Scan-directed mini-incision focused parathyroidectomy: how accurate is accurate enough?

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ABSTRACT

INTRODUCTION Mini-incision focused parathyroidectomy (MI-FP) is advocated as an alternative to bilateral neck exploration (BNE), owing to its reduced morbidity. The site and side of the affected gland is identified preoperatively using a combination of ultrasound and sestamibi scans. However, the acceptable degree of inter-scan concordance required to prompt MI-FP without compromising accuracy is undetermined.

METHODS Accuracy of preoperative imaging was determined both individually and in combination for all parathyroidectomies (2007–2014). A grading system (excellent, good, poor) was devised to describe the interscan concordance, which was validated by the operative and histological findings.

RESULTS Eighty-nine patients (17 male, 68 female) underwent parathyroidectomy (MI-FP 44, BNE 45). The accuracy of scans interpreted individually was 53% for ultrasound and 60% for sestamibi, with no difference according to surgical technique ($P = 0.43$, $P = 1$, respectively). The proportion of interscan concordance was: excellent – 35%, good – 40%, poor 25%. Combined accuracy was 100% for both excellent and good grades but only 13% for those graded poor. Similar rates of normocalcaemia were observed for MI-FP and BNE, while postoperative hypocalcaemia was five times higher in those undergoing BNE.

CONCLUSIONS Reduction in the inter-scan concordance from *excellent* to *good* does not compromise accuracy. MI-FP could be successfully performed in up to 75% of patients – 25% higher than recommended in national guidelines. Focused parathyroidectomy does not compromise surgical and endocrinological outcomes but boasts a far superior complication rate.

KEYWORDS

Focused parathyroidectomy – Primary hyperparathyroidism – Sestamibi – Ultrasound

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Introduction

Bilateral neck exploration (BNE) has been the traditional surgical technique for parathyroidectomy until the turn of the 21st century. Indeed, it is still the technique of choice for surgical treatment of secondary or tertiary hyperparathyroidism, where all parathyroid glands are equally affected. However, a focused approach is increasingly advocated in cases of primary hyperparathyroidism, where the most common pathology is a single-gland adenoma or hyperplasia.¹ The British Association of Endocrine and Thyroid Surgeons (BAETS) guidelines suggest that around 50% of patients will not be suitable for a focused approach, due mainly to discordant scans or coincidental concomitant thyroid disease. Concomitant thyroid pathology requiring surgery can be expected in around 20–30% of patients with primary hyperparathyroidism.^{2–3} This would suggest that, with advancing radiological capabilities, a 70–80% rate of focused parathyroidectomy is not an unreasonable aspiration. Focused

parathyroidectomy is reported to be both efficacious in the long-term and associated with reduced morbidity,^{4–5} while the expected minimum standard for achieving normocalcaemia is greater than 95%.¹ By and large, mini-incision focused parathyroidectomy (MI-FP) is a very safe procedure, which has demonstrated its long-term efficacy (recurrence of 2.5% or less) and reduced adverse-effect profile in the face of persistent scrutiny.^{5,6}

The term ‘focused parathyroidectomy’ is vague and has been used to describe several techniques ranging from unilateral exploration, mini-incision (MI-FP), endoscopic and robotic surgery.^{7–8} Table 1 summarises the differences between the various surgical techniques. Irrespective of the type of focused parathyroidectomy technique, the focused approach is facilitated by the preoperative identification and localisation of the affected parathyroid gland, to both side and site, using radiological imaging. The most commonly used imaging modalities are ultrasound and sestamibi radioisotope scans; the latter can be performed either as a standard

Table 1 Summary of different techniques of parathyroidectomy

Technique	Size (cm)	Incision(s)	Location	Surgical approach
Bilateral neck exploration	7.5–12.5		Collar/neck	Midline through strap muscles
Focused parathyroidectomy:				
Unilateral exploration	5–7.5		Collar/neck	Midline through strap muscles
Mini-incision	2–2.5		Anterior border of sternocleidomastoid	Lateral to strap muscles
Robotic or endoscopic	Single or multiple small incisions totalling 4–6cm		Axillary infraclavicular	
Trans-mammary	Subcutaneous plane is developed superficial to the pectoralis major muscle fascia and the heads of the sternocleidomastoid			

radioisotope scan or in tandem with a single photon emission computed tomography (SPECT) scan. Some patients with concurrent thyroid disease or malignancy may also undergo standard computed tomography (CT) for further imaging of the neck. Historically, the primary function of the sestamibi scan was to demonstrate the presence of ectopic parathyroid tissue, although with improved imaging techniques and reporting, a role for sestamibi scans in localising the affected gland has developed.^{9–11} In some quarters, a negative sestamibi scan is not considered a contraindication for focused parathyroidectomy.¹² However, a key issue of concern is the wide variation of accuracy, due in part to the operator-dependant nature of ultrasound and the complexities of sestamibi scans.¹³ It is well established that when sestamibi and ultrasound scans are reviewed in combination the accuracy is improved substantially and is consistently above 90% when the findings from the two modalities are concordant.^{13–14}

How the preoperative imaging findings might translate into changing practice and improved surgical and endocrinological outcomes is less well understood. Throughout the published literature, there is a wide variation in the definition of ‘combined accuracy’ and in determining the positive predictive value of the scans in combination. In most cases, specificity to both side (left or right) and site (superior or inferior) is considered the gold-standard definition of accuracy. However, the crucial factor that is often absent is the proportional concordance between the scans. For example, it is possible to achieve a high accuracy, nearing 100%, while maintaining a low concordance between the scans, thus eliminating the populations that skew the rate of accuracy. The main surgical challenge remains unchanged; that is, *How to appropriately manage those whose dual-scan concordance is less than perfect?* With this in mind, the acceptable degree of accuracy, according to interscan concordance, remains undetermined. Moreover, appropriate interpretation of accuracy according to concordance holds the key to determining the most appropriate surgical technique (focused parathyroidectomy or BNE) for individual patients.

Methods

A retrospective review was undertaken of all parathyroidectomies performed since MI-FP was commenced at our unit (2007–2014). All patients were considered eligible for MI-FP apart from those who had undergone previous neck surgery. Preoperative imaging modalities and reports were identified for all patients and a clinical decision on the appropriateness for MI-FP was made without using an objective assessment tool. Where possible and considered appropriate, MI-FP was advocated as the primary surgical technique of choice. Radiological, endocrinological, surgical and histopathological outcomes were reviewed and defined accordingly. Statistical analysis was undertaken where appropriate with a *P*-value of <0.05 denoting statistical significance.

Surgical technique

A technique similar to that described by Agarwal⁴, whose results have been widely replicated, was used for all patients.^{15–16} The patient was positioned and prepared in the standard fashion for any thyroid/parathyroid procedure: this included use of a head ring for increased neck extension to maximise exposure of the surgical field with a slight tilt to the contralateral side. A 2cm incision was made over the anterior border of the sternocleidomastoid muscle at the predetermined level according to the likely position of the affected parathyroid gland. Subplatysmal flaps were elevated using sharp and blunt dissection, with dissection continued laterally to the strap muscles and medially to the sternocleidomastoid muscle to reach the posterolateral aspect of the thyroid lobe. The recurrent laryngeal nerve was identified and preserved. Intravenous methylene blue was not administered to assist in localising the affected parathyroid gland. The parathyroid gland was excised, maintaining meticulous haemostasis throughout the procedure. Use of frozen section was determined clinically on a case by case basis where subjective assessment of the gland appearance, weight and anatomical location were deemed unsatisfactory. A standard closure in layers was performed with no drains left in place.

Radiological outcomes and grading system

The accuracy of preoperative imaging was determined both individually and in combination. A three-tiered grading system (excellent, good, poor) was devised to describe the interscan concordance, which was validated by the findings outlined in the operation notes and histopathological reports. The criteria for the grading system were simplicity, objectivity and reproducibility. A fourth tier was considered unhelpful, as it would have increased the risk of a type II statistical error. Scan reports were independently reviewed by two of the authors who were blinded to the surgical technique. Where discrepancies occurred, the senior author provided a third and final opinion. In order to reduce inter- and intra-observer bias ambiguous, vague and noncommittal reports were automatically considered to be poor. Excellent concordance was demonstrated by specificity of both the side (left or right) and site (superior or inferior). Good concordance reflected side and site specificity from one scan but no contradictory findings from the second scan. Poor concordance was defined as nonspecific or inaccurate scan reports or contradictory scans. Equal weighting was given to both imaging modalities in the grading system. Proportional concordance was defined as the concordance according to each of the three classification grades.

Endocrinological, surgical and histopathological outcomes

The BAETS guidelines recommend success rates of 95% and above for achieving normocalcaemia in MI-FP. In addition to this, we reviewed success rates of normocalcaemia within 30 days as well as rates of postoperative hypocalcaemia. All complications and conversions from MI-FP to BNE were reviewed and reported. Histopathological findings and the rate of use of intraoperative frozen section was documented.

Results

Eighty-nine patients, the majority female (17 male, 68 female) underwent parathyroidectomy during the study period. There was a roughly equal division of patients undergoing MI-FP compared with BNE (44 MI-FP, 45 BNE) with a similar mean age in both groups (MI-FP, 58 years; BNE 59 years). The accuracy of scans interpreted individually was 53% for ultrasound ($P = 0.43$, χ^2) and 60% for sestamibi ($P = 1$, χ^2), with no difference according to surgical technique). Table 2 outlines the combined accuracy according to interscan concordance.

The mean preoperative adjusted calcium levels were 2.83 mmol/L and 2.81 mmol/L ($P = 1$, t -test) for MI-FP and BNE, respectively. The mean preoperative parathyroid hormone levels were 85.47 pmol/L and 104.64 pmol/L ($P = 0.59$, t -test) for MI-FP and BNE, respectively. There was no statistical difference according to surgical technique in relation to postoperative normocalcaemia (Table 3). Rates of postoperative normocalcaemia exceeded the minimum standard according to the BAETS guidelines, with 100% success in the MI-FP group.

Postoperative complications were higher in the BNE group, with hypocalcaemia the main source of morbidity

Table 2 Combined scan accuracy and proportional concordance according to grade of concordance

	Grade of concordance		
	Excellent	Good	Poor
Proportional concordance (%)	35	40	25
Accuracy (%)	100	100	13

Table 3 Endocrinological outcomes

Normocalcaemia	Outcomes (%)		
	MI-FP	BNE	<i>P</i> value
Within 30 days	91	93	0.71 ^a
Total	100	98	1 ^b

^a χ^2 ; ^b Fisher's exact

(one patient in the MI-FP group and 5 in the BNE group). In the MI-FP group, bleeding occurred in one patient (drop in haemoglobin of 2 g/dl) and one had a small pneumothorax, which was treated conservatively. One patient in the BNE group developed a postoperative chest infection. Only one patient undergoing MI-FP required conversion to full BNE. Rates of frozen section were 26/44 (MI-FP) and 29/45 (BNE), with virtually identical pathological findings (Table 4).

Discussion

This study demonstrates that the accuracy of preoperative imaging is only as important as the represented proportional concordance between the scans. When a good grading of concordance is considered the minimum acceptable standard, the proportion of patients with 100% accuracy increases from 35% to 75%. This suggests that the proportion of patients eligible for focused parathyroidectomy could be as high as 75% – a significant increase (50% relative, 25% absolute) above national guidelines. Rigid adherence to a standard of concordance consistent with the excellent grading is likely to unnecessarily exclude a substantial volume of patients from focused parathyroidectomy and expose them to excess morbidity. This is particularly pertinent for an increasingly elderly population, with soft symptoms, who stand to benefit most from a surgical procedure with lower rates of morbidity. The proportion of patients with truly symptomatic primary hyperparathyroidism (classic symptoms of urinary calculi, bone pain or fracture, hypercalcaemic crisis or neuropsychiatric symptoms) is in the region of 20%.^{17–18} Indeed the soft symptomatic nature of primary hyperparathyroidism is such that almost two-thirds of this cohort remains in the community untreated.¹⁹ It is this cohort of patients that may be unaware of the potential

Table 4 Pathological outcomes

	MI-FP (n)	BNE (n)
Single gland	42	37
Multi-gland	0	5
Malignant:		
Papillary thyroid	1	1
Parathyroid	0	1
Tissue unidentifiable	1	0
Inconclusive	0	1
Frozen section	26/44	29/45

quality of life improvements gained from focused parathyroidectomy for soft symptomatic primary hyperparathyroidism. They are also less likely to be concerned with the cosmetic appearance of a 2cm scar on the lateral part of the neck.

Our grading system was similar but not identical to that used by Philippon *et al* in an analysis of discordant scans of primary hyperparathyroidism patients in Marseille, France.²⁰ They also described a three-group approach where group 1 (positive concordant imaging) and group 3 (negative imaging) corresponded to our excellent and poor grades, respectively. However, the criteria for Philippon *et al*'s second group were slightly more relaxed, whereby patients with 'only one positive image or both positive but with different results' was considered acceptable.²⁰ However, this was supplemented by their use of intraoperative parathyroid hormone (IOPTH) measurement. In our study, we adopted a more stringent classification criteria (where no contradictory findings were considered acceptable) in order to robustly defend our validation in the absence of routine IOPTH measurement. In both studies, the same ultrasound and sestamibi scan combination was used, while site and side specificity of the affected gland were absolute criteria for positive radiological reporting. Similar results were experienced by the French group: 70% of patients with primary hyperparathyroidism would have been eligible for focused parathyroidectomy. In this instance, a relative increase of 43% of patients previously considered to have discordant scans may have undergone successful focused parathyroidectomy. These results are comparable to those reported in our study (50% relative increase) while our conclusions and use of our classification system are further supported by Kunstman *et al*.²¹

IOPTH measurement is considered by some to be an invaluable adjunct and a prerequisite for demonstrating successful focused parathyroidectomy. Its role is controversial and it has as many critics as there are advocates.²² When combined with preoperative radiological localisation, sensitivity rates of 100% are achievable and can lead to cure rates of 98.5%.^{23–24} Miller *et al* concluded that focused parathyroidectomy (with IOPTH) could be performed successfully in 78% of cases. Focused parathyroidectomy without IOPTH

has been demonstrated to be safe and successful.²⁵ Reliable access to reproducible IOPTH monitoring is not consistent across the country and is dependent upon the particular assay technique used and the competencies and resources in place at the laboratory. Such resources are predominantly focused in tertiary endocrine surgery units and not always available in district general hospitals, where a significant proportion of endocrine surgery is still performed. Timeliness of the IOPTH measurement (which can be up to 1 hour, or longer if the neck is reopened) is also worth considering, given the greater constraints on financial resources in the healthcare sector. The much improved sensitivity of radiological imaging in recent years means that a further focused parathyroidectomy to remove a double adenoma is not an unreasonable treatment option compared with full bilateral neck exploration. While multi-gland disease may occur in up to 16% of the population with primary hyperparathyroidism,²⁶ these risks would ordinarily be explained to all patients undergoing focused parathyroidectomy. One major advantage of this study is that the outcome of the grading system is not reliant on access to IOPTH and its strength lies in clarifying the clinical conundrum of managing patients with discordant scans in a simple, reliable and non-invasive manner.

One patient in our series was reported to have undergone full conversion to BNE. In this case, a hot spot behind the right thyroid was reported by the sestamibi scan, with a concordant lesion seen on ultrasound. Upon the initial focused exploration, no abnormal parathyroid gland was seen, however a thyroid nodule was identified on the right. A full BNE was performed, which did not reveal the affected parathyroid gland. Given the negative neck exploration, the thyroid nodule was excised, with histological examination demonstrating papillary thyroid cancer. The original sestamibi images were independently reviewed again by a second radiologist and on this occasion ectopic parathyroid tissue was demonstrated in the mediastinum. Despite the radiological images being reviewed at the time of surgery, the full images were not available to the surgeon and the lower part of the images, which demonstrated the ectopic parathyroid gland, were excluded. This was explained by a different configuration of the computer hardware used in the radiology department from the remainder of the hospital.

Two other patients were also reported to have malignancy – both were reviewed at the thyroid cancer multi-disciplinary team meeting and a second opinion of the histology was sought. The first case was reported to be in keeping with papillary thyroid cancer and the patient underwent subsequent right hemi-thyroidectomy 2 months after the initial focused procedure. He was followed up according to the local cancer protocol. The second patient had primary parathyroid carcinoma, which was confirmed by second histological opinion from the regional cancer centre. In this instance, further neck-clearance surgery was not performed, owing to the patient's comorbidities and high anaesthetic risk. Postoperatively, all blood values normalised and interval follow-up CT scans did not show any recurrent malignant disease. Further to this, histological findings from one other patient was inconclusive, but she experienced a

normalisation of her calcium levels postoperatively and was managed as a standard parathyroidectomy for single-gland disease.

Pneumothorax is an unusual complication during parathyroidectomy. In this instance, a focused right inferior parathyroidectomy was performed. A pre-operative magnetic resonance scan was required in addition to ultrasound and sestamibi because identification of the affected gland was difficult. A difficult operative procedure was anticipated. At the time of surgery, there was a breach of the right pleura with no air leak and no respiratory or ventilator problems while under general anaesthesia. Postoperative chest x-ray demonstrated pneumomediastinum, but no pneumothorax. Clinically, the patient complained only of mild pleuritic chest pain, and had mild surgical emphysema on the right side of the neck but no evidence of respiratory compromise. This complication was managed conservatively and, following a satisfactory repeat chest x-ray the next day, she was discharged on the second postoperative day.

One disadvantage of MI-FP via the lateral approach is the ability to accurately determine the appropriate craniocaudal level of the incision. This is not an issue in unilateral exploration as the larger (5–7cm) cervicotomy scar allows full access to the side of the neck in question, albeit with the associated morbidity alluded to earlier. While the preoperative imaging, in particular ultrasound, can provide some degree of correlation with surface anatomy, the positions of the patient on the operating table and in the radiology suite are different, resulting in a varied surface anatomical landmark. To overcome this, either the surgeon requires training in ultrasound in order to repeat the process intraoperatively²⁷ or a predetermined and jointly agreed reporting protocol is required, with mention of anatomical relationships to specific surface anatomy landmarks (e.g. sternocleidomastoid, midline, or clavicle). A different approach would be for the patient to undergo preoperative wire-guided localisation in a similar manner to breast surgery for small ductal carcinoma in situ.^{28–29} However, the additional resources, time and skill level required to perform this with a satisfactory degree of accuracy may negate the very principals of MI-FP.

Arguably, the greatest advantage of MI-FP over BNE is the combined attributes of equal efficacy with significantly lower complications. Postoperative hypocalcaemia was much higher in the BNE group despite the virtually identical histological findings of single gland disease. While bleeding and infection are recognised complications, pneumothorax is infrequently associated with this procedure.

Conclusions

MI-FP is an established procedure with an efficacy comparable to BNE and a favourable complication rate. Even in the presence of multi-gland disease, repeat focused parathyroidectomy may be preferable to BNE when improved radiological techniques and reporting are employed. Focused parathyroidectomy could benefit many more patients than at present if the preoperative imaging is interpreted in the manner outlined by this study. This study provides an

alternative and reliable method of treating patients with primary hyperparathyroidism with discordant scans, and validates work previously undertaken in this area.

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