



Different Results of Reoperations for Persistent and Recurrent Primary Hyperparathyroidism

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Abstract

Background: To report results of reoperation for hypercalcemia after parathyroidectomy for primary Hyperparathyroidism (HPT).

Methods: Two groups: Group 1: Persistent (PHPT), Group 2: Recurrent (RHPT).

Results: 81 patients, 60% in group 1 and 40% in group 2 were included. Ultrasound, MIBI Scan, 4D CT scan, and MRI localization rate was 84%, 86%, 91%, and 88% respectively. 93% of abnormal parathyroid gland(s) were operated *via* a cervicotomy and 7% *via* a mediastinal approach. Parathyroid adenoma was showed in 80% and 72% and parathyromatosis in 2% and 9 % in group 1 and group 2 respectively (statistically significant difference). We noted a statistically significant difference in the presence of supernumerary and mediastinal gland (4% vs. 13% and 8% vs. 22%) in groups 1 and 2 respectively. Cure rate was 94% in both groups.

Conclusion: Parathyroid adenoma is more common in group 1, whereas parathyromatosis, supernumerary and mediastinal gland are more common in group 2. The cure rate of reoperation was 94%.

Keywords: Primary hyperparathyroidism; Persistent hyperparathyroidi; Recurrent hyperparathyroidism; Localization studies; Surgery

Introduction

Primary Hyperparathyroidism (HPT) is the third most common endocrine disease and the leading cause of hypercalcemia. It is more common in postmenopausal women and its overall incidence displays great variability within populations. Parathyroidectomy is the treatment of choice with a cure rate of 95% to 98% with an experience hand. Surgical failure is the most common complication of surgery for HPT [1-3]. According to some data, the annual reoperation rate for all parathyroidectomies varies between 3.6 and 4.8%. In addition, 5% to 20% of all parathyroid surgeries performed for HPT in reference centers are reoperations for persistent and recurrent disease. [4-14]. The 6-month postoperative period for hypercalcemia is used to differentiate between persistent (PHPT) and recurrent HPT (RHPT). PHPT is defined as the persistence of hypercalcemia or reappearance of hypercalcemia within the first 6 months after parathyroidectomy, and recurrence of hypercalcemia after a normocalcemic period of more than 6 months is defined as RHPT. A common cause of failure is inadequate resection of the parathyroid adenoma, parathyroid hyperplasia and an ectopic location of the parathyroid gland. While parathyroid adenomas are predominantly located in the neck, 6% to 30% are ectopic [3,15-19].

This paper aimed to report the outcome of reoperation for hypercalcemia after parathyroidectomy for primary hyperparathyroidism and compared the results in persistent and recurrent cases.

Patients and Methods

Patient's selection

Between January 1997 and December 2024, all consecutive unselected patients operated for HPT were retrospectively included. The study was approved by an institutional review board. The diagnosis of HPT was based on elevated serum calcium levels in combination with inappropriate elevation of a serum Parathormone (PTH) level. Exclusion criteria were: normocalcemic HPT, secondary, tertiary and familial hyperparathyroidism, and any of the multiple endocrine neoplasia syndromes. The following data were collected: age at time of diagnosis, gender, dysphonia, preoperative calcium

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and PTH levels, type of operation, surgical findings, histopathologic results, hospital stay, and postoperative calcium levels.

In all patients already operated on, we collected the previous operative report (unilateral or bilateral exploration, localization and number of excised parathyroid glands(s), biopsy or marking of the remaining glands, intraoperative dosage of PTH), the results of the anatomopathology and the postoperative biological assessment of calcemia. Preoperative indirect laryngoscopy was performed in all patients to assess vocal cord mobility.

High resolution real-time Ultrasonography (US) and color-Doppler sonography with Technetium (Tc) 99 m Sestamibi Scan (MIBI) were the first diagnostic procedures performed by the radiologist. A four-dimensional Computed Tomography (4D CT) and/or Magnetic Resonance Imaging (MRI) of the neck and mediastinum was performed when the US and MIBI were negative or discordant.

All operations were performed by one surgeon (BA). Focal parathyroidectomy was conducted in patients in whom preoperative radiological studies localized one abnormal parathyroid gland. Bilateral Neck Exploration (BNE) was made when the preoperative examination was failed to localize the lesion, discordant, and when justified by the surgical findings. The mediastinal approach is performed when at least one radiological localization study definitively shows the presence of an adenoma in the deep mediastinum. This approach included sternotomy, thoracotomy, minithoracotomy, and thoracoscopy. Two groups were established in order to further assess the discrepancy between 2 groups: Group 1 included all patients operated for PHPT: defined as persistent hypercalcemia following parathyroid surgery, or recurrence of hypercalcemia within 6 months of surgery; and Group 2 regrouped patients operated for RHPT: defined as the recurrence of HPT more than 6 months after parathyroidectomy that initially normalized calcemia.

Anatomic localization of the gland(s), preoperative and postoperative calcium levels, presence of polyglandular disease and pathologic findings were collected. Parathyroid pathologies were classified as adenoma, hyperplasia, parathyromatosis, or carcinoma.

Statistical analysis

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

Results

Between January 1997 and December 2024, 1361 patients underwent parathyroidectomy for HPT. There were 1075 women (79%) and 286 men, with a mean age of 58 years (range: 11-92 years). 81 patients (6%), reoperated for PHPT ($n=49$; 60%) or RHPT ($n=32$; 40%) meeting the inclusion criteria, were included. Of these, 54 patients were operated on for HPT in other institutions and referred to our hospital for reoperation for postoperative hypercalcemia. Both sex groups were comparable regarding median age (57 years for women, 61 years for men, $p = 0.629$). Preoperative vocal cord evaluation (indirect laryngoscopy in all reoperated patients) showed a right vocal cord palsy in one patient operated in another hospital.

The average preoperative serum calcium and PTH levels were 2.79 mmol/l and 142 pg/ml respectively. High resolution US, MIBI scan, 4D CT scan, and MRI were performed preoperatively in 81, 77, 53, and 11 patients respectively. Two patients with persistent hypercalcemia and

Table 1: Comparison of variables of patients in Groups 1 and 2.

Patients	Group 1	Group 2	P value
n=81	49	32	NA
Gender(F/M)	76%/24%	77%/23%	NS
Age	18-89 years	21-87 years	NS
Ca: mmol/l	2.69	2.73	NS
PTH: pg/ml	136	149	NS
Adenoma	39(80%)	23(72%)	<.003
Polyglandular lesions	9(18%)	6(19%)	NS
Parathyromatosis	1(2%)	3(9%)	<.0001
Supernumerary gland	2(4%)	4(13%)	<.0002
Mediastinal localization	4(8%)	7(22%)	<.0002
Cure rate	0.94	0.94	NS

non-abnormal gland visualized with non-invasive localization tests underwent arteriography of the neck and mediastinum vessels ($n=1$), which revealed the location of an adenoma in the left jugulocarotid sheath, and the other patient underwent selective venous sampling (neck and mediastinum), which lateralized the lesion to the right cervical region. The US, MIBI Scan, 4D CT, and MRI localization rate was 84%, 86%, 91%, and 88% respectively.

All patients who had a localized one abnormal parathyroid gland, in cervical region, underwent a focal parathyroidectomy with intraoperative dosage of 1-84 PTH (one dosage before incision and the second dosage 10 minutes after excision of the abnormal parathyroid gland). BNE was made when the examination failed to localize the lesion, and when justified by the surgical findings or intraoperative dosage of PTH.

The mediastinal approach is performed when at least one radiological localization study definitively shows the presence of an adenoma in the deep mediastinum.

Minimally invasive mediastinal surgical techniques

Right thoracoscopy: performed under general anesthesia with selective orotracheal intubation, along with the placement of a nasogastric tube. Low-pressure CO₂ (10 mm) insufflations was used. The patient is positioned in an inclined at a 45-degree angle backward lateral decubitus, with the arm elevated and supported on a suspension frame. The operation was conducted with 3 trocars: two 10 mm and one 5 mm were inserted into the chest through intercostals spaces II, IV and VII. The surgical started with intraoperative identification and confirmation of the diagnosis, continued with a dissection using Ligasure sealing system Maryland forceps, excision of the abnormal gland, and extraction of the resected specimen using an endobag. Exsufflation of CO₂ at the end of procedure without pleural drainage.

A right minithoracotomy

A 2-4 inches small incision was performed between the ribs, on the right side of the chest, closed to the nipple line. This approach avoids the need to cut through the breastbone (sternotomy), leading to reduced pain, smaller scars, and faster recovery times.

11 patients (14%) had a Mediastinal Parathyroid Adenoma (MPA). Of these 5 and 6 patients were operated by cervical and mediastinal approaches (sternotomy $n=3$, thoracotomy $n=1$, minithoracotomy $n=1$, and thoracoscopy $n=1$) respectively. Undescended abnormal parathyroid gland was found in 4 patients (3 on the right and one on

the left side of the neck) and one abnormal gland was found in the left jugulocarotid sheath in 2 patients. In all the patients, the recurrent nerves were visualized and preserved. All the abnormal parathyroid gland(s) was or were excised (three-and-the half parathyroidectomy associated to thymectomy when all parathyroid glands were excised) and frozen sections were obtained. Other visualized normal glands were only marked with a clip or long silk suture. Definitive pathology study was obtained for all resected tissues.

Following appropriate surgical treatment and pathologic assessment, there were parathyroid adenomas in 62 patients (76%), polyglandular lesions in 15 patients (19%), and parathyromatosis in 4 patients (5%). Among polyglandular lesions, 10 lesions were identified as parathyroid hyperplasia (12%) and 5 of two or more adenomatous lesions each (7%). The weights of the adenomas ranged from 57 to 15768 mg, and mean size in greatest diameter was 27 mm (7 mm to 46 mm). The supernumerary gland was noted in 6 patients (7%).

76 patients (94%) were cured during a median follow-up period of 48 months (range 6 to 321). 31 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 4 patients. In this series, no patient developed persistent hypoparathyroidism, permanent recurrent laryngeal nerve palsy or compressive neck haematomas. 5 patient (6%) developed hypercalcemia within few months to few years after surgery.

The hospital stay was one day, 2 days, and more than 2 days in 90%, 6%, and 4% of cases respectively. Postoperative Intensive Care Units (ICU) stay for 24 to 48 hours was necessary in 4 patients.

Comparison of groups 1 and 2

There were 49 patients in Group 1 and 32 patients in Group 2. 11 patients (14%) had an MPA, 4 in group1(8%), and 7(22%) in group 2(statistically significant difference). Of these 5 and 6 patients were operated by cervical (45%) and mediastinal (55%) approaches (sternotomy n=3, thoracotomy n=1, minithoracotomy n=1, and thoracoscopy n=1) respectively. For all the series, 93% of abnormal parathyroid gland(s) were operated via a cervicotomy and 7% via a mediastinal approach. We noted the same distribution of gender in the 2 groups. Both sex groups were comparable regarding median age (56 years for women, 58 years for men, $p = 0.44$). Patient enrollment and assessment in groups was summarized in Table 1. The average preoperative PTH and serum calcium levels were 136 and 149 pg/ml, and 2.69 and 2.73 mmol/l in group 1 and 2 respectively. We did not note any significant differences in the mean preoperative serum calcium and PTH levels in the two groups. The postoperative outcomes, cure rates, and polyglandular lesions were comparable in the two groups. Parathyroid adenoma and parathyromatosis were showed in 80% and 72%, and in 2% and 9% of patients (statistically significant difference) in group 1 and group 2 respectively. We noted a statistically significant difference in the presence of supernumerary gland (4% vs. 13%) and mediastinal localization (8% vs. 22%) in groups 1 and 2 respectively. The cure rate was 94 % in groups 1 and 2. All the patients operated on for parathyroidomatosis, had a persistent(n=3) or recurrent(n=1) postoperative hypercalcemia.

Discussion

In our series, parathyroid adenoma and parathyromatosis were showed in 80% and 72%, and in 2% and 9% of patients (statistically significant difference) in group 1 and group 2 respectively. We

noted a statistically significant difference in the presence of supernumerary gland (4% vs. 13%) and mediastinal localization (8% vs. 22%) in groups 1 and 2 respectively. The cure rate was 94 % in the two groups. Pathologic results showed parathyroid adenomas, polyglandular lesions, and parathyromatosis in 76%, 19%, and 5% of cases respectively. In the literature, the causes of PHPT/RHPT are adenoma, parathyroid hyperplasia, parathyroid carcinoma, and other causes (parathyromatosis, autograft relapse) in 68%, 28%, 3%, and 1% of cases respectively. The cure rate varied from 80 to 97% [7,9-11,14].

In HPT, the persistent disease rate is reported in between 2% and 22% and the recurrent disease rate between 1% and 15% in literature. The incidence of PHPT is more common than RHPT (rate of PHPT: 60% - 85% vs rate of RHPT: 15% to 40%). The most common cause of development of per HPT is due technical problems in first surgery (failure to remove an abnormal parathyroid adenoma, lack of experience of surgeon). The most common cause of the reHPT is the multiple gland disease. reHPT could be occurred in case of hyperplasia or could be occurred due to supernumerary parathyroid gland. Other etiologies included: parathyroid carcinoma, parathyromatosis, metachronous parathyroid adenoma [4-14].

Localization studies with pre-operative imaging methods should be performed in all patients with perHPT and reHPT before reoperation [20-29]. In these cases, the sensitivity of USG varies between 38 and 72% and its Positive Predictive Value (PPV) ranges between 70 and 93%. The sensitivity of MIBI combined with SPECT/CT varied from 74% to 96% and PPV from 86% to 100% [20-23]. The sensitivity of 4D-CT in reoperative cases is 64% to 98% and is significantly higher than both scintigraphy and USG in lateralizing recurrent cases (77.4%, 46%, and 38.5%, respectively). For some authors, 4D dynamic MRI can accurately localize single gland disease 92% and multi-gland disease 74% [20,24]. In our series, the US, MIBI Scan, 4D CT, and MRI localization rate was 84%, 86%, 91%, and 88% respectively. F-Fluorocholine PET/CT has demonstrated a high preoperative detection rate for abnormal parathyroid glands, proving to be more accurate than cervical ultrasound and 99 m Tc-sestamibi scintigraphy particularly in patients with recurrent PHPT with negative or equivocal conventional imaging findings. In a meta-analysis comparing the diagnostic relevance of 18F-Fluorocholine and 11C-methionine, the sensitivity of fluorocholine was higher (92% vs. 80%, $p < 0.01$), and its PPV (94% vs. 95%, $p = 0.99$) was similar [25-30]. In reoperation, US-guided fine needle aspiration of the suspected parathyroid gland preoperatively may be useful by providing cytology and PTH levels. Selective venous catheterization is rarely used via the femoral vein and assessment of PTH in venous blood drained from the neck and mediastinum. Its sensitivity in P-HPT/R-HPT is 83.3% for solitary adenomas and 91.6% for parathyroid hyperplasia. Cervico-mediastinal arteriography could be used but the indication is very rare now a days [7,9-11,14,31-35].

Owing to the different embryological origin and more extensive migration, the inferior parathyroid glands are more frequently ectopic than the superior ones. The most common ectopic locations include the anterior mediastinum, retro tracheal/paraesophageal space, middle mediastinum, or within the substance of the thyroid gland, and carotid sheath. Ectopic inferior parathyroids are most frequently found in the anterior mediastinum, usually embedded in the thymus gland, while superior parathyroids are generally found in the posterosuperior mediastinum. Less commonly, MPAs may be located in the aorto-pulmonary window, and rarely in the pericardium and

right dome of the diaphragm [7-10,14-19]. The MPA showed in 14% of our patients.

Surgical indications for PHPT and RHPT are not different from the surgical indications for HPT. The risk of complications secondary to reoperation is markedly high, with up to 10% permanent RLN paralysis and up to 20% permanent hypoparathyroidism report [7,9,14]. When deciding on surgery for reoperative parathyroidectomy, the risk/benefit balance should be considered. The success rate of reoperation 80% to 97% (94% in our series). While surgery should be considered in patients with significant ongoing symptoms, significantly elevated Ca, non-operative treatment can be considered for patients who are mildly asymptomatic and have no systemic findings. While most MPAs can be resected via a cervical incision, it is not possible in 2% to 5% of cases [36-39] (7% in our series). Median sternotomy and lateral thoracotomy are the traditional methods for cases of deep mediastinal adenoma. Various minimally invasive approaches can be utilized, including thoracoscopy, video assisted thoracoscopic surgery, robotic-assisted thoracic surgery, the prevertebral cervical approach, and the subxiphoid approach. The overall success rate was reported as up to 98% to 100% [38,40-47]. Several useful intraoperative tools (like gamma probe, frozen section, intraoperative parathyroid hormone monitoring, visual identification of parathyroid by near-infrared autofluorescence angiography or indocyanine green angiography, intraoperative US, and bilateral jugular venous sampling) [16,48-52]. Facilitate accurate parathyroid assessment, but no tool can replace the surgeon's judgment and experience. Auto transplantation and cryopreservation should be considered when hypoparathyroidism occurs after parathyroidectomy or when the target parathyroid in reoperation is the only viable parathyroid tissue remaining. For patients who are poor surgical candidates, angiographic ablation or medical therapy such as cinacalcet can be used to treat hyperparathyroidism.

There are limitations to our study. This series is limited by its retrospective nature and the small sample size. Unfortunately, it is difficult to perform a prospective randomized control trial and the number of patients with hypercalcemia after parathyroidectomy is relatively low given that the success rate of the operation for HPT is very high.

Conclusion

Surgical failure is the most common complication of surgery for HPT. In the pre-operative evaluation, the initial diagnosis should be confirmed biologically in all patients who are evaluated with a pre-diagnosis of PHPT and RHPT. Localization studies with preoperative imaging methods was mandatory in all patients with PHPT and RHPT with a confirmed diagnosis and surgical indication. Non-invasive localization studies are very effective, which make the indication for invasive tests very rare at present. Parathyroid adenoma is more common in group 1, whereas parathyromatosis and supernumerary gland are more common in group 2. The cure rate of reoperation varied from 80 to 97%, 94% in this series.

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