ARE THYROID NODULES AN OBSTACLE TO MINIMAL INVASIVE PARATHYROID SURGERY? A SINGLE-CENTER STUDY FROM AN ENDEMIC GOITER REGION

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Abstract

Context. Minimally invasive parathyroidectomy (MIP) procedure has become a widely accepted alternative to the standard four-gland exploration nowadays.

Objective. The aim of this study was to evaluate patients with primary hyperparathyroidism (PHPT), who had been treated with thyroidectomy and bilateral neck exploration (BNE), rather than MIP alone, due to coexisting thyroid nodules and to determine the benefits of simultaneous thyroidectomy and the possible negative outcomes of not performing this additional procedure.

Design. There were 185 patients who were operated for PHPT at our clinic from January 2014 to November 2016.

Subjects and Methods. 50 patients meet inclusion criteria: have thyroidectomy at the same time of parathyroid surgery, have concordant findings of parathyroid adenoma localization at preoperative MIBI-SPECT and the cervical US and have not had malignancy on fine needle aspiration biopsy (FNAB).

Results. The mean age of the patients was 55.3±10.4, and female to male ratio was 7:1. All patients had parathyroidectomy with BNE and thyroidectomy: 11 (22%) patients had micropapillary thyroid cancer (mPTC), 2 (4%) had papillary thyroid cancer (PTC).

Conclusion. The results were inconclusive in clearly demonstrating which patients presenting with coexisted thyroid nodules should undergo thyroidectomy, rather than MIP, and which should be monitored for thyroid nodules after MIP. However, we consider that in cases who are not clearly indicated for thyroidectomy, MIP followed by monitoring of thyroid nodules can be the treatment approach.

Key words: Primary hyperparathyroidism, thyroid nodules, thyroid cancer, minimally invasive parathyroid surgery.

INTRODUCTION

Primary hyperparathyroidism (PHPT) occurs due to over secretion of parathyroid hormone (PTH) by one or more pathological parathyroid glands and causes

hypercalcemia, hypercalciuria, and hypophosphatemia. It is the third most common endocrine disorder, with a prevalence of 0.1 % in the general population (1). Treatment for PHPT has been defined as complete excision of the involved parathyroid tissue or tissues. Traditional surgical management is the identification of all four parathyroid glands with bilateral neck exploration (BNE) through a transverse cervical incision. Today, minimally invasive parathyroidectomy (MIP) has become a widely accepted alternative to the standard four-gland exploration (2). However, this procedure requires accurate preoperative localization of parathyroid adenoma.

The coexistence of thyroid nodule and PHPT presents difficulties with localization of parathyroid adenoma using imaging techniques. In PHPT patients, two imaging examinations are routinely performed for the MIP procedure: cervical ultrasonography (US) and 99m Tc-sestamibi scan (MIBI) (3). Single photon emission computed tomography (SPECT) has further improved adenoma localization and detection rates (4, 5). The prevalence of concomitant thyroid disease in patients undergoing neck exploration has been reported to range from 17 to 84 % for primary hyperparathyroidism (6) and 2 to 17.6 % for malignant thyroid pathology (4, 7). In these patients, some studies have recommended thyroid resection concomitant with parathyroidectomy to minimize complications of reoperative surgery, such as recurrent laryngeal nerve palsy and permanent hypocalcemia (8-12).

Turkey is an endemic goiter region due to iodine deficiency (13). In Turkey, nodular thyroid disease is an important public health issue, with the prevalence of multinodular and nodular goiter being reported as 42% and 14.6%, respectively (14). In line with this high rate of multinodular goiter, concomitant thyroid disease in PHPT patients has also reached 84 % (7).

The aim of this study was to evaluate patients with PHPT, who had been treated with thyroidectomy

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and BNE, rather than MIP alone, due to coexisting thyroid nodules. We aim to determine the malignancy rate, possible predictive factors for malignancy, the benefits of simultaneous thyroidectomy and the possible negative outcomes of not performing this additional procedure.

MATERIALS AND METHODS

From January 2014 to November 2016, 185 patients with PHPT were operated on the Breast and Endocrine Surgery Clinic of Ankara Numune Research and Education Hospital, Turkey. Of the 185 patients, 77 underwent thyroidectomy during the same procedure and 54 of these patients had concordant findings of parathyroid adenoma localization at preoperative MIBI-SPECT and cervical US. Nineteen patients that did not have concordant findings on imaging studies and four patients that had malignancies revealed by fine needle aspiration biopsy (FNAB) were excluded. Thus, a total of 50 patients were included in further evaluation. Additionally, 40 patients who underwent MIP alone have been included to this study as control group.

The patients' data were retrospectively obtained from hospital records. Demographic and clinical information including age, gender, and history of neck surgery and radiation exposure was noted. Parathyroid surgery had been performed with BNE in all patients. The patients in control group underwent traditional open MIP through a unilateral 2.5 cm transverse cervical incision. Frozen section examination had been undertaken for all excised parathyroid tissue. Concomitant thyroid procedures included lobectomy, total thyroidectomy, completion thyroidectomy, or total thyroidectomy with central neck dissection.

All 50 patients had undergone cervical US for thyroid nodules and parathyroid adenomas by experienced endocrinologists at our hospital. US-guided FNAB was also performed on patients who have consented for thyroid surgery with one or more suspicious features at one or more nodules on cervical US, including solid components, marked hypoechogenicity, microlobulations or irregular margins, microcalcifications, and a taller-than-wider shape in nodules. From the cervical US, the dimension of the most suspicious nodule, the number of suspicious features, and localization of the nodules were recorded.

All the patients underwent 99mTc-sestamibi scan and single photon emission computed tomography (MIBI-SPECT) for parathyroid localization at our

nuclear medicine clinic. Preoperative laboratory values obtained before surgery comprised calcium, PTH, vitamin D 25-OH, thyroid stimulating hormone (TSH), and glomerular filtration rate (GFR). PTH measurement method was immunoassay with monoclonal PTH specific antibody, and for 25 OH Vitamin D measurement method was electrochemiluminescence.

Concomitant thyroid disease includes benign and malignant nodules, Hashimoto's thyroiditis, toxic and nontoxic multinodular goiters. Hyperthyroidism, pressure of the enlarged nodule to airway, too many counts of nodule which cannot be followed up by FNAB, patients' desire for additional thyroid surgery, and Bethesda 3 FNAB result, constituted indications for thyroidectomy in this study. The treatment management of all PHPT patients including mentioned patients was decided by an endocrinology council attended by representatives of surgery, endocrinology, and nuclear medicine clinics in accordance with the latest published guidelines (15, 16).

Postoperative complications of thyroidectomy with BNE, such as persistent disease, recurrent disease, recurrent nerve palsy, and neck hematoma were also evaluated. All patients' postoperative calcium levels after 24 hours from surgery were also recorded.

Statistical analyses were performed using SPSS 17.0 (SPSS Inc, Chicago, IL). The normality of data distribution was assessed by the Kolmogorov-Smirnov test. All values were expressed as mean $\pm$ SD or counts (percentage) unless otherwise specified. Comparisons were made using the chi-square test or Fisher's exact test for categorical data and the Mann-Whitney U test for continuous variables.

Ethical approval was not sought for this research due to its retrospective nature.

RESULTS

Fifty patients were included in this study, with a mean age of 55.3 ± 10.4 , and the female-to-male ratio was 7:1. All patients had undergone parathyroidectomy with BNE. Additional procedures undertaken were: total thyroidectomy for 39 patients (78%), lobectomy for five patients (10%), total thyroidectomy with central lymph node dissection for three patients (6%), and completion thyroidectomy for three patients (6%). All procedures were carried using an open approach (scar length >2 cm).

All patients had multinodular goiter on preoperative neck ultrasound and five (10%) had hyperthyroidism according to preoperative laboratory

findings. The results of preoperative FNAB were as follows: insufficient for two patients (4%), non-diagnostic for 18 patients (36%), benign for 14 patients (28%), and atypia of undetermined significance/follicular lesion of undetermined significance for eight patients (16%) (Table 1).

According to the final pathology reports on thyroid specimens, 11 (22%) patients had micropapillary thyroid cancer (mPTC), two (4%) had papillary thyroid cancer (PTC), nine (18%) had thyroiditis, 27 (54%) had nodular hyperplasia, and one had a follicular adenoma. The final pathology reports on parathyroid specimens revealed single adenoma in 39 patients (78%), double adenoma in two patients (4%), hyperplasia in four patients (8%), and normal parathyroid in five patients (10%). There was no persistence or recurrence in the five patients with normal parathyroid. Overall, persistent PHPT after surgery was seen only in two patients, who were found to have another adenoma during reoperation. There was no recurrence in any of the patients. Detailed information about the patients is summarized in Table 1.

There were no statistical differences between patients with thyroid malignancy and benign thyroid lesions concerning demographic features (age and gender), preoperative laboratory findings (calcium, vitamin D, PTH, and phosphorus), and suspicious thyroid nodule size (Table 2). Thirty-five patients (70%) had a parathyroid adenoma on the same side with the suspicious thyroid nodule. Of these patients, nine (18%) had malignancy and 26 (52%) had benign thyroid lesions (Table 3). There was no statistical difference between the two groups ($p>0.05$).

Two patients (2%) had persistent PHPT and required reoperation two months after the first surgery. After one month from the first operation MIBI-SPECT scan showed a second adenoma at contralateral side to the first adenoma in first patient and at the mediastinum in the second patient. Both patients' second adenoma could not be seen at first scan. The second adenoma had been found in the carotid sheath at second operation which could be defined as an ectopic location in the first patient. In the second patient, a second adenoma was found at mediastinum with sternotomy. The final

Table 1. Features of patients

Feature	n (%)			
Age	Mean: 55.3 ±10.4 (28-85)			
Sex	Female	44 (88%)		
	Male	6 (12%)		
	Insufficient (Bethesda I)	2 (4%)		
	Non-diagnostic (Bethesda I)	5 (10%)		
FNAB	2 or more non-diagnostic (Bethesda I)	13 (26%)		
	Benign (Bethesda II)	14 (28%)		
	Atypia of undetermined significance/follicular lesion of undetermined significance (Bethesda III)	8 (16%)		
Preoperative disease	Multinodular goitre	50 (100%)		
	Hyperthyroidism	5 (10%)		
	Total thyroidectomy	39 (78%)		
	Lobectomy	5 (10%)		
Surgery types	Total thyroidectomy with central lymph node dissection	3 (6%)		
	Completion thyroidectomy	3 (6%)		
	Thyroiditis	9 (18%)		
Final pathology report of the thyroid	Nodular hyperplasia	27 (54%)		
	Follicular adenoma	1 (2%)		
	mPTC	11 (22%)		
	PTC	2 (4%)		
Side of thyroid pathology to parathyroid adenoma	Same side	35 (70%)	Benign	mPTC
	Contralateral side	15 (30%)	26 (52%)	8 (16%)
			Benign	PTC
			8 (16%)	1 (2%)
			6 (12%)	1 (2%)
Parathyroid pathology	Single adenoma	39 (78%)		
	Double adenoma	2 (4%)		
	Hyperplasia	4 (8%)		
	Parathyroid	5 (10%)		
Complications	Recurrent nerve palsy	0 (0%)		
	Neck hematoma	0 (0%)		

Table 2. Preoperative findings

		Mean	p value
Age (years)	Benign	57 ±10	0.086
	Malignant	51 ±12	
Preoperative P (mg/dL)	Benign	2.59 ±0.58	0.438
	Malignant	2.46 ±0.47	
Preoperative Vit D (ng/mL)	Benign	14.6 ±12.4	0.319
	Malignant	16.59 ±10.46	
Preoperative PTH (pg/mL)	Benign	217.03 ±161.3	0.748
	Malignant	278.33 ±365.68	
Suspicious nodule size (mm)	Benign	15.97 ±13.57	0.684
	Malignant	15.73 ±15.19	

Table 3. Final pathology reports of the patient

		Malignant n(%)	Benign n(%)	Total n(%)	p*
Sex	Female	11 (22%)	33 (66%)	44 (88%)	0.643
	Male	2 (4%)	4 (8%)	6 (12%)	
Counter side to parathyroid adenoma		4 (8%)	11 (22%)	15 (30%)	0.602
Same side with parathyroid adenoma		9 (18%)	26 (52%)	35 (70%)	
Total		13 (26%)	37 (54%)	50 (100%)	

pathology report confirmed double adenoma in both two patients. Overall, there were no recurrences of the disease, recurrent nerve palsy or neck hematoma after surgery.

There were 32 (80%) females and 8 (20%) males in the control group who underwent MIP alone. Mean age of control group was 54.1 (24-86). 23 (57.5%) patients had concomitant thyroid nodule but they did not undergo thyroidectomy due to singularity, lower diameter (Mean: 0.76 cm Min-Max: 0.3-1.7), and Bethesda 2 FNAB results of nodules. 17 (42.5%) patients had no thyroid nodule. All these patients had concordant findings on US and MIBI-SPECT. Only one (2.5%) patient had persistent disease after MIP due to double adenoma which could have been diagnosed after reoperation. After reoperation there was no persistence or recurrence. There was no recurrence of the disease, recurrent nerve palsy or neck hematoma in the control group.

The rates of postoperative hypocalcemia (<8.5 mg/dL) in thyroidectomy with BNE group and control group were 22% and 15% respectively. There was no statistical difference between groups considering postoperative hypocalcemia (p=0.432).

DISCUSSION

The traditional surgical procedure for PHPT is BNE. The cure rates of this procedure at endocrine neck surgery clinics have increased to 95%. In this study, the cure rate for the selected patients was 98%. MIP is a widely accepted procedure due to the similar

success rates to BNE and has many advantages, such as smaller incision, shorter operative time, lower complication rate, reduced postoperative pain, and outpatient setting (2). However, MIP requires a careful and proper preoperative localization of lesions, which may increase the cost. Despite all the developments in imaging techniques, the multigland disease may still be missed and may require reoperation (17).

Most important obstacles to MIP are negative or discordant findings on imaging studies. Zheng *et al.* reported that concordant preoperative sestamibi and ultrasound findings present as a reliable localization technique when used together (12). In the literature, coexistence of thyroid nodules and carcinoma rates varies between 3.3% and 17.4%, and the guidelines of the American Thyroid Association do not consider PHPT as a risk factor for PTC (16, 18), but the preferred modality for the treatment of these patients is thyroidectomy since it avoids increased complications of reoperative surgery. However, these procedures may still lead to complications, such as transient hypocalcemia and temporary recurrent laryngeal nerve palsy, as well as longer hospital stay and operative times compared to MIP (6, 19).

In this study, we evaluated patients with PHPT who had been treated by thyroidectomy and BNE, because of coexisting thyroid nodules. All of these selected patients have concordant findings at US and MIBI-SPECT for parathyroid adenoma and have thyroid nodules with FNAB results that were not further than Bethesda category III or below (Table 1). It was the presence of parathyroid adenomas that made surgery

necessary for these patients. Without a diagnosis of PHPT, these patients would have only been followed up using US and repeated FNAB. From this perspective, our treatment success was based on accurate detection of malignancy. In the literature, malignancy rates generally range from 3.3% to 17.4% (18). However, Scerrino *et al.* reported a high malignancy rate (32.9%) in an endemic goiter region, but discrimination of mPTC was not included in this study (20). In the current study, two patients had PTC and a considerable number of patients (n=11) had mPTC, and the overall malignancy rate was 26%. The high malignancy rate confirms that thyroidectomy was necessary for the treatment of these patients. In view of the excellent prognosis of mPTC (21) and the prevalence of this disease reaching 35.6% in autopsy series (22), performing a procedure that will make the patient dependent on hormone replacement therapy for his/her remaining life is questionable. In addition, in a previous study, the overall malignancy rate and the prevalence of mPTC of our clinic were reported to be 30.1% and 17.2%, respectively (23). These rates are similar to those we obtained in the current study.

In this study, when the patients' preoperative findings were considered, there were no statistical differences between the patients with thyroid malignancy and benign thyroid lesions. This may indicate that preoperative findings except for FNAB have limited contribution to decisions regarding the treatment of coexisting thyroid nodules in this patient group. In control patient group there were 23 patients who had concomitant thyroid nodules but treated with MIP alone due to benign FNAB results. Absence of persistence, recurrence or postoperative complication in this patient group may also support this hypothesis.

Postoperative hypoparathyroidism and hypocalcemia are observed more often in patients with simultaneous thyroidectomy than after simple parathyroidectomy (6, 19). The rate of hypocalcemia in thyroidectomy group was higher than in MIP group in this study. But there was no statistical difference. With this finding and absence of persistence or recurrence of hypoparathyroidism may indicate that postoperative hypoparathyroidism and hypocalcemia are not intimidating complications in high volume-experienced centers for thyroidectomy with BNE.

There are some limitations of this study due to retrospective nature, such as the number of cases was low depending on multiple patient selection criteria, and insufficient follow-up data of control patient group which has been followed up for coexisted thyroid nodules after MIP.

In conclusion, we evaluated patients that underwent additional thyroidectomy, rather than only MIP, due to coexisting thyroid nodules. The results were inconclusive in clearly demonstrating which patients presenting with coexisted thyroid nodules should undergo thyroidectomy, rather than MIP, and which should be monitored for thyroid nodules after MIP. However, we consider that in cases who are not clearly indicated for thyroidectomy, MIP followed by monitoring of thyroid nodules can be the treatment approach.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Press DM, Siperstein AE, Berber E, Shin JJ, Metzger R, Monteiro R, Mino J, Swagel W, Mitchell JC. The prevalence of undiagnosed and unrecognized primary hyperparathyroidism: a population-based analysis from the electronic medical record. *Surgery*. 2013;154(6):1232-1237.
2. Laird AM, Libutti SK. Minimally invasive parathyroidectomy versus bilateral neck exploration for primary hyperparathyroidism. *Surgical oncology clinics of North America*. 2016;25(1):103-118.
3. Greilsamer T, Blanchard C, Christou N, Drui D, Ansquer C, Le Bras M, Cariou B, Caillard C, Mourrain-Langlois E, Delemazure AS, Mathonnet M, Kraeber-Bodere F, Mirallic E. Management of thyroid nodules incidentally discovered on MIBI scanning for primary hyperparathyroidism. *Langenbecks Arch Surg*. 2015;400(3):313-318.
4. Ryan S, Courtney D, Timon C. Co-existent thyroid disease in patients treated for primary hyperparathyroidism: implications for clinical management. *Eur Arch Otorhinolaryngol*. 2015;272(2):419-423.
5. Neagoe RM, Sala DT, Pascanu I, Voidazan S, Wang L, Lansdown M, Cvasciuc IT. A Comparative Analysis of the Initial East European Center Experience with A Western High-Volume Center for Open Minimally Invasive Parathyroidectomy (O mip) As Treatment of Primary Hyperparathyroidism. *Acta Endocrinologica-Bucharest* 2016; 12(3):297-302.
6. Kiernan CM, Schlegel C, Kavalukas S, Isom C, Peters MF, Solórzano CC. Does concomitant thyroidectomy increase risks of parathyroidectomy? *J Surgical Research*. 2016;203(1):34-39.
7. Kosem M, Algun E, Kotan C, Harman M, Ozturk M. Coexistent thyroid pathologies and high rate of papillary cancer in patients with primary hyperparathyroidism: controversies about minimal invasive parathyroid surgery. *Acta Chir Belg*. 2004;104(5):568-571.
8. Auguste LJ, Attie JN. Completion thyroidectomy for initially misdiagnosed thyroid cancer. *Otolaryngol Clin North Am*. 1990;23(3):429-439.
9. Goretzki PE, Simon D, Frilling A, Witte J, Reinert C, Grussendorf M, Horster FA, Roher HD. Surgical reintervention for differentiated thyroid cancer. *Br J Surg*. 1993;80(8):1009-1012.
10. Levin KE, Clark AH, Duh QY, Demeure M, Siperstein AE, Clark OH. Reoperative thyroid surgery. *Surgery*. 1992;111(6):604-609.
11. Shaha AR, Jaffe BM. Parathyroid preservation during thyroid surgery. *Am J Otolaryngol*. 1998;19(2):113-117.

12. Zheng YX, Xu SM, Wang P, Chen L. Preoperative localization and minimally invasive management of primary hyperparathyroidism concomitant with thyroid disease. *J Zhejiang Univ Sci B*. 2007;8(9):626-631.
13. Ay N, Oz A, Alp V, Bahadır M, V, Yilmaz V, Dinc B, Ay D. The Thyroid Cancer Incidence in An Endemic Goiter Region and the Relationship of Thyroid Cancer with Nodule Diameter. *Acta Endocrinologica-Bucharest* 2015; 11(4):444-448.
14. Aydin Y, Besir FH, Erkan ME, Yazgan O, Gungor A, Onder E, Coskun H, Aydin L. Spectrum and prevalence of nodular thyroid diseases detected by ultrasonography in the Western Black Sea region of Turkey. *Med Ultrason*. 2014;16(2):100-106.
15. Wilhelm SM, Wang TS, Ruan DT, Lee JA, Asa SL, Duh QY, Doherty GM, Herrera MF, Pasicka JL, Perrier ND, Silverberg SJ, Solorzano CC, Sturgeon C, Tublin ME, Udelsman R, Carty SE. The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism. *JAMA Surg*. 2016;151(10):959-968.
16. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016;26(1):1-133.
17. Cherenko S, Dinets A, Bandura G, Sheptuha S, Larin O. Multiglandular parathyroid gland disease: an incidental discovery in normocalcemic patients during thyroid surgery. *Acta Endocrinologica-Bucharest*. 2017;13(3):349-355.
18. Cinamon U, Levy D, Marom T. Is Primary Hyperparathyroidism a Risk Factor for Papillary Thyroid Cancer? An Exemplary Study and Literature Review. *International archives of otorhinolaryngology*. 2015;19(01):042-045.
19. Riss P, Kammer M, Selberherr A, Scheuba C, Niederle B. Morbidity associated with concomitant thyroid surgery in patients with primary hyperparathyroidism. *Annals of surgical oncology*. 2015;22(8):2707-2713.
20. Scerrino G, Attard M, Piccolo CL, Attard A, Melfa G, Raspani C, Zarcone M, Bonventre S, Mazzola S, Gulotta G. The coexistence of primary hyperparathyroidism and thyroid nodules: should the preoperative work-up of the parathyroid and the thyroid diseases be specifically adjusted? *Il Giornale di Chirurgia*. 2016;37(3):123.
21. Hay ID, Hutchinson ME, Gonzalez-Losada T, McIver B, Reinalda ME, Grant CS, Thompson GB, Sebo TJ, Goellner JR. Papillary thyroid microcarcinoma: a study of 900 cases observed in a 60-year period. *Surgery*. 2008;144(6):980-988.
22. Harach HR, Franssila KO, Wasenius VM. Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study. *Cancer*. 1985;56(3):531-538.
23. Özden S, Erdoğan A, Simsek B, Saylam B, Yıldız B, Tez M. Clinical course of incidental parathyroidectomy: Single center experience. *Auris Nasus Larynx*. 2017.