ORIGINAL ARTICLE

Early, Postinjection MIBI-SPECT as the Only Preoperative Localizing Study for Minimally Invasive Parathyroidectomy

Pinhas P. Schachter, MD; Nidal Issa, MD; Mordechai Shimonov, MD; Abraham Czerniak, MD; Mordechai Lorberboym, MD

Hypothesis: Early, postinjection technetium Tc 99m sestamibi scintigraphy–single-photon emission computed tomography (MIBI-SPECT) can be used as the only localizing study for focused parathyroidectomy in patients with primary hyperparathyroidism.

Design: During a 26-month period, 82 consecutive patients with primary hyperparathyroidism underwent a standard planar scan using a double-tracer subtraction technique for localization. On the morning of surgery, each patient received radiolabeled technetium Tc 99m sestamibi for intraoperative detection and validation. We performed an early, postinjection SPECT study for comparison with the planar study.

Results: The SPECT study revealed a sensitivity of 96% vs 78% for the planar study. The SPECT study was helpful in locating adenomas in 10 patients with multinodular goiter disease, of whom 3 patients had ectopic adenomas and 2 patients had 2 adenomas each. A significant correlation was noted between uptake ratio and preoperative parathyroid hormone levels ($r = 0.41$; $P = .04$). No recurrent or persistent hyperparathyroidism was reported during a follow-up period of at least 6 months.

Conclusions: Our results encourage the use of preoperative SPECT as the only localizing study on the morning of the operation, both to select patients for minimally invasive radioguided surgery and to provide accurate 3-dimensional information on deeply seated or ectopic adenomas. This approach lowers the costs of preoperative localization and intraoperative validation to a single study. The intraoperative gamma probe technique enables the surgeon to focus the search, provides instant feedback regarding the progress of the operation, reduces surgical trauma and complications, and yields better cosmetic results.

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From the Departments of Surgery A (Drs Schachter, Issa, Shimonov, and Czerniak) and Nuclear Medicine (Dr Lorberboym), Edith Wolfson Medical Center, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel.

PRIMARY HYPERPARATHYROIDism is a common endocrine disorder with an annual incidence of 0.2 to 0.5 per 1000 people.[1,2] Surgical exploration by experienced endocrine surgeons, identification of 4 parathyroid glands, and resection of all diseased parathyroid tissue have evolved as the gold standard in the treatment of this disease.[3] Because about 90% of patients have a solitary parathyroid adenoma, a simpler operative procedure would be desirable. The advent of improved localizing studies like high-resolution ultrasonography and particularly technetium Tc 99m sestamibi (MIBI) scintigraphy has permitted unilateral exploration or even localized, focused parathyroidectomies.[4-9] Intraoperative nuclear scanning and measurement of parathyroid hormone (PTH) levels with a quick PTH assay constitute a valid method for assuring complete removal of diseased parathyroid tissue.[10-19] Although preoperative localizing studies and intraoperative validation tests add to the cost of the procedure,[20] limited radioguided surgery can significantly reduce operation time and total cost. This technique enables direct approach through a minimal incision, instant feedback during the progress of the operation, and validation of any excised tissue.[21] Furthermore, the intraoperative gamma probe technique has been shown to minimize surgical trauma and complications and achieve better cosmetic results.[4] The routine use of MIBI scintigraphy–single-photon emission computed tomography (MIBI-SPECT) before initial surgery is still controversial. The purpose of our study is to compare the diagnostic value of early, postinjection SPECT with planar parathyroid imaging in patients with primary hyperparathyroidism and to consider using early, postinjection SPECT as the only preoperative localizing study.

METHODS

The study cohort consisted of 82 consecutive patients with primary hyperparathyroidism (54

Serum Calcium (Ca) and Parathyroid Hormone (PTH) Levels

	PTH,* pg/mL	Ca, mg/dL†		
		1	2	3
Mean	180.2	11.6	9.4	9.25
Range	72-400	10-17	8-11.4	8-11.2

SI conversion factors: To convert calcium to millimoles per liter, multiply by 0.25; PTH to picomoles per liter, 0.1053.

*These are for the PTH levels before surgery (normal, 10.65 pg/mL).

†Ca 1 indicates serum levels before surgery (normal, 8.5-10.3 mg/dL); Ca 2, serum levels 8 hours after surgery; and Ca 3, serum levels 24 hours after surgery.

women and 28 men; mean age, 63.5 years; range, 18-84 years) who had parathyroid surgery by 1 surgeon during a 26-month period. Serum calcium levels were obtained before surgery and 8 and 24 hours after surgery (**Table**). Intact serum PTH levels and urinary calcium output levels (24 hours) were available for all patients prior to surgery. Most patients underwent a localizing study, ultrasonography, and/or planar scintigraphy performed as part of the endocrinologist's workup.

SCINTIGRAPHY

All patients underwent planar and SPECT parathyroid scintigraphy 2 to 5 days before surgery on an outpatient basis. Anterior 10-minutes planar images of the neck and chest were acquired at 10 minutes and 120 minutes after the intravenous injection of 740 MBq of MIBI using a gamma camera with a large field of view that was equipped with a parallel-hole collimator. Immediately after the first planar image, a SPECT study was performed using 60 projections of 30 seconds each in a 180° anterior arc from the right lateral to 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 at full width, half maximum. In addition, a dual-isotope technique was performed using a delayed (120 minutes) 10-minute image after the injection of 370 MBq of Tc 99m pertechnetate. The thyroid counts in the pertechnetate image were normalized to those in the MIBI image and subtracted from the corresponding early MIBI image. On the morning of surgery, each patient underwent reinjection with 740 MBq of MIBI for intraoperative localization and validation. A SPECT study, as previously described, was performed prior to sending the patient to the operating room for comparison.

INTERPRETATION

The SPECT study was compared with the planar dual-phase technique (prolonged MIBI retention) and double-tracer subtraction technique (computer-generated subtraction image). A distinct focus of increased or separate 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 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, right thyroid lobe, and region of maximal thyroid gland activity. A count ratio of parathyroid to thyroid was determined using the mean counts in each region of interest (parathyroid left, parathyroid right, and parathyroid maximum for the left thyroid lobe, right thyroid lobe, and maximum thyroid activity, respectively).

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 medial part of the carotid sheath. The gamma detection device guided the dissection of the parathyroid adenoma.

In instances of concomitant thyroid disease, recurrent hyperparathyroidism, or more than 1 parathyroid adenoma, standard neck exploration was performed through a collar incision. A midline incision in the fascia and the lateral retraction of the strap muscles exposed the thyroid gland. The gamma probe was used to identify all "hot" parathyroid glands prior to excision of the enlarged one(s). Frozen sections were obtained for glands with an equivocal appearance.

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

STATISTICAL ANALYSIS

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

RESULTS

Minimally invasive radioguided parathyroidectomy was performed in 52 patients, including 4 patients with recurrent hyperparathyroidism. Three patients were converted to formal neck exploration because of small adenomas that were not "convincing" enough clinically and/or after frozen section examination. Conventional neck exploration was performed in 30 patients: 21 patients who needed surgery for concomitant thyroid disease, 4 patients with 2 adenomas demonstrated before surgery, and 5 patients with persistent primary hyperparathyroidism following previous neck exploration (1 patient with parathyroid hyperplasia).

Among the 82 patients, planar scintigraphy using delayed imaging and the dual-isotope technique correctly identified 64 adenomas (78%). These adenomas were also correctly identified with SPECT, providing further 3-dimensional information for the surgeon. Additionally, 15 more adenomas were identified with SPECT for a sensitivity of 96%. The SPECT study was superior to planar imaging in 10 patients with multinodular goiter (MNG), 3 patients with ectopic adenomas, and 2 pa-

tients with 2 adenomas each. **Figure 1** and **Figure 2** show planar MIBI and SPECT images of a patient with concomitant MNG. Ectopic adenomas were identified in 6 patients (7%), and MNG was present in 21 patients (26%). Interestingly, gland size did not significantly affect the detectability of the SPECT study compared with planar imaging, although the smallest adenoma (170 mg) was missed with planar imaging. The MIBI retention was noted in only 49 adenomas (60%), whereas the remaining adenomas demonstrated a rapid washout.

The mean±SD uptake ratios of parathyroid counts for the left thyroid lobe, right thyroid 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=0.41; P=.04). Otherwise, no significant correlation was found between parathyroid activity ratios and any of the blood chemistry or clinical variables.

The mean adenoma weight was 1.14 g (range, 0.17-6.0 g). There was no correlation between gland size and parathyroid uptake. Only 4 of 82 patients had transient symptoms of hypocalcemia following surgery. As expected, clinical symptoms following surgery showed a significant inverse association with calcium levels after surgery (r=–0.4; P=.03). Five patients (4 from the bilateral exploration group and 1 from the focused parathyroidectomy group) experienced symptomatic postoperative hypocalcemia and required oral treatment for 1 to 2 weeks. No laryngeal nerve injuries were encountered. No recurrent or persistent hyperparathyroidism was reported during a follow-up period of at least 6 months.

COMMENT

Surgical treatment by an experienced endocrine surgeon can cure primary hyperparathyroidism in most patients (up to 98% of cases) without the aid of any preoperative imaging.[22] The surgical approach varies between bilateral neck exploration, unilateral neck exploration, and radioguided, focused parathyroidectomy. The pros and cons of each procedure are still widely debated; success rates, operative time, complications, cost, and cosmetic results are all considered. Our experience reveals that a patient-tailored approach should be adopted, taking into consideration the educated patient's choice regarding his or her preferred surgical procedure.

Because a solitary parathyroid adenoma is the most frequent cause of primary hyperparathyroidism (80%-90%), bilateral neck exploration seems an overtreatment in most cases. A wide exploration distorts the normal anatomy of the neck, carries a higher rate of complications,[23] and has a poorer cosmetic result.[24] In accordance with the criteria proposed by Sidhu et al,[25] bilateral neck exploration is indicated when (1) there is no preoperative localization; (2) concomitant thyroid abnormalities are present; (3) parathyroid hyperplasia is suspected; and (4) patients have more than 1 parathyroid adenoma. Unilateral neck exploration and in particular focused parathyroidectomy are dependent on reliable, accurate preoperative and intraoperative localization and validation.

Figure 1. Early MIBI planar imaging shows a large multinodular goiter with increased activity in the enlarged left thyroid lobe.

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 MIBI trapping.[26,27] Planar MIBI parathyroid imaging is associated with a large number of equivocal or false-negative study results.[28,29] In our study, planar imaging identified only 78% of the adenomas. A major limitation is related to the presence of thyroid nodules that often have high MIBI avidity and can therefore mimic a parathyroid lesion, yielding false-positive scintigraphic results, particularly when using the dual-phase MIBI technique.[30] Several authors have reported various effects of thyroid abnormalities on the sensitivity of the scan,[30-32] discouraging the use of preoperative MIBI-SPECT and the intraoperative gamma probe technique in patients with concomitant MNG.[33] Our series included a relatively high proportion of patients (26%) with concomitant MNG. Whereas MNG lowered the sensitivity of planar imaging in our patients, it did not affect the high sensitivity of SPECT. This discrepancy is explained by the fact that most adenomas were posterior to the thyroid gland and therefore difficult to identify with planar imaging. Although oblique views have been advocated for parathyroid adenomas superimposed on the thyroid (behind the thyroid lobe), this technique is not efficient in demonstrating an intrathyroid parathyroid adenoma. Despite the relative accuracy of planar parathyroid imaging, intrathyroid adenomas with low MIBI uptake, ectopic adenomas, and double adenomas may be overlooked. More important, depth information and a 3-dimensional image of the adenoma are lacking with this technique, a crucial factor for the surgeon in planning and performing limited surgery.

A small number of oxyphil cells in some adenomas may account for rapid washout of MIBI from the adenoma. Thus, delayed imaging may be nondiagnostic

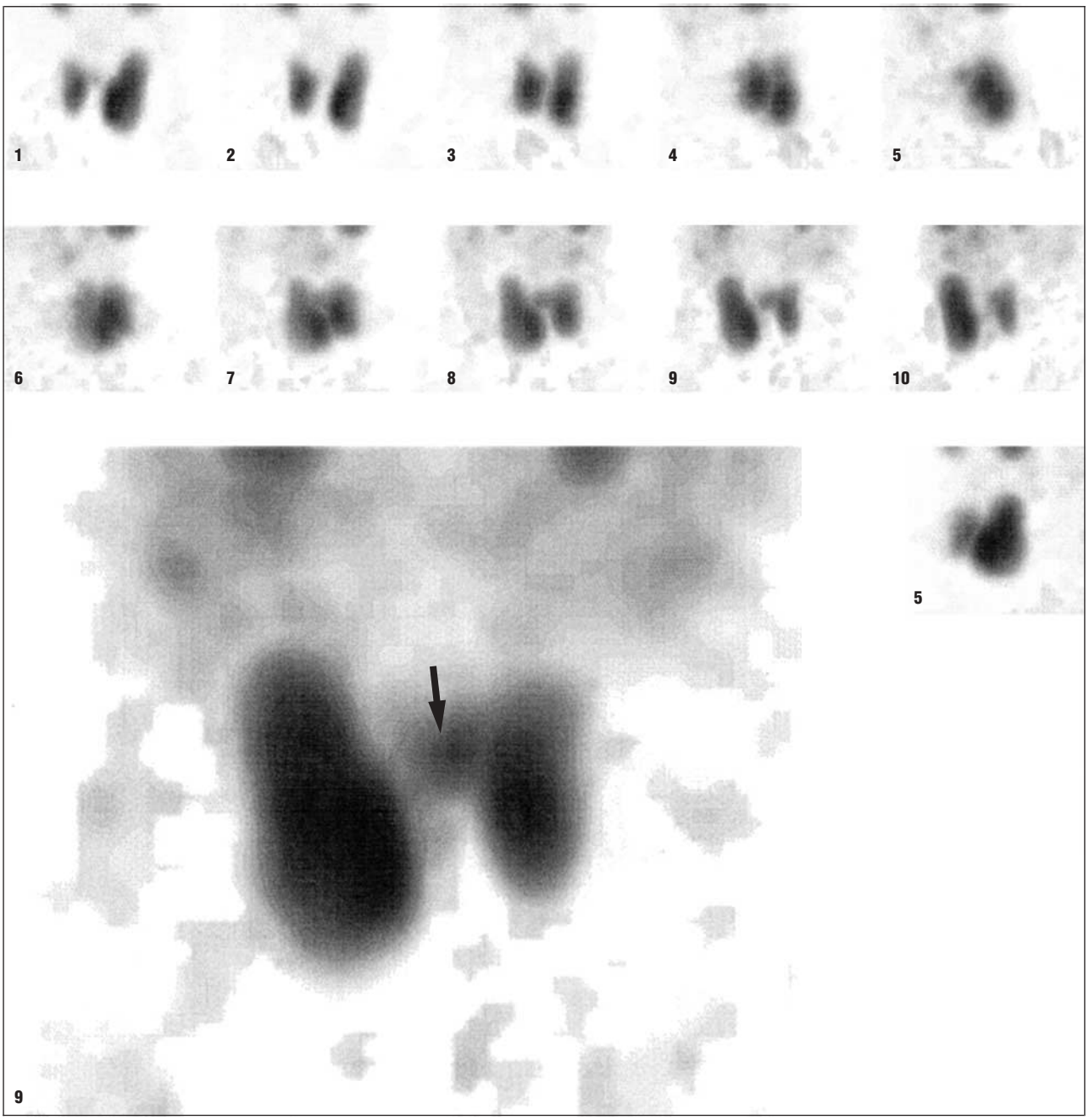

Figure 2. Three-dimensional volume–rendered images from the same patient show a small parathyroid adenoma attached to the posterior aspect of the right upper thyroid lobe (arrow).

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 on the morning of surgery was most useful for localizing parathyroid adenomas and was superior to delayed dual-phase imaging. Delayed SPECT is not recommended because it may cause unnecessary delay in surgery and yield false-negative results due to rapid washout.

The weight of the adenoma had no significant effect on the higher sensitivity of SPECT in our study, although Takebayashi et al[34] used semiquantitative analysis with planar imaging (including only 9 parathyroid adenomas) and found a greater ratio of parathyroid to thyroid counts in larger glands. The use of quantification analysis in our study showed that high PTH levels before surgery predicted significantly higher uptake of 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 more from radioguided surgery.

Intraoperative quick PTH assay has gained wide acceptance as a validation of the success of localized surgical procedures. However, recent studies reveal limited additive value (about 2%) at the cost of performing unnecessary general explorations in about 13% of patients who have been cured by the local procedure.[35] It also adds significantly to operating time and cost.

Our data encourage the use of preoperative MIBI-SPECT as the only localizing study on the morning of the operation, not only to select patients who are candidates for minimally invasive radio-guided surgery[33] but also to provide accurate 3-dimensional information on deeply seated or ectopic adenomas. This approach lowers the costs of preoperative localization and intraoperative validation to a single study. The intraoperative gamma probe technique enables the surgeon to focus the search, provides instant feedback regarding the progress of the operation, reduces surgical trauma and complications, and yields better cosmetic results.

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Corresponding author: Pinhas P. Schachter, MD, Department of Surgery A, Edith Wolfson Medical Center, Holon 58100, Israel (e-mail: pini_sc@yahoo.com).

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