

Detectability and surgical outcomes in parathyroid surgery – a single-centre experience

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Abstract

The incidence of primary hyperparathyroidism and referrals for the removal of parathyroid adenomas are increasing. Factors that improve the detectability, and ultimately the surgical outcome, are the focus of this retrospective study. We included 117 patients who had parathyroid operations with intraoperative monitoring of parathyroid hormone (PTH). Sestamibi, ultrasound and, in selected cases, fusion with computed tomograms (CT), were done to locate the lesion preoperatively. Concentrations of calcium and PTH before and after operation, specimen weight, and preoperative vitamin D concentrations, were assessed. The sensitivity of sestamibi and ultrasound for the preoperative location of adenomas was 92% and 80%, respectively. Sestamibi located them more accurately in patients with low preoperative concentrations of vitamin D ($p=0.037$) and with heavier adenomas ($p<0.001$). We found no significant association between the preoperative concentrations of PTH and detectability on preoperative scans ($p=0.058$). Postoperative follow up showed that 97% of the 117 patients were biochemically cured. Accurate location helps to lower morbidity as it facilitates a targeted approach. Further studies are needed to explore the role of vitamin D in the location of parathyroid adenomas before parathyroidectomy.

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Introduction

Primary hyperparathyroidism is an endocrine disorder in which autonomous overproduction of parathyroid hormone (PTH) results in derangement of the calcium metabolism. It is diagnosed when a patient has hypercalcaemia with an inappropriately normal or raised concentration of PTH. It is the third most common endocrine disorder after diabetes mel-

litus and osteoporosis,¹ and is reported more commonly in women than in men. It is often diagnosed in asymptomatic patients on routine biochemical testing.²

Indications for surgical referral include a calcium concentration that is 0.25 mmol/L above the upper limit, impaired renal function with creatinine clearance of less than 60 ml/min (or eGFR of less than 60 ml/min), reduced bone mineral density; and previous vertebral or low-impact fracture. The long-term benefits of parathyroidectomy include bone protection and prevention of renal complications.³

Many patients with primary hyperparathyroidism, however, report non-specific musculoskeletal symptoms and neurocognitive psychiatric impairment.⁴ Besides biochem-

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ical cure by normalisation of calcium concentrations, parathyroid surgery helps with a variety of non-specific symptoms which, in some cases were the main motivation for referral.^{4–7} Familial hypocalcaemic hypercalcaemia (FHH), which is a rare autosomal dominant condition that can mimic primary hyperparathyroidism, must be differentiated from primary hyperparathyroidism, as there is no parathyroid adenoma. A calcium-creatinine clearance ratio (CCCR) of less than 0.01 is indicative of the condition, but the results can be influenced by a number of factors including renal function and age. Genetic testing for calcium-sensing receptor protein may be used for diagnosis of FHH. Many centres target screening for FHH in patients with long-standing hypercalcaemia, minimal symptoms, and when scans show no definite adenoma.

Vitamin D deficiency is common among patients with primary hyperparathyroidism and is associated with a more advanced biochemical and clinical presentation of the disease, so adequate replacement is recommended.^{8–13} The impact that this deficiency has on the incidence of prolonged hypocalcaemia, despite normal postoperative concentrations of parathyroid hormone, is not clear. Prolonged hypocalcaemia is known as hungry bone syndrome. Some authors suggest that patients deficient in vitamin D have an increased risk of this postoperatively, but others have found no significant association between deficiency and postoperative hypocalcaemia.⁹ Although vitamin D sufficiency is not a prerequisite before parathyroid surgery, normal concentrations may prevent confusion about the aetiology of persistently raised PTH concentrations after successful parathyroidectomy.¹⁴

Bilateral neck exploration can identify adenomas or hyperplasia of the parathyroid gland, and enable their removal, particularly when several glands are affected. Improved scans and intraoperative monitoring of PTH allow for a more targeted, unilateral approach with similar long-term results and low morbidity.^{15,16} We have therefore retrospectively assessed the factors that influence the outcome of parathyroid surgery, and focused on the accuracy of preoperative location.

Material and methods

We retrospectively analysed data on patients who were treated surgically between 2014 and 2017 for primary hyperparathyroidism by the same surgeon. Preoperative data (symptoms, and calcium and serum PTH concentrations) were assessed together with the postoperative biochemical results and preoperative vitamin D concentrations when available.¹⁷ Preoperative location was compared with the actual intraoperative findings. We also assessed factors that may influence accurate visualisation of the adenoma on preoperative scans (scintigraphy and ultrasound). Ideally scintigraphy preceded ultrasound to enable a more targeted ultrasound examination. Tc 99 m sestamibi (MIBI) was used with early 15-minute and

2-hour delayed planar acquisitions, the latter supplemented with SPECT acquisitions. The scans were assessed by an experienced radionuclide radiologist.

Ultrasound scans with 12 and 7.5 MHz lineal array probes were assessed by an experienced clinical radiologist who was a specialist in ultrasound of the head and neck. In cases of doubt, computed tomographic images (CT) of the neck and mediastinum were fused with the MIBI SPECT acquisitions.

Before the operation, the multidisciplinary team discussed the preoperative scans and biochemical results. Patients with unilateral tumours were operated on through access in the neck with intraoperative monitoring of PTH.¹⁸ Those whose tumours were not clearly located had bilateral exploration of the neck. We recorded the intraoperative PTH.^{18,19} Before operation the baseline PTH was measured and a further sample was taken 30 minutes after removal of the adenoma. A decline in PTH from baseline indicated correct removal.²⁰ We also used frozen sections to confirm diagnosis of parathyroid tissue, and recorded the weight of the specimens. When there was no drop in PTH, the neck was explored further and the tests repeated, particularly when several glands were affected. We recorded agreement between the locations found on preoperative imaging and the actual findings. The preoperative results were considered as true positive (TP) when the scans detected the adenoma in the same site as it was found during the operation. When found in a different site than the scans suggested, it was considered a false positive (FP). An adenoma that had not been detected by the scans but was identified at operation was considered a false negative (FN), and cases in which no adenoma was found preoperatively or intraoperatively were considered true negatives (TN). Sensitivity was calculated as TP/(TP + FN), and positive predictive value as TP/(TP + FP). Specificity was calculated as TN/(TN + FP) and negative predictive value as TN/(TN + FN).

Patients were followed up after a minimum of two months and besides the clinical examination, which included flexible nasoendoscopy, we took blood for biochemical examination.

The statistical tests and graphic illustrations were done with the aid of Matlab (Mathworks) and Numbers ('09 version 2.3 Apple Inc). The data were analysed by Pearson's correlation coefficient and the Mann Whitney U test. The correlation coefficient (R^2), 95% CI, area under the curve (AUC), and p values were calculated. Probabilities of less than 0.05 were considered significant.

Results

In total, 117 patients were included in this retrospective study (median (range) age 66 (51–80) years). Fifteen (13%) were male and 102 (87%) female. Most were symptomatic ($n = 73$, 62%), although 24 (20%) had no disease-specific symptoms. Only 23 patients (20%) had osteoporosis confirmed by bone densitometry. Most ($n = 102$, 87%) cases were discussed by the multidisciplinary team before operation.

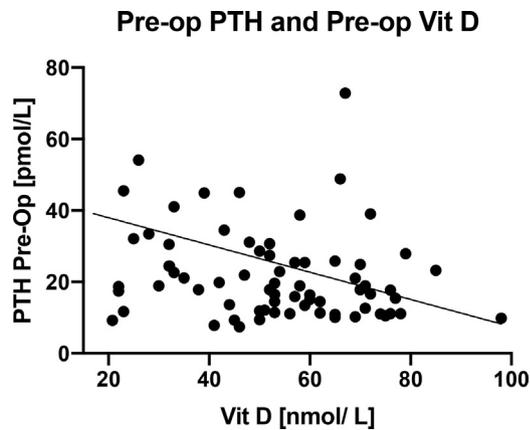


Fig. 1. Inverse linear relation between preoperative concentrations of vitamin D and parathyroid hormone (PTH) (R^2 0.07, 95% CI - 0.70 to - 0.05, $p=0.021$).

Preoperative investigation and biochemical examination

Most patients (73%) had a 24-hour urine collection that showed increased calcium excretion. The eGFR was low (mean (range) 73 (27-117) ml/min), which indicated reduced renal function (reference range at local laboratory more than 90 ml/min). The mean (range) preoperative collected calcium concentration was raised (2.82 (2.58- 3.73) mmol/L; reference range at local laboratory 2.1-2.6 mmol/L). Concentrations of PTH were inappropriately raised at a mean (range) of 24 (7.2-179) pmol/L (reference at local laboratory 1.6 - 7.2 pmol/L). The preoperative vitamin D concentrations were measured in 79 (67%) of the patients (mean (range) preoperative concentration 53 (32-79) nmol/L; reference range at local laboratory 75-200 nmol/L). An inverse linear relation was found between concentrations of preoperative vitamin D and PTH, so concentrations of PTH were higher in patients deficient in vitamin D (R^2 0.07, $p=0.02$, 95% CI - 0.70 to - 0.05) (Fig. 1).

A total of 16 patients (14%) were given a calcium-mimetic agent such as cinacalcet to control the concentration of calcium preoperatively, and it was discontinued in all cases postoperatively.

Accuracy of location

All patients had sestamibi and ultrasound scans preoperatively. A total of 29 (25%) required CT for further assessment.

Preoperative sestamibi gave results that were true positive in 95 cases (81%) and false positive in 12 (10%). Sestamibi gave a false negative result in eight (7%), and in two (2%) the adenoma was not identified on MIBI or during operation (true negative). The sensitivity of the sestamibi scans was calculated to be 92% with a positive predictive value of 88%. The specificity was 14% with a negative predictive value of 20%.

In 84 cases (72%) the ultrasound findings were true positive and corresponded with the intraoperative findings. The

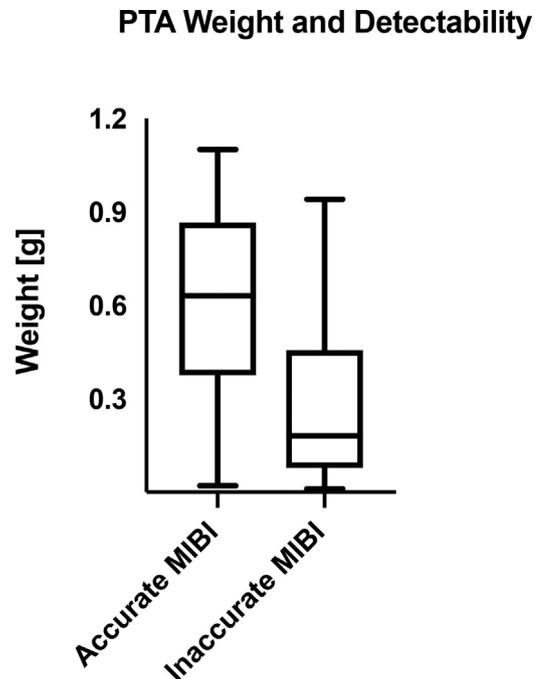


Fig. 2. Improved detectability of heavier adenomas on sestamibi scans (AUC=0.79, 95% CI: 0.67 to 0.90, $p<0.001$).

sensitivity of ultrasound for the location of adenomas was 80% with a positive predictive value of 86%. The specificity was 18% with a negative predictive value of 13%. Location by ultrasound agreed with sestamibi findings in 65% of cases.

Adenomas were most often found in the right lower pole of the thyroid ($n=48$, 42%), followed by the left lower pole ($n=40$, 35%), left upper pole ($n=21$, 18%), and right upper pole ($n=6$, 5%).

There was no significant association between preoperative concentrations of PTH and detectability on preoperative sestamibi scans (AUC=0.62, 95% CI: 0.50 to 0.74, $p=0.05$). The accuracy of location on sestamibi was higher in patients with heavier specimens (AUC=0.79, 95% CI: 0.67 to 0.90, $p<0.001$) (Fig. 2). The mean (range) weight of the adenomas was 0.85 g (0.004 - 9.78 g). There was a significant linear association between weight and preoperative concentration of PTH (R^2 0.40, 95% CI 9.0 to 14.30, $p<0.001$) (Fig. 3), but weight was not significantly associated with preoperative concentration of vitamin D (R^2 0, $p=0.6$). We found a weak association between preoperative vitamin D and detectability of adenoma on sestamibi scan (AUC = 0.68, 95% CI: 0.53 to 0.83, $p=0.038$). Location on sestamibi was more accurate in patients with lower preoperative concentrations of vitamin D (Fig. 4).

Heavier adenomas were often located accurately on ultrasound sonography (AUC=0.66, 95% CI: 0.54 to 0.77, $p=0.011$) (Fig. 5). Vitamin D concentrations were not significantly associated with detectability on ultrasound scans (AUC 0.53, 95% CI: 0.36 to 0.70, $p=0.72$). Multigland disease was identified intraoperatively in only three (3%) patients whose PTH concentrations did not drop sufficiently

Association Specimen Weight and PTH Level

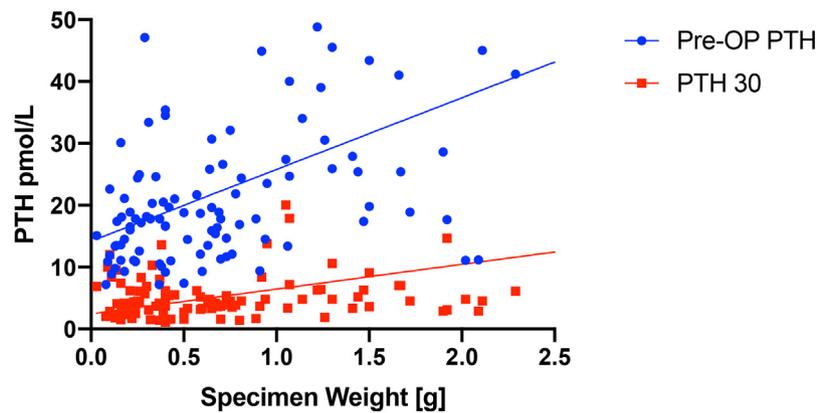


Fig. 3. Significant linear association between weight of the adenoma and preoperative and postoperative parathyroid hormone (PTH) concentrations (blue: R^2 0.40, 95% CI 9.0 to 14.3, $p < 0.001$; red: R^2 0.36, 95% CI 3.0 to 5.0, $p < 0.001$).

Pre-op Vit D and Detectability

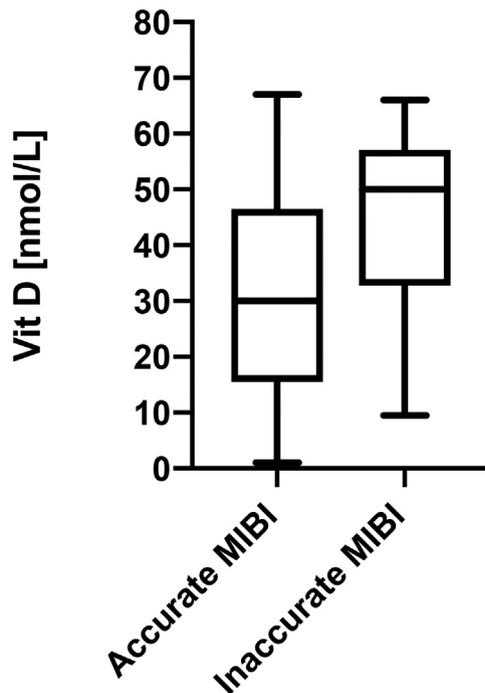


Fig. 4. Association between preoperative concentrations of vitamin D and detectability of adenomas on sestamibi scans (AUC = 0.68, 95% CI: 0.53 to 0.83, $p = 0.038$).

after removal of the first adenoma, but did so after further exploration of the neck and removal of a second adenoma.

Postoperative biochemical results

Postoperative follow up in surgical care was after a mean (range) of 65 (43–295) days. In most patients ($n = 113$, 97%) the concentration of calcium had returned to normal (mean (SD) 2.42 (0.3) mmol/L).

Weight and Detectability on USS

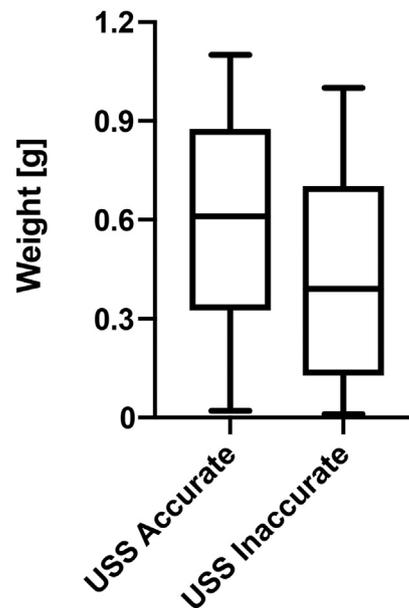


Fig. 5. Improved detectability of heavier adenomas on ultrasound sonography (USS) (AUC = 0.66, 95% CI: 0.54 to 0.77, $p = 0.011$).

Generally, there was a reduction in PTH of 71% postoperatively. The higher the preoperative PTH and the heavier the specimen, the more the PTH dropped 30 minutes after removal of the adenoma (R^2 0.90, 95% CI 0.67 to 0.76, $p < 0.001$) (Figs. 3 and 6).

In four patients (3%) the adenoma could not be found during the operation and the intraoperative concentration of PTH did not drop sufficiently. Two were rescanned with CT fusion and discussed again by the multidisciplinary team. In both, a single adenoma was found in a second operation, after which PTH declined sufficiently, and calcium concentrations returned to normal. In the third patient, PTH and calcium eventually returned to normal, and in the fourth, who decided

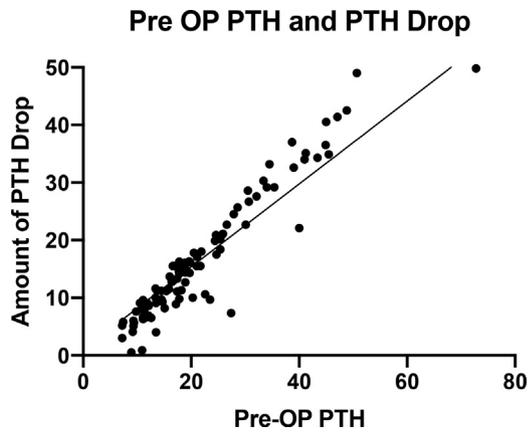


Fig. 6. Association between preoperative concentrations of parathyroid hormone (PTH) and the amount they drop 30 minutes after parathyroidectomy (R^2 0.90, 95% CI 0.67 to 0.76, $p < 0.001$).

not to have a further operation, concentrations of both PTH and calcium improved from baseline.

In a further three (3%) patients calcium remained high after the adenomas had been removed. In all three, histological examination of frozen sections confirmed that the specimens were parathyroid tissue, but PTH concentrations dropped by a mean (range) of only 21% (5% - 51%) after removal. Two patients were treated with calcium-mimetic medication (cinacalcet) and the remaining patient was treated elsewhere.

Hypercalcaemia therefore persisted in only four patients (3%) postoperatively.

Discussion

Multimodal location techniques and intraoperative monitoring of PTH help to reduce morbidity, and maintain high rates of cure in parathyroidectomy.¹⁹

Preoperative location allows for a unilateral approach when a single gland is affected, but when several are affected, or when scans do not agree, bilateral exploration is required.²¹ The use of nerve monitors helps to reduce morbidity caused by inadvertent injury to the recurrent laryngeal, and external branches of the superior laryngeal nerves. We used flexible nasoendoscopy to evaluate the vocal cords before and after operation. Overall, we found a reduction in unilateral vocal cord mobility in three patients (3%) who had temporary postoperative hoarseness that improved with speech and language therapy. This agrees with reported incidences of postoperative neuropraxia of the recurrent laryngeal nerve.²² In our study 97% of patients were biochemically cured, which is similar to that reported in other case series.²³

Although reported by other authors, we did not find a significant association between PTH concentration and detectability on preoperative scans.¹⁹ Larger adenomas were detected better on both ultrasound and sestamibi scans, but the imaging methods that are currently used are not infalli-

ble, and more advanced techniques such as 4-dimensional CT are being proposed for accurate location particularly when several glands are affected.²⁴ Sestamibi scans had a positive predictive value of 88%, but a low specificity (14%). The sensitivity of ultrasound for the detection of adenomas was 80% with a positive predictive value of 86%. The sensitivities and specificities observed in our study agree with those reported elsewhere.²⁵

We found a significant association between preoperative concentrations of vitamin D and the detectability of adenomas on sestamibi scans (AUC = 0.68, 95% CI: 0.53 to 0.83, $p = 0.038$). We also found high concentrations of PTH in patients with low preoperative concentrations of vitamin D ($p = 0.02$). To the best of our knowledge no previous study has assessed the role of vitamin D in the preoperative location of adenomas. Vitamin D replacement before operation is controversial so our findings may have important clinical implications. Our study was, however, limited by the fact that preoperative vitamin D concentrations were known in only 79 patients (67%). Further studies are needed to explore its role in preoperative localisation of adenomas in parathyroid surgery.

Conflict of interest

We have no conflicts of interest.

Ethics approval

Not required. Reviewed by the Research Department of Western Sussex Hospitals NHS Foundation Trust. Patients' permission not applicable.

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