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ORIGINAL ARTICLE

Use of preoperative ultrasonography adenoma size measurements for accurate localization estimation in parathyroid adenomas

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Abstract

Background: It is known that Primary hyperparathyroidism (pHPT) is the most common cause of hypercalcemia. It is characterized by high serum calcium and parathyroid hormone (PTH) levels. Also, hyperactivity is seen in one or more of the parathyroid glands and preoperative ultrasonography (USG) usually localizes the location of parathyroid adenomas. In this study, the factors that affect the success of parathyroid surgery have been investigated.

Methods: In total, the medical records of 245 patients with pHPT who underwent parathyroidectomy have been reviewed, retrospectively. In order to confirm the location of hyperactive parathyroid gland and the factors that affect the success of laboratory methods have been examined by using imaging techniques.

Results: As a result, false localization is found in 7.8% (19) of the patients. The weight calculated by using the preoperative USG measurements has been approximately similar to the macroscopic weight ($p = 0.651$). When the preoperative USG results in patients with false localization have been analyzed, it is seen that the lesion diameter was significantly less than 12 mm and the calculated weight was significantly less than 39 g ($p = 0.005$ and $p < 0.001$).

Conclusion: It has been concluded that a second-line imaging should be used to obtain an accurate localization in patients with a small lesion suspected of being a parathyroid adenoma on preoperative USG. In addition, an intraoperative PTH (IOPTH) should be used to increase the success rate of the surgery in patients who cannot undergo a second-line imaging.

Keywords: Minimal Invasive Parathyroidectomy, Primary Hyperparathyroidism, Ultrasonography, Parathormone.

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INTRODUCTION

Primary hyperparathyroidism (pHPT) is the most common cause of hypercalcemia in the outpatient setting. It is characterized by hyperactivity of one or more parathyroid glands accompanied by high serum calcium levels and inappropriate PTH levels in postmenopausal women (1). While a single solitary adenoma causes pHPT in 70% to 80% of the cases, two or more glands are responsible for the disease in 20% to 30% of the cases (2,3). Parathyroid carcinoma is rarely the cause of pHPT (4,5). The only curative treatment for patients with pHPT is a surgical resection of the parathyroid adenoma that is responsible for the disease. The success rate of surgical treatment increases up to 97% thanks to the preoperative localization and the assessment of intraoperative PTH levels (6,7) and it is demonstrated by the normalization of serum calcium and PTH levels. The presence of hypercalcemia in the first 6 (six) months after surgery (3 to 6% of patients) indicates the presence of persistent or recurrent pHPT (7,8). Repeated surgical procedures might lead to an increase in complications. While recurrent laryngeal nerve (RLN) paralysis is observed in 0.3% to 0.6% of the patients with the initial surgical procedure, RLN paralysis is observed in 3% to 9% of the recurrent surgical procedures (9). In addition, the risk of permanent hypocalcemia is 7% to 8% at the first surgery and increases, reaching up to 13%, at repeated surgery (9,10). Intraoperative parathyroid hormone monitoring (IOPTH) is recommended to increase the number of minimally invasive parathyroidectomy (MIP) procedures and to prevent the development of permanent hypoparathyroidism (10). Preoperative localization studies include neck ultrasonography (US), sestamibi scintigraphy, C11-methionine PET-CT, selective venous parathyroid hormone sampling, 4D MRI imaging, and 4D CT of the parathyroid gland (2,11,12). It is reported that the sensitivity of USG is 65.5% to 87.5%, the sensitivity of MIBI is 60% to 77%, the sensitivity of 4D CT is 80% to 85.7%, and the sensitivity of 4D MRI is 85% in accurately detecting the localization of parathyroid adenoma (11-15). The exploration of 4 glands or bilateral neck exploration (BNE) in parathyroidectomy surgery increases the success rate of the surgery (16). However, in order not to increase the risk of complications and to shorten the duration of the surgery, the routine preoperative US would reduce the number of patients with BNE in chosen cases (17). However, the sensitivity of USG decreases in adenomas smaller than 1 cm (18). In order for minimally invasive parathyroidectomy to be successful, a very good localization study should be performed in the preoperative period (19). In this study, it is aimed to investigate the factors that affect the success of parathyroid surgery.

MATERIALS AND METHODS

Initially, 266 patients who were older than 18 years and underwent parathyroidectomy at the Department of General Surgery between 1st March, 2019 and 28th February, 2022 have been included in this study. The study was initiated with the approval of the Ankara City Hospital Clinical Research Ethics Committee, numbered 2266, until 29.12.2021. The medical records which belong to the patients have been reviewed, retrospectively. As a result, it is seen that 21 of the patients had undergone a surgery for secondary hyperparathyroidism before and these patients have been excluded from the study. Finally, a total of 245 patients who underwent parathyroidectomy for primary hyperparathyroidism have been included in the study. Age, gender, and preoperative biochemical parameters such as calcium (preoperative and 6 hours after surgery), phosphorus, albumin, and alkaline phosphatase levels of the patients were obtained via their medical records. Parathormone levels (preoperatively, 10 minutes after the surgical removal of the parathyroid adenoma, and 6 hours after the surgery) were also recorded. On preoperative imaging, the correct location of the parathyroid adenoma and its dimensions were also determined and recorded. The macroscopic size of the parathyroid gland, the pathology of the thyroidectomy (for those who decided to undergo thyroidectomy in the Endocrine Council), and the pathology of the parathyroid gland were recorded in each patient's follow-up form. The weight of the parathyroid glands was calculated by using the formula V (mm3) = L (mm) x W (mm) x H (mm) x $\pi/6$ of the ellipsoid volume of the adenomas, which was obtained three-dimensionally by imaging methods. The calculated volume was multiplied by 1mg/mm3 to find the weight of the adenoma, assuming that the adenoma had the density of water. W (mg) = 1mg/mm3 x V adenoma (mm3) (20).

In our hospital, the preoperative examinations of parathyroid adenoma are performed by endocrinologists. During the preoperative endocrine council (in which at least one person from our clinic participates) the USG examination is re-done. The results of these examinations and the decision of the council are regularly recorded in the hospital information system. When the presence of a

large adenoma is detected in our clinic and an obvious adenoma is detected during the surgery in the location determined by the endocrinologists with preoperative USG, some surgeons perform a frozen pathology study in addition to GIBTH, while others are satisfied with the frozen result only. In the presence of small adenomas and in the absence of adenomas in the location determined by endocrinologists with preoperative USG, frozen results with IOPTH are expected. If there is no decrease in PTH on IOPTH, 4 glands are examined to find the adenoma.

In this study, data analysis is performed by using SPSS software (25.0, IBM Corp., Armonk, NY). To present descriptive statistical analyses, numbers, percentages, means, and standard deviations are used. When the age of the patient, the longest dimension of the parathyroid gland on USG, the preoperative PTH level, and the PTH level 6 hours after the surgery in both groups with and without preoperative correct localization of the parathyroid glands have been examined by using the Kolmogorov-Smirnov test, it is found that the data shows a normal distribution among the groups ($p > .05$). Besides, when adenoma weight calculated by its size on USG and the PTH values at 10 minutes after the removal of the adenoma have been examined by using the Kolmogorov-Smirnov test, it is seen that the data does not show a normal distribution among the groups ($p < .001$). Therefore, the significance of the difference between the groups has been analyzed by using Mann-Whitney U test for adenoma weight, PTH data at 10 minutes and PTH data at 6 hours postoperatively. The significance of the difference between the groups in preoperative PTH and adenoma longest length data has been analyzed by using independent t-test. For the accurate localization, the ROC curve has been plotted with these data, and cut-off values have been determined for each. The significance of the difference between the weights calculated based on the USG measurements and the macroscopic weight has been analyzed by using the Wilcoxon test.

RESULTS

The mean age of the patients included in the study was 53.20±12.6 years. Of the patients, 78% (191) were female and 22% (54) were male. Prior to the surgery, 61.2% (150) of the patients were scheduled for MIP and 38.8% (95) of them were scheduled for 4 gland exploration and/or thyroid surgery. Among these patients, MIP could not be performed in 19 patients who were preoperatively planned as MIP, because the adenoma could not be found (11) or an intraoperative decrease in PTH level was not detected (8). For this reason, the incision was extended and the operations were continued as 4-gland exploration. It was observed that one patient with parathyroid carcinoma underwent thyroid lobectomy in addition to the parathyroidectomy, and one other patient underwent bilateral total thyroidectomy (BTT). Patients who underwent parathyroidectomy were followed for at least 6 months. Double parathyroid adenoma was present in 5.3% (13) of the patients who underwent parathyroidectomy. The presence of a double parathyroid adenoma was discovered during the surgery in 3.3% (8) of the patients and parathyroid hyperplasia was found in 9.4% (23) of the patients. To increase the success of minimally invasive parathyroidectomy in our clinic, the exploration of 4 parathyroid glands was started in patients who did not have a decrease in PTH measured 10 minutes after the removal of the parathyroid gland during surgeries. An intraoperative quick PTH was tested in 61.2% (150) of the patients, but not in 38.8% of them. In 8 of the patients who underwent MIP, the presence of a double adenoma was discovered by performing 4-gland explorations because the quick PTH value tested 10 minutes after the removal of the parathyroid gland did not decrease sufficiently. After at least 6 months of follow-up, 90.2% (221) of the patients had a normal serum PTH and calcium levels. It was observed that 7.8% (19) of the patients had preoperative misdiagnosis or inadequate localization studies. During the postoperative follow-up, 5 patients had elevated PTH levels that returned to normal after the surgery and the imaging (MR or 4DCT) demonstrated the presence of a second adenoma. While 2 of these patients underwent reoperation, 3 of the patients were referred to a thoracic surgery because one of them had an adenoma located on the aortic knob and the other had an intra-thymic adenoma. The other patient with a substernal parathyroid adenoma did not wish to undergo surgery because of concomitant systemic disease. Of the adenomas, 10.9% (28) were located in the right superior lobe, 33.7% (87) in the right inferior lobe, 10.1% (26) in the left superior lobe, 39.9% (103) in the left inferior lobe, 2.7% (7) were intrathyroidal, and 2.7% (7) were in other locations.

Firstly, the measurements have been analyzed. When the weight calculated from the three-dimensional measurements of the adenoma in the preoperative USG and the macroscopic three-dimensional measurements

and weight measurements at pathological examination were compared by using the Wilcoxon test, it is seen that there has been no significant difference between the two groups (p = 0.651). A comparison of the weight calculated from the USG measurements of the adenoma and the macroscopic weight is shown in **Table 1**.

Table 1. The comparison of the weight calculated by the USG measurements of the adenoma and the macroscopic weight

	N	Mean	Std. Deviation	Minimum	Maximum	Mean Rank	*P* Value
Macroscopic Weight	245	1.2	1.7	0.1	13.7	119.5	0.651
Weight calculated according to measurements on USG	245	1.1	1.3	0.1	10.3	116.5	

Wilcoxon test used

The patients included in the study were then divided into two groups, those with the correct localization and those without in order to analyze the effect of adenoma diameter and volume on correct localization. The longest diameter of the parathyroid measured on USG and the calculated parathyroid weight were significantly lower in the patients with preoperatively mis-localized ($p < 0.005$ and $p < 0.001$, respectively). In the analysis performed with the preoperative serum PTH levels, it is seen that there has been no difference between the groups (p = 0.079). PTH and calcium levels examined 6 hours after surgery were significantly lower in the patients who were correctly localized preoperatively ($p< 0.0001$, $p < 0.001$, respectively). A comparison of several parameters of correct adenoma localization is shown in **Table 2**.

Tables 2. The comparison of several parameters on the correct localization of the adenoma

Incorrect localization?		N	Test Value	P Value
Longest diameter on USG	No	226	2.8	0.005*
	Yes	19		
Calculated weight	No	226	1076.5	< 0.001**
	Yes	19		
Preoperative PTH	No	226	1.8	0.079*
	Yes	19		
Postoperative PTH	No	226	325.5	< 0.001**
	Yes	19		
Postoperative Calcium	No	226	1134.5	0.001**
	Yes	19		

**Independent-T test used. **Mann-Whitney U test used.*

The cut-off value for adenoma diameter measured on preoperative USG was 12 mm (AUC: 0.739, sensitivity: 0.668, specificity: 0.684). The ROC curve for the longest adenoma size according to whether the correct localization was performed preoperatively is shown in **Figure 1**. The cut-off value for the preoperative adenoma weight measured in the preoperative USG was 39 gr (AUC: 0.749, sensitivity: 0.673, specificity: 0.684). The ROC curve for the size of the adenoma weight calculated according to whether the correct localization was performed preoperatively is shown in **Figure 2**. The cut-off value of PTH was set at 182 pg/mL to accurately localize the

parathyroid adenoma preoperatively. It was observed that the location of the adenoma was better localized when the PTH level was above 182 pg/mL (AUC: 0.647, sensitivity: 0.584, specificity: 0.632). The sensitivity for correct gland removal was 0.97 and the specificity was 0.90 in the patients with a 50% or greater reduction in IOPTH compared to preoperative PTH (136/140). The cut-off value for IOPTH was 39 pg/mL. In patients with a value below this, the correct removal of the gland (86/140), the sensitivity and specificity were calculated to be 0.61 and 0.60. The ROC curve was plotted for PTH measured at hour 6 postoperatively. The cut-off for PTH at hour 6 was 41 pg/mL (AUC: 0.925, sensitivity: 0.842, specificity: 0.841). Similarly, the cut-off for postoperative calcium at hour 6 was 9.2 mg/dL (AUC: 0.736, sensitivity: 0.632, specificity: 0.726). A comparison of the cut-off values of several parameters in determining the correct localization of the adenoma is shown in **Table 3**. The effective parameters in determining the preoperative correct localization of the adenoma are shown in **Table 4**.

Tables 3. The comparison of the cut-off values of several parameters in determining the correct localization of the adenoma

			Preoperative Correct localization		P value
			Yes	No	
Adenoma Longest Diameter	< 12 mm	N	78	13	0.003
		%	85.7	14.3	
	≥12 mm	N	148	6	
		%	96.1	3.9	
Adenoma weight	< 39 gr	N	74	13	0.002
		%	85.1	14.9	
	≥ 39 gr	N	152	6	
		%	96.2	3.8	
Preoperative PTH Level	<182 pg/mL	N	94	12	0.068
		%	88.7	11.3	
	≥182 pg/mL	N	132	7	
		%	95	5	
Postoperative PTH Level	≥ 41 pg/mL	N	37	16	<0.001
		%	69.8	30.2	
	< 41 pg/mL	N	189	3	
		%	98.4	1.6	
Postoperative Calcium Level	≥ 9.2	N	62	12	0.001
		%	83.8	16.2	
	< 9.2	N	164	7	
		%	95.9	4.1	
Total		N	226	19	
		%	92.2	7.8	

Pearson Chi-Square test used.

Tables 4. The effective parameters in determining the preoperative correct localization of the adenoma

Parameters	AUC	Sensitivity	Specificity
Preop. PTH ≥ 182 pg/mL	0.65	0.58	0.63
Longest diameter ≥12mm	0.74	0.67	0.68
Adenoma weight ≥ 39 gr	0.75	0.67	0.68
Postop. 6th hour PTH < 41 pg/mL	0.93	0.84	0.84
Postop. 6th hour Ca++ < 9.2 mg/dL	0.74	0.63	0.73

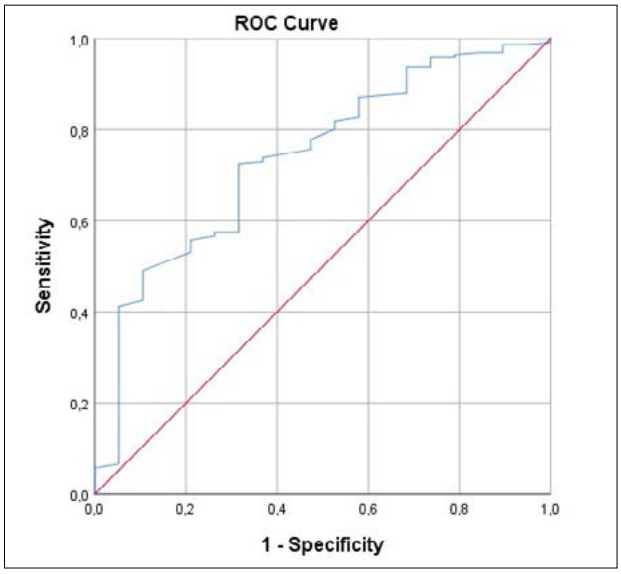

Figure 1. ROC curve for the longest adenoma size according to whether the correct localization was performed preoperatively.

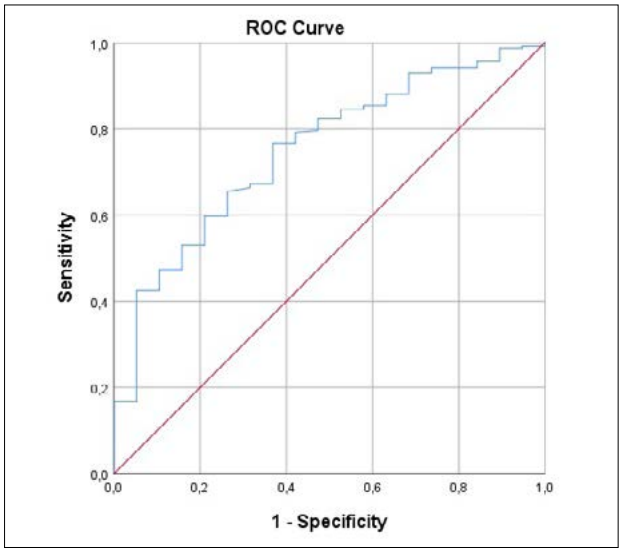

Figure 2. ROC curve for the size of the adenoma weight calculated according to whether the correct localization was performed preoperatively.

The sensitivity decreases down to 0.58 and the specificity increases up to 0.79 when the adenoma weight is considered to be 50 gr, which is the cut-off value reported in previous studies in the literature (20).

It has been observed that the preoperative MIBI has never been performed in 80 patients. The localization of 81.2% (134/165) of the adenomas was accurately determined by MIBI.

DISCUSSION

This study is based on the analysis of a cohort of 245 patients with pHPT who underwent surgery at a single center over a 3-year period. It has been determined that when parathyroid adenomas are minimally enlarged, the localization becomes difficult. The serum PTH level and the weight of the gland are important in determining its location (21,22). Calva-Cerqueira et al. (21) have reported that the sensitivity of imaging decreased in patients with preoperative serum PTH levels below 101 pg/mL. There have been excellent cure rates (97-99%) which are reported for parathyroidectomy performed by experienced endocrine surgeons, regardless of the size of the parathyroid adenoma (23). However, persistent/recurrent pHPT is seen in 2 to 10% of the patients with pHPT after surgery (24,25). Goodsell et al. (25) have determined that the presence of a double adenoma was associated with persistent/recurrent pHPT. In a recent study, Mazotas et al. (26) have concluded that the presence of a double parathyroid adenoma do not increase postoperative recurrence; however, persistent pHPT has been reported to be more common in patients with a double parathyroid adenoma.

First-line imaging modalities, including USG and technetium-99m sestamibi, were initially used to localize parathyroid adenomas because of their high accuracy rates. Preoperative USG is a valuable tool for preoperative localization of parathyroid adenoma. However, its use in the detection of double adenoma or multi-gland disease is limited. The sensitivity of USG decreases down to 78.5% in single adenoma, 34.9% in multi-gland disease, and 16.2% in double adenoma. The sensitivity of sestamibi scintigraphy decreases down to 88.4% for single adenoma, 44.5% for multiglandular hyperplasia, and 30% for double adenoma (27,28). Dy et al. (29) have reported that the postoperative cure rate was 89% in patients with negative USG results and negative MIBI. Therefore, in cases where USG and technetium-99m sestamibi imaging

are insufficient, 4-dimensional CT and MRI, which are second-line imaging modalities, are used. The correct localization of preoperative double adenoma on 4D MRI has been reported to be 85% in pHPT cases (11). Acar et al. (30) have determined that 4D CT and 4D MRI successfully localized the parathyroid adenoma with a rate of 52.9% and 84%, respectively.

It is recommended to examine the paraoesophageal and paratracheal regions, as well as the anterior and posterior mediastinal regions to locate a minimally enlarged parathyroid adenoma in patients examined with USG and MIBI. It is also recommended to use 18 F-fluorocholine-PET-CT or C11-methionine-PET-CT (91-100% sensitivity) in addition to 4D CT and 4D MRI to locate these adenomas (31,32). In the presence of a suspicious adenoma in the neck on USG, surgery should be started with MIP, and after the removal of the mass thought to be an adenoma, a quick PTH should be studied (33,34). It should be noted that if a good preoperative localization is not performed, IOPTH monitoring and selective venous PTH measurement would increase the duration of the operation and the cost (35).

The size of parathyroid adenomas affects the success rate of localization studies for pHPT. Stucken et al. (36) have shown that the weight of the parathyroid gland can be accurately estimated by preoperative USG and 4D CT. Similarly, our study has demonstrated that there has been no significant difference between the weight of the parathyroid gland calculated by using the three dimensions measured by USG and the pathological weight. It has been reported that the localization sensitivity decreases when the weight of the parathyroid adenoma calculated by 4D CT which is less than 50 mg (20,36). This study determines that in patients with preoperative USG measurements of less than 12 mm in the longest diameter of the parathyroid gland and less than 50 mg in weight, second-line studies are required to differentiate the normal parathyroid tissue from adenoma.

IOPTH measurements were taken 10 minutes after the removal of the lesion thought to be a parathyroid adenoma during surgery. A 50% or greater decrease in preoperative PTH or an IOPTH of 35 pg/mL or less is considered to be the indication of correct adenoma removal (92-98.8%) (37,38). In this study, the sensitivity of correct adenoma removal is found to be 97% in patients with a 50% reduction in IOPTH. Similarly, the PTH level at the 6-hour postoperative cut-off of 41 pg/mL had a sensitivity of 84%, but did not contribute to the correct adenoma removal. The addition of IOPTH to focused parathyroidectomy has shown similar long-term results compared to bilateral neck exploration (39).

The limitation of the study is that it is a retrospective study. Therefore, the same standard procedure cannot be applied to each patient. The importance of the study is that the endocrine surgery is very common in our clinic and the records are kept on a regular basis.

As a result, it can be stated that most parathyroid adenomas can be accurately localized with preoperative USG and MIBI. Second-line imaging should be performed when the suspected adenoma lesion is less than 12 mm in longest diameter and the calculated weight on USG is less than 39 g. Also, parathyroidectomy should be planned after second-line imaging in patients in whom parathyroid adenomas are not found outside the neck (retrosternal, infraclavicular, mediastinum, etc.). IOPTH should be studied in these patients, and bilateral neck exploration should be performed in patients who do not have a 50% decrease in PTH.

Declarations

The authors have no conflicts of interest to declare. The authors declared that this study has received no financial support.

This study was approved by the clinical research Ethics Committee of the Ankara City Training and Research Hospital (Date: 29.12.2021, Number: 2266)

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