Patterns of disease in patients at a tertiary referral centre requiring reoperative parathyroidectomy

CJ McIntyre¹, JLY Allen², VA Constantinides¹, JE Jackson¹, NS Tolley¹, FF Palazzo^{1,2}

¹Hammersmith Hospital, Imperial College Healthcare NHS Trust, UK

²Imperial College London, UK

ABSTRACT

INTRODUCTION

Reoperative parathyroidectomy is required when there is persistent or recurrent hyperparathyroidism following the initial surgery (at least 5% of parathyroidectomies nationally). By convention, 'persistent disease' is defined as the situation where the patient has not been cured by the first operation. The term 'recurrent hyperparathyroidism' is used when the patient was confirmed to be biochemically cured for six months from the first operation but has hyperparathyroidism after this date. Reoperative surgery is associated with higher rates of postoperative complications as well as a greater rate of failure to cure. The aim of our study was to review our departmental experience of reoperative parathyroidectomy, with a view to identify patterns of disease persistence and recurrence.

METHODS Using a departmental database, patients were identified who had undergone reoperative parathyroidectomy between 2006 and 2014. All the pre, intra and postoperative information was documented including the operative note so as to record the location of the abnormal parathyroid gland found at reoperation.

RESULTS Almost two-thirds (63%) of patients had negative, equivocal or discordant conventional imaging so secondary investigative tools were required frequently. The majority of abnormal glands were found in eutopic locations. The most common locations for ectopic glands were intrathyroidal, mediastinal and intrathymic. A third (33%) of the patients had multigland disease and over a quarter (28%) had coexisting thyroid disease.

CONCLUSIONS Persistent hyperparathyroidism represents a challenging patient subgroup for which access to all radiological modalities and intraoperative parathyroid hormone monitoring are required. Patient selection for reintervention is a key determinant in the reoperation cure rate.

KEYWORDS

Parathyroidectomy – Parathyroid adenoma – Primary hyperparathyroidism – Parathyroid glands – Parathyroid disorders

Accepted 14 March 2015

CORRESPONDENCE TO

Charlotte McIntyre, E: charlotte.mcintyre87@gmail.com

Primary hyperparathyroidism (HPT) is caused by a single adenoma in approximately 90%, multigland disease including adenomas or hyperplasia in 10% and parathyroid carcinoma in under 1% of cases.¹ Parathyroidectomy remains the definitive cure of primary HPT and the procedure of choice in refractory tertiary HPT in renal failure patients both before and after renal transplantation. Failure to cure HPT at the first operation (persistent HPT) is reported to occur in 5% of cases, both in the literature and in national registry data, but this is very probably underreported.^{2,3} In contrast, patients with recurrent HPT will have been biochemically cured (normal serum calcium and accommodated parathyroid hormone) for more than six months since the initial operation.

Patients who have ongoing HPT despite a previous operation are candidates for a reoperative parathyroidectomy. This surgery is associated with higher rates of

postoperative complications as well as a lower chance of being cured.^{4,5} The aim of our study was to review our departmental experience of reoperative parathyroidectomy with a view to identifying patterns of disease persistence and recurrence.

Methods

Using the departmental database, patients were identified who had undergone reoperative parathyroidectomy between October 2006 and May 2014. The standard data sought when contemplating parathyroid reintervention were reviewed, including the biochemical diagnosis, presence of symptoms, evidence of end organ damage and reassessment of indications for surgery in the context of the new risk–benefit analysis (Fig 1). The available information from the first intervention was also examined,

including the preoperative biochemistry, imaging, initial operative note and pathology report. Furthermore, the imaging modalities used and their contribution to the decision on surgical reintervention were noted. The operative note from the reintervention was used to identify the location of the abnormal parathyroid gland and correlate this with the imaging findings, and postoperative biochemistry was used to confirm cure.

Results

Over 700 parathyroidectomies were performed during the study period and 46 reoperative cases were identified for which all the data required were available. The demographics of the 46 patients (Table 1) were typical of those seen in parathyroid disease; there were more than twice as many women as men and the median age at reoperation was 62 years (range: 20–80 years). Thirty-six patients were referred from outside of the hospital’s geographical area while the remaining ten had had their initial operation in the trust at some time in the past. Five patients had already undergone two prior unsuccessful operations. The majority

of patients with primary HPT had sporadic disease. However, three patients had a confirmed diagnosis of multiple endocrine neoplasia type 1. At the original operation, 40 patients had a bilateral neck exploration with 6 having more focused surgery: unilateral neck exploration (*n*=4) and minimally invasive parathyroidectomy (*n*=2).

Concurrent thyroid disease and previous thyroid surgery was seen in 28% of the patients: multinodular goitre (*n*=7), Hashimoto’s thyroiditis (*n*=2), hemithyroidectomy for suspicious nodule (*n*=2), Graves’ disease (*n*=1) and papillary thyroid carcinoma (*n*=1). Thirty-five patients had persistent primary HPT, six had recurrent disease and five had unresolved renal HPT.

All patients had repeat ultrasonography and sestamibi imaging unless this had already been performed prior to referral. We routinely use single photon emission computed tomography (CT) in sestamibi imaging. Patients whose conventional imaging was discordant, equivocal or negative proceeded to have contrast CT (more recently with a four-dimensional [4D] CT protocol) and/or selective venous sampling with/without arteriography. We defined conventional concordant imaging as ultrasonography and sestamibi imaging locating the gland at the same location (ie left/right and superior/inferior). The true positive rate was defined as when the imaging modality correctly identified the location of the abnormal parathyroid gland found at surgery. For selective venous sampling without arteriography, the true positive rate was defined as when the gland was correctly regionalised to either the left or the right side of the upper or lower neck. Table 2 summarises the image modalities used and the true positive rates encountered.

In order to calculate the positive predictive value (PPV) of the imaging modalities, we defined a false positive as when the imaging reported the abnormal parathyroid gland to be in the wrong location. These cases were not included in the imaging reported as ‘negative’. Where the imaging showed an abnormal gland in the left lower neck and the surgical findings indicated a left superior adenoma, this was documented as a false positive. Table 3 summarises the PPV of the imaging modalities used for all abnormal glands and for ectopic glands.

Table 1 Patient demographics	
Total number of patients	46
Male-to-female ratio	13:33
Median age	62 years
Age range	20–80 years
Number of prior procedures	
1	41
2	5
Persistent hyperparathyroidism	35
Recurrent hyperparathyroidism	6
Renal hyperparathyroidism	5

Table 2 Summary of imaging studies performed		
Modality	Number performed	True positive rate
<i>Non-invasive</i>		
Sestamibi imaging	42	48%
Ultrasonography	39	36%
Computed tomography	17	47%
<i>Invasive</i>		
Selective venous sampling +/- angiography	18	94%

Table 3 Positive predictive value (PPV) of imaging modalities		
Modality	PPV for all abnormal glands	PPV for ectopic adenomas
<i>Non-invasive</i>		
Sestamibi imaging	53%	67%
Ultrasonography	57%	50%
Computed tomography	55%	50%
<i>Invasive</i>		
Venous sampling	75%	100%
Angiography	91%	100%

Synchronous or metachronous multigland disease was found in a third of patients (ie a histologically proven pathological gland at the initial operation and at least one abnormal gland removed at reintervention confirmed by histopathology). Ten patients were found to have multiple adenomas and four patients had four-gland disease. In

four patients, a supernumerary gland was found, and one patient presented with localised and therefore excisable parathyromatosis. At reoperation, the abnormal glands were found at the locations shown in Figure 2 and Table 4.

Table 4 Location of parathyroid glands at reoperation

Location	n
Eutopic	31
Left superior	7
Left inferior	5
Right superior	11
Right inferior	5
Undescended inferior	3
Ectopic	15
Intrathyroidal	4
Mediastinal	4
Intrathymic	3
Adjacent to the submandibular gland	2
In the carotid sheath	1
In the sternohyoid muscle (parathyromatosis)	1

At 3-month follow-up review, all 46 patients were biochemically cured (normocalcaemia with an appropriate level of parathyroid hormone with corrected vitamin D) of their disease. There were no long-term complications and fibreoptic laryngoscopy was routinely performed postoperatively.

Discussion

First-time parathyroid surgery in the UK comes with a high cure rate and very contained complication rates (persistent hypercalcaemia 4.7%, recurrent laryngeal nerve palsy 0.8%, reoperation for haemorrhage 0.5%, mortality 0.2%).⁶ Preoperative conventional localisation studies are now standard practice in first-time surgery and, when concordant, they are associated with a high cure rate.⁷ Patients without localised disease on preoperative imaging are more likely to have multigland disease and are less likely to be cured.^{8,9} Consequently, these patients are more likely to need reoperation although this seems to apply less to high volume parathyroid surgeons, where complications are also less common.¹⁰

Among our patients undergoing reoperation, 63% had negative, equivocal or discordant conventional imaging. The true positive rate of ultrasonography and sestamibi imaging in this group was 36% and 48% respectively. This is considerably lower than reported in first-time surgery, reflecting that this patient subgroup is more likely to have multigland disease, smaller volume disease or concurrent thyroid disease, which are all known to lower the efficacy of localisation studies.^{11–14} Over a quarter (28%) of the patients in our series had concurrent thyroid disease. 4D CT is currently the second-line investigation for patients with negative conventional parathyroid imaging. It is derived from three-dimensional CT with an added dimension looking at changes in perfusion of contrast over

time.¹⁵ One study reports that 4D CT has a sensitivity of 89% and a PPV of 74% in localising abnormal parathyroid glands not localised with ultrasonography or sestamibi imaging.¹⁶

Complications related to parathyroid arteriography and venous sampling include groin haematoma, contrast medium related anaphylaxis, contrast medium induced acute renal failure and cerebrovascular accident. While the risks are all small, these invasive studies are reserved for those patients in whom disease has not been localised on conventional imaging. In our current series, selective venous sampling (with and without arteriography) was performed in 18 patients, and proved very effective in localising the disease with true positive rates of 94% and 89% respectively. However, this is a highly operator dependent technique, and the importance of the radiological technical expertise together with knowledge of parathyroid embryology and positional variation cannot be overemphasised. Some patients in whom the abnormal glands were localised successfully with this modality had undergone unsuccessful selective venous sampling elsewhere prior to referral.

Intraoperative parathyroid hormone (IOPTH) monitoring is used frequently in cases of reoperative parathyroid surgery and it was used in all cases in our series. Curative resection of the abnormal parathyroid is associated with a fall in the IOPTH level by 50%. If the IOPTH does not fall, the surgeon should continue exploring for other parathyroid glands. Unfortunately, IOPTH monitoring also has its downsides and it is associated with an interpretation learning curve. Potential false positive results may be caused by technical error, haemolysis or removal of asymmetrically enlarged abnormal glands in unsuspected multigland disease.¹⁷

Our finding that 33% of reoperative patients had multigland disease is in keeping with the literature and underlines the importance of four-gland visualisation at first-time surgery when localisation studies are not unequivocally positive.^{18,19} A common pitfall is the identification and removal of one abnormal parathyroid gland in a patient with negative localisation studies with a bilateral exploration of the neck but without confident visualisation of the remaining glands. Indeed, most patients in our series had undergone bilateral neck surgery and yet the abnormal parathyroid glands found at reoperation were nevertheless mostly in the neck (91%), and three of the four glands found in the mediastinum were accessible through a standard cervical incision.

The vast majority of the abnormal glands were in eutopic locations (ie where one might expect to find a parathyroid gland), including descended superior and undescended inferior glands found along their normal tract of descent. The most common locations for ectopic glands were intrathyroidal, mediastinal and intrathymic. Although rare, supernumerary glands are of clinical importance because they do represent a significant cause of persistent/recurrent HPT.²⁰ In this series, 10% of the abnormal glands were considered supernumerary. Consequently, if a patient is found to have four normal glands of normal appearance intraoperatively, then it is important to consider the possibility of a supernumerary gland.

Conclusions

Persistent HPT represents a challenging problem that requires careful assessment as well as the availability of all the necessary radiological and intraoperative adjuncts to achieve a favourable outcome. Most patients requiring reoperative parathyroidectomy need additional imaging. Consequently, optimal radiology and careful patient selection allow a cure rate comparable with first time surgery.

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