT. The CT was performed with 110 kV and the effective mAs was adjusted using the Care Dose 4D® system.

Image processing entailed subtraction of the $^{123}$I-thyroid image from the MIBI-Tc99 m thyroid and parathyroid image. The final visualization displays the CT merged $^{99m}$Tc-sestamibi thyroid and parathyroid image, the $^{123}$I -thyroid image as well as the subtraction image on the Syngovia® station (Siemens®). The field of view included the cervical and thoracic area (from the angle of the mandibule to the heart).

### *Image interpretation*

For cervical US images, a positive finding was defined by an ovoid homogeneous hypoechogenic gland, with peripheral vascularization. Concerning scintigraphic planar pinhole images, a positive finding was defined as residual $^{99m}$Tc-sestamibi activity after normalization and subtraction. For pinhole images, doubtful uptake foci were classified according to the following diagnostic confidence score: 1 = negative, 2 = doubtful but probably negative (doubtful residual uptake foci after subtraction in a non-typical area of parathyroid distribution), 3 = doubtful but probably positive (doubtful residual uptake foci after subtraction in a typical area of parathyroid distribution), 4 = positive. Scores 1 and 2 will be considered as negative and 3 and 4 as positive.

On SPECT-CT, a positive finding was defined as residual $^{99m}$Tc-sestamibi activity after subtraction, corresponding to a tissular formation. The formations were classified as superior (P4 derived) if they were posterior and located within the superior two-thirds of the thyroid lobe. They were classified as P3 derived if they were anterior and developed at the tip of the inferior pole of the thyroid lobe or along the thyrothymic tract. Other locations included adenomas that were described as anterior or posterior.

### *Disease status*

Cure was defined irrespective of the surgical strategy by normalization of serum calcium and serum PTH values in concordance with the vitamin D status at least 6 months after parathyroidectomy. Uniglandular disease (UGD) was defined when only a single abnormal gland was removed and the patient was cured. When more than one gland was involved histologically (adenoma or hyperplasia), the patient was considered to have multiglandular disease (MGD). This category also included cases with multiple adenomas or multiple parathyroid gland hyperplasia. Patients who were not cured after excision of a single lesion were also considered to have MGD.

### *Statistical analyses*

Outcomes from imaging modalities cervical US and PS were classified as UGD, MGD or negative, and were compared to defitive diagnoses post-operatively.

As previously published [6], the results of cervical US or PS were analyzed as follows:

True positive (TP): diagnosis of UGD with final UGD disease status.

False positive (FP): diagnosis of UGD with final MGD disease status.

True negative (TN): diagnosis of MGD or a negative result with final MGD disease status.

False negative (FN): diagnosis of MGD or a negative result with final UGD disease status.

According to our criteria, positive predictive value (PPV) was the probability that the imaging investigation correctly predicted UGD and the negative predictive value (NPV) was the probability that imaging investigation correctly excluded UGD.

These results were used to calculate the sensitivity (Se), specificity (Sp), PPV, NPV and accuracy.

Between-group comparisons were performed using Chi 2 or fisher's exact test for qualitative variables and Student's t-test or Mann-Whitney *U* test for continuous variables (expressed as mean ± S.D. or median with interquartile range (IQR) if appropriate). The extended McNemar test was used to compare sensitivities of the different imaging modalities. The P values of ~0.05 were taken to be statistically significant. All statistical analyses were performed using SPSS 17.0 Software.

## Results

### *Patients and imaging findings*

Ninety patients were included in the study. Two hundred seventy-seven patients were not included in the study due to: absence of neck US performed in our institution (n = 137), absence of follow-up data (n = 109, patients managed in different institutions following imaging) or presence of renal HPT or MEN1 disease (n = 11). Among the remaining 114 cases, 90 were operated and constituted the study population.

Patient and gland characteristics are detailed in Table 1. Seventy-two patients had true UGD and 18 had MGD (2 abnormal glands in 14 cases and 3 abnormal glands in the latter 4 cases). No major ectopia were identified. Cervical US and pinhole scintigraphy were concordant in 66/90 cases (73.3%) for a single, multiple or absence of gland abnormalities in 63, 2 and 1 cases, respectively. In the remaining discordant cases, 5 were negative by US but displayed single gland abnormalities by pinhole scintigraphy, and 6 cases had multiple gland pathology by pinhole scintigraphy but were classified as UGD by US (Table 2, Fig. 1).

### *Performance of PS and cervical US*

Sensitivities and specificities of neck US, planar pinhole scintigraphy with subtraction, planar pinhole and SPECT/CT with subtraction, and all modalities combined (US + pinhole + SPECT/CT) were 91.7%/38.9%, 88.9%/72.2%, 93%/66.7% and 84.72%/77.78%, respectively (Table 3). The use of a concordance between cervical US and PS (pinhole and SPECT/CT) as a criterion for directing a focused approach provides the highest specificity (with p = 0.023 in comparison to cervical US alone) (Table 3).

### *Added value of subtraction SPECT/CT*

Interestingly, pinhole was considered as doubtful for 22 foci in 19 patients (11 with a diagnostic confidence score of 2 and 11 with a score of 3) and has been reclassified by SPECT/CT in several cases.

In 7 cases of doubtful single foci on pinhole, SPECT/CT with subtraction was able to reclassify 5 cases as UGD, with 4 out of the 5 cases having a final UGD disease status (Figs. 1–3) while MGD was the final disease status for the 5th case. In the remaining 2 doubtful cases, SPECT/CT was negative in both but final disease status was UGD in one case, and MGD in the other.

In 9 patients, pinhole identified a typical abnormal parathyroid uptake and a second doubtful focus. These doubtful foci were accurately reclassified by SPECT/CT in 8 cases with a true double adenoma in one case and non-parathyroid foci in 7 cases (5 thyroid, 2 non-specific). In the remaining case, the examination result of all-modalities-combined was concluded as MGD (despite the fact that only one gland was observed on SPECT/CT) because of the confidence score for the doubtful focus being at 3. This patient was eventually found to have MGD post-operatively.

In 2 patients, pinhole identified 2 doubtful foci (confidence scores 2 and 3 each). In one case, SPECT/CT was negative and the all-modalities-combined examination was concluded as UGD based on the 1 focus with a confidence score of 3. In the second case, SPECT/CT was concordant with the pinhole findings. In both cases, patients were found to have 2 abnormal parathyroid glands (MGD status).

Finally, in one case, pinhole identified a typical abnormal parathyroid uptake and 2 additional doubtful foci (confidence scores 2 and 3) SPECT/CT was positive for a single gland pathology but the examination was concluded as MGD according to the pinhole. The final disease status was MGD with 2 abnormal glands on pathological examination.

**Table 2**
Head-to-head comparison between $^{123}I/^{99m}Tc$-sestamibi subtraction pinhole scintigraphy and neck US.

| | | Subtraction pinhole | | |
|---|---|---|---|---|
| | | UGD | MGD | Negative |
| Neck US | UGD | 63 | 6 | 8 |
| | MGD | 1 | 2 | 3 |
| | Negative | 5 | 1 | 1 |

## Discussion

To the best of our knowledge, this is the first study that evaluates the diagnostic performance of $^{123}I/^{99m}Tc$-sestamibi subtraction planar pinhole scintigraphy with SPECT/CT in primary hyperparathyroidism for identifying UGD eliglible for MIP.

The principal conclusions that can be drawn from this study include: Firstly; our dual isoptope subtraction SPECT/CT acquisition and reconstruction protocol generates volumetric high-quality image. Secondly; the combination of cervical US and subtraction PS (pinhole + SPECT/CT) offers a higher specificity than that of neck US alone, which is required for selecting patients for focused

**Table 1**
Patient and tumor characteristics.

| | |
|---|---|
| Median age (in year) | 64.5 (min = 16, max = 84) IQR [56,73] |
| Sex | Male 22/90 Female 68/90 |
| Median calcemia (in mmol/L) | 2.6 (min = 2.3, max = 3.9) IQR [2.5,2.7] |
| Median PTH level (in pmol/L) | 13 (min = 4.6 max = 140) IQR [11,18.3] |
| Transverse cervicotomy | 35 |
| Focused surgery | 55 |
| Cervicotomy conversion | 3 |
| UGD | 72 |
| MGD | 18 |
| Median gland weight (in mg) | 700 (min = 130, max = 8650) IQR [450, 1330] |

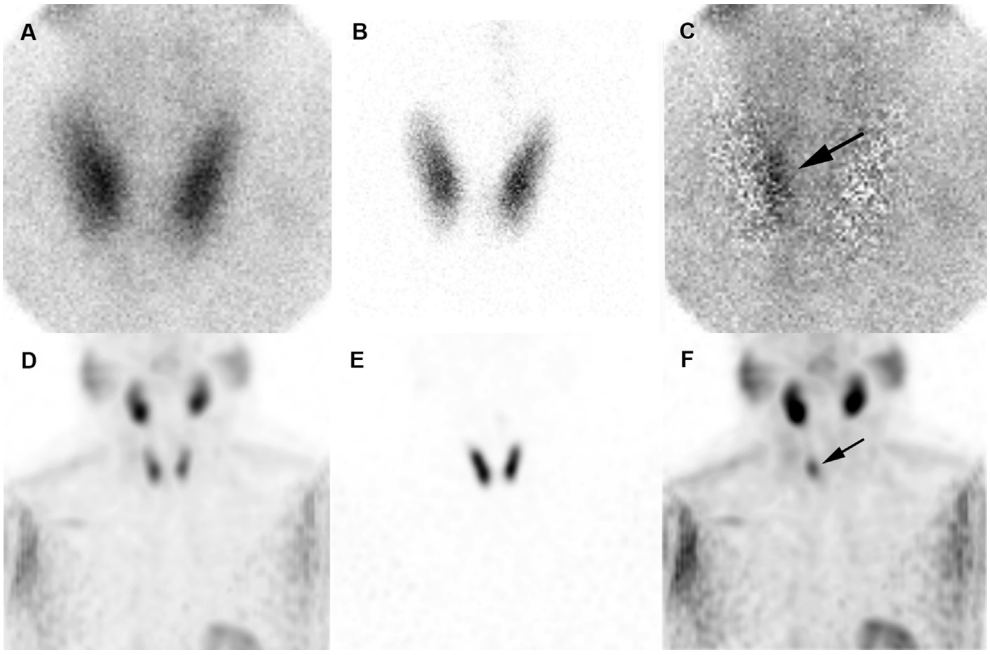


**Fig. 1.** Pinhole and SPECT subtraction PS in a patient with UGD. A: $^{99m}$Tc-sestamibi pinhole, B: $^{123}$I pinhole, C: $^{123}$I/$^{99m}$Tc-sestamibi subtraction pinhole, D: $^{99m}$Tc-sestamibi SPECT (attenuation corrected), E: $^{123}$I SPECT (attenuation corrected), F: $^{123}$I/$^{99m}$Tc-sestamibi subtraction SPECT (attenuation corrected). The parathyroid adenoma is visible in panels C and F (arrows).

parathyroidectomy with limited numbers of surgical conversions. Thirdly; doubtful uptake foci on pinhole scintigraphy in presence of negative subtraction SPECT/CT (absence of thyroid uptake) should be considered as positive.

Although our acquisition and reconstruction protocol has not been validated yet for clinical routine, it provides high quality subtraction images with very useful information. With this application, we showed that the use of tomographic acquisition with parallel-hole collimators LEHR on a double detector SPECT/CT camera, in a double isotope mode, provides two perfectly superimposable volumes after reconstruction and a high quality subtraction image. This protocol can therefore be set up easily in any department of nuclear medicine. Subtraction tomoscintigraphic protocol was also evaluated in one study, with excellent results, with sensitivities and specificities for pinhole and SPECT/CT subtraction of 75%/90% and 86%/100% respectively.[17] They used a $128 \times 128$ matrix and 36 projections of 50 s realizing at 30 min acquisition, the reconstruction was performed by OSEM iterative reconstruction (4 subsets and 10 iterations), then filtred with a Butterworth spatial filter (cut off frequency 0.3cmj1). The two volumes were attenuation corrected using the patient's CT. We used the same projection matrix but decided to upgrade the tomographic image quality with 64 projections of 30 s for 32 min of acquisition, the reconstruction was also performed with a OSEM iterative reconstruction (6 iterations and 8 subsets) with a Gaussian filter and CT-based attenuation correction.

Although bilateral parathyroid exploration should no longer be considered as the only option for all patients with primary hyperparathyroidism (pHPT), it has demonstrated excellent results (98% success rate, most of ectopic glands being removed via a cervical route) with low morbidity. In high-volume surgical centers, focused parathyroidectomy and bilateral cervicotomy are performed in daily routine, depending on parathyroid imaging findings (concordant vs discordant for a single gland abnormality) and whether concomitant thyroidectomy is to be performed. Therefore, the aim of preoperative imaging is to limit the number of surgical conversions. The present study shows that a combination of cervical US and PS + SPECT/CT offers a higher specificity than cervical US alone: 77.78% versus 38.89% ($p = 0.074$), which is optimal for guiding towards MIP. Other studies have shown that neck US and SPECT/CT has incremental values in accurately localizing solitary parathyroid adenomas over either technique alone.[6,18]

Based on our longstanding experience in parathyroid imaging, dual isotope planar pinhole cervical acquisition (at 3-cm distance

**Table 3**
Performances of neck US, PS, and US + PS for predicting UGD.
Comparison of sensitivities and specificities for 1 versus 2: $p = 0.773$ and $p = 0.077$, for 1 versus 3: $p = 1.00$ and $p = 0.182$, for 2 versus 3: $p = 0.248$ and $p = 1.00$, for 1 versus 4: $p = 0.074$ and $p = 0.023$.

| Different scenarios | TP | FP | TN | FN | Se (95% CIs) | Sp (95% CIs) | PPV (95%CIs) | NPV (95%CIs) | Accuracy (95%CIs) |
|---|---|---|---|---|---|---|---|---|---|
| 1- Neck US | 66 | 11 | 7 | 6 | 91.67 (82.99 −96.12) | 38.89 (20.30 −61.38) | 85.71 (76.2 −91.83) | 53.85 (29.14 −76.79) | 81.11 (71.82 −87.86) |
| 2- Subtraction Pinhole | 64 | 5 | 13 | 8 | 88.89 (79.58 −94.26) | 72.22 (49.13 −87.50) | 92.75 (84.13 −96.87) | 61.90 (40.88 −79.25) | 85.56 (76.84 −91.36) |
| 3- Subtraction Pinhole + subtraction SPECT/CT | 67 | 6 | 12 | 5 | 93.06 (84.75 −97.00) | 66.67 (43.75 −83.72) | 91.78 (83.21 −96.18) | 70.59 (46.87 −86.72) | 87.18 (79.43 −93.04) |
| 4- Neck US + Subtraction Pinhole + subtraction SPECT/CT | 61 | 4 | 14 | 11 | 84.72 (74.68 −91.25) | 77.78 (54.78 −91.00) | 93.85 (85.22 −97.58) | 56.00 (37.07 −73.33) | 83.33 (74.31 −89.63) |

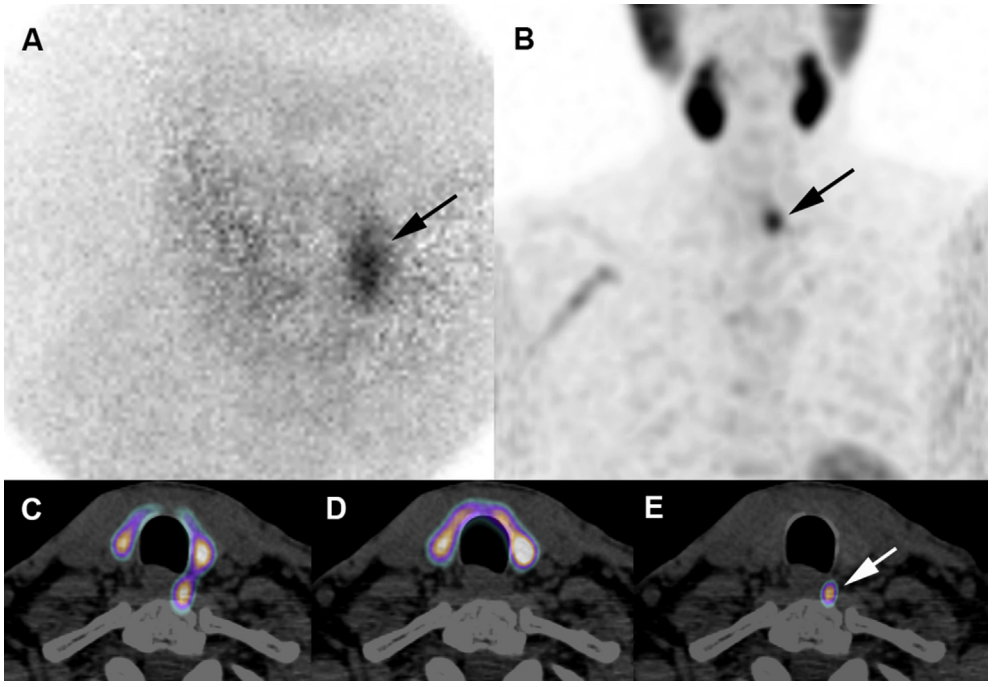


**Fig. 2.** Pinhole, SPECT and SPECT/CT subtraction PS in a patient with UGD. A: $^{123}I/^{99m}Tc$-sestamibi subtraction pinhole, B: $^{123}I/^{99m}Tc$-sestamibi subtraction SPECT (attenuation corrected), C: Axial $^{99m}Tc$-sestamibi SPECT/CT, D: Axial $^{123}I$ SPECT/CT, E: Axial $^{123}I/^{99m}Tc$-sestamibi subtraction SPECT/CT. The parathyroid adenoma is visible in panels A, B and E (arrows).

from thyroid cartilage for 20 min) is very sensitive tool. This has been confirmed by this study. The major role of SPECT/CT is to identify major ectopia (none were observed in the present study), provide anatomical 3D information for cervical adenomas for choosing the most suited surgical approach (mini-open anterior route for P3-derived adenomas vs endoscopy for posterior adenomas (mainly P4-derived)) and reclassify doubtful foci identified on pinhole imaging.[19,20] In cases of doubtful foci on pinhole, 3 situations have been observed: 1- positive SPECT/CT with reclassification of doubtful foci as true abnormal parathyroid glands; 2- positive SPECT/CT with reclassification of doubtful foci as thyroid abnormalities; 3- Negative SPECT/CT. In the latter situation, the rate of TP findings was dependent on the confidence score on pinhole images: 2/5 in grade 2 and 4/4 in grade 3. Therefore, we recommend considering only grade 3 uptake foci as parathyroid abnormalities, even if SPECT/CT is negative.

We acknowledge several limitations of the present study such as its retrospective nature, the highly selected population (A 30-yrs

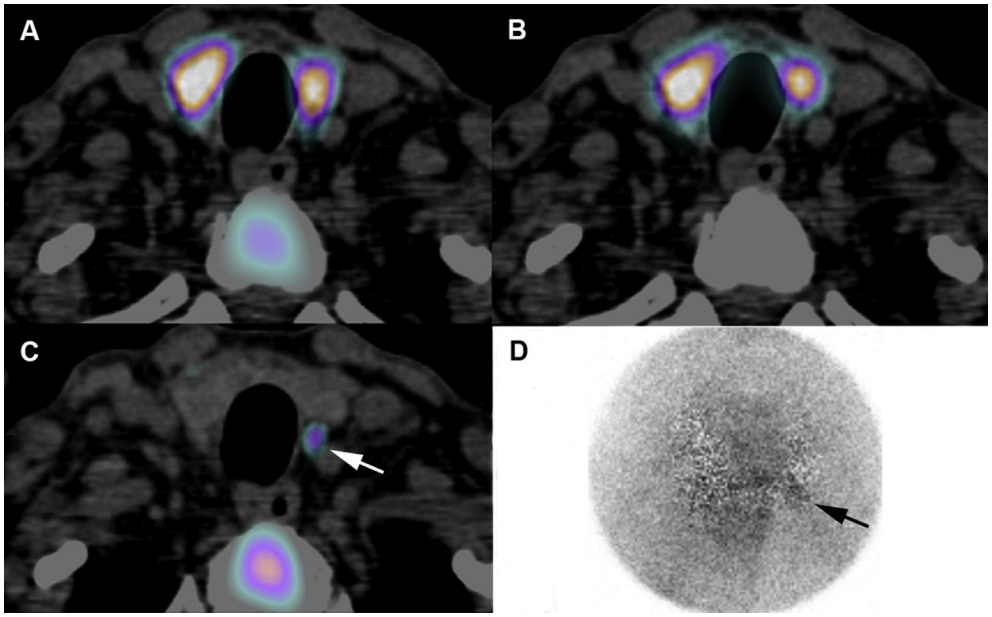


**Fig. 3.** Doubtful foci on pinhole image. A: Axial $^{99m}Tc$-sestamibi SPECT/CT, B: Axial $^{123}I$ SPECT/CT, C: Axial $^{123}I/^{99m}Tc$-sestamibi subtraction SPECT/CT, D: $^{123}I/^{99m}Tc$-sestamibi subtraction pinhole. The doubtful foci on $^{123}I/^{99m}Tc$-sestamibi subtraction pinhole (D, arrow) was reclassified by subtraction SPECT/CT (C, arrow) as a true positive finding.

experienced radiologist) and the exclusion of non-operated patients. However, the aim of the study was to describe the clinical value of an optimal combined imaging approach. Furthermore, our PS protocol can easily be transferred to other centers and takes less than 1-h per patient. In our optinion, $^{18}$F-fluorocholine PET/CT should be performed in rare cases with discordant imaging findings between US and PS (parathyroid abnormalities on both imaging modalities), and in cases with negative findings on PS (expecially negative pinhole) after ruling out potential differential diagnoses.

## Conclusions

In conclusion, subtraction SPECT/CT provides informative images that can accurately reclassify doubtful foci detected on planar pinhole imaging. The combination of cervical US and SPECT/CT with concordant findings of a solitary gland disease remains the most specific approach for orienting towards MIP and deserves to be compared to $^{18}$F-fluorocholine in clinical trials.[8]

## Conflicts of interest

The authors declare no conflict of interest.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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