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Sensitivity of localization studies performed by various radiologists in the evaluation of parathyroid lesions

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ABSTRACT

Objective. Preoperative imaging studies are commonly used in the diagnosis of primary hyperparathyroidism to increase the success rate of surgery. In the present study, we aimed to correlate surgical outcomes with the sensitivity of localization studies that were performed by various radiologists. ***Methods.*** One hundred eighty-nine patients with preoperative diagnosis primary hyperparathyroidism were included. A total of 174 patients in whom hypercalcemia had been cured by parathyroidectomy, were evaluated retrospectively. In total, 184 lesions were excised from these 174 patients. Ultrasonography (USG) and technetium-99m-methoxy isobutyl isonitrile (99mTc-MIBI) imaging yielded correctly localized lesion in 74 and 108 patients, respectively. ***Results.*** The specificity of USG and 99mTc-MIBI imaging were similar (95.9% and 95.0%, respectively). However, the sensitivity was not satisfactory (45.9% for USG, 62.4% for 99mTc-MIBI). The gland size was not significant for the rate of lesion detection by 99mTc-MIBI scan or USG. Significant differences were not observed between the preoperative serum parathormone, serum calcium or 24-hour urine calcium excretion levels and the success rate of localization with either USG or 99mTc-MIBI. ***Conclusions.*** Radiologist experience in ultrasonographic parathyroid imaging was found to affect sensitivity. Therefore, surgeons, radiologists and endocrinologists that perform ultrasonographic evaluation should have extensive experience.

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Keywords: Primary hyperparathyroidism, parathyroidectomy, localization studies, ultrasonography, technetium-99m-methoxy isobutyl isonitrile

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Introduction

Primary hyperparathyroidism is characterized by hypercalcemic clinical manifestations that emerge as a result of excess parathyroid hormon (PTH) secretion from the parathyroid gland. Its prevalence increases with age and reaches to 2% in the population that is between 50 and 60 years of age [1, 2]. Most patients are asymptomatic. The increase in routine measurement of serum calcium levels has increased early diagnosis and estimates of primary hyperparathyroidism prevalence [3]. Solitary parathyroid adenoma is the most common cause of primary hyperparathyroidism (80-85%), followed by diffuse or nodular hyperplasia (10-15%), multiple parathyroid adenoma (2-5%), and carcinoma (<1%) [4]. Depending on its severity, hypercalcemia can lead to several complications, particularly in the renal, gastrointestinal, cardiovascular, neurologic and musculoskeletal systems. Surgery is the only curative therapy that can relieve short- and long-term complications related to hypercalcemia [5]. Preoperative localization studies are important for enhancing surgical success. However, they do not involve diagnostic criteria because the methods employed yield both false negative and false positive results.

Ultrasonography (USG) and technetium-99m-methoxy isobutyl isonitrile (99mTc-MIBI) imaging are primary imaging techniques in preoperative evaluation. USG is an inexpensive, sensitive and specific modality that does not expose the patient to radiation. Although the sensitivity and specificity of 99mTc-MIBI imaging is higher than those of USG, it involves low levels of radiation exposure. Unlike USG, 99mTc-MIBI imaging is not operator dependent [6]. The sensitivities of these modalities vary among centers, with a mean preoperative USG sensitivity of 76% (48-98%) for USG and of 79% (61-100%) for 99mTc-MIBI imaging [7]. However, the sensitivity of USG and 99mTc-MIBI imaging decreases to 34.8% and 44.4%, respectively, in multiglandular disease and to 16.2% and 29.9%, respectively, in double parathyroid adenomas. These decreases in multiglandular disease and double adenoma may be related to small gland sizes or insufficient investigation by the radiologist following the detection of an abnormal parathyroid gland [7, 8]. Gland size and volume are the most powerful independent factors that affect the success of localization methods. Accordingly, a correlation between both preoperatively high serum PTH and calcium levels and the success of localization method has been reported [9]. The presence of ectopic pathological gland does not affect the sensitivity of 99mTc-MIBI imaging but negatively affects USG sensitivity [10, 11]. In addition to all these factors, radiologist experience in imaging the parathyroid gland plays an important role [7].

In the present study, we aimed to investigate the factors influencing the sensitivity of preoperative localization methods and compare the results to the literatüre.

Methods

In our study, we included patients who were diagnosed with primary hyperparathyroidism between 2005 and 2016 and operated on in our center. This study was approved by the Institutional Review Board of the Uludağ University. Patient data were collected from electronic files. The preoperative presenting complaints and biochemical results of 189 patients were analyzed. Curative result rates were evaluated with serum PTH and calcium levels on postoperative day 1 and at 3 and 12 months during follow-up. Among those patients whose hypercalcemia was treated after surgery, the preoperative sensitivity, specificity, true positivity and true negativity of USG and 99mTc-MIBI measurements by different radiologist were assessed. The correlations between each of sensitivity rate and specificity rate in imaging studies and macroscopic measurement of postoperatively resected lesions in pathological assessment were evaluated. In addition, the correlation between imaging method success and preoperative biochemical parameters were analyzed.

Statistical Analysis

Statistical analysis was performed using the computer software SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). The chi-square test was used for the comparison of categorical data, whereas the Mann-Whitney U test or Student t-test were used for the comparison of numerical data as appropriate. Demographic characteristics and preoperative frequency data were expressed as the means and standard deviations (SD) and percent (%) where appropriate. The sensitivity and specificity of the preoperative examinations were calculated manually with the number of true and false scores according to

the postoperative results. A $p < 0.05$ was considered statistically significant.

Results

Among the 189 patients, 162 (85.7%) were female and 27 (14.3%) were male. The mean age was 53.2 ± 12.2 years. There were 63 (33.3%) symptomatic patients diagnosed as primary hyperparathyroidism while they were investigated for seconder osteoporosis (13.2%) and urolithiasis (9.5%). Three patients had multiple endocrine neoplasia (MEN) syndrome. Twelve (6.3%) patients were administered bisphosphonate therapy because of preoperative severe hypercalcemia. The mean preoperative serum calcium level was 11.5 ± 1.0 mg/dl, and the mean preoperative serum PTH level was 414 ± 527 pg/ml. Table 1 shows the patients' demographic and preoperative biochemical data.

We performed a total of 199 surgeries because of persistent hyperparathyroidism, 11 patients were operated on twice, and 1 patient was operated on triple. Two of the patients had been referred to our hospital after noncurative first surgery at their centers. We obtained a curative result in 162 (86.6%) of 187 hypercalcemic patients whose first operation was at our center. Among the 11 patients who underwent a second surgery, 72.7% had a curative result. Considering all the operations, 92.0% of 189 patients were treated with surgery (Table 2). In histopathological evaluation, solitary adenoma was observed in 178 patients, double adenoma was observed in 9 patients, and parathyroid carcinoma was observed in 1 patient. One patient underwent 3.5-gland parathyroidectomy because of multiple gland hyperplasia (Table 3). In the other MEN patients it is observed that dominant adenoma was resected on the first operation and other glands were not checked during surgery. So these patients had to be reoperated. The sensitivity of the imaging modalities was calculated by comparing the results of the preoperative localization studies with the resected side in patients with curative surgery. Among the 174 patients who underwent curative surgery, USG had been performed with 155 patients, and 99mTc-MIBI imaging had been performed with 167 patients. USG localized lesions correctly in 74 (47.7%) patients, whereas 99mTc-MIBI imaging did so in 108 (64.4%) patients. The sensitivity rate was 45.9% for USG and 62.4% for 99mTc-MIBI imaging. The specificity rate was 95.9% for USG and 95.0% for 99mTc-MIBI imaging (Table 4).

In our study, patient gender did not affect

Table 1. Demographic characteristic of patients and preoperative laboratory findings

	Patients (n = 189)
Sex	
Male	27
Female	162
Age (years)	53.2 ± 12.2 (19 - 88)
Asymptomatic	126
MEN	3
Pre-op calcium (RR: 8.4-10.2 mg/dL)	11.5 ± 1.0 (10.2 - 18.5)
Pre-op phosphorus (RR: 2.4-4.4 mg/dL)	2.4 ± 0.5 (0.8 - 4.1)
Pre-op creatinine (RR: 0.7-1.1 mg/dL)	0.74 ± 0.20 (0.48 – 1.8)
Pre-op PTH (RR: 15-68.3 pg/mL)	414 ± 527 (71 - 4262)
Pre-op vitamin D (RR: >30ng/L)	14.7 ± 8.9 (2.1 – 54)
Pre-op 24 h U Ca (RR: <400 mg/day)	388 ± 253 (60 - 2062)
Associated thyroid disease	63

Data were expressed as the means ± standard deviations (range) and number. MEN = multiple endocrine neoplasia, Pre-op = preoperative, PTH = parathormone, 24 H U ca = 24-hour urine calcium excretion

Table 2. Results of operation

	Cure rates
1st operation (n = 187)	165 (86.6%)
2nd operation (n = 11)	8 (72.7%)
3rd operation (n = 1)	1 (100%)

Data were expressed as number (percent).

Table 3. Histopathological features

	Patients (n = 155)
Single adenoma	178
Double adenoma	9
Single gland hyperplasia	0
Multi-gland hyperplasia	1
Carcinoma	1
Non-pathological gland	9

Table 4. Results of preoperative localization studies

	USG (n = 155)	^{99m}Tc-MIBI (n = 167)
True positive	74	108
False positive	6	8
False negative	87	65
True negative	143	153
Sensitivity (%)	45.9	62.4
Specificity (%9	95.9	95.0

USG = ultrasonography, ^{99m}Tc-MIBI = technetium-99m-methoxy isobutyl isonitrile

Table 5. Comparisons of patients with positive and negative USG or MIBI results

	USG			^{99m}Tc-MIBI		
	positive	*negative*	*p-value*	*positive*	*negative*	*p-value*
Sex (M/F)	12/61	14/87	NS	18/87	8/61	NS
Age	51.9 ± 12.3	53.4 ± 12.2	NS	52.6 ± 12.0	53.0 ± 12.6	NS
PTH	436.6 ± 448.2	342.4 ± 375.9	NS	391 ± 375	367 ± 458	NS
Ca	11.6 ± 1.2	11.3 ± 1.0	NS	11.5 ± 1.18	11.2 ± 0.92	NS
P	2.39 ± 0.66	2.54 ± 0.53	NS	2.41 ± 0.59	2.57 ± 0.58	NS
24-h U Ca	386 ± 196	350 ± 302	NS	387 ± 217	333 ± 320	NS
Size (mm)	22.3 ± 11.1	20.3 ± 9.3	NS	22.1 ± 10.6	19.7 ± 9.1	NS

Data were expressed as the means ± standard deviations and number. USG = ultrasonography, ^{99m}Tc-MIBI = technetium-99m-methoxy isobutyl isonitrile, PTH = parathyroid hormone, Ca = calcium, P = phosphorus, 24-h Ca = 24-hour urine calcium excretion, NS = non-significant ($p > 0.05$)

sensitivity ($p>0.05$). There was no significant association between gender and imaging modality success ($p>0.05$). Analysis of the correlations between preoperative biochemical parameters and imaging modality success revealed no significant association between preoperative serum calcium, PTH, phosphorus or 24-hour urine calcium excretion levels and successful localization. Parathyroid gland size did not affect the success of the imaging modality (Table 5).

Discussion

Parathyroid adenoma and hyperplasia are the most common causes of primary hyperparathyroidism; parathyroid carcinomas are very rare [3]. Primary hyperparathyroidism due to adenoma is common in older women [1, 2]. The surgical resection of the adenoma is the only curative therapy in the patients with primary hyperparathyroidism. Parathyroid adenomas are typically small in size and can go undetected by preoperative imaging methods in some cases [12, 13]. The main therapeutic approach is to detect and resect the adenoma during operation with neck exploration even if the adenoma is not detected preoperatively. The preoperative localization of the adenoma and the surgeon's experience are crucial to the success of surgery [7].

Among the 189 subjects in our study, 162 were female (F/M: 6/1). Three patients had hyperplasia, and one patient had parathyroid carcinoma; these findings are consistent with the literature. In the literature, the

curative operation rate is greater than 95% in experienced centers. In our study, this rate was 92.0%, which is slightly lower than that of experienced centers. It was thought that our success rate should increase with experience. The slightly lower rate observed in the present study may also be due to the exclusion of patients who had no postoperative follow-up at our center. Patients that were operated on and cured may have discontinued outpatient follow-up postoperatively.

The preoperative detection rate of parathyroid adenoma varies among imaging methods and studies. Reviews have indicated that USG and 99mTc-MIBI imaging are the most sensitive methods [5]. The sensitivity and specificity of USG are reported to be 56-100% and 50-99%, respectively [12]. For 99mTc-MIBI imaging, they are 56-100% and 83-99%, respectively [12]. In our study, the sensitivity and specificity of 99mTc-MIBI imaging are consistent with those reported in the literature. The sensitivity of 99mTc-MIBI imaging may reach very high levels if used carefully, and the specificity of this method is high. The positive predictive value obtained for USG in the present study is consistent with the literature, and the false positive rate was low. However, the sensitivity of USG was low, and the false negative rate for USG was high.

It has been reported that adenomas are preoperatively detected more with USG than 99mTc-MIBI, especially when USG is performed by experienced hands [13]. The rate of curative surgery is high in patients with adenomas that were localized preoperatively. In addition, in these patients, the need for wide neck exploration during surgery and the rate of complications decrease. However, the resection of adenomas via minimal surgical intervention with local anesthesia is reported to be possible [14].

Surgery is the only curative therapy, and bilateral neck exploration is considered the gold standard surgical approach. All the parathyroid glands can be evaluated by this procedure, and the rate of curative surgery is approximately 95% [7, 15]. The rate of curative surgery decreases for adenomas that cannot be localized with preoperative imaging methods [16]. Therefore, there is a correlation between surgical success and the sensitivity of localization studies. In our study, for USG, the true positive rate was 47.7%, the false negative rate was 56.1% and sensitivity was 62.4%; for 99mTc-MIBI imaging, the corresponding values were 64.6%, 38.9% and 62.4%. Although 99mTc-MIBI imaging was superior to USG in our study, some studies have reported that USG is superior to 99mTc-MIBI imaging [17]. USG, performed by experienced radiologist, may be superior to 99mTc-MIBI [17]. Sensitivity increases when the two modalities are used together. In addition, radiologist experience is an important factor affecting sensitivity [18, 20]. The lower sensitivity of USG and 99mTc-MIBI observed in our study relative to their sensitivity in previous studies might reflect the fact that the imaging studies were performed by different radiologists not all of whom are experienced in parathyroid imaging.

In the literature, gland size and volume are reported to be most powerful independent factors influencing successful localization [7]. It is known that small lesions are more difficult to localize than large lesions in USG. However, the difficulty in detecting small lesions in 99mTc-MIBI imaging might be explained by lower intracellular radiotracer uptake in small lesions [17]. In our study, size did not significantly affect the USG and 99mTc-MIBI imaging results.

Some studies have reported that preoperative serum PTH and calcium level were both higher in patients whose imaging study results are positive [9]. Vassy *et al.* [20] found that PTH and calcium levels did not affect 99mTc-MIBI imaging results in 37 patients with primary hyperparathyroidism. We did not observe a significant correlation between any of preoperative serum PTH, serum calcium, and 24-hour urine calcium excretion levels and successful localization in our study.

There is concomitant thyroid pathology in 20-30% of patients with primary hyperparathyroidism [21]. The presence of thyroid pathology decreases the sensitivity of both USG and 99mTc-MIBI imaging [22-24]. In 99mTc-MIBI imaging, this decrease in sensitivity might be associated with a delay in wash-out in multinodular goiter and Hashimoto's thyroiditis, whereas in USG, this decrease might be associated with the limitation of sonographic evaluation of adenoma because of a multinodular thyroid gland. However, it has been reported that benign and malign thyroid diseases might cause false positive results [22-24]. In our study, 33% of patients had concomitant thyroid disease. There was no significant difference in sensitivity of either USG or 99mTc-MIBI imaging between patients with thyroid nodule and without thyroid nodule.

Conclusions

In conclusion, the treatment of primary hyperparathyroidism is surgical resection in parathyroid adenomas and surgical resection of almost the entire parathyroid gland, leaving minimal residual tissue, in parathyroid hyperplasia. Surgery should be performed by operators specialized in parathyroid surgery. Preoperative localization of a lesion is not an indication for surgery, but it increases the rate of curative surgery and decreases surgical complications. Therefore, it is important to carefully evaluate patients using a multidisciplinary approach involving a surgeon, an endocrinologist and a radiologist.

Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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