RESEARCH ARTICLE

Impact of concurrent thyroid pathology on surgical intervention for primary hyperparathyroidism

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OBJECTIVES: Minimally-Invasive Parathyroidectomy (MIP) is the gold standard treatment of primary hyperparathyroidism in single-gland disease with adequate pre-operative localization. The study aim was to evaluate the effect of concomitant thyroid pathology on the accuracy of pre-operative localization for primary hyperparathyroidism and impact on the surgical approach.

METHODS: A retrospective cohort analysis of patients undergoing surgical intervention for parathyroid disease in a tertiary referral center from 1999 to June 2014 was conducted.

RESULTS: Of 429 parathyroidectomies performed on 424 patients, coexistent thyroid pathology was identified in 68 patients (16%). The sensitivity of pre-operative localization of parathyroid pathology in these patients was considerably lower than in patients without concurrent thyroid disease: ultrasonography 55% vs 63%, 99mTc-sestamibi scintigraphy 50% vs 60% and CT 47% vs 49%. Single-gland disease was present in 58 patients (85%), but correctly identified on pre-operative imaging in only 43%. Of these 58 patients, 45 (66%) required Bilateral Neck Exploration (BNE), with MIP in 23 (34%) with a conversion rate of 13%. All conversions resulted from intra-operative identification of thyroid disease. Of the remaining open procedures, 40 (88%) were conducted with simultaneous thyroid lobectomy/total thyroidectomy, 2 (4%) due to multi-nodular goitre, and 3 to thyroiditis and thyroid nodules/cysts. The biochemical cure rate was 100%. In 84 months median follow-up, no patient experienced persistent or recurrent hypercalcemia, or required re-intervention.

CONCLUSION: Concurrent thyroid pathology reduces the sensitivity of pre-operative localization of parathyroid pathology and results in higher rates of open parathyroidectomy in single-gland disease.

Key Words: *Parathyroid; Thyroid; Localization; Radioguided; ioPTH; Minimally-invasive parathyroidectomy*

Abbreviations: ioPTH: Intra-Operative Parathyroid Hormone; PHPT: Primary Hyperparathyroidism

Hyperparathyroidism refers to the clinical condition produced by the excessive production of Parathyroid Hormone (PTH) by one or more of the parathyroid glands. The effect of elevated PTH is a hypercalcemic state, that if left untreated, results in a range of patient symptoms and long term sequelae, ranging from constipation and depression to renal stones and osteoporosis.

Surgery remains the only curative therapy for Primary Hyperparathyroidism (PHPT) [1]. Traditionally, this entailed a bilateral neck exploration of all four parathyroid glands to identify the source of pathology. With single-gland adenoma representing the primary etiology of PHPT however, there has been a move away from this exploratory approach in favor of targeted Minimally Invasive Parathyroidectomy (MIP) [2]. To enable this shift in practice, pre-operative localization and intra-operative adjuncts are increasingly relied upon to accurately localize parathyroid pathology, to inform surgical strategy and to confirm excision of the pathologic gland.

Currently, the use of ultrasonography in conjunction with ^{99m}Tc-Sestamibi scintigraphy (^{99m}Tc-sestamibi) is advised for optimal pre-operative localization of parathyroid pathology [3-5]. In cases of equivocal ultrasound and ^{99m}Tc-sestamibi, suspected ectopic parathyroid or previous parathyroid surgery, 4-dimensional computerized tomography (4D-CT) or Magnetic Resonance Imaging (MRI) are advocated [6,7]. Intra-operatively, the use of multiple adjuncts for parathyroid localization is reported in the literature, including video-assistance, radio-guidance, frozen section and intra-operative PTH monitoring [8-11].

The reported incidence of concomitant thyroid pathology in PHPT is highly variable, ranging from 17-84% [12-16]. This co-existent pathology may complicate the management of PHPT by negatively impacting the efficacy of pre-operative localization and in certain cases obviate the potential for minimally invasive surgery due to the requirement of synchronous thyroid intervention [3,12,17-20].

The goal of this study was to determine the frequency of concomitant thyroid pathology in a consecutive series of patients presenting for operative management of PHPT in a single tertiary referral Centre over a 15-year period. Further to this, the impact of this concomitant thyroid disease on the surgical management of PHPT was assessed, including the accuracy of pre-operative imaging techniques, intra-operative adjuncts employed, surgical intervention, pathology identified and rate of biochemical cure.

METHODS

A retrospective cohort analysis of all patients undergoing surgical intervention for parathyroid disease in a tertiary referral Centre from January 1999 to June 2014 was conducted. Patients undergoing Para thyroidectomy were identified by analyzing theatre logbooks and consultant operating lists. Further data regarding individual patient radiology, biochemistry and histopathology were obtained by examining hospital imaging and laboratory systems, Picture Archiving and Communication System (PACS MediWeb) and Patient Administration System (PAS) respectively.

All procedures were conducted by one of two Consultant General and Endocrine surgeons. Patients were predominantly referred by endocrinologists to the out-patients' department. Some were referred to after radiological investigations were performed with an identified pathological gland. Other patients were reviewed primarily and were referred for the standard pre-operative workup of ultrasonography and ^{99m}Tc-sestamibi, with measurement of PTH and corrected calcium. When findings were inconclusive either a CT (+/- SPECT) or MRI were arranged

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for further investigation. All patients were discussed at the multi-disciplinary team meeting to develop a pre-operative management strategy.

As cases were identified retrospectively, all patients were known to have parathyroid disease. When analyzing the sensitivity and specificity of pre-operative localization, Table 1 outlines the potential findings. As all patients were known to have the parathyroid disease, there were no true negative findings, precluding the calculation of specificity.

TABLE 1
Sensitivity and specificity of pre-operative localization

Finding	Meaning
True positive	Identification and localisation of the pathological parathyroid gland(s) where the disease is present
False positive	Identification and localisation of the pathological parathyroid gland(s) where no disease is present
True negative	Identification and localisation of the healthy parathyroid gland(s) where no disease is present
False negative	Identification and localisation of the healthy parathyroid gland(s) where the disease is present
Inconclusive	Unable to comment on the appearance of the parathyroid gland due to the presence of thyroid disease

When analyzing operative cure rate, patient corrected calcium level was utilized. This was calculated using the following formula:

$$\text{Corrected Calcium (mmol/L)} = \text{Measured Calcium (mmol/L)} + 0.2 \times (40 - \text{measured albumin(g/L)})$$

All patient data was retained in an anonymized fashion on a Microsoft Excel database and data analysis conducted using MiniTab software (v17).

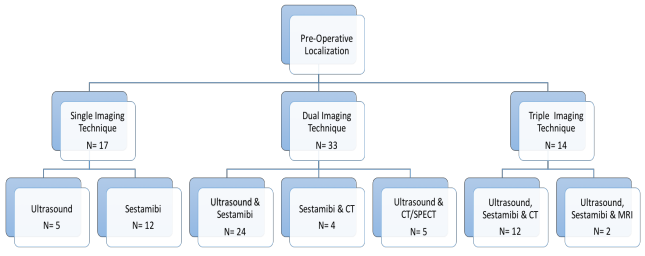

Figure 1) *Radiological investigations utilized for pre-operative localization*

RESULTS

Demographics

A total of 429 parathyroidectomies were performed on 424 patients during this 15-year period. Co-existing thyroid pathology was identified either radiologically or histologically in 68 patients (16%). Of these 68 patients, 58 were female (85%) with 10 males (15%), representing a median age of 67 years (range 40-87 years). Interestingly, 5 of these patients presented with symptomatic thyroid disease (7%), with PHPT being diagnosed incidentally.

Pre-operative biochemical analyses

On admission for surgical intervention, mean patient corrected serum calcium level was 2.73 mmol/L, ranging from 2.18-3.48 mmol/L (median 2.67 mmol/L) with mean patient serum PTH level 255.7 pg/ml, ranging from 29.6-2195 pg/ml, SD 360.87 (Table 2).

Pre-operative localisation

Complete imaging data was available on 94% of patients studied (n=64). Overall, ^{99m}Tc-sestamibi was performed in 57 patients (84%), followed by ultrasonography (n=48,71% patients), CT (n=19,28% patients) and SPECT (n=3,4%), with MRI employed in 2 patients (3%). A single imaging modality was employed in 17 patients (27%), dual radiological investigation in 33 patients (52%), with 14 patients requiring three radiological investigations (Figure 1). Of patients who had a single radiological investigation, ^{99m}Tc-sestamibi was employed most frequently (n=12,71%), with a minority of patients undergoing ultrasonography alone (n=5,29%). Concerning dual radiological investigation, ultrasound and ^{99m}Tc-sestamibi were employed in combination most frequently (n=24,67%), followed by ^{99m}Tc-sestamibi with CT (n=4,12%), ultrasound with SPECT (n=3,9%) and ultrasound with CT (n=2,6%). Of those patients undergoing three imaging techniques, ultrasound in conjunction with ^{99m}Tc-sestamibi and CT was utilized most frequently (n=12,86%) with two patients having ultrasound, ^{99m}Tc-sestamibi and MRI (n=2,14%).

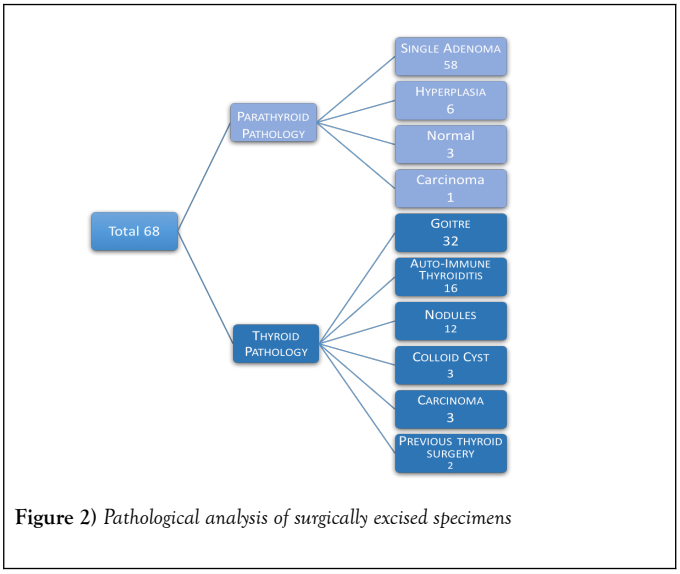

Figure 2) *Pathological analysis of surgically excised specimens*

TABLE 2
Pre and post-operative biochemistry results

Biochemistry	Timepoint	Corrected mean	Range	SD
Calcium (mmol/L*)	Pre-op	2.73	2.18-3.48	0.2
	Post-op	2.3	1.87-2.71	0.2
PTH (pg/ml†)	Pre-op	255.7	29.6-2195	361
	Post-op	47	6-191.1	47

* milimoles per litre; † picograms per millilitre

To determine accuracy, pre-operative imaging data was compared with operative and pathological findings. In isolation, ultrasonography was found to be most effective, with a sensitivity of 55%. This was followed by ^{99m}Tc-sestamibi, with a sensitivity of 50% and CT, sensitivity 47% (Table 3)

[1]. MRI and SPECT returned a false negative result in the two and three cases respectively in which they were utilized.

Regarding the identification of single-gland disease specifically, it was present in 58 patients (85%). Ultrasonography had a sensitivity of 54% and ^{99m}Tc-sestamibi having a sensitivity of 52%, with the single-gland disease being correctly identified in only 43% of cases. The use of ultrasound in conjunction with ^{99m}Tc-sestamibi produced a combined sensitivity of 53%. Comparing the sensitivity of these imaging techniques in patients with concomitant thyroid pathology (n=68) to the patients in our series without concurrent thyroid disease (n=356), the respective sensitivity was higher in patients without concurrent thyroid disease: ultrasonography 55% vs 63%, 99mTc-sestamibi 50% vs 60% and CT 47% vs 49%.

TABLE 3
Imaging modalities used for pre-operative localization with sensitivity

Imaging Modality	No. patients	True positive %	False negative %	Inconclusive %	Falsely localising %	Sensitivity
Ultrasound	48	37 (n=17)	30 (n=14)	33 (n=16)	2 (n=1)	55%
^{99m}Tc-Sestamibi Scintigraphy	54	46 (n=25)	46 (n=25)	7 (n=4)	0 (n=0)	50%
CT	19	37 (n=7)	42 (n=8)	16 (n=3)	5 (n=1)	47%

Surgical approach

All procedures were conducted by one of two Consultant General and Endocrine surgeons in a tertiary referral centre.

Of the 68 patients with concomitant thyroid pathology undergoing Parathyroidectomy for PHPT, BNE was employed in 45 patients (66%), with a minimally-invasive approach in the remaining 23 patients (34%), with a conversion rate of 13 % (n=3). Of the 45 open procedures, 5 were patients with four-gland hyperplasia, whereby 40 were patients with the single-gland disease. These findings differ from the surgical approach identified in our cohort of patients without concurrent thyroid disease, whereby MIP was employed most frequently in 54% of patients (n=231) with BNE in 45% (192), with a lower conversion rate of 8% (n=19).

Single-gland disease

Of this series of 68 patients, the single-gland disease was present in 58 patients (85%) but was pre-operatively correctly identified in only 25 patients (43%). Of these 58 patients, an open approach was mandated in 28 (48%) due to the requirement of concurrent thyroidectomy/lobectomy. MIP was employed in 21 patients (36%), with three cases converted to an open approach, two due to the requirement of lobectomy and one for the purpose of thyroid nodule excision. BNE was employed in the remaining 14 patients (24%) due to failed pre-operative localization. Of these BNEs, an ectopic parathyroid gland was identified in three patients, two intrathyroidal and one in the superior mediastinum.

Thyroid intervention

A total of 48 patients required thyroid surgical intervention (71%), including hemi thyroidectomy/lobectomy (n=27), total thyroidectomy (n=13), thyroid biopsies (n=4) and thyroid nodule excision (n=4). The indication for surgical intervention in these cases included multi-nodular goitre, thyroiditis, intra-thyroidal parathyroid (n=4) and thyroid carcinoma (n=3).

Sole parathyroid intervention

Twenty patients did not require intervention for thyroid pathology (30%). Eighteen of these twenty patients had multi-nodular goitre (90%), one patient had chronic thyroiditis and one, thyroidal cysts. Of these 20 sole parathyroid interventions, 14 were conducted via a minimally-invasive approach (70%), with the remainder conducted via an open approach (30%) due to inconclusive pre-operative localization, as the presence of thyroid disease obscured pathological parathyroid gland localization.

Intra-operative adjuncts

Complete data regarding intra-operative adjunct utilization was available on 64 patients (94%). Adjuncts employed include frozen section (n=55,81%), ioPTH monitoring (n=33,52%), radio-guidance (n=8,12%) and video-assistance (n=2,3%). Of these, ioPTH and frozen section were concurrently utilized in 25 patients (45%), with radio-guidance in 2 (4%). Intra-operative PTH monitoring (ioPTH), was available in our institution from 2006 to 2012 inclusively, at which point the service was discontinued. During this period, of the 39 cases of concurrent thyroid and parathyroid disease operated upon, ioPTH was employed in 33 (85%). In each case, ioPTH confirmed the successful removal of parathyroid pathology by identifying a PTH drop of >50% from baseline by 10 mins post-resection. In 8 of these cases, radio-guidance was utilized in conjunction with ioPTH.

Pathology

Single-gland adenoma was the cause of PHPT in the majority of cases (n=58, 85%), followed by parathyroid hyperplasia (n=6,9%), with parathyroid carcinoma identified in 1 patient and normal parathyroid tissue in the remaining three. These three 'normal' reports included the proviso 'clinical correlation advised' and each patient had abnormally raised serum PTH and corrected calcium pre-operatively that was restored to within normal ranges post-operatively.

Three patients had ectopic parathyroid adenomata (n=4%): two were intrathyroidal adenomata, with the final ectopic adenoma located in the superior mediastinum. Open surgery was required for the mediastinal parathyroid, which mandated a sternotomy, and one of the intrathyroidal adenomata, with a minimally-invasive approach in the final case. The mean mass of adenoma excised was 1.04 g (SD 1.6 g, median 607 mg, range 0.04-10 g).

For cases in which thyroid surgery (lobectomy or total thyroidectomy) was performed, multi-nodular goitre was the most frequent pathology (n=32,47% patients), followed by thyroiditis (n=16, 24% patients), solitary thyroid nodules (n=12, 18% patients), carcinoma (papillary n=2, follicular n=1, 4% patients) and thyroidal cysts (n=3, 4%) (Figure 2). The remaining two patients had undergone previous thyroidectomy (1 hemi thyroidectomy, 1 total thyroidectomy). Regarding the three papillary carcinoma cases, one was diagnosed incidentally intra-operatively at the time of Para thyroidectomy, whereby an area of the thyroid was grossly abnormal and it was decided to perform a lobectomy, while the other two were diagnosed pre-operatively in conjunction with PHPT.

Outcome

Mean corrected calcium levels dropped from 2.73 mmol/L pre-operatively (median 2.67 mmol/L, SD 0.2 mmol/L) to 2.3 mmol/L post-operatively (median 2.29 mmol/L, SD 0.2 mmol/L). Mean PTH levels dropped from 255.7 pg/ml pre-operatively (range 29.6-2195 pg/ml, SD 360.87) to 47 pg/ml post-operatively (range 6-191.1 pg/ml, SD 47 pg/ml) (Table 2).

During a median follow-up of 84 months, no patient experienced recurrent hypercalcemia, or required re-operative intervention. The median Length of Hospital Stay (LOS), was 3 nights, ranging from day case surgery to 29 days (Table 4). Three patients required hospital stays of 15, 21 and 29 days, all of which were due to co-morbidities (renal disease) rather than as a result of their surgical intervention. Overall, the operative approach did not affect LOS, with MIP requiring a mean stay of 4 nights (median 3, range 0-29), and open-approach requiring 4.5 nights (median 3, range 1-21 nights). However, when patients with stays longer than 7 days (due to co-morbidities rather than surgical intervention) are excluded, mean stay for MIP patients drops to 2 nights, with patients requiring an open-approach remaining at a mean of 4 nights. When further analyzed, comparing LOS between MIP conducted prior to 2009 and subsequent to 2009, the average LOS is seen to reduce from 4 nights to 1 night.

TABLE 4
Length of patient stay

Length of stay (Number of nights)	Number of patients
Day case	1
1	7
2	18
3	10
4	10
5	4
6	3
7	3
9	1
10	1
11	1
21	1
15	1
29	1

DISCUSSION

This study highlights the incidence and impact of concurrent thyroid disease on pre-operative localization and surgical intervention for primary hyperparathyroidism in a tertiary referral Centre. In a consecutive series of 424 patients requiring 429 Para thyroidectomies over a 15-year period, concurrent thyroid pathology was identified in 16% of patients. This is at the lower end of the 17-84% range of incidence currently reported in the literature [12-16]. Of these 68 patients, 71% required concurrent surgical intervention for their thyroid disease, which reflects the 33-100% concurrent intervention rate reported by others [12,13,21,22]. While the majority of thyroid pathology comprised multi-nodular goitre and thyroiditis, the incidence of thyroid malignancy identified was 4% (n=3), which is in keeping with the variable incidence of concurrent thyroid carcinoma in association with PHPT currently reported in the literature [23,24]. This is an interesting observation as recent literature suggests a noteworthy increased risk of papillary thyroid carcinoma in association with PHPT24. Excluding known associations Eg: MEN syndrome, further authors have reported an association between PHPT and an increased incidence of malignancy overall, including breast, renal, colonic and skin malignancies [25,26]. While potential environmental risk factors and genetic pre-dispositions have been proposed, a definitive association between PHPT and overall malignancy has yet to be identified. Of the three cases identified in this series, two were papillary thyroid carcinoma with one follicular variant carcinoma. The follicular variant carcinoma presented on a background of multi-nodular goitre, with concurrent four-gland parathyroid hyperplasia producing the hyperparathyroidism. Two cases were diagnosed pre-operatively in conjunction with PHPT, with each patient undergoing a total thyroidectomy at the time of parathyroid adenoma excision, and one was diagnosed intra-operatively, whereby an area of the thyroid was seen to be grossly abnormal and it was decided to perform a lobectomy. The rate of parathyroid malignancy in this series was 1%, which is in keeping with international experience [12,23,27-29].

The requirement for simultaneous thyroid surgery in this series mandated a more invasive surgical approach than the minimally-invasive technique routinely conducted for cases of isolated primary hyperparathyroidism with well-localized pathology [30-32]. While single-gland adenoma was responsible for 85% of parathyroid pathology in this series, 66% of parathyroid resections were conducted via an open approach. Further to this, a 13% conversion rate to the open approach was identified, due to the identification of thyroid pathology intra-operatively that required excision. This is notably higher than the 8% conversion rate identified in the cohort without concurrent thyroid disease.

Of the 20 cases requiring sole parathyroid intervention, 14 were conducted via a minimally-invasive approach (70%), with the remainder conducted via an open approach (30%). An open approach was required in these patients due to inconclusive pre-operative localization of pathological parathyroid gland as a result of pathological thyroid gland obscuring visibility. This falls short of the findings reported by Schneider, Mazeh [32], whereby MIP was employed in 86% of 1,083 cases of isolated PHPT, with an open approach utilized in only 14%. This highlights the higher rate of open Para thyroidectomy required in the presence of co-existent thyroid disease, irrespective of whether simultaneous thyroid intervention is required.

The sensitivity of pre-operative parathyroid localization in this series was seen to decrease by approximately 10% in cases of concurrent thyroid and parathyroid disease (section 3.3). It must be noted, however, that the overall sensitivity of ultrasonography and ^{99m}Tc-sestamibi identified in this unit was below expected, particularly for patients without concurrent thyroid disease [12,33]. The lack of a dedicated radiologist with a specialist interest in parathyroid and thyroid imaging may have contributed to the low sensitivity of this imaging series overall. It was interesting to note also that 17 patients were imaged with a single imaging modality, primarily ^{99m}Tc-sestamibi (n=12). Two of these patients required conversion from MIP to four-gland exploration due to requirement of hemi thyroidectomy and thyroid nodule excision, with half of the remainder n=7 undergoing minimally-invasive Parathyroidectomy, and half (n=7) undergoing an open approach. While isolated 99mTc-sestamibi scanning has been advocated as the most accurate imaging modality for directing targeted parathyroid intervention, its sensitivity is known to be reduced in the setting of co-existent thyroid disease [34,35]. The question remains as to whether a direct open approach may have been performed in this series had an ultrasound been performed to identify the co-existent thyroid disease. The American Association of Endocrine Surgeons guidelines recommends ultrasonography, in the hands of a dedicated parathyroid ultrasonographer in conjunction with 99mTc-sestamibi for pre-operative localization, as dual imaging increases localization accuracy, improves sensitivity and is the most cost-effective imaging protocol [30].

Regarding intra-operative adjuncts, the frozen section was employed most frequently in this institution, followed by ioPTH, radio-guidance, and video-assistance. Although ioPTH was implemented almost routinely during the period in which it was available, this service was removed from the hospital in 2012. Despite the reduced availability of intra-operative adjuncts and the decreased sensitivity of pre-operative localization of parathyroid pathology, the rate of operative success for the management of PHPT in these 68 patients with co-existent thyroid disease equaled 100%. This adds to the findings of Mownah, Pafitanis [36] who report the safety of ioPTH omission in cases of focused, isolated Para thyroidectomy. No patient experienced persistent or recurrent hypocalcaemia or required re-operative intervention during a median follow-up of 84months (range 33-180 months). This success is attributed to surgeon experience, the increased use of the open Para thyroidectomy/BNE and the application of available intra-operative adjuncts.

CONCLUSION

Concurrent thyroid pathology reduces the sensitivity of pre-operative localization in hyperparathyroidism and results in higher rates of open Para thyroidectomy in single-gland disease. The use of ultrasonography performed by a dedicated radiologist specializing in thyroid/parathyroid imaging, in conjunction with ^{99m}Tc-sestamibi scintigraphy to assess for co-existent thyroid pathology could enable an optimized surgical approach and is advocated in current guidelines. While ioPTH functions as an intra-operative adjunct it is not essential for successful surgical outcome. Primary operative success can be achieved in the hands of experienced surgeons, with the use of intra-operative adjuncts and the appropriate surgical approach.

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