Differences in Accuracy of ^{99m}Tc-Sestamibi Scanning Between Severe and Mild Forms of Primary Hyperparathyroidism

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Preoperative localization of the parathyroids using ^{99m}Tc-sestamibi scanning has not yet been established as a routine diagnostic procedure for primary hyperparathyroidism. Several studies have demonstrated a variable degree of accuracy (70%–98%) in asymptomatic patients. **Methods:** We evaluated the accuracy of this technique in 64 patients who underwent scanning between January 2000 and January 2005 according to the clinical manifestations of the disease. **Results:** The study included 25 asymptomatic patients (group I), 18 nephrolithiasis patients without overt bone disease (group II), and 21 patients with severe bone involvement and osteitis fibrosa cystica (group III). Mean serum calcium in groups I, II, and III was 10.98 ± 0.02, 11.32 ± 0.17, and 13.35 ± 0.35 mg/dL, respectively. Mean serum parathyroid hormone in groups I, II, and III was 135.45 ± 13.50, 165.85 ± 15.06, and 579.6 ± 628.4 pg/mL, respectively. The ^{99m}Tc-sestamibi scan results were positive in 64% of the patients in group I, in 83% of those in group II, and in 100% of those in group III. Of the patients with severe bone disease, 70% showed increased uptake on the initial images, whereas in the other groups, increased uptake was seen only on the delayed images, as expected. **Conclusion:** Our data show a high degree of accuracy for the use of ^{99m}Tc-sestamibi scanning as a localizing procedure in severe primary hyperparathyroidism.

Key Words: ^{99m}Tc-sestamibi; parathyroid; accuracy; hyperparathyroidism

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Primary hyperparathyroidism (PHPT) is a relatively common disease characterized by an increase in the synthesis and secretion of parathyroid hormone (PTH) by one or more of the parathyroid glands, with a resultant increase in the serum concentration of calcium. The literature suggests that PHPT occurs in approximately 1 of 500 women and 1 of 2,000 men per year in their fifth to seventh decades of life. Excessive secretion of PTH is most frequently caused by a parathyroid adenoma (80%–85% of cases), hyperplasia involving more than 1 gland and usually all 4 glands (10%–15% of cases), or, rarely, parathyroid carcinoma (0.5%–1% of cases) (*1*).

Patients with PHPT may clinically present with nephrolithiasis, bone involvement, or neuropsychiatric disease or may be asymptomatic. Many aspects distinguish mild from severe PHPT. PHPT with severe skeletal involvement is characterized as osteitis fibrosa cystica (which is observed as demineralization on radiographs), bone mineral density (BMD) is extremely low, and bone turnover extremely high (*2*). In Brazil, PHPT is perceived as an asymptomatic ailment in about half the patients, whose PHPT is diagnosed during a routine laboratory assessment (*3*). In other series, asymptomatic patients account for 80% of those diagnosed with the condition (*4*). In patients from Western industrialized societies, milder forms of these classic features will be present in only 30%–40% of patients diagnosed with PHPT (*4*).

In laboratory tests, patients with PHPT reveal increased PTH, calcium, and alkaline phosphatase levels; decreased phosphorus levels; and usually increased urinary calcium excretion. In these patients, low serum levels of vitamin D have been reported to be related to the severity of the disease in terms of biochemical indices, bone turnover, and bone density measurements (*5*). Markers of bone resorption such as CTx (carboxyterminal cross-linking telopeptide of bone collagen, or serum C-telopeptide) and NTx (amino-terminal cross-linking telopeptide of bone collagen, or urinary N-telopeptide) are degradation products of collagen and are useful in monitoring bone loss. Measurement of CTx and NTx is convenient and specific for bone resorption, which reflects the rate of bone turnover.

The treatment of choice for adenoma is surgical excision. Postsurgical normalization of PTH and calcium levels and improvement of renal, musculoskeletal, and circulatory function could be achieved in 95% of patients when the surgery was performed by an experienced surgeon (*6*).

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Surgical failure may result from ectopic glands, involvement of multiple glands, supernumerary glands, a small tumor, or the surgeon's failure to recognize the gland involved (*7*).

Ultrasonography, CT, MRI, and scintigraphy have been widely used in the preoperative localization of abnormal parathyroid glands. ^{201}Tl- or ^{99m}Tc-scintigraphy has been used since the early 1980s, but its use declined after the advent of novel technetium agents, mainly ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin, which offer lower radiation exposure and higher detection efficacy (*8*). The advent of the ^{99m}Tc-sestamibi scan in the early 1990s changed the management of PHPT. Although ^{99m}Tc-sestamibi has been used extensively for parathyroid imaging, the mechanism for its uptake by parathyroid cells remains unclear. It has been suggested that the electrical potential of the plasma and mitochondrial membrane regulates uptake of ^{99m}Tc-sestamibi and that tissues rich in mitochondria are avid for it. An increased blood flow is implicated in the uptake of ^{99m}Tc-sestamibi and may account for uptake by parathyroid and thyroid neoplasms (*9*).

A parathyroid ^{99m}Tc-sestamibi scan or other localizing methods are normally ordered for patients with PHPT recurrence after parathyroidectomy with the aim of detecting ectopic or residual glands to guide the surgeon in a second operation. A routine parathyroid scan before the first operation has been used to localize involved glands, which may improve the surgical success rate and reduce complications, leading to a less invasive procedure (*7*). Several studies have demonstrated a high degree of accuracy for ^{99m}Tc-sestamibi scanning in detecting the parathyroids preoperatively, with a better result than is obtained with ultrasound, CT, or MRI (*10*). However, few studies have clarified a possible association between the clinical forms of PHPT and the accuracy of ^{99m}Tc-sestamibi scanning of the parathyroid.

The aim of this study was to assess the accuracy of ^{99m}Tc-sestamibi scanning of the parathyroid for the various presentations of PHPT: asymptomatic patients, patients with nephrolithiasis, and patients with severe bone disease and osteitis fibrosa cystica.

MATERIALS AND METHODS

Patients

We studied 64 consecutive patients with PHPT diagnosed at our institution between January 2000 and January 2005, who underwent ^{99m}Tc-sestamibi parathyroid imaging and had no thyroid nodule on ultrasound in the area of ^{99m}Tc-sestamibi uptake. The diagnostic criteria for HPTP were based on hypercalcemia (total calcium levels $\geq$ 10.3 mg/dL) associated with high or inappropriately normal intact PTH levels.

The patients were divided into 3 groups. Group I comprised asymptomatic patients, characterized as those with PHPT without evidence of nephrolithiasis, bone disease, classic neuromuscular symptoms (proximal muscle weakness, atrophy, hyperreflexia, or gait disturbances), or the typical neuropsychiatric syndrome (mental confusion, depression, or symptoms of acute hypercalcemia). Given the elevated incidence of symptomatic PHPT in Brazil (*2*,*3*), we divided the symptomatic group into patients with renal disease and patients with bone disease (osteitis fibrosa cystica). Group II comprised patients with renal disease, always presenting with episodes of renal colic with evidence of solitary calculi or showing features of nephrocalcinosis without overt bone disease. In PHPT, the severity of disease in patients with nephrolithiasis is intermediate between that in asymptomatic patients and that in patients with severe bone disease. Group III comprised patients with severe bone disease causing bone pain and pathologic fractures and having typical features of osteitis fibrosa cystica. Patients with osteitis fibrosa cystica are characterized by severe skeletal involvement, demineralization on radiography, extremely low BMD, and extremely high bone turnover.

Serum calcium and phosphorus were measured using an autoanalyzer (Cobas-Mira Plus; Roche). Serum PTH was measured by automated immunochemiluminometric assay (Diagnostic Products Corp.). According to these tests, the reference range for serum calcium is 8.6–10.3 mg/dL, serum phosphorus is 2.5–4.5 mg/dL, and serum PTH is 10–65 pg/mL. In addition, we evaluated levels of 25-hydroxyvitamin D and their correlation with the levels of PTH hormone and biochemical markers of bone remodeling. Serum 25-hydroxyvitamin D was measured by radioimmunoassay after extraction of vitamin D metabolites (DiaSorin, Inc.). The reference range for serum 25-hydroxyvitamin D according to this test is 12–68 ng/mL. NTx excretion was determined by enzyme-linked immunosorbent assay. Assay values were corrected for creatinine. The reference range for urine NTx according to this test is 50–60 nmol/mmol of creatinine in premenopausal women, 15–120 nmol/mmol of creatinine in postmenopausal women, and 6–65 nmol/mmol of creatinine in men. CTx was assayed using an autoanalyzer immunoassay CrossLaps kit (Elecsys; Roche) according to the manufacturer's instructions. The reference range for serum CTx according to this test is 50–450 pg/mL in premenopausal women, 90–680 pg/mL in postmenopausal women, and 70–480 pg/mL in men. All markers were measured on fasting patients, and for the NTx test second-void morning urine samples were used, as is standard practice for the resorption markers.

To further evaluate patients with PHPT and its bone and renal complications, we measured renal function and daily urinary calcium excretion and performed renal ultrasonography and bone densitometry. The BMD was determined at the lumbar spine (L2, L3, and L4), femoral neck, and distal third of the nondominant radius, with use of dual-energy x-ray absorptiometry (Lunar Corp.). The precision error in vivo as a percentage coefficient of variation was 0.9% for the lumbar spine, 1.2% for the femoral neck, and 2% for the distal radius. The data on bone density are reported as *t* scores.

All tests were performed at Dilab Laboratories.

Image Acquisition

Before scintigraphy, all patients underwent a careful clinical examination to verify the presence of palpable thyroid nodules and underwent neck ultrasonography to evaluate the thyroid and parathyroid glands. Patients who had a nodular thyroid lesion in the area of the ^{99m}Tc-sestamibi uptake were excluded from the study.

After a 740-MBq (20-mCi) intravenous injection of ^{99m}Tc-sestamibi, anterior planar images of the neck and upper chest were acquired with a 256 × 256 matrix at 5 min (early phase) and 2 h (delayed phase), using a large-field-of-view dual-head γ-camera (Siemens) equipped with a low-energy, high-resolution, parallel-hole collimator. The energy windows were set to 140 keV ± 5%.

The zoom factor was 1.45. All interpretations were performed by 2 experienced nuclear medicine physicians. The scan findings were considered positive for parathyroid disease when an area of increased uptake that persisted on late imaging was found.

Statistical Analysis

Results were expressed as percentages or mean ± SD. The χ^2 test and Fisher exact test were used to compare percentages of positive scans among the groups. The Wilcoxon test was used to compare means. Probability values below 0.05 were defined as significant.

RESULTS

Group I accounted for 39.04% of the sample, 80% of the group being female. The mean age was 66.75 ± 0.63 y, serum calcium 10.98 ± 0.02 mg/dL, serum phosphorus 2.79 ± 0.29 mg/dL, PTH 135.45 ± 13.50 pg/mL, serum 25-hydroxyvitamin D 26.97 ± 4.13 ng/mL, urinary calcium 213.21 ± 42.7 mg, *t* score for lumbar spine BMD –2.02 ± 0.15, *t* score for femoral neck BMD –2.03 ± 0.28, and *t* score for distal third radius BMD –2.23 ± 0.74.

Group II accounted for 28.12% of the sample, 77.7% of the group being female. The mean age was 55.8 ± 5.09 y, serum calcium 11.32 ± 0.17 mg/dL, serum phosphorus 2.56 ± 0.47 mg/dL, PTH 165.85 ± 15.06 pg/mL, serum 25-hydroxyvitamin D 20.02 ± 0.56 ng/mL, urinary calcium 303.45 ± 58.9 mg, *t* score for lumbar spine BMD –1.83 ± 0.85, *t* score for femoral neck BMD –1.81 ± 0.38, and *t* score for distal third radius BMD –1.79 ± 0.04.

Group III accounted for 32.81% of the sample, 47.6% of the group being female. Mean age was 38.7 ± 4.38 y, serum calcium 13.35 ± 0.35 mg/dL, serum phosphorus 1.99 ± 0.29 mg/dL, PTH 579.6 ± 628.4 pg/mL, serum 25-hydroxyvitamin D 15.91 ± 1.11 ng/mL, urinary calcium 285.5 ± 67.1 mg, *t* score for lumbar spine BMD –4.25 ± 0.24, *t* score for femoral neck BMD –5.44 ± 1.37, and *t* score for distal third radius BMD –5.33 ± 0.69.

The mean NTx in groups I, II, and III was 51.3 ± 6.4 nmol/mmol of creatinine (9 patients), 154.1 ± 62.9 nmol/mmol of creatinine (10 patients), and 501.5 ± 201 nmol/mmol of creatinine (16 patients), respectively. The mean CTx in groups I, II, and III was 752.6 ± 496.3 pg/mL (16 patients), 727.3 ± 220.4 pg/mL (8 patients), and 2,210.2 ± 375.4 pg/mL (5 patients), respectively.

The baseline characteristics of the study groups are summarized in Table 1.

All 64 patients underwent parathyroid ^{99m}Tc-sestamibi scanning. The findings were positive in 64% of the patients in group I, in 83% of those in group II, and in 100% of those in group III. Of patients with severe bone disease, 70% showed increased uptake on early images, in contrast to patients in the other groups, who showed increased uptake only on delayed images. Figures 1 and 2, the scintigraphic images of 2 patients with osteitis fibrosa cystica (group III), show that uptake in the parathyroid gland was increased on early images.

Of the 25 asymptomatic patients, 12 (48%) filled the surgical criteria of the National Institutes of Health Workshop on asymptomatic PHPT (*11*). These 12 asymptomatic patients of group I, 18 symptomatic patients with nephrolithiasis (group II), and 21 symptomatic patients with bone disease (group III) underwent parathyroidectomy. Thus, 51 scintigraphic examinations were verified by subsequent sur-

TABLE 1
Clinical Characteristics, Laboratory Values, and BMD Values of the 64 Patients, Stratified by Study Group

Feature	Group I (asymptomatic)	Group II (renal stone disease)	Group III (osteitis fibrosa cystica)	*P*	Reference range
Age (y)	66.75 ± 0.63	55.8 ± 5.09	38.7 ± 4.38	<0.01	
Sex ratio (M:F)	1:4	2:7	11:10	<0.01	
Serum calcium (mg/dL)	10.98 ± 0.02	11.32 ± 0.17	13.35 ± 0.35	<0.01	8.6–10.3
Serum phosphorus (mg/dL)	2.79 ± 0.29	2.56 ± 0.47	1.99 ± 0.29	<0.01	2.5–4.5
Serum PTH (pg/mL)	135.45 ± 13.50	165.85 ± 15.06	579.6 ± 628.4	<0.01	10–65
Serum 25-hydroxyvitamin D (ng/mL)	26.97 ± 4.13	20.02 ± 0.56	15.91 ± 1.11	<0.01	12–68
Urine NTx (nmol/mmol of creatinine)	51.3 ± 6.4	154.1 ± 62.9	501.5 ± 201	<0.05	50–60*, 15–120†, 6–65‡
Serum CTx (pg/mL)	752.6 ± 496.3	727.3 ± 220.4	2,210.2 ± 375.4	<0.05	50–450*, 90–680†, 70–480‡
BMD *t* score					
Lumbar spine	−2.02 ± 0.15	−1.83 ± 0.85	−4.25 ± 0.24	<0.01	
Femoral neck	−2.03 ± 0.28	−1.81 ± 0.38	−5.44 ± 1.37	<0.01	
Distal radius	−2.23 ± 0.74	−1.79 ± 0.04	−5.33 ± 0.69	<0.01	

Data are mean ± SEM.
*Premenopausal women.
†Postmenopausal women.
‡Men.

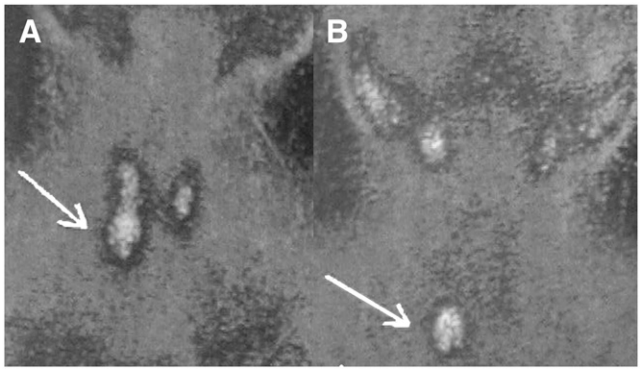

FIGURE 1. ^{99m}Tc-Sestamibi scan of patient with osteitis fibrosa cystica (group III): early (A) and delayed (B) images of right inferior parathyroid adenoma (arrows) weighing 6.5 g before initial surgery.

gery. Of these, 49 (96%) had histologic confirmation of a single adenoma and 2 (4%) of parathyroid carcinoma. The mean size of the resected parathyroid glands was 2 ± 1.2 g (range, 0.9–3.0 g) in group I, 2.5 ± 2.8 g (range, 0.8–6.0 g) in group II, and 6.8 ± 4.2 g (range, 2.8–12 g) in group III. Parathyroid glands tend to be larger in patients with osteitis fibrosa cystica and renal stone disease than in asymptomatic patients. Although the size of the parathyroid did not significantly differ between groups I and II, the parathyroid was significantly larger in group III than in the other groups ($P < 0.001$).

DISCUSSION

Parathyroid scintigraphy has been used mainly for screening for ectopic glands in patients who have recurrent hyperparathyroidism or whose initial surgical exploration failed to detect any parathyroid lesion. Traditionally, surgical management has been a bilateral exploration of the neck with identification of the 4 parathyroid glands and removal of the enlarged gland. Many experts believe that, in the hands of an experienced surgeon, preoperative localizing procedures are unnecessary, as the success rate may

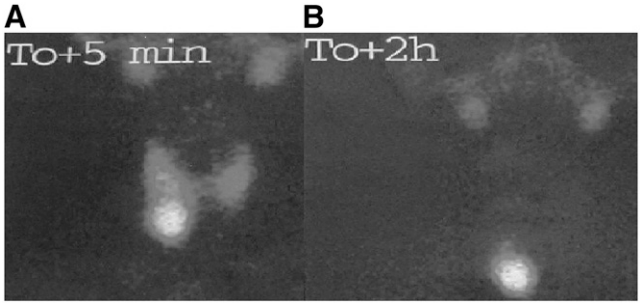

FIGURE 2. ^{99m}Tc-Sestamibi scan of patient with osteitis fibrosa cystica (group III). (A) Initial image, obtained 5 min after intravenous injection of ^{99m}Tc-sestamibi, shows increased uptake in parathyroid gland. (B) Delayed image, obtained at 2 h, shows right inferior parathyroid adenoma weighing 12 g before initial surgery.

be as high as 98% (*12*). With the increased use of minimally invasive parathyroidectomy, this localizing procedure has become increasingly popular (*13*). This surgical approach has advantages such as a smaller incision; less surgical trauma; a procedure, anesthetic exposure, and hospital stay that are briefer; less postsurgical pain; better cosmetic results; and lower overall cost (*14*).

In our study, asymptomatic PHPT patients accounted for around 39% of the entire patient sample, in contrast to other series, in which asymptomatic patients accounted for 80% of those diagnosed with the condition (*4*). Severe bone involvement—osteitis fibrosa cystica—corresponded to 32.81% of the sample, in contrast to literature reports that this form is extremely rare (*12*). Patients with nephrolithiasis accounted for 28.12% of the sample, slightly higher than the incidence (around 20%) reported in the literature (*12*). Studies being conducted in Western countries show that less than 20% of the patients display symptomatic PHPT (*15*). In contrast to these findings, studies in countries such as India, China, and Brazil still show an elevated incidence of symptomatic cases (*5,15–17*). In China and India, around 98% of patients with PHPT show severe osteitis fibrosa cystica and 100% of them have vitamin D deficiency (25-hydroxyvitamin D levels < 25 ng/mL) (*15*). Late diagnosis, related to limited access to routine measurement of calcium levels or poor acknowledgment of PHPT, as well as the possible high prevalence of vitamin D deficiency in these countries, may lead to a more symptomatic clinical profile (*5*).

In our study, symptomatic patients presented with lower levels of 25-hydroxyvitamin D. Asymptomatic patients had a mean 25-hydroxyvitamin D value of 26.97 ± 4.13 ng/mL. Patients with severe bone disease presented with the lowest 25-hydroxyvitamin D values (15.91 ± 1.11 ng/mL). In patients with asymptomatic PHPT, several studies have shown that rates of disease activity, such as levels of PTH hormone and biochemical markers of bone remodeling, correlate inversely with levels of 25-hydroxyvitamin D (*5,17,18*). Data from the literature indicate that vitamin D deficiency may stimulate hyperactivity of the parathyroid glands, leading to more cases of symptomatic disease.

Mean NTx and CTx levels were high in all groups studied, correlating with the bone loss observed, and usually fell markedly after parathyroidectomy. These markers were significantly higher in patients with osteitis fibrosa cystica.

BMD by dual-energy x-ray absorptiometry is an important means of assessing bone involvement in PHPT. Most patients present with varying degrees of bone loss, which is most apparent in sites with a predominance of cortical bone, such as the distal radius and femoral neck (*4,12*). In our study, patients with osteitis fibrosa cystica presented with greater bone loss (*t* score, –5.44 for the femoral neck and –5.33 for the distal radius).

^{99m}Tc-Sestamibi scan results were positive in 100% of patients with severe bone disease, in 64% of patients in group I (asymptomatic), and in 83% of patients in group II (nephrolithiasis). Figure 3 summarizes the statistical results

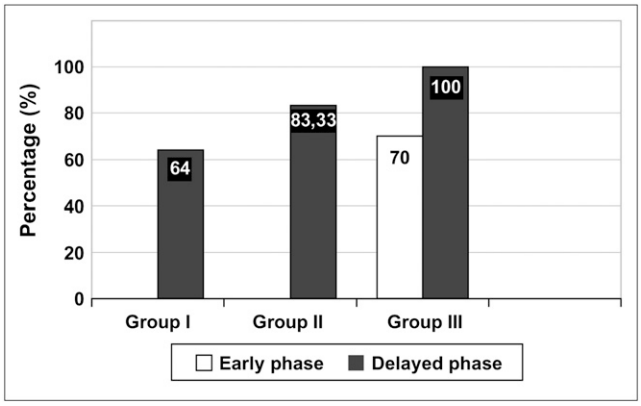

FIGURE 3. Comparison of ^{99m}Tc-sestamibi scans of parathyroid among the 3 clinical groups of PHPT at 5 min (early phase) and 2 h (delayed phase). Accuracy of technique increases in more severely affected patients, approaching 100%. Of patients with severe bone disease (group III), 70% showed increased uptake on early images, in contrast to patients in the other groups, who showed increased uptake only on delayed images.

for the accuracy of ^{99m}Tc-sestamibi scanning during the early and delayed phases in the 3 clinical forms of PHPT. Our findings corroborated those reported in the literature, and in the more severely affected patients, the sensitivity of the technique approached 100%. Studies have shown a sensitivity ranging from 79.1% to 98% for detecting parathyroid adenomas (*7,19–21*). In our study, most parathyroid lesions were adenomas (96%).

Accurate detection of hyperfunctioning glands depends also on some related factors that can influence ^{99m}Tc-sestamibi uptake. Increases in both perfusion and functional activity and targeting of abundant mitochondria-rich oxyphil cells seem to be relevant mechanisms of uptake (*22*). A relationship has been observed between the intensity of focal uptake in the parathyroid glands and the cell-cycle phase for patients with secondary hyperparathyroidism (*22*). A correlation between higher uptake and the active growing phase shows that scintigraphy accurately reflects the functional status of hyperplastic parathyroid glands. Serum calcium levels may modify radiotracer kinetics by influencing membrane potential (*22,23*). Lower calcium and PTH levels seem to correlate with less sensitive ^{99m}Tc-sestamibi scanning (*24*). In addition, P-glycoprotein or multidrug-resistance–associated protein expression may play an important role in false-negative parathyroid scintigraphy results. Parathyroid adenomas that express either P-glycoprotein or the multidrug-resistance–related protein are less likely to accumulate ^{99m}Tc-sestamibi (*25*). If the lipophilic cationic radiotracers used in parathyroid scintigraphy are transported by the same mechanism as the anticancer drugs, they will quickly be eliminated from the parathyroid glands containing P-glycoprotein or expressing multidrug-resistance–related protein and the images will be negative for uptake. In parathyroid glands with no P-glycoprotein or multidrug-resistance–related protein expression, the radiotracers remain in the cells, making it easier to detect them by scintigraphy (*22*). Mitochondria-rich oxyphil cells presumably account for ^{99m}Tc-sestamibi scan uptake in parathyroid lesions. Fewer oxyphil cells, and hence fewer mitochondria, may explain both lower uptake and rapid washout of ^{99m}Tc-sestamibi from some lesions (*25*).

Data on the use of SPECT for detecting hyperfunctioning parathyroid lesions have also been reported (*26,27*) and are encouraging, because the method showed a preoperative sensitivity higher than that of conventional planar scintigraphic procedures. However, these data refer only to preliminary studies. The data of our study, which did not use SPECT, suggest that in patients with PHPT and severe bone disease, ^{99m}Tc-sestamibi planar imaging can be highly accurate in detecting parathyroid adenoma. This accuracy could have been due to the fact that patients with osteitis fibrosa cystica present with larger parathyroid lesions that are associated with higher calcium and PTH levels and comprise cells of higher perfusion and functional activity.

CONCLUSION

The use of ^{99m}Tc-sestamibi to guide parathyroidectomy has been studied with encouraging results. ^{99m}Tc-Sestamibi scanning was highly accurate for localizing parathyroid lesions in severe PHPT. This study provided additional information supporting the use of ^{99m}Tc-sestamibi scanning. However, these suggestions need to be confirmed by further studies in a larger number of patients.

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