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Ectopic and Eutopic Located Parathyroid Lesions: Do They Behave Differently? How Can We Monitor Them? What Should We Look for?

ORIGINAL ARTICLE

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ABSTRACT

Objective: Hyperparathyroidism (HPT) is a frequent endocrine disorder that progresses with an increase in the parathormone (PTH) synthesis and secretion from the chief cells in one or more glands. The common methods used in the imaging of parathyroid adenomas are the ultrasonography and Tc-99m sestamibi scintigraphy (MIBI) scintigraphy. We aimed to investigate the determining characteristics and availability of the MIBI scintigraphy technique in detecting eutopic and ectopic localized parathyroid adenomas.

Materials and Methods: This is a retrospective study. A total of 59 patients diagnosed with primary HPT between 2002 and 2010 using parathyroid scintigraphy with Tc99m MIBI imaging and dual-phase dual-isotope technique, which was reported as parathyroid adenoma, were enrolled into this study. To determine the radiopharmaceutic retention, an early parathyroid-to-thyroid ratio (early PT/T), late parathyroid-to-thyroid ratio (late PT/T), early-to-late ratio (E/L), and the retention index (RI) were calculated.

Results: The lesions were divided into two groups: ectopic (n=28) and eutopic (n=37). When biochemical parameters were compared, there was not any statistically significant difference in the physiological parameters excluding the PTH levels. We determined that the level of PTH is the only biochemical parameter that is directly associated with the positivity of MIBI. Moreover, our findings revealed that the E/L ratio is negatively correlated with Ca^{+2} and P, while the RI ratio exhibited a positive association with Ca^{+2} and P in the ectopic group.

Conclusion: We concluded that the MIBI is currently the best imaging method to diagnose parathyroid adenomas. The ideal imaging protocol should include a combination of a single photon emission computerized tomography study that is not prolonged over 1 h with an early and late planar (15 min and 2 h, respectively) imaging.

Keywords: Parathyroid, ectopic, MIBI, imaging

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INTRODUCTION

Hyperparathyroidism (HPT) is a frequent endocrine disorder that progress with an increase in the parathormone (PTH) synthesis and secretion from the chief cells in one or more glands. It is divided into three etiological classes as primary, secondary, and tertiary.

Primary hyperparathyroidism (PHPT) is a result of an excessive autonomous secretion of PTH from one or more parathyroid glands. In the fifth, sixth, and seventh decades of life, the annual incidence is reported as 1/500 for women and 1/2000 for men. In 80%–90% of patients, one adenoma was found, and on the other hand, in 5%–10% of patients and 10%–15% of patients, respectively, double adenomas and four-gland hyperplasia were found (1).

The disease can be diagnosed clinically by measuring the serum PTH, and Ca^{+2} and phosphorus (P) levels. There is no need for imaging techniques in the diagnostic stage. However, during the treatment, some of the asymptomatic patients and all symptomatic patients are treated primarily by surgery. The PHPT surgery selection criteria are presented in Table 1 (2). An early surgical resection using the minimally invasive parathyroidectomy (MIP) technique is becoming a commonly used practice. Because of this trend in the approach in patients with HPT, the identification of the number and the localization of parathyroid glands that cause the disease are becoming increasingly important (3).

The most common methods used in the imaging of parathyroid adenomas are ultrasonography (USG) and Tc-99m sestamibi scintigraphy (MIBI). The sensitivity of USG and MIBI for detecting parathyroid adenomas ranges between 80% (77%–83%) and 84% (80%–87%), respectively (4). In a different study, it was reported that MIBI is more sensitive than USG in detecting parathyroid adenoma (5). It was shown that MIBI is an eminent method to determine the localization of parathyroid adenomas preoperatively, and it can provide certain information to the surgeon about the adenomas that cannot be detected with standard radiological procedures (3). Consequently,

Table 1. Current recommendations for surgery in asymptomatic PHPT (2)

Serum calcium (>upper limit of normal)	1.0 mg/dL (0.25 mmol/L)
Skeletal	A. BMD by DEXA: T-score <−2.5 at the lumbar spine, total hip, femoral neck, or distal 1/3 radius*
	B. Vertebral fracture by x-ray, CT, MRI, or VFA
Renal	A. Creatinine clearance <60 cc/min
	B. 24-h urine for calcium >400 mg/d (>10 mmol/d) and increased stone risk in the biochemical stone risk analysis**
	C. Presence of nephrolithiasis or nephrocalcinosis by x-ray, ultrasound, or CT
Age, years	<50

BMD, bone mineral density; DEXA, dual-energy x-ray absorptiometry; CT, computed tomography; MRI, magnetic resonance imaging; VFA, vertebral fracture assessment. *Consistent with the position established by the ISCD, the use of Z-scores instead of T-scores is recommended in evaluating BMD in premenopausal women and men younger than 50 years. **Most clinicians will first obtain a 24-h urine for calcium excretion. If marked hypercalciuria is present (>400 mg/d [>10 mmol/d]), further evidence of calcium-containing stone risk should be sought by a urinary biochemical stone risk profile, available through most commercial laboratories. In the case of abnormal findings indicating an increased calcium-containing stone risk and marked hypercalciuria, a guideline for surgery is met.

both USG and MIBI have a high sensitivity for solitary parathyroid adenoma; however, negative imaging studies can be made inevitably (6). We aimed to investigate the determination characteristics and the availability of MIBI imaging to determine eutopic and ectopic localized parathyroid adenomas.

MATERIALS and METHODS

Patients: Patients diagnosed with PHPT between January 1, 2002, and August 30, 2010, using parathyroid scintigraphy with MIBI and imaging with a dual-phase dual-isotope technique, reported as parathyroid adenoma, were enrolled into this study. We retrospectively scanned the data of 387 patients who were referred for MIBI imaging to evaluate parathyroid adenoma. From the hospital patient record and automation system, the PTH, Ca^{+2}, P, urea, and creatinine levels and the USG data of all patients during scintigraphy were obtained. Surgery notes and pathology results of all patients who underwent parathyroidectomy were also obtained from medical records and added to the study. The cases that had missing biochemical parameters and pathological confirmation were excluded. Images were evaluated for compliance with the Turkish Society of Nuclear Medicine Parathyroid Scintigraphy Procedure Guideline (7) and the Europe Nuclear Medicine Society standard imaging protocol (8). Images that did not match the protocol, were not optimal due to patient movement or other reasons, and were reported as suspicious were left out of the study. Finally, 59 patients aged 20–82 years (mean age, 53.3; median age, 48) were included in the study. There were 14 males (24%) and 45 females (76%). The process of patient selection is presented in Figure 1. Lesions from each imaging according to localization were divided into two groups: ectopic and eutopic.

The Consent Statement of the Subject and Ethical Approval: All patients were informed about the process and consequences of the procedure before the scintigraphy protocol. All patient data were allowed to be used in scientific studies. This study was approved by the local ethics board (TUTFEK2009/139).

Imaging Protocol: In all studies, after applying 20–25 mCi Tc99m MIBI, at 15 min and 2 h, planar imaging was made, and after a complete MIBI washout, 5 mCi Tc99m pertechnetate were given and thyroid scintigraphy was performed. All MIBI images were obtained from the Philips BrightView gamma camera (Philips Medical Systems, Cleveland, USA) and the Siemens E.CAM gamma camera (Siemens Healthcare GmbH, Erlangen, Germany). In addition, early (1 h) single photon emission computerized tomography (SPECT) and 4 h planar MIBI imaging (if needed) were performed. According to the anatomical definition (9), adenomas posterior to the bilateral lower and upper thyroid lobes adjacent to the thyroid gland were accepted as eutopic; adenomas that were out of these areas were accepted as (neck, mediastinum, and intrathyroid; all intrathyroid lesions were pathologically confirmed as parathyroid adenomas) ectopic.

Following a visual assessment of the image, to determine the radiopharmaceutic retention and excretion in the early and late phases of a dual-phase imaging protocol, counting was made after drawing the same-sized region of interest (ROI) around the lesion for each phase from the early and late images of all lesions (at 15 min and 2 h). The base activity counting was made without changing the ROI sizes, for cases with one adenoma from the symmetric thyroid tissue and for cases with bilateral adenoma from the shoulder muscle tissue abroad. For ectopic and eutopic lesions, four different scintigraphic parameters were calculated. An early parathyroid-to-thyroid ratio (early PT/T), late parathyroid-to-thyroid ratio (late PT/T), early-to-late ratio (E/L), and the retention index (RI) were calculated as follows:

PT/T=Parathyroid/Thyroid E/L=Early/Late

RI=[(Late PT/T)-(Early PT/T)]/(Early PT/T)x100

Statistical Analysis

Statistical correlation between scintigraphic parameters and three biochemical parameters (serum PTH, and calcium and phosphor levels) were evaluated. For ectopic and eutopic localized lesions, statistical differences for these parameters were tested. The statistical analysis was made using the STATISTICA AXA 7.1 statistical program (serial number, AXA507C775506FAN3). Compliance with the normal data distribution that could be measured was made with the Kolmogorov–Smirnov test, and when there was no compliance, the Mann–Whitney U test was used for group comparison. Also, the t-test was applied when assuming the normal distribution.

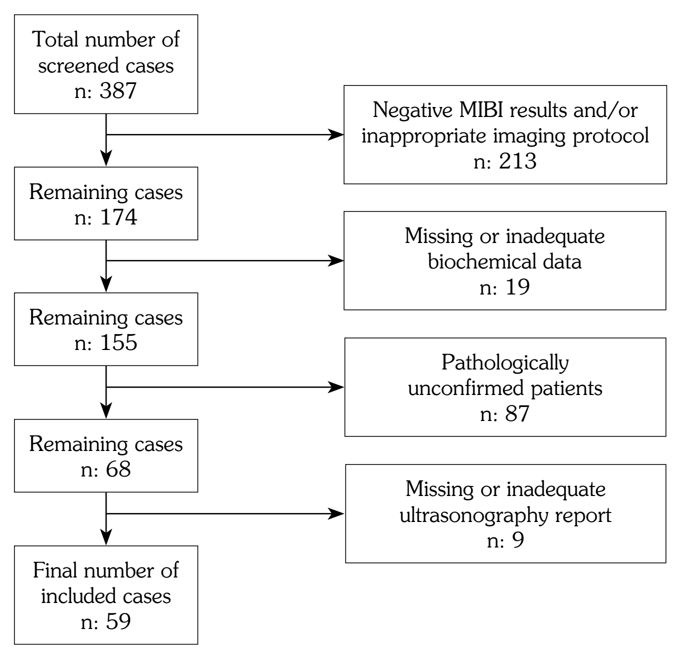

Figure 1. Lesions from each imaging according to localization were divided into two groups: ectopic and eutopic

To evaluate the relation between the variables, Spearman's rho correlation analysis was used. For definitive statistics, the median (interquartile range [IQR]) values, and the mean±standard deviation (SD) was given. A p-value <0.05 was considered to represent a significant difference for all statistics.

RESULTS

A total of 59 patients were included in the study. The mean age of patients for the ectopic group was 55.43±15.23 years, and it was 51.62±11.33 in the eutopic group. Of the 65 identified lesions, 28 were (43%) ectopic, and 37 were (57%) eutopic. Fifty-four had one adenoma, 4 had two adenomas, and 1 had three parathyroid adenomas (91.5%, 6.8%, 1.7%, respectively). According to the localization, 28 adenomas were determined as ectopic and 37 of as eutopic.

When biochemical parameters were compared between the two groups with either eutopic or ectopic parathyroid adenoma, there was not statistically significant difference excluding the PTH levels (Table 2). Since the PTH data were non-normally distributed, we described the PTH levels with the median and interquartile range. The PTH levels were 65–2500 pg/mL, with a median of 222 pg/mL (25^{th} percentile, 160 pg/mL; 75^{th} percentile, 561 pg/mL) for the ectopic group. For the eutopic group, the PTH levels were 73–1222 pg/mL, with a median of 151 pg/mL (IQR, 119–303 pg/mL). Since all other parameters fit the normal distribution, they were expressed as the mean±SD. Mean Ca^{+2} levels were 10.53±1.51 mg/dL and 10.68±0.998 mg/dL for the ectopic and eutopic groups, respectively.

Regarding the association between scintigraphic and biochemical parameters in the ectopic group, a positive and medium level association was determined between RI and the Ca^{+2} and P levels, which was statistically significant. In addition, although an association between the RI with the PTH level was at a positive direction, it was weak and statistically non-significant (Table 3). Moreover, there was a statistically significant relationship between the early PT/T rate and Ca^{+2} value, which was at a negative direction and the medium level. Although the association between P and the PTH levels was similarly negative, it was not statistically significant. On the other hand, the late PT/T values were not significantly affected by biochemical parameters (Table 3). Furthermore, we determined a negative association between the E/L values and the Ca^{+2} and P levels, which was statistically significant, while there was no remarkable relationship between the E/L values and the PTH levels, which was very weak and similarly negative (Table 3).

Table 2. Assessment of difference between the two study groups regarding the parameters presented in this table

	RI	Early PT/T	Late PT/T	E/L	PTH (pg/mL)	Ca^{+2} (mg/dL)	p (mg/dL)
Ectopic	17.8±17.5	1.1±0.4	1.16±0.2	0.8±0.1	222 (IQR=160-561)	10.53±1.51	2.6±0.8
Eutopic	20.2±24.9	1.2±0.4	1.3±0.3	0.8±0.1	151 (IQR=119-303)	10.68±0.998	3±0.8
P-value	0.865	0.175	0.803	0.219	**0.001**	0.102	0.075

RI: Retention index; PT: Parathyroid; T: Thyroid; E: Early; L: Late; PTH: Parathyroid hormone; Ca^{+2}, calcium; P: Phosphorus; IQR: Interquartile range. A p-value <0.05 was considered to represent a significant difference for all statistics

Table 3. Association between parameters in the group of patients with ectopic parathyroid adenomas

	Ca^{+2}	P	PTH
RI	**rho=0.325. p=0.013**	**rho=0.410. p=0.003**	rho=0.143. p=0.272
Early PT/T	rho=-0.403. p=0.002	rho=-0.268. p=0.058	rho=-0.126. p=0.332
Late PT/T	rho=-0.188. p=0.158	rho=-0.085. p=0.555	rho=-0.077. p=0.556
E/L	**rho=-0.311. p=0.017**	**rho=-0.318. p=0.023**	rho=-0.058. p=0.658

RI: Retention index; PT: Parathyroid; T: Thyroid; E: Early; L: Late; PTH: Parathyroid hormone; Ca^{+2}: Calcium; P: Phosphorus; rho: Spearman's rank correlation coefficient; p: Level of significance. A p-value <0.05 was considered to represent a significant difference for all statistics

Table 4. Association between parameters in the group of patients with eutopic parathyroid adenomas

	Ca^{+2}	P	PTH
RI	rho=0.200. p=0.131	rho=0.101. p=0.480	rho=0.065. p=0.618
Early PT/T	rho=-0.074. p=0. 580	rho=-0.267. p=0.058	rho=-0.072. p=0.584
Late PT/T	rho=0.145. p=0.279	rho=-0.240. p=0.090	rho=0.012. p=0.929
E/L	rho=-0.200. p=0.131	rho=-0.101. p=0.480	rho=-0.065. p=0.618

RI: Retention index; PT: Parathyroid; T: Thyroid; E: Early; L: Late; PTH: Parathyroid hormone; Ca^{+2}: Calcium; P: Phosphorus; rho: Spearman's rank correlation coefficient; p: Level of significance. A p-value <0.05 was considered to represent a significant difference for all statistics

At the same time, our assessment revealed that scintigraphic parameters including RI, early PT/T, late PT, and E/L were not significantly affected by biochemical values such as Ca^{+2}, P, and PTH in the eutopic group (Table 4).

DISCUSSION

Since the success of MIP is highly correlated with the correct location of the adenoma, preoperative imaging techniques have become increasingly important in recent years. A number of scintigraphic methods were improved for preoperative pinpoint of hyperfunctional parathyroid glands in the past decade. Although there are few researchers who directly compared the reliability of different methods, a clear protocol has not been improved yet for the MIBI parathyroid scintigraphy in medical literature. Comparison between different methods revealed that no method is significantly better than any other.

The majority of studies on parathyroid scintigraphy compare the sensitivity of SPECT and planar imaging systems. Although the sensitivity is higher in SPECT (11%–20%) than in planar imaging in a number of studies, the difference between them is not statistically significant (10). Moreover, two studies suggested that there is no difference between using SPECT and planar imaging (11, 12).

The current hot topic for researchers is to improve scintigraphy revealing parallel changes in positive invasion patterns with both biochemical and pathological processes. We also focused on two main targets. The first target was to determine whether there was any difference between ectopic and eutopic parathyroid adenomas considering the radiopharmaceutical absorption and elimination by early and late imaging, and to develop an easily obtainable and repeatable parameter to use when selecting the most suitable imaging protocol for every single patient. Second, we aimed to evaluate the plausible association between scintigraphic results obtained with the MIBI parathyroid scintigraphy in patient groups (having either ectopic or eutopic parathyroid adenomas) and biochemical parameters that are routinely studied in the same patient groups, and to assess whether these biochemical parameters differ due to localization of parathyroid adenomas.

The main principle of the MIBI parathyroid imaging is based on differences in the amount and duration of radiopharmaceutical absorption by the parathyroid and thyroid tissues. Moreover, the amount of radiopharmaceutical absorption by the parathyroid tissue is positively correlated with the weight and size of the parathyroid gland and how the parathyroid gland is functional (13, 14). Therefore, the rate of the PT/T obtained from interested areas including adenoma and neighboring normal tissue will reveal the amount of absorption of radiopharmaceutics by the lesion. Common consensus in the nuclear medicine literature is that the rate of the PT/T increases with time after the MIBI injection (15). In compliance with this consensus, we determined that there was a significant difference between the values of early PT/T and late PT/T in both the eutopic and ectopic groups, whereas the enhancement in the PT/T values was more remarkable in the late period. Therefore, we suggest that the use of prolonged scintigraphic imaging (2 h, or 4 h in special cases) will advance the sensitivity and specificity of this imaging method by improving the identification of parathyroid adenomas and their differential diagnosis from thyroid nodules. However, it should be kept in mind that early imaging at 15 min is essential to catch parathyroid adenoma with multidrug resistance gene encoding P-glycoprotein that leads to early elimination of MIBI from parathyroid adenoma (16, 17). We suggest that the ideal imaging protocol should include both the early and late imaging.

An intact PTH level reveals a functional condition of the parathyroid gland. An association between the MIBI absorption in parathyroid adenoma and the amount of oxyphilic cells consisting of a number of mitochondria was suggested. These cells also synthesize PTH, which may be involved in the pathophysiology of HPT. Therefore, the relationship can be postulated between the absorption of MIBI and the PTH level. In this study, we did not find any significant association between the PTH level and RI, and the mean of early PT/T or late PT/T values in both groups. Other studies presented different findings about the association between the MIBI absorption and PTH levels regarding the same scintigraphic parameters including the RI, early PT/T, or late PT/T values in parathyroid adenomas. In 2016, Koberstein et al., and, in 2018, Beheshti et al., suggested a positive correlation between the serum PTH values and a positive MIBI scan (13, 18). Similarly, Hung et al., revealed that the sensitivity of test reaches 100% when the level of serum intact PTH is over 200 pg/ml (19).

Moreover, Siegel et al., suggested a positive correlation between the PTH values and gland`s weight studied to identify the threshold of the PTH level enabling to take positive imaging in 2006 (20). In their study, the mean PTH level was calculated as 367 pg/ml (normal range, 46–3231 pg/ml) for a real positive imaging, while it was determined as 148 pg/ml (normal range, 46–390 pg/ml) for the pseudo negative and positive imaging, and the difference was found to be statistically significant (20).

In contrast, Melloul et al., postulated that there was no correlation between the MIBI absorption and PTH levels in parathyroid adenomas (21). Although we did not determine any correlation between the PTH level and scintigraphic parameters, significant differences were found in the mean PTH values between two groups. Considering that there is an association between the gland function and the cellular response, and the PTH levels were higher in the ectopic group, we hypothesized that there may be changes in the number of receptor and their function that make different the cellular response to PTH in this group. Further studies are required to clarify whether the same possible molecular or cellular change is also the cause of the ectopic location of the parathyroid gland.

Considering the association of the RI, PT/T, or E/L rates with Ca^{+2} and P, no significant association was detected between these parameters in the eutopic group, suggesting that the levels of Ca^{+2} and P are associated, at least partially, with the MIBI absorption independent of PTH, and this association should be considered prior to scintigraphic imaging. We proposed that the difference regarding the RI and E/L rates between the two patient groups may be caused by structural differences (receptor structure or sensitivity) at the cellular level in glands, revealing a unique embryological migration. These structural differences may also explain the behavioral difference seen during the late embryonic period. More advanced research needs to be conducted to assess whether this hypothesis is true.

There are a few previous studies examining the association between the Ca^{+2} and P levels and the MIBI positivity. Findings published in 2008 by Erbil et al., suggested that there was no correlation between the parameters (including the values of PTH and Ca^{+2}, the weight of the gland) and the ectopic localization of parathyroid adenoma (22). In the same study, the association was postulated between the weight of the gland and the USG and MIBI positivity. A study examining the MIBI absorption and the volume of tumor and biochemical markers (PTH, Ca^{+2}, P) by Çermik et al., revealed that the MIBI absorption is higher in the late phase compared to the early phase (23). Moreover, an increase in the weight of the gland and the serum PTH level was found in all parathyroid adenomas compared with the normal, while there was no statistically significant correlation between the phase of imaging, volume of the lesions, and levels of Ca^{+2} and PTH (23). Çermik et al., also suggested that the MIBI absorption is not always correlated with the content of oxyphilic cells and additionally postulated that the number of oxyphilic cells is not the only factor affecting the MIBI absorption (23). Conversely, in 2012, Ciappuccini et al., showed that the adenoma size, serum calcium levels, and serum PTH levels most likely affect the MIBI scintigraphy results (24).

Our second aim was to determine any differences between ectopic and eutopic parathyroid adenomas regarding four scintigraphic and three biochemical parameters. In addition, another purpose of our study was to examine whether any of these parameters could be a marker to be focused on when we need to take images of ectopic parathyroid adenoma. In conclusion, we found a statistically significant difference only in the PTH levels ($p=0.027$) between the patient groups when we considered the analysis of results obtained by seven parameters. When we examined the scientific literature, we could not find any study investigating scintigraphic or biochemical tools to predict ectopic adenoma before imaging. The study by Koberstein et al., in 2016 showed that the MIBI SPECT was a useful imaging tool for both the groups (18). Liddy et al., compared the ability of USG and MIBI scintigraphy in 2016 and found that MIBI images were more sensitive and accurate in detecting ectopic adenomas (5). In current study, since all the included cases were positive for adenoma, we did not investigate the efficacy of MIBI scanning on detecting adenomas. We only investigated whether biochemical and scintigraphic parameters have changed according to the localization of adenomas. Our findings are consistent with previously reported results on Ca^{+2} values, while they are controversial when we considered the level of PTH in the same study performed on the changes on parameters due to lesion localization (22). We suggest that these differences in results may be due to different features of the patient population included in the study. Subjects included in the study by Erbil et al., agreed to be operated on for their parathyroid adenomas. However, our study included individuals who were randomly evaluated for any parathyroid adenoma due to PHPT.

Moreover, we evaluated all patients with or without the indication for parathyroid surgery. Differences between the two studies may be caused by changes in parameters regarding age, the metabolic condition, and the level of PTH in between the two groups.

Furthermore, in another study evaluating PHPT, the incidence of parathyroidectomy and the association of PHPT with age and gender were conducted by Richerta et al., based on the population of patients taken from Switzerland (25). They suggested that the incidence of PHPT significantly increases with age and the difference between two genders becomes clearer with the increase in age (24). The incidence of parathyroid adenomas starts increasing at the age of 40 and reaches significantly increased rates in patients 65 and older, peaking after the age of 80. This alteration that occurs with age may explain the difference between the study results.

CONCLUSION

Considering the information presented in this paper, we concluded that the MIBI scanning is currently the best imaging method for the localization of parathyroid adenomas. The ideal imaging protocol should include a combination of the SPECT study that is not prolonged over 1 h with an early and late planar (at 15 min and 2 h, respectively) imaging. We determined that the level of PTH is the only biochemical parameter that is directly associated with the MIBI positivity. Moreover, our findings revealed that the rate of E/L was negatively correlated with Ca^{+2} and P, while RI exhibited a positive association with Ca^{+2} and P. Previous studies also suggested that the content of oxyphilic cells was not the single and the most important parameter affecting the MIBI absorption.

The biochemical parameters including the Ca^{+2} and P levels are not clearly predictive of scintigraphy results and the localization of adenomas. However, serum PTH values should be considered in ectopic parathyroid adenomas prior to scintigraphic imaging. The possibility of ectopic parathyroid adenomas should be kept in mind, especially when the blood levels of PTH are high.

Imaging protocols and radionuclides used in the imaging of the parathyroid gland have changed, and different protocols have been developed by researchers over time. Currently, the Tc99m MIBI is commonly used as a chosen radiopharmaceutical agent in the imaging of parathyroid and thyroid tissues. The Tc99m MIBI imaging is based on the differences in the mechanisms and the amount of the radiopharmaceutical agent's uptake by the parathyroid and thyroid glands and the duration of its elimination from these tissues. Specialists in nuclear medicine who conduct imaging and analyze its results should be cautious and consider the uptake and elimination principles of Tc99m MIBI when they decide on the use of either planar or the SPECT imaging method.

Ethics Committee Approval: This study was approved by the local ethics board (TUTFEK2009/139).

Informed Consent: All patients were informed about the process and consequences of the procedure before the scintigraphy protocol. All patient data were allowed to be used in scientific studies.

Peer-review: Externally peer-reviewed.

Author Contributions: Conceived and designed the experiments or case: ÜK, AS. Performed the experiments or case: ÜK. Analyzed the data: ÜK. Wrote the paper: ÜK. All authors have read and approved the final manuscript.

Conflict of Interest: The authors have no conflict of interest to declare.

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