# Defining failure after parathyroidectomy for primary hyperparathyroidism: case series

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## Abstract

*Objective*: To identify the cause of operative failure in patients who have undergone parathyroid surgery for primary hyperparathyroidism.

*Design*: Retrospective case review.

*Participants*: Patients who had undergone a primary procedure for primary hyperparathyroidism between July 2003 and December 2007. Cases with incomplete post-operative serum calcium data were excluded.

*Main outcome measure*: Operative failure was defined as failure to achieve normalisation of serum adjusted calcium levels post-operatively.

*Results*: A total of 220 primary procedures were conducted over 4.5 years. Data were not available for 16 patients. Thirteen procedures (6.4 per cent) were considered failures, and these cases were individually reviewed and classified according to the reason for failure.

*Conclusion*: Establishing the cause of failure following surgery for primary hyperparathyroidism can be a complex task. In some instances, diagnostic uncertainty remains despite detailed biochemical and radiological assessment. This paper outlines our approach to maximising the cure rate at primary surgery.

**Key words:** Parathyroid Hormone; Primary Hyperparathyroidism; Hypercalcaemia; Parathyroid Adenoma; Parathyroidectomy

## Introduction

Primary hyperparathyroidism is caused by autonomous, hyperfunctioning parathyroid tissue. The condition has a prevalence of approximately 3 per 1000 in the general population and predominantly affects women aged 55–75 years.[1] Parathyroid adenomas and multi-gland hyperplasia account for approximately 85 and 14 per cent of cases, respectively, while parathyroid adenocarcinomas are the underlying aetiology in less than 1 per cent.[2] Parathyroidectomy is the 'gold standard' treatment, and operative success is generally defined as long-term normalisation of the serum calcium level. Recently cited success rates range from 95.5 to 100 per cent for primary procedures.[3-5]

A recent audit of parathyroidectomies performed for primary hyperparathyroidism in our department suggested a low success rate, prompting a more detailed evaluation of the apparent failures. This paper presents these cases and explores the challenges faced in identifying the cause of persistent hypercalcaemia.

## Materials and methods

A retrospective review of medical records was undertaken for all parathyroidectomies performed for primary hyperparathyroidism from July 2003 to December 2007, through the Hull thyroid clinic. The start date was chosen to coincide with the introduction of routine intra-operative parathyroid hormone (PTH) monitoring in our department.

All operations were performed by a single consultant (RJAE), or trainees directly supervised by that consultant.

Minimally invasive parathyroidectomy was undertaken when double imaging, using high definition ultrasound and Technetium (99m Tc) sestamibi scans, demonstrated concordant localisation of a solitary hypersecreting parathyroid gland. A bilateral neck exploration was used in the absence of concordant imaging or when minimally invasive parathyroidectomy failed to locate the gland. Three to three and a half gland excision was undertaken when parathyroid hyperplasia was clinically diagnosed at operation.

Three serum samples were taken for intra-operative PTH monitoring. These were taken immediately prior to skin incision, immediately after the removal of the abnormal parathyroid tissue, and 15 minutes after the second sample. The criterion used to indicate curative excision consisted of a fall in the intra-operative PTH level of 50 per cent or more between the first and last assays.

Histopathology reports and biochemical results were reviewed for all primary procedures. Post-operative PTH levels and serum adjusted calcium levels were measured at the first out-patient follow-up appointment, which took place an average of 5.3 months after surgery (range, one to 40 months). Parathyroid hormone levels of 7–53 pg/ml were considered normal. Operative failure was defined as a persistently elevated serum adjusted calcium level of greater than 2.60 mmol/l (normal range, 2.20–2.60 mmol/l) at post-operative out-patient assessment.

## Results and analysis

In total, 231 parathyroidectomies for primary hyperparathyroidism were performed over the four and a half year period. Of these, 220 were primary procedures and 11 were revision cases. For the purposes of this study, only the primary procedures were analysed. Patient ages ranged from 14 to 88 years (mean, 56.7

years). One hundred and ninety-five (84.4 per cent) patients were female and 36 (15.6 per cent) were male.

### Failures

Out-patient serum calcium levels were available for 92.7 per cent ($n = 204$) of primary case patients. Based on our failure criterion, a total of 13 primary procedures (6.4 per cent) were identified as apparent failures (Table I). A minimally invasive technique was used in one of these cases, while the remaining 12 patients underwent bilateral neck exploration.

### Classification of parathyroidectomy failures

All non-curative parathyroidectomies were categorised according to the histological result into two main groups: (1) no abnormal parathyroid tissue excised (six cases, 46.2 per cent); and (2) abnormal parathyroid tissue excised (seven cases, 53.8 per cent) (Table I). Following a detailed review of medical records, all

TABLE I
PARATHYROIDECTOMY FAILURES: BIOCHEMICAL PARAMETERS AND OUTCOMES

| Case | Age (y) | Sex | Pre-operative | | Intra-operative | | | Post-operative | | | Histology | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Ca | PTH | PTH1 | PTH2 | PTH3 | Ca1* | Ca2† | PTH† | | |
| *Group 1* | | | | | | | | | | | | |
| 1 | 45 | F | 2.71 | 123 | 90 | 75 | 106 | 2.99 | 2.80 | – | Thyroid tissue | Missed solitary adenoma |
| 2 | 42 | F | 3.04 | 238 | – | – | – | – | 3.06 | – | Thyroid tissue & thymic remnant | Missed solitary adenoma |
| 3 | 42 | M | 2.83 | 24 | 42 | 42 | 30 | 2.69 | 2.70 | 48 | Normal parathyroid | Probable missed solitary adenoma |
| 4 | 57 | F | 2.65 | – | – | – | – | 2.37 | 2.69 | 73 | Normal parathyroid | Probable missed solitary adenoma |
| 5 | 23 | M | 2.92 | 85 | – | – | – | 2.84 | 2.97 | 64 | Normal parathyroid | Familial hypercalcaemic hypocalciuria |
| 6 | 39 | F | 2.73 | 53 | – | – | – | 2.60 | 2.70 | – | Normal parathyroid | Familial hypercalcaemic hypocalciuria |
| *Group 2* | | | | | | | | | | | | |
| 7 | 54 | F | 2.91 | 140 | – | – | – | 2.66 | 2.84 | – | Parathyroid adenoma | Missed 2nd & 3rd adenomas |
| 8 | 62 | F | 2.92 | 63 | 72 | 44 | 22 | 2.46 | 2.65 | 10 | Parathyroid adenoma | Probable missed adenoma |
| 9 | 61 | F | 2.56 | – | 91 | 374 | 158 | 2.63 | 2.67 | 95 | Parathyroid adenoma | Probable missed second adenoma |
| 10 | 63 | F | 2.65 | 123 | 97 | 102 | 102 | 2.67 | 2.61 | 96 | Parathyroid hyperplasia | Under-treated multi-gland hyperplasia |
| 11 | 50 | F | 2.67 | 115 | 67 | 88 | 75 | 2.67 | 2.66 | 82 | Parathyroid adenoma & hyperplasia | Under-treated multi-gland hyperplasia |
| 12 | 80 | F | 2.68 | 100 | 165 | 106 | 30 | 2.52 | 2.61 | 108 | Parathyroid hyperplasia | Under-treated multi-gland hyperplasia |
| 13 | 19 | F | 2.77 | 136 | 103 | – | 49 | 2.46 | 2.67 | – | Parathyroid adenoma | Under-treated multi-gland hyperplasia |

Serum adjusted calcium (Ca) concentrations are given as mmol/l; parathyroid hormone (PTH) concentrations are given as pg/ml. Group 1 = no abnormal parathyroid tissue excised; group 2 = abnormal parathyroid tissue excised. *Within 24 h post-parathyroidectomy; †at out-patient follow up. Y = years; PTH1 = 1st PTH assay; PTY2 = 2nd PTH assay; PT3 = 3rd PTH assay; Ca1 = 1st Ca assay; Ca2 = 2nd Ca assay; F = female; M = male; – = data unavailable

failed cases were further classified according to their final outcome (see Table II), and were discussed individually under each diagnostic category.

### Case reviews

*Missed adenomas.* Failure to identify one or more parathyroid adenomas during the initial operation was the confirmed cause of post-operative hypercalcaemia in three patients. In two of these cases, a missed solitary adenoma was found at revision surgery. The first patient (case one) had an adenoma removed following an unsuccessful minimally invasive parathyroidectomy. In the second patient (case two), a superior mediastinal adenoma was identified using double imaging after a failed primary bilateral neck exploration, and this was subsequently removed by video-assisted thoracoscopic surgery. The third patient (case seven) was ultimately found to have a triple adenoma; a bilateral neck exploration was performed initially, yielding a parathyroid adenoma. First and second revision procedures were preceded by single and double imaging, respectively, and demonstrated a solitary lesion in each case. Adenomas were removed in both revision operations. Excision of the final adenoma, lying in the left retro-oesophageal position, was curative.

Missed adenomas were the presumed cause of failure in a further four patients. Failure to find a solitary adenoma was suspected in two of these patients. In both instances, bilateral neck exploration was performed after 24-hour urinary calcium excretion levels proved normal. In one patient (case three), all four glands were identified and an enlarged right superior parathyroid gland was excised, weighing 200 mg; however, this gland was histologically normal. In the second patient (case four), both inferior parathyroid glands appeared enlarged intra-operatively and were removed, while both superior glands looked normal and were left. The two excised glands were reported as normal. In both patients, double imaging was undertaken to investigate post-operative hypercalcaemia. Technetium (99m Tc) sestamibi scanning showed no active uptake of technetium in the neck or mediastinum, and no adenomas were identifiable on ultrasound. The most likely diagnosis in these cases was thought to be missed microadenomas.

A presumed diagnosis of a missed second adenoma was made for two patients who had solitary adenomas excised at primary surgery. One patient (case eight) underwent removal of an adenoma, and the remaining glands were identified and clipped. Borderline hypercalcaemia was observed over a 12-month period during out-patient follow up, and the patient was treated conservatively. The second patient (case nine) underwent bilateral neck exploration, and four glands were successfully identified. An enlarged parathyroid was removed and an adenoma was confirmed. Elevated serum PTH and calcium levels were recorded after surgery. A Technetium (99m Tc) sestamibi scan was performed but did not demonstrate a second adenoma. A missed second adenoma with a false negative scan result was the presumed cause of operative failure.

*Multi-gland hyperplasia.* Four patients who had failed surgery were diagnosed intra-operatively with multi-gland hyperplasia. Two patients (cases 10 and 11) underwent less than three-gland excision as the fourth parathyroid could not be identified. A third patient (case 12) had three glands removed and the remaining parathyroid gland clipped. A fourth patient (case 13), known to have multiple endocrine neoplasia type I, also underwent three-gland excision as the fourth gland could not be identified. In this last patient, double imaging was subsequently carried out for post-operative hypercalcaemia, and demonstrated an intrathyroidal parathyroid. A left thyroid lobectomy was performed; 12 months later, the patient remained normocalcaemic.

*Misdiagnoses.* In the current series, diagnostic error prior to surgery accounted for two (14.3 per cent) failed procedures (cases five and six). Twenty-four-hour urine calcium measurements were undertaken after parathyroidectomy, and confirmed familial hypercalcaemic hypocalciuria in both patients.

### Parathyroid hormone measurements

Intra-operative PTH immunoassays were documented for 68.1 per cent ($n = 139$) of all primary operations. Of the patients receiving curative procedures, intra-operative PTH levels decreased by 50 per cent or more in 125 cases, correctly predicting success, while in six cases the level fell by less than half.

The intra-operative PTH level was measured in 61.5 per cent ($n = 8$) of defined surgical failure patients. In five of these cases, there was a reduction of less than half, correctly indicating failure. In the remaining three cases, the intra-operative PTH level fell by more than 50 per cent, suggesting operative success. Under-treated multiple gland hyperplasia accounted for two of these cases. The third patient was suspected of having a missed adenoma, but did not undergo revision surgery.

Post-operative PTH levels were identified in 60.8 per cent ($n = 124$) of all primary cases. A total of 116 patients received curative surgery and had post-operative PTH levels measured; of these, 44 patients (37.9 per cent) were found to have elevated PTH levels. Of patients receiving non-curative procedures, post-operative PTH samples were identified in eight cases (61.5 per cent).

| TABLE II |
|---|
| CLASSIFICATION OF DIAGNOSTIC OUTCOMES |
| (1) No abnormal parathyroid tissue excised |
| – Missed adenoma (solitary or multiple adenomas) |
| – Under-treated multiple gland hyperplasia |
| – Misdiagnosis |
| (2) Abnormal parathyroid tissue excised |
| – Missed adenoma (multiple adenomas) |
| – Under-treated multiple gland hyperplasia |

In six of these cases, the post-operative hormone levels were raised, while in two the levels were normal.

## Discussion

One would assume, from reading published series of primary parathyroidectomies, that the cause of a failed operation could be identified with relative ease, whether it be a misdiagnosis, missed adenoma or under-treated multiple gland hyperplasia. In contrast, we found that determining the aetiology of such failures was in some cases a more complex task, and in over one-quarter of failed procedures a degree of diagnostic uncertainty remained despite detailed biochemical and radiological assessment.

### Familial hypercalcaemic hypocalciuria

Familial hypercalcaemic hypocalciuria is a rare genetic disorder producing asymptomatic hypercalcaemia. It has an estimated prevalence of 1 in 78 000.[6] However, due to the skewed nature of the patient population referred to the tertiary clinic, most with previously diagnosed hyperparathyroidism, the incidence in this population will be much higher. The condition has an autosomal dominant inheritance with high penetration. It is caused by a mutation in the calcium receptor sensing gene, which is expressed in multiple end-organs but particularly in the parathyroid gland and renal tubule.[7] This abnormality leads to partial resistance of the parathyroid glands and kidneys to the normal effects of extracellular calcium, producing a shift in the set-point for calcium homeostasis. Familial hypercalcaemic hypocalciuria is characterised by mild hypercalcaemia, an inappropriately normal PTH level and hypocalciuria. It is this latter feature which usually helps to distinguish the condition from primary hyperparathyroidism. Urinary calcium levels are normal or elevated in primary hyperparathyroidism, in contrast to the low calcium excretion rate found in familial hypercalcaemic hypocalciuria, and 24-hour urinary calcium measurement provides a fairly reliable method of diagnosis. A calcium:creatinine ratio of less than 0.01 is considered to be more than 80 per cent sensitive and 88 per cent specific for the disease.[7] The condition is considered benign, as affected individuals do not develop bone demineralisation or the renal complications associated with primary hyperparathyroidism, and life expectancy appears to be normal. Treatment involves reassurance and counselling.

It has been suggested that only asymptomatic hypercalcaemic patients should be screened for familial hypercalcaemic hypocalciuria.[8] However, the symptoms associated with hypercalcaemia are common to many other conditions, and in this series alone one patient with familial hypercalcaemic hypocalciuria presented with symptoms suggestive of hypercalcaemia. Reliance on this presented selection criterion for screening would inevitably lead to further cases being missed. We would therefore advocate 24-hour urinary calcium analysis in all patients undergoing parathyroidectomy for primary hyperparathyroidism.

In addition to measuring urinary calcium pre-operatively, we would also recommend testing serum vitamin D levels in all patients with hyperparathyroidism and inappropriately normal serum calcium. If vitamin D levels are below normal or in the lower third of the normal range, then replacement therapy should be instituted. This will either unmask primary hyperparathyroidism or else return the calcium levels to normal in cases of secondary hyperparathyroidism due to hypovitaminosis D. Omission of routine vitamin D testing is likely to increase the number of unnecessary parathyroidectomies performed to treat hyperplasia.

### Missed adenomas

Adenomas were missed in procedures that failed to identify a solitary adenoma, or in cases in which multiple adenomas had not been recognised pre-operatively. In a series of 1112 bilateral neck explorations conducted for primary hyperparathyroidism, Allendorf et al. found that multiple adenomas accounted for 14.1 per cent of cases.[9] This compares to a prevalence of 3.8 per cent published by Carty et al. in a study of 360 patients.[3] Double adenomas make up the vast majority of multi-gland disease, while triple adenomas are rare. In the present series, one case of triple adenoma was confirmed. Similarly, Muira also reported a single case in a series of 115 patients with primary hyperparathyroidism.[10]

In order to minimise the risk of missing adenomas in patients with multi-gland disease, and to avoid negative neck explorations due to intrathoracic adenomas, our experience suggests that, once primary hyperparathyroidism has been confirmed, all patients should undergo pre-operative double imaging, comprising high definition ultrasound and Technetium (99m Tc) sestamibi scanning. When double imaging results are concordant, minimally invasive parathyroidectomy can be performed. In our experience, however, when given the choice, many patients opt for a four-gland exploration in order to avoid the additional hospital attendances required for imaging investigations.

### Multi-gland hyperplasia

Under-treatment of multiple gland hyperplasia with three-gland excision, when a fourth gland appeared clinically normal, resulted in failure to achieve normocalcaemia in three cases. We would therefore advocate treating all patients with clinically diagnosed parathyroid hyperplasia using three and a half gland removal, in order to maximise the chances of achieving long-term normocalcaemia.

### Parathyroid hormone levels

Intra-operative PTH levels are used as a guide to determine whether parathyroid gland excision has been adequate prior to wound closure. A fall of 50–60 per cent in the intra-operative PTH level, comparing the pre-operative baseline to the final assay, is generally

considered a reliable marker of adequate gland excision.[3,11–13] In the presented series, the sensitivity and specificity of intra-operative PTH immunoassay as an indicator of operative success were 95.4 and 62.5 per cent, respectively. This compares with a 92 per cent sensitivity reported by Westerdahl and Bergenfelz in a study of 269 parathyroidectomies followed up for an average of 3.6 years.[11] Failure of intra-operative PTH levels to fall sufficiently following removal of an adenoma should alert the surgeon to the possibility of multiple gland hyperplasia or a missed adenoma.

- **Parathyroid adenomas and hyperplasia account for approximately 99% of all primary hyperparathyroid cases, and parathyroidectomy is the gold standard treatment**
- **In primary hyperparathyroidism, operative success rates in achieving long term normocalcaemia are reported as high as 95–100%, particularly of single gland disease; however, with the inclusion of diagnostic uncertainties, errors and multi-gland disease, seemingly lower success rates are evident**
- **A diagnostic work-up should include double imaging, comprising high definition ultrasound and Technetium sestamibi scans, to assist in identifying ectopic and multiple adenomas**
- **To minimise the risk of unnecessary surgery we also advocate pre-operative serum vitamin D and 24-hour urinary calcium measurements in all patients referred for parathyroidectomy, to exclude hypovitaminosis D and familial hypercalcaemic hypocalciuria respectively**
- **Parathyroid hyperplasia should be treated with a minimum of 3.5 gland removal to maximise the cure rate at primary surgery**
- **Despite detailed biochemical and radiological tests the cause of persistent post-operative hypercalcaemia can be difficult to establish in a minority of patients, and in these cases a multi-disciplinary team approach should be sought**

In contrast, we found post-operative PTH values to be less reliable for detecting operative failure, with a sensitivity of 62.1 per cent and a specificity of 75.0 per cent. The occurrence of elevated post-operative PTH levels following curative surgery is well known, occurring in as many as 48 per cent of parathyroidectomy cases; this phenomenon accounts for the low specificity when using post-operative PTH levels as a screening tool for surgical failure.[3,14] Factors implicated in this biochemical abnormality include high pre-operative PTH levels, advanced age, deficiencies in vitamin D and calcium, and post-operative renal dysfunction.[9,15] Disease recurrence occurs in approximately 5 per cent of such cases.[15] We would suggest waiting at least three months before undertaking a post-surgical review, in order to enable residual parathyroid function to recover and hence more accurately to assess surgical success.

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