The Role of Parathyroid Scintigraphy in the Differential Diagnosis of Primary Hyperparathyroidism

Primer Hiperparatiroidizmin Ayırıcı Tanısında Paratiroid Sintigrafisinin Rolü

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ABSTRACT Objective: Primary hyperparathyroidism mostly develops due to a solitary parathyroid adenoma, less frequently due to other parathyroid lesions (hyperplasia and carcinoma). The aim of our study is to determine the efficiency of parathyroid gland scintigraphy in the differential diagnosis of primary hyperparathyroidism. **Material and Methods:** This study included 27 patients (21 F, 6 M; mean age ± SE: 55 ± 3 years) with a diagnosis of primary hyperparathyroidism. All patients underwent parathyroid ultrasonography (USG). Then, Tc-^{99m} MIBI dual-phase and Tl-^{201} chloride/Tc-^{99m} pertechnetate subtraction scintigraphies were acquired in 18 and 9 cases, respectively. After parathyroid surgery, the excised tissues were examined by histopathology. **Results:** While parathyroid pathology was detected by scintigraphic and histopathological examinations in 24 out of 27 patients, it was not detected in 3 patients. Preoperative parathormon (PTH) levels were between 79 and 2500 pg/mL (median: 388 pg/mL) and serum Ca levels were between 9.8 and 15.5 mg/dL (mean ± SE: 12 ± 0.3 mg/dL). Postoperative PTH levels were measured as between 2.6 and 339 pg/mL (median: 12 pg/mL), serum Ca levels were between 5.7 and 11.8 mg/dL (mean ± SE: 9 ± 0.3 mg/dL). The mean weight of the parathyroid glands was 2.6 g. The sensitivity, specificity and accuracy of parathyroid scintigraphy were all found to be 100%. When we compared USG findings with the pathology results, the sensitivity, specificity and accuracy of USG were 100%, 18.7% and 50%, respectively. **Conclusion:** Parathyroid scintigraphy is a reliable and useful non-invasive method for the localization and differential diagnosis of parathyroid lesions, and it aids the clinician in choosing the treatment modality for primary hyperparathyroidism patients.

Key Words: Parathyroid neoplasms; technetium Tc ^{99m} sestamibi; thallium chloride

ÖZET Amaç: Primer hiperparatiroidizm en sık soliter paratiroid adenomu daha az sıklıkla paratiroid hiperplazisi ve karsinomu nedeni ile gelişir. Bizim çalışmamızın amacı, primer hiperparatiroidizmin ayırıcı tanısında paratiroid bezi sintigrafisinin etkinliğini belirlemektir. **Gereç ve Yöntemler:** Çalışma primer hiperparatiroidizm tanısı almış 27 hastadan (21 K, 6 E; ort yaş ± SE 55 ± 3 yıl) oluşmaktadır. Bütün hastalara paratiroid ultrasonografisi (USG) uygulandı. Ardından Tc-^{99m} MIBI çift-faz ve Tl-^{201} klorid/Tc-^{99m} perteknetat çıkarma sintigrafileri sırasıyla 18 ve 9 hastada çalışıldı. Paratiroid cerrahisi sonrası, çıkartılan dokular histopatolojik olarak incelendi. **Bulgular:** Sintigrafik ve histopatolojik incelemeleri yapılan 27 hastanın 24'ünde paratiroid patolojisi saptanırken 3 tanesine saptanmadı. Preoperatif parathormon (PTH) düzeyleri 79 ve 2500 pg/mL arasında (medyan: 388 pg/mL) ve serum Ca düzeyleri 9.8 ve 15.5 mg/dL arasında (ort ± SE: 12 ± 0.3 mg/dL) ölçüldü. Postoperatif parathormon (PTH) düzeyleri 2.6 ve 339 pg/mL arasında (medyan: 12 pg/mL), ve serum Ca düzeyleri 5.7 and 11.8 mg/dL arasında (ort ± SE: 9 ± 0.3 mg/dL) idi. Paratiroid bezlerinin ortalama ağırlığı 2.6 g olarak saptandı. Paratiroid sintigrafisinin sensitivite, spesifite ve doğruluğu %100 bulundu. Histopatoloji sonuçları ile karşılaştırdığımızda, USG'nin sensitivite, spesifite ve doğruluğu sırasıyla %100, %18.7 and %50 olarak hesaplandı. **Sonuç:** Paratiroid sintigrafisi, paratiroid lezyonlarının ayırıcı tanısında ve lokalizasyonunda güvenilir, kullanışlı, noninvaziv bir yöntemdir ve klinisyene primer hiperparatiroidizm vakalarının tedavi seçiminde yol göstericidir.

Anahtar Kelimeler: Paratiroid tümörleri; teknesyum Tc ^{99m} sestamibi; talyum klorid

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After diabetes mellitus and hyperthyroidism, primary hyperparathyroidism is the third most frequent endocrine disease.[1] Primary hyperparathyroidism most often develops due to a solitary parathyroid adenoma (84%), less frequently due to multiple parathyroid gland disease (15%) and rarely due to a parathyroid carcinoma (1%),[2] and treatment includes bilateral total neck exploration.[3] Today, with the widespread use of preoperative ultrasonography (USG) and Tc-^{99m} MIBI parathyroid scintigraphy for the detection and localization of parathyroid lesions, treatment has shifted to minimally invasive surgery.[3,4] In this new treatment paradigm, the success of the surgery depends on the sensitivity and specificity of the imaging method as well as on the surgeon's experience.[5] The sensitivity of USG depends on the size and location of the hyperfunctional gland and whether the mediastinal gland can be detected.[6] Though the sensitivity of parathyroid scintigraphy is expected to be associated with the size of the parathyroid tissue, it has been reported that large parathyroid lesions may not be shown. In these studies, it was revealed that the detectability of the lesion was related to its function as much as its size.[7,8] Different radiotracers have been used for parathyroid imaging. The major imaging methods have used Tl-^{201}, Tc-^{99m} MIBI or Tc-^{99m} tetrofosmin for evaluating parathyroid lesions. These are all myocardial perfusion tracers and are taken up also by hyperfunctioning parathyroid glands and by thyroid glands. Therefore, a second tracer, which is taken up by the thyroid gland only, such as Tc-^{99m} pertechnetate or I-123 is necessary for the differentiation between two glands. Radioactive iodine is an ideal physiological tracer because it is selectively trapped and organified by the thyroid.[9] The Tc-^{99m} pertechnetate is trapped but it is not organified by the thyroid. Because of Tc-^{99m} pertehnetate's low cost and ready availability from Mo-99/Tc-^{99m} generator system, it has been as an useful alternative to radioiodine for thyroid detection.[9] The visual comparison of distribution of the two tracers and the digital subtraction the thyroid gland from the parathyroid improve the detection of parathyroid lesion. As a blood flow agent Tl-^{201} is taken up by both benign and malignant tumors which include hyperfunctioning parathyroid tissue, and also, normal thyroid tissue shows uptake. Tc-^{99m} MIBI is a lipophilic cation and the mechanism of uptake is probably related to high cellularity and tumor vascularity.[9] It was distributed into the thyroid and the parathyroid like Tl-^{201}. Tc-^{99m} MIBI uptake in parathyroid tissue is lower than Tl-^{201}, but the ratio between the parathyroid and thyroid tissue is higher. The uptake of MIBI remains constant in parathyroid tissue (possibly due to mitochondrial binding or reduced PgP expression) whereas there is a washout from the thyroid.[2] The introduction of Tc-^{99m} MIBI dual-phase parathyroid scintigraphy[10] replaced the Tl-^{201}/Tc-^{99m} pertechnetate subtraction method. In preoperative imaging, detection of multiple parathyroid gland diseases and ectopic parathyroid tissue are very important in preventing inappropriate, minimally invasive surgery.[3] The scintigraphic detection of thyroid malignant nodules also prevents the confusion with parathyroid adenomas, which is common.[11-13] In addition, MIBI scintigraphy can also prevent unnecessary referring patients for parathyroid surgery due to increased parathormon (PTH) which is secondary to the thyroid tissue inflammation.[14] In the literature, it has been shown that 20% of the parathyroid glands have ectopic localization, and therefore, they cannot be excised in the first neck operation.[15] Recently, it has also been reported that the success rate of the first operation is 95%, but this success rate falls to ≤ 80% in the second operation.[16] In cases that underwent reoperation, the risk of operation-associated complications, such as permanent hypoparathyroidism or laryngeal nerve paralysis (13%-66%) are increased at least 10 times compared to the first operation (<1%).[12,17-20]

The aim of this study is to determine the efficiency of parathyroid gland scintigraphy in the differential diagnosis and localization of hyperfunctional parathyroid glands in patients with hyperparathyroidism using histopathology as the gold standard.

MATERIAL AND METHODS

Twenty-seven patients (21 female, 6 male; mean age ± SE: 55 ± 3 years) with a preliminary diagno-

sis of primary hyperparathyroidism were enrolled in this retrospective study. None of the patients had undergone neck surgery. All of the patients underwent preoperative USG (LOG IQ 200 PRO, Version 3, GE; Milwaukee, Wisconson) parathyroid examination using lineer probe with 7.5 Hz image frequency in our department. Following the USG, Tc-^{99m} MIBI (740 MBq) dual-phase parathyroid (n= 18) or Tl-^{201} chloride/Tc-^{99m} pertechnetate (74 MBq/185 MBq) parathyroid subtraction scintigraphy (n= 9) (GE-Milenium Acq, Entegra) was acquired with a low-energy all-purpose (LEAP) collimator. For the 18 patients undergoing the dual-phase parathyroid scintigraphy, 10 minutes after the IV injection of Tc-^{99m} MIBI, planar anterior neck images were acquired with the patient in supine position, for 300 seconds, and then 2 hours later, planar anterior neck and mediastinum images were acquired for 300 seconds using a 128 x 128 pixel matrix and with 1.33 zoom factor. The Tl-^{201}/Tc-^{99m} subtraction scintigraphy was used in 9 patients; 10 minutes after the Tl-^{201} chloride IV injection, the Tc-^{99m} pertechnetate was intravenously injected. After a period of 15 minutes, anterior views of the neck and the mediastinum were acquired with the patient in supine position, for 600 seconds using a 128 x 128 matrix and a 140 keV and 80 keV photopeak with a 20% energy window and 1.33 zoom factor. After the acquisition, the subtracted parathyroid image was obtained semi-automatically using the system software. In addition, all scintigraphic parathyroid images were blindly evaluated by 2 nuclear medicine physicians (one with more experience than the other). For each neck and mediastinum image, if there were one or more observed regions of extrathyroidal increased focal activity, then the image was considered to be positive for parathyroid pathology (parathyroid adenoma or hyperplasia, ectopic tissue). Within one week following scintigraphic imaging, all of the patients underwent minimally invasive parathyroid surgery or bilateral total neck surgery. The excised pathological tissue(s) was histopathologically examined. After the fresh pathological tissues were separated from the lipid layer, the dimensions were measured and weighed. In addition, PTH and serum calcium (Ca) levels were measured before and immediately after the operation.

RESULTS

Of the 27 patients, parathyroid gland pathology was detected in 24 patients using scintigraphic and histopathological examinations, but the parathyroid lesion was not detected in 3 cases (Figure 1). During histopathological examination, a benign thyroid pathology was detected in 1 of these 3 cases with normal scintigraphy and USG. Ectopic parathyroid tissue was not observed in any of our cases. The preoperative PTH levels were measured between 79 and 2500 pg/mL (median: 388 pg/mL); Ca levels were between 9.8 and 15.5 mg/dL (mean ± SE: 12 ± 0.3 mg/dL); postoperative PTH levels were between 2.6 and 339 pg/mL (median: 12 pg/mL); and Ca levels were between 5.7 and 11.8 mg/dL (mean ± SE: 9 ± 0.3 mg/dL). The weight of the abnormal parathyroid glands was between 0.40 and 6.5 g (mean ± SE: 2.6 ± 0.3 g). Using the histopathological results as the gold standard, the sensitivity, specificity and accuracy of parathyroid gland scintigraphy were all found to be 100% (Table 1). Though a parathyroid lesion was not detected in 3 cases using parathyroid scintigraphy and histopathology, neck surgery was performed based on the other clinical findings. When we evaluated the adenoma and hyperplasia separately (Table 2), 2 patients' pathological diagnoses were hyperplasia, but they were diagnosed with parathyroid adenoma based on the scintigraphy. All of the other scintigraphic and pathological results were compatible (Figure 2, 3). When we compared the results of the parathyroid gland USG with the histopathology, the USG sensitivity, specificity and accuracy were calculated as 46%, 100% and 50%, respectively (Table 3).

DISCUSSION

A preliminary diagnosis is performed in cases with hyperparathyroidism based on clinical findings and elevated Ca-PTH in the serum.[2,4] Imaging was used to measure the presence and localization of the parathyroid gland rather than for diagnosis. A normal parathyroid gland cannot be seen because it is

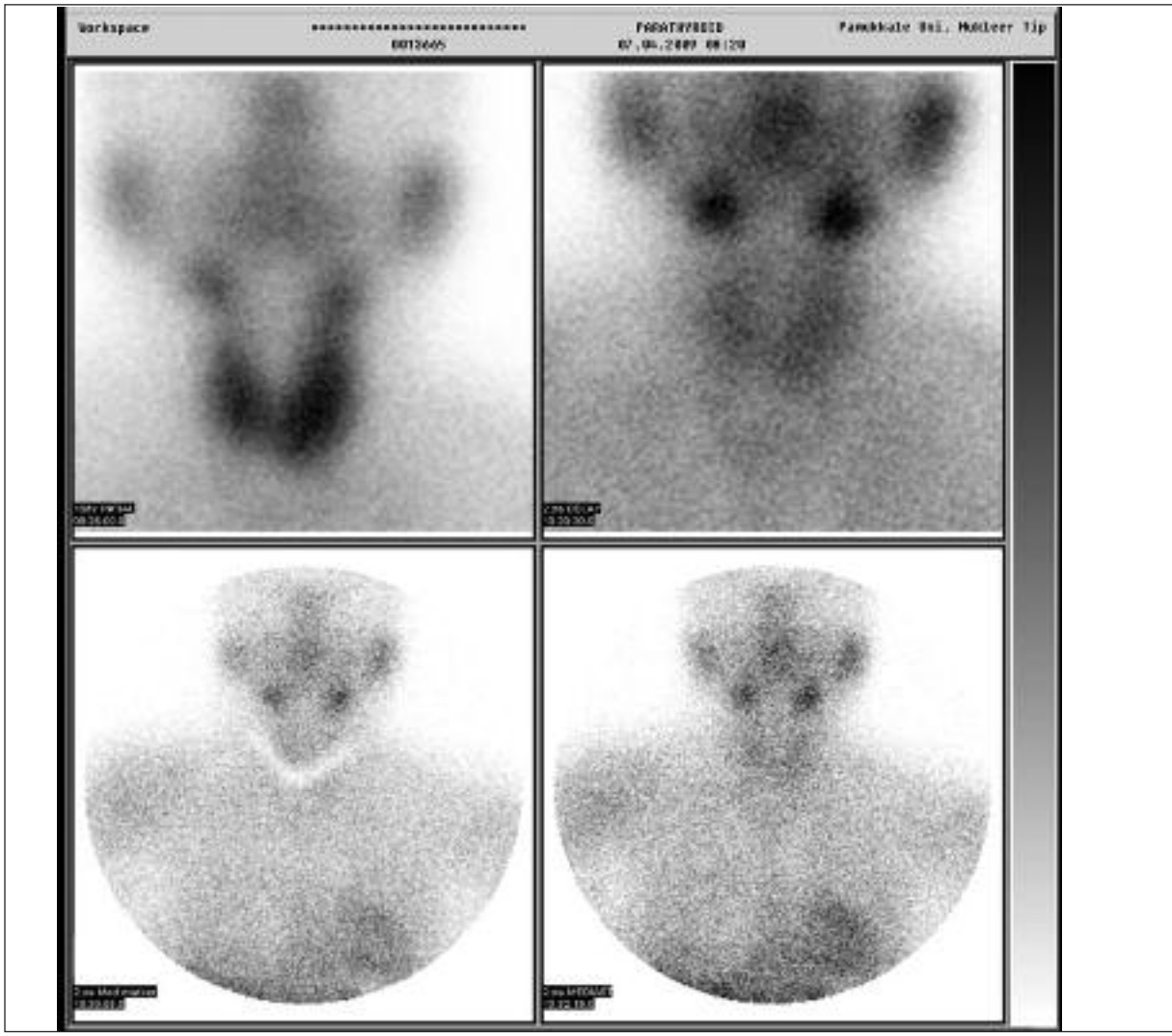

FIGURE 1: Tc-^{99m} MIBI parathyroid scan of a patient showed normal thyroid gland on the early planar thyroid image (left superior). The planar scintigraphic images of thyroid gland and the histopathological examination were regarded as negative for the localization of parathyroid adenoma on the late planar neck image (right superior) and on the late planar mediastinum images with and without sternal marker (inferior row).

TABLE 1: The scintigraphic and histopathological results of total parathyroid lesions.

		Histopathology		
		Normal (n)	Parathyroid lesion (n)	Total (n)
Scintigraphy	Normal	3	0	3
	Parathyroid lesion	0	24	24
Total		3	24	27

TABLE 2: The classification of parathyroid lesions detected by histopathology and scintigraphy.

		Histopathology		
		Adenoma(n)	Hyperplasia(n)	Total (n)
Scintigraphy	Adenoma	17	2	
	Hyperplasia	0	5	
Total		17	7	24

very small (20-50 mg). Currently, even patients with mild primary hyperparathyroidism (mild hypercalcemia and a mildly elevated serum PTH level) undergo surgery because the parathyroidectomy improves a patient's quality of life. Generally, these types of patients are candidates for minimally

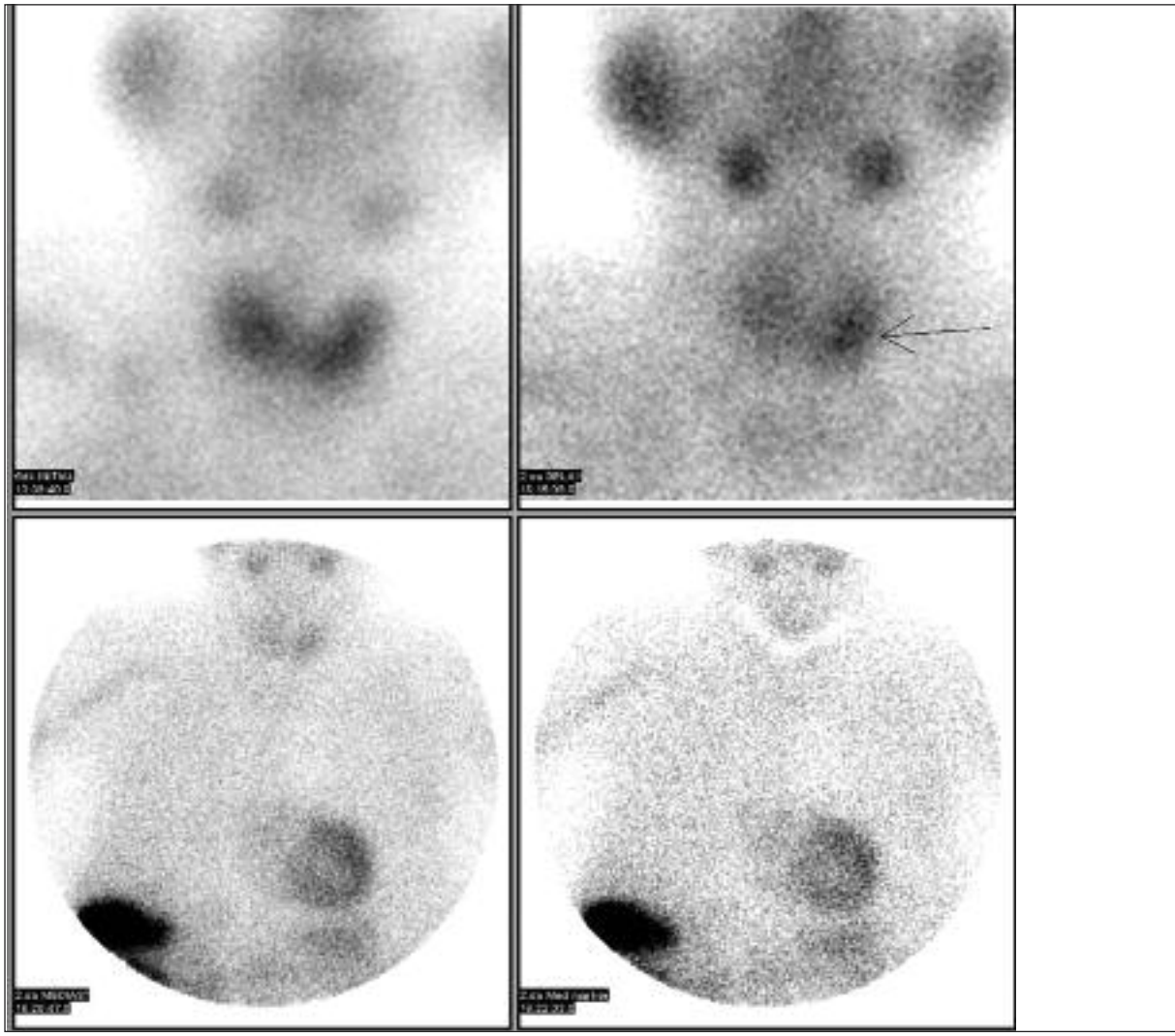

FIGURE 2: The early planar image of the Tc-^{99m} MIBI scan delineates the thyroid gland (left superior). The late planar neck image of the Tc-^{99m} MIBI scan (right superior) showed focal uptake below the left thyroid lobe and reported as parathyroid adenoma. The histopathological examination was compatible with scintigraphy. The activity distribution on the late planar mediastinum images with and without sternal marker (inferior row) was normal.

invasive surgery because their glands are slightly enlarged in proportion to their serum PTH and Ca levels.[4,21] All of our preliminary hyperparathyroidism cases were diagnosed based on clinical and/or laboratory evaluation; parathyroid lesions that were detected with scintigraphy or neck surgery were applied accordingly.

Parathyroid scintigraphy and USG are the dominant imaging techniques used in the detection of parathyroid lesions. Combined interpretation of scintigraphy and USG can enhance the diagnosis of parathyroid lesions and clinical decision making.[2] The tracers utilized in routine parathyroid scintigraphy like Tl-^{201}, Tc-^{99m} MIBI and also Tc-^{99m} tetrofosmin are taken up not only by the hyperfunctioning parathyroid glands but also by thyroid gland. A second tracer, which is taken up by the thyroid only, such as Tc-^{99m} pertechnetate or I-123, provides digitally subtraction from the parathyroid scan to remove the thyroid activity.[2] In the past, Tl-^{201}/Tc-^{99m} pertechnetate subtraction parathyroid scintigraphy was frequently used, but the increased use of Tc-^{99m} MIBI for this purpose has caused a decline in the popularity of Tl-^{201}/Tc-^{99m} pertechnetate subtraction. Tc-^{99m} MIBI imaging was first performed as the subtraction technique

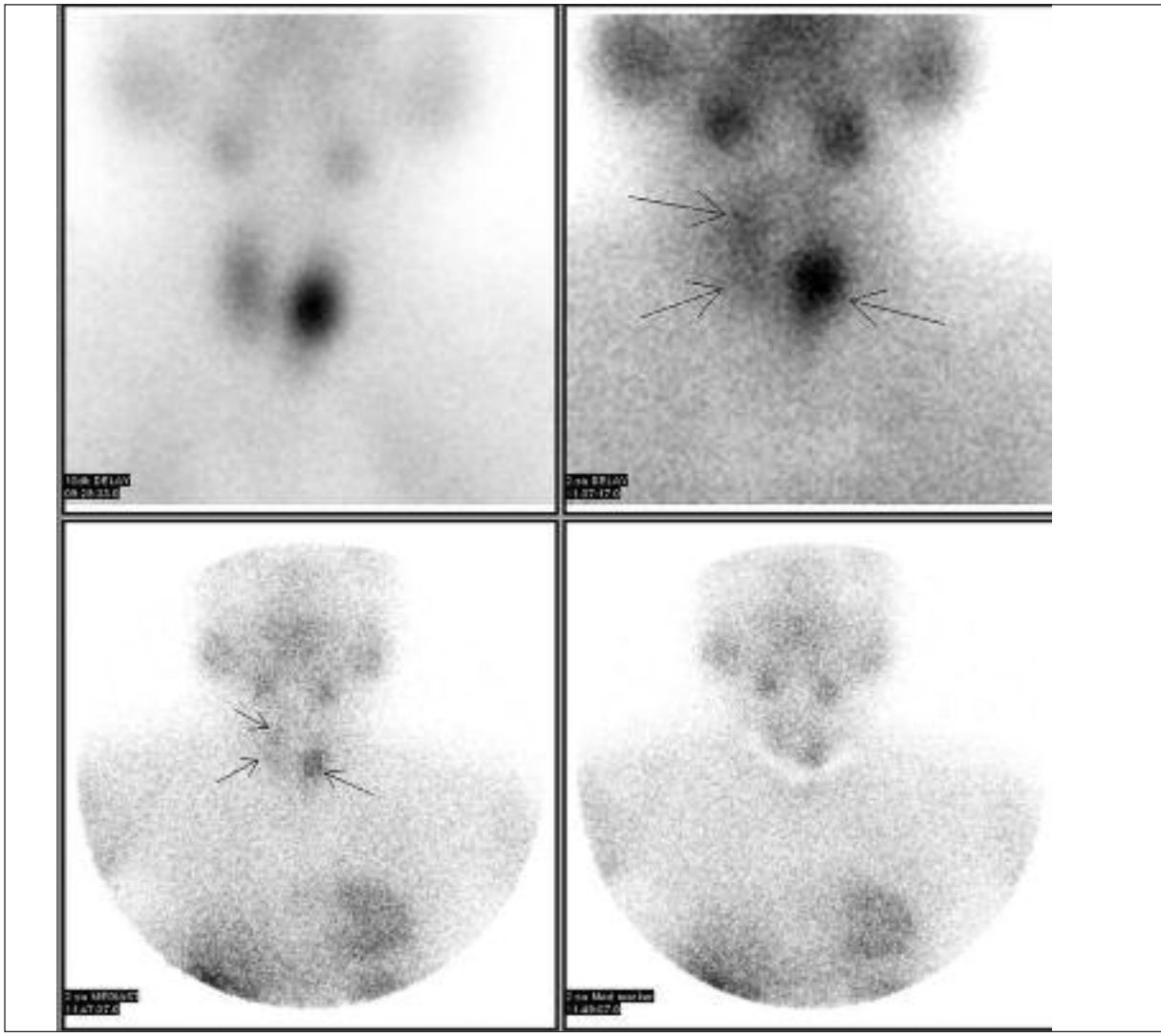

FIGURE 3: The Tc-99m MIBI early (left superior) and late parathyroid scan (right superior) revealed three enlarged parathyroid glands one located on the left and two located on the right thyroid lobe. The mediastinum planar images of Tc-^{99m} MIBI with and without mediastinal marker (inferior row) showed also the same pathological parathyroid gland activity uptakes with normal mediastinal activity. Postsurgical histopathology confirmed the scintigraphic findings of parathyroid hyperplasia.

using I-123 to outline the thyroid.[10] However, it is expensive and requires a delay between administration and imaging.[2] Another tracer for parathyroid imaging is Tc-^{99m} tetrofosmin, which is similar as Tc-^{99m} MIBI but its kinetic is different from sestamibi.[22,23] Its uptake in the thyroid and parathyroid do not demonstrate differential washout.[22]

According to the literature, the sensitivity of Tl-^{201}/Tc-^{99m} pertechnetate subtraction scintigraphy has been found to be between 38% and 92%, and these values are comparable to the parathyroid USG sensitivity.[20,21] The sensitivity and specificity of Tc-^{99m} MIBI dual-phase scintigraphy were reported to be between 90% and 100%.[24-29] In the related

TABLE 3: The ultrasonographic (USG) and histopathological results of parathyroid lesions.

		Histopathology		
		Normal	**Parathyroid pathology**	**Total**
USG	Normal	3	13	16
	Parathyroid pathology	0	11	11
	Total	3	24	27

studies, the lesion-to-background activity ratio was found to be lower in the Tl-^{201} scan, and the image quality of the Tc-^{99m} MIBI was reported to be better.[24,25] In addition, the reduced radiation dose is another advantage for the patients who underwent a Tc-^{99m} MIBI (WB: 0.0041 mGy/MBq) study compared to a Tl-^{201} (WB: 0.055 mGy/MBq) study.[2] In correlative studies with histopathology, Tl-^{201}/Tc-^{99m} pertechnetate subtraction scintigraphy and USG were shown to decrease diagnostic accuracy in cases with a coincidental thyroid nodule.[25] In addition, in patients with decreased or suppressed thyroid function due to thyroid medication or contrast agent administration, Tl-^{201}/Tc-^{99m} pertechnetate subtraction scintigraphy is not reliable.[25,30] In our study, the sensitivity, specificity and accuracy of the scintigraphic imaging of parathyroid lesions were all found to be 100%. The sensitivity of Tl-^{201}/Tc-^{99m} subtraction parathyroid scintigraphy was similar with Tc-^{99m} MIBI. We think that, probably low number of patients caused much higher sensitivity, specificity and accuracy for Tl-^{201}/Tc-^{99m} subtraction scintigraphy in our study than previously reported data. And also, our patients were without thyroid pathology, therefore Tl-^{201} was taken up higher by hyperfunctioning parathyroid glands than thyroid, faster washout from normal thyroid tissue and consequently the sensitivity of Tl-^{201} increased. We prefer Tc-^{99m} MIBI imaging (18/27) to Tl-^{201}/Tc-^{99m} subtraction scintigraphy (9/27), which was also observed in our study and in general application. A pinhole and HRES collimator are used to increase spatial resolution and improve sensitivity of planar parathyroid scintigraphy. SPECT method could be optimised by using the LEAP or pinhole collimator.[2] However it is also reported that the higher level of false positive parathyroid lesions due to the use of pinhole SPECT in the presence of thyroid nodules and irregular thyroid lobes.[3] Therefore, the clinical applications of these methods are rare. We generally perform planar parathyroid scintigraphies by LEAP collimator as in this study. If we detect any suspicious lesion, we acquire SPECT study or use pinhole collimator for imaging. We can't use HRES collimator is another option if available planar imaging with LEAP collimator to obtain parathyroid images and a comparison with USG. We suggest the use of pinhole collimator or SPECT method only to confirm doubtful results of planar views.

Although thyroid disease is prevalent in our region no patients with defined or suspected thyroid nodules are present in our study group. However, one benign thyroid pathology (i.e., a nodule-like structure having follicles containing colloid) was detected in one of our cases, but the parathyroid lesion was identified by histopathology and not with Tl-^{201}/Tc-^{99m} pertechnetate subtraction scintigraphy. In addition, in the same case, the thyroid lesion was also not detected by USG with 7.5 Hz image frequency lineer probe. In USG, this lesion was described as a pseudo-nodule having isoechogenic structure with a size of almost 0.4 cm.

In previous studies, a positive correlation was identified between radiopharmaceutical uptake in parathyroid lesions and the lesion dimensions and the function level (serum PTH and Ca values).[21,25,28] It was reported that it is difficult to detect the tissues ≤ 200 mg.[25,28,31,32] Some authors reported that no relationship was found between the accurate scintigraphic detection of the lesions and the lesion's dimensions.[33] In these studies, it was reported that a rapid, significant decrease in postoperative PTH value and Ca level (<10 mg/dL) compared to preoperative measurements are an important indication of a successful surgery.[18,34] Rarely PTH elevation may persist for a prolonged period after parathyroidectomy due to Vitamin D deficiency, compromised renal function or bone remineralization.[35] In our study, we detected a prominent decrease in PTH and Ca values (median ± SE: pre-op 388 and post-op 12 pg/mL, mean ± SE: pre-op 12 ± 0.3 and post-op 9 ± 0.3 mg/dL, respectively) immediately following the operation, which indicated the successful removal of the parathyroid lesions. The total weight of parathyroid glands of the 2 patients (2 glands in each) that were diagnosed as hyperplasia by pathological examination but were evaluated as adenoma in scintigraphy, were very

small (< 200 mg): 60 and 80 mg. These values were much lower than the mean weight of the parathyroid glands (mean ± SE: 260 ± 30mg). In these 2 cases, the pre-op PTH values were 110 pg/mL and 719.30 pg/mL, and the preop Ca levels were 10.10 mg/dL and 14.20 mg/dL. The PTH levels were almost 2 to 10 times higher than the normal limit (68 pg/mL). Therefore, as demonstrated in previous studies, we believe that not only the dimensions of the lesion but also the content of the functional tissue is important in the differential diagnosis of hyperplasia and adenoma by scintigraphy. We conclude that more-functional parathyroid tissue may be better visualized with scintigraphy when compared to less-functional tissue, and in the event of multiple hyperplasia, this tissue may be falsely reported as adenoma.

CONCLUSION

Parathyroid scintigraphy is a reliable, accurate and useful method in the differential diagnosis and localization of parathyroid lesions in primary hyperparathyroidism, and this non-invasive method helps the clinician and the surgeon determine the treatment method. The sensitivity, specificity and accuracy of the scintigraphic imaging of parathyroid lesions were almost same for both Tl-^{201}/Tc-^{99m} pertechnetate subtraction scintigraphy and Tc-^{99m} MIBI dual-phase scintigraphy. However, Tc-^{99m} MIBI dual-phase scintigraphy is superior to Tl-^{201}/Tc-^{99m} pertechnetate subtraction scintigraphy, because it is easy available and inexpensive to produce and has a low whole-body radiation dose. For that reason, Tc-^{99m} MIBI dual-phase parathyroid scintigraphy is currently preferred.

REFERENCES

1. Dugonjic S, Aidinovic' B, Cerovic S, Jankovic Z. Validity of dual tracer ^{99m}Tc-tetrofosmin and ^{99m}Tc-pertechnetate subtraction parathyroid scintigraphy in patients with primary and secondary hyperparathyroidism. Vojnosanit Pregnl 2009;66:949-53.
2. Hindie E, Ugur Ö, Fuster D, O'Doherty M, Grassetto G, Urena P, et al. 2009 EANM Parathyroid Guidelines. Eur J Nucl Med Mol Imaging; 2009;36:1201-16.
3. Carlier T, Oudoux A, Mirallie E, Seret A, Daumy I, Leux C, et al. ^{99m}Tc-MIBI Pinhole SPECT in primary hyperparathyroidism: comparison with conventional SPECT, planar scintigraphy and ultrasonography. Eur J Nucl Med Mol Imaging; 2008;35:637-43.
4. Henry JF, Iacobone M, Mirallie E, Deveze A, Pili S. Indications and results of video-assisted parathyroidectomy by a lateral approach in patients with primary hyperparathyroidism. Surgery 2001;130:999-1004.
5. Roka R, Pramhas M, Roka S. Primary Hyperparathyroidism: Is there a role for imaging? Eur J Nucl Med Mol Imaging 2004;31:1322-4.
6. Mariani G, Gulec SA, Rubello D, Boni G, Puccini M, Pelizzo MR, et al. Preoperative localization and radioguided parathyroid surgery. J Nucl Med 2003;44:1443–58.
7. Arbab AS, Koizumi K, Toyama K, Arai T, Arak T. Ion transport systems in the uptake of 99Tcm-tetrofosmin, 99Tcm-MIBI and ^{201}Tl in a tumour cell line. Nucl Med Commun 1997;18: 235-40.
8. Chen CC, Skarulis MC, Fraker DL, Alexander R, Marx SJ, Spiegel AM. Technetium-^{99m}-sestamibi imaging before reoperation for primary hyperparathyroidism. J Nucl Med 1995;36: 2186-91.
9. Ziessman HA, O'Malley JP, Thrall JH. The Requisities Nuclear Medicine. 71-113, Mosby, Philadelphia, 2006
10. Coakley AJ, Ketle AG, Wells CP, O'Doherty MJ, Collings REC. Technetium-^{99m}-sestamibi: a new agent for parathyroid imaging. Nucl Med Commun 1989;10:791-4.
11. Bonjer HJ, Bruining HA, Pols HAP, de Herder WW, van Eijck CHJ, Breeman WAP, et al. Intraoperative nuclear guidance in benign hyperparathyroidism and parathyroid cancer. Eur J Nucl Med Mol Imaging; 1997;27:246-51.
12. Mitchell BK, Kinder BK, Cornelius E, Stewart AF.Primary hyperparathyroidism: preoperative localization using technetium-sestamibi scanning. J Clin Endocrinol Metab 1995;80:7-10.
13. Erdem S, Kirac S, Duman Y. Malign tiroid nodüllerinde Tl-^{201} tutulumu: Olgu sunumu. Ulusal Endokrinoloji Dergisi 1994,4:37-40.
14. Yüksel D, Fenkçi S, Kıraç FS, Akalın EN, Yaylalı O. Hashimoto Tiroiditli Hastalarda tiroitteki Tc-^{99m} Tetrofosmin Tutulumu ve Atılımındaki Değişiklikler. Turkiye Klinikleri J Med Sci 2010,30:115-22.
15. Casara D, Rubello D, Piotto A, Pelizzo MR. ^{99m}Tc-MIBI radio-guided minimally invasive parathyroid surgery planned on the basis of a preoperative combined ^{99m}Tc-pertechnetate/^{99m}Tc-MIBI and ultrasound imaging protocol. Eur J Nucl Med Mol Imaging; 2000;27: 1300-4.
16. Pitt SC, Panneerselvan R, Sippel RS, Chen H. Radioguided parathyroidectomy for hyperparathyroidism in the reoperative neck. Surgery 2009;146:592-9.
17. Jarhult J, Nordenstrom J, Perbeck L. Re-operation for suspected primary hyperparathyroidism. Br J Surg 1993;80:453-6.
18. Geatti O, Shapiro B, Orsolon PG, Proto G, Guerra UP, Antonucci F, et al. Localization of parathyroid enlargement: experience with technetium-^{99m} methoxyisobutylisonitrile and thallium-^{201} scintigraphy, ultrasonography and computed tomography. Eur J Nucl Med Mol Imaging; 1994;21:17-22.
19. Thompson G, Grant C, Perrier N, Hormon R, Hodgson S; Ilstrup D et al. Reoperative parathyroid surgery in the era of sestamibi scanning and intraoperative parathyroid hormon monitoring. Arch Surg 1999;134:699-704.
20. Udelsman R. Six hundred fifty-six consecutive explorations for primary hyperparathyroidism. Ann Surg 2002;235:665-70.

21. Caillard C, Sebag F, Mathonnet M, Gibelin H, Brunaud L, Loudot C, et al. Prospective evaluation of quality of life (SF-36v2) and nonspesific symptoms before and after cure of primary hyperparathyroidism (1-year follow-up). Surgery 2007;141:153–9.

22. Fjeld JG, Erichsen K, Pfeffer PF, Clausen OP, Rootwelt K. Technetium-^{99m}-tetrofosmin for parathyroid scintigraphy: a comparison with sestamibi. J Nucl Med 1997;38:831-4.

23. Yüksel D, Fenkçi S, Kıraç FS, Akalın EN, Yaylalı O. Hashimoto Tiroiditli Hastalarda Tiroitteki Tc-^{99m} Tetrofosmin Tutulumu ve Atılımındaki Değişiklikler. J Med Sci 2010;30:115-22.

24. Coakley AJ. Parathyroid imaging. Nucl Med Commun 1995;16:522-33.

25. Staudenherz A, Abela C, Niederle B, Steiner E, Helbich T, Puig S, et al. Comparison and histopathological correlation of three parathyroid imaging methods in a population with a high prevalance of concomitant thyroid diseases. Eur J Nucl Med Mol Imaging; 1997;24:143-9.

26. Blanco I, Carril JM, Banzo I, Quirce R, Gutierrez C, Uriarte I, et al. Double-phase Tc-^{99m} sestamibi scintigraphy in the preoperative location of lesions causing hyperparathyroidism. Clin Nucl Med 1998;23:291-7.

27. Caixas A, Berna L, Piera J, Rigla M, Matias-Guiu X, Farrerons J, et al. Utility of ^{99m}Tc-sestamibi scintigraphy as a first-line imaging procedure in the preoperative evaluations of hyperparathyroidism. Clin Endocrinol 1995;43:525-30.

28. Melloul M, Paz A, Koren R, Cytron S, Feinmesser R, Gal R. ^{99m}Tc-MIBI scintigraphy of parathyroid adenomas and its relation to tumour size and oxyphil cell abundance. Eur J Nucl Med Mol Imaging; 2001;28:209-13.

29. Froberg AC, Valkema R, Bonjer HJ, Krenning EP. ^{99m}Tc- tetrofosmin or ^{99m}Tc- sestamibi for double-phase parathyroid scintigraphy? Eur J Nucl Med Mol Imaging; 2003;30:193-6.

30. McBiles M, Lambert AT, Cote MG, Kim SY. Sestamibi parathyroid imaging. Semin Nucl Med 1995;25:221-34.

31. Takebayashi S, Hidai H, Chiba T, Takagi Y, Nagatani Y, Matsubara S. Hyperfunctional parathyroid glands with ^{99m}Tc-MIBI scan: semiquantitative analysis correlated with histological findings. J Nucl Med 1999;40:1792-7.

32. Coakley AJ. Parathyroid localization – how and when? Eur J Nucl Med Mol Imaging; 1991;18:151-2.

33. Thompson GB, Mullan BP, Grant CS, Gorman CA, van Heerden JA, O'Connor MK, et al. Parathyroid imaging with technetium-^{99m}-sestamibi: an initial institutional experience.Surgery 1994;116:966-72.

34. Casara D, Rubello D, Pelizzo MR, Shapiro B. Clinical role of ^{99m}TcO4/MIBI scan, ultrasound and intra-operative gamma probe in the performance of unilateral and minimally invasive surgery in primary hyperparathyroidism. Eur J Nucl Med Mol Imaging; 2001;28:1351-9.

35. Aktaran Ş, Akarsu E. Prolonged Elevation Of Parathyroid Hormone In Normocalcemic Patient After Hyperparathyroidism: association With Vitamin D: Case Report. Turkiye Klinikleri J Med Sci 2008;28:580-3.