Impact of preoperative imaging on surgical approach for primary hyperparathyroidism: Data from single institution in India

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ABSTRACT

Context: Preoperative localization of parathyroid adenoma is essential in deciding the surgical approach of parathyroidectomy. **Aim:** To describe clinical and biochemical profile, evaluate preoperative imaging modalities and surgical approach in patients with primary hyperparathyroidism (PHPT). **Methodology:** This was a retrospective study conducted at the single institution. All patients who underwent evaluation and surgery for PHPT from 2011 to 2015 were included in the study. **Results:** A total of 100 patients underwent surgery for PHPT. Mean (standard deviation) age was 51.6 (15.9) years with female to male ratio of 1.7:1. Forty patients had severe symptoms, and sixty had mild to moderate symptoms. The sensitivity of technetium-99m hexakis (2-methoxyisobutylisonitrile) (MIBI) scan and ultrasonography (USG) neck in identifying abnormal parathyroid gland was 93% (93/100) and 98% (98/100), respectively. The MIBI scan results of 90/93 (96.7%) patients corresponded with their surgical findings whereas preoperative USG findings of 96/98 patients (98%) showed correlation with operative findings. Intraoperative intact parathyroid hormone (IOPTH) levels at 10 min postexcision were measured in forty patients (minimally invasive parathyroidectomy = 38, bilateral neck exploration = 1, and unilateral neck exploration = 1). All patients except two had <50% fall in IOPTH. Adenoma weight was positively correlated with preoperative intact PTH. **Conclusion:** We found that USG has higher sensitivity (98%) than MIBI scan (93%) in localizing abnormal parathyroid gland. Moreover, USG had a higher preoperative localization accuracy (93%) than MIBI scan (90%), allowing to choose an appropriate surgical approach. A higher proportion of patients (60%) had mild/asymptomatic form of PHPT.

Key words: India, primary hyperparathyroidism, surgery, ultrasonography

INTRODUCTION

Primary hyperparathyroidism (PHPT) is defined as hypercalcemia resulting from the overproduction of parathyroid hormone (PTH) by one or more hyperfunctioning parathyroid glands. Classical PHPT patients present with recurrent renal stones, bone disease, peptic ulcer disease, pancreatitis, and proximal muscle weakness, whereas the asymptomatic form of PHPT is most commonly detected by elevated serum calcium on routine biochemical evaluation. With the introduction of the multichannel serum autoanalyzer in the 1970s, diagnoses of asymptomatic PHPT have risen in the West.[1] In contrast, classic symptoms of PHPT continue to be common in the East (80–100%) including India.[2]

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However, a rise in asymptomatic form has been reported recently in some Asian countries.[3] An asymptomatic form of PHPT was found in a significant percentage of North Indian patients in our recently published study.[4] Surgical treatment (parathyroidectomy) remains the treatment of choice for all symptomatic PHPT cases. Medical management of asymptomatic PHPT patients is controversial. The guidelines from the Third International Workshop on the management of asymptomatic PHPT clarified the indications of surgery in asymptomatic PHPT patients.[5]

Since the first parathyroidectomy performed by Mandl in 1925 in Vienna, bilateral neck exploration (BNE) under general anesthesia had been considered the standard of care for removal of hyperfunctioning parathyroid glands. Surgical techniques of parathyroid gland excision have evolved in last two decades allowing a focused or minimally invasive parathyroidectomy (MIP), thus avoiding BNE and its concomitant morbidity.[6,7] The philosophy of minimally invasive operative approach relies heavily on accurate preoperative localization. Technetium-99m hexakis (2-methoxyisobutylisonitrile) (99-mTc MIBI) scans and ultrasonography (USG) are the most widely used imaging modalities of choice for preoperative localization, whereas magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT) add more reliable anatomical information for good surgical planning. Intraoperative PTH (IOPTH) assays are being employed with ever-increasing frequency during parathyroid surgery as an intraoperative adjunct to determine whether additional hyperfunctioning PTH-secreting glands remain *in situ*.

The aim of the present retrospective study was to evaluate in detail the clinical presentation, biochemical profile, preoperative imaging modalities, and the surgical approach used in PHPT patients who underwent surgery from the year 2011 to 2015.

Methodology

All patients who underwent surgery for PHPT from 2011 to 2015 at our tertiary care hospital were retrospectively reviewed. Patients with secondary and tertiary hyperparathyroidism (HPT) were excluded. Patients were diagnosed as having symptomatic PHPT, if they had following symptoms or signs classically associated with hypercalcemia or PTH: Proximal muscle weakness, nephrolithiasis or nephrocalcinosis, pancreatitis, fragility fractures, and bone deformity. Patients lacking specific symptoms or signs traditionally associated with hypercalcemia or PTH excess were diagnosed as having asymptomatic or mildly symptomatic PHPT.

Data collection included personal history, family history, physical examination, and biochemical tests. These tests included fasting blood sample for total serum calcium, serum albumin, creatinine, inorganic phosphorus, alkaline phosphatase (ALP), intact PTH (iPTH), and 25-hydroxyvitamin D3 (25[OH] D). Serum calcium was adjusted for serum albumin using the following formula: Corrected serum calcium = total serum calcium (mg/dL) + 0.8 × (4 – patient's serum albumin [g/dL]). Serum total calcium, inorganic phosphorus, and creatinine concentrations and total ALP activity were measured using automated techniques. The normal laboratory ranges for adults were 8.4–10.2 mg/dL for total serum calcium, 2.5–4.5 mg/dL for serum phosphorus, and 30–120 U/L for serum ALP. Serum iPTH (normal laboratory range: 15–68 pg/mL) was measured using a chemiluminescent microparticle assay (Abbott architect i1000 SR, Abbott Laboratories, Chicago, IL, USA), and serum 25(OH)D was measured using a chemiluminescent microparticle assay (Abbott architect i1000 SR). USG neck and 99-mTc MIBI scintigraphy were performed in all patients. USG of the neck was primarily used not only to confirm the results of Tc-99m-MIBI scintigraphy but also to detect any suspicious thyroid nodule that could alter the imaging and surgical strategy. USG of the neck was performed by a single radiologist. MRI and CT of the neck were obtained when clinically indicated.

Surgery was performed in those patients who met the criteria for parathyroidectomy.[5] MIP included focused mini-incision (between the sternocleidomastoid and the infrahyoid muscles). When concordant results were obtained on USG and MIBI scan, MIP was performed. If only one test was positive, stage-wise, surgical neck exploration was done (MIP or unilateral exploration or bilateral exploration, depending on intraoperative findings). If both tests were negative, a BNE was performed. The weight, size, and number of parathyroid glands resected were recorded. Intraoperative PTH monitoring was introduced in 2014 at our center; therefore, IOPTH levels were obtained in patients operated in the year 2014 and 2015. The successful operation was defined using the Miami Criteria: A fall in PTH levels of >50% at 10 min postexcision compared to the pre-skin-incision level.[8]

If the patient was found to have intrathyroid nodule in preoperative USG, partial thyroidectomy was combined, if indicated depending on preoperative fine-needle aspiration cytology. If preoperative or intraoperative findings warranted extended resection (e.g., adhesion of parathyroid to surrounding structures) then *en bloc* resection was done in view of suspicion of malignancy. All specimens were confirmed as parathyroid tissue on frozen section. The histopathologic diagnosis of surgically dissected tumor specimens was established using conventional histologic criteria. Postoperative hypocalcemia was managed by intravenous calcium gluconate infusion and oral calcium and calcitriol depending on the severity of hypocalcemia.

Ethical clearance for this study was obtained from the appropriate institutional review boards.

Statistical analyses

Statistical analyses were performed using the SPSS software (version 11.5, Chicago, IL, USA). The data are expressed as mean ± standard deviation (SD), except for data that did not have a normal distribution, which are expressed as median (range). Variables were tested for normality using the Kolmogorov–Smirnov Z-statistic. Correlations were analyzed with the Spearman's rank correlation coefficient.

Results

A total of 100 patients underwent surgery for PHPT between the year 2011 and 2015. All patients had sporadic PHPT except one patient who had HPT-jaw tumor syndrome (HPT-JT). Table 1 shows the baseline clinical profile of all patients. Mean (SD) age was 51.6 (15.9) years, range (14–81).

Of the 100 patients, 37% were males and 63% were females with female to male ratio of 1.7:1. Among them, forty had severe symptoms attributable to the disease and sixty had mild to moderate symptoms. Among the severe symptoms, renal calculi (16%) dominated, with a close second in pancreatitis (14.0%). Other symptoms were acute kidney injury (5%), fractures (3%), and proximal muscle weakness (2.0%).

Table 2 presents biochemical variables of all the patients.

MIBI scan localized parathyroid adenoma in 93% of the cases. Most common site of localization on MIBI scan was the right inferior parathyroid adenoma (44/93).

Ultrasound neck localized parathyroid adenoma in 98% of the cases. Most common site of localization on ultrasound neck was the right inferior parathyroid adenoma (45/98).

SPECT-CT was performed in five patients with doubtful imaging on the USG and MIBI scan.

The sensitivity of MIBI scan and USG neck in identifying abnormal parathyroid gland in our study was 93% (93/100) and 98% (98/100), respectively. Of the seven MIBI negative patients, USG localized single adenoma (SA) in five patients (SA final diagnosis), multigland disease (MGD) in one patient (MGD final diagnosis), and one patient could not be localized by either MIBI or USG. Of the two patients not localized by USG, one was MIBI positive (SA) and one was not localized by either MIBI or USG. Among 92 patients who were localized both by USG and MIBI, concordance rate between MIBI and USG was 95.6% (88/92). Three out of four patients with discordant results had MGD on USG and single gland localization with MIBI scan (final diagnosis MGD in two and SA in one) and one patient had left inferior parathyroid localization with USG and left superior parathyroid localization with MIBI scan (final diagnosis left superior parathyroid adenoma).

Table 1: Clinical profile (*n*=100)

Variable	Frequency (%)
Age (years), mean±SD	51.6±15.9
Male:female ratio	1:1.7
Symptoms, frequency (%)	
Severe	40
Mild	60
Fragility fracture history	3.0
Pancreatitis	14
Acute kidney injury	5.0
Proximal muscle weakness	2.0
Renal calculi	16

SD: Standard deviation

Table 2: Biochemical profile[a]

Variable	Total (*n*=100)	
	Mean±SD	Median (range)
Age (years)	51.6±15.9	53.0 (14-81)
Serum iPTH (pg/mL)		350.8 (77-4181)
Postoperative iPTH (pg/mL)		17.0 (1-1581)
Serum calcium (mg/dL)	12.1±1.5	11.8 (10.3-20.3)
Postoperative calcium (mg/dL)	9.4±1.1	9.5 (6.0-11.9)
Serum 25(OH) D (ng/mL)		18.9 (3-126)
Serum alkaline phosphatase (U/L)		120.0 (59-2304)
Adenoma weight (g)	3.7±3.4	3.0 (0.2-14.8)

[a]Results are expressed as mean±SD for data with normal distributions and median (range) for nonnormally distributed data. iPTH: Intact parathyroid hormone, 25(OH)D: 25-hydroxyvitamin D, SD: Standard deviation

Ninety-five patients were a candidate for MIP based upon single gland localization with both MIBI scan and USG (*n* = 89), with USG only in MIBI negative patients (*n* = 5) and with MIBI scan only (*n* = 1). Four patients underwent BNE, reasons: One preoperatively not localized (final diagnosis, parathyroid hyperplasia) and three with a preoperative diagnosis of MGD on USG (final diagnosis, MGD in two and SA in one). One patient underwent unilateral neck exploration based on USG localization of the right inferior and right superior parathyroid adenoma (final diagnosis of the right inferior and right superior parathyroid adenoma). The MIBI scan results of 90/93 (96.7%) patients corresponded with their surgical findings. However, preoperative USG findings of

96/98 patients (98%) showed correlation with operative findings.

Intraoperative iPTH levels at 10 min postexcision were measured in forty patients (MIP = 38, BNE = 1, and unilateral neck exploration = 1). All patients except two had >50% fall in IOPTH. One patient with <50% fall in iPTH had MGD on USG and therefore underwent unilateral neck exploration with the removal of two adenomas. However, consent was not given for further exploration. In the second patient, BNE was done but all other three glands were normal and iPTH was normal at the end of the procedure; hence, the decision was taken for one abnormal gland removal only. Twenty-two patients had hypocalcemia in the postoperative period. Out of these, 14 were severely symptomatic requiring intravenous calcium and 8 were mild to moderately symptomatic.

Median (range) adenoma weight was 3.0 (0.2–14.8) grams. Using Spearman's correlation coefficient, adenoma weight was positively correlated with preoperative iPTH and IOPTH at 10 minutes. Moreover, there was a significant positive correlation between preoperative iPTH and ALP.

Discussion

Surgery for PHPT has evolved in recent times with the advent of better localization modalities and minimally invasive surgical techniques. Since single gland enlargement is the most common cause of PHPT, robust localization strategies are a must for the success of minimally invasive surgical parathyroidectomy. Our study is first in India to describe in detail the clinical and biochemical features, preoperative localization, and type of surgery performed with histopathological characteristics in patients with PHPT in such large number.

Mean age was 51.6 years with female predominance which is in accordance with the data from the West and our previously published study. Forty percent of patients had severe/classical symptoms, rest of the patients (60%) were either asymptomatic or had mild symptoms which included generalized bone pains, polyarthralgias, constipation, and mood swings. Asymptomatic PHPT is the predominant form in the West.[9] Although symptomatic PHPT continues to be the predominant form in the East, an increasing number of asymptomatic PHPT patients are being described recently from some Asian countries.[3] Our recent study reported a high proportion of asymptomatic patients which is in stark contrast to existing Indian studies on PHPT that showed that symptomatic PHPT is the predominant form.[4] Similarly, this study also showed that more than 50% of patients had mild/asymptomatic form. Even in the group of patients who had severe symptoms, none of them had bone deformities described in classical PHPT. Reasons for this higher proportion of mild/asymptomatic form of PHPT could be the wide application of routine biochemical checkups done at our center in screening high serum calcium levels and possibly better nutritional status of these patients as the majority was affluent. 25(OH)D estimations were available in 68 patients out of which 37 (54%) were vitamin D deficient (25(OH)D <20 ng/ml). Median 25(OH)D level was 18.9 ng/ml and no correlation was found between 25(OH)D level and symptomatology, adenoma weight, iPTH, or serum calcium levels.

Identification and localization of abnormal parathyroid gland are must to decide the surgical approach: MIP vs. BNE. MIBI and USG are the well-established methods for the preoperative localization of abnormal parathyroid gland. A meta-analysis reported sensitivities and specificities of 68–95% and 75–100%, respectively, for MIBI[10] and 34–92% and 92–97%, respectively, for USG.[11] Combining MIBI and USG may increase the sensitivity further to 95%.[12] Our study demonstrated a higher sensitivity of USG (98%) in localizing abnormal parathyroid gland as compared to aforementioned meta-analysis, as well as few recently published studies. Among seven patients who were MIBI negative, USG could localize SA in five and MGD in one patient. Ninety-three of 100 patients (93%) patients had a correct preoperative USG localization and could have been selected for MIP, only based on USG. Whereas, 90% patients had correct preoperative MIBI localization. MGD was misdiagnosed as SA with MIBI scan in three patients. One reason for the misdiagnosis of MGD as SA in MIBI scan is that all concentration may be focused on a single enlarged gland in MGD, missing other small lesions.

In experienced hands, USG is a highly sensitive technique. Higher sensitivity of USG as compared to MIBI has also been reported by others. A Korean Study found that sensitivity of MIBI scan was only 73.6% but that of USG was 90.6% in the localization of pathologic glands.[13] Similarly, excellent results were reported in a study of 77 patients in whom USG correctly localized the adenoma to a specific quadrant of the neck in 87% and to a specific side of the neck in 94%, with an overall sensitivity of 89%.[14] Similar to our results, in a study of 36 PHPT patients, the addition of USG led to the successful identification of the abnormal parathyroid gland in 19/36 (53%).[15]

Mihai *et al.* summarized the results of a large number of patient series available with different conclusions on imaging in PHPT.[16] Some support initial USG, followed by MIBI in doubtful cases.[17] Some advocate initial MIBI followed by USG in equivocal cases.[18] Many surgeons still prefer to use USG along with MIBI scan not only to localize abnormal parathyroid gland but also to evaluate the thyroid gland for synchronous nodules for which it is exquisitely sensitive technique.[19] However, the presence of concomitant thyroid nodules reduces the true positive results of both USG and MIBI scans[20] as it happened in one of our patients who was diagnosed as MGD with USG, but the final diagnosis was two benign thyroid nodules and single parathyroid adenoma. In five of the doubtful cases, we performed SPECT-CT. SPECT-CT has an advantage of diagnosing the correct position in some deep-seated adenomas like deep in tracheoesophageal groove or retroesophageal.

MIP has many advantages over BNE and has been associated with better cosmetic results from a smaller incision, quicker operative time, uneventful recovery, and a reduced risk of developing hypocalcemia and recurrent laryngeal nerve injury.[21] The use of IOPTH in combination with preoperative imaging has been useful to surgeons in performing MIP. Nussbaum *et al*. first described the measurement of IOPTH in parathyroidectomy.[22] Compared with baseline PTH level, a decline of 50% or more in IOPTH means that hyperfunctioning parathyroid tissue has been excised.[23]

Various IOPTH criteria (Halle, Miami, Rome, and Vienna) in MIP are used and each criterion has a distinguishing limitation.[24] Above all, the Miami Criteria, i.e., a decline in IOPTH of 50% or more at 10 min after excision, showed an acceptable sensitivity and specificity in detecting multiple gland disease.[8] There is a lot of controversy regarding the use of IOPTH. In recent years, there has been some suggestion that measurement of IOPTH may not be needed to perform MIP in all patients, especially when the results of preoperative USG and sestamibi are concordant and suggest single-gland disease.[25-27]

In our study, IOPTH levels were measured in forty patients, and all patients except one showed >50% decline in iPTH. Thirty-eight out of these forty patients were already a candidate for MIP based on preoperative localization. Two patients had MGD on the preoperative US and were the candidates for BNE. IOPTH remains useful in patients with discordant or negative preoperative localization studies to limit dissection and prevent operative failures due to MGD.

The intraoperative frozen section is a must for parathyroidectomy to confirm that excised tissue is parathyroid as sometime it may be confused with thyroid nodule or paratracheal lymph node.

Intraoperative findings may guide the surgeon to suspect a parathyroid carcinoma-like adhesion to surrounding structures as there is no confirmatory test to diagnose parathyroid carcinoma preoperatively. We found two of our cases as parathyroid carcinoma on the final histopathology. We did an *en bloc* resection in both the cases depending on the intraoperative findings.

On histopathology, 93 patients had SA, 3 patients had a double adenoma, 2 patients had hyperplasia, and 2 patients had parathyroid carcinoma. Twenty-two patients had hypocalcemia in the postoperative period. None of the patients had recurrent laryngeal nerve palsy.

The main limitation of the study was that follow-up serum calcium levels were not available to define curative parathyroidectomy. Another limitation is that it was a retrospective study.

In the present study, preoperative localization of SA by MIBI scan and USG allowed MIP to be performed in 95 PHPT patients, thereby avoiding unnecessary BNE. US in addition avoided MIP in patients who were candidates for BNE by localizing MGD preoperatively. Sestamibi scans continue to be the preferred method of imaging. However, high-frequency ultrasound has emerged as a very sensitive method if performed by an experienced investigator as done by a single radiologist at our center.

Conclusion

We found the higher sensitivity of USG (98%) than MIBI scan (93%) in localizing abnormal parathyroid gland. Moreover, USG had a higher preoperative localization accuracy (93%) than MIBI scan (90%), allowing to choose an appropriate surgical approach. A higher proportion of patients (60%) had a mild/asymptomatic form of PHPT.

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Conflicts of interest
There are no conflicts of interest.

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