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ORIGINAL SCIENTIFIC REPORT

Long-term Cure of Primary Hyperparathyroidism After Scan-Directed Parathyroidectomy: Outcomes From A UK Endocrine Surgery Unit

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Abstract

Background Two-decades ago, the advent of sestamibi scintigraphy led to an enthusiastic acceptance of minimally invasive parathyroidectomy (MIP) in most surgical centres. More recently, concerns have been raised about the efficacy of limited neck exploration and some surgeons proposed bilateral neck exploration to be (once again) the gold standard operation for primary hyperparathyroidism in 2020s.

Methods A departmental database was used to identify patients who had MIP after concordant dual localisation with sestamibi scintigraphy and ultrasound scans. Long-term follow-up data were obtained from electronic patient records to ascertain any further treatment for recurrent disease and confirm most recent biochemical status. Patients with negative localisation scans and those with familial disease were excluded from analysis.

Results Between June 2001 and August 2014 a total of 404 patients (108 M:296F, median age 63 years, range 17–90 years) underwent MIP and had normalisation of calcium in first 6 weeks after the operation. Information on electronic patient records were missing in 14 patients; therefore, data on 390 patients were analysed. During median follow-up of 78 months (IQR: 21.25–111.75 months), 375 patients had normocalcaemia (2.36 mmol/L, IQR: 2.29–2.44 mmol/L) at a median 75 months, (IQR: 20–118 months) after their operation. Overall, 15 (3.85%) patients had biochemical evidence of recurrent disease (2.70 mmol/L IQR: 2.63–2.75 mmol/L) at 92 months (Range: 6–196) after initial operation. Of these, 5 (1.28%) patients underwent a second parathyroid procedure.

Conclusion Recurrence after scan-directed unilateral neck exploration occurred in 4% of patients after a long disease-free interval. Only one patient had recurrent disease within 1-year of primary surgery. The data suggest that bilateral neck exploration at the time of initial operation, in this selected cohort, is unlikely to have uncovered multi-gland disease and prevent disease recurrence. Focused parathyroidectomy in patients with convincing localisation studies should continue.

Introduction

Over the last few decades, primary hyperparathyroidism (PHPT) has become a common clinical condition that typically presents asymptomatically and is diagnosed biochemically. Although selection criteria for referral for surgical cure continue to be debated, PHPT is a surgically reversible disease with parathyroidectomy. If not treated, it is likely to progress to end organ damage and to impact on

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quality of life through a multitude of neurocognitive symptoms.

In the 1990s, standard bilateral neck exploration (BNE) without preoperative localisation studies was expected to have an approximate cure rate of 95% [1–3], the commonest causes for failure to cure patients being ectopic located glands, failure to recognised multiglandular disease, failure to localise the gland and regrowth of an incompletely resected gland [4]. Evolvement in radiological imaging, striving to reduce postoperative morbidity, patient demand for minimal access surgery and a drive for economical efficiency have led to a shift of the operative strategy away from a BNE to a focused scan-directed approach—the minimally invasive parathyroidectomy (MIP). Numerous studies showed MIP did not have reported inferior cure rates to the traditional BNE [5]. Furthermore, other adjuncts to assess functional status such as intraoperative PTH measurement [6] and gamma probes [7] were also utilised by some to reduce the risk of missed MGD but with an additional financial cost.

Recently, over the preceding decade there has been a perceived gradual move away from MIP with the "pendulum" swinging back towards BNE, primarily due to the concerns of inferior long-term recurrence rates of MIP [8–10].

Starker et al. reported that after a targeted parathyroidectomy, if proceeded to a BNE 25% of patients would have another adenoma, which provided evidence and supported against MIP due to missed multiglandular disease [11]. However, McGill et al. [8] found no difference in cure rate comparing BNE and focused parathyroidectomy suggesting that the other adenoma is non-functional and did not require excision, providing an argument against BNE at time of the indexed procedure.

Remarkably, analysis of data on over 13,000 parathyroidectomy recorded on the UK Registry of Endocrine and Thyroid Surgery (UKRETS) between 2010 and 2015 [12] has shown that 15% of patients whom had concordant nuclear medicine and ultrasound imaging went onto to have non-targeted surgery [12]. Moreover, the audit shows there is a diverse spectrum of operative approaches within high/median volume surgeons (> 50 parathyroidectomy per year). On one end of the scale are many performing MIP and on other end many performing BNE-only in first time surgery. Such contemporary national findings corroborate that there is an increase tendency towards abandoning scan-directed parathyroidectomy.

Our unit adopted in the early 2000s a scan-directed targeted approach without intra operative parathyroid hormone analysis for patients undergoing first time surgery for PHPT and favourable short-term outcomes in the first 200 patients have already been published [13]. The aim of this study is to examine recurrence outcomes during long-term follow-up so that an informed decision could be made on whether or not to continue to utilise this approach.

Methods

Patient cohort

A retrospective cohort study of consecutive patients undergoing scan-directed parathyroidectomy was undertaken as part of an institutional audit of outcomes after endocrine surgery.

Patients operated between June 2001 and August 2014 were identified using a departmental database of parathyroid surgery. Those with known familial disease, secondary, tertiary, or re-operative cases were excluded from analysis. As were any patients that underwent a concomitant thyroid operation or thoracic procedure to remove an ectopic mediastinal adenoma.

Persistent disease was defined as elevated adjusted calcium within 6 months of the initial operation. Recurrence was defined as an elevated adjusted calcium any time after 6 months postoperatively, with calcium being greater than our laboratory's upper reference limit of normal (2.50 mmol/L). Simultaneous PTH levels were obtained at the surgeon's preference.

Surgical management

All patients underwent preoperative localization with 99mTc-labelled sestamibi imaging and ultrasonography of the neck. Patients underwent MIP when the two localization studies were concordant.

Sestamibi scans were performed using the single-agent washout technique. Patients were given 600 MBq 99mTc-labelled sestamibi. Single frontal planar images were obtained at 10 min and 2 h after isotope administration. Single-photon emission tomography images were obtained at 2 h. Patients were imaged using a Sopha© DST-XL γ camera (General Electric; Paris, France) with a low-energy, high-resolution parallel collimator and pictures were obtained with a 256 × 256 matrix. Ultrasonography was performed by a single experienced operator using a small-footprint high-resolution 15-MHz linear array probe (Sequoia^{TM}; Accuson, Mountain View, California, USA).

Laryngeal mask general anaesthesia with propofol and a superficial cervical block on the side of the localized adenoma were employed.

All operations were undertaken by or under the supervision of two consultant General and Endocrine surgeons, Mr Greg Saddler and Mr Radu Mihai. A 20-mm transverse incision was made in a skin crease directly over the localized parathyroid gland, along the medial border of the

sternomastoid muscle [14]. The sternomastoid muscle was mobilized laterally and the strap muscles medially to reveal the lateral margin of the thyroid gland. The parathyroid adenoma was then identified and dissected out; ioPTH measurements or frozen-section analysis were not performed.

All patients were considered for discharge on the day of surgery, or the following morning if surgery was performed in the afternoon. Calcium tablets were provided to be taken when needed and patients were given instructions on how to identify the symptoms of hypocalcaemia.

Statistical analysis

Categorical data were explored using the Chi-squared test and continuous variables compared using Mann–Whitney test. Differences were considered to be statistically significant when the P value was less than 0.05. Cumulative survival was calculated according to the method of Kaplan and Meier. Data analyses were performed with the Statistical Package for Social Sciences (SPSS) version 23 (SPSS, Chicago, IL, USA).

Results

A total of 404 patients had concordant preoperative localisation imaging and received a scan directed targeted parathyroidectomy between June 2001 and August 2014. Fourteen patients were excluded from analysis due to missing electronic patient records; therefore, 390 patients compiled the final cohort for analysis (Fig. 1).

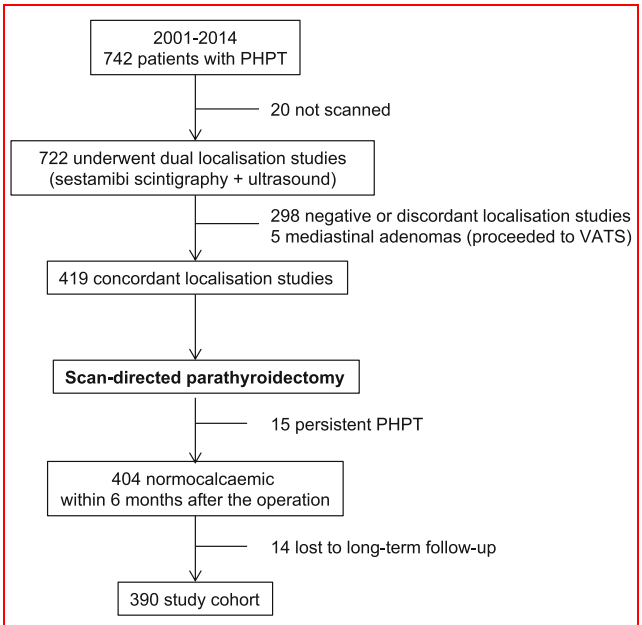

Fig. 1 Flowchart of patient cohort

The overall median follow-up time for the cohort was 78 months (IQR: 21–112 months). During this period, 15 (3.85%) patients had disease recurrence. No patients had treatment for permanent hypocalcaemia. Some 254 (65.13%) patients had a simultaneous postoperative serum PTH values recorded.

Table 1 presents the patient demographics of the cohort related to recurrence. The group with recurrent disease were younger, had a lower median preoperative adjusted calcium and PTH compared to the group with no recurrence although this did not reach statistical significance. The gland weight was lighter and the size was smaller in the recurrent cohort but did not reach statistical significance. There were no patients with normocalcaemic or normohormonal hyperparathyroidism in the cohort.

The group with recurrence had a longer median follow up time of 22.40 months, $p = 0.045$. The overall cumulative risk of normocalcaemia at 1, 5 and 10 years was 99.68% (CI: 98.59%; 1.00%), 98.95% (CI: 97.73%; 100%) and 91.56% (CI: 86.86%; 96.26%), respectively. Only one patient had persistent disease with the majority of the remaining patients having recurrences after 5 years. Figure 2 shows normocalcamia rate over time for the entire cohort. During the follow up time 60 (15.38%) patients had died after a median follow up time of 86 months (IQR 40–120 months).

The outcomes of patients that had recurrence are shown in Fig. 3. There were 15 patients that had not been cured from primary surgery. Of these 8 patients did not undergo a further surgical procedure to achieve cure. The reasons were: 5 due to patient choice and 3 due to metastatic disease (breast, ovarian, and lung). It is unknown if a bilateral exploration at the time of primary surgery would have prevented disease recurrence in this contemporary subset of patients. However, the failure did not impact on our service with further investigations or operations.

Five patients went on to have further procedures and were cured at last follow up. Of these, 2 had a parathyroid adenoma on the same localised side as the primary surgery, 1 had a adenoma on the contralateral side, 1 had regrowth of a previously excised parathyroid adenoma, the remaining patient had 2 further cervical explorations after having a thyroid nodule excised on the primary surgery before the adenoma was found on the localised side. For the patients that had recurrences and were cured with further surgery, a bilateral neck exploration would have potentially prevented three recurrences (one adenoma on contralateral side and two adenoma on ipsilateral side).

Of the final two patients that remained hypercalcaemic, one was diagnosed with MEN1 and underwent a subtotal parathyroidectomy and the final patient had three further

Table 1 Demographics, pre and post operative biochemistry, histopathology and cure for patients undergoing scan directed parathyroidectomy

	Recurrence *n = 15*	No recurrence *n = 375*	*p*
Female/Male	14/1	270/105	0.055
Age (y) (IQR)	60.5 (48.8–73.0)	62 (53.2–74.6)	0.233
Pre Op A.Ca (mmol/L)	2.83 (2.71–2.99)	2.88 (2.75–3.03)	0.173
Pre Op PTH (pmol/l)	14.25 (10.90–25.90)	14.9 (10.10–18.90)	0.298
Histology			
Gland size (mm)	21 (17.25–26.25)	18 (14–23.50)	0.10
Weight (mg)	890 (367–1075)	1000 (510–1800)	0.12
Post Op A.Ca (mmol/L)	2.70 (2.63 -2.75)	2.36 (2.29–2.44)	
Post Op PTH (pmol/l)	14.9 (12.62–17.30)	4.9 (3.70–7.65)	0.00065
Follow up time (months)	97.26 (71–118)	74.86 (21–115)	0.045
Time to recurrence (months)	92 (6–196)		

Numbers in parentheses are 25th and 75th percentiles

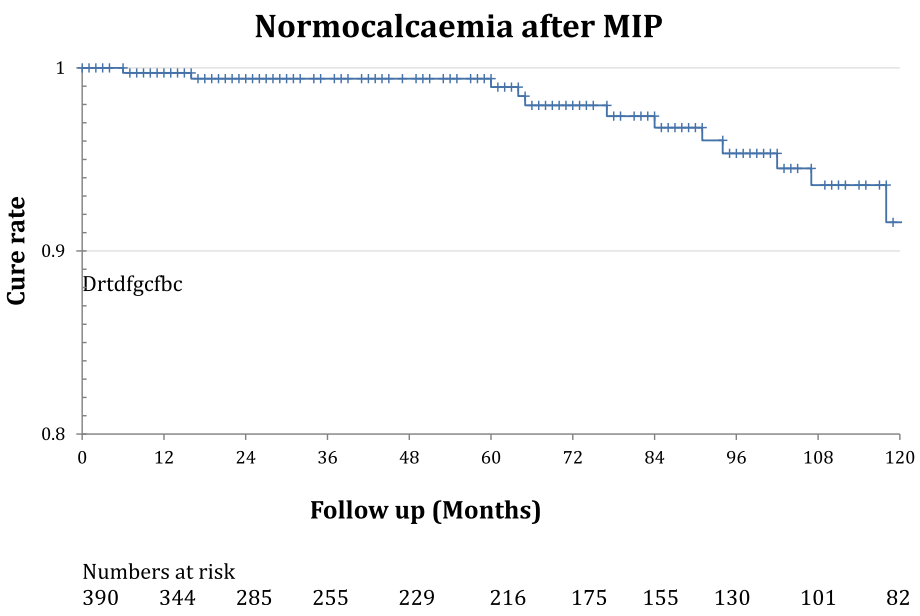

Fig. 2 Risk of recurrence after MIP

neck explorations with four pathological parathyroid glands excised but still remained with persistent disease.

Discussion

This study reports long-term results after scan directed parathyroidectomy, with 96% of a large cohort of patients remaining normocalcaemic during a median follow up time of 78 months.

Of those that did have recurrent disease, all but one were identified 5 years after undergoing primary surgery. Only one patient had a recurrence within 6 months of primary surgery with the reason for failure uncertain. This was a 73-year-old female who did not wish to have any further surgery or investigation. Furthermore, only 3 patients would have been cured if they had undergone a successful bilateral neck exploration at the indexed procedure (two adenoma on contralateral side and one ipsilateral adenoma). Four of the reoperated patients would not have been cured even if they underwent a BNE as the indexed procedure, as technical issues were the cause of failing rather than missed MGD (regrowth of gland, missed gland for thyroid nodule, asynchronous disease in MEN1 and one patient who we do not have a cause of failure). Assuming that BNE has a cure rate of 95%, exposing the entire cohort

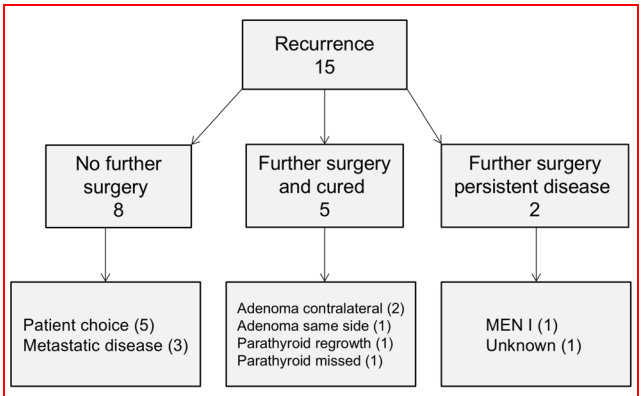

Fig. 3 Outcomes of patients with recurrent disease

to BNE would not have significantly impacted on our long-term cure rate and as such scan directed parathyroidectomy has a role in a scan-localised cohort of patients.

Our long-term recurrence rates are comparable to those reported within the UKRETS for persistent hypercalcaemia (6 months follow up) for first time-targeted surgery which is 4% [15].

The results of our study are in keeping with other studies investigating long-term normocalcaemia with MIP. Thier et al. from Lund, Sweden reported a cohort of 292 patients with a median follow up of 5 years with a rate of 1.1% persistent disease [16]. In contrast to our study they used IOPTH and also incorporated patients who did not have 2 positive preoperative localisation tests, which differs from our cohort. Ishii et al., in a systematic review of cure and recurrence following MIP reported in 5282 patients, mean recurrence and cure rates of 1.6 and 96.9%, respectively, with a mean follow up of 33 months which is similar to our experience but with a shorter follow up time [17]. Interestingly, they found recurrence rates were lower in patients who did not have IOPTH, 0.2 vs. 1.5%, $p < 0.001$. Such results were most likely achieved due to the stern patient selection and utilising MIP for double concordant preoperative imaging. This supports our findings and outcomes of others who perform MIP without IOPTH. Norlen et al. from Sydney, Australia, who had longer patient follow up, reported in a multicentre retrospective study that the recurrence rate at 5 years was similar in an intention to treat analysis comparing focused parathyroidectomy (2.7%) vs. BNE (1.7%) and although there was a trend to a higher recurrence rate at 10 years in the group who had MIP, this was not statistically significant [18]. More recently, one of the units in the Australian multicentre study showed a persistent/reoperation rate of 2.2% with a median follow up of 44 months, without IOPTH, with no difference between patients that underwent bilateral exploration vs. focused parathyroidectomy [19]. Implying patient selection by a experienced multidisciplinary unit for MIP can achieve equivalent outcomes to BNE.

Previous reports have shown concern with inferior long-term outcomes of MIP compared with excellent cure rates from BNE and have lead some to abandon MIP [9, 20, 21]. However, there has correspondingly been reservations abandoning MIP [22]. Notably, the results from the largest experience derive from an extremely specialist unit with a yearly surgeon volume (> 1000 parathyoidectomies) that is not achieved in the UK by any member units in BAETS [12]. Additionally, several meta-analyses have reported that MIP does not have statistically significantly inferior persistent and recurrence rates compared to BNE. Ospina et al. showed the cure rate for MIP was 97% (95% CI 96–98%) compared with 98% (95% CI 97–98%) for BNE, $p = 0.25$ [23]. More recently, Jinih et al. comparing focused parathyroidectomy against bilateral exploration found the persistence disease rate was 2.27 vs. 2.39%, OR 0.89 (95% CI 0.58–1.35), $p = 0.58$ and for recurrence 1.25 vs. 0.79%, OR 1.08 (95% CI 0.59–2.00), $p = 0.15$ [24].

We do not routinely use frozen section in parathyroid surgery at our institution. This is due to the fact that it is a time consuming and labour intensive procedure that does not reveal additional information about parathyroid disease. Indeed, frozen sections can differentiate between parathyroid tissue and lymph node/thyroid tissue and would have prevented just one patient in our cohort from having thyroid tissue excised and therefore does not add value in our scan directed cohort. IOPTH could have theoretically prevented 4 out of the 5 patients who underwent a reoperation and were cured from having a second procedure. This is a modest 1.02% of patients of the scan directed cohort and so we cannot justify its routine use as the estimated running costs of routine practice is likely to be greater than the cost of reoperation of 4 patients over the study period which is in keeping with the findings by Norlen et al. [18].

Our study adds to the literature as with the meta-analysis by Jinih et al. there was heterogeneity between length of follow up and over 80% of the studies comprised patients that had functional assessment with IOPTH. As we did not use IOPTH there were no patients that were excluded from analysis that would have been converted to a BNE if it had been utilised and the test positive. Additionally, the meta-analysis by Ospina et al. study included patients that also underwent radio guided/gamma probe surgery, video-assisted parathyroidectomy, and endoscopically assisted approach that our cohort did not.

We acknowledge that unfortunately some patients do have recurrent disease, which occurs several years after surgery. The challenge remains in which patients to follow up for an extended period of time when the majority of patients are cured, extended follow up of all could incur

cost and overburden in surgical outpatient clinics and cause patient inconvenience. Risk factors for recurrent disease after MIP have been reported as: age > 65, raised calcium and (≥ 9.8 mg/dl), raised PTH, and the addition of at least 1 preoperative imaging study that conflicted with the operative findings [25, 26]. Within our cohort of double localised patients we were unable to validate these parameters to predict recurrent disease.

This study has several limitations, which are inherent with all single centre retrospective studies. Nonetheless, the data does represent a high volume UK centre with a consistent approach to a selected cohort of patients undergoing parathyroidectomy with long-term follow-up data. Not all of the patients had PTH measurement on follow up initially at the start of the study, however there is no consensus on PTH measurements at follow up after 6 months in other centres [17]. Furthermore, the laboratory values for calcium and analysis methods did not change over the time period with the definition of recurrence remaining consistent through the study period adding strength to our study.

In conclusion our experience of scan directed parathyroidectomy supports and validates the surgical strategy to continue to offer patients that have preoperative localisation, a scan-targeted operation in a UK regional endocrine unit with low and acceptable long-term recurrence rates.

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