

Sestamibi Scans and Intraoperative Parathyroid Hormone Measurement in the Treatment of Primary Hyperparathyroidism

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Objective: To assess the value of preoperative sestamibi scanning and intraoperative parathyroid hormone (IOPTH) measurement in the treatment of patients with primary hyperparathyroidism due to multiple gland disease (MGD).

Design: Retrospective medical record review.

Setting: Tertiary care academic medical center.

Patients: The study population comprised 383 consecutive patients who underwent surgery for primary hyperparathyroidism at Long Island Jewish Medical Center, New Hyde Park, NY, between June 1, 1999, and January 31, 2002.

Interventions: Sestamibi scanning, IOPTH measurement, bilateral parathyroid exploration, and minimally invasive parathyroid surgery.

Main Outcome Measures: Rate of postoperative persistent hyperparathyroidism.

Results: A total of 376 patients met the requirements for inclusion in the study. There were 275 women (73%) and 101 men (27%). Of the patients, 325 (86%) had single adenomas, 28 (7%) had double adenomas, 16 (4%) had 3 or more abnormal glands, and 1 had parathyroid cancer. There were 9 cases (2%) of persistent or recurrent hypercalcemia after surgery. Duration of follow-up ranged from 1 to 37 (median, 7) months. The sensitivity of sestamibi scanning for detecting MGD was 23%, and the positive predictive value was 63%. Using the requirement that the IOPTH level fall by 50% from the first baseline and into the normal range, MGD was distinguished from solitary adenoma in 36 (88%) of 41 cases.

Conclusions: The combination of preoperative sestamibi scanning and IOPTH measurement is effective in identifying cases of MGD and allows successful minimally invasive parathyroidectomy in most patients.

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IN THE LAST DECADE THERE HAS been a major change in surgery for primary hyperparathyroidism (PHPTH). Bilateral exploration (B/L) with identification of all parathyroid glands has been the standard operation with success rates of 95% or more.¹⁻⁵ Minimally invasive parathyroidectomy (MIP) in which only the single, abnormal parathyroid is identified and excised, with no attempt to visualize the remaining glands, is becoming increasingly popular.⁶⁻⁹

Parathyroid scanning with technetium Tc 99m sestamibi was introduced in 1989 and has become the standard preoperative imaging modality for patients with PHPTH.¹⁰⁻¹² The sensitivity of sestamibi scanning is reported to be 87% for the detection of single adenomas but only 55% for detection of multiple gland disease (MGD).¹¹ The intraoperative mea-

surement of parathyroid hormone (PTH) was introduced in 1988 and has been used to confirm complete removal of hyperfunctioning parathyroid tissue at surgical exploration for hyperparathyroidism.^{6-9,13,14} It has been proposed that complete removal of abnormal parathyroid tissue can be accurately predicted by a 50% decrease in intraoperative PTH (IOPTH) levels.¹⁴ Using preoperative localization and IOPTH measurement, many surgeons are performing MIP with results comparable with B/L.⁶⁻⁹

The ability of these studies, alone or in combination, to accurately distinguish single from MGD is a source of controversy.¹⁵ As MIP gains popularity, preoperative identification of those patients with MGD becomes more important. This study was undertaken to evaluate the use of sestamibi scanning and IOPTH measurement in the surgical management of

Table 1. Comparison of Sestamibi Scanning Results With Surgical Findings in 376 Patients Operated on for PPHTH

Sestamibi Scanning Results*	No. of Patients	Surgical Findings†		
		Negative	Single	Multiple
No scan	1	0	1	0
Negative	2	1	1	0
Equivocal	30	2	20	8
Single	294	2	275	17
Single-?-double	33	1	23	9
Multiple	16	0	6	10
Total	376	6	326	44

Abbreviation: PPHTH, primary hyperparathyroidism.

*Definitions: negative, no abnormal uptake identified; equivocal, a suggestion of ≥ 1 foci of abnormal uptake but not clearly identified; single, a clearly identified focus of abnormal uptake; single-?-double, 1 clearly identified focus of abnormal uptake and 1 less definitive suggestion of another; multiple, multiple clear foci of abnormal uptake.

†Definitions: single, 1 abnormal hypercellular parathyroid; multiple, >1 abnormal hypercellular parathyroid.

PPHTH, particularly as they are applied to those patients with MGD.

METHODS

This study is a retrospective medical record review of 383 consecutive patients who underwent surgery for PPHTH at Long Island Jewish Medical Center, New Hyde Park, NY, between June 1, 1999, and January 31, 2002. Patients were excluded if they had familial hyperparathyroidism, any of the multiple endocrine neoplasia syndromes, recurrent or persistent hyperparathyroidism after previous parathyroid surgery, evidence of renal insufficiency, or inadequate follow-up. The remaining 376 patients make up the subjects of this study. Each operation was performed by 1 of 3 attending surgeons. The following data were collected: age at time of surgery, sex, preoperative and postoperative calcium and PTH levels, sestamibi scan results, IOPTH data, type of operation, surgical findings, and histopathologic results.

Preoperative sestamibi scanning was performed at the Long Island Jewish Medical Center on 375 of the 376 patients. The following protocol was used for sestamibi imaging: patients were injected with 25 to 30 mCi (925-1110 MBq) of technetium Tc 99m sestamibi. Early, late, and 3-dimensional single-photon emission computed tomographic images were obtained. Patients were also injected with 5 mCi (185 MBq) of technetium Tc 99m pertechnetate for thyroid imaging. The early and late sestamibi images and the thyroid images were background subtracted and normalized. The thyroid image was then subtracted from the late sestamibi image.

Scan results were categorized as follows: "negative" indicates that there was no abnormal uptake identified; "single," that a single focus of abnormal uptake was definitively identified; "multiple," that more than 1 focus of abnormal uptake was definitively identified; "equivocal," that a suggestion of 1 or more foci of abnormal uptake were seen but not conclusively demonstrating a hyperfunctioning parathyroid; and "single-?-double," that there was a single definite focus of abnormal uptake identified and 1 less definitive suggestion of another.

The sensitivity and positive predictive value (PPV) of the sestamibi scan for detection of MGD were calculated using the following definitions and formulas. True positives (TP) are cases in which the scan reports MGD and MGD is found at surgery. False positives (FP) are cases in which the scan reports MGD and MGD is not found at surgery. False negatives (FN) are cases

in which the scan does not report MGD but MGD is found at surgery.

$$(1) \quad \text{Sensitivity} = \text{TP}/(\text{TP} + \text{FN})$$

$$(2) \quad \text{PPV} = \text{TP}/(\text{TP} + \text{FP})$$

The QuiCK-IntraOperative Intact PTH Assay (Nichols Institute Diagnostics, San Juan Capistrano, Calif) was used during all procedures. Blood samples were drawn either from an indwelling intravenous or a radial arterial catheter. Samples were taken at the following times: at baseline 1 (before skin incision or induction of anesthesia); at baseline 2 (preexcision after identification but before removal of an abnormal gland); at 5 and 10 minutes after gland excision; and at variable intervals thereafter. In cases of MGD, samples were generally drawn at 10-minute intervals after each gland was excised.

The operations performed are grouped into 3 categories. Minimally invasive parathyroidectomy is performed through a small incision over the single abnormal gland that is exposed and excised. No attempt is made to identify additional glands. In unilateral explorations (UNI), both glands on the explored side are identified. Bilateral exploration is the traditional bilateral cervical parathyroid exploration, attempting to identify all 4 glands. Specimens were judged by the pathologists to be abnormal based on gross and histological criteria including weight, cellularity, fat depletion, and morphology.

In general, MIP was only attempted on those patients with a single well-localized focus of abnormal uptake on the preoperative sestamibi scan. Patients with more than 1 focus of uptake on preoperative imaging generally underwent B/L, even if the second focus was equivocal. Conversion from MIP to UNI or B/L was required when there was failure to identify the abnormal gland or when the IOPTH level did not decrease appropriately. A decrease in IOPTH level by 50% from baseline 1 and into the normal range (<65 pg/mL) was used to indicate successful removal of all abnormal parathyroid tissue.

RESULTS

There were 275 women (73%) and 101 men (27%), ranging in age from 15 to 89 (median, 58) years. Of these patients, 325 (86%) had single adenomas, 28 (7%) had double adenomas, 16 (4%) had 3 or more abnormal glands, and 1 had parathyroid cancer. There were 6 cases (2%) in which no abnormal parathyroid tissue was identified.

Of the 376 patients, 249 (66%) underwent MIP, 40 (11%) underwent UNI, and 87 (23%) underwent B/L. Thirty-three cases (12%) that were begun as MIP were converted to B/L because of failure of the IOPTH level to decrease appropriately after removal of a single gland (22 cases), because of inability to identify an abnormal gland (6 cases), because of inadequate exposure caused by an enlarged thyroid (3 cases), and because a second abnormal parathyroid gland was seen (2 cases).

Duration of follow-up ranged from 1 to 37 (median, 7) months. All patients had at least 1 set of postoperative laboratory tests, usually 2 weeks after surgery. Of the 376 patients, 282 (75%) had at least 4 months of follow-up and 231 (61%) had at least 6 months of follow-up.

The results of the preoperative sestamibi scans and the subsequent findings at surgery are summarized in **Table 1**. The sensitivity for the detection of MGD was 23%, and the PPV was 63%.

Table 2. Data From Patients After Failed Parathyroid Exploration

Patient No.	Preoperative Measurements		Operation	No. of Glands Identified	IOPTH Baseline Measurements, pg/mL		Final IOPTH Measurement, pg/mL	Follow-up, mo	Most Recent Measurements	
	Calcium, mg/dL	PTH, pg/mL			1	2			Calcium, mg/dL	PTH, pg/mL
1	12.5	279	B/L	4	138	158	139	7	10.2	166
2	10.5	69	B/L	3	65	56	43	37	9.5	58
3	12.4	230	B/L	2	154	171	82	25	10.2	74
4	11.6	92	B/L	3	110	135	125	11	11.5	104
5	10.3	93	MIP	1	187	240	44	2	10.9	91
6	11.4	148	MIP	1	97	91	45	6	10.4	59
7	11.4	175	MIP	1	137	118	62	11	10.6	77
8	11	53	MIP	1	61	66	27	5	10.6	59
9	11	106	MIP	1	99	113	49	10	10.7	68

Abbreviations: B/L, bilateral exploration; IOPTH, intraoperative parathyroid hormone; MIP, minimally invasive parathyroidectomy; PTH, parathyroid hormone. SI conversion: To convert calcium to millimoles per liter, multiply by 0.25.

At surgery, 44 patients were found to have MGD, 41 of whom underwent B/L and 3 of whom underwent UNI. Of the 3 patients who underwent UNI, 2 had their procedures terminated after removal of 2 abnormal glands and satisfactory decrease in IOPTH level. The third patient had a single gland removed, and an ipsilateral hemithyroidectomy was performed for a separate indication. A second hypercellular intrathyroidal parathyroid gland was identified on the final pathologic examination.

The IOPTH data from the 41 patients with MGD who underwent B/L were analyzed to determine the ability of the assay to identify cases of MGD. An average of 3.7 glands per patient were identified. By using the IOPTH criteria for successful parathyroidectomy, MGD would have been distinguished from adenoma, on the basis of the assay alone, in 36 (88%) of 41 cases. Surgery was started as MIP and converted to B/L in 16 of these 41 cases because of failure to meet the IOPTH criteria. The remaining 25 patients had planned B/L because their scans indicated something other than a single focus of abnormal uptake.

Of the 376 patients, 9 had persistent PHPTH following surgery. The relevant data from these 9 patients is summarized in **Table 2**. Of these 9 failures, 4 underwent B/L and 5, MIP. In addition, there were 6 cases in which no abnormal parathyroid tissue was removed. All of these patients underwent B/L. Only 1 of these cases is among the 9 failures (patient 4, Table 2). The remaining 5 patients have remained eucalcemic with normal postoperative PTH levels.

COMMENT

Primary hyperparathyroidism has traditionally been treated with bilateral cervical exploration and removal of all grossly enlarged glands. This operation has a success rate of 95% to 98% and a low incidence of associated morbidity.¹⁻⁵ In approximately 85% to 92% of cases, PHPTH is caused by a single adenoma.^{1,2,16,17} Therefore, many surgeons have advocated more limited surgical approaches. In 1993, Worsey et al¹⁸ described 371 patients with PHPTH treated surgically, without preopera-

tive imaging or IOPTH measurement. They arbitrarily began their operations on the right side and terminated the procedure if a single adenoma and another normal gland was found. Unilateral exploration was possible in 125 of 371 patients, and they reported only 1 case of persistent disease in this group. However, it was not until the advent of accurate preoperative localization and IOPTH measurement that more limited approaches to parathyroid surgery became more widely accepted.⁶⁻⁹

The use of sestamibi scanning for the detection of abnormal parathyroid tissue was first introduced in 1989.¹⁰ Since that time, sestamibi scanning has become the most commonly used technique in parathyroid imaging.^{11,12} Ishibashi et al¹⁹ prospectively studied various imaging modalities in 20 patients undergoing surgery for hyperparathyroidism. They found that the sensitivity and specificity were 83% and 83% for sestamibi scanning, 78% and 40% for ultrasound, and 80% and 60% for magnetic resonance imaging. In a review of 26 case series in the literature, Pattou et al¹¹ established that the sensitivity of sestamibi scanning in the detection of single parathyroid adenomas is 87%.

The ability of any imaging modality to accurately predict MGD is much more limited. Heller et al²⁰ compared the ability of high-resolution ultrasound, thallium-201/technetium Tc 99m subtraction scintigraphy, and magnetic resonance imaging to detect MGD in 16 patients who underwent B/L for PHPTH. High-resolution ultrasound identified 28% of abnormal glands; thallium-201/technetium Tc 99m subtraction scintigraphy identified 35%; and magnetic resonance imaging identified 53%. None of the studies predicted the presence of MGD in more than 30% of these 16 patients. Sestamibi scanning is also limited in its ability to detect MGD. In a review of 19 case series in the literature, Pattou et al¹¹ established that in cases of MGD, sestamibi scanning has a sensitivity of 55%.

Our results are similar to those quoted above, demonstrating the low sensitivity of sestamibi scanning for MGD. In the 44 patients with MGD, the sestamibi scan correctly identified the presence of MGD in 23% of cases. This is less than the 55% quoted in the review by Pattou et al.¹¹ In that study, calculations were based on the num-

ber of glands detected, whereas in our study calculations are based on the number of patients with MGD. Furthermore, if scans with “single-?-double” had been combined with the “multiple” scans in the calculation, the sensitivity would have been 44%. When the sestamibi scan definitively reported MGD, MGD was found at surgery in 63% of cases.

In 1988, Nussbaum et al¹³ introduced the IOPTH assay. Subsequent work by Irvin et al¹⁴ established the parameters and criteria for using the assay to predict adequate parathyroidectomy and postoperative normocalcemia. In their review of 23 patients who were successfully operated on for PHPTH, Irvin et al¹⁴ found that after excision of all abnormal parathyroid tissue, the mean \pm SD decrease in IOPTH level was $78\% \pm 16\%$. The equipment used had a variability of 8%. Therefore, 54% ($78\% - 16\% - 8\%$) was used as the criterion to indicate a successful operation. In a later study, this was changed to 50% of either baseline 1 or baseline 2, and the assay was reported to predict postoperative normocalcemia with 94% sensitivity, 100% specificity, and 95% accuracy.²¹

The combination of preoperative sestamibi localization and IOPTH measurement has permitted MIP for PHPTH. Udelsman et al⁶ described 100 patients with PHPTH operated on with MIP as the initial approach. All patients had preoperative sestamibi scans, and IOPTH assay was used to confirm adequacy of the procedure. Five cases of MGD were detected by failure of the IOPTH level to fall appropriately. Of 100 patients, 1 was mildly hypercalcemic after surgery but with normal PTH level.

Carty et al⁹ report a similar experience with 67 patients with PHPTH treated using a unilateral approach guided by preoperative sestamibi scans and IOPTH measurement. They successfully performed unilateral surgery in 63 of 67 patients. In 3 cases, failure of the IOPTH level to decrease appropriately prompted conversion to B/L, and MGD was subsequently identified. In 1 case, the IOPTH level continued to be elevated after B/L and thus predicted persistence of disease. Carty et al⁹ required that the IOPTH level fall 50% from baseline and into the normal range (<65 pg/mL) to be satisfied that their procedure was adequate. These are essentially the same criteria used in our series.

These studies demonstrate good results with MIP, and follow-up data on these procedures is encouraging. Carneiro and Irvin²² reviewed 144 patients with PHPTH treated with MIP guided by preoperative sestamibi scan and IOPTH measurement. At 6 to 85 (mean, 27.6) months, they report recurrent or persistent disease in 2 (1%) of 144 patients.

In 85% to 92% of cases, PHPTH is caused by single adenoma and in the remaining 8% to 15%, by MGD.^{1,2,17} The results in our series are similar. Long-term success in a large series of patients treated with MIP will depend on the consistent ability to identify those patients with MGD. The limited sensitivity of sestamibi scanning in cases of MGD has been established in the literature and reproduced in the present study. This places additional importance on the ability of IOPTH measurement to detect MGD and prevent failure when both sides of the neck are not explored.

Recently, the ability of IOPTH measurement to detect occult MGD has been challenged. Gauger et al¹⁵ re-

viewed 20 cases of double adenomas identified at B/L, in which IOPTH was measured but not used to guide surgical decision making. They found that in 55% of the cases, measurement of IOPTH to indicate removal of all abnormal parathyroid tissue would have resulted in failure to detect the second adenoma. By contrast, in a smaller series, Stratmann et al²³ found that the IOPTH measurement accurately predicted the presence of MGD in 8 of 8 patients with PHPTH suspected of having a solitary adenoma on preoperative sestamibi scans.

The criterion of a 50% decrease in IOPTH level from the higher of the 2 baseline values was developed from a retrospective review of successful operations.¹⁴ Manipulation of the parathyroid glands by palpation or during exploration can cause a surge of PTH release and result in a misleading transient elevation of the IOPTH level.²⁴ It seems illogical to accept that an elevated PTH value, albeit 50% less than a previous baseline value, should be indicative of cure. Persistent elevation of IOPTH level above the normal range would intuitively seem to indicate the continued presence of abnormal parathyroid tissue in the patient. Therefore, we used the requirement that the IOPTH level decrease by 50% from baseline 1 and into the normal range for the assay (<65 pg/mL).

In our series, if the criteria of Irvin et al¹⁴ had been used, only 24 (59%) of 41 cases of MGD would have been identified. Using our criteria, MGD was distinguished from solitary adenoma in 36 (88%) of 41 cases. This is a statistically significant difference ($P=.005$ by Fisher exact test).

Of the 9 patients with persistent PHPTH, 4 underwent B/L. In patient 1, the final IOPTH level measured did not decrease below baseline 1 or into the normal range despite removal of 2 abnormal glands. The assay correctly predicted failure. In patient 2, the IOPTH level decreased but not by 50% from either baseline after removal of an abnormal gland. Failure was predicted by the assay in this case as well.

In patient 3, only 2 glands were identified despite B/L, and only 1 was clinically abnormal. In this case, the IOPTH level decreased by 50% from baseline 2 but not by 50% from baseline 1 or into the normal range. Failure would not be predicted by the criteria of Irvin et al¹⁴ but was predicted by our more stringent requirements. Patient 4 had 3 glands removed. All were normal pathologically. The IOPTH levels did not meet any criteria, and thus failure was predicted by the assay. Because these 4 patients underwent B/L, failure cannot be attributed to MIP or the IOPTH assay.

Patients 5 through 9 underwent MIP with a single gland removed. In patient 5, the IOPTH level decreased by 76.5% from baseline 1 and into the normal range; thus failure was not predicted by the assay. This patient had a second sestamibi scan that showed a lesion on the non-operated side that was not seen on the first scan. The patient underwent a second exploration with removal of a second adenoma. During this operation, the IOPTH level decreased from 137 to 7 pg/mL. The patient remains normocalcemic.

In patients 6 through 9, the IOPTH level decreased by just barely 50% from baseline 1 and into the normal range. Postoperatively, these 4 patients have been per-

sistently hypercalcemic with slowly rising PTH values. These 4 failures were not predicted by the assay. This suggests that a 50% decrease in IOPTH level may not be adequate and that a stricter requirement may be needed to detect MGD. However, if the criteria are made more sensitive, it is likely that more patients who truly have single adenomas may be subjected to unnecessary B/L.

There were 6 cases in which all parathyroid tissue removed was pathologically normal. All of these patients underwent B/L. One of these cases had persistent PHPTH (patient 4, Table 2), which was predicted by the IOPTH assay. Two patients had 3.5 glands excised, with a satisfactory fall in IOPTH level. They have remained eucalcemic after surgery. In the remaining 3 cases, review of the preoperative and postoperative laboratory data suggests that the diagnosis of PHPTH may have been incorrect.

As a result of these data, we suggest the following algorithm: when the preoperative sestamibi scan is equivocal, indicates a single focus of abnormal uptake, or a single focus with a possibility of a second, the surgical approach should be MIP. In each of these circumstances, the pathologic condition is most often found to be a solitary adenoma. The operation is converted to a B/L if the IOPTH level does not decrease by more than 50% from baseline 1 and into the normal range after removal of 1 abnormal gland. Patients whose sestamibi scans show MGD should undergo conventional B/L.

The entire series was reevaluated to predict the likely outcome if this proposed algorithm had been followed in all cases. In the 5 cases in which the IOPTH assay failed to detect MGD, 2 of the scans showed MGD and 1 showed a poorly localized lesion near the midline. These 3 cases would have undergone B/L. The remaining 2 cases would have failed because they would have undergone MIP, and abnormal parathyroid glands would have been left behind. In the 9 cases that actually failed, the outcome would presumably have been the same. However, in 4 of these 9 cases that involved B/L, failure cannot be attributed to MIP or IOPTH assay. We therefore estimate that following the above algorithm would have resulted in only 11 failed explorations (2.9%) in 376 cases, while minimizing the number of unnecessary B/Ls.

CONCLUSIONS

Preoperative sestamibi scanning and IOPTH measurement allow for successful MIP, with cure rates comparable with traditional results using B/L. The IOPTH assay provides confirmation that all hyperfunctioning parathyroid tissue has been removed. Adding the requirement that the final PTH level be lower than 65 pg/mL improved the sensitivity, allowing accurate identification of MGD in 88% of cases. However, it is clearly not a perfect tool. In many of our failures, the IOPTH level fell by just barely 50%. Further study is needed to better define the parameters that will optimize the effectiveness of IOPTH assay in guiding parathyroid surgery.

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