Preoperative Technetium Tc 99m Sestamibi SPECT Imaging in the Management of Primary Hyperparathyroidism in Patients With Concomitant Multinodular Goiter

Mordechai Lorberboym, MD; Tiberiu Ezri, MD; Pinhas P. Schachter, MD

Hypothesis: Preoperative parathyroid and thyroid imaging using technetium Tc 99m sestamibi scintigraphy—single-photon emission computed tomography (Tc 99m MIBI SPECT) and technetium Tc 99m sodium pertechnetate, respectively, in patients with parathyroid adenomas and concomitant multinodular goiters enables the selection of those suitable for minimally invasive radio-guided surgery.

Design: One hundred thirty patients with primary hyperparathyroidism were treated surgically during a 30-month period. Forty-one of these 130 patients had an associated multinodular goiter. All patients underwent planar and SPECT parathyroid scintigraphy using Tc 99m MIBI, and thyroid scintigraphy with technetium Tc 99m pertechnetate 2 to 5 days before surgery. On the morning of surgery each patient was reinjected with Tc 99m MIBI for intraoperative localization and validation. Minimally invasive radio-guided parathyroidectomy was performed using a handheld gamma-detection device with a thyroid probe. Removed glands were submitted for histopathologic examination for comparison with the scintigraphic results. Quantitative analysis of parathyroid activity was performed.

Results: Minimally invasive, radio-guided parathyroidectomy was successfully performed in 21 (51%) of 41 patients who had a concomitant multinodular goiter. The remaining 20 patients underwent standard neck exploratory surgery because of associated thyroid disease; 5 of them had malignant thyroid disease. Among the 41 patients planar scintigraphy correctly identified 28 adenomas (68%). Single-photon emission computed tomographic imaging identified an additional 11 adenomas for a sensitivity of 95% and a specificity of 100%. Moreover, SPECT imaging correctly identified malignant thyroid nodules in 4 of 5 patients. Technetium Tc 99m MIBI retention was noted in only 25 adenomas (61%) while the remaining adenomas demonstrated a rapid washout. The average uptake ratio of parathyroid counts to maximum thyroid activity was significantly correlated with parathyroid hormone levels before surgery (P = .04).

Conclusions: Our data encourage the use of preoperative SPECT imaging of parathyroid adenomas in patients who have multinodular goiters to select those suitable for minimally invasive radioguided surgery. This technique also offers important information regarding thyroid nodules that are suspicious for malignancy. The intraoperative gamma-probe technique enables the surgeon to focus his or her search, provides instant feedback regarding the progress of the operation, reduces surgical trauma and complications, and yields better cosmetic results. Patients with higher presurgical parathyroid hormone levels may especially benefit from radioguided surgery.

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MINIMALLY INVASIVE parathyroid surgery (MIPS) for primary hyperparathyroidism (HPT) is gaining wide acceptance. A prerequisite for MIPS is preoperative localization of the hyperfunctioning parathyroid gland.1 Concomitant thyroid disease, in particular multinodular goiter (MNG), is common, ranging from 20% to 75% in endemic regions.2,5 A major limitation related to parathyroid imaging using ultrasonography, or technetium Tc 99m sestamibi scintigraphy (Tc 99m MIBI), or both is the presence of concomitant thyroid nodules that often are MIBI avid and can, therefore, mimic a parathyroid lesion, causing false-positive scintigraphic results.6 Several authors found different effects of thyroid abnormalities on the sensitivity of the scan.6-8 For this reason, some physicians discourage the use of preoperative Tc 99m MIBI scintigraphy and the gamma-probe technique in patients with hyperparathyroidism who have a concomitant MNG.9 However, studies...
comparing sensitivity, specificity, and positive predictive values show ultrasonography to be inferior to Tc 99m MIBI scintigraphy in detecting parathyroid adenomas in patients with concomitant MNG.10

In addition, the rate of malignancy in thyroid nodules associated with MNG may reach 10% and correct preoperative identification of suspicious nodules is mandatory.11-13 A thyroid scan with technetium Tc 99m pertechnetate is useful to evaluate “cold” nodules, and fine-needle aspiration biopsy of the thyroid is a common procedure to search for malignancy. However, manually or ultrasonography-guided fine-needle aspiration of multiple, nonpalpable nodules is technically difficult, yielding results that are not always equivocal.14

The purpose of our study was to prospectively evaluate minimally invasive, radioguided parathyroidectomy in patients with concomitant MNG and the additive value of combined parathyroid-thyroid imaging using Tc 99m MIBI–single-photon emission computed tomography (Tc 99m MIBI SPECT) and technetium Tc 99m pertechnetate in developing an index of suspicion for potentially malignant thyroid lesions that require surgical management.

METHODS

During a 30-month period we prospectively evaluated 130 patients with primary HPT who were surgically treated in our department. The study population included 41 of 130 patients who had primary HPT associated with an MNG (30 women and 11 men; mean age, 63.5 years; age range, 32-84 years). Gland weight was recorded after surgery. The removed parathyroid glands of all of the patients had a histopathologic examination for comparison with the scintigraphic results.

SCINTIGRAPHY

All of the patients underwent planar and SPECT parathyroid scintigraphy 2 to 5 days before surgery. Anterior planar images of the neck and chest were acquired for 10 minutes and at 10 minutes and 120 minutes after intravenous injection of 20 mCi (740 MBq) of Tc 99m MIBI, using a large-field-of-view gamma camera equipped with a parallel-hole collimator. Immediately after the first planar image, a SPECT study was acquired using 60 projections of 30 seconds each over a 180° anterior arc from the right lateral to the left lateral position in a 128 × 128 matrix at 3° angular steps. In addition, a delayed (120 minutes) 10-minute image was performed after the injection of 10 mCi (370 MBq) of technetium Tc 99m sodium pertechnetate. On the morning of surgery, each patient was reinjected with 20 mCi (740 MBq) of Tc 99m MIBI for intraoperative localization and validation. A SPECT study, as previously described, was acquired for comparison prior to sending the patient to the operating room.

INTERPRETATION

The SPECT study was compared with the planar technique. A distinct focus of increased or separate Tc 99m MIBI uptake relative to thyroid tissue on early images, late images, or both was considered positive for abnormal parathyroid tissue. In each case a 3-dimensional image was created from the SPECT data and presented to the surgeon before the operation. For quantitative analysis a region of interest was drawn around the diseased parathyroid gland, and a region of interest of similar size was drawn in the left thyroid lobe (P/L), right thyroid lobe (P/R), and in the region of maximal thyroid gland activity (P/M). A count ratio of parathyroid to thyroid was determined using the average counts in each region of interest (ie, P/L, P/R, and P/M).

TECHNIQUE OF RADIOGUIDED PARATHYROIDECTOMY

Minimally invasive radioguided parathyroidectomy was performed through a 2.0- to 2.5-cm low transverse incision. A handheld gamma-detection device (Navigator; US Surgical Corp, Norwalk, Conn) with a thyroid probe (US Surgical Corp) was used to direct the skin incision and the dissection through the strap muscles. The thyroid gland was revealed and retracted medially exposing the carotid sheath. The gamma-detection device was used to guide the dissection of the parathyroid adenoma.

In instances of concomitant thyroid pathology that required surgical management, in particular when a malignant lesion was suspected, standard neck exploratory surgery was performed through a collar incision. A midline incision in the fascia and lateral retraction of the strap muscles exposed the thyroid gland. The gamma-detection device was used to identify all “hot” parathyroid glands prior to excision of the enlarged one and for localization of the hot thyroid nodule. Frozen-section examination was obtained for parathyroid glands with an equivocal appearance and for all suspect thyroid nodules (hot nodules were marked for examination).

Radioactivity contained within the resected adenoma was determined ex vivo and compared with background radioactivity in the neck. Frozen sections were not obtained if the resected tissue appeared clinically to be an adenoma. The mean time for the entire procedure was 30 minutes (range, 20-40 minutes) for the minimally invasive procedure and 60 minutes (40-70 minutes) for the formal exploration of the neck. Most patients were admitted for a 24-hour stay after the operation to watch for complications. All patients had a histopathologic examination of the removed parathyroid glands for comparison with the scintigraphic results.

STATISTICAL ANALYSIS

Analysis of data was performed using SPSS statistical analysis software (1999 version; SPSS Inc, Chicago, Ill). Descriptive statistics were calculated and are reported as mean ± SD. Normality of distribution of variables was determined using the Kolmogorov-Smirnov test. Pearson correlation coefficients were calculated to describe intervariable associations. All tests were 2-sided and considered statistically significant at P < .05.

RESULTS

Among the 41 patients, planar scintigraphy using delayed imaging and dual isotope technique correctly identified 28 adenomas (68%). Single-photon emission computed tomographic imaging correctly identified those adenomas thereby providing additional 3-dimensional information for the surgeon. Additionally, 11 more adenomas were identified on SPECT, for a sensitivity of 95%, a specificity of 100%, and a positive predictive value of 1 (Table 1). Single-photon emission computed tomography was superior to planar imaging in identifying 3 patients with small adenomas lying just posterior to a large MNG and in 8 patients with MIBI-avid thyroid nodules.
that often mimic ectopic adenomas. Moreover, SPECT imaging correctly identified malignant thyroid nodules in 4 of 5 patients, being cold on technetium Tc 99m pertechnetate imaging but showing avid uptake of Tc 99m MIBI (Figure 1 and Figure 2). The parathyroid adenomas were usually more posterior in location and could, therefore, be separated from the malignant nodules.

Gland size did not affect significantly the detectability of the SPECT studies compared with planar imaging. Technetium Tc 99m MIBI retention was noted in only 25 adenomas (61%) while the remaining adenomas demonstrated a rapid washout.

Minimally invasive, radioguided parathyroidectomy was successfully performed in 21 patients (51%) with concomitant MNG. One patient was converted to standard neck exploratory surgery because of a suspicious thyroid nodule that proved to be malignant. The remaining 20 patients had concomitant thyroid disease requiring surgery. 4 of them with malignant thyroid disease and 2 with inconclusive Tc 99mMIBI-SPECT localization. The Tc 99m MIBI-SPECT failed to demonstrate a small adenoma (95 mg) adjacent to a “warm” thyroid nodule and the second patient had a huge MNG, which displaced the parathyroid adenoma in an anterior position. Both adenomas were revealed at surgery and resected.

The mean uptake ratios of parathyroid counts to the P/L, P/R, and P/M were 1.22±0.40, 1.30±0.42 and 0.81±0.33, respectively. Statistical analysis showed that the uptake ratio of parathyroid to P/M was significantly 0.81±0.33, respectively. Statistical analysis showed that the uptake ratio of parathyroid to P/M was significantly correlated with parathyroid hormone (PTH) levels be-

In our study planar imaging correctly identified 95% of the adenomas in 39 patients. This discrepancy is explained by the fact that most adenomas were posterior to the thyroid gland and, therefore, difficult to identify on planar imaging. More importantly, depth information and 3-dimensional location of the adenoma are crucial factors for the surgeon in planning and performing a limited surgery.

Table 1. Sensitivity of Parathyroid Scintigraphy Methods

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<th>Method</th>
<th>Sensitivity, %</th>
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<tr>
<td>Dual-phase technique</td>
<td>60</td>
</tr>
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<td>Combined planar techniques</td>
<td>78</td>
</tr>
<tr>
<td>Early Tc 99m MIBI–SPECT imaging</td>
<td>96</td>
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Abbreviation: Tc 99m MIBI–SPECT, technetium Tc 99m sestamibi scintigraphy–single-photon emission computed tomography.

The association of primary HPT and thyroid pathology, in particular MNG, is common (26%) in our recently published series and it requires not only careful localiza-

tion of parathyroid adenoma but also meticulous preoperative assessment of suspicious nodules to direct intraoperative biopsy. An experienced endocrine surgeon performing bilateral neck exploratory surgery can cure primary HPT in most patients (up to 98% of cases) without the aid of any preoperative imaging. Since a solitary parathyroid adenoma is the most frequent cause of primary HPT, unilateral neck exploratory surgery seems an overtreatment in most cases. Exploratory surgery of a wide area distorts the normal anatomy of the neck, carries a higher rate of complications, and yields poorer cosmetic results. In accord with the criteria proposed by Sidhu et al, bilateral neck exploratory surgery is indicated when (1) there is no preoperative localization; (2) concomitant thyroid pathology is present; (3) parathyroid hyperplasia is suspected; and (4) patients have more than 1 parathyroid adenoma. The surgical approach, however, varies between bilateral neck exploratory surgery, unilateral neck exploratory surgery, and guided, focused parathyroidectomy. Pros and cons for each procedure are still widely debated. Issues like success rates, operative time, complications, cost, and cosmetic results are considered.

Our experience reveals that a patient-tailored approach should be adopted, considering the educated patients’ choice regarding his or her preferred surgical procedure. Unilateral neck exploratory surgery and even more so focused parathyroidectomy are dependent on reliable, accurate preoperative and intraoperative localization and validation, especially in the presence of concomitant thyroid pathology.

Parathyroid adenomas typically have a high metabolic rate for their size and show high avidity for labeled MIBI. The presence of mitochondria-rich oxyphil cells and increased vascularity presumably accounts for Tc 99m MIBI trapping. However, planar Tc 99m MIBI parathyroid imaging is associated with a large number of equivocal or false-negative studies. Additionally, false-positive results may occur in the presence of thyroid nodules that are MIBI avid and can, therefore, mimic a parathyroid lesion, particularly when using the dual-phase Tc 99m MIBI technique. Several authors reported various effects of thyroid abnormalities on the sensitivity of the scan, discouraging the use of preoperative Tc 99mMIBI scintigraphy and intraoperative gamma-probe technique in patients with concomitant MNG.

In our study planar imaging correctly identified only 68% (28) of the parathyroid adenomas while SPECT imaging correctly identified 95% of the adenomas in 39 patients. This discrepancy is explained by the fact that most adenomas were posterior to the thyroid gland and, therefore, difficult to identify on planar imaging. More importantly, depth information and 3-dimensional location of the adenoma are crucial factors for the surgeon in planning and performing a limited surgery.

In addition, the SPECT correctly identified malignant nodules in 4 of 5 patients, being cold on technetium Tc 99m pertechnetate imaging but showing avid uptake of MIBI. The malignant nodules could be easily separated from the parathyroid adenomas by their conspicuous anterior location. The overall malignancy rate in thyroid nodules among patients with MNG may reach

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10% and multinodularity of a goiter is no longer considered an indicator of probable benign disease.\textsuperscript{6,14,24}

Moreover, a large proportion of histologically malignant nodules are nonpalpable. Chest radiography, high-resolution ultrasonography, and computed tomography help to delineate the size and extent of a goiter in evaluating compression symptoms\textsuperscript{2} and a fine-needle aspiration biopsy of the thyroid is the procedure of choice to search for malignancy. We routinely use ultrasonography to diagnose MNGs; it has been our experience [and others\textsuperscript{10,25}] that ultrasonography has relatively lower sensitivity and specificity compared with MIBI scintigraphy for identification of parathyroid adenoma in patients with MNG.

A thyroid scan with technetium Tc 99m pertechnetate is a useful and simple test to evaluate cold thyroid nodules while Tc 99m MIBI scintigraphy is a highly accurate test for localization of parathyroid adenomas\textsuperscript{26-28} with a high target-background ratio. Our study suggests an important additive contribution of the SPECT study not only in localization of the parathyroid adenoma but also in the differentiation between a suspect thyroid nodule and a parathyroid gland.

A small number of oxyphil cells in some adenomas may account for rapid washout of Tc 99m MIBI from the adenoma. Thus, delayed imaging may be nondiagnostic when similar washout rates between thyroid and parathyroid tissue are observed. In our study only 61% of the adenomas showed retention of activity on delayed images. We found that early SPECT imaging on the morning of surgery was most useful for localizing parathyroid adenomas and is superior to delayed dual-phase imaging. Delayed SPECT is not recommended, as it may cause unnecessary delay in surgery and may yield false-negative results due to rapid washout.

The weight of the adenoma had no significant effect on the higher sensitivity of SPECT imaging in our study, although Takebayashi et al\textsuperscript{29} used semiquantitative analysis with planar imaging (including only 9 parathyroid adenomas) and found a greater ratio of parathyroid-thyroid counts in larger glands. The use of quantification analysis in our study showed that high PTH levels before surgery predicted a significantly higher uptake of Tc 99m MIBI in the adenoma. This relationship between the intensity of tumor uptake and hormonal function suggests that patients with higher preoperative PTH levels may benefit better from radioguided surgery.

Our data strongly supports the use of preoperative SPECT imaging of parathyroid adenomas in patients with MNGs. This technique has a significant effect on the op-

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**Figure 1.** Standard image of a 55-year-old woman with a multinodular goiter. A, The early technetium Tc 99m sestamibi scintigraphic (MIBI) image shows a “hot” focus in the lower pole of the left lobe (black arrow) consistent with a parathyroid adenoma and a second focus in the upper pole of the left lobe (white arrow), a histologically confirmed thyroid carcinoma. B, Delayed MIBI image shows persistent activity in the carcinoma but significant washout from the adenoma. Arrows indicate same locations as noted in Figure 1A. C, The technetium Tc 99m sodium pertechnetate scan shows neither activity in the region of the adenoma nor in the carcinoma (circles).

**Figure 2.** A 3-dimensional volume rendered technetium Tc 99m sestamibi scintigraphic image from the same patient as in Figure 1 shows distinct foci of activity associated with the carcinoma (top arrow) and the adenoma (bottom arrow).

**Table 2. Serum Calcium and Parathyroid Hormone Levels**

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<tr>
<th>PTH Level, pg/mL</th>
<th>Serum Calcium Level, mg/dL†</th>
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<tr>
<td>At 1</td>
<td>At 2</td>
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<tr>
<td>180.2 (72.0-400.0)</td>
<td>11.6 (10.0-17.0)</td>
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Abbreviation: PTH, serum parathyroid hormone levels before surgery (reference range, 10-65 pg/mL).

SI unit conversion factor: To convert parathyroid hormone values to picomoles per liter, multiply by 0.1053; calcium values to millimoles per liter, multiply by 0.25.

*Data are given as the mean (range).
†1 indicates serum calcium levels before surgery (reference range, 8.5-10.3 mg/dL); 2, serum calcium levels 8 hours after surgery; and 3, serum calcium levels 24 hours after surgery.
erative time and success of surgery. It is important not only in helping to select patients who are candidates for minimally invasive radioguided surgery\(^9\) and provide accurate 3-dimensional information, but it can also identify thyroid nodules suspicious for malignancy. The intraoperative gamma-probe technique enables the surgeon to focus his or her search, provides instant feedback regarding the progress of the operation, reduces surgical trauma and complications, and yields better cosmetic results.

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