10.5005/jp-journals-10002-1106
ORIGINAL ARTICLE

Dual Localization with Ultrasound and Iodine 123 and Technetium (^{99m}Tc) Sestamibi Scintigraphy is Superior to Single Imaging Modalities in Facilitating Minimally Invasive Parathyroidectomy for Primary Hyperparathyroidism

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ABSTRACT

Primary hyperparathyroidism is caused by a single parathyroid adenoma in the majority of patients. Localization of parathyroid adenomas prior to surgery has the benefit of allowing a minimally invasive approach. Over the years, multiple imaging modalities have been employed in an attempt to identify the site preoperatively, with varying degrees of success. In this study, we explore the accuracy of a combination of ultrasound and nuclear medicine planar scintigraphy with iodine-123 and technetium (99mTc) sestamibi. A retrospective study of consecutive series of 117 patients undergoing minimally invasive parathyroidectomy was carried out. Inclusion criteria incorporated clinical and biochemical evidence of primary hyperparathyroidism. All patients had at least one form of imaging: Ultrasound or nuclear medicine scintigraphy or both. The accuracy was compared with surgical findings. Gland weight was also related to imaging accuracy. A total of 101 patients underwent surgery for primary hyperparathyroidism. There was no significant difference between ultrasound and scintigraphy ability to localize a parathyroid adenoma (p = 0.738). The combination of ultrasound and scintigraphy was superior at preoperative localization compared to ultrasound (p = 0.039) or scintigraphy alone (p = 0.0078). Gland weight had no significant bearing on the accuracy of the scan (ultrasound, p = 0.89; scintigraphy, p = 0.16). Dual localization with ultrasound and scintigraphy in primary hyperparathyroidism is superior to a single imaging technique. Dual localization facilitates minimally invasive parathyroidectomy.

Keywords: Hyperparathyroidism, Localization, Parathyroidectomy, Sestamibi, Ultrasound.

How to cite this article: Lyon A, Komolafe OO, Wilson CR, Doughty JC. Dual Localization with Ultrasound and Iodine 123 and Technetium (^{99m}Tc) Sestamibi Scintigraphy is Superior to Single Imaging Modalities in Facilitating Minimally Invasive Parathyroidectomy for Primary Hyperparathyroidism. World J Endoc Surg 2012;4(3):93-98.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Primary hyperparathyroidism (PHPT) is caused by an isolated adenoma in one of the four parathyroid glands in most cases (80-90%), however, it has been reported that one in 20 of these patients will have a second gland affected.[1] Parathyroidectomy is the only curative option for both asymptomatic and symptomatic patients. Even asymptomatic patients have been shown to benefit from surgery, with improved cardiovascular function and diabetic control.[2,3]

The traditional approach to parathyroid surgery has been bilateral neck exploration of all four glands via a collar incision under general anesthetic. Minimally invasive parathyroidectomy (MIP) has now become an accepted and even preferable alternative. The predominance of single gland disease has facilitated this change in practice. Cure rates have been shown to be at least as good in MIP compared with bilateral neck exploration[4,5] with a lower complication rate.[5-7]

MIP is dependent on accurate preoperative gland localization, with various imaging modalities currently employed. The two most prevalent modalities are nuclear medicine sestamibi-technetium 99m scintigram scanning and ultrasonic scanning. Sestamibi scanning has been shown in various studies to be 72 to 88% sensitive for the detection of parathyroid adenomas.[8-12] Ultrasound has a sensitivity for detection of parathyroid adenomas of up to 89% in experienced hands.[13-15] The aim of this paper is to see if a combination of both methods improves preoperative localization, compared to each in isolation.

MATERIALS AND METHODS

Patients

A series of 117 patients underwent minimally invasive parathyroidectomy between January 2003 and September 2009. All patients, with documented elevation of serum calcium and PTH, underwent preoperative localization with nuclear medicine planar scanning, neck ultrasound or both. Eight patients were excluded as they had been diagnosed with secondary hyperparathyroidism and, therefore, required excision of all four glands; four patients were excluded as they had tertiary hyperparathyroidism. Two patients were excluded due to a lack of complete intraoperative and follow-up data. Two patients were excluded as they had undergone previous parathyroid surgery. A total of 101 patients were analyzed (Fig. 1).

Imaging

Ultrasound scanning was carried out by a single experienced head and neck radiologist. Scans reporting a lesion at the mid thyroid level were analyzed as being superior parathyroid glands, as this is more likely.[16] Standard protocol for nuclear medicine scanning was followed to demonstrate areas of Tc99m sestamibi uptake outwith the thyroid in the neck and upper chest (Fig. 2).

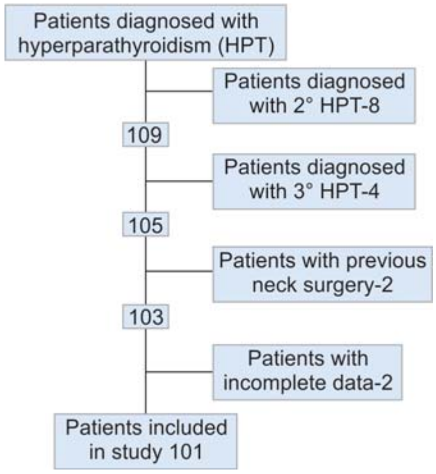

Fig. 1: Patient selection

Surgery

All imaging was reviewed by the surgeon prior to operation in order to plan the procedure. All procedures were performed by two consultant surgeons, or under their direct supervision, by senior surgical trainees. MIP comprised of a 2.5 cm incision in a skin crease halfway between the cricoid cartilage and sternal notch. The pole highlighted by the preoperative study was then explored. Intraoperative parathyroid hormone levels were monitored in order to confirm removal of adenoma and ensure no further adenomas remained *in situ*. A drop greater than 50% of the initial sample 10 minutes after excision was considered to signify successful treatment.

The particular incision allows for access to any of the four poles as well as the retrosternum in the event of inaccurate imaging, rather than resorting to multiple

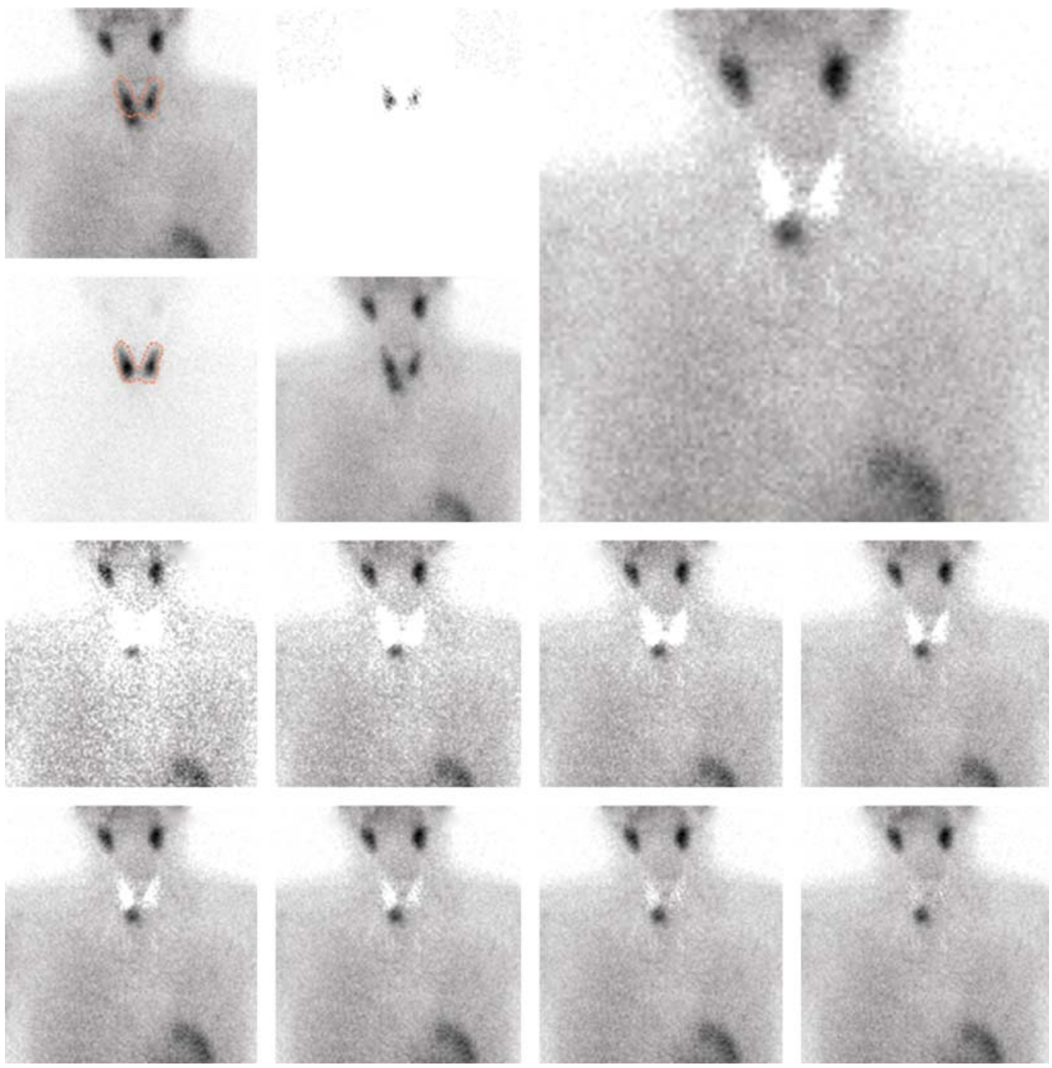

Fig. 2: Nuclear medicine planar imaging with I-123 and Tc99m sestamibi with evidence of right inferior parathyroid adenoma

incisions, and also results in good cosmesis. If the gland identified by imaging was normal–no fall in PTH, the other gland on the same side was excised. If there is no fall in PTH, the contralateral side, and retrosternum are explored through the same incision, until the postexcision parathyroid hormone levels returned to <50% of the pre-excision level, prior to closing the neck. All surgical specimen were analyzed by a histopathologist with a special interest in thyroid and parathyroid disease.

Data Analysis

Data analysis was performed with IBM SPSS Version 20. The data was examined for sensitivity, positive predictive value (PPV) and relationship of gland weight to scan accuracy. Multigland disease was also examined to clarify if this had an impact on scan accuracy. Data was analyzed for statistical significance using the Wilcoxon signed rank test. The null hypothesis assumed that there was no statistical difference between nuclear medicine study and ultrasound in their ability to localize parathyroid adenoma. Probability (p) value of <0.05 was considered statistically significant.

RESULTS

A total of 101 patients underwent surgery for primary hyperparathyroidism, 65 patients were female, 36 male, with a mean age of 56 years (range, 26-84 years). Median adjusted calcium levels were 2.87 mmol/L (IQR, 2.75-2.99 mmol/l) preoperatively and 2.37 mmol/L (IQR, 2.28-2.5 mmol/l) postoperatively. There was a statistically significant difference between the groups ($p < 0.001$). Median PTH levels were 14.1 ng/l (IQR, 10.4-20.4 ng/l) preoperatively and 5.1 ng/l (IQR, 3.35-7.0 ng/l) postoperatively ($p < 0.001$).

Preoperative Localization

Preoperative ultrasound was performed in 75 patients and nuclear medicine scintigraphy was performed in 94 patients. Sixty-seven patients had both scans performed (Table 1). Ultrasound identified the correct pole of an abnormal gland in 39 patients (56%) and the correct side in 49 (65%).[11] Fifteen percent misleading ultrasound scan results occurred–four of these were localized to the wrong side; seven of the 11 patients had thyroid pathology identified on scan (two thyroid nodules and five multinodular goiters), scintigraphy correctly identified the pathological parathyroid gland in seven of these 11 patients. The remaining 15 patients (20%) had a negative scan result.

Nuclear medicine planar scanning identified the correct pole of an abnormal gland in 49 patients (53%), and the correct side in 66 (70%). Twenty-two patients (24%) had a negative scan result. Six patients (6%) had the contralateral side incorrectly identified–three of these patients had thyroid disease.

Where both scans were performed, 25 were misleading, this is due to scans being discordant. When scan results match, only in one case did they identify the incorrect side.

Gland Histology

Eighty-six patients had excision of a histologically confirmed adenoma. Seven patients diagnosed with primary hyperparathyroidism were found on histology to have gland appearances in keeping more with hyperplasia, rather than adenoma. Furthermore, five patients had normal glands removed. These patients are shown in Table 2. Three patients had carcinoma of the parathyroid on histology—we have previously reported these cases.[4] One patient had a concomitant thyroid cancer identified and excised intraoperatively.

Multiglandular Disease

None of the 19 patients who had more than one gland excised were found to have multiglandular disease on histology. Seven patients had two or more areas localized preoperatively with either ultrasound or nuclear medicine scan. Ultrasound highlighted two or more possible adenoma locations preoperatively in four of these seven patients (two patients had two or more glands removed). Nuclear medicine scanning highlighted two or more areas in the other three of the seven patients (one of these patients had more than one gland removed). There were no patients having both scans which concorded in showing multigland disease.

Inconclusive Scan Results

Of the 15 patients who had no abnormality identified on ultrasound, 11 had a straightforward procedure with one

Table 1: Accuracy of imaging in all patients with a preoperative diagnosis of primary hyperparathyroidism

	Ultrasound (%)	*Sestamibi (%)*	*Both (%)*
Total	75 (100)	94 (100)	67 (100)
Accurate pole	39 (53)	49 (52)	21 (31)
Accurate side	49 (65)	66 (70)	31 (46)
Misleading*	11 (15)	22 (24)	29 (43)
Negative	15 (20)	6 (6)	7 (11)

*Where scans not predictive of pole, or side, or discordant gland removed (six of which were aided by a correctly localizing nuclear medicine scan). Three patients required two or more glands removed, histology suggested hyperplasia in two patients and normal gland tissue in one patient (Table 2). One patient had an adenoma removed from an unusual retrosternal location. There were 22 negative nuclear medicine scans. Eighteen of these patients had an ultrasound scan, 11 of these scans correctly demonstrated the affected side, facilitating surgery. However, five of these patients did require more than one gland removed (histology suggested carcinoma in one patient and normal glandular tissue in another). Seven patients had negative ultrasound and nuclear medicine scans, four of these had a single gland removed. The fifth patient had hyperplasia on histology, the sixth had normal glandular tissue removed and the seventh patient had two glands removed, one of which was an adenoma.

Localization of Adenomas

The accuracy of imaging for all patients with primary hyperparathyroidism is shown in Table 1, and for those with histologically confirmed parathyroid adenomas in Table 3. Table 3 demonstrates, like Table 1, that there were a large number of discordant scan when both modalities were preformed. However, when scans concur this leads to the high sensitivity and PPV demonstrated in Tables 4 and 5. The nuclear medicine scan revealed a high PPV as there were few false positives, it had a lower sensitivity due to the number of negative scans. Table 5 demonstrates that where the scans correlated to the correct side, there were no inaccuracies. There was no significant difference between ultrasound and nuclear medicine scan ability to localize a parathyroid adenoma ($p = 0.738$). The combination of both modalities was superior at preoperative localization compared to ultrasound ($p = 0.039$) or nuclear medicine scan alone ($p = 0.0078$). There was no statistically significant difference between the first 50% of scans reported and the second 50% (ultrasound, $p = 0.27$; nuclear medicine scan, $p = 0.19$). Gland weight had no significant bearing on the accuracy of the scan (ultrasound, $p = 0.89$; nuclear medicine scan, $p = 0.16$).

DISCUSSION

The parathyroid glands are known to be variable in location, hence, the classical approach of bilateral lateral neck exploration, and on occasion the superior mediastinum has to be explored. We believe that successful minimally invasive parathyroidectomy is completely dependent on accurate preoperative imaging, coupled with intraoperative confirmation that all the hypersecretory parathyroid tissue has been excised. Intraoperative PTH monitoring is standardized. However, the results for individual imaging modalities vary wildly. Our study was designed to see if

Table 2: Histology of nonadenoma patients

Histology	*Ultrasound*	*Scintigram*	*Glands removed*	*Intraop PTH decrease >50%*	*Long-term sequelae*
Hyperplasia	Negative	Negative	Left upper, Left lower	Yes	Nil
Hyperplasia	Negative	Right upper	Right upper, Left upper, Left lower	Yes	Nil
Hyperplasia	Left lower	Right lower, multinodular goiter	Right lower	Yes	Short-term oral calcium
Hyperplasia	Not performed	Negative	Left upper, Right upper	Yes	Nil
Hyperplasia	Not performed	Negative	Four glands	Yes	Long-term calcium and vitamin D supplements
Hyperplasia	Not performed	Right lower	Four glands	Yes	Reimplantation left upper in brachioradialis
Hyperplasia	Not performed	Right lower	Right lower	Yes	Nil
Normal gland	Negative	Negative	Left lower, Right upper, Two glands clipped	Yes	Nil, resolution hypercalcemia
Normal gland	Right lower	Right lower	Right upper, lymph node	No	Repeat curative procedure after SPECT/CT
Normal gland	Left lower	Left lower	Left upper	No	Repeat curative procedure after SPECT/CT
Normal gland	Left lower	Negative	Left lower, Left upper, right lower	No	Long-term monitoring borderline hypercalcemia
Normal gland	Right lower	Right lower	Left lower and left thyrothymic tract	No	Nil, resolution hypercalcemia, long-term vitamin D supplementation

combining the two most prevalent imaging modalities could improve accuracy.

Ultrasound localized the correct side in 65% of patients in all cases of primary hyperparathyroidism in our study. A negative ultrasound scan result occurred in 20% of patients. Accuracy of ultrasound is dependent on physical characteristics of the gland, morphology of the patient's neck and presence of adjacent lesions in the thyroid. These variables have a great bearing on the images obtained ultrasonically, and can make such scans difficult to interpret, which is why the experience and skill of the ultrasonologist is crucial.[16]

In our study, 24% of nuclear medicine scans were negative. Negative scintigram scans have been postulated to occur in patients who have altered cell type ratio within the parathyroid adenoma. Sestamibi is taken up by mitochondria. The amount of sestamibi uptake in parathyroid adenomas correlates with gland size and type of cell composition, with greater uptake seen in adenomas with a predominance of oxyphil cells rather than chief cells.[17,18] The rates of reported negative scans in our study is within previous reported ranges from 72 to 89%.[8-15,19] If both scans were performed and were concordant, the accuracy rates were superior to single imaging modalities.

There was no great interobserver variability; moreover, the sensitivities of the first half of all scans and the second half were comparable indicating a consistent approach to reporting. We found no relationship between gland weight and sensitivity or PPV of nuclear medicine scanning or ultrasound or the combination of both.

Table 3: Accuracy of imaging in patients with histologically-proven parathyroid adenomas

	Ultrasound (%)	*Sestamibi (%)*	*Both (%)*
Total	65 (100)	80 (100)	59 (100)
Accurate pole	36 (55)	48 (60)	23 (39)
Accurate side	43 (66)	59 (74)	29 (49)
Misleading*	10 (15)	4 (5)	25 (42)
Negative	12 (19)	17 (21)	5 (9)

*Where scans not predictive of pole, or side or discordant

Table 4: Sensitivity of scans in patients with adenoma

	Correct pole	*Correct side*
Ultrasound sensitivity	0.75	0.78
Scintigram sensitivity	0.74	0.77
Both scans' sensitivity	0.82	0.85

Table 5: Positive predictive values for scans in patients with adenoma

	Correct pole	*Correct side*
Ultrasound PPV	0.78	0.81
Scintigram PPV	0.92	0.94
Both scans' PPV	0.77	1.0

PPV: Positive predictive value

Multiglandular disease is thought to be evident in 5% of all patients diagnosed with primary hyperparathyroidism secondary to parathyroid adenoma.[1] Within our patient population, there was little evidence of multiglandular disease. Preoperative imaging did not support multiglandular disease; no patients who underwent both scans had multiple areas identified on both. Furthermore, histology did not identify any evidence of multiple adenomas in patients having more than one gland removed. Scans with more than one area highlighted did occur in seven patients. However, four of these only required a single gland excision, confirmed by the fall in intraoperative PTH, and none of the other three had any histological evidence of multigland disease.

Within the patient population, only four patients (4%) required neck reexploration. Two of these patients had initial surgery with normal histological glands removed, further localization procedures were carried out and resulted in successful adenoma removal. The other two patients were diagnosed with carcinoma and required further surgery; one patient due to recurrence and another had persistently elevated PTH levels with atypical features on initial histology.

Nuclear medicine scintigraphy and ultrasound are the most commonly used techniques employed for preoperative localization. This paper has demonstrated the benefits of employing a dual localization technique in order to supplement a less invasive procedure for the patient. Although a proportion of patients did have inconclusive or discordant scans, the use of intraoperative parathyroid hormone monitoring resulted in excellent cure rates for this group of patients.

As this is a retrospective study, there may have been some bias when the scans were reported. Areas of development for the future include examining ways of improving sensitivity of both ultrasound and nuclear medicine scintigraphy, this of course depends on technological advances, which will hopefully continue as minimally invasive parathyroidectomy continues to be advanced as a safe and economical technique.

There is no doubt that the 'gold-standard' would be an appropriately-powered multilimbed randomized trial comparing the various imaging modalities in isolation and combination. However, as is often the case in surgery, technological advances have opened up new techniques and options prior to validation in any randomized studies. We believe that our study, within the limits of its design, adds to the weight of evidence about preoperative imaging for parathyroid surgery.

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