

Comparison of Technetium-99m-MIBI, Technetium-99m-Tetrofosmin, Ultrasound and MRI for Localization of Abnormal Parathyroid Glands

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Abnormal parathyroid tissue can be identified by radionuclide imaging with either ^{99m}Tc -MIBI or ^{99m}Tc -tetrofosmin. This study compared the relative sensitivity of these two agents to localize parathyroid hyperplasia and adenoma. **Methods:** Twenty patients with primary ($n = 9$) or secondary ($n = 11$) hyperparathyroidism were studied with ^{99m}Tc -MIBI and ^{99m}Tc -tetrofosmin parathyroid imaging, ultrasonography and MRI. Radionuclide images of the neck were acquired 10 min and 2–3 hr after radiopharmaceutical injection. The images were visually evaluated for abnormal focal areas of increased tracer localization in the neck and mediastinum. A parathyroid gland/normal thyroid tissue activity ratio (referred to as the P/T uptake ratio) was calculated for each positive scan. **Results:** Of the 46 parathyroid glands surgically explored, the overall sensitivity and specificity of MIBI imaging were 83% and 83% (38/46); tetrofosmin imaging 87% and 83% (40/46); ultrasonography 78% and 40% (36/46); and MRI 80% and 60% (37/46), respectively. Both radiopharmaceuticals performed well in the nine patients found to have adenoma. The sensitivity and specificity of MIBI imaging were 100% and 100% (9/9); tetrofosmin imaging 100% and 100% (9/9); ultrasonography 78% and 67% (7/9); and MRI 100% and 100% (9/9), respectively. In the 37 glands with hyperplasia, MIBI imaging had a sensitivity of 78% and specificity of 75%; tetrofosmin imaging 84% and 75%; ultrasonography 78% and 43%; and MRI 73% and 60%, respectively. **Conclusion:** All imaging techniques localized abnormal parathyroid glands. The radiotracers have equal sensitivity for the localization of abnormal parathyroid glands. The sensitivity of these tracers was high as compared to ultrasonography or MRI.

Key Words: parathyroid glands; technetium-99m-MIBI; technetium-99m-tetrofosmin; ultrasound; magnetic resonance imaging

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Localization of abnormal parathyroid glands preoperatively can reduce operative time, postoperative morbidity and the requirement for repeat surgery. Despite the best surgical efforts, a 5% surgical failure or recurrence rate still remains after parathyroid surgery (1). Imaging techniques for localizing abnormal parathyroid glands include ultrasonography, CT, MRI and $^{201}\text{Tl}/^{99m}\text{Tc}$ -pertechnetate or $^{201}\text{Tl}/^{123}\text{I}$ subtraction imaging (2–7). In 1989, a new approach using the myocardial imaging radiopharmaceutical ^{99m}Tc -MIBI (8) was reported for the localization of parathyroid glands (9). Several investigators confirmed the use of this technique for identifying abnormal parathyroid glands using either MIBI alone or with subtraction imaging (10–14). Recently, ^{99m}Tc -tetrofosmin (15), an agent developed for myocardial perfusion imaging, was also found to localize in abnormal parathyroid glands (16).

Often, parathyroid lesions are defined by comparing early to

late ^{99m}Tc -MIBI images, due to differential retention of the agent in the abnormal gland. Early and late imaging appears significantly more sensitive for the scintigraphic localization of parathyroid glands than combined $^{201}\text{Tl}/^{99m}\text{Tc}$ subtraction imaging. Giordano et al. (17) reported that the image quality with ^{99m}Tc -tetrofosmin of both the raw and ^{99m}Tc -pertechnetate subtracted images was always superior compared with that with ^{201}Tl . Furthermore, we reported that ^{99m}Tc -tetrofosmin parathyroid scintigraphy was a suitable agent for localization of parathyroid glands. In our series, examination of the histology suggested that prolonged retention of tetrofosmin in abnormal glands may not depend on the number of mitochondria-rich oxyphil cells (18) raising the possibility of a different mechanism of retention of tetrofosmin than other agents. The similarity of ^{99m}Tc -tetrofosmin to MIBI in its myocardial behavior and the preliminary evidence confirming its localization in abnormal parathyroid tissue suggests that a comparison of the technetium-labeled agents in patients with known parathyroid disease would be worthwhile. In addition, it would be helpful to define the role of radionuclide imaging in comparison to that of ultrasound and MRI. This article describes this comparison in patients with abnormal parathyroid glands.

MATERIALS AND METHODS

Study Population

The study population consisted of 20 patients (14 women, 6 men; age range 19–69 yr; mean age 47 yr), 9 had primary hyperparathyroidism and 11 had secondary hyperparathyroidism due to dialysis dependent renal failure. The duration of hemodialysis was 149.2 ± 73.2 mo, and the frequency of the sessions was three times per week. Hyperparathyroidism was suspected in all patients on the basis of either elevated parathyroid hormone (PTH) assays, laboratory results or, in patients with kidney stones, symptoms relating to complications of primary or secondary hyperparathyroidism. The 11 hemodialysis patients were resistant to vitamin D therapy and vitamin D pulse therapy, while the nine patients with primary hyperparathyroidism had hypercalcemia and kidney stones.

All patients were imaged with ultrasonography, MRI and radionuclide techniques such as MIBI and tetrofosmin to study the parathyroid glands. Parathyroidectomy was performed in all 20 patients within 1 mo of radionuclide imaging. The locations, weight and histopathologic findings of the excised glands were recorded for each patient. Informed consent was obtained from all the patients as part of the protocol approved by the Institutional Clinical Subpanel on Human Studies.

Laboratory Data

Immunoreactive intact PTH was measured in all patients using the Allegro intact PTH kit (Nichols Institute Diagnostics, San Juan

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Capistrano, CA). The serum concentration of calcium (σ -cresolphthalein complexone, Iyatron Co., Tokyo, Japan) and phosphate (Enzyme assay, Kyowa Co., Tokyo, Japan) were also measured. Intact PTH concentrations ranged from 92–2399 pg/ml (mean 777.4 ± 651.4 pg/ml; normal range 10–65 pg/ml). Serum calcium and phosphate ranged from 6.8–15 mg/ml (mean 10.8 ± 1.6 mg/ml; normal range 8.5–10.5 mg/ml) and from 1.7–8.6 mg/ml (mean 4.1 ± 2.0 mg/ml; normal range 2.5–4.5 mg/ml), respectively.

Imaging Studies

Radionuclide Imaging. Imaging with ^{99m}Tc -MIBI and ^{99m}Tc -tetrofosmin was separated by 3 days. Each agent was administered intravenously (about 600 MBq ^{99m}Tc -MIBI and about 740 MBq ^{99m}Tc -tetrofosmin. Anterior images of the neck were recorded with a small field-of-view camera at 10 min and 2–3 hr after injection both in analog form on film, and digitally (256×256) on a dedicated computer system equipped with a low-energy, general-purpose, parallel-hole collimator. Each image was acquired for 10 min with a 15% window centered on the 140 keV photopeak. About 500,000 counts were recorded in each image. In addition, a large field-of-view gamma camera and computer system equipped with a low-energy, high-resolution, parallel-hole collimator was concomitantly used to record anterior images of the mediastinum at about 1 hr after the injection of the radiotracer.

Ultrasound. All patients underwent ultrasonography within 2 days of radionuclide imaging. A real-time scanner with a 7.5 MHz annular array probe (Toshiba SSA250A, Tokyo, Japan) was used to identify abnormal parathyroid glands.

MRI. All patients underwent MRI within 1 wk of radionuclide imaging using a 1.5 T superconducting magnet (Magnex 150HP Shimadzu Co., Kyoto, Japan or Phillips Gyroscan TS-II, Best, The Netherlands) and a neck coil. Imaging parameters were as follows: conventional spin-echo T1-weighted sequences, T2-weighted sequences and proton-density sequences; 5-mm section thickness without interslice gap; 256×256 acquisition matrix. T1-weighted images were also acquired after administration of gadolinium-DTPA in all patients not receiving hemodialysis. Also, short time inversion recovery (STIR) was applied to acquire images with fat suppression.

Data Analysis

Visual Analysis. Two observers, blinded to the patients' clinical findings and the results of ultrasonography and MRI, evaluated the images for the presence of abnormal increased uptake in the region of the thyroid bed or mediastinum. Early and late ^{99m}Tc -MIBI and ^{99m}Tc -tetrofosmin images were displayed side-by-side on a computer. Scans were scored as positive or negative for parathyroid localization and categorized as slight or intense uptake compared to thyroid uptake on late image.

The initial image, acquired 10 min after radiotracer injection, was referred to as the thyroid phase image, and the second image, at 2–3 hr, was referred to as the parathyroid phase image as previously described by Taillefer et al. (10). Technetium-99m-MIBI images were independently reviewed of the ^{99m}Tc -tetrofosmin data. The scans were read independently, and the results were compared. When there was disagreement, the readers discussed the findings and reached a consensus opinion.

Quantitative Analysis. Areas of increased uptake thought to represent parathyroid lesions on the neck images recorded at 2–3 hr were used to delineate regions of interest (ROIs) over the normal thyroid parenchyma and the areas of persistent increased uptake corresponding parathyroid glands. Average counts per pixel in the late (parathyroid) images were divided by average counts per pixel in the thyroid images to calculate the parathyroid gland/normal

TABLE 1
Comparison of Technetium-99m-MIBI, Technetium-99m-Tetrofosmin, Ultrasonography and MRI Studies in the 20 Patients

	Histology	Sensitivity (%)	Specificity (%)
^{99m}Tc -MIBI	Adenoma (n = 9)	100	100
	Hyperplasia (n = 37)	78	75
	Total (n = 46)	83	83
^{99m}Tc -tetrofosmin	Adenoma (n = 9)	100	100
	Hyperplasia (n = 37)	84	75
	Total (n = 46)	87	83
Ultrasonography	Adenoma (n = 9)	78	67
	Hyperplasia (n = 37)	78	43
	Total (n = 46)	78	40
MRI	Adenoma (n = 9)	100	100
	Hyperplasia (n = 37)	73	60
	Total (n = 46)	80	60

thyroid tissue activity ratio (referred to as the P/T uptake ratio) (10).

Ultrasound

Any hypoechoic mass adjacent, inferior or superior to the thyroid lobes was considered a positive indication of the presence of abnormal parathyroid gland. The scans were interpreted by a single observer, blinded to the result of other imaging studies.

MRI

Two observers, blinded to the result of other imaging studies, evaluated the MR images for the presence of abnormal parathyroid glands in the area of the thyroid bed or other ectopic regions. Abnormal appearance on T1- or T2-weighted images, enhancement after administration of gadolinium-DTPA and STIR images with fat suppression were used as the criteria for identifying parathyroid glands.

Statistical Analysis

All quantitative data are expressed as mean \pm s.d. Quantitative data comparisons were performed using an unpaired Student's t-test. A probability level of < 0.05 was considered significant.

RESULTS

Parathyroidectomy was performed in all 20 patients within 1 mo after MIBI and tetrofosmin imaging. Nine patients had parathyroid adenomas (9 glands) and 11 patients had hyperplasia (37 glands) for a total of 46 glands. One patient with secondary hyperparathyroidism underwent repeat surgery, which revealed an ectopic parathyroid gland. Of the 46 parathyroid glands, which were explored surgically, the sensitivity and specificity of MIBI imaging were 83% and 83% (38/46); tetrofosmin imaging 87% and 83% (40/46); ultrasonography 78% and 40% (36/46); and MRI 80% and 60% (37/46) (Table 1).

With respect to adenoma (n = 9), the sensitivity and specificity of MIBI imaging were 100% and 100% (9/9); tetrofosmin imaging 100% and 100% (9/9); ultrasonography 78% and 67% (7/9); and MRI 100% and 100% (9/9), whereas the sensitivity and specificity in hyperplasia (n = 37) of MIBI imaging were 78% and 75%; tetrofosmin imaging 84% and 75%; ultrasonography 78% and 43%; and MRI 73% and 60% (Table 1). The excised weight of the parathyroid adenomas and hyperplasia ranged from 0.16–20.6 g (mean: 2.9 ± 5.4 g).

The ^{99m}Tc -MIBI and ^{99m}Tc -tetrofosmin scans demonstrated focal uptake in all patients, but not in all lesions (Figs. 1–4). The P/T uptake ratio was measured in the visually positive lesions. Slight focal uptake (P/T ratio < 1.4) was seen in 26 (68%) of 38 glands in MIBI positive scans and 33 (83%) of 40

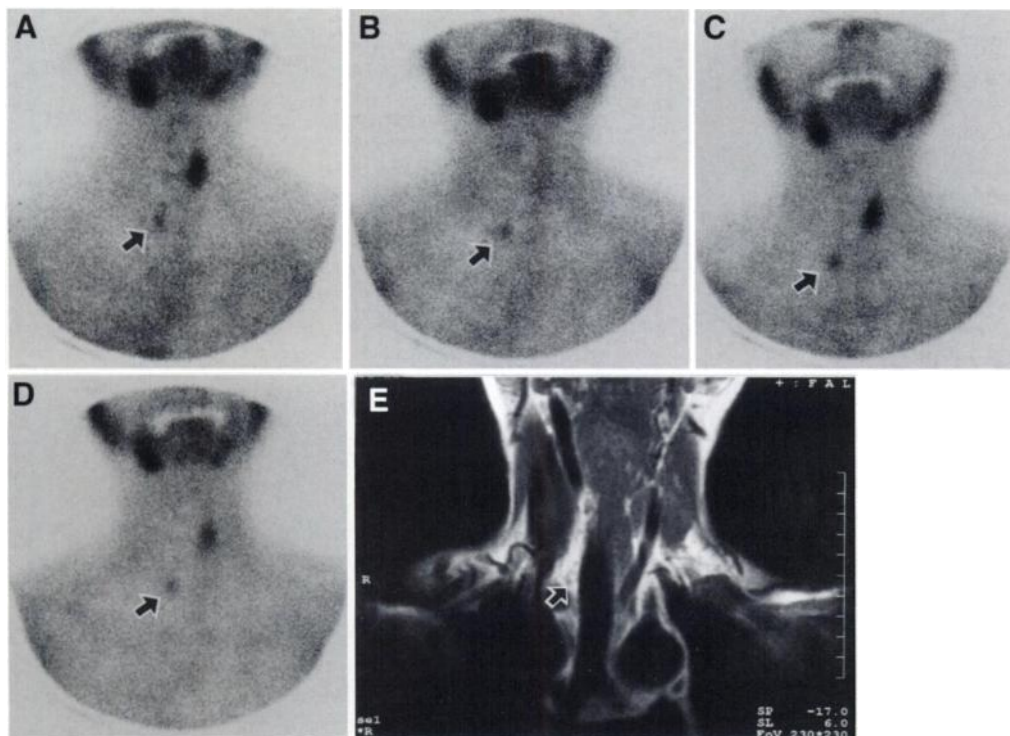


FIGURE 1. A 52-yr-old woman with an adenomatous ectopic parathyroid gland. Technetium-99m-MIBI imaging: (A) Early image showing the hemi-thyroid parenchyma increased uptake associated with an area of atypical focal uptake (arrow) in the thymus. (B) Late image showing thyroid uptake appears decreased while residual uptake in the ectopic parathyroid gland (arrow) in the thymus is visible. Technetium-99m-tetrofosmin imaging: (C) Early image showing the ectopic parathyroid gland (arrow) can be seen in the thymus to the same degree as with ^{99m}Tc -MIBI imaging. (D) On the late image, as with ^{99m}Tc -MIBI imaging, the ectopic parathyroid (arrow) is clearly visible on late images. (E) MRI image (T1-weighted image) showing a mass (arrow) in the thymus. At surgery, the patient was found to have an adenomatous parathyroid gland in that location. The weight was 0.8 g.

glands in the tetrofosmin scans. The P/T uptake ratio ranged from 1.10–1.36 (mean 1.18) with MIBI and 1.10–1.36 (mean 1.19) with tetrofosmin. More intense focal uptake (P/T uptake ratio > 1.4) was seen in 12 (32%) of 38 glands with MIBI and 7 (18%) of 40 glands with tetrofosmin (Table 2). There was no significant difference ($p = \text{ns}$) between the total P/T uptake ratio in the ^{99m}Tc -MIBI scans and the ^{99m}Tc -tetrofosmin positive scans (Table 2).

DISCUSSION

Current methods to help the endocrine surgeons localize abnormal parathyroid glands include scintigraphy, ultrasonography, CT and MRI. The imaging modalities are not equally sensitive for the detection of abnormal glands. Depending on the circumstance, one technique may be preferable. When the

thyroid gland is diffusely enlarged, for example, ultrasound is less useful because high resolution transducers have limited path length through the gland (19). For example, one patient with a normal sized thyroid had one abnormal gland detected by ultrasound, while radionuclide imaging and MRI both detected two abnormal parathyroid glands (Fig. 2). Radionuclide techniques did better with adenoma than hyperplasia, while all techniques detected parathyroid adenomas and hyperplasia, radionuclide imaging appears better at localizing adenomas. Hyperplasia was detected to a similar degree with all procedures, but the specificity of radionuclide imaging was higher than that of ultrasound and MRI. MRI has a high incidence of false-positive results, especially for cervical glands (20).

Early and late ^{99m}Tc -MIBI imaging (9–10) has replaced

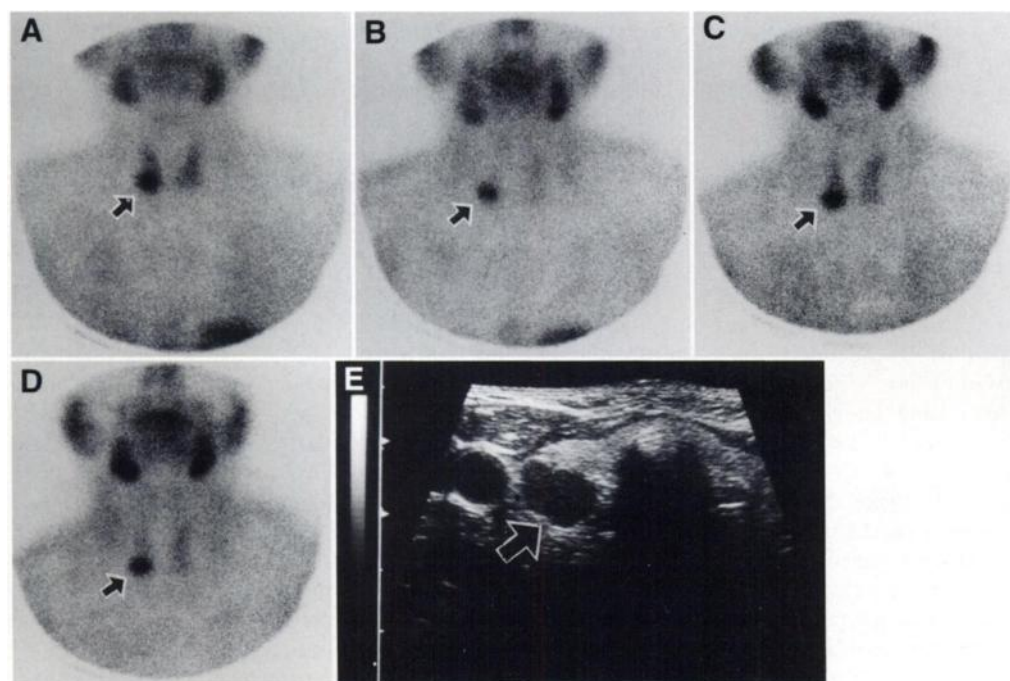


FIGURE 2. A 65-yr-old woman with hyperplastic parathyroid glands. Technetium-99m-MIBI imaging: (A) Early image showing an uniform thyroid uptake with a more intense focal uptake (arrow) in the right lower neck. (B) Late image showing decreased thyroid uptake and focal uptake (arrow) in the right lower neck. Technetium-99m-tetrofosmin imaging: (C) Early image showing increased thyroid uptake associated with focal uptake (arrow) in the right lower neck. (D) Late image demonstrating intense focal uptake (arrow) in the right lower neck. (E) Ultrasonography demonstrating the parathyroid gland as a hypoechoic mass (arrow). The weights of four hyperplastic parathyroid glands ranged from 0.33–2.1 g.

TABLE 2

Focal Uptake in Positive Scans of Technetium-99m-MIBI and Technetium-99m-Tetrofosmin Imaging in the Twenty Patients

	^{99m} Tc-MIBI (38 glands)	^{99m} Tc-tetrofosmin (40 glands)	p value
Slight uptake	1.18 ± 0.09	1.19 ± 0.08	ns
Intense uptake	2.21 ± 0.92	1.84 ± 0.67	ns
Total	1.51 ± 0.70	1.31 ± 0.37	ns

Data are expressed as mean ± s.d.

ns = not significant.

Tl/Tc subtraction scintigraphy as the radionuclide procedure of choice for parathyroid imaging. O'Doherty et al. (11) showed that ^{99m}Tc-MIBI, on the average, washed out of the thyroid more rapidly than from abnormal parathyroid glands explaining the rationale behind the procedure. Taillefer et al. (10) described a double-phase ^{99m}Tc-MIBI parathyroid study where early images defined the thyroid gland and abnormal parathyroid glands, while later images identified the abnormal parathyroid glands. This approach avoids many of the drawbacks of Tl/Tc subtraction protocols. Further, although it is believed that the single radiotracer, double-phase ^{99m}Tc-MIBI technique is quite useful, easy to perform and provides striking images of high quality, a recent report suggests that late imaging alone was not reliable and early ^{99m}Tc-MIBI images should be used in conjunction with ¹²³I for ^{99m}Tc-MIBI subtraction scintigraphy (14). However, Lee et al. (13) reported that double-phase ^{99m}Tc-MIBI imaging was a promising method for localization of parathyroid adenomas although localization of multiple hyperplastic glands remained a challenge. Since our study was designed to compare ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin imaging, ¹²³I/^{99m}Tc-MIBI subtraction was not performed.

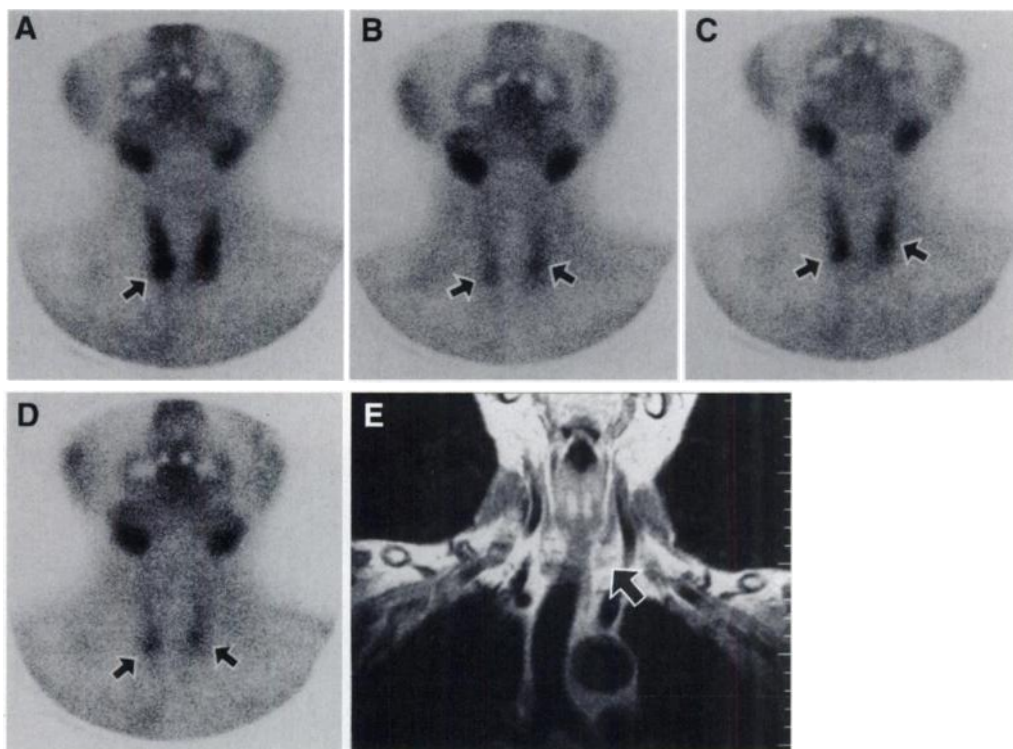
Since the initial report of Ishibashi et al. (16) on ^{99m}Tc-tetrofosmin for parathyroid imaging, there has been a question about which technetium agent would offer better parathyroid lesion detection. This study compared these two agents: MIBI and tetrofosmin. Comparable imaging times were used for both

radiopharmaceuticals, although the administered doses were slightly different. The sensitivity of MIBI and tetrofosmin imaging was high, and, when evaluated over the entire group of patients with adenoma and hyperplasia, the results were similar with the two agents, but ultrasound failed to detect two ectopic parathyroid of the nine glands as well as previously described using ^{99m}Tc-MIBI by Ishibashi et al. (21). Piga et al. (22) reported that the sensitivity of hyperplastic parathyroid using ^{99m}Tc-MIBI was 74%. Our data are consistent with their results. However, the specificity of ultrasonography and MRI was lower than that of radionuclide techniques.

There was no statistically significant difference ($p = ns$) between the total P/T uptake ratio in ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin positive scans. Although there was no statistically significant difference in the two radiotracers, the number of parathyroid glands with intense focal uptake was greater with MIBI than tetrofosmin imaging. This difference is also reflected in the higher P/T uptake ratio of MIBI.

Two patient studies illustrate the quality of data obtained with the two radiopharmaceuticals. Images of a patient with secondary hyperparathyroidism are presented in Figure 3. The early ^{99m}Tc-tetrofosmin image demonstrates two focal areas of uptake while the ^{99m}Tc-MIBI images reveals greater uptake in the left lower pole lesion. Late ^{99m}Tc-MIBI imaging showed slight focal uptake in the left upper and lower neck, and very slight focal uptake in the right lower neck. In another patient (Fig. 2), early ^{99m}Tc-MIBI imaging demonstrated focal uptake in the right and left lower neck, the former of which was difficult to localize on the late image. Further, early ^{99m}Tc-tetrofosmin imaging showed slight focal regions of uptake in the right and left lower neck while late images showed obvious slight focal uptake in the same regions. While the radiopharmaceuticals have similar overall sensitivity, these cases illustrate subtle, but possibly important, differences in their behavior. Our data suggest that while the timing of the scans for tetrofosmin is different, tetrofosmin imaging provides high quality images in patients with abnormal parathyroid glands. In primary hyperparathyroidism, secondary to adenomas, the two radiotracers

FIGURE 3. A 63-yr-old woman with hyperplastic parathyroid glands. Technetium-99m-MIBI imaging: (A) Early image showing an uniform thyroid uptake with focal uptake (arrows) in the right and left lower neck. (B) Late image showing the decreased thyroid uptake associated with a very slight focal uptake (arrows) in the right lower neck and slight focal uptake (arrow) in the left lower neck. Technetium-99m-tetrofosmin imaging: (C) Early image showing two parathyroid glands (arrow) in the right and left lower neck. (D) Late image demonstrating the decreased thyroid uptake with two focal areas of uptake (arrow) in the right and left lower neck. (E) A gadolinium-enhanced T1-weighted MRI image showing a round mass (arrow) associated with slight enhancement in the right lower neck. Exploratory surgery revealed hyperplastic parathyroid glands. The weights were 0.5–1.3 g.



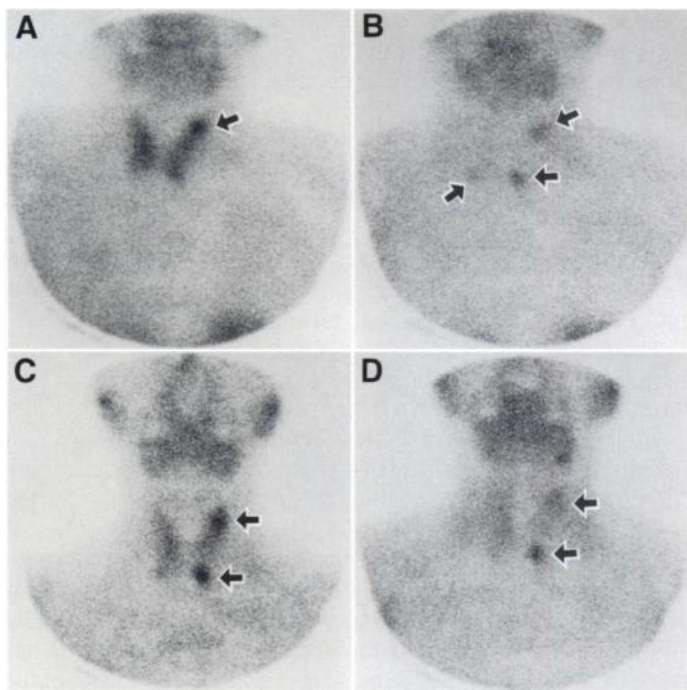


FIGURE 4. A 49-yr-old woman with hyperplastic parathyroid glands. Technetium-99m-MIBI imaging: (A) Early image showing a uniform thyroid uptake with more intense focal uptake (arrow) in the left upper neck. (B) Late image showing the decreased thyroid uptake, slight focal uptake (arrow) in the left upper and lower neck, and very slight focal uptake (arrow) in the right upper neck. Technetium-99m-tetrofosmin imaging: (C) Early image showing increased thyroid uptake associated with intense focal uptake (arrow) in the left lower neck and with focal uptake (arrow) in the left upper neck. (D) Late image demonstrating intense focal uptake in the left lower neck (arrow) and slight focal uptake (arrow) in the left upper neck. Exploratory surgery revealed four hyperplastic parathyroid glands in that location. The weights were 0.33–15.5 g (left upper 0.33 g, left lower 15.5 g, right upper 0.43 g, right lower 0.6 g).

appear equally useful to localize parathyroid glands. In patients with secondary hyperparathyroidism, the findings may be subtle, and the role of radionuclide imaging versus that of MRI remains to be determined.

CONCLUSION

This study suggests that ^{99m}Tc -MIBI and ^{99m}Tc -tetrofosmin have equal sensitivity for the localization of abnormal parathyroid glands. The sensitivity of these tracers was high as compared to ultrasonography or MRI.

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