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THE IMPORTANCE OF PREOPERATIVE PARATHYROID GLAND LOCALIZATION

İbrahim Tayfun Şahiner*
Hitit University School of Medicine, Department of General Surgery, Erol Olçok Training and Research Hospital, Çorum, Turkey *Corresponding Author

Murat Kendirci
Hitit University School of Medicine, Department of General Surgery, Erol Olçok Training and Research Hospital, Çorum, Turkey

ABSTRACT To assess the localization, surgical techniques and outcomes in patients undergoing surgery for hyperparathyroidism. Seventeen patients who underwent surgery due to hyperparathyroidism were evaluated. Demographic data, biochemistry results, radiological and scintigraphy localization studies were recorded. Also assessed were the surgical techniques as well as the results of the frozen sections and histopathological examinations. Of the 17 patients, 12 had primary and five had secondary hyperparathyroidism. Ultrasound and scintigraphy were used in 91.7% and 75% of the patients for localization, respectively. Minimally invasive parathyroidectomy, and thyroidectomy+parathyroidectomy was performed in 83.3% and 16.7% of the patients, respectively. Histopathological examination showed the presence of adenoma in 83.3% of the patients, and hyperplasia in 16.7%. In patients with secondary hyperparathyroidism in whom adequate localization with Spect CT/scintigraphy cannot be achieved, other imaging studies should be utilized to be able to remove all parathyroid tissues.

KEYWORDS : hyperparathyroidism, parathyroidectomy, ultrasound, parathyroid surgery

INTRODUCTION

Primary hyperparathyroidism (pHPT) is defined as the development of hypercalcemia and associated clinical manifestations due to excessive parathormone secretion as a result of the presence of an adenoma, hyperplasia, or carcinoma, alone or in combination, in the parathyroid glands [1]. On the other hand, (sHPT) arises from parathyroid hyperplasia from a number of causes including chronic renal failure (CRF), while (tHPT) is due to the acquired autonomy of one of the parathyroid glands [2,3].

Parathyroid surgery for HPT is not a frequently performed surgical procedure due to its low incidence. In the past, diagnosis of pHPT was mostly made after development of obvious clinical signs of the condition, while more recently further diagnostic work-up for high calcium levels detected during routine laboratory tests allow more frequent identification of this condition which is referred to as asymptomatic HPT [4].

Ultrasound (US) and sestamibi scintigraphy represent the two imaging modalities most frequently utilized to localize the parathyroid glands pre-surgically. If these fail to detect the localization, further imaging with SPECT CT/scintigraphy, computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) may be used for this purpose [1,5,6].

In the present study, adequacy of pre-surgical localization of parathyroid glands in accurately determining the surgical anatomical localization as well as the success rates of parathyroid surgery and surgical techniques were examined in a group of patients scheduled for surgery due to a diagnosis of hyperparathyroidism.

MATERIALS AND METHODS

After ethic committee approve (2017/29) 17 patients undergoing pHPT or sHPT surgery between 2011-2016 at the Department of General Surgery, Erol Olçok Research and Training Hospital, Hitit University were retrospectively evaluated. Age, gender, and the characteristics of clinical presentation were recorded. Prior to surgery calcium (Ca), parathyroid hormone (PTH), phosphorus (P), and alkaline phosphatase (ALP) levels were determined, while at 6 months of follow-up calcium, phosphorus, and parathyroid hormone levels were re-checked in those who had had sHPT

High-resolution cervical US (CUS) and sestamibi scintigraphy were performed to localize parathyroid glands, while cases with sHPT were assessed using Spect CT/scintigraphy. If these failed to localize the glands, CT and MRI were performed. Presence of additional thyroid lesions was ascertained using thyroid US. In addition, an abdominal US (ABUS) was performed to check for the presence of complications associated with hyperparathyroidism such as urinary stones and a bone densitometry was performed to determine those with a T score below -2.5.

Those with parathyroid adenoma only underwent open minimally invasive parathyroidectomy (OMIP), while those with multi-nodular goiter (MNG) underwent thyroidectomy plus parathyroidectomy. In those with sHPT bilateral neck exploration (BNE), removal of four parathyroid glands and auto implantation of ½ parathyroid gland into sternocleidomastoid, and labelling with metal clips were performed. All procedures were carried out under general anesthesia. In those patients with a surgical indication, frozen biopsy was done and the definitive diagnoses were based on the results of histopathological examination.

RESULTS

Of the 12 patients with pHPT 10 (83.3%) were female and 2 (16.7%) were male, with a mean age of 56 years (range: 28-75 years). Nine patients (75%) were over 50 years of age, while three (25%) were below that age.

Eight of the cases clinically presenting with pHPT (66.7%) had asymptomatic hypercalcemia detected during routine examinations, and four (33.3%) had classical symptoms (fatigue, diffuse body pain, and nausea. Five cases had been referred to our center due to sHPT arising from CRF.

Pre- and post-surgery biochemistry results in patients with pHPT are shown in Table 1. As depicted in the table, the PTH level before surgery was 278 pg/ml vs. 28.7 pg/ml after surgery, and the corresponding calcium concentrations were 11.9 mg/ml and 8 mg/dl, respectively.

Among patients with pHPT, CUS was able to accurately localize the parathyroid glands in 91.7% (n=11), while it failed in 8.3% (n=1). Parathyroid scintigraphy showed scintigraphy involvement in nine patients (75%), while 2 (16.7%) were involved, and scintigraphy could not be performed in one subject (8.3%). In all patients with scintigraphy involvement, the lower pole of the thyroid was the site of involvement. No patients with pHPT required further imaging with CT, MRI, or Spect CT/scintigraphy etc. for lesion localization.

Thyroid US in this patient group showed MNG in seven (58.3%) normal thyroid in four (33.3%), and recurrent nodular goiter in one (8.3%). Of the overall patient group, 66.7% had additional thyroid pathology.

Bone densitometry in in L1-L4 in patients with pHPT showed a T score of < -2.5 in six (50%), and > -2.5 in two (16.7%), while four patients (33.3%) had no bone densitometry measurement.

Pre-operative ABUS was normal in 11 patients (91.7%), while 1 (8.3%) had renal stones.

Surgically, an OMIP procedure was performed in seven (58.3%) (Figure 1) while bilateral thyroidectomy+parathyroidectomy was performed in three (25%) patients with additional thyroid pathology, and 2 (16.7%) had unilateral thyroidectomy + parathyroidectomy.

Figure 1: Removal of the parathyroid gland

Tissue identification with frozen section was done intraoperatively in seven patients (58.3%), while this was not deemed necessary in five (41.7%). Frozen section examinations all revealed the presence of parathyroid tissue. (Figure 2)

Figure 2: Parathyroid adenoma examined by frozen section

Histopathological examination of the surgical specimens in pHPT patients showed the presence of parathyroid adenoma in 10 patients (83.3%), while 2 (16.7%) had parathyroid hyperplasia. Among those subjects undergoing thyroidectomy due to additional thyroid pathology, 3 (25%) had incidental papillary micro carcinoma, while two (16.7%) had nodular goiter. Parathyroid was localized in the lower pole of the thyroid gland in all cases.

TABLE – 1 Biochemistry results of the patients

No	Preoperative				Postoperative				6. Month		
	Ca	Pth	P	ALP	Ca	Pth	P	ALP	Ca	P	Pth
1	13,8	302	2,3	137	8,2	2,60	2,8	53	-	-	-
2	12,5	245	2,4	167	7,4	5,40	5,5	96	-	-	-
3	11,8	287	2,2	395	6,5	2,50	5,5	150	-	-	-
4	11,2	149	2,4	96	8	3	3,4	81	-	-	-
5	12	146	2,2	111	8,8	4,90	3,6	81	-	-	-
6	10	215	2	380	8,9	118	3,3	60	-	-	-
7	11,9	185	1,1	197	7,9	13,5	1,7	143	-	-	-
8	10,7	65	2,9	83	7,7	34,3	2,8	80	-	-	-
9	11,5	165	3,3	376	8,3	39	2,3	105	-	-	-
10	12,8	651	2	497	8	37,9	4,4	102	-	-	-
11	12,7	562	1,9	234	7,8	14	1,8	161	-	-	-
12	13	367	1,9	110	8,7	69,5	2,5	110	-	-	-
13*	11,8	1521	5,8	2710	8,3	70	3,2	261	8,3	2,6	205
14*	10,7	2403	6	538	6,7	13,2	4,2	1240	7,5	3,5	8,5
15*	10,3	1856	6,4	469	4,3	1,3	4	133	6,1	4,2	30
16*	11,4	1241	6,3	269	6,7	3,8	2,5	46	9	4	1,2
17*	10,7	2218	8	399	6,6	350	8,1	465	9,1	5,2	35620

* sHPT

Ca: Calcium (N:8-10.5 mg/dl) P: phosphorus (N:2,5-4,5mg/dl), ALP: Alkaline phosphatase (N:35-104 U/L), Pth: Parathormone (N:15-65 pg/ml)

Of the five patients referred to our clinic due to sHPT, 4 (80%) were male and 1 (20%) was female, with a mean age of 42 years (35-63). Four patients were less than 50 years of age, and one was greater than 50 years of age. All patients were undergoing hemodialysis for an average duration of 8 years.

Parathyroid glands could be detected with CUS in four patients (80%), while it was not possible to localize parathyroid glands in one patient (20%) with this method.

In all patients with sHPT, parathyroid glands were assessed with Spect CT/scintigraphy, with no involvement in three patients (60%), vs. involvement in two (40%). Except for renal parenchymal injury, no other pathological findings could be detected with ABUS. Of the patients undergoing a TUS due to possible additional thyroid pathology, 3 (60%) had MNG.

L1-L4 T score in bone densitometry measurements in sHPT patients showed a t score < -2.5 in two (40%), while three (33.3%) had no bone densitometry measurements.

Surgery in sHPT patients involved BNE + removal of four parathyroid glands + and auto implantation of ½ of a parathyroid gland into sternocleidomastoid muscle. Intraoperatively, five patients with sHPT required frozen section examination, all of which subsequently proved to be parathyroid hyperplasia

DISCUSSION

Hyperparathyroidism is a clinical condition that results from excessive secretion of parathormone from the chief cells of the parathyroid gland associated with increased blood PTH, Ca levels, and decreased P levels [7-9]. Solitary parathyroid adenoma, parathyroid hyperplasia, multiple parathyroid adenomas, and parathyroid carcinoma are responsible for 80-85%, 10-15%, 2-3%, and 1% of the cases with pHPT. Five to 10% of parathyroid adenomas have an ectopic localization, 95% being within the thymus, and 5% being mediastina [7-10]. Of the cases with pHPT in our study, 10 (83.3%) had parathyroid adenoma, and two (16.7%) had parathyroid hyperplasia, thought to be consistent with previous reports.

The incidence of hyperparathyroidism in the general population is between 0.1 and 0.3%, and postmenopausal women over 40 years of age have an increased risk for developing this condition [9, 11]. Accordingly, 83.3% of our patients with pHPT were female, and 75% were over 50 years of age.

The most common clinical sign of pHPT is asymptomatic hypercalcemia. These patients are generally identified during routine biochemical screening [12]. On the other hand, symptomatic patients mostly present with fatigue and weakness [7, 11]. In our study, 8 of the patients (66.7%) were diagnosed following detection of asymptomatic hypercalcemia during routine screening, while 4 patients (33.3%) had classical symptoms (fatigue, weakness, diffuse body pain, nausea). Again, in line with previous reports, patients operated after detection of asymptomatic hypercalcemia represented the majority of our participants [9, 13-15].

High resolution cervical US (CUS) and/or Spect CT, CT, MRI, PET, and venous sampling methods are used to localize the parathyroid glands [1, 5-7, 16-20]. Accurate pre-surgical localization of the parathyroid glands has gained more significance after widespread acceptance of OMIP as the surgical intervention of choice. Also, due to the progressive decrease in surgical success rates after each intervention for persistent or recurrent hyperparathyroidism, correct localization has become even more important. Initially, sestamibi scintigraphy and CUS are recommended for this purpose [6, 19, 21]. CUS has been reported to provide a specificity and sensitivity of 95% and 75-80%, respectively [20]. Among our participants, high resolution CUS was able to successfully localize the parathyroid glands in 91.6% of pHPT patients, consistent with the figures reported in the literature. Although left lower pole of the thyroid was initially suggested as the site of localization in one patient, an intrathymic localization, the second most common site of ectopic, was subsequently found.

The reported specificity and sensitivity for scintigraphy is 90% and 75%, respectively. Scintigraphy is an important tool to detect the localization of ectopic parathyroid glands [6, 19]. In this study, scintigraphy was able to correctly define the localization of parathyroid glands in 75% of the cases. Presence of additional thyroid lesions reduces the specificity and sensitivity of hyperparathyroidism. In two of our patients' scintigraphy images could not be obtained, and in both of these patient's additional thyroid disease was present.

The lower sensitivity rate observed in our study as compared to previous reports was explained based on additional thyroid conditions. In a single patient, CUS was considered adequate and no scintigraphy was performed. Combined use of these two modalities has been reported to provide a specificity and sensitivity of up to 97% for the localization of the parathyroid glands [21, 22].

When localization is not possible with US and scintigraphy and/or ectopic localization is suspected or in patients with previous parathyroid surgery who have persistent or recurrent parathyroid disease other imaging modalities such as CT, MRI and Spect CT/scintigraphy should be preferred [5, 21, 22]. In our study, CT, MRI, or Spect CT/scintigraphy were not required in pHPT patients.

In approximately up to 70% of the patients' bone cysts, Brown's tumor, pathological fractures, or bone pain may be seen due to demineralization and osteoclastic activity of the skeletal system [9, 13]. In 75% of our patients the T score at L1-L4 was < -2.5 with bone densitometry, demonstrating the presence of osteoporosis and/or osteoporosis, which are among the end organ effects associated with pHPT. In patients, presenting with urinary signs and symptoms such as polydipsia, polyuria, or hypertension several pathological findings such as nephrolithiasis or urolithiasis may be demonstrated. Such signs and symptoms occur in nearly 15 to 20% of the patients [1, 23]. In this study, 8.3% of the pHPT patients had nephrolithiasis. Additionally, gastrointestinal complaints such as nausea, vomiting, peptic ulceration, or constipation may occur in approximately 5% of the cases [9].

Bilateral neck exploration (BNE) or unilateral neck exploration (UNE) may be associated with an increased rate of temporary or persistent complications, as these modalities require unnecessary exploration [24-26]. Absence of a difference between BNE and Open minimally invasive parathyroidectomy (OMIP) in terms of recurrent or persistent hyperthyroidism and in terms of success rate has led to widespread acceptance of the latter technique. Also, OMIP is a feasible and safe technique associated with low morbidity and good cosmetic results that may be performed as day-surgery, leading to reduced costs and more frequent use by the surgeons. In our study, all seven patients with no additional thyroid disease underwent OMIP and they were discharged on postoperative day 1 without complications.

Enbloc ipsilateral thyroidectomy + parathyroidectomy is recommended to prevent recurrences in patients with parathyroid cancer. In our series, there were no patients with parathyroid carcinoma.

Concurrent occurrence of pHPT and medullary thyroid cancer is common in subjects with MEN-2A, while co-occurrence with non-medullary thyroid carcinomas can be seen in 2.4 to 3.7% of the patients [7-9, 11]. In the present study, incidental thyroid micro papillary cancers were detected at a higher frequency (25%) than reported in the literature, and this was considered to represent a coincidental finding [27]. Two of these patients underwent total thyroidectomy, precluding the need for additional surgery, while total thyroidectomy was performed in a patient who previously had unilateral thyroidectomy.

These surgical procedures should not be taken as guarantee for the removal of the parathyroid gland with the pathological condition, and the diagnosis should be confirmed intraoperatively to avoid recurrent and/or persistent disease. For this purpose, a quick intraoperative PTH assay may be utilized and a PTH level less than 50% of the pre-operative level should be considered as an indication of successful intervention [28]. Generally, previous reports have not recommended routine use of this approach and advised its use when localization is problematic based on scintigraphy, US or MRI results. Additionally, a frozen section examination may also be performed, which confirms the presence of parathyroid tissue, without differentiating between adenomas and hyperplasia [22, 28-30]. In this study, a frozen section was considered necessary in 58.3% of the pHPT patients. In all of these cases, frozen section confirmed the diagnosis intraoperatively by demonstrating the presence of parathyroid tissue.

In addition, parathyroid glands may be removed under intraoperative radioisotope guidance using the portable gamma probe. A basal activity exceeding 20% in the excised adenoma suggests a solitary parathyroid adenoma. This also facilitates the detection of ectopic adenomas [17, 18, 25]. Thus, without the need for frozen section or quick PTH assays, removal of the pathological parathyroid gland may be performed.

While the success rates in surgery is between 95 and 99% for experienced parathyroid surgeons, this figure is down to 70 to 80% among less experienced surgeons, particularly in BNE procedures. In our study, the success rate in parathyroid surgery among pHPT patients was 100%, with no recurrent or persistent disease during follow-up.

In this study, 80% of the five patients developing sHPT after CRF were male, and 80% were under 50 years of age. Despite the absence of active complaints at presentation, this was probably due to the frequent occurrence of symptoms such as abdominal pain, bone pain, or itching in CRF patients that are also commonly observed in sHPT. All of these patients were diagnosed during the routine laboratory work-up of the hemodialysis program. Of the patients undergoing bone densitometry, two had a T score of less than -2.5 and 80% were under 50 years of age, suggesting the presence of premature osteoporosis.

CUS was able to localize the parathyroid glands in four patients (80%), while this technique failed in one patient (20%).

Of the patients undergoing Spect CT/scintigraphy, 3 (60%) was involved, while two were involved. All patients without involvement had MNG as the additional thyroid condition. Presence of additional thyroid pathology was thought to prevent the involvement in Spect CT/scintigraphy. Furthermore, removal of 99mTc-MIBI in the hyperplasic parathyroid gland occurs at a higher rate than normal. A histopathological diagnosis of parathyroid hyperplasia in all sHPT patients was also thought to contribute to the absence of involvement.

The surgical technique in sHPT or tHPT involves the assessment of parathyroid glands by BNE + total removal of all four gland + auto implantation of the ½ of an intact gland into forearm or strep muscles or removal of the ½ of an intact gland [25, 31, 32]. In our study, five patients with sHPT had BNE + removal of four parathyroid glands + auto implantation of ½ parathyroid into the sternocleidomastoid muscle and labelling of this site with metal clips. Our aim was to facilitate the detection of viable auto implanted tissue in scintigraphy examinations performed during longer follow-up. In three patients, the viability of the parathyroid glands auto implanted into the sternocleidomastoid muscle was ascertained by normal or near-normal PTH levels, while detection of a PTH level of 1.2 pg/dl at 6 months of follow-up was considered to indicate loss of viability in the auto implanted parathyroid tissue. It was not possible to assess the viability of the auto implanted parathyroid tissue due to elevated PTH caused by persistent disease. Other than auto implantation technique, ½ of an intact parathyroid gland may be left in place, although it could be potentially disadvantageous when repeated surgery is needed due to recurrent or persistent disease. Auto implantation may be performed either in the sternocleidomastoid muscle or in the forearm subcutaneously. In this study, forearm auto implantation was avoided due to the presence of arterio-venous shunts in the forearm region.

In all sHPT patients, pathological examination showed the presence of parathyroid hyperplasia. Thus, 17 patients, 12 with pHPT, and 5 with sHPT, had surgery. Of these, OMIP was carried out in 7; also 5 cases with additional thyroid lesions had bilateral and/or unilateral thyroidectomy + parathyroidectomy and 5 others with sHPT had BNE + removal of 4 parathyroid glands + auto implantation of ½ thyroid gland into the sternocleidomastoid muscle. A single patient had persistent disease after surgery. Overall, our success rate was 94%. The major clinical finding at presentation was asymptomatic hypercalcemia detected during routine laboratory work-up in patients with pHPT. Histopathology showed the presence of parathyroid adenoma in 83% and parathyroid hyperplasia in 16% of the cases with pHPT, while all patients with sHPT had parathyroid hyperplasia. When one considers the ever-increasing trend toward minimally invasive surgery, more significance is now placed on the pre-surgical localization of parathyroid glands. Also, despite the decreased sensitivity of scintigraphy and CUS due to additional thyroid disease, our results suggest that these two modalities alone or in combination should be adequate for localization in most of the cases.

CONCLUSIONS

In sHPT patients with inadequate localization with Spect CT/scintigraphy, complete removal of parathyroid glands should be possible with localization studies with PET, CT, or MRI or intraoperative venous sampling or radio-guided selective parathyroidectomy techniques.

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