

The Role of Technetium-99m-Sestamibi Parathyroid Scintigraphy in the Detection and Localization of Parathyroid Adenomas in Patients with Hyperparathyroidism: Comparison with Technetium-Thallium Subtraction Scan and Ultrasonography

Nuri Arslan* Seyfettin Ilgan* Muammer Urhan* Alper Özgür Karaçalıoğlu* İsmail Arslan**
Emel Öztürk* Bengül Günel* Hikmet Bayhan*

Gülhane Military Medical Academy and Medical Faculty, Ankara

* Department of Nuclear Medicine

** Department of General Surgery

Dual radionuclide imaging using a combination of ^{201}Tl with $^{99\text{m}}\text{Tc}$ -pertechnetate is recognized as a useful procedure in the preoperative localization of parathyroid adenomas. Recently, $^{99\text{m}}\text{Tc}$ -MIBI scintigraphy has been introduced as an alternative to subtraction scintigraphy. The purpose of this study was to evaluate the role of $^{99\text{m}}\text{Tc}$ -MIBI dual-phase (early and late imaging) parathyroid scan in the detection and localization of parathyroid adenomas and to compare the results with subtraction scintigraphy and ultrasonography. Eighteen patients that had suspicious clinical or laboratory findings for hyperparathyroidism were included in this study. $^{99\text{m}}\text{Tc}$ -MIBI imaging and ultrasonography were performed for all patients prior to surgical exploration. A positive $^{99\text{m}}\text{Tc}$ -MIBI scan for parathyroid adenoma was defined as an area of increased focal uptake that persisted on late imaging. Nine out of 18 patients underwent subtraction scintigraphy, also. $^{99\text{m}}\text{Tc}$ -MIBI, ultrasonography and $^{201}\text{Tl}/^{99\text{m}}\text{Tc}$ subtraction scintigraphy showed a sensitivity of 94% (17/18) 88% (16/18), and 66% (6/9), respectively. We obtained concordant results for 5 patients with parathyroid adenoma using any imaging modality. ^{201}Tl subtraction scintigraphy correctly detected a parathyroid adenoma, undetected with both MIBI and ultrasonography. In conclusion, $^{99\text{m}}\text{Tc}$ -MIBI dual-phase imaging was found more sensitive and accurate for the detection and localization of parathyroid adenomas. $^{201}\text{Tl}/^{99\text{m}}\text{Tc}$ subtraction scintigraphy is considered as a helpful second line imaging modality for patients who have a negative result with $^{99\text{m}}\text{Tc}$ -MIBI scintigraphy, when there is clinical suspicion of hyperparathyroidism.

KEY WORDS Primary hyperparathyroidism, parathyroid scintigraphy, $^{99\text{m}}\text{Tc}$ -MIBI, $^{201}\text{Tl}/^{99\text{m}}\text{Tc}$ -pertechnetate subtraction, ultrasonography

Introduction

Primary hyperparathyroidism is characterized by increased synthesis of parathyroid hormone, which

produces an elevated serum calcium level and a decline in serum inorganic phosphates. The vast majority of hyperparathyroidism cases are due to single or multiple hyperfunctioning adenomas (80-85%) (1). Different imaging techniques have been used for detection of abnormal parathyroid glands such as ultrasonography (US), computerized tomography, magnetic resonance imaging, and radio

Correspondence address:

Nuri Arslan, M.D.
G.A.T.A. ve Askeri Tıp Fakültesi, Nükleer Tıp Anabilim Dalı
06018 Etlik- Ankara, TURKEY
Tel: + 90. 312. 321 36 83
e-mail: nuria@gata.edu.tr

nuclide imaging (2-5). Among the several radionuclides available for parathyroid imaging, the accepted method has been subtraction scintigraphy with combined use of [^{99m}Tc] pertechnetate and [^{201}Tl] thallous chloride (6,7).

^{99m}Tc -MIBI has recently been introduced for myocardial perfusion imaging as an alternative to ^{201}Tl (8). Utility of dual phase ^{99m}Tc -MIBI imaging for the detection of parathyroid adenomas has been reported in previous reports (9,10). The aim of this study was to evaluate the clinical utility of ^{99m}Tc -MIBI dual-phase parathyroid scintigraphy in the preoperative detection and localization of parathyroid adenomas in patients with known hyperparathyroidism, and to compare the results with US and $^{201}\text{Tl}/^{99m}\text{Tc}$ -pertechnetate subtraction study. Histopathologic diagnosis was used as the golden standard for all patients.

Materials and Methods

Patients

Between 1995-1998, 18 consecutive patients (13 female, 5 male; age: 24-77, mean: 47 years) with biochemical confirmation of hyperparathyroidism based on an elevated inappropriate level of parathyroid hormone (PTH) associated with elevation of serum calcium concentration were enrolled in this study. Total serum calcium levels were determined by colorimetric method (Sigma Diagnostics, Inc., MO, USA) using an automated analyzer system. ^{99m}Tc -MIBI dual-phase scintigraphy and US were performed in 18 patients, and $^{201}\text{Tl}/^{99m}\text{Tc}$ subtraction scintigraphy in 9. The clinical presentations were complicated by additional neck pathologies in 5 patients (one chronic lymphocytic thyroiditis, one papillary thyroid cancer and three diffuse goiters). Two patients had previously undergone neck surgery, owing to thyroid disease. Histopathologic correlation was obtained in every patient.

Preoperative intact PTH levels were determined for all patients using immunoradiometric assay method (Diagnostics Products Corporation, CA, USA). The assay's detection limit, defined as the concentration two standard deviations above the response at zero dose, was approximately 1.0 pg/ml

in a range of 15 to 3000 pg/ml. Intra-assay and inter-assay variation was lower than 6% and 6.6% respectively.

Ultrasonography

Thyroid and neck US of all patients was performed with a dedicated unit (GE Medical Systems) using a 7.5 MHz linear probe. Hypoechogenic or anechogenic lesions behind the thyroid gland were considered as enlarged parathyroid adenoma.

^{99m}Tc -MIBI Parathyroid Imaging

Planar imaging of the neck and upper portion of the thorax (and mediastinum) was performed by using a large-field-of-view (LFOV) gamma camera equipped with a low energy, high resolution collimator (GE 400 ACT/STARCAM, GE Medical Systems, Milwaukee, WI). Each patient received an intravenous injection of 740 MBq of ^{99m}Tc -MIBI (Cardiolite, Du Pont Merck Pharmaceutical Co., N. Billerica, MA). Three sets of images were obtained in the anterior view (10 min/view) with the patient in the supine position, the initial set at 20 min, the second set at 2 hr, and the third set 3 hr after the injection of the tracer. A positive ^{99m}Tc -MIBI scan for parathyroid adenoma was defined as an area of increased focal uptake which persisted on late imaging, contrary to the uptake in the normal thyroid tissue which progressively decreases with time (differential washout).

$^{201}\text{Tl}/^{99m}\text{Tc}$ -pertechnetate Dual Radiotracer Parathyroid Imaging

In 9 of the 18 patients, a second radionuclide imaging modality was performed using a dual tracer with a LFOV gamma camera equipped with a low-energy high-resolution collimator. Any thyroxine medication was stopped for at least 3 weeks prior to scintigraphy. Twenty minutes after the subsequent injection of 100 MBq of ^{99m}Tc -pertechnetate, 74 MBq of ^{201}Tl was injected. After the injection of ^{201}Tl , planar imaging of the neck and upper portion of the thorax was performed with dual isotope acquisition. All of the images were normalized by equalizing counts per pixel of each image to another. ^{201}Tl and ^{99m}Tc -pertechnetate images overlapped and a single image was

obtained by using computer subtraction technique. Any area of increased uptake was considered as parathyroid adenoma after the subtraction procedure.

Statistical Analysis

All data are expressed as mean plus or minus one standard deviation. Sensitivity was defined as the number of true positives divided by the sum of true positives and false negatives. Accuracy was defined as the sum of true positives and true negatives divided by the sum of the number of the patient population.

Results

Preoperative serum PTH levels in the 18 patients ranged from 105 to 2000 pg/ml (mean: 480 ± 612 ; PTH normal range 12-72 pg/ml). Serum calcium levels ranged from 10.1 to 13.9 mg/dl (mean: 11.3 ± 1.02 ; normal range 8.5-10.4 mg/dl). Serum phosphate levels (Menagent Fosfofix, MENARINI Diagnostics) ranged from 2 to 3.9 mg/dl (mean: 2.87 ± 0.44 ; normal range 3-4.5 mg/dl).

The mean time interval between the completion of imaging and surgery was 25 days (range of 10-65 days). According to the histopathologic results, 18 patients were found to have solitary parathyroid adenoma. The greatest diameter of the detected parathyroid adenoma ranged from 0.8 to 2.8 cm (mean: 1.9 ± 0.5 cm) according to US findings. ^{99m}Tc -MIBI scintigraphy and US correctly identified and localized 17 out of 18 and 16 out of 18 adenomas, with a sensitivity of 94% and 88% respectively.

In the subgroup of 9 patients on whom $^{201}\text{Tl}/^{99m}\text{Tc}$ scintigraphy was performed as a second radionuclide imaging, $^{201}\text{Tl}/^{99m}\text{Tc}$ parathyroid scintigraphy and ^{99m}Tc -MIBI dual phase imaging correctly localized 6 out of 9 and 8 out of 9 parathyroid adenomas with a sensitivity of 66% and 88%, respectively (Fig. 1-3). In the patient who had a false-negative result with ^{99m}Tc -MIBI and US, $^{201}\text{Tl}/^{99m}\text{Tc}$ subtraction scintigraphy correctly detected and precisely localized a parathyroid adenoma (2.2 x 0.9 cm) in the left lower neck (Fig. 4-5) (Case 8, Table 1). The results of imaging

Figure 1. ^{99m}Tc -MIBI parathyroid imaging (planar anterior view) obtained at 20 min (A), and 2 hr (B) and 3 hr (C) after the injection. The thyroid parenchyma was visualized with an increased focal uptake (short thick arrow) in the left lower neck (A-C) that persisted on late imaging.

Figure 2. $^{201}\text{Tl}/^{99m}\text{Tc}$ subtraction scintigraphy of the thyroid and parathyroids showed increased focal tracer accumulation (short thick arrows) in the left lower neck concordant with ^{99m}Tc -MIBI dual phase imaging.

Figure 3. Ultrasonographic examination revealed a hypoechoic, extra thyroidal lesion (thin short arrows) located inferior to the thyroid gland, oval in shape and elongated, indicating enlarged (21x16 mm) parathyroid adenoma.

Table 1. Histopathologic diagnosis, lesion size, serum parathormone (PTH) and calcium levels and the results of three different imaging modalities for patients suspicious for hyperfunctioning parathyroid adenoma.

Case	PTH (pg/ml)	Ca (mg/dl)	US	²⁰¹ Tl/ ^{99m} Tc subtraction	^{99m} Tc-MIBI scintigraphy	Histopathologic Diagnosis	Lesion Size (mm)
1	145	10.8	+	+	+	P. Adenoma	23x12
2	158	12.4	+	-	+	P. Adenoma	15x8
3	2000	10.9	+	-	+	P. Adenoma	17x6
4	718	10.3	+	-	+	P. Adenoma	13x9
5	2000	10.6	+	+	+	P. Adenoma	28x15
6	182	11	+	+	+	P. Adenoma	20x12
7	816	10.8	+	+	+	P. Adenoma	25x5
8	524	13.9	-	+	-	P. Adenoma	22x9
9	907	13	+	+	+	P. Adenoma	21x16
10	125	10.3	+	NP	+	P. Adenoma+TMPC	28x17
11	107.8	12.2	+	NP	+	P. Adenoma	20x15
12	120.8	11.5	+	NP	+	P. Adenoma	13x9
13	238	12.1	-	NP	+	P. Adenoma	11x5
14	117	11	+	NP	+	P. Adenoma	8x5
15	120	10.6	+	NP	+	P. Adenoma	23x15
16	114	10.1	+	NP	+	P. Adenoma	24x8
17	105	10.7	+	NP	+	P. Adenoma	20x7
18	150	11.3	+	NP	+	P. Adenoma+CLT	22x17

NP: not performed, +: positive for parathyroid adenoma, -: negative for parathyroid adenoma, CLT: Chronic Lymphocytic Thyroiditis, TMPC: Thyroid Micro Papillary Cancer

Figure 4. ^{99m}Tc-MIBI parathyroid imaging (planar anterior view) obtained at 20 min (A), and 2 hr (B) and 3 hr (C) after the injection showed normal and relatively uniform thyroid uptake with no evidence of increased tracer accumulation indicating parathyroid adenoma.

Figure 5. ²⁰¹Tl/^{99m}Tc subtraction scintigraphy of the thyroid and parathyroids showed increased focal tracer accumulation (short thick arrows) in the left lower neck discordant with ^{99m}Tc-MIBI dual phase imaging.

modalities, lesion size, serum PTH and calcium levels and histopathologic diagnosis of all patients are presented in Table 1.

The accuracy of ^{99m}Tc -MIBI dual-phase imaging, US and $^{201}\text{Tl}/^{99m}\text{Tc}$ subtraction study in the detection and localization of parathyroid adenomas was found to be 94%, 88%, and 66% respectively.

Discussion

Surgery for primary hyperparathyroidism is successful in 95% of patients, but ectopic glands and anatomic variations in location are causes of surgical failure (11). Localization of hyperfunctioning parathyroid tissue prior to surgery may shorten operation time.

Although, US is found to be performed easily, it has a low sensitivity especially after previous neck surgery due to alterations in neck anatomy (12). Moreover, US is accepted as an operator dependent methodology. ^{201}Tl -chloride has been reported as an agent used to visualize parathyroid glands (13), related to increased cellular density and vascularity of parathyroid adenomas. Although dual radionuclide imaging with $^{201}\text{Tl}/^{99m}\text{Tc}$ -pertechnetate has shown satisfactory results (6,7,14), many technical aspects of the procedure have not been completely resolved as yet. Patient motion, image misregistration, and intrathyroidal lesions such as adenomas, carcinomas or thyroiditis are the main drawbacks for dual radionuclide imaging. On the other hand, recently administered radiographic contrast material or thyroid hormone may interfere with pertechnetate imaging, and will compromise the use of subtraction techniques.

^{99m}Tc -MIBI, with its cationic charge and lipophilicity, is passively transferred across the cell membrane and concentrated in the mitochondria (15). In addition to myocardial perfusion studies (8), it has also been widely used for the detection and localization of hyperfunctioning parathyroid adenomas (9,10,16). It has been speculated that mitochondria-rich oxyphilic cells make a logical target for the prolonged retention of ^{99m}Tc -MIBI, usually observed in abnormal parathyroid glands (17).

In our study, the sensitivities obtained with US and $^{201}\text{Tl}/^{99m}\text{Tc}$ -pertechnetate subtraction scintigraphy were similar to reported series (6,11). In our study, dual-phase ^{99m}Tc -MIBI scintigraphy revealed the highest sensitivity and accuracy (94% and 94%) for the detection and localization of abnormal parathyroid glands among the three imaging modalities. These findings are similar to previous reports (11,12,16). The higher sensitivity with ^{99m}Tc -MIBI may be partly due to a higher target-to-background ratio, but also to the superior physical characteristics of ^{99m}Tc versus ^{201}Tl .

In some patients, dual-phase ^{99m}Tc -MIBI imaging may be hampered by an inhomogeneous thyroid wash-out that prevents a clear delineation of the focal tracer retention in the parathyroid adenoma. Moreover, prolonged retention of ^{99m}Tc -MIBI may occur in various types of thyroidal lesions such as thyroiditis, adenoma and carcinoma (18, 19). On the other hand, ^{99m}Tc -MIBI imaging offers the advantages of being easier to perform and to interpret, and is not affected by patient motion. Furthermore, thyroid hormone substitutor or contrast media does not hamper its thyroid uptake.

In conclusion, the results of our study confirmed that dual-phase ^{99m}Tc -MIBI parathyroid imaging and US could be useful in the preoperative detection and localization of parathyroid adenomas. However, in selected cases where the ^{99m}Tc -MIBI differential wash-out analysis fails to give a definitive diagnosis, as in one of our patients, it might be valuable to use a thyroid selective agent to subtract thyroid activity in order to improve the sensitivity and accuracy of the parathyroid scintigraphy.

References

1. Fine EJ. Parathyroid imaging: its current status and future role. *Semin Nucl Med* **17**: 350-359, 1987.
2. Peck WW, Higgins CB, Fisher MR, Ling M, Okerlund MD, Clark OH. Hyperparathyroidism: comparison of MR imaging with radionuclide scanning. *Radiology* **163**: 415-420, 1987.
3. Aufferman W, Gooding GAW, Okerlund MD. Diagnosis of recurrent hyperparathyroidism: comparison of MR imaging and other imaging techniques. *AJR Am J Roentgenol* **150**: 1027-1033, 1988.

4. Miller DL, Doppman JL, Shawler TH, Krudy AG, Norton JA, Vucich JJ, Morrish KA, Marx SJ, Spiegel AM, Aurbach GD. Localization of parathyroid adenomas in patients who have undergone surgery. Part 1. Non-invasive imaging methods. *Radiology* **162**: 133-137, 1987.
5. Reading CC, Charboneau JW, James EM. High-resolution parathyroid sonography. *AJR Am J Roentgenol* **139**: 539-546, 1982.
6. Ferlin G, Borsato N, Camerani M, Conte N, Zotti D. New perspectives in localizing enlarged parathyroids by technetium-thallium subtraction scan. *J Nucl Med* **24**: 438-441, 1983.
7. Young AE, Gaunt JJ, Groft DN, Collins REC, Wells CP, Coakley AJ. Localization of parathyroid adenomas by thallium-201 and technetium-99m subtraction scanning. *Br Med J (Clin Res Ed)* **286**: 1384-1386, 1983.
8. Taillefer R, Lambert R, Dupras G, Gregoire J, Leveille J, Essiambre R, Phaneuf DC. Clinical comparison between thallium-201 and Tc-99m-methoxy isobutyl isonitrile (hexamibi) myocardial perfusion imaging for detection of coronary artery disease. *Eur J Nucl Med* **15**: 280-286, 1989.
9. O'Doherty MJ, Kettle AG, Wells P, Collins RE, Coakley AJ. Parathyroid imaging with Technetium-99m-sestamibi: preoperative localization and tissue uptake studies. *J Nucl Med* **33**: 313-318, 1992.
10. Taillefer R, Boucher Y, Potvin C, Lambert R. Detection and localization of parathyroid adenomas in patients with hyperparathyroidism using a single radionuclide imaging procedure with Technetium-99m-sestamibi (double-phase study) *J Nucl Med* **33**: 1801-1807, 1992.
11. Casas AT, Burke GJ, Sathyanarayana, Mansberger AR Jr, Wei JP. Prospective comparison of technetium-99m-sestamibi/iodine-123 radionuclide scan versus high-resolution ultrasonography for the preoperative localization of abnormal parathyroid glands in patients with previously unoperated primary hyperparathyroidism. *Am J Surg* **166** (4): 369-73, 1993.
12. Staudenherz A, Abela C, Niederle B, Steiner E, Helbich T, Puig S, Kaserer K, Becherer A, Leitha T, Kletter K. Comparison and histopathologic correlation of three parathyroid imaging methods in a population with a high prevalence of concomitant thyroid disease. *Eur J Nucl Med* **24**: 143-149, 1997.
13. Fukunaga M, Morita R, Yonekura Y, Dokoh S, Yamamoto I, Fujita T, Torizuka K, Kawamura J. Accumulation of 201Tl-chloride in a parathyroid adenoma. *Clin Nucl Med* **4**: 229-230, 1979.
14. Hauty M, Swartz K, McClung M, Lowe DK. Technetium-thallium scintiscanning for localization of parathyroid adenomas and hyperplasia. A reappraisal. *Am J Surg* **153**: 479-486, 1987.
15. Delmon-Moingeon LI, Piwnicka-Worms D, Van der Abbeele AD, Holman BL, Davison A, Jones AG. Uptake of the cation hexakis (2-methoxyisobutylisonitrile)-technetium-99m by human carcinoma cell lines in vitro. *Cancer Res* **50**(7):2198-202, 1990.
16. Lee VS, Wilkinson RH Jr, Leight GS Jr, Coogan AC, Coleman RE. Hyperparathyroidism in high-risk surgical patients: evaluation with double-phase technetium-99m sestamibi imaging. *Radiology* **197**(3): 627-33, 1995.
17. Benard F, Lefebvre B, Beuvon F, Langlois MF, Bisson G. Rapid wash-out of technetium-99m-MIBI from a large parathyroid adenoma. *J Nucl Med* **36**: 241-243, 1995.
18. Kitapçı MT, Taştekin G, Turgut M, Caner B, Kars A, Barışta I, Bekdik C. Preoperative localization of parathyroid carcinoma using Tc-99m MIBI. *Clin Nucl Med* **18**: 217-219, 1993.
19. Schiepers C, Riet HV, Mortelmans L, Roo MD. Limitations of parathyroid imaging with Tc-99m/Tl-201 subtraction and early/delayed Tc-99m MIBI imaging. *Clin Nucl Med* **21**: 502-503, 1996.