Original research

Retrospective evaluation of the pre- and postoperative factors influencing the sensitivity of localization studies in primary hyperparathyroidism

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HIGHLIGHTS

- Preoperative localization of a suspected adenoma is essential to perform mini invasive surgery in primary hyperparathyroidism.
- The main factors predicting a low reliability of preoperative localization studies are concomitant thyroid disease and discordant studies.
- In such cases a mini invasive approach is possible but intraoperative PTH monitoring is mandatory.

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ABSTRACT

Introduction: Over the last decades, mini-invasive surgery has become increasingly common for treatment of primary hyperparathyroidism; such approach requires preoperative localization of a suspected parathyroid adenoma. Neck ultrasound (US) and technetium-99 m sestamibi (MIBI) scan are the main imaging studies used for this purpose. The aim of the present study is to evaluate what pre- and postoperative factors may alter the reliability of localization studies.

Methods: A retrospective analysis on 212 patients with preoperative diagnosis of primary hyperparathyroidism was conducted. Data collected included demographic data, preoperative workup, operative findings and follow-up. Univariate logistic regression was performed on pre- and postoperative variables.

Results: US sensitivity was 62.4% and MIBI sensitivity 78.9%. Cure rate after parathyroidectomy was 98.1%. Univariate logistic regression demonstrated that US sensitivity was impaired by lower levels of serum calcium (p < 0.0001), multi-gland disease (p = 0.011) and co-existence of thyroid disease (p = 0.001); MIBI sensitivity was impaired by lower levels of serum calcium (p = 0.001) and multi-gland disease (p < 0.0001).

Conclusions: Mild hypercalcaemia, multi-gland disease and co-existing thyroid disease are the main factors affecting sensitivity of preoperative imaging studies. In such patients a mini-invasive approach is possible but the use of intraoperative PTH monitoring is mandatory to reduce the risk of unsuccessful surgery.

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1. Introduction

Primary hyperparathyroidism (PHP) is the third most frequent endocrine disorder, with a prevalence estimated to be 1% in the over-65 population. Its incidence has increased consistently over recent decades due to the diffusion of screening blood calcium test. Surgery provides the only curative treatment for PHP, reducing both short and long term complications linked to hypercalcaemia. For many years, bilateral neck exploration has been considered the gold standard procedure because it permits the identification and concurrent treatment of multiglandular disease (MGD), thought to be the main cause of persistent PHP [1−3]. Over the last two decades, the use of mini-invasive parathyroidectomy (MIP) has
become increasingly common, with equivalent cure and lower complication rates compared with traditional exploration [4–7]. The main requirement for MIP is the preoperative localization of a suspected parathyroid adenoma ascertained from imaging studies. The literature reports preoperative ultrasound (US) scan to have an average sensitivity of 76% (range 48–89%), while that of technetium-99 m sestamibi (MIBI) scans is 79% (range 61–100%). This wide range of sensitivity rates raises questions about the reliability of these tests, with some authors suggesting a surgical bilateral approach in all patients with PHP. The aim of this retrospective study was to assess the accuracy of US and MIBI scans and to analyse pre- and postoperative factors that may alter the success of localization studies in patients with PHP.

2. Patients and methods

Having gained ethics approval from our Institutional Board Review we performed a retrospective review of 264 patients who had undergone parathyroidectomy to treat PHP between January 2002 and December 2012 within the Unit of General Surgery at the University of Cagliari, Italy. Only patients with preoperative diagnosis of PHP were included in the study: 21 patients were excluded due to preoperative suspicion of adenoma caused by morphological alteration of the parathyroid glands during neck surgery for other pathologies; 9 patients with persistent or recurrent PHP were excluded. The data analysed included: age, sex, coexisting thyroid pathology, serum calcium and parathyroid hormone (PTH) levels, the results of preoperative localization studies, surgical procedure, histopathological features and follow up.

Neck US and MIBI scans were performed preoperatively. All patients underwent MIP or bilateral exploration; a bilateral approach was preferred in cases of associated thyroidectomy or discordant preoperative localization studies. Intraoperative PTH determination at 10' and 20' after gland excision is routinely used in our Unit for both bilateral and mini invasive approaches. In cases of negative intraoperative PTH test during MIP, bilateral exploration was performed.

During patient follow-up, serum calcium and PTH levels were tested once a day during hospitalization, once a week for the first month following hospital discharge and then every 6 months. Persistent or recurrent hyperparathyroidism was defined as high levels of PTH detected within or after 6 months post-surgery, respectively.

2.1. Preoperative localization studies

The results of US and MIBI studies were retrospectively assessed. Patient outcome were categorized based on the results of localizing studies and operative findings as follows:

- True positive (TP) result: a single pathological gland found during surgical exploration on the same side where a single abnormality was identified by a scan, and the patient was cured. In cases of MGD a TP result was considered if two or more abnormalities and the patient cured by the excision of just a single gland.
- False positive (FP) result: the absence of any pathology as revealed by surgical exploration of the side of the neck where a scan had indicated a single abnormality or only one enlarged gland revealed by neck exploration where a scan had indicated two or more abnormalities and the patient cured by the excision of just a single gland.
- False negative (FN) result: one or more pathological gland found despite the lack of any such indication from imaging studies; results in which surgical exploration found a second enlarged gland when only a single abnormality had been identified by a scan; results in which a single gland was identified by both imaging studies and neck exploration, but the patient was not cured, implying the presence of an unrecognized pathological gland.

Due to the varying localization of the parathyroid glands, no distinction between superior and inferior glands was considered for this assessment.

Definitions:

- Sensitivity : TP Result/(TP Result + FN Result)
- Positive Predictive Value : TP Result/(TP Result + FP Result)

2.2. Statistical analysis

Univariate logistic regression analysis was performed to assess the influence of pre- and post-operative variables (age, gender, calcium and PTH serum level, concomitant thyroid disease, histopathological features) on localization study outcome. Continuous data are expressed as mean ± standard error of the mean (SEM).

3. Results

Two-hundred and twelve patients with preoperative diagnosis of PHP were included in the study; 34 (16%) were male and 178 (84%) female; the mean age was of 58.8 ± 12.7 years. Associated thyroid disease was present in 95 (44.8%) cases. Full demographic data and preoperative data are reported in Table 1.

All patients had undergone preoperative US scan; 180 (84.9%) patients underwent a MIBI scan. Overall, US scans had a sensitivity of 62.4% and a positive predictive value (PPV) of 92.6%; MIBI demonstrated a sensitivity of 78.9% and a PPV of 89.9% (Table 2).

Surgical treatment entailed bilateral exploration in 96 (45.3%) patients (in 89 of these parathyroidectomy was associated with a thyroid resection) and a MIP in 116 (54.7%). The mean operative time was 96 ± 39.1 min and the mean postoperative length of stay was 2.4 ± 0.8 days.

Cure rate after parathyroidectomy was 98.1%. Surgical failure was the outcome in 4 patients: 3 patients presented persistent hyperparathyroidism and 1 recurrent hyperparathyroidism (Table 3).

Histopathological examination demonstrated single-gland disease in 194 (91.5%) cases and multi-gland disease in 17 (8%) patients. In one case (0.5%), no pathological glands were found in the specimen; the patient presented a persistent hyperparathyroidism and refused to undergo any further surgical procedure, thus it was not possible to categorize the patient as having either single or

**Table 1**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n = 212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>34 (16%)</td>
</tr>
<tr>
<td>Female</td>
<td>178 (84%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.8 ± 12.7 (19–86)</td>
</tr>
<tr>
<td>Familial HP</td>
<td>4 (1.9%)</td>
</tr>
<tr>
<td>Pre-op Calcemia (mg/dl)</td>
<td>11.4 ± 1.3 (9.4–17.4)</td>
</tr>
<tr>
<td>Pre-op PTH (pg/mL)</td>
<td>315.9 ± 322.3 (26–2500)</td>
</tr>
<tr>
<td>Associated thyroid disease</td>
<td>95 (44.8%)</td>
</tr>
<tr>
<td>Follow up (months)</td>
<td>74.7 ± 23.2 (3–125)</td>
</tr>
</tbody>
</table>

HP: hyperparathyroidism; PTH: parathyroid hormone.
multi gland disease. The full histopathological features of all patients are reported in Table 4. An ectopic gland was identified in 8 (3.7%) patients; among these, MIBI correctly identified the site in 7 cases (87.5%) and US in 3 (37.5%).

Univariate logistic regression demonstrated that lower levels of serum calcium and multi-gland disease impaired the detection of abnormal parathyroid glands both by US and MIBI; the co-presence of thyroid disease impaired detection by US but not by MIBI. The effects of age, sex and preoperative PTH upon abnormal parathyroid detection by US and MIBI did not reach statistical significance. Receiver operating curves (ROC) determined an Area Under the Receiver Operating Curve (AUC) of 78% for US and 82% for MIBI, suggesting a good predictability for detection of an abnormal parathyroid gland by each study (Table 5).

As reported in Table 6, US sensitivity was consistently lower in patients with thyroid disease (46.7% vs 75%), MGD (18.7% vs 66.5%) and discordant results from preoperative localization studies (18.3% vs 90.1%); MIBI sensitivity was significantly impaired by multi gland disease (26.7% vs 92.6%) but not by thyroid disease or discordant results.

4. Discussion

Traditional bilateral exploration has long been considered the gold standard in PHP surgery, with cure rates standing at above 95% [1–3]; the advantage of this approach consists in the possibility to identify all the parathyroid glands, allowing contemporary detection and treatment of multiglandular disease or ectopic glands.

Over the last few decades, MIP has become a popular approach for the treatment of PHP. Many authors have reported advantages in terms of postoperative complications, hospitalization and cosmetic results due to the smaller incision and limited dissection compared to the traditional bilateral exploration approach, and similar cure rate [4–10]. Jaskowiak et al. [11] and Yen et al. [12] assessed large samples of patients presenting persistent or recurrent PHP and found that the two main causes of unsuccessful primary surgery were a single missed parathyroid adenoma, due to ectopic localization, and multiglandular disease. Thus the accurate preoperative localization of suspected glands is essential in order for mini invasive parathyroid surgery to obtain success rates comparable to those associated with the traditional approach.

US and MIBI scans are the main non-invasive studies used for this purpose. The reported sensitivity of US ranges between 48% and 89% and for MIBI the figure stands between 61% and 100% [2,13–19]. The wide range of these results should be taken into account when considering a minimal invasive procedure. A few studies have also investigated whether preoperative or post-operative factors can influence the reliability of US and MIBI; the present study fits into this context.

A systematic review by Ruda et al. [2], involving the retrospective analysis of more than 20,000 patients, demonstrated lower sensitivities for both US and MIBI scans in relation to the detection of multi gland hyperplasia (34.8% and 44.4% respectively) and double adenomas (16.2% and 29.9%) versus single pathological glands (78.5% and 88.4%), in accordance with other studies [3,20,21]. Our study confirms this observation: in cases of multiglandular disease, the sensitivities of US and MIBI were 18.7% and 26.7%, respectively. Possible reasons that could explain the lower accuracy in double adenomas and multi gland disease are the smaller size of the glands and, for US, operator satisfaction after smaller size of the glands and, for US, operator satisfaction after的小。

An ectopic localization of a pathological gland would correlate with a negative US result [15,22], but not a negative MIBI scan [23]. In fact, ectopic glands are often localized in mediastinal or para- or retro-tracheal areas, where ultrasound has low accuracy due to physical limits. In the present study, ultrasound investigations were associated with a negative results in 5 out of 8 ectopic parathyroid lesions, with a sensitivity of 37.5%, while MIBI scans detected 7 of them (sensitivity 87.5%).

A large prospective study [18] of 1000 bilateral explorations for hyperparathyroidism, including primary and secondary disease, identified BMI, serum calcium and PTH levels at presentation, and gland size as factors that influenced US and MIBI sensitivity. According to multivariate analysis, gland size and volume were found to be the strongest independent predictors of a successful localization. Furthermore, Kebebew et al. [24] found a correlation between calcium and PTH serum levels and US and MIBI detection rates of pathological glands. These data have been confirmed by other studies which have found higher serum PTH levels in patients with positive MIBI scans versus those with negative scans [13,25,26]. In the present study, only preoperative calcaemia was shown to influence US and MIBI accuracy, while preoperative PTH, sex and age did not result as statistically significant factors.

Other studies have underlined a direct correlation between PTH serum levels and gland weight [13,23,27]; indeed a strong relationship between gland weight and positive localization has been demonstrated [16,28,29]. It is clear that a small lesion size makes localization by US difficult, while an association between higher BMI and lower US sensitivity could be explained by less US wave penetration through fat tissue.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n = 212)</th>
</tr>
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<tbody>
<tr>
<td>Single gland adenoma</td>
<td>166 (78.3%)</td>
</tr>
<tr>
<td>Single gland hyperplasia</td>
<td>22 (10.4%)</td>
</tr>
<tr>
<td>Parathyroid carcinoma</td>
<td>6 (2.8%)</td>
</tr>
<tr>
<td>Double adenoma</td>
<td>4 (1.9%)</td>
</tr>
<tr>
<td>Multiple gland hyperplasia</td>
<td>12 (5.7%)</td>
</tr>
<tr>
<td>No pathological gland</td>
<td>2 (0.9%)</td>
</tr>
<tr>
<td>Ectopic gland</td>
<td>8 (3.7%)</td>
</tr>
<tr>
<td>Single gland disease</td>
<td>194 (91.5%)</td>
</tr>
<tr>
<td>Multiple gland disease</td>
<td>17 (8%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (0.5%)</td>
</tr>
</tbody>
</table>

US: neck ultrasound scan; MIBI: 99mTc-Sestamibi scan.
Several hypotheses have been proposed to explain false negative MIBI scan results: for example, smaller adenoma sizes and weights tend to decrease the uptake of radiotracer into the cells [13]. Some authors have reported that a gland size of less than 2 cm is the threshold value below which MIBI scans become difficult to interpret [16].

The different parathyroid cell types, considered to represent different stages of the life cycle of parathyroid cells, influence MIBI scan accuracy. The ability of each cell type to incorporate MIBI is related to mitochondrial content: chief and oxyphil cells are rich in mitochondria and exhibit greater MIBI uptake, while clear and adipose cells have a low mitochondrial content and lower MIBI uptake. Many studies support the correlation between parathyroid cell type and localizability; the factors correlating with positive localization are: a high content of chief cells [30] and oxyphil cells [13,16,28,31,32], the absolute number of mitochondria, and a ratio of oxyphil to clear cells greater than 1 [33]. On the other hand, clear cell predominance correlates with a higher incidence of inconclusive localization results [32].

Another factor that should be taken into account, as reported from a number of studies [23,34,35], is the importance of an experienced US operator; in some cases, a skilled operator should even be able to locate an adenoma in MIBI-negative patients [13]. The strong association between parathyroid and thyroid pathology is well known [18,24,36–40], especially in geographic regions presenting endemic goitre where the prevalence of thyroid disease ranges from 25 to 52% among patients with PHP. In our study we identified concomitant disease in 45.4% patients. In accordance with other studies [15,18,41,42] we found a strong correlation between coexisting thyroid disease and incorrect US localization, with a US sensitivity of 46.7% in patients with concomitant thyroid disease compared with 75% in those presenting parathyroid pathologies only. Indeed, thyroid nodules can be misidentified as parathyroid lesions and vice versa; furthermore, central compartment nodes, frequently seen in patients with thyroiditis, can be mistaken for parathyroid glands [43,44]. When using MIBI, the presence of a thyroid nodule with a late wash-out can resemble a parathyroid nodule in the final images, resulting in a decrease in MIBI sensitivity. Moreover, the influence of TSH-suppression therapy has been reported to affect MIBI scan accuracy due to changes in thyroid metabolism and uptake [45].

This loss of localization accuracy in thyroid disease is a considerable problem, especially for US, such that some authors [41] deem bilateral exploration to be essential in patients with concomitant thyroid disease due to the reduced US sensitivity. We believe that patients with concomitant thyroid disease should be carefully evaluated preoperatively by means of both US and MIBI scans; a mini-invasive approach is also possible, but intraoperative PTH monitoring is mandatory due to the low sensitivity of preoperative localization studies.

Many authors have emphasized that the combination of a US and MIBI scan is the most effective method for localizing parathyroid adenomas [15]. In our experience, discordant studies are associated with high sensitivity (90.1%) and discordant studies correlate with lower, but acceptable levels of MIBI sensitivity (79.3%), but very poor US sensitivity (18.3%).

As previously reported by our group [46,47] the incidence of multiglandular disease in discordant studies is high (12%): in such cases, a mini-invasive approach can only have a successful outcome if combined with intraoperative PTH measurement; otherwise, bilateral exploration is mandatory in order to avoid persistent hyperparathyroidism due to missed multiglandular disease.

Furthermore, it is interesting to note that none of the patients with negative US and MIBI scans in our study were found to have a multiglandular disease. Other studies [46,48] noted that a patient with a negative MIBI scan were more likely to have a single adenoma rather than multiple gland disease; in such patients, a mini-invasive approach could be considered, starting exploration on one side and — if negative — continuing with bilateral exploration.

### 5. Conclusions

A mini-invasive approach in PHP treatment requires careful preoperative evaluation using both US and MIBI scans. In the patient population assessed, concomitant thyroid disease and mild hypercalcaemia were found to be the two most important preoperative factors influencing the outcome of preoperative localization studies. Thus, intraoperative PTH assessment is recommended in patients presenting these two conditions. With regard to discordant studies, US sensitivity was found to be very low, with the results of MIBI scans instead being more reliable. Negative preoperative localization studies do not preclude a mini-invasive approach because the possibility of multiglandular disease is very low in these patients.

### Ethical approval

Ethical approval was requested and obtained from the “University of Cagliari” ethical committee.

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All Authors have no source of funding.


