
Incremental Diagnostic Value of Preoperative ^{99m}Tc -MIBI SPECT in Patients with a Parathyroid Adenoma

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The purpose of this prospective study was to evaluate the diagnostic value of early parathyroid SPECT combined with quantitative analysis as compared with planar imaging in patients undergoing minimally invasive radioguided surgery.

Methods: A total of 52 consecutive patients with primary hyperparathyroidism underwent planar and SPECT parathyroid scintigraphy 2–5 d before surgery. Each patient had a single-tracer dual-phase technique using ^{99m}Tc -methoxyisobutylisonitrile (^{99m}Tc -MIBI) and a double-tracer subtraction technique using a delayed ^{99m}Tc -pertechnetate scan. Immediately after the first ^{99m}Tc -MIBI planar image, a SPECT study was acquired. Before radioguided parathyroidectomy, each patient was reinjected with ^{99m}Tc -MIBI. Serum calcium levels were available for all patients before surgery and at 8 and 24 h after surgery. Serum parathyroid hormone (PTH) levels were also available for all patients. Quantitative analysis was performed using the average count ratio of parathyroid to left thyroid lobe, right thyroid lobe, and maximum thyroid activity. All patients had histopathologic examination of the removed glands. **Results:** The average time for radioguided surgery was 30 min (range, 20–40 min). Post-surgical calcium levels correlated significantly with the adenoma weight ($r = 0.5$; $P = 0.016$). Combined planar scintigraphy correctly identified 41 adenomas (79%). SPECT increased the sensitivity to 96%. SPECT was superior to planar imaging in 9 patients, mainly in patients with ectopic adenomas or with multinodular goiters. Gland size did not affect significantly the detectability of SPECT. ^{99m}Tc -MIBI retention was noted in only 31 adenomas (60%). The average uptake ratios of parathyroid counts to the left lobe, right lobe, and maximum thyroid activity were 1.20 ± 0.42 , 1.29 ± 0.45 , and 0.84 ± 0.35 , respectively. The latter ratio was significantly correlated with PTH levels before surgery ($r = 0.408$; $P = 0.04$). **Conclusion:** Our data indicate that early preoperative SPECT in patients with primary hyperparathyroidism is essential for accurate localization of parathyroid adenomas and for the selection of patients who are candidates for minimally invasive radioguided surgery. Planar parathyroid imaging is less sensitive compared with SPECT, and washout kinetics of ^{99m}Tc -MIBI are unreliable in the dual-

phase technique. Patients with higher presurgical PTH levels may especially benefit from radioguided surgery.

Key Words: parathyroid; adenoma; ^{99m}Tc -methoxyisobutylisonitrile; SPECT; radioguided surgery

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PPrimary hyperparathyroidism is a common endocrine disorder with an annual incidence of 0.2–0.5 per 1,000 population. Despite the high success rate achieved at neck exploration by experienced endocrine surgeons, more accurate preoperative localization and intraoperative guidance are required to enable selective minimal surgery and to reduce the operative failure rate (1,2). Moreover, repeated exploration is associated with a higher rate of complications, including recurrent laryngeal nerve paralysis and hypoparathyroidism (3).

Anatomic imaging modalities including ultrasonography, CT, and MRI have a relatively low sensitivity for detection of parathyroid adenomas (4,5). Parathyroid scintigraphy using either the single-tracer dual-phase technique or the double-tracer subtraction technique provides high-quality imaging and reproducible scintigraphic findings (6). The previously used imaging approach combining ^{201}Tl and ^{99m}Tc subtraction scintigraphy showed only 45%–75% sensitivity. In contrast, ^{99m}Tc -methoxyisobutylisonitrile (^{99m}Tc -MIBI) scintigraphy has a higher target-to-background ratio and is more effective for the localization of adenomas (7–9).

However, the sensitivity of the subtraction method using either ^{123}I - or ^{99m}Tc -pertechnetate as the thyroid agent may be limited by a pertechnetate (or iodine)-avid intrathyroid parathyroid adenoma (10,11). The other common imaging technique is single-tracer dual-phase scintigraphy, which is based on the differential washout of ^{99m}Tc -MIBI from thyroid and parathyroid tissue. However, the washout of ^{99m}Tc -MIBI from thyroid and parathyroid tissue is unpredictable and it may be washed out rapidly from parathyroid adenomas. Several studies found that the dual-phase technique is

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unreliable, with sensitivities as low as 55% (12). In addition, this method is a time-consuming procedure that requires the patient to remain in the nuclear medicine department for several hours.

Despite the relatively high accuracy of planar parathyroid imaging, intrathyroidal adenomas with low ^{99m}Tc -MIBI uptake and ectopic adenomas may be overlooked. Another limitation for planar ^{99m}Tc -MIBI scintigraphy is a nodular goiter, because thyroid nodules are frequently ^{99m}Tc -MIBI avid and can cause false-positive scintigraphic results. More important, depth information and 3-dimensional (3D) location regarding the adenoma are lacking, a crucial factor in planning a limited surgery.

The routine use of ^{99m}Tc -MIBI SPECT before initial surgery is still controversial. The purpose of our study was to prospectively compare the diagnostic value of early postinjection SPECT combined with semiquantitative analysis with planar parathyroid imaging in patients with primary hyperparathyroidism.

MATERIALS AND METHODS

The study cohort consisted of 52 consecutive patients with primary hyperparathyroidism (38 women, 14 men; mean age, 63.5 y; range, 32–84 y) who had parathyroid surgery to treat primary hyperparathyroidism. Serum calcium levels were taken before surgery and at 8 and 24 h after surgery (Table 1). Serum parathyroid hormone (PTH) levels were available for all patients before surgery. Gland weight was recorded after surgery, and each patient had a histopathologic examination of the removed glands for comparison with the scintigraphic results.

Scintigraphy

All patients underwent planar and SPECT parathyroid scintigraphy 2–5 d before surgery. Anterior planar images of the neck and chest were acquired for 10 min, at 10 and 120 min after intravenous injection of 740 MBq ^{99m}Tc -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 s each, over a 180° anterior arc from the right lateral to the left lateral position in a 128 × 128 matrix at 3° angular steps. Transaxial, coronal, and sagittal slices 1 pixel thick were reconstructed using a third-order Metz filter set to 8-mm full width at half maximum. In addition, a dual-isotope technique was performed using a delayed (120 min) 10-min image

after the injection of 370 MBq ^{99m}Tc -pertechnetate. The thyroid counts in the pertechnetate image were normalized to those in the ^{99m}Tc -MIBI image and subtracted from the corresponding early ^{99m}Tc -MIBI image. Before undergoing a radioguided parathyroidectomy each patient was reinjected with 740 MBq ^{99m}Tc -MIBI and sent to the operating room.

Interpretation

The SPECT study was compared with the combined planar dual-phase technique (prolonged ^{99m}Tc -MIBI retention) and the double-tracer subtraction technique (computer-generated subtraction image). A distinct focus of increased or separate ^{99m}Tc -MIBI uptake relative to thyroid tissue on either early or late images (or both) was considered positive for abnormal parathyroid tissue. In each case, a 3D image was created from the SPECT data and presented to the surgeon before the operation. For quantitative analysis, a region of interest (ROI) was drawn around the diseased parathyroid gland, and an ROI of similar size was drawn in the left thyroid lobe, right thyroid lobe, and in the region of maximal thyroid gland activity. A count ratio of parathyroid to thyroid was determined using the average counts in each ROI (P/L, P/R, and P/M for the left thyroid lobe, right thyroid lobe, and maximum thyroid activity, respectively).

Technique of Radioguided Parathyroidectomy

Minimally invasive radioguided parathyroidectomy was performed under general anesthesia. A handheld γ -detection device (Navigator; U.S. Surgical Corp.) using a parathyroid probe (U.S. Surgical) was used to determine the incision location and to direct the dissection. A 1.5- to 2.5-cm collar incision was performed. The dissection continued through the fascia and strap muscles directly toward the adenoma. Radioactivity contained within the resected adenoma was determined ex vivo and compared with background neck radioactivity. Frozen sections were obtained only for borderline cases (3 patients). In 3 patients with scintigraphic identification of the adenoma, the local surgery was extended into a wider exploration. The average operating time was 30 min (range, 20–40 min). Most patients were admitted for a 24-h stay after surgery to evaluate for complications.

Statistical Analysis

Analysis of data was performed using SPSS statistical analysis software (SPSS Inc.). Descriptive statistics were calculated and are reported as mean \pm 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 significant at $P < 0.05$.

RESULTS

Among the 52 patients, planar scintigraphy using delayed imaging and dual-isotope technique correctly identified 41 adenomas (79%). SPECT correctly identified those adenomas, providing additional 3D information for the surgeon. Additionally, 9 more adenomas were identified on SPECT, for a sensitivity of 96% (Table 2). SPECT was superior to planar imaging in 6 patients with multinodular goiters (MNGs) and in 3 patients with ectopic adenomas. Figure 1 illustrates a patient with an adenoma lying posterior to the right lower thyroid pole, and Figure 2 shows a patient with a small adenoma just behind a large MNG. Altogether,

TABLE 1
Serum Calcium and PTH Levels

Parameter	Ca 1* (mg%)	Ca 2† (mg%)	Ca 3‡ (mg%)	PTH§ (pg/mL)
Mean	11.6	9.4	9.25	180.2
Range	10–17	8–11.4	8–11.2	72–400

*Calcium levels before admission (normal, 8.5–11.0 mg%).
†Calcium levels 8 h after surgery.
‡Calcium levels 24 h after surgery.
§Serum PTH levels before surgery (normal, 10–65 pg/mL).

TABLE 2
Sensitivity of Parathyroid Scintigraphy Methods

Method	Sensitivity (%)
Dual-phase technique	60
Combined planar techniques	79
Early ^{99m} Tc-MIBI SPECT	96

ectopic adenomas were identified in 6 patients (11%) and MNGs were present in 16 patients (31%). Interestingly, gland size did not affect significantly the detectability of the SPECT studies compared with planar imaging, although the smallest adenoma (170 mg) was missed by planar imaging. ^{99m}Tc-MIBI retention was noted in only 31 adenomas (60%), whereas the remaining adenomas demonstrated a rapid washout. The average uptake ratios of parathyroid counts to the left lobe, right lobe, and maximum thyroid activity were 1.20 ± 0.42 , 1.29 ± 0.45 , and 0.84 ± 0.35 , respectively. Statistical analysis showed that the uptake ratio of parathyroid to maximum thyroid activity was significantly correlated with PTH levels before surgery ($r = 0.408$; $P = 0.04$). Otherwise, no significant correlation was found between parathyroid activity ratios and any of the blood chemistry or clinical variables. The average adenoma weight was 1.14 g (range, 0.17–4.0 g). There was no correlation between gland size and parathyroid uptake. Only 4 of 52 patients had transient symptoms of hypocalcemia after surgery. As expected, clinical symptoms after surgery showed significant inverse association with calcium levels after surgery ($r = -0.4$; $P = 0.03$). No laryngeal nerve injuries were encountered.

DISCUSSION

Experienced endocrine surgeons can cure primary hyperparathyroidism with bilateral neck exploration in most pa-

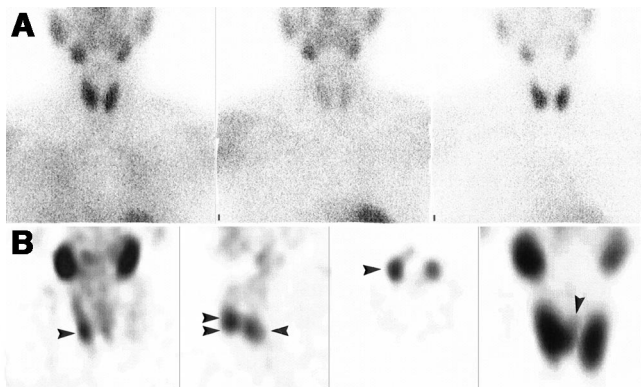


FIGURE 1. A 63-y-old woman with primary hyperparathyroidism. (A) Early ^{99m}Tc-MIBI planar image (left) shows relatively uniform activity in thyroid gland and uniform washout on delayed image (middle). Pertechnetate scan (right) is congruent with early ^{99m}Tc-MIBI scan. (B) Coronal (left), sagittal (middle left), and transaxial (middle right) representative SPECT slices and 3D volume-rendered image (right) show posterior location of adenoma (arrowhead) just behind lower pole of right thyroid lobe (double arrowheads).

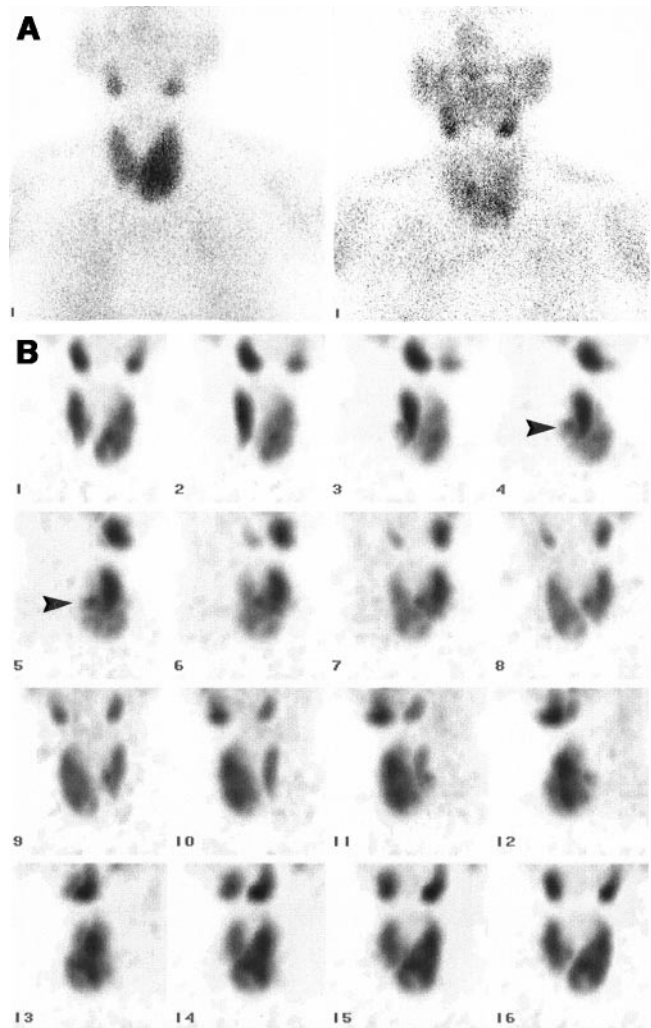


FIGURE 2. A 75-y-old man with primary hyperparathyroidism. (A) Early ^{99m}Tc-MIBI planar image (left) shows large MNG with irregular increased activity in left lobe. Delayed image (right) shows nonuniform washout. (B) 3D-volume rendered images show small adenoma attached to posterior aspect of right lower lobe (arrowhead).

tients (up to 95% of cases) without the aid of any preoperative imaging (13,14). However, morbidity and the rate of failed surgery can be high in less experienced hands (15,16). Considering that a solitary parathyroid adenoma is the most frequent cause of primary hyperparathyroidism (in 80%–85%), bilateral neck exploration is considered overtreatment in most cases: It increases the risk of recurrent laryngeal nerve injuries and the likelihood of hypoparathyroidism. In addition, a wide exploration distorts the normal anatomy of the neck, causing a high rate of complications at repeated exploration. In fact, bilateral neck exploration has been advocated only when parathyroid hyperplasia or double adenomas are suspected.

The intraoperative γ -probe technique can reduce surgical trauma and is considered most useful in patients with ectopic adenomas (13) and in patients with a normal thyroid

gland (17). The prevalence of ectopic adenomas was reported to be as high as 20% (18), and this condition represents one of the most frequent causes of surgical failure. The γ -probe enables the surgeon to focus the search and provides instant feedback about the progress of the operation (19).

Parathyroid adenomas typically have a very 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 ^{99m}Tc -MIBI trapping (20,21). However, a small number of oxyphil cells in some adenomas may account for rapid washout of ^{99m}Tc -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 60% of adenomas showed retention of activity on delayed images. We found that early SPECT was most useful for localizing parathyroid adenomas and is superior to delayed dual-phase imaging. Delayed SPECT is not recommended because it may cause unnecessary delay in surgery and may yield false-negative results due to rapid washout. Planar ^{99m}Tc -MIBI parathyroid imaging is associated with a large number of equivocal or false-negative studies (10,22). In our study, only 79% of the adenomas were identified by planar imaging. Another major limitation is related to the presence of concomitant thyroid nodules that often are ^{99m}Tc -MIBI avid and, therefore, can mimic a parathyroid lesion, causing false-positive scintigraphic results, particularly using the dual-phase ^{99m}Tc -MIBI technique (23). Several authors found different effects of thyroid abnormalities on the sensitivity of the scan (23–25). For this reason, some physicians discourage the use of preoperative ^{99m}Tc -MIBI scintigraphy and the γ -probe technique in patients with hyperparathyroidism who have a concomitant MNG (17). However, although an MNG lowered the sensitivity of planar imaging in our patients, it did not affect the high sensitivity of SPECT, despite the high proportion of patients (31%) with MNGs. This discrepancy is explained by the fact that most adenomas were posterior to the thyroid gland (12/16 patients; 75%) and, therefore, were difficult to identify on planar imaging. Two other adenomas were ectopic, 1 of which had a false-negative SPECT result. The weight of the adenoma had no significant effect on the higher sensitivity of SPECT. Although oblique views have been advocated for parathyroid adenomas superimposed on the thyroid (behind the thyroid lobe), this technique is not useful for an intrathyroid parathyroid adenoma and should be replaced by SPECT. Norman et al. claims that surgeons should be extremely cautious in deciding intraoperatively that a positive MIBI scan is a false-positive scan (19). Our experience is in accordance with this conclusion that when properly applied, conducted, and interpreted, there is no such thing as a false-positive MIBI scan.

The literature contains both supportive and conflicting claims for the use of SPECT in parathyroid adenomas. Chen et al. (12) claims that SPECT does not provide additional

information, whereas others assert that tomographic ^{99m}Tc -MIBI scintigraphy allows topographic localization without improving the detection rate (20). Neumann et al. (26), who used double-phase SPECT MIBI in patients with hyperparathyroidism, defined a positive study as a focal increased activity showing preferential retention of activity over time and, not surprisingly, found a low sensitivity of 55% for localization of adenomas before surgery. In contrast, Moka et al. (27) found a sensitivity of 95% by the use of a SPECT technique compared with 87% sensitivity of planar imaging, even though tomographic imaging was performed 120 min after injection (when many adenomas are already washed out). However, the exact topographic quadrant position was achieved in only 88%.

Our data support the use of preoperative SPECT before the initial operation, not only to select patients who are candidates for minimally invasive radioguided surgery (17) but also to provide accurate 3D information on deeply seated or ectopic adenomas. The aim is to avoid, or at least to reduce, the frequency of surgical failures. The use of quantification analysis in our study showed that high PTH levels before surgery predicted significantly higher uptake of ^{99m}Tc -MIBI in the adenoma. This relationship between the intensity of tumor uptake and the hormonal function suggests that patients with higher presurgical PTH levels may benefit more from radioguided surgery. Takebayashi et al. (28) used semiquantitative analysis with planar imaging (including only 9 parathyroid adenomas) and found a higher ratio of parathyroid-to-thyroid counts in larger glands.

CONCLUSION

Our data indicate that preoperative SPECT in patients with primary hyperparathyroidism is highly important for accurate localization of parathyroid adenomas and for the selection of patients who are candidates for minimally invasive radioguided surgery, including patients with a nodular goiter. Planar imaging has a much lower sensitivity compared with SPECT. The washout kinetics of ^{99m}Tc -MIBI are unreliable in the dual-phase technique. SPECT is mandatory for 3D evaluation of parathyroid adenomas, and it should be the primary preoperative imaging method.

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