

Re-explorative Parathyroid Surgery for Persistent and Recurrent Primary Hyperparathyroidism

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ABSTRACT

Primary hyperparathyroidism (HPT) is treated by parathyroidectomy. Excision of abnormal parathyroid tissue is curative in the majority of cases. Postoperative persistent or recurrent HPT has been reported up to 30%. The purpose of this study was to evaluate the role of imaging techniques and determine the efficacy of reexplorative surgery. A total of 306 patients underwent parathyroidectomy between 2000 and 2009. Twelve patients (3.9%) were not cured. Two patients declined further treatment, the other 10 patients underwent further investigation and surgery. Imaging and results of redo surgery together with associated complications were evaluated. All 10 patients were investigated with sestamibi, which accurately localized aberrant parathyroid tissue in three cases and ultrasound scans which also localized three cases. CT was useful in one of the three cases for which it was used. PET and MRI were not helpful. Twelve glands were resected, six adenomas, five hyperplastic and one normal gland. Nine of the 10 reoperated patients became normocalcemic. Complications included a bilateral recurrent laryngeal paresis. In total, 317 operations were performed and 303 of 306 (99%) patients were cured. Redo surgery for HPT is challenging and carries higher risks than primary surgery. Sestamibi and ultrasound scans are the most helpful imaging modalities. When there is concordance a targeted approach may be considered, otherwise a more extensive dissection is required. Redo parathyroid surgery should be considered, even if scans are unhelpful, for patients who are symptomatic or young or have a persistently high calcium level.

Keywords: Primary hyperparathyroidism, Hyperparathyroidism, Hypercalcemia, Ultrasound, Sestamibi scan, Parathyroid gland Redo parathyroidectomy, Recurrent hyperparathyroidism, Persistent hyperparathyroidism.

INTRODUCTION

Primary hyperparathyroidism (HPT) and malignancy are the two most common causes of hypercalcemia. The incidence of primary HPT is 25 to 30 cases per 100,000 in the general population and is 2 to 3 times higher in women.¹ Solitary parathyroid adenoma accounts for the majority of cases (85%) with parathyroid hyperplasia the cause for the rest.^{2,3} Surgical excision of the abnormal parathyroid gland or glands is curative in 95% of cases although cure rates as low as 70% have been reported.⁴ Parathyroidectomy is associated with low morbidity when performed by an experienced surgeon.⁵ Continuing post-operative hypercalcemia may be due to persistent HPT (defined as elevated serum calcium levels within 6 months of surgery) or recurrent HPT (elevated calcium levels 6 months or more after surgery). Treatment failure after surgery is due to a missed adenoma in the majority of cases⁶ or else the presence of previously unrecognized multiglandular disease.⁷

Redo parathyroid surgery is technically challenging and is associated with a higher morbidity than primary parathyroidectomy. Tissue fibrosis causes anatomical distortion of the normal planes. This can result in difficulty identifying any remaining abnormal parathyroid tissue as well as key structures such as the recurrent laryngeal nerves. Imaging techniques are available to aid the accurate localization of

remaining parathyroid tissue, particularly adenomas, prior to redo surgery. These techniques include nuclear medicine (NM) scans, ultrasound (US) scans, computed tomography (CT) and magnetic resonance imaging (MRI). The purpose of this study was to evaluate the role of imaging techniques in facilitating the surgical procedure and to assess the efficacy of redo parathyroid surgery in patients with continuing HPT following previous parathyroidectomy in our institution.

PATIENTS AND METHODS

During the decade from January 2000, 306 patients underwent parathyroidectomy for primary HPT at St Peter's Hospital, Surrey, UK. Twelve patients were not permanently cured of their hypercalcemia; 11 had persistent and one (case 5) recurrent HPT. Before considering redo surgery, the diagnosis of continuing primary HPT was reconfirmed. Measurements were made of serum parathyroid hormone levels (PTH), calcium and vitamin D together with screening for familial hypocalciuric hypercalcemia. Patients were assessed for malignancy which can cause paraneoplastic hypercalcemia.

For the purpose of this study the medical records, operation notes, imaging, histology and biochemistry results of those patients with postoperative hypercalcemia were reviewed. Patients underwent further imaging to try to localize residual

parathyroid tissue. Reexplorative parathyroid surgery was performed and the results including complications evaluated.

RESULTS

Primary Surgery

Primary parathyroid exploration was carried out using a standard cervical approach. In later years, after 2006, a minimally invasive targeted approach was employed if both US and NM scans were concordant. Intravenous methylene blue dye and frozen section analysis were only used in those cases in whom the preoperative scans were negative and therefore had failed to localize parathyroid tissue. In this series of 306 patients, there were no cases of recurrent laryngeal nerve palsy. One patient developed a postoperative cervical hematoma which required surgical evacuation.

Blood calcium levels were measured on the first post-operative day and 6 months after surgery. A total of 294 patients (96%) were cured of their HPT by the primary operation. Twelve patients (3.9%) were hypercalcemic after primary surgery, of whom seven were female, two older patients, asymptomatic from their persistent hypercalcemia, declined further surgery (Table 1). The mean age at primary operation for these 12 patients was 59 years (range 16 to 75). The mean length of time from primary to redo surgery was 11 months.

Localization Studies Prior to Redo Parathyroidectomy

Ten patients who underwent redo surgery had technetium (Tc)-99-m-labeled 2-methoxy-isobutyl-isonitrile (sestamibi) scintigraphy preoperatively (Table 2). Sestamibi scanning identified a potential location for aberrant parathyroid tissue in four patients, and was correct in three cases [1, 2 (Fig. 1) and 4]. In case 9, where the sestamibi scan suggested aberrant

parathyroid tissue on the left, three hyperplastic glands (one on the left and two others on the right) were identified intra-operatively. The remaining six scans were negative.

Patients also underwent an US scan prior to surgery (Table 2). In three cases (1, 5 and 10), the scans were accurate in identifying the gland. However, in the remaining seven cases, US did not assist in preoperative localization. In cases 1 and 5, the US performed prior to primary parathyroidectomy had not accurately identified the parathyroid glands. There was concordance between the US and sestamibi scan in only one case (case 1).

Three patients also underwent CT scanning, one patient had an MRI scan, and two had positron emission tomography (PET) scans. Of all these imaging studies, only CT scan aided correct localization of a parathyroid adenoma (patient 4).

During redo surgery all patients had methylene blue dye administered. In four patients, an intraoperative radioprobe was also used to help to locate parathyroid tissue.

Anatomical Location of Excised Parathyroid Tissue following Redo Surgery

In total, 12 glands were resected, of which six were adenomas, five showed hyperplastic parathyroid tissue and one was reported as a normal gland. One specimen was found to be a thyroid nodule; none showed parathyroid carcinoma (Table 1).

Out of the six adenomas, five were ectopic. Two adenomas were within the thyroid gland (patients 1 and 2). One adenoma was found in the anterior mediastinum separate from the thymus (patient 4), one was intrathymic (patient 10) and one lay at the tracheoesophageal groove (patient 3). This patient as well as having an ectopic gland had double adenomas. One of these adenomas was found at primary surgery in the right side superior to the inferior thyroid artery and the other at the ectopic location in the tracheoesophageal groove during the second operation.

Table 1: Histology and outcome of patients who underwent redo parathyroid surgery

Case number	Histology from 1st operation	Histology from 2nd operation	Outcome
1	Normal parathyroid tissue	Adenoma within right lobe of thyroid	Normocalcemic
2	Normal parathyroid tissue	Adenoma within left lobe of thyroid	Normocalcemic
3	Right-sided adenoma	Right-sided adenoma at tracheoesophageal groove	Normocalcemic
4	Normal parathyroid tissue	Normal tissue	Continued persistent hypercalcemia Underwent 3rd operation, adenoma located in superior mediastinum Now hypocalcemic
5	Right-sided parathyroid hyperplasia	Right-sided hyperplastic parathyroid tissue	Bilateral recurrent laryngeal nerve palsy hypocalcemia
6	Left-sided parathyroid hyperplasia	Right-sided hyperplastic parathyroid tissue	Normocalcemic
7	Left-sided parathyroid hyperplasia	Right-sided thyroid nodule, no parathyroid tissue	Persistent hypercalcemia, declined further surgery
8	Right-sided thyroid nodule and normal parathyroid tissue	Left-sided adenoma	Normocalcemic
9	Normal parathyroid tissue	Hyperplasia of 3 parathyroid glands (2 left, 1 right)	Normocalcemic
10	Thymus tissue, no parathyroid tissue	Adenoma within thymus on right of superior mediastinum	Normocalcemic

SURGICAL OUTCOMES

Following redo surgery, two patients remained persistently hypercalcemic (Table 1). One patient (case 4) went on to have a third operation and is now normocalcemic. The other declined a third operation and remains hypercalcemic (patient 7). Thus 10 patients had 11 operations and 9 of them were rendered normocalcemic. Mean follow-up was 37 months (range 10-87 months). After a total of 317 operations, 303 of 306 patients (99%) were cured of hyperparathyroidism.

COMPLICATIONS

Following the 11 redo procedures carried out on 10 patients, one patient suffered bilateral recurrent laryngeal nerve paresis requiring a tracheostomy for 5 months. Her voice has completely recovered (case 5). A second patient suffered a right vocal cord weakness; his voice recovered with speech therapy (case 4). Thus, 3 of 22 cords at risk were affected (14%). There were no wound infections or hematomas. Two patients still require calcium and vitamin D supplementation.

DISCUSSION

Persistent and recurrent HPT are associated with failed initial surgery, abnormal anatomical variants or abnormal biology of the disease.⁸

Parathyroid and redo parathyroid operations are technically challenging procedures and several studies have concluded that more experienced surgeons have greater operative success with these cases.⁹ An association between volume and outcome in parathyroid surgery has been claimed, suggesting inexperienced surgeons may perform inadequate exploration, resection or both.¹⁰ In our series, 12 patients (3.9%) were not biochemically cured following primary surgery, an incidence which is comparable to reported rates in the literature.

Ectopic and supernumerary glands contribute to the failure of primary parathyroid surgery. The embryological development of the branchial pouches can result in a range of locations for the parathyroid glands.¹¹ The superior parathyroid glands arise from the fourth branchial pouch. Due to minimal descent during development, their positions are relatively constant and fewer than 2% of the superior glands are found in an ectopic location.¹² The inferior parathyroid glands are more likely to be ectopic as they develop from the third branchial pouch and descend, together with the thymus, a greater distance. Ectopic glands have been found at redo surgery in the thymus, thyroid gland, tracheoesophageal groove or paraesophagus, mediastinum,

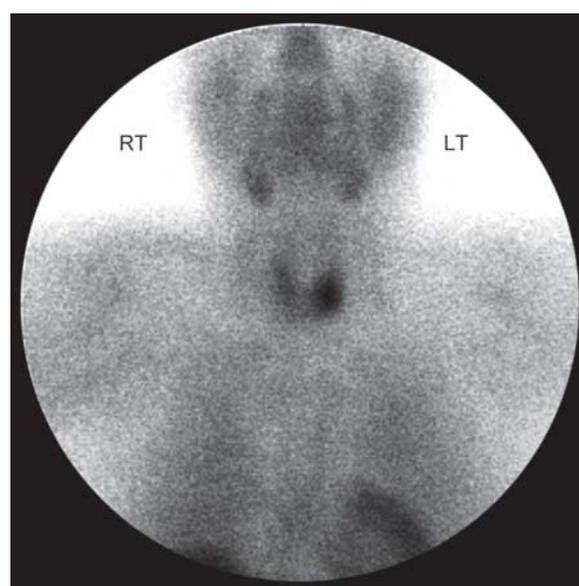


Fig. 1: Sestamibi scan of patient 2, demonstrating increased left side uptake, therefore localizing the aberrant parathyroid tissue to the left side of the neck

Table 2: Investigations and results of patients who underwent redo parathyroid surgery

Case number	Ultrasound before 1st operation	Sestamibi scan before 1st operation	Ultrasound before 2nd operation	Sestamibi scan before 2nd operation	CT/MRI/PET before 2nd operation	Location of lesion
1	Negative (FN)	Negative (FN)	Right-sided lesion within thyroid (TP)	Right-sided uptake (TP)	Not done	Right lobe of thyroid
2	Left-sided lesion (TP)	Left-sided uptake (TP)	Negative (FN)	Left-sided uptake (TP)	Not done	Left lobe of thyroid
3	Negative (FN)	Negative (FN)	Negative (FN)	Negative (FN)	CT/MRI/PET not helpful	Right tracheoesophageal groove
4	Negative (FN)	Negative (FN)	Negative (FN)	Lesion in superior mediastinum (TP)	CT: 8 mm nodule in superior mediastinum	Lesion not located on 2nd operation, found in superior mediastinum on 3rd operation
5	Negative (FN)	Negative (FN)	Right-sided lesion (TP)	Negative (FN)	Not done	Right sided
6	Negative (FN)	Negative (FN)	Negative (FN)	Negative (FN)	Not done	Right sided
7	Negative	Negative	Negative	Negative	CT/PET not helpful	Lesion not located
8	Right-sided lesion (FP)	Right-sided uptake (FP)	Negative (FN)	Negative (FN)	Not done	Declined further surgery
9	Right-sided lesion (FP)	Right-sided uptake (FP)	Negative (FN)	Left-sided uptake (FP)	Not done	Left sided
10	Negative (FN)	Negative (FN)	Right-sided lesion (TP)	Negative (FN)	Not done	3 parathyroid glands (2 left, 1 right) Adenoma within thymus on right of superior mediastinum

FN: False-negative; FP: False-positive; TP: True positive

carotid sheath, base of skull and lateral to the carotid artery.¹³ The tracheoesophageal groove is the most common location of missed glands¹⁴ and it has been suggested that a reluctance to dissect near the recurrent laryngeal nerve may be a key factor in the failure to appreciate abnormal parathyroid glands in this position.³ In our series, there were five cases of ectopic glands; two of these were within the mediastinum and were accessed via a cervical incision in keeping with other published studies.¹⁵ There was also one case of double adenomata, which has a reported incidence of 1.9 to 12%.^{16,17} In our patient, one abnormal parathyroid gland was found on the right side and duly excised but, as a result, a second abnormal gland also on the right tracheoesophageal groove went undetected.

In this series, there was only one case of recurrent HPT which occurred in a patient with parathyroid hyperplasia. Hyperplasia accounts for 15% of primary HPT, but up to 20 to 40% of reoperative cases from residual hyperplastic tissue.^{8,16}

Recurrence secondary to hyperplasia may also be due to parathyromatosis from incomplete resection during the first operation. Parathyromatosis is a rare cause of recurrent hypercalcemia and is secondary to capsular rupture and spillage of parathyroid cells during parathyroidectomy. This results in the dissemination of multiple foci of hyperfunctioning parathyroid tissue in the neck or mediastinum.⁸ Clearance of this ectopic tissue is difficult, if not impossible and a cure is rare. For this reason care should be used when removing abnormal parathyroid tissue to avoid spillage of cells.¹⁸

Preoperative localization studies are essential in the evaluation of persistent or recurrent HPT. In our study, all patients undergoing redo surgery had sestamibi and US scanning although neither was always helpful. Sestamibi aided the correct localization in three cases, and in one patient the result was a false-positive. Although these numbers are small they suggest that the imaging of our patients has been less helpful than in other studies some of which have demonstrated a positive yield rate of around 60 to 80% using sestamibi.¹⁹ Sestamibi scans have also been reported to be able to detect ectopic parathyroid adenomas with an accuracy of over 90%.^{20,21} Smaller adenomas or adenomas with a low mitochondrial content may result in rapid washout of tracer, resulting in a false-negative result.²²

US is a fast and safe procedure but it is dependent on the operator and the equipment. The sensitivity of US has been reported to be as low as 22% and as high as 82%.²³ Patients with multinodular thyroid disease, a short and thick neck or an adenoma in the retroesophageal, mediastinal or tracheoesophageal groove are more likely to yield a false-negative result.²⁴ Ultrasound is a sensitive investigation for intrathyroid glands, which account for 10% of ectopic glands,¹³ and accurately identified one intrathyroid lesion prior to redo surgery in our series. Parathyroid glands are more readily identified when there is concordance between the sestamibi and US scans.

CT and MRI have a true positive rate of 50 to 70% for patients with persistent or recurrent disease.¹⁵ These imaging modalities are less operator-dependent compared to US and can identify glands in the mediastinum and retroesophageal

region more readily than US. CT scan exposes the patient to radiation and to contrast. Artefacts are common if surgical clips have been used during the primary operation. PET has been used in several small studies, one demonstrated an accuracy of 79% for adenomas and 29% for hyperplasia identification.²⁵ The number of CT, MRI and PET scans done in this series was small but were not found to be very helpful.

Four-dimensional computer tomography (4D-CT) is a relatively novel technique that allows for functional and anatomical localization of hyperfunctioning parathyroid tissue by performing multislice imaging paired with timed contrast enhancement of the neck structures.²⁶ A study of 45 patients who had previously undergone reoperative parathyroidectomy showed that 4D-CT had a sensitivity of 88% in localization compared to 54% for sestamibi imaging.²⁷ This technique appears promising.

Invasive localization studies have been employed in some institutions. Venous sampling might be expected to be less helpful in patients who have already had parathyroid surgery where the venous anatomy may be distorted. Nevertheless an accuracy of around 90%^{19,28} has been reported. The method is invasive and carries the risks of contrast medium.

Immunoassays for parathyroid hormone with short incubation times and results available within 15 minutes have allowed intraoperative monitoring of the success of parathyroid surgery. One study demonstrated its use in redo parathyroidectomy surgery, increasing the success rate from 76 to 94%.²⁹ Another study has highlighted that although sampling PTH intraoperatively at 5 minutes posttissue excision has a high positive-predictive value (99.5%), it has a low negative-predictive value (19.5%), which can lead to unnecessary explorations and longer operative time. Instead the study advocates measurement of PTH day 1 postoperatively as an indicator of biological recovery to predict successful parathyroidectomy and not intraoperative measurement. The technique carries little benefit in primary parathyroidectomy where the results reach 95% success or more. In redo parathyroidectomy quick assay PTH measurement might be considered helpful but good results, as shown by this study, can be obtained without it.

Patients with negative scans were still considered for redo surgery if the patient was in favor of reexploration and it was considered clinically appropriate. These patients require a thorough surgical exploration of the neck which may be aided by the use of methylene blue administration and the preoperative administration of sestamibi with subsequent use of an intraoperative radioprobe.

CONCLUSION

Patients with persistent hypercalcemia after a failed initial operation must be carefully evaluated by review of their previous medical records and further imaging before reexplorative parathyroid surgery is considered.

Sestamibi and US scanning are the most useful imaging modalities to identify residual parathyroid tissue. If both scans

are concordant then a targeted approach can be considered, but if not, then a wider and more extensive surgical exploration is necessary. Redo parathyroid surgery is challenging and carries complications. While redo operations must be considered in patients with persistent hypercalcemia, even when preoperative imaging is unhelpful, such surgery should be reserved for those who are symptomatic, the young or those with excessively high calcium levels (> 2.8 mmol/l). Following this policy has allowed us to cure 99% of our patients of their HPT with no cases of permanent voice change.

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