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Research Article

Complications and Cure Rates of Parathyroidectomy for Primary Hyperparathyroidism with Negative Localization Studies

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ABSTRACT

Purpose: This paper evaluates the outcomes of parathyroidectomy for primary hyperparathyroidism with negative localization studies.
Methods: All patients with primary hyperparathyroidism with negative preoperative ultrasound and MIBI scan who underwent parathyroidectomy were retrospectively included. Three groups were defined. Group 1 included the patients with negative ultrasound and MIBI. Group 2 included the patients with negative ultrasound and positive MIBI. Group 3 included the patients with positive ultrasound and negative MIBI.
Results: In Group 1, 51% and 86% of patients had one adenoma and atypical localizations respectively. Unique adenoma and atypical localizations were showed in 87% and 93% of patients in Group 2 respectively. In Group 3, 83% and 17% of patients had one adenoma and atypical localizations respectively. No cervical hematoma was noted. Transient recurrent laryngeal nerve palsy occurred in 2 patients. Seven patients required postoperative calcium supplementation for 2 to 5 months, and one had recurrent hypercalcemia at follow-up. Cure rate was 98,3%.
Conclusion: When US and MIBI were negative, multiple lesions and atypical localizations were frequent. The success rate and postoperative complications were not affected with this event.

Introduction

Primary hyperparathyroidism (PHPT) is a common disorder. Bilateral neck exploration (BNE) was the treatment of choice for PHPT with a success rate of more than 95% [1-5]. The introduction of the preoperative localization studies has led to the development of minimally invasive parathyroidectomy (MIP) where only the affected gland is identified and excised [6-8]. MIP has clear benefit in terms of operative duration, shorter hospital stays, overall cost, higher patient satisfaction, less postoperative pain, smaller incisions, better cosmetic outcomes, less associated morbidity, and becoming the gold standard treatment [9-16]. The ability to perform MIP relies upon successful localization of the diseased gland(s) preoperatively by many techniques [17-19]. These techniques include neck ultrasound (US), dual phase planar technetium-99 m (99mTC) sestamibi scans (MIBI), MRI, single photon emission computed tomography (SPECT), combined SPECT/CT and four dimensional CT scans (4D CT) [20-25]. A combination of imaging modalities is often used as no single imaging modality is 100% sensitive or specific [17, 18, 26, 27]. Despite advancements in imaging technique, a subset of patients with non-localizing abnormal gland(s) will require the traditional method of BNE [18, 19, 28-35]. Decreased intraoperative success and overall cure rates and increased in the rates of common postoperative complications have been described in non-localizing imaging for PHPT [30-32]. The aim of this study was to determine our institution's cure and complications rates of parathyroidectomy in PHPT with negative MIBI and US.

Materials and Methods

I Patients Selection

Between January 2000 and December 2018, all consecutive unselected patients who were admitted for parathyroidectomy for PHPT with negative preoperative MIBI and/or US were retrospectively considered

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for the study. The study was approved by an institutional review board. The diagnosis of primary hyperparathyroidism was based on three elevated serum calcium levels in combination with inappropriate elevation of a serum PTH level. Exclusion criteria were patients with secondary causes of hyperparathyroidism, familial hyperparathyroidism, any of the multiple endocrine neoplasia syndromes, recurrent or persistent hyperparathyroidism after previous parathyroid operation, and if US and MIBI lead to identify the same one adenoma. The following data were collected: age at time of operation, gender, preoperative calcium and parathyroid hormone (PTH) levels, type of operation, surgical findings, histopathologic results, and postoperative calcium and PTH levels.

High resolution real-time US and colour-Doppler sonography were the first diagnostic procedure performed by the radiologist. For US, the patient was scanned in supine position with the neck extended. Scanning was performed from high in the neck at the carotid bifurcation to as low as feasible in the base of the neck. High frequency transducers of 10 MHz were used, in combination, in some cases, with lower frequency transducer (7.5 MHz). A routine real-time sonography combined with colour-Doppler imaging was used. Transverse and longitudinal views were recorded. Routine search of parathyroid glands is usually directed along the posteromedial aspect of the thyroid close to tracheoesophageal groove and includes the entire thyroid gland and the anterior neck from the thyroid cartilage to the sternal notch and from the midline to the jugular veins. Parathyroid adenomas are typically hypo echogenic compared with the thyroid gland and are solid in sonographic appearance. Adenomas tend to be oval, bean-shaped, or oblong. Classically, an echogenic plane between the parathyroid lesion and the thyroid gland is helpful in distinguishing the lesion from a thyroid nodule. Doppler study reveals hypervascularity.

Technetium (Tc) 99m sestamibi scan was performed in some cases especially where no definite results could be obtained by US. For MIBI scan, a dual-head gamma camera system (ADAC Vertex Plus; ADAC Laboratories, Milpitas, CA) was used for parathyroid imaging with a low-energy, high-resolution parallel hole collimator. For the dual-phase MIBI study, 20 mCi 99mTc-MIBI was administered intravenously. Fifteen minutes after injection, the first image of the neck was acquired for 10 minutes. A second image, targeting the mediastinum, was obtained for 10 minutes. These 2 images were repeated at 1 and again at 2 and at 3 hours after administration of 99mTc-MIBI. All operations were performed by one surgeon (BA) via a transverse cervicotomy. Patients in whom preoperative US or MIBI localized one abnormal parathyroid gland underwent unilateral surgical exploration of the neck under local anaesthesia with intraoperative dosage of 1-84 PTH**.** BNE under general anaesthesia was made when the preoperative examination failed to localize the lesion, and when justified by the surgical findings.

Reported categorical outcomes include detection of abnormal parathyroid(s), anatomic localization of the gland(s), preoperative and postoperative calcium and PTH levels (postoperative, at 6 months, and at follow up), presence of polyglandular disease and pathologic findings. Following the results of both imaging tests, three groups were established in order to further assess the discrepancy between imaging techniques: Group 1 included all patients with negative US and MIBI, Group 2 regrouped patients having negative US and positive MIBI and Group 3 included patients with positive US and negative MIBI. Surgical anatomic localizations were subdivided in 2 groups: Typical or normal localizations (TL) and atypical localizations (AL). Parathyroid disorders characteristics were classified as adenoma, hyperplasia, or carcinoma. Final pathology results were reported in two different groups: one adenomatous lesion (A) and polyglandular disease (P) comprising hyperplastic lesion and at least 2 adenomatous lesions.

II Statistical Analysis

Discrepancy was evaluated by comparing outcomes between the groups using 2x2 Fisher's exact test; statistical significance for comparison between nominal variables was set at $p<0.05$.

Results

From January 2000 to December 2018, 74 patients with primary hyperparathyroidism and negative US or MIBI underwent parathyroidectomy. There were 51 women (69%) and 23 men, with a mean age of 57 years (range: 24-83 years). Both sex groups were comparable regarding median age (56 years for women, 58 years for men, $p = 0.629$). The average preoperative PTH and serum calcium levels were 137pg/ml and 2.67 mmol/l respectively. High resolution real-time US and colour-Doppler sonography were performed preoperatively in 72 patients. Technetium (Tc) 99m sestamibi scan was performed in 60 patients, mainly when no definite result was obtained by US. Average size of the adenomas on US examination was 18 mm(range, 7-67mm). Patients with correct ultrasonography localization had an adenoma in the anterior part of the neck (typical) compared to the adenoma in mediastinum or in the posterior part or in the retroesophageal groove (atypical) with negative or incorrect localization. Other factors– including patient age, sex, side (right versus left) of adenoma, position (upper versus lower) of the adenoma, size of adenoma, preoperative highest serum calcium, PTH, urinary calcium, serum alkaline phosphatase levels had no significant association with the accuracy of US.

I Surgical Anatomy

In all the patients, the preservation of the recurrent nerves was the rule. When found, adenomas were excised, hyperplasia of parathyroid glands were removed (three-and-the half parathyroidectomy associated to thymectomy) and frozen sections for parathyroid tissue were obtained. Biopsy specimens of normal macroscopic glands were not obtained in patients with excision of an obvious adenoma, whereas other visualized glands were only marked with a clip or long silk suture. When vascularization of a parathyroid gland seemed compromised, it was selectively resected and auto transplanted in the homolateral sternocleidomastoid muscle. Definitive pathology study was obtained for all resected tissues (weight and size of the lesion were measured).

In patients with a missing superior parathyroid gland, a careful exploration of the retro-pharyngeal area, tracheooesophageal groove, and posterior superior mediastinum was performed. With a missing inferior parathyroid gland, the root of the neck, thymus (thymectomy), and anterior superior mediastinum were carefully explored. The next step in patients with a missing superior or inferior parathyroid gland was opening of the carotid sheath. The final procedure in all patients with a missing and presumably diseased parathyroid gland was ipsilateral partial or total thyroid lobectomy with trunk ligation of inferior thyroid artery.

The four parathyroid glands were identified in each patient who underwent BNE. Morphologic features of abnormal parathyroid glands included: enlarged size (>50 mg), irregular shape, dark colour or hypervascularization, firm consistency with lack of compressibility, and absence of surrounding fatty tissue typical of a suppressed parathyroid gland. Specimens were considered by the pathologist to be abnormal based on gross and histological criteria including: weight, cellularity, fat depletion, and morphology. Surgery assessments of PHPT revealed 51 atypical localization of abnormal parathyroid(s) (51/74=69%) and 23 typical localizations (23/74=31%). Following appropriate surgical treatment and pathologic assessment, there were 53 parathyroid adenomas (72%) and 21 polyglandular lesions (28%). Among polyglandular lesions, 13 lesions were identified as parathyroid hyperplasia (17%) and 8 resected specimens presenting at least two adenomatous lesions each (11%). The weights of the adenomas ranged from 53 to 4312 mg, and mean size in greatest diameter was 18 mm. Table 1 summarize the relation between negative US, negative MIBI, surgical localizations, and final pathology.

Table 1: Relation between negative US, negative MIBI, surgical localizations and final pathology.

	Negative Ultrasound (n=52)	**Negative MIBI(n=43)**
Female	32(62%)	31(72%)
Atypical locations	46(88%)	33(77%)
Typical locations	6(12%)	10(23%)
Adenoma	32(62%)	24(56%)
Multiple lesions	20(38%)	19(44%)

No patient was lost to follow-up. Within days following surgery, all patients had calcium levels in the normal range, 63 patients normalized their previously elevated PTH levels. 9 patients required postoperative calcium supplementation for 2 to 5 months, and all were normocalcemic at the time of the last clinic visit with median follow-up of 48 months (range 12 to 216). One patient had recurrent hypercalcemia 2 years after surgery. Cure rate was 98,6%. Two patients had transient recurrent laryngeal nerve palsy. No cervical haematoma neither permanent palsies of the recurrent laryngeal nerve were noted. Sixteen patients: two without US and 14 without MIBI, were therefore excluded from further analysis. Among the remaining 58 patients(who had US and MIBI), 52 and 43 had a negative US and MIBI respectively. The median preoperative total calcium and PTH levels were 2.67 mmol/L and 132 mIU/mL respectively for the abnormal multiple glands patients and were 2.71mmol/L and 136 mIU/mL respectively for the remaining patients. These differences are not statistically significant ($p = 0.601$ and $p = 0.665$ for calcium and PTH respectively).

As per intraoperative findings, the hyperparathyroidism was due to a solitary adenoma in 37 patients (64%), and polyglandular diseases in 21 patients (36%).Atypical localizations showed in 47 patients (81%) : abnormal gland(s) were found in the anterior mediastinum (n=8), in the posterior mediastinum (n=12), in the tracheoesophageal groove or retroesophageal space (n=19), on intrathymic (n=5), near the carotid artery bifurcation (n=1), and within the thyroid gland (n=2). On pathologic examination the average size of the adenoma was 17 mm (range, 7-66 mm), and average weight was 1930 mg (range, 83-46300 mg). No patient was lost to follow-up. 57patients (98.3%) were cure during a median follow-up period of 48 months (range 12 to 216). 53 patients had normal PTH levels. 7 patients required postoperative calcium supplementation for 2 to 5 months, and all were normocalcemic at the time of the last clinic visit. Transient recurrent laryngeal nerve palsy occurred in 2 patients. In this series, no patient developed neck haematomas or persistent hypoparathyroidism or had permanent recurrent laryngeal nerve injuries. One patient (1.7%) developed hypercalcemia 2 years after surgery.

II Comparison of Groups 1, 2, and 3

There were 37 patients in Group 1, 15 patients in Group 2 and 6 patients in Group 3.Both sex groups were comparable regarding median age (56 years for women, 58 years for men, $p = 0.42$). Patient enrollment and assessment in groups was summarized in (Tables 2 & 3).

Table 2: Relation between negative preoperative studies and surgical localizations.

	Groupe 1(n= 37) Double Negative	**Groupe 2 (n=15) US(-) and MIBI(+)**	**Groupe 3(n=6) US(+) and MIBI(-)**
Female	25(68%)	7(47%)	6(100%)
Atypical locations	32(86%)	14(93%)	1(17%)
Typical locations	5(14%)	1(7%)	5(83%)
Total	37(100%)	15(100%)	6(100%)

Table 3: Relation between negative preoperative studies and final pathology.

	Groupe 1(n= 37) Double Negative	**Groupe 2 (n=15) US(-) and MIBI(+)**	**Groupe 3(n=6) US(+) and MIBI(-)**
Female	25(68%)	7(47%)	6(100%)
Adenoma	19(51%)	13(87%)	5(83%)
Multiple lesions	18(49%)	2(13%)	1(17%)
Total	37(100%)	15(100%)	6(100%)

Patients in Group 1 (n=37) underwent BNE under general anaesthesia because a double negative preoperative localization studies. The anatomic distribution of abnormal gland(s) was: anterior mediastinum (n=5), posterior mediastinum (n=7), the tracheoesophageal groove or retroesophageal space (n=15), intrathymic (n=3), and near the carotid artery bifurcation (n=1), intra thyroid (n=1). No Unsuccessful cervical exploration occurred. The exploration of the different cervical spaces averaged 92 minutes (range, 35-182 minutes). Patients in Groups 2 and 3 (n=21) underwent minimally invasive parathyroidectomy by unilateral neck exploration under local anaesthesia with intraoperative dosage of 1-84 PTH. Three patients in this group required conversion to BNE under general anaesthesia because of failure of a significant decrease in intraoperative quick PTH assay (n=2) after excision of the adenoma. In one patient, frozen section study revealed hyperplastic parathyroid glands on the same side, and the procedure was extended to a bilateral exploration. The anatomic distribution of abnormal gland(s) was: anterior mediastinum (n=3), posterior mediastinum (n=5), in the tracheoesophageal groove or retroesophageal space (n=4) intrathymic (n=2), and intra thyroid (n=1). The mean operative time was 13 minutes (range, 7-39 minutes).

Comparison between Groups 1 and 2 yielded significant differences in pathology findings: 13% of patients in group 2 had a polyglandular disease compared to 49% of patients in Group 1 (p=0.004).Comparison between Groups 1 and 3 showed significant differences in anatomic localization as there were 86% and17% of atypical localizations respectively (p<0.001).Comparison between Groups 2 and 3 showed significant differences in sex (p= 0.046) and anatomic localization (p<0.001). 53% of male patients were in Group 2 and zero (0%) patient in Group 3. There were17% of atypical localizations in Group 3 compared to 93% of patients in Group 2.

Discussion

In this study, we found that ectopic localizations (86%) and polygland diseases (49%) were independently associated with double negative preoperative US and MIBI Scan in PHPT. Our experience corroborates several reports of a significantly increased incidence of MGD (21.7-84%) in patients with double negative imaging in patients with PHPT [19, 29, 32, 34]. In our series, BNE was performed if no positive result was seen in any imaging technique. These patients typically required BNE(more extensive surgery) for suitable disease control. In our patients, there was no difference in the rates of common postoperative complications between groups. Additionally, while previous studies have associated non-localizing hyperparathyroidism with lower cure rates, cure rates at our institution have been comparably high between patients with nonlocalized and localized disease at 98.3% and 98.9%, respectively [31]. In contrast, some authors, found a markedly decreased cure rate of 89% in patients with both a negative MIBI scan and a negative ultrasound [30, 31]. Gland size in our series was smaller in patients with negative US and/or negative 99mTc sestamibi compared to those with positive imaging without reaching statistical significance.

In our series, 87% of patients in Group 2 and 83% of patients in Group 3 had a single adenoma and underwent parthyroidectomy by MIP with intraoperative dosage of 1-84PTH. A unilateral MIP procedure was successful after an intra-operative PTH drop of at least 50% of its initial value to confirm the absence of other abnormal glands. The usefulness of iOPTH in MIP was also validated by many other authors [9, 36-39]. At our institution, US and MIBI scans are most often used to localize hyperfunctioning gland(s). Previous studies have suggested the sensitivities for MIBI and US to range from 54% to 88% and 59% to 92.5% respectively [6, 9, 35]. Combining these two imaging modality increases the sensitivity of localization. In this series, 8% of patients undergoing initial surgery for PHPT failed to localize on pre-operative imaging (double negative). Previous studies show rates of 14% to 32% [18, 33-35]. The precise reasons for equivocal or negative studies remain unclear. The successful identification of a parathyroid adenoma with ultrasound is dependent on the operator's proficiency, neck girth, lesion size, presence of thyroid disease and ectopic gland [8, 9, 17, 23, 27, 28].

In our series, among the patients with negative US, 88% had abnormal parathyroid gland(s) situated in AL. 99mTc-MIBI SPECT/CT scans has difficulty localizing adenomas when thyroid nodules are present, when parathyroid adenomas are small, or if there is multi gland disease and the degree of necrosis and apoptosis. Other factors include accuracy of imaging modality, imaging technique, and the discipline and experience of the interpreter [40-47]. Some authors demonstrated that radionucleotide retention in 99mTc sestamibi scans is related to oxyphil cell content and a pathologic study by others showed a higher proportion of chief cells in the glands of patients with non-localizing scans [33, 41]. Singer *et al.* found that centers that perform a high volume of MIBI imaging may achieve higher levels of scan sensitivity (82% within their institution versus 67% at outside facilities) [42]. Interpretation of the imaging may also vary based on the level of experience of the physician who is interpreting the film as well as their specialty (surgeon vs. radiologist). Adenoma weight of more than 600 mg and oxyphil cell content of more than 20% were independent factors for a positive MIBI scan for some authors [40]. Several studies have reported lower preoperative PTH and calcium levels in patients with nonlocalized PHPT [44]. While our series uncovered no difference in preoperative calcium and PTH levels in patients with double negative imaging. Some authors showed that negative MIBI scan was associated with an increased rate of multiglandular disease and a lower cure rate [31]. In contrast to this finding, other studies did not find any association between negative MIBI scan and mutliglandular disease; Their *et al.*, identified a single adenoma in 94.2% of patients [37]. Our study showed that the rate of multiglandular disease in patients with negative MIBI was 44% but success cure rate was not affected.

Recently, various imaging modalities such as 4D-CT, PET/CT, and MRI have been used with mixed success. 4D-CT is traditionally reserved for patients with unclear SPECT/CT results with a continued suspicion for adenoma [24, 29]. Some authors recommend reserving 4D-CT for certain situations such as cases with ectopic glands, especially in patients suspected to have adenoma but have unidentified lesions on initial imaging. However, 4D-CT has been shown to miss smaller adenomas as well and may not be the best alternative [17]. Historic cure rates for parathyroidectomy before the introduction of preoperative imaging were approximately 95%; as our study demonstrates, cure rates continue to be high regardless of preoperative imaging status. The only localization required for a patient with primary hyperparathyroidism is the localization of an experienced endocrine surgeon [29]. There are limitations to our study. This series is limited by its retrospective nature and the small sample size. Unfortunately, it not possible to perform a prospective randomized control trial in which patients are randomized to be localized or non-localized.

Conclusion

According to our results, US and MIBI must be performed preoperatively in PHPT in order to realize a MIP. Non-localization of parathyroid glands was not associated with decreased surgical cure rate or increased surgical morbidity. BNE is the treatment of choice with double non-localizing disease. MIP with intraoperative dosage of 1-84 PTH is the treatment of choice when US and/or MIBI was positive (more than 83% of patients had one adenoma).

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None.

Conflicts of Interest

None.

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