J of Nuclear Medicine Technology, first published online August 23, 2018 as doi:10.2967/jnmt.118.209767

SPECT-CT-guided ultrasound for parathyroid adenoma localisation - a one stop approach

AUTHORS:

1. Dr Philip Touska; MBBS, BMedSci(Hons), MRCS, FRCR

    Department of Radiology, St. George's Hospital, Blackshaw Road, Tooting, London, SW17 0QT, UK

2. Dr Alison Elstob; MBBS, MRCS, FRCR

    Department of Radiology, St. George's Hospital, Blackshaw Road, Tooting, London, SW17 0QT, UK

3. Dr Nikhil Rao; MBBS

    Department of Radiology, City Hospital Birmingham, Dudley Road, Birmingham, West Midlands, B18 7QH, UK

4. Dr Arum Parthipun; MBBS, MRCP, FRCR

    Department of Nuclear Medicine, Royal Free London NHS Foundation Trust, London, NW3 2QG, UK

SHORT RUNNING TITLE:

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Conflicts of interest: None declared.

Financial disclosures: None declared.

CORRESPONDING AUTHOR:

Dr Arum Parthipun MBBS, MRCP, FRCR

Department of Nuclear Medicine, Royal Free London NHS Foundation Trust,

London, NW3 2QG, UK

Email: arum.parthipun@nhs.net,

Tel: +44 7968 186 577

Corresponding author not in training.

ACKNOWLEDGMENTS

The authors would like to thank all of the staff at the department of radiology at St. Helier Hospital and our colleagues in the department of pathology and head and neck surgery.

ETHICAL APPROVAL

The institutional review board approved this retrospective study and the requirement to obtain informed consent was waived in accordance with NHS Health Research Authority guidelines.

Preliminary data presented at the European Congress of Radiology (ECR) in March 2016.

Word count 3,389

Abstract:

Rationale: To evaluate the accuracy of one-stop (single patient attendance) SPECT-CT-guided ultrasound in the localisation of parathyroid adenomata (PTA). Secondary aims included analysing the effect of multiple PTA and concurrent thyroid disease on sensitivity.

Methods: Patients with hyperparathyroidism that had undergone parathyroidectomy were identified over a 5 year period. Pathological correlation with results from pre-operative sestamibi SPECT-CT followed by targeted ultrasound of the neck was performed. The number of glands, location and presence of concurrent thyroid disease were reviewed.

Results: 146 patients were included (88% single gland, 7% multigland and 5% negative explorations). The sensitivity and specificity of SPECT-CT-guided ultrasound were 83% and 96% respectively. The sensitivity was higher for single gland (87%) as compared to multigland disease (70%). The addition of ultrasound significantly increased the sensitivity of the technique ($p<0.001$). The presence of concurrent thyroid disease (nodules/thyroiditis) did not adversely affect sensitivity (85% CI 74.2-93.1%) compared with normal or atrophic glands (82% CI 72.3-89.7%).

Conclusion: SPECT-CT guided ultrasound represents a useful means of localising PTA, thereby aiding the decision to undertake minimally-invasive or exploratory surgery. The one-stop approach offers patient convenience and enables the radiologist to use the additive benefits of both modalities to optimise localisation. The technique is less sensitive in multi-gland disease, but concurrent thyroid disease does not adversely affect sensitivity.

Keywords

Parathyroid adenoma; parathyroidectomy; parathyroid scintigraphy, 99mTc sestamibi, ultrasound

INTRODUCTION

Primary hyperparathyroidism is a frequently-encountered, endocrinological disorder characterised by excessive secretion of parathyroid hormone and consequent hypercalcaemia. The condition results in a protean, but well-established, constellation of clinical features, ranging from renal tract calcification and pancreatitis to neuropsychiatric disorders and cardiac arrhythmias. It is most commonly caused by parathyroid adenomata or hyperplastic glands, which may be single (80-85%) or multiple (10-15%) (*1*). More infrequently, it may occur in the setting of familial syndromes, such as multiple endocrine neoplasia, or parathyroid carcinoma. Curative management and restoration of normal calcium homeostasis may be achieved by parathyroidectomy, which involves resection of the affected gland or glands. Historically, the procedure of choice was an open, four-gland exploration. However, the advent of preoperative localisation studies has enabled selective, minimally-invasive parathyroidectomy. This technique significantly reduces operative risk and is associated with an improved aesthetic result and reduced recovery time (*2,3*). Therefore, it has become increasingly important for medical imagers to provide accurate pre-operative localisation information, which can be used to determine surgical technique.

Variation in parathyroid gland anatomy presents a significant challenge to imaging-based localisation; therefore, an appreciation of the relevant embryology is of paramount importance. The superior parathyroid glands, derived from the 4th branchial pouch, have a fairly constant position, typically lying on the posterior surface of the upper thyroid gland and dorsal to the recurrent laryngeal nerve (*4*), but the positions of the inferior parathyroid glands, derived from the 3rd branchial pouch, are more likely to be variable, occurring along the path of descent of the parathymic complex.

Supernumerary glands occur in approximately 5% of cases and are typically located in the region of the thymus and thyrothymic ligament (*5*).

The roles of imaging in pHPT

The first role of imaging in primary hyperparathyroidism involves identification of cases of multigland disease, which would obviate a minimally-invasive approach and require exploration. Such cases may have existing risk factors, such as multiple endocrine neoplasia or a familial predisposition. The second role of imaging involves anatomical localisation, which requires an appreciation of the relevant anatomy and embryology. The third role involves identification of occult thyroid disease, which may alter surgical management (for example, requiring a concurrent thyroidectomy).

AIMS

The primary aim was to determine the sensitivity and specificity of a one-stop approach to parathyroid localisation using SPECT-CT guided ultrasound within our institution. Secondary aims included determining whether the techniques were additive and whether sensitivity and specificity were adversely affected by the presence multiple glands or concurrent thyroid disease.

METHODS

Patient selection

The records of patients that had undergone parathyroidectomy for primary hyperparathyroidism were reviewed from October 2009 to March 2015. This 5.4 year period corresponded with the use of SPECT-CT guided ultrasound as the standard parathyroid localisation technique at our institution. Local pathology databases were utilised to identify the details of patients that had undergone parathyroidectomy for primary hyperparathyroidism. The picture archiving and communication system and radiology information system databases were used to retrieve imaging reports. Pre- and post-operative calcium and parathyroid hormone levels were also reviewed to confirm operative success.

Imaging technique

One-stop (single attendance) pre-operative SPECT-CT guided ultrasound was the standard protocol during the evaluation period. This involved a single operator utilising the SPECT-CT findings to guide ultrasound scanning and ultimately reviewing both examinations together to reach a diagnosis.

The parathyroid scintigraphy was performed following an intravenous injection of 750MBq of 99mTc sestamibi. Imaging was performed using a Siemens Truepoint Symbia T6 SPECT-CT scanner (Siemens Healthcare GmbH, Erlangen Germany). Planar imaging of the neck and upper mediastinum was performed at 15 minutes and 150 minutes after tracer injection. Planar images were acquired with an LEHR collimator, a 256 x 256 matrix and a 2.29 zoom factor over 10 minutes. A SPECT-CT acquisition was performed during the delayed phase using 110kV, 190mAs and 3mm slice thickness. Radionuclide scans were called positive if increased uptake seen on early imaging showed retention on delayed scans relative to the thyroid and localised to a nodule in a typical location for a parathyroid adenoma on CT.

Following review of the SPECT-CT images, a targetted ultrasound scan was performed using a 14MHz high-resolution linear probe on a GE Logiq E9 ultrasound scanner (GE Healthcare, Chalfont St Giles, UK). This involved evaluating the location of abnormal uptake identified on SPECT-CT on ultrasound to confirm the presence of a parathyroid adenoma and to note its anatomical location; the neck was also subsequently scanned for any additional abnormal glands not visible on SPECT-CT. In the event that no abnormal glands were localised on SPECT-CT, ultrasound was used to scan the neck for adenomata in all possible locations accessible on ultrasound. Typical ultrasound features of a parathyroid adenoma are of a hypoechoic nodule, usually separate from the thyroid, in a typical location. Additional sonographic features include hypervascularity and a separate vascular pedicle.

The SPECT-CT findings were reviewed by a single experienced consultant (attending) radiologist with specialist training in radionuclide imaging, who performed the subsequent ultrasound examinations on all patients.

Figure 1 demonstrates an example of the multimodality approach to parathyroid gland localisation.

Statistical analysis

Pre-operative imaging results were considered to be true positives if they correctly identified the number of diseased glands and localised them to the correct side (right, left or bilateral). In order to establish true positivity, radiological reports were compared with the subsequent surgical pathology results. Like Patel et al. (*6*) and Witteveen et al. (*7*), non-identification of normal glands on the unaffected side was considered to represent a true negative result. False positives were defined as abnormal glands suggested on imaging in a location where none were found at surgery.

Secondarily, localisation was also considered in terms of quadrants, as defined by Hinson et al.(*8*), where the patient's midline served to divide the gland into left and right and a line through the mid-thyroid served to divide superior from inferior. True positives were defined as abnormal glands localised to correct quadrants and true negatives as the non-identification of normal glands in the remaining quadrants.

The sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of the localisation techniques were obtained using MedCalc statistical software (Medcalc.org, version 16.2.1, MedCalc Software, Ostend, Belgium). Comparison of the sensitivities of SPECT-CT+ultrasound and SPECT-CT alone was conducted using McNemar's test; a p-value of ≤0.05 was taken to indicate statistical significance.

The sensitivity and specificity of combined SPECT-CT and ultasound in patients with a normal thyroid gland were compared with those with Hashimoto's thyroiditis, mulitnodular goitre, atrophic thyroid gland and benign nodules using a Fisher's exact test; a p-value of ≤0.05 was taken to indicate statistical significance.

SAS® Studio 3.4 (SAS Institute Inc., Cary, NC, USA) was used to calculate the p-value with a 95% confidence interval.

The institutional review board approved this retrospective study and the requirement to obtain informed consent was waived in accordance with NHS Health Research Authority guidelines.

RESULTS

Demographics

Pathological and radiological data were available for a total of 148 patients that had undergone parathyroidectomy for primary hyperparathyroidism during the specified time period. SPECT-CT combined with ultrasound was carried out in 146 cases and SPECT-CT alone in 2 cases; these 2 cases were therefore excluded from further analysis. Of the remaining 146 patients, 115 were female and 31 male (ratio of 3.7:1). The median age was 62 (range: 23-88 years).

Based on the surgical and pathological data, single adenomata were most common, with multigland disease being uncommon (table 1). No abnormal glands were found in 8 cases (5%).

Imaging Modalities

Overall, SPECT-CT guided ultrasound (SPECT-CT followed by ultrasound carried out by the same radiologist) correctly identified the number and laterality of abnormal glands in 123 cases, yielding an overall sensitivity of 83% (Table 2). Upon analysing the technique’s sensitivity for correctly localising abnormal glands to a particular quadrant, the sensitivity fell slightly (77%) when compared to lateralisation alone; however, specificity remained high at 97% (Table 2). Of note, in 11 cases, the quadrant could not be established from the patients’ postoperative electronic records, so that they could not be correlated with preoperative imaging. Therefore, these cases were excluded, leaving a total of 135 cases to be analysed.

Ultrasound scanning helped localise lesions not identified by SPECT-CT in 13 cases (9%). These were subsequently proven true positives at surgery. Additionally, in 1 case, ultrasound successfully resolved two adjacent adenomata, initially thought to represent a single lesion on SPECT-CT. Therefore, the additional component of ultrasound improved overall sensitivity (sensitivity of 83% for SPECT-CT + ultrasound vs. sensitivity of 75% for SPEC-CT alone; $p < 0.005$ using McNemar's test) (Table 2).

Ultrasound was unable to confirm the presence of a lesion in 18 cases (12%) which were positive on SPECT-CT. Again, these were proven to be true positives at surgery. In these cases, failure of localisation was attributed to the deep or atypical locations of abnormal glands (figure 2), or to patient factors (such as inability to extend the neck). Examples of discrepant cases on SPECT-CT and ultrasound are shown in figure 3.

Single and multigland disease

The data revealed a reduced sensitivity for SPECT-CT guided ultrasound in determining the correct side and gland number in the setting of multigland disease (70%, CI 34.8-93.3%; n=10), when compared to single gland disease (87%, CI 79.6-92.1%; n=128).

Co-existing thyroid disease

The thyroid was reported as unremarkable or atrophic in 86 cases (59%) and abnormal (nodular or ultrasonographic evidence of thyroiditis) in 60 cases (41%). Among the latter, 4 patients (7%) were recommended to undergo fine needle aspiration as a result of their ultrasound examinations. The presence of concurrent thyroid disease did not adversely affect the sensitivity and specificity of SPECT-CT guided ultrasound for lateralising diseased glands (Table 3).

DISCUSSION

This study represents a large series reviewing the sensitivity and specificity of SPECT-CT guided ultrasound in the preoperative localisation of diseased parathyroid glands. The rationale of the technique is to offer patients the convenience of a single hospital attendance; it also offers the radiologist the opportunity to use SPECT-CT to guide their ultrasound examination. This enables the provision of as much anatomical information as possible to the operating surgeon, including the visibility of the adenoma for intraoperative ultrasound. Subsequently, a minimally-invasive procedure can be offered in cases of clear single gland disease, avoiding the risks associated with four gland exploration.

Our results yielded an overall sensitivity of 83% for all abnormal glands and 87% for single adenomata; the specificity was 96%. These results are comparable with the literature (*9-11*); however, are slightly lower than some authors' studies, which quote sensitivities of up to 96% (*6,12,13*). The reason for this is uncertain, but could reflect the limitations of retrospective data acquisition. Indeed, our institution treats a large population of patients with tertiary hyperparathyroidism (which is associated with a lower lesion detection rate compared to primary hyperparathyroidism) and whilst every effort was made to exclude such cases, it is possible that some were included due to errors in the clinical documents used to identify patients. It is also possible that the single phase SPECT-CT acquisition technique used in this study could have contributed to a slightly lower sensitivity (this is discussed subsequently).

Precise definition of gland localisation is important, particularly as misclassification of superior and inferior parathyroid glands may be unhelpful to the surgeon, given the differing relationship to the recurrent laryngeal nerve. In this study, sensitivity was also calculated using the quadrant method suggested by Hinson et al.; its lower value (77%) reflects the difficulties of applying a system of localisation retrospectively and does not reflect the true sensitivity of the technique, as a superior parathyroid adenoma may lie deep to inferior pole of the thyroid, leading to discrepancy between the radiological and surgical interpretation. A classification proposed by Perrier and colleagues seeks to provide more reliable nomenclature. It involves identifying multiple discrete cervical regions (A-G), which correspond with typical parathyroid locations (*14*). It has the potential benefit of improving communication of gland location between radiologists and surgeons, but is yet to be widely used in the UK.

As observed in other studies, there was a higher diagnostic sensitivity for localising single gland disease (87%) in comparison to multigland disease (70%). The reduced sensitivity was thought to be related to reduced gland weight and oxyphil content in hyperplastic glands (*15-17*). However, more recent studies have found no correlation between lesion weight and the reduced sensitivity of Tc-99m MIBI SPECT-CT studies in multigland disease (*18,19*).

This study highlights the utility of multimodality imaging. In our study, the additional use of ultrasound identified 13 cases (9%), which were occult on SPECT-CT, resulting in a significant increase in sensitivity. The cause of non-detection by scintigraphy may relate to poor uptake by the lesion or early washout. A study by Lavely et al. (*20*) found a significant improvement in sensitivity if both early and delayed SPECT-CT acquisitions were obtained, as opposed to the early planar and delayed phase SPECT-CT acquisition technique used in our institution. It is therefore possible that the sensitivity could have been increased further using this method.

The added value of multimodality imaging in adenoma detection is supported in the literature. However, there has been suggestion that a single modality, such as ultrasound, could be used in the first instance, with the second modality only employed as an adjunct in cases where the ultrasound was equivocal or negative (*21,22*). Conversely, our data suggests that SPECT-CT could be used as the initial technique, with ultrasound used in the instance that an adenoma is not identified, as a slightly higher proportion of adenomata were occult on ultrasound as compared to SPECT-CT. However, ultrasound offers several additional benefits to support its routine use with SPECT-CT. In addition to its low cost, lack of ionising radiation and rapidity, its high spatial resolution enables resolution of adjacent adenomata, which may appear to represent a single gland on SPECT-CT. It also enables identification and characterisation of thyroid disease that may mimic an adenoma on scintigraphy or require concurrent management.

In our experience, the ultrasound examination adds greater confidence in localising adenomas that are visualised on SPECT-CT. Anecdotally there are cases where the SPECT-CT findings are equivocal due to possible early washout of sestamibi, and the ultrasound scan allows interrogation of these specific areas. In our study, the radiologist is not blinded to the results of the SPECT-CT when performing the ultrasound, so it was not possible to quanify this.

Finally, ultrasound is also helpful to surgeons performing subsequent intra-operative ultrasound and may add detail in specifying anatomical location. If there are discordant imaging findings between SPECT-CT and ultrasound, then intraoperative parathyroid hormone monitoring is proven to improve localisation of adenomas (*23,24*).

Overall, the presence of pre-existing thyroid disease does not seem to impair the detection of parathyroid adenomas, with no deleterious effect upon the diagnostic sensitivity of SPECT-CT guided ultrasound in the presence of thyroid lesions. This is likely to be attributable to the use of combined modalities, as ultrasound can be of assistance in differentiating intrathyroidal lesions, which have uptake on SPECT and scintigraphy is useful in cases where lesions are obscured on ultrasound by large multinodular goitres. Ultrasound may also be used to evaluate incidental thyroid pathology; in our series, 4 patients were referred for fine needle aspiration as a result of their ultrasound examinations.

Limitations

Owing to the retrospective nature of the study, the authors were reliant upon the quality of documentation and, as highlighted above, there can be discrepancies between the radiological and surgical nomenclature of glands.

It was also not possible to compare the different modalities in isolation (ultrasound alone vs. SPECT-CT) as a single combined protocol was used. The radiologist was not blinded to the results of the SPECT-CT when performing the ultrasound examination. In fact, this was felt to be one of the strengths of the technique as the SPECT-CT could be used to target specific areas with ultrasound in order to improve confidence in reporting findings on SPECT-CT and ultrasound combined. However, this could bias the results of the SPECT-CT.

Additionally, the study focused upon patients undergoing surgery, so did not identify those with positive scans that did not undergo surgery, perhaps due to patient choice or other comorbidities.

CONCLUSION

SPECT-CT guided ultrasound offers a reliable means of localising parathyroid adenomata in primary hyperparathyroidism and the one-stop approach offers patient convenience and aids diagnostic confidence. The modalities in combination demonstrate a significant increase in sensitivity. Furthermore, concurrent thyroid disease does not impair localisation of parathyroid adenomas. However, pre-operative localisation is more accurate with single adenomas, compared to multigland disease, which correlates with the published literature.

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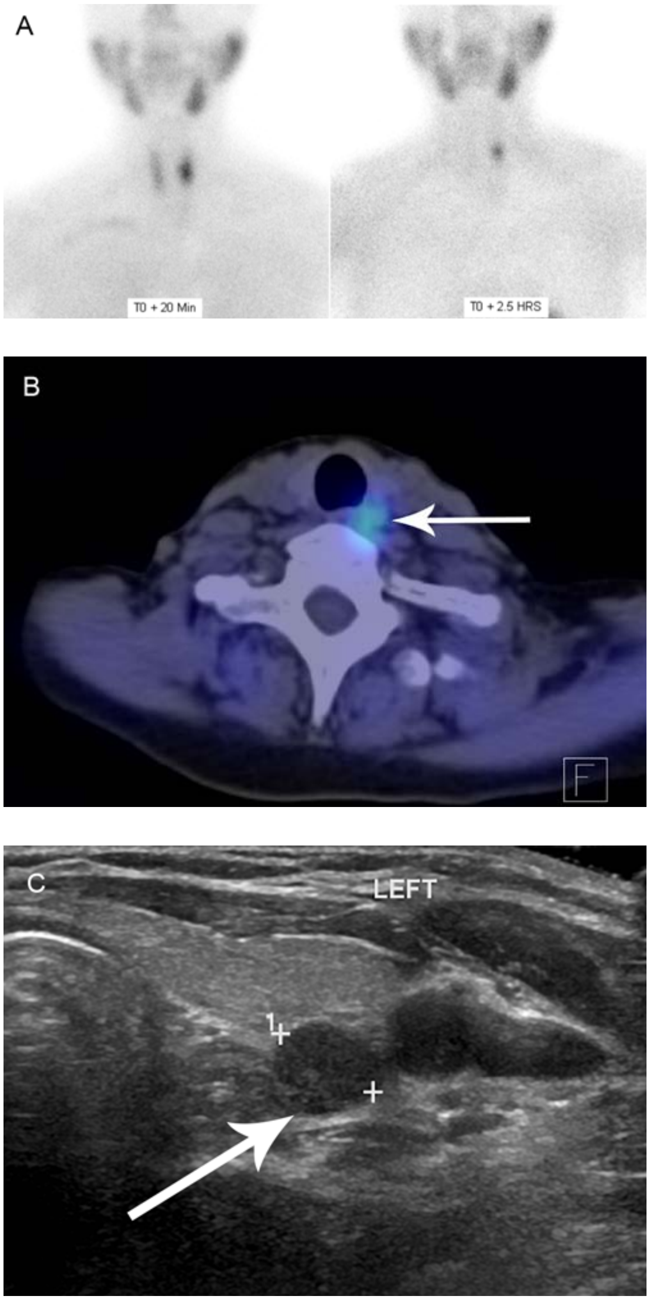

Figure 1. Example of the multimodality approach to parathyroid localisation.

A left superior parathyroid adenoma is diagnosed using both Tc99m sestamibi SPECT-CT and ultrasound. A) Planar radionuclide imaging performed after Tc99m sestamibi injection at 20 minutes and 2.5 hours after injection. The planar image demonstrates tracer retention after 2.5 hours. B) The fused SPECT-CT image confirms localisation of an adenoma (arrow) posterior to the left lobe of the thyroid. C) Shows the tracer uptake corresponds to a single hypoechoic nodule (arrow) posterior to the left thyroid lobe in the midgland region. Parathyroid adenomas have a characteristic feeding artery that can often be seen on doppler examination (not shown on this image).

	Anatomical location	% cases
1	Retrotracheal	22.2%
2	Deep tracheo-oesophageal groove	27.7%
3	Retrosternal	27.7%
4	Posterior to common carotid artery	5.5%
5	Retro-oesophageal	5.5%
6	Obscured by MNG	5.5%

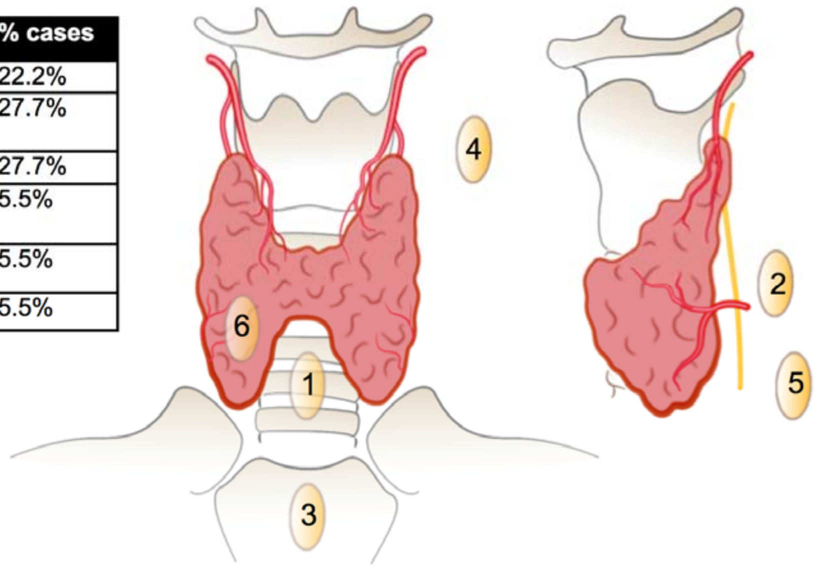

Figure 2. Adenomas not identified on ultrasound categorised by anatomical location.

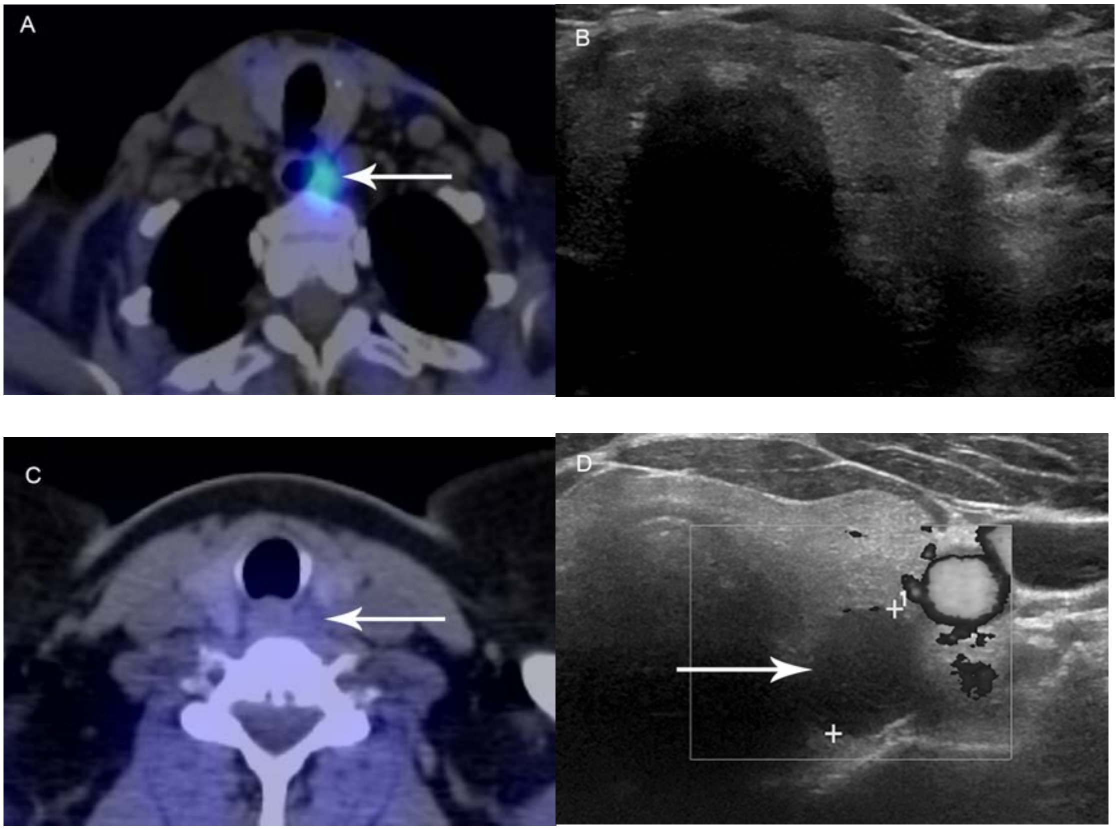

Figure 3. Examples of discrepancies between modalities. Series of images demonstrating discrepancies between the modalities. A) Avid tracer uptake is seen on fused SPECT-CT images within a left superior parathyroid adenoma (arrow), which is located deep in the tracheo-oesophageal groove. This is not visible on the corresponding ultrasound (B) due to acoustic shadowing from the trachea, but was subsequently located at surgery. C) Fused SPECT-CT image reveals no tracer retention in a nodule posterior to the left lobe of the thyroid (arrow). D) There are characteristic appearances of this nodule (arrow) on ultrasound for a parathyroid adenoma, which has exhibited early washout with sestamibi. This was subsequently confirmed at surgery.

TABLES

TABLE 1. Number of diseased glands by frequency

Number of Diseased glands	Frequency
Single	128 (88%)
Multigland ≥2	10 (7%)
Negative exploration	8 (5%)
Total	**146**

TABLE 2. Sensitivity, specificity, NPV and PPV according to analysis and modality

Analysis	Modality	Sensitivity	Specificity	NPV	PPV
Laterality & gland number (n = 146)	**SPECT-CT + ultrasound**	83% (CI 75.5-88.3%)	96% (CI 91.1-98.4%)	84% (CI 77.5-89.3%)	95% (CI 90.2-98.3%)
	SPECT-CT*	75% (CI 66.8-81.5%)	96% (CI 91.3-98.5%)	79% (CI 72.4-84.8%)	95% (CI 89.0-98.1%)
Quadrant & gland number (n = 135)	**SPECT-CT + ultrasound**	77% (CI 68.9-83.4%)	97% (CI 94.5-98.3%)	92% (CI 89.1-94.5%)	89% (CI 82.5-94.2%)
	SPECT-CT*	70% (CI 61.5-77.1%)	97% (CI 94.8-98.4%)	90% (CI 86.7-92.7%)	89% (CI 81.9-94.3%)

**Results for SPECT-CT alone analysed by disregarding ultrasound component of the examination. CI = 95% confidence interval*

TABLE 3. The effect of thyroid disease on localisation of parathyroid adenomas with combined SPECT-CT and ultrasound

	Sensitivity	**Specificity**	**NPV**	**PPV**
Normal (n=86)	82%	97%	85%	96%
Atrophic (n=5)	100% (p=0.383)	100% (p=0.847)	100%	100%
Benign nodules (no glandular enlargement) (n=20)	76% (p=0.194)	100% (p=0.556)	79%	100%
Hashimoto's thyroiditis (n=4)	100% (p= 0.462)	100% (p=0.875)	100%	100%
Multinodular goitre (n=60)	94% (p=0.069)	96% (p=0.429)	93%	97%