Combined ultrasound and Sestamibi scintigraphy provides accurate preoperative localisation for patients with primary hyperparathyroidism

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ABSTRACT

INTRODUCTION Minimally invasive parathyroidectomy has advantages over the traditional bilateral neck exploration for the surgical treatment of primary hyperparathyroidism. It requires accurate localisation of the parathyroid pathology prior to surgery. The best method of preoperative localisation in a district general hospital setting is not well understood.

METHODS All patients who underwent parathyroidectomy for primary hyperparathyroidism from 2008 to 2016 were identified from a prospectively maintained database. Operative findings were correlated with radiological and histological results. Sensitivity and specificity of ultrasound, sestamibi scintigraphy and the two together were calculated for diagnostic precision and compared.

RESULTS One hundred and eighty-four patients met the inclusion criteria, of whom 81.5% had a histological diagnosis of a parathyroid adenoma. Ultrasound had higher sensitivity than sestamibi scintigraphy. Used together, ultrasound and sestamibi scintigraphy performed better than either ultrasound or sestamibi scintigraphy alone ($P < 0.001$). Twenty-two of 184 cases had no lesion located by either ultrasound or sestamibi scintigraphy preoperatively. Where neither ultrasound nor sestamibi scintigraphy located the lesion, additional computed tomography led to the excision of parathyroid pathology in one in ten patients.

CONCLUSION The combination of ultrasound and sestamibi scintigraphy provides the highest sensitivity of preoperative localisation. This approach led to a high success rate of minimally invasive parathyroidectomy. Where preoperative localisation is not achieved with ultrasound or sestamibi scintigraphy, computed tomography adds little additional benefit. In this setting other modalities of localisation such as selective venous sampling, intraoperative methylene blue or intraoperative parathyroid hormone levels could be considered.

KEYWORDS

Radionuclide Imaging – Parathyroidectomy – Ultrasonography – Parathyroid neoplasms – Hyperparathyroidism – primary

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Introduction

There has been a worldwide increase in the prevalence of primary hyperparathyroidism, a disease diagnosed in patients with hypercalcaemia and elevated or inappropriately normal plasma parathyroid hormone level.^{1–3} In the developed world, primary hyperparathyroidism is diagnosed increasingly in asymptomatic patients, through routine biochemical screening.⁴ Common sequelae of hypercalcaemia secondary to primary hyperparathyroidism, such as impaired renal function, nephrolithiasis and osteopenia are potentially avoidable if treated early.^{5–7}

Parathyroidectomy is the only known cure for primary hyperparathyroidism.^{8–10} Since Felix Mandl performed the first successful parathyroidectomy in 1925, the traditional approach to parathyroid surgery has been bilateral neck exploration.¹¹ More recently minimally invasive parathyroidectomy has been shown to have similar cure rates to bilateral neck exploration.^{12–14} The technique is designed to minimise tissue dissection, hasten recovery time, decrease postoperative pain and reduce scarring. As a result, it is associated with lower costs, fewer complications and better cosmetic results.^{15,16} Minimally invasive parathyroidectomy is established as a safe and effective

technique, but it requires accurate localisation of the parathyroid adenoma(s) prior to surgery.^{8,10} The best method of preoperative localisation in the setting of a district general hospital is not well understood.

Preoperative localisation is made more complex by the variable location of parathyroid glands: the two inferior glands are less anatomically consistent than the superior glands owing to their longer embryological migration.^{17,18} Solitary parathyroid adenomas are the cause in approximately 80% of cases; other causes include multiglandular hyperplasia, synchronous adenomas or, rarely, carcinoma (1%).⁵ A popular combination of imaging modalities for locating parathyroid glands preoperatively is sestamibi scintigraphy and ultrasound, with a limited role for computed tomography (CT).^{8,19}

Sestamibi scintigraphy uses a radioisotope which accumulates in mitochondria and collects in cells with a high metabolic rate, such as parathyroid adenoma.^{18,20,21} It is widely available, relatively inexpensive and requires less ionising radiation than CT. Accuracy depends on the size and cytology of the adenoma, the preoperative serum calcium and parathyroid hormone levels, and can be confounded by thyroid nodules and multinodular goitres. Rates of accuracy range from 80% to 95%.^{22,23} High diagnostic accuracy can be obtained from ultrasound imaging by experienced sonographers.^{8,18,21} Rates of ultrasound accuracy range from 70% to 85%, although reviews suggest that ultrasound has a higher positive predictive value than sestamibi scintigraphy and may be used alone.^{22,24} The aim of this study was to determine the most accurate preoperative localisation technique in primary hyperparathyroidism in a district general hospital setting.

Materials and methods

Patient records were analysed at a district general hospital in England. All patients who underwent parathyroidectomy for primary hyperparathyroidism from 2008 to 2016 were identified from a prospectively maintained database. Radiological and histological data were obtained from the hospital's electronic databases. Surgical site was ascertained from review of the operation note. Results of the preoperative imaging modalities were correlated with operative findings. The ultrasound scans were performed by a group of specialist head and neck radiologists, with extensive experience of parathyroid imaging.

Patients with preoperative radiology results from both ultrasound and sestamibi scintigraphy modality were included. If a patient required re-exploration, only data from the initial surgery were included. Patients with missing or indeterminate histology, missing surgical site details or missing radiology data were excluded.

Where histological analysis concluded the presence of pathological parathyroid tissue, operative site was considered the gold standard for comparison to imaging location. 'Successful excision' was defined as: macroscopic identification of an abnormal parathyroid gland at time of surgery

with histological confirmation of the lesion. 'Pathological parathyroid tissue' was defined as parathyroid adenoma, hyperplasia, oxyphil or carcinoma. Sensitivity and specificity of single (ultrasound or sestamibi scintigraphy) and two-image (ultrasound and sestamibi scintigraphy) modalities were calculated for diagnostic precision and compared. To assess the concordance between imaging modalities the anatomical location identified for each test was categorised into one of: left, left upper, left lower, right, right upper, right lower, ectopic or not localised.

Surgical technique

All surgery was performed by a single surgeon. The operative technique included a 3-cm midline collar incision and focused exploration of the side indicated by the preoperative imaging. In the case of no preoperative localisation, each parathyroid region was examined sequentially starting with the most likely position. Intraoperative frozen section was used on a case by case basis in the case of diagnostic uncertainty.

Statistical technique

Categorical data were expressed as number and a percentage. The sensitivity and specificity of the imaging tests, performed on each patient (paired data), were compared using McNemar's test and exact McNemar's test when the data were limited. Cohen's κ was used to assess agreement between the two imaging modalities. Statistical significance was accepted for P -values less than 0.05. Data handling was conducted using Microsoft Excel 2015. Statistical calculations were performed with IBM SPSS Statistics version 25.0.

Results

A total of 212 patients underwent parathyroidectomy between 2008 and 2016, and 184 patients met inclusion criteria (Fig 1). The mean age was 66 years and 82% were female; 81.5% had a final histological diagnosis of parathyroid adenoma (Table 1).

Ultrasound had a higher sensitivity than sestamibi scintigraphy, but the difference was not statistically significant ($P = 0.25$; Table 2). Their specificity was the same (Table 3). The sensitivity and specificity of the ultrasound and sestamibi scintigraphy together was compared only with ultrasound alone, which performed slightly better than sestamibi scintigraphy. The sensitivity of the combined ultrasound and sestamibi scintigraphy was statistically different from the sensitivity of ultrasound ($P < 0.001$; Table 4). There was no statistical difference in terms of their specificity ($P = 0.25$; Table 5). The sensitivity, specificity and accuracy of each test is shown in Table 6.

Where both preoperative imaging results were positively concordant, the likelihood of successful surgical excision was 97% (69/71). In cases with a lack of concordance between tests, the likelihood of successful excision was 89% (82/92). In the case of an image negative case, the

Table 1 Demographic and characteristics of study patients.

	Patients
<i>Patient characteristic</i>	
Female gender, <i>n</i> (%)	150 (81.5)
Age, years (IQR)	66.0 (56.8–74.4)
<i>Biochemical profile</i>	
Preoperative adjusted serum calcium, mmol/l	
median (IQR)	2.74 (2.65, 2.85)
mean (IQR)	2.38 (2.29, 2.45)
Preoperative serum PTH, ng/l, median (IQR)	119.5 (88.5, 174.7)
<i>Histological diagnosis</i>	
Parathyroid:	
Adenoma, <i>n</i> (%)	150 (81.5)
Oxyphil adenoma, <i>n</i> (%)	6 (3.2)
Carcinoma, <i>n</i> (%)	4 (2.2)
Hyperplasia, <i>n</i> (%)	3 (1.6)
Normal, <i>n</i> (%)	2 (1.1)
No pathological tissue found, <i>n</i> (%)	19 (10.3)

IQR, interquartile range; PTH, parathyroid hormone.

chance of successful removal was 57% (12/21). Cohen's κ was calculated to determine the level of agreement between ultrasound and sestamibi scintigraphy. There was weak agreement between the two imaging modalities ($\kappa = 0.323$).

Of the 184 cases, 21 were image negative. Ten of these cases underwent traditional neck CT, with one case showing an abnormal parathyroid gland (Fig 2).

Table 2 Comparison between ultrasound and sestamibi scintigraphy among the 163 cases with parathyroid pathology.

Sestamibi scintigraphy	Ultrasound	
	True positive	False negative
True positive	87	18
False negative	27	31

Table 3 Comparison between ultrasound and sestamibi scintigraphy among the 21 cases without parathyroid pathology.

Sestamibi scintigraphy	Ultrasound	
	True positive	False negative
True positive	9	3
False negative	3	6

Discussion

This study demonstrates that over eight years in a district general hospital in England, the technique of combining ultrasound scanning and sestamibi scintigraphy for preoperative localisation led to successful parathyroidectomy in 88.6% of patients. Ultrasound is more sensitive than sestamibi scintigraphy (sensitivity 0.70 vs 0.64). Combined ultrasound and sestamibi scintigraphy was superior to ultrasound and sestamibi scintigraphy on their own. Successful excision of a parathyroid lesion is more likely with accurate preoperative localisation (97% vs 57%).

Table 4 Comparison between ultrasound and ultrasound and sestamibi scintigraphy among the 163 cases with parathyroid pathology.

Ultrasound and sestamibi scintigraphy	Ultrasound	
	True positive	False negative
True positive	114	18
False negative	0	31

Table 5 Comparison between ultrasound and ultrasound and sestamibi scintigraphy among the 21 cases without parathyroid pathology.

Ultrasound and sestamibi scintigraphy	Ultrasound	
	True positive	False negative
True positive	12	3
False negative	0	6

Minimally invasive parathyroidectomy should be offered to all suitable patients and relies on successful localisation

of the parathyroid lesion(s) preoperatively.^{25–28} Ultrasound and sestamibi scintigraphy are two popular imaging modalities for preoperative localisation, with most studies quoting little difference in the accuracy of these modalities.²⁵ It is well recognised that ultrasound and sestamibi scintigraphy perform differently depending on gland characteristics. Ultrasound can give more accurate anatomical information and gland detail if the adenoma is located in a eutopic (normal) position. Conversely, sestamibi scintigraphy reveals superior physiological information and can locate ectopic or deeper glands. Combining the different attributes results in increased accuracy of preoperative localisation and, accordingly, current guidelines recommend dual ultrasound and sestamibi scintigraphy scans.^{25,29} In addition to being the most accurate and informative imaging option, combined localisation with sestamibi scintigraphy and ultrasound has been shown to be the most cost-effective strategy.¹⁰ In our study, ultrasound scans were performed by a group of specialist head and neck radiologists with extensive experience of parathyroid imaging. Sensitivity and specificity of ultrasound in this study are comparable to other literature sources; demonstrating that ultrasound is still accurate in the context of a district general hospital.^{19,30}

There were ten patients in this study who were image negative after ultrasound and sestamibi scintigraphy and

Table 6 Sensitivity, specificity and accuracy of single and combined imaging modalities.

Modality	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy
Ultrasound	0.70 (0.62–0.77)	0.57 (0.34–0.78)	0.68 (0.61–0.75)
Sestamibi scintigraphy	0.64 (0.57–0.72)	0.57 (0.34–0.78)	0.64 (0.56–0.71)
Ultrasound and sestamibi scintigraphy	0.81 (0.74–0.87)	0.71 (0.47–0.89)	0.80 (0.73–0.85)

CI, confidence interval

went on to have a CT. Only one of these patients had a pathological parathyroid gland identified on CT. Traditional CT has been shown to be relatively poor at localising parathyroid adenomas, with an accuracy of 40–70%.^{18,21} Our study reinforces that in this small but important subgroup of patients, CT only offers further minimal information. There are other preoperative localising modalities available. Four-dimensional CT (4D-CT) uses repeated

imaging over time. Some evidence suggests that 4D-CT is more accurate and sensitive than ultrasound or sestamibi scintigraphy and may be beneficial in revision parathyroid surgery.^{51,52} However, 4D-CT has a considerably heavier dose of ionising radiation compared with traditional CT. Other diagnostic techniques include intraoperative parathyroid hormone venous sampling,⁵³ contrast-enhanced ultrasonography⁵⁴ and intraoperative methylene blue.⁵⁵

Figure 3 Recommended patient management following biochemical diagnosis of primary hyperparathyroidism.

The use of intraoperative ultrasonography performed by the surgeon has the potential to visualise location directly and to provide excellent spatial feedback.⁸

The limitations of this study include those common to all retrospective, observational studies. The study excluded patients undergoing revision surgery and therefore is unable to comment on the best imaging strategy in this context. Our definition of 'surgical cure' is a pathological histological diagnosis which, when excised, resulted in normalisation of serum calcium level.

Conclusion

This study demonstrates that dual imaging with ultrasound and sestamibi scintigraphy is a very effective preoperative localisation strategy in the majority of patients and is associated with a high minimally invasive parathyroidectomy success rate in a district general hospital setting. There remains a small cohort of patients in whom additional techniques may be required for further preoperative localisation. Fig 3 outlines our current recommendation for patient management from time of biochemical diagnosis of primary hyperparathyroidism.

References

1. Yu N, Donnan PT, Murphy MJ, Leese GP. Epidemiology of primary hyperparathyroidism in Tayside, Scotland, UK. *Clin Endocrinol (Oxf)* 2009; **71**(4): 485–493.
2. Abood A, Vestergaard P. Increasing incidence of primary hyperparathyroidism in Denmark. *Dan Med J* 2013; **60**(2): A4567.
3. Fraser WD. Hyperparathyroidism. *Lancet* 2009; **374**(9684): 145–158.
4. Silverberg SJ, Clarke BL, Peacock M *et al*. Current issues in the presentation of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. *J Clin Endocrinol Metab* 2014; **99**(10): 3,580–3,594.
5. Stenström G, Heedman PA. Clinical findings in patients with hypercalcaemia: a final investigation based on biochemical screening. *Acta Med Scand* 1974; **195**(6): 473–477.
6. Mundy GR, Cove DH, Fiske R. Primary hyperparathyroidism: changes in the pattern of clinical presentation. *Lancet* 1980; **1**(8182): 1,317–1,320.
7. Udén P, Chan A, Duh QY *et al*. Primary hyperparathyroidism in younger and older patients: symptoms and outcome of surgery. *World J Surg* 1992; **16**(4): 791–798.
8. Udelsman R, Åkerström G, Biagini C *et al*. The surgical management of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. *J Clin Endocrinol Metab* 2014; **99**(10): 3,595–3,606.
9. Bilezikian JP, Brandi ML, Eastell R *et al*. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. *J Clin Endocrinol Metab* 2014; **99**(10): 3,561–3,569.
10. Wilhelm SM, Wang TS, Ruan DT *et al*. The American Association of Endocrine Surgeons guidelines for definitive management of primary hyperparathyroidism. *JAMA Surg* 2016; **151**(10): 959–968.
11. Johnson NA, Tublin ME, Ogilvie JB. Parathyroid imaging: technique and role in the preoperative evaluation of primary hyperparathyroidism. *AJR Am J Roentgenol* 2007; **188**(6): 1,706–1,715.
12. Bergenfelz A, Lindblom P, Tibblin S, Westerdaal J. Unilateral versus bilateral neck exploration for primary hyperparathyroidism: a prospective randomized controlled trial. *Ann Surg* 2002; **236**(5): 543–551.
13. Grant CS, Thompson G, Farley D, van Heerden J. Primary hyperparathyroidism surgical management since the introduction of minimally invasive parathyroidectomy: Mayo Clinic experience. *Arch Surg* 2005; **140**(5): 472–479.
14. Russell CF, Dolan SJ, Laird JD. Randomized clinical trial comparing scan-directed unilateral versus bilateral cervical exploration for primary hyperparathyroidism due to solitary adenoma. *Br J Surg* 2006; **93**(4): 418–421.
15. Meyer A, Brabant G, Behrend M. Surgical treatment of primary hyperparathyroidism. *Eur J Med Res* 2005; **10**(7): 287–291.
16. Kunstman JW, Udelsman R. Superiority of minimally invasive parathyroidectomy. *Adv Surg* 2012; **46**: 171–189.
17. Wang C. The anatomic basis of parathyroid surgery. *Ann Surg* 1976; **183**(3): 271–275.
18. Kunstman JW, Kirsch JD, Mahajan A, Udelsman R. Clinical review: parathyroid localization and implications for clinical management. *J Clin Endocrinol Metab* 2013; **98**(3): 902–912.
19. Khan AA, Hanley DA, Rizzoli R *et al*. Primary hyperparathyroidism: review and recommendations on evaluation, diagnosis, and management: a Canadian and international consensus. *Osteoporos Int* 2017; **28**(1): 1–19.
20. Mihai R, Gleeson F, Buley ID *et al*. Negative imaging studies for primary hyperparathyroidism are unavoidable: correlation of sestamibi and high-resolution ultrasound scanning with histological analysis in 150 patients. *World J Surg* 2006; **30**(5): 697–704.
21. Mihai R, Simon D, Hellman P. Imaging for primary hyperparathyroidism: an evidence-based analysis. *Langenbecks Arch Surg* 2009; **394**(5): 765–784.
22. Ruda JM, Hollenbeak CS, Stack BC. A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. *Otolaryngol Head Neck Surg* 2005; **132**(3): 359–372.
23. Kobylecka M, Płazińska MT, Chudziński W *et al*. Comparison of scintigraphy and ultrasound imaging in patients with primary, secondary and tertiary hyperparathyroidism: own experience. *J Ultrason* 2017; **17**(68): 17–22.
24. Coelho MC, de Oliveira E Silva de Moraes NA, Beuren AC *et al*. Role of imaging tests for preoperative location of pathologic parathyroid tissue in patients with primary hyperparathyroidism. *Endocr Pract* 2016; **22**(9): 1,062–1,067.
25. Inabnet WB, Fulla Y, Richard B *et al*. Unilateral neck exploration under local anesthesia: the approach of choice for asymptomatic primary hyperparathyroidism. *Surgery* 1999; **126**(6): 1,004–1,010.
26. Westerdaal J, Bergenfelz A. Unilateral versus bilateral neck exploration for primary hyperparathyroidism: five-year follow-up of a randomized controlled trial. *Ann Surg* 2007; **246**(6): 976–981.
27. Udelsman R, Lin Z, Donovan P. The superiority of minimally invasive parathyroidectomy based on 1650 consecutive patients with primary hyperparathyroidism. *Ann Surg* 2011; **253**(3): 585–591.
28. Sackett W BB, Reeve T, Delbridge L. Worldwide trends in the surgical treatment of primary hyperparathyroidism in the era of minimally invasive parathyroidectomy. *Arch Surg* 2002; **137**: 1,055–1,059.
29. Treglia G, Trimboli P, Huellner M, Giovanella L. Imaging in primary hyperparathyroidism: focus on the evidence-based diagnostic performance of different methods. *Minerva Endocrinol* 2018; **43**(2): 133–143.
30. Ebner Y, Garti-Gross Y, Margulis A *et al*. Parathyroid surgery: correlation between pre-operative localization studies and surgical outcomes. *Clin Endocrinol (Oxf)* 2015; **83**(5): 733–738.
31. Chazen J, Gupta A, Dunning A, Phillips C. Diagnostic accuracy of 4D-CT for parathyroid adenomas and hyperplasia. *Am J Neuroradiol* 2012; **33**(3): 429–433.
32. Mortenson MM, Evans DB, Lee JE *et al*. Parathyroid exploration in the reoperative neck: improved preoperative localization with 4D-computed tomography. *J Am Coll Surg* 2008; **206**(5): 888–895.
33. Ito F, Sippel R, Lederman J, Chen H. The utility of intraoperative bilateral internal jugular venous sampling with rapid parathyroid hormone testing. *Ann Surg* 2007; **245**(6): 959–963.
34. Cantisani V, Wilson SR. CEUS: Where are we in 2015? *Eur J Radiol* 2015; **84**(9): 1,621–1,622.
35. Patel H, Chadwick D, Harrison B, Balasubramanian S. Systematic review of intravenous methylene blue in parathyroid surgery. *Br J Surg* 2012; **99**(10): 1,345–1,351.