Detection and Localization of Parathyroid Adenomas in Patients with Hyperparathyroidism Using a Single Radionuclide Imaging Procedure with Technetium-99m-Sestamibi (Double-Phase Study)

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Dual radionuclide imaging using a combination of ^{201}Tl with either $^{99m}TcO_4^-$ or ^{123}I is recognized as a useful procedure in the preoperative localization of parathyroid adenomas. Recently, ^{99m}Tc-sestamibi (MIBI) has been introduced for myocardial perfusion imaging as an alternative to ^{201}Tl. The purpose of this prospective study was to evaluate parathyroid scan using early and late imaging following MIBI injection. Twenty-three patients (21 F, 2 M, mean age: 57 yr) with a clinical and biologic diagnosis of hyperparathyroidism were submitted to a MIBI study prior to surgical exploration of the neck. Cervico-thoracic planar imaging (anterior view, 10 min/view) was performed at 15 min and at 2–3 hr after an intravenous injection of 20–25 mCi of MIBI. A positive 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 over time (differential washout). Surgical exploration of the neck, performed between 1 day and 72 days (average: 16 days) after the MIBI study, showed a parathyroid adenoma in 21 patients and hyperplasia in two patients. MIBI scan correctly detected and localized 19/21 adenomas (90%). In conclusion, parathyroid imaging using a single radionuclide with MIBI (early and late study with differential washout analysis) is a promising procedure in the preoperative detection and localization of parathyroid adenomas in patients with primary hyperparathyroidism.

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Hyperparathyroidism is a condition characterized by an excess secretion of parathyroid hormone by adenomatous or hyperplastic glands (*1*). Between 80% to 95% of patients with hyperparathyroidism have a solitary adenoma of the parathyroid glands. Different imaging techniques have been used for detection of abnormal parathyroid glands such as high resolution ultrasonography, computerized tomography, arteriography, venous sampling or magnetic resonance imaging (*2–5*). Radionuclide procedures have been also involved in the detection and localization of parathyroid adenomas (*6–7*). Among the several different techniques available for parathyroid radionuclide imaging, the most common is the use of a dual-radioisotope procedure combining of [^{201}Tl]thallous chloride with either [^{99m}Tc]pertechnetate or ^{123}I (*8*). However, there are some controversies regarding the optimal technical aspects of this procedure, including the relative amount of injected dose of radiotracers, the order of injection of the radiotracers, the computer subtraction technique and computer alignment procedures. The use of a single radionuclide method would be very useful to solve these technical limitations.

Technetium-99m-sestamibi has recently been introduced for myocardial perfusion imaging as an alternative to ^{201}Tl (*9–12*). The purpose of this prospective study was to evaluate parathyroid scintigraphy using a single radiotracer method with ^{99m}Tc-sestamibi, in the preoperative detection and localization of parathyroid adenomas in patients with known hyperparathyroidism.

PATIENTS AND METHODS

Patient Population

Over an 18-mo period, 23 consecutive patients with biochemical confirmation of hyperparathyroidism (inappropriate level of parathyroid hormone associated with elevation of serum calcium concentration) were prospectively studied with ^{99m}Tc-sestamibi planar parathyroid scintigraphy. All these patients were scheduled to undergo surgical exploration of the neck. Histopathologic correlation was obtained in every patient. Eight of these patients also had a [^{201}Tl]thallous chloride/^{99m}Tc-sodium pertechnetate dual radiotracer parathyroid scan before the surgery.

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Preoperative serum parathyroid hormone levels were determined for all patients using a radioimmunoassay that measured the intact PTH. The results of ^{99m}Tc-sestamibi (detection and specific localization of parathyroid adenomas) were known to the surgeon preoperatively. All parathyroid glands were identified at surgery and the gross surgical findings, location of parathyroid adenomas, weight of excised glands and histopathologic findings were recorded for each patient.

^{99m}Tc-Sestamibi Parathyroid Imaging

The labeling efficiency of ^{99m}Tc-sestamibi was assessed by thin layer chromatography before the intravenous injection. The percentage of ^{99m}Tc-sestamibi labeling was always more than 95%. Patients were injected with 20–25 mCi of ^{99m}Tc-sestamibi without any specific preparation. Planar imaging of the neck and upper portion of the thorax (and mediastinum) was done in the anterior view with the patient supine and the head and neck extended and immobilized. Other optional views (anterior oblique or lateral views) were performed only when judged necessary. Analog images were acquired with a preset-time mode of 10 minutes for each image using a large field-of-view scintillation camera with a low energy, high resolution, parallel hole collimator. The zoom factor varied from 1.0 to 1.5. Digital data (128 × 128 matrix) were also acquired during 10 min. Two sets of images were obtained, the initial set at 10–15 min and the second set at 2–3 hr after the injection of the radiotracer.

^{201}Tl/[^{99m}Tc]Pertechnetate Dual Radiotracer Parathyroid Imaging

In 8 of the 23 patients, a second radionuclide imaging of the parathyroids was performed using a dual tracer scintigraphic procedure with [^{201}Tl]thallous chloride and ^{99m}Tc-sodium pertechnetate. The patient was positioned under the scintillation camera after the intravenous injection of 2–3 mCi of ^{201}Tl. An anterior view of the neck and upper thorax was obtained 15–20 min later, for a duration of 10 min. After recalibration of the gamma camera and without movement of the patient, a dose of 5 mCi of ^{99m}Tc-pertechnetate was injected and a second image was acquired. Subtracted images were then generated using the computerized data.

Data Analysis

Localization studies with ^{99m}Tc-sestamibi were evaluated and the results were made available to the surgeon before the surgery. For the purpose of the study, all images were retrospectively read by two blinded observers without knowledge of the results of surgery and histopathologic diagnosis in each patient.

The initial image, obtained at 10–15 min after the injection of ^{99m}Tc-sestamibi, was used as the "thyroid" phase of the study since this radiopharmaceutical is rapidly concentrated in the thyroid parenchyma. The second image performed between 2–3 hr after the injection corresponded to the delayed or "parathyroid" phase.

Both initial and delayed analog images of a given patient were placed side by side for comparison. A positive ^{99m}Tc-sestamibi study for the presence of a parathyroid adenoma was defined as a focal area of increased uptake of the radiotracer in projection of the thyroid bed and surrounding areas or mediastinum which showed either a relative progressive increase over time or a fixed uptake which persisted on delayed imaging, contrary to the uptake in the surrounding normal thyroid tissue which progressively decreases over time (differential washout analysis). Observers were asked to give the exact location of the parathyroid adenoma: right or left side; upper, lower or ectopic location. The interpretation of the scintigraphic data was done only on the analog images, obtained in the anterior view.

On a second reading session performed many weeks after the initial one, the same blinded observers randomly interpreted early and delayed parathyroid images separately. They were asked to read a single image at a time (early or delayed) and to give the location of the adenoma.

Digital images were used only to evaluate the parathyroid adenoma/normal thyroid tissue uptake ratios as part of the differential washout analysis. One region of interest (ROI) was drawn over the area of persistent increased uptake corresponding to the parathyroid adenoma and a second one over the normal thyroid parenchyma. The parathyroid adenoma/normal thyroid tissue ratio was then calculated for both early and delayed imaging.

Technetium-99m-sestamibi parathyroid scintigraphy results, surgical reports, and pathologic findings were analyzed for each patient. Pathologic reports were reviewed for the histology of the lesions as the size or weight determinations of the parathyroid adenomas. These data were compared with the findings at the surgery with attention directed to the exact anatomic location of adenomas. The ^{99m}Tc-sestamibi study was judged to be accurate only if the parathyroid adenoma was precisely located. Accurate lateralization alone was not sufficient for the determination of the procedure sensitivity.

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. A paired Student's t-test was used to analyze the differences in uptake ratios.

RESULTS

Patient Population

Twenty-three patients were included in this study. There were 21 women and 2 men; their ages ranged from 31 to 87 yr with a mean age of 57 yr. It was the first neck exploration for all patients. Preoperative serum parathyroid hormone levels ranged from 7 to 31 pmol/liter (mean 16 ± 7 pmol/liter, normal range = 1.0–6.4 pmol/liter). Serum calcium levels ranged from 2.50 to 3.92 mmol/liter (mean 2.91 ± 0.28 mmol/liter, normal range = 2.12–2.58 mmol/liter).

The mean time interval between ^{99m}Tc-sestamibi parathyroid scintigraphy and the surgery was 16 days (range of 1–72 days). Thallium-201/[^{99m}Tc]pertechnetate dual-tracer parathyroid imaging, performed in eight patients, was separated from the ^{99m}Tc-sestamibi study by a mean time interval of 4 days (2–12 days).

Correlation Between Surgical and Scintigraphic Findings

From the operative and histologic results, 21 patients were found to have solitary parathyroid adenomas and two had parathyroid hyperplasia. The weight of parathyroid adenomas varied from 150 mg to 8.0 g (mean of 1.6 ± 0.9 g).

Technetium-99m-sestamibi parathyroid scintigraphy correctly identified and precisely localized 19 out of the 21 adenomas: 8 in right lower neck, 7 in left lower neck, 2 in right upper neck and 2 in left upper neck (Figs. 1–6). The sensitivity of ^{99m}Tc-sestamibi study to localize parathyroid adenomas was 90% (19/21). In two patients, ^{99m}Tc-sestamibi study detected an area of persistent increased uptake, but the final scintigraphic diagnosis did not exactly correspond to the surgical findings. In one patient, the ^{99m}Tc-sestamibi scan showed a right lower neck lesion while the surgery detected a right upper neck adenoma of 175 mg. In the second patient (Fig. 7), the ^{99m}Tc-sestamibi study demonstrated two areas of increased

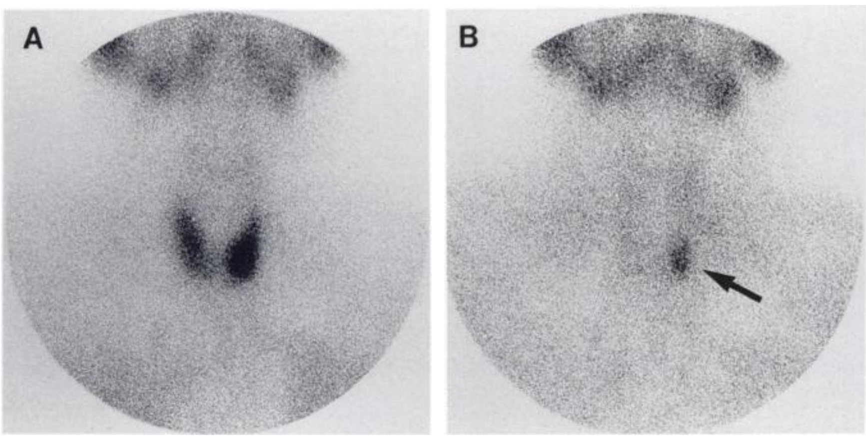

FIGURE 1. Technetium-99m-sestamibi parathyroid imaging (planar anterior view) obtained at 15 min (A) and 2 hr (B) postinjection. (A) The thyroid parenchyma is visualized with an increased focal uptake in the left lower neck. (B) On delayed imaging, only the parathyroid adenoma (400 mg) is clearly seen (left lower neck, arrow).

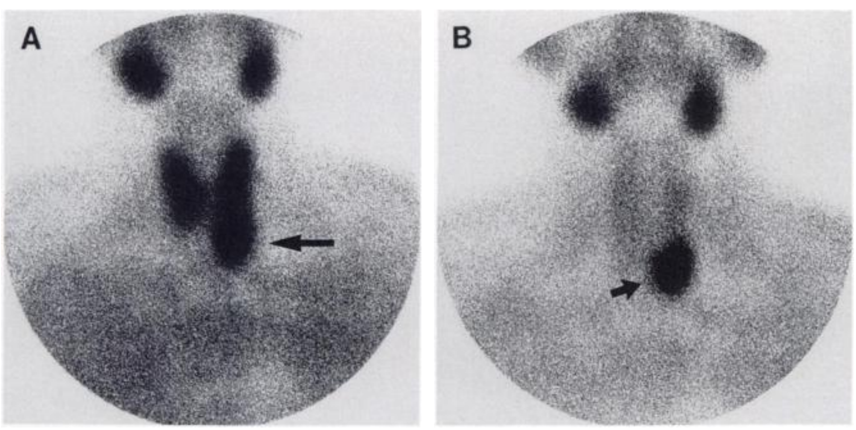

FIGURE 2. The early ^{99m}Tc-sestamibi imaging shows a uniform thyroid distribution and an increased focal uptake in the left lower neck (arrow). (B) On delayed imaging (2 hr) the parathyroid adenoma (3.5 g) is well visualized at the same level (arrow).

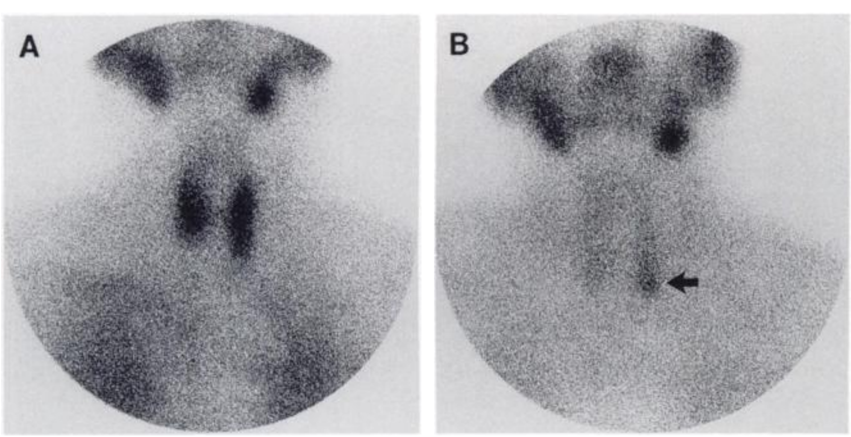

FIGURE 3. (A) The early ^{99m}Tc-sestamibi scintigraphy shows a normal and relatively uniform thyroid uptake. (B) However, on delayed imaging (2.5 hr), there is an increased focal uptake in the left lower neck corresponding to a parathyroid adenoma (300 mg) at this level (arrow).

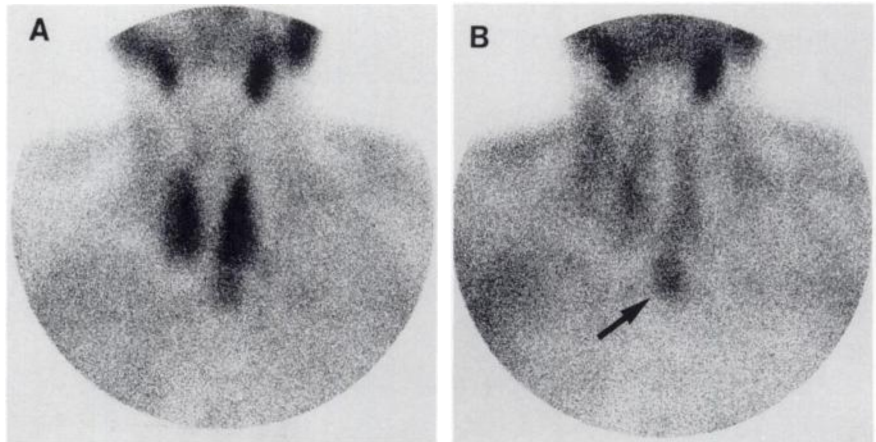

FIGURE 4. (A) Early ^{99m}Tc-sestamibi parathyroid imaging showing a uniform thyroid uptake with a slight focal uptake in the left lower neck (under the left thyroid lobe). (B) The delayed image demonstrates an inverse pattern, the thyroid uptake decreased over time while the relative uptake in the parathyroid adenoma (2.5 g) increased (arrow).

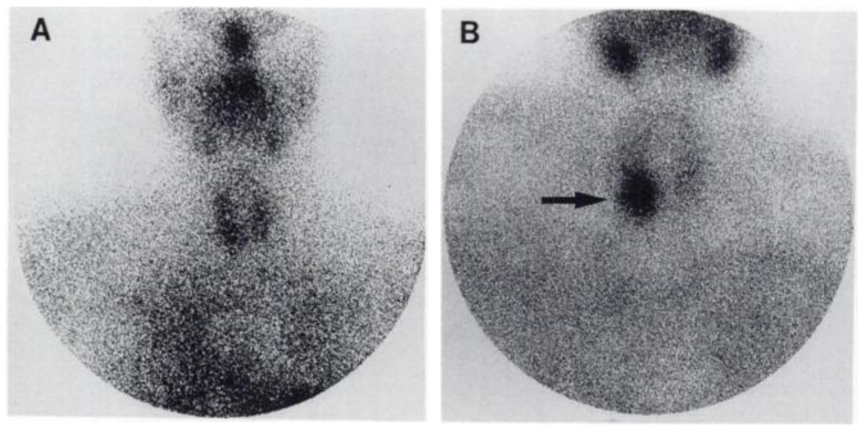

FIGURE 5. (A) Thallium-201 cervicothoracic scintigraphy showing a relatively uniform thyroid uptake except for a slight assymetry in the right lower neck (which was considered as being within normal range on ^{201}Tl/[^{99m}Tc]pertechnetate dual radiotracer scintigraphy). (B) A delayed ^{99m}Tc-sestamibi parathyroid imaging was obtained 3 days later and showed a significant lesion at the same level (arrow). Surgery revealed a right lower neck parathyroid adenoma (2.0 g).

uptake, one, larger and more intense involving the left lower neck; the second one, smaller and less intense, at the level of the right lower neck. Surgery revealed a follicular adenoma of the left thyroid lobe (2 × 1.5 cm) and a parathyroid adenoma of the right lower neck (400 mg).

Surgery detected two cases of parathyroid hyperplasia. In one patient, the ^{99m}Tc-sestamibi study was completely normal, while the other showed a very slight focal uptake in the left lower neck. The final interpretation of the ^{99m}Tc-sestamibi scan in this particular case was that the study was probably normal.

Although the initial image, obtained at 10–15 min after the injection of ^{99m}Tc-sestamibi, was used mainly as an anatomical reference ("thyroid phase") for the second set or delayed imaging, the observers were asked to interpret independently the initial images only. The criterion for a

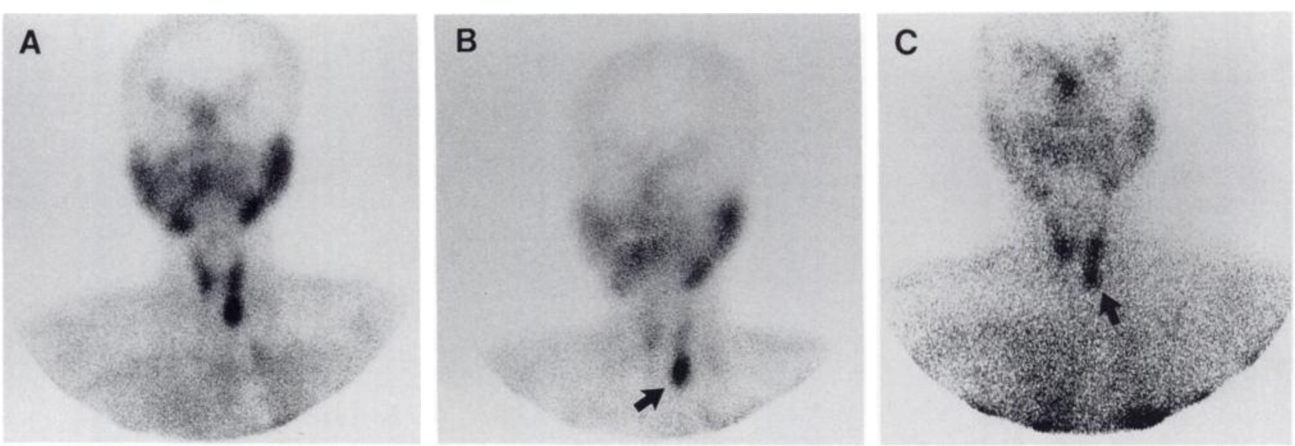

FIGURE 6. Early (A) and delayed (B) ^{99m}Tc-sestamibi imaging showing a left lower neck parathyroid adenoma (arrow). The same lesion was seen on a ^{201}Tl scan (C) performed 4 days later. The parathyroid adenoma/normal thyroid tissue activity ratio is much more increased with ^{99m}Tc-sestamibi. Surgery revealed a 1.5 g parathyroid adenoma.

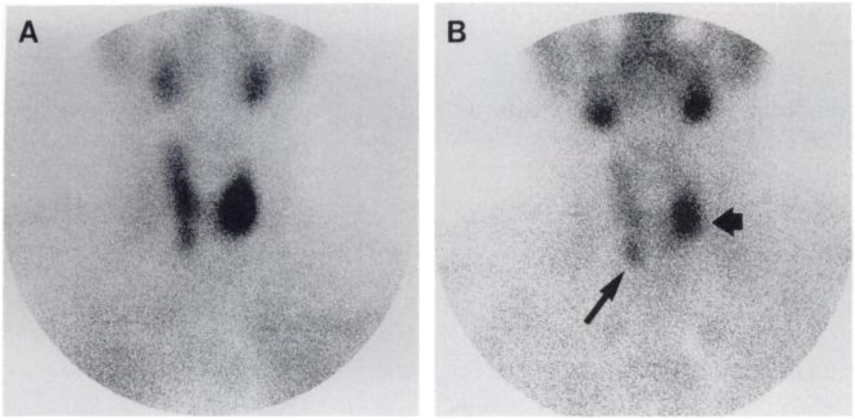

FIGURE 7. Early (A) and delayed (B) ^{99m}Tc-parathyroid imaging in a patient with a follicular adenoma of the left thyroid lobe (arrow head) and a small parathyroid adenoma (425 mg) of the right lower neck (arrow). This case illustrates a "false-positive" ^{99m}Tc-sestamibi uptake for parathyroid adenoma in the left thyroid lobe.

positive study for parathyroid adenoma on the initial imaging was a relative focal increased uptake. This was seen in 15 of the 21 patients (sensitivity of 71%) with parathyroid adenomas.

Parathyroid adenoma/normal thyroid tissue activity ratio was quantitatively determined in 15 patients in whom complete (both early and delayed imaging) computerized data were available. This ratio was 1.24 ± 0.23 for the initial phase and 1.46 ± 0.20 for the delayed phase ($p < 0.001$).

Technetium-99m-sestamibi parathyroid imaging results were compared to dual radionuclide (^{201}Tl/[^{99m}Tc]pertechnetate) parathyroid study obtained in eight patients. Surgery detected the parathyroid adenomas in all these patients. The ^{99m}Tc-sestamibi study correctly localized the adenomas in all of them (sensitivity = 100%) while the dual radionuclide procedure showed an adenoma in six of eight patients (sensitivity = 75%).

DISCUSSION

Although an experienced surgeon will be able to localize up to 90%–95% of parathyroid adenomas during an initial neck exploration for primary hyperparathyroidism, failure to identify the tumor may result in significant morbidity for the patient (*13,14*). Furthermore, a preoperative localization procedure may help to shorten operative and anesthesia time by directing the surgeon to the site of the lesions.

Several techniques with various degrees of accuracy have been evaluated for the preoperative localization of parathyroid adenoma in patients with biochemically proven hyperparathyroidism: intraoperative vital staining methods (*15*), cineesophagography, thermography (*16*), mediastinography, computerized axial tomography (*17*), arteriography, selective venography, ultrasonography (*18*) and more recently, magnetic resonance imaging (*3,19*), digital subtraction arteriography and needle aspiration combined with high-resolution ultrasonography (*20*). The introduction of nuclear medicine procedures was based on the concept of using metabolic markers directed to specific tissues.

Cobalt-57 B12 vitamin (*21*), ^{75}Se-methionine (*22*) and ^{131}Ce-chloride (*23*) have been successively used for parathyroid imaging. In the late 1970s, [^{201}Tl]thallous chloride had been reported as an agent to visualize parathyroid glands (*24*). Increased cellular density and vascularity of parathyroid adenomas have been postulated as main reasons for increased ^{201}Tl uptake in these lesions. The addition of [^{99m}Tc]pertechnetate imaging to provide the computerized subtraction of the normal thyroid gland ^{201}Tl uptake was introduced a few years later (*25–26*). Since then, several studies on ^{201}Tl/[^{99m}Tc]pertechnetate dual-radiotracer parathyroid scintigraphy have been reported in the literature (*27–29*). In a review of the literature on this topic, performed few years ago by Hauty et al. (*30*) and regrouping 14 studies with a total of 317 patients with primary hyperparathyroidism who have been operated upon, the accumulated sensitivity of parathyroid scintigraphy to detect parathyroid adenomas was 82%. The diagnostic accuracy was 78%, the positive predictive value 94% and the false-positive rate was 5%.

Although the dual radionuclide parathyroid scintigraphy has shown satisfactory results and good diagnostic accuracy, many technical aspects of the procedure are either still somewhat controversial or not completely resolved in the literature (*6*); for example: the involved radiotracers ([^{99m}Tc]pertechnetate or ^{123}I), the order of injection of tracers (^{201}Tl before or after [^{99m}Tc]pertechnetate), the relative injected activities of the tracers (related to the tracers and their injection order), the value of computer subtraction techniques (increased sensitivity, decreased specificity) and the computer alignment and display procedures. Furthermore, it is essential that the head and neck of the patient remain immobile during the image acquisition.

Recently, Coakley et al. (*31*) reported the use of ^{99m}Tc-sestamibi as a new agent for parathyroid imaging. Conceptualizing that ^{99m}Tc-sestamibi has been introduced as an alternative to ^{201}Thallium for myocardial perfusion imaging, they studied five patients who underwent surgery for proven hyperparathyroidism. Their ^{99m}Tc-sestamibi parathyroid imaging protocol was as follows: Ten 2-min frames were acquired after intravenous injection of 5 mCi of

^{99m}Tc-sestamibi. Images were compared to a standard ^{201}Tl/[^{99m}Tc]pertechnetate dual-radiotracer protocol. Four patients had a parathyroid adenoma correctly localized by both dual radionuclide and ^{99m}Tc-sestamibi parathyroid imaging. In three patients, the abnormal parathyroid gland was more easily detected (both qualitatively and quantitatively) with ^{99m}Tc-sestamibi imaging than with dual radionuclide procedure. The same group (*32*) more recently reported their experience with this procedure. On a total of 40 parathyroid adenomas, 37 were localized with ^{201}Tl and 39 with ^{99m}Tc-sestamibi.

The results of our study confirmed that ^{99m}Tc-sestamibi parathyroid imaging can be useful in the preoperative detection and localization of parathyroid adenomas in patients having proven hyperparathyroidism (sensitivity of 90%). The double-phase ^{99m}Tc-sestamibi parathyroid study is simple to perform and does not require the immobilization of the patient. Furthermore, computerized data have not been used for the scintigraphic diagnosis. The use of a single radiopharmaceutical study overcomes all the drawbacks related to dual radiotracer procedure, as previously mentioned. The late phase of ^{99m}Tc-sestamibi scan is sufficient to detect parathyroid adenoma. However, the early phase is helpful and used as an anatomical reference to locate the abnormal focus of persistent uptake since the normal thyroid tissue is usually only faintly seen on the delayed imaging. The parathyroid adenoma/normal thyroid parenchyma activity ratios confirmed the highest lesion detectability of the late phase of the study. This indicates that the washout of ^{99m}Tc-sestamibi from parathyroid adenoma is slower than the one from surrounding thyroid tissue. This differential washout constitutes the rationale of the use of ^{99m}Tc-sestamibi for parathyroid single radiotracer scintigraphy.

Criteria used in our study to define a positive ^{99m}Tc-sestamibi scintigraphy for parathyroid adenoma was rigorous; the exact scintigraphic location of the adenoma was essential. In one patient who had a ^{99m}Tc-sestamibi study considered as "false-negative" for adenoma location, the scan showed a right lower neck lesion while the surgery detected a right upper neck adenoma. Chan et al. (*33*) showed that such "misinterpretation" is thought to be due to the prolapse of the adenoma arising from the upper gland toward the lower pole of the thyroid, thereby mimicking a lower neck lesion on the ^{201}Tl/[^{99m}Tc]pertechnetate scan.

The most common cause of false-positive localization of ^{201}Tl during parathyroid imaging is its uptake in thyroid adenomas. As seen in one of our patients, ^{99m}Tc-sestamibi uptake was "falsely" increased in a follicular adenoma, resulting in a false-positive study. Although the clinical experience with this new agent is somewhat limited, palpation of thyroid gland will remain mandatory (as for dual tracer procedure) and further radionuclide thyroid evaluation may be helpful whenever thyroid lesions are detected or suspected on physical examination. Further studies will be needed to evaluate the incidence and the degree of ^{99m}Tc-sestamibi uptake in various types of thyroid lesions for a better understanding of potential false-positive parathyroid studies. In addition, in selected cases where the ^{99m}Tc-sestamibi differential washout analysis fails to give a "definitive" diagnosis, it might be valuable to use a thyroid selective agent to subtract thyroid activity (as with dual radiotracer parathyroid imaging) in order to improve the accuracy of the procedure.

More accurate data on ^{99m}Tc-sestamibi thyroid uptake and washout will improve parathyroid imaging. It might help to determine the optimal time after the injection to obtain initial and delayed imaging. In this study we have used a dose of 20–25 mCi on the basis of previous experience with ^{99m}Tc-sestamibi myocardial perfusion imaging. With a better understanding of the thyroid and parathyroid kinetics of ^{99m}Tc-sestamibi, the injected dose can probably be decreased. Furthermore, in vitro studies will be needed in order to determine the mechanisms of ^{99m}Tc-sestamibi uptake in parathyroid adenomas.

In conclusion, single radionuclide parathyroid imaging with ^{99m}Tc-sestamibi (early and late study with differential washout analysis) is a promising procedure in the preoperative detection and localization of parathyroid adenomas in patients with primary hyperparathyroidism.

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EDITORIAL

Parathyroid Imaging—Current Status and Future Prospects

The prevalence of hyperparathyroidism seems to be increasing (*1*). Some of this apparent increase is due to the earlier detection of hypercalcemia through the routine measurement of serum calcium in clinical chemistry screens. This increasing prevalence of suspected hyperparathyroidism, as indicated by an elevated serum calcium detected on a routine screen, may be no more than a lead time bias induced by the detection of a chemical abnormality in presymptomatic patients. Some presymptomatic hyperparathyroidism may not ever become clinically significant. The role of further diagnostic work-up of patients with hypercalcemia is controversial, because there have been very few studies on the implications of presymptomatic hyperparathyroidism. Further diagnostic studies, which attempt preoperative localization of abnormal parathyroid tissue in patients with suspected hyperparathyroidism, present an even greater problem in efficacy. As many as 90%–95% of individuals with symptomatic hyperparathyroidism and hypercalcemia will be readily treated by an experienced surgeon without preoperative localization of the abnormal gland (*1–3*). The question becomes: does every patient with a chemically detected hypercalcemia, who may indeed have an occult parathyroid adenoma, warrant further diagnostic studies directed toward the localization of that prospective parathyroid lesion? Some authors have questioned whether every patient with asymptomatic hyperparathyroidism even needs surgical removal of the offending gland (*4*). With this background, we need to assess the propriety and utility of alternative schemes designed to locate a parathyroid lesion preoperatively.

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There is a long history of nuclear medicine efforts to diagnose and locate abnormal parathyroid tissue. Sisson and Beierwaltes, in 1962, attempted the use of radiocyanocobolamine with only modest results (*5*). Subsequently, Potchen (1963) demonstrated prospects for ^{75}Se localization of parathyroid tissue (*6*). This too had only minimal clinical utility. The utility of selenomethionine was dependent upon tissue blood activity changes over time. The time-dependent variation in tissue activity contrast is similar to the time-dependent relative thyroid parathyroid activity with ^{99m}Tc-sestamibi reported in this issue (*7*).

In addition to these early radioisotopic approaches, other techniques had been attempted for the preoperative localization of hyperactive parathyroid adenomas. Esophageal displacement, as seen on the barium