Preoperative Sestamibi Scanning and Surgical Findings at Bilateral, Unilateral, or Minimal Reoperation for Recurrent Hyperparathyroidism After Subtotal Parathyroidectomy in Patients With Multiple Endocrine Neoplasia Type 1

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Hypotheses: Preoperative parathyroid radioisotope scanning is of little or no value in patients with multiple endocrine neoplasia type 1 when 4 or more hypertrophied glands are present. Scanning using technetium Tc 99m sestamibi and single photon emission computed tomography will achieve a high level of sensitivity and specificity after 3 or more glands have previously been removed, justifying limited surgical reexploration.

Design: In a prospective study, the preoperative documented report of the predicted site of residual parathyroid was compared with the surgical findings in 13 patients having 19 scans and 17 reoperations.

Setting: All patients belonged to one family, previously described as Tasman family 1, and were confirmed by genetic testing as having multiple endocrine neoplasia type 1. In 10 of 13 patients, reexploration was being undertaken more than 10 years after the first operation.

Main Outcome Measures: Scanning was regarded as successful when the documented preoperative report correctly predicted the side and quadrant in which a gland was found at surgery. Surgery was regarded as successful when calcium levels decreased to or below normal levels and were maintained.

Results: All 13 scans before first reexploration were successful in identifying the location of a residual parathyroid. From a statistical viewpoint, this equates to 100% sensitivity and 92% specificity. However, despite accurate localization of 1 residual gland in every patient, 7 supernumerary glands in 4 patients and 1 parathyroid remnant in a fifth patient were not localized so that sensitivity in locating all glands in every patient was only 61%. Scans performed for persistent hypercalcemia 48 to 72 hours after reexploration in 2 patients were unsuccessful in demonstrating any residual parathyroid. Scans performed 3 months after surgery in the same 2 patients and a third patient were successful, with sensitivity and specificity of 100%. Apart from patient 11, who awaits reexploration, normocalcemia was eventually achieved in every patient, with 11 of 12 having an initial period of hypocalcemia.

Conclusions: Three months after reexploration and trimming or resection with transplant of half a gland left at first operation, sestamibi scanning achieved sensitivity and specificity of 100% in locating supernumerary parathyroids in patients with multiple endocrine neoplasia type 1 and persistent hypercalcemia. Before first reexploration, however, scans rarely provided new information, predominantly showing only the hypertrophied half-gland remnant.

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CONTemporary techniques of radioisotope localization make it possible to predict the site of most parathyroid adenomas but are reportedly rarely successful in demonstrating multiple gland disorder.1,2

In our experience, solitary adenomas are not a manifestation of multiple endocrine neoplasia type 1 (MEN 1),2 and preoperative localization studies are not indicated. The only appropriate initial management is bilateral neck dissection plus exploration of the mediastinal areas accessible through the incision, followed by subtotal parathyroidectomy or total parathyroidectomy and implantation.

There are few data on the evaluation of preoperative isotope localization in patients with MEN 1 when hyperparathyroidism recurs after removal of 3 or more glands, and this is addressed in this study.

All patients have been confirmed by genetic testing as having MEN 1. We regard this as an essential background to publication and consider that much confusion about the pathological features and outcome of hyperparathyroidism in MEN 1 has arisen from inclusion.
PATIENTS AND METHODS

The geographic location on the island of Tasmania of a large documented kindred with MEN 1 affords extensive experience of the disorder.7 Seventy-three members of one family have had 1 or more neck explorations for hyperparathyroidism in the last 16 years. One of us (J.J.S.) was present at every initial operation and, with one exception, at all reexplorations. Facilities to measure parathyroid hormone levels intraoperatively were not available.

None of the patients in this review had any form of organ imaging to attempt localization before initial surgery, and none had any other form of imaging before reexploration. In every case, 3 or more glands had been removed, usually leaving a remnant of about 25 mg in the neck. The glands involved were documented in surgery records and pathology reports, and 2 metal clips were attached to the adjacent thyroid at the margins of the preserved remnant.

Diagnosis of recurrent hyperparathyroidism was based on elevation of serum ionized calcium concentration on at least 2 occasions, with high or inappropriately normal serum parathyroid hormone levels.

Sestamibi, 800 MBq, was administered intravenously. Ten minutes after injection, a zoomed planar view of the neck and the anterior mediastinum was performed for 5 minutes using ultra–high-resolution collimation. A single photon emission computed tomographic (SPECT) study of this imaging field was performed immediately after the planar image on a triple-head gamma camera, taking 120 views using 128 matrix and total imaging time of 1600 seconds. Images were processed with filtered back projection and Butterworth filtering tailored to the image statistics. The planar and SPECT images were repeated 2 hours after radiotracer administration. Visual analysis was performed to look for areas of abnormally increased radiotracer accumulation and areas of delayed washout. Localization was regarded as successful when the preoperative scan correctly predicted not only the side of the parathyroid (regarded as successful in a previous study7) but also whether it was in the normal upper or lower position.

in some studies of data from patients with MEN 2 and from those with parathyroid adenomas coincidentally associated with other endocrine tumors. Teh et al5 previously reported that 1 female from Tasman family 1 had a parathyroid adenoma but, on genetic testing, does not have MEN 1. We have now identified an additional 4 patients in this family with hyperparathyroidism but not MEN 1. One man has a prolactinoma and hyperparathyroidism but not MEN 1.

RESULTS

The 13 patients in this study are the total number from Tasman family 1 seen with recurrent hyperparathyroidism and undergoing reoperation between July 1996 and July 1999. Patients 1 through 12 had 3½ or 4½ glands removed at the initial operation. Patient 13 had 3 glands removed.

Evidence of persistent or recurrent hyperparathyroidism has been based on ionized calcium levels rather than on total or albumin-corrected calcium levels.

The Table summarizes isotope localization, operative findings, and outcome for 19 scans and 17 reoperations in 13 patients.

The numbers are small, and some patients had additional complex problems that affected the timing of surgery. So that the basis of management and choice of limited or comprehensive reexplanation is apparent, these require more detailed presentation.

In 11 patients, results of isotope scanning coincided with operative records in showing parathyroid tissue at the known site of the remnant from the first operation.

INITIAL BILATERAL REEXPLORATION
(PATIENTS 1 THROUGH 6)

In patient 1, isotope scanning localized a parathyroid on the left side from which 2 glands had been removed completely but did not show any parathyroid tissue on the right side, where 1½ glands had been removed and a remnant left behind. Bilateral neck exploration revealed a supernumerary gland on the left side that was markedly larger than the remnant still present and viable on the right side.

Bilateral neck exploration was also performed on patients 2 through 6. In patients 2, 3, and 4, surgery revealed no evidence of supernumerary glands, and removal of the remnant resulted in a successful outcome.

Patient 5 had initial parathyroidectomy at age 15 years and recurrent hypercalcemia with renal calculi at age 28 years. Sestamibi scanning confirmed a hypertrophied remnant at the left inferior position that was removed at surgery together with a fifth gland not demonstrated by the isotope. Calcium levels normalized transiently, but by 72 hours after surgery she was again hypercalcemic and another sestamibi scan showed no evidence of additional parathyroid tissue. The neck wound was reopened and explored together with the mediastinum, and a tiny sixth gland was removed, but hypercalcemia persisted.

Three months later, a third sestamibi scan now showed a seventh gland. Through a small incision using a directional isotope probe, the gland was located in a few minutes and removed with successful response.

Patient 6 had a similar course to patient 5, but, on this occasion, when bilateral exploration and removal of a hypertrophied remnant and 1 supernumerary gland was unsuccessful and another sestamibi scan was negative, the patient was not immediately reexplored. Three months later, a third sestamibi scan now showed another supernumerary gland, and its removal through a limited incision using a directional isotope probe had a successful outcome.
The sestamibi scan of patient 12 demonstrated a large lesion in the right lower lobe of the thyroid, where a parathyroid remnant had been preserved. Surgery revealed a 2.5-cm diameter follicular adenoma of the thyroid with an adjacent parathyroid remnant less than 5 mm in diameter. It is not possible to say if the isotope had shown both lesions or only the large thyroid adenoma. In patient 13, isotope scan correctly located a missed fourth gland after removal of 3 glands at first exploration.

The addition of SPECT imaging to sestamibi scanning has been reported\(^3\) to be associated with significantly improved results and was routine throughout this series.

In a recently published series\(^4\) in which SPECT was rarely used, 4 of 12 patients with multiple parathyroid gland enlargement had negative preoperative scans. In 8 patients, the scans were judged successful in that they predicted the side (although not necessarily the quadrant) in which 1 enlarged gland was found.

In our study, a residual gland or remnant was accurately located not only in terms of side but also correct quadrant in 13 of 13 patients before first reexploration, with probably one false-positive localization of an immediately adjacent follicular thyroid adenoma.

However, 5 of 13 patients were ultimately found to have 8 additional parathyroids that were not localized. In purely statistical terms, scanning that correctly located a lesion in every patient achieved sensitivity of 100% and specificity of 92%, but only 68% of all parathyroid glands present were displayed, and all glands present were located in only 8 (61%) of 13 patients. Moreover, scanning for first reoperation was only moderately valuable in that it demonstrated an unsuspected supernumerary gland only in patient 1 and a previously unlocated gland.

### Parathyroid Glands Predicted by Scan and Found by Surgery

<table>
<thead>
<tr>
<th>Patient No./Age, y</th>
<th>Site Predicted by Scan</th>
<th>Operation</th>
<th>Number</th>
<th>Area</th>
<th>Glands Found</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left inferior</td>
<td>1/39</td>
<td>Bilateral</td>
<td>2nd</td>
<td>Left inferior (5th), right superior (remnant)</td>
<td>Success</td>
<td></td>
</tr>
<tr>
<td>Right inferior</td>
<td>2/54</td>
<td>Bilateral</td>
<td>2nd</td>
<td>Left inferior (remnant)</td>
<td>Success</td>
<td></td>
</tr>
<tr>
<td>Right inferior</td>
<td>3/58</td>
<td>Bilateral</td>
<td>2nd</td>
<td>Left inferior (remnant)</td>
<td>Success</td>
<td></td>
</tr>
<tr>
<td>Left superior</td>
<td>4/46</td>
<td>Bilateral</td>
<td>2nd</td>
<td>Left superior (remnant)</td>
<td>Success</td>
<td></td>
</tr>
<tr>
<td>Left inferior</td>
<td>5/28</td>
<td>Bilateral</td>
<td>2nd</td>
<td>Left inferior (remnant), right superior (5th)</td>
<td>Failed</td>
<td></td>
</tr>
<tr>
<td>None demonstrated</td>
<td></td>
<td></td>
<td>3rd</td>
<td>Bilateral plus mediastinum</td>
<td>Failed</td>
<td></td>
</tr>
<tr>
<td>Right inferior</td>
<td>6/37</td>
<td>Bilateral</td>
<td>2nd</td>
<td>Left inferior (remnant), left superior (5th)</td>
<td>Failed</td>
<td></td>
</tr>
<tr>
<td>None demonstrated*</td>
<td></td>
<td></td>
<td>3rd</td>
<td>Minimal left inferior</td>
<td>Success</td>
<td></td>
</tr>
<tr>
<td>Left inferior</td>
<td>7/58</td>
<td>Right side</td>
<td>2nd</td>
<td>Right superior (remnant)</td>
<td>Success</td>
<td></td>
</tr>
<tr>
<td>Left inferior</td>
<td>8/57</td>
<td>Right side</td>
<td>2nd</td>
<td>Right inferior (remnant)</td>
<td>Success</td>
<td></td>
</tr>
<tr>
<td>Right inferior</td>
<td>9/48</td>
<td>Right side</td>
<td>2nd</td>
<td>Right inferior (remnant)</td>
<td>Success</td>
<td></td>
</tr>
<tr>
<td>Left inferior</td>
<td>10/46</td>
<td>Minimal left inferior</td>
<td>2nd</td>
<td>Left inferior (remnant)</td>
<td>Success</td>
<td></td>
</tr>
<tr>
<td>Right inferior</td>
<td>11/40</td>
<td>Minimal right inferior</td>
<td>2nd</td>
<td>Right inferior (remnant)</td>
<td>Failed</td>
<td></td>
</tr>
<tr>
<td>Left inferior*</td>
<td>12/25</td>
<td>Right side</td>
<td>2nd</td>
<td>Right inferior (remnant), adjacent follicular thyroid adenoma</td>
<td>Success</td>
<td></td>
</tr>
<tr>
<td>Right inferior</td>
<td>13/60</td>
<td>Right side</td>
<td>2nd</td>
<td>Right inferior (4th)</td>
<td>Success</td>
<td></td>
</tr>
</tbody>
</table>

* Surgery delayed.
in patient 13. In the other 11 patients, parathyroid was predicted to be present at a site documented as the remnant preserved at previous surgery (although this information was not available to the reporting physician).

The outstanding value of scanning was found after failure of a second or third operation. Missed supernumerary glands were identified in 4 patients when scanning was performed 3 months after reoperation, and their accurate localization was confirmed in the 3 who had undergone further exploration. A hypocalcemic outcome in each case, until transplant became functional, suggested that they were the only remaining glands, giving a sensitivity and specificity of 100% in this situation.

Scanning did not show these glands before the first reoperation and in 2 of these patients when carried out immediately after surgery. It seems possible that inappropriate timing was responsible for some of the failed scans in the California series, in which many patients had been transferred to a tertiary care center after failed surgery elsewhere.

Our experience suggests that supernumerary glands are missed at first exploration not only because they are supernumerary and ectopic but because they are small. In 4 of 5 patients, at reexploration the glands were smaller than the preserved remnant. In the fifth patient, scanning showed a large supernumerary gland but not the smaller remnant. At initial explorations, fragments of one gland approximately 4 × 3 × 2 mm were left. Assuming that these fragments grow no faster than missed supernumerary glands, the latter at the time of initial surgery would have been even smaller.

Apparently preferential concentration of isotope in the largest gland might indicate functional dominance at one site. This was also apparent in a single case in which sestamibi scanning was performed in a family member before first exploration. High concentration of isotope before and after washout was obvious in a gland with a maximum diameter of 22 mm. Preoperative and even the most careful postoperative scrutiny did not detect any concentration at all in 2 other glands with maximum diameters of 15 mm or a fourth smaller but histologically equally hyperplastic gland. This graphically demonstrates the limitation of sestamibi scanning in hyperparathyroidism. All initial explorations should be performed or supervised by an experienced parathyroid surgeon however convincing the isotope study. In our opinion, this applies equally in sporadic hyperparathyroidism, in which 15% of patients will have multiple adenomas or hyperplasia that might not be demonstrated by sestamibi scanning. One member of this family remained normocalcemic until her death from heart disease 2 years later after 8 glands were found and 7½ were removed at initial exploration.

The increased technical difficulties and high complication rates of reexploration of scarred neck tissue have engendered a philosophy that the ideal timing for reoperation is 48 hours after failed parathyroidectomy. This needs reappraisal following the observation that scanning was not helpful at this time, whereas, a few weeks later, residual glands were accurately localized and extracted through minimal incisions.

Of 73 patients from Tasman family 1 who had surgery in Hobart, Tasmania, Australia, 63 (86%) had 4 parathyroids, 7 (10%) had 5 parathyroids, and only 3 (4%) had more than 5 parathyroids. Eight (67%) of 12 patients with recurrence after removal of 3½ or more glands were successfully treated by removal of the known remnant plus, on one occasion, a supernumerary gland demonstrated by sestamibi scanning.

The use of minimal access or unilateral parathyroidectomy led to failure in 2 of 10 operations (patients 7 and 11) when sestamibi scanning showed only a single focus, whereas more than 1 parathyroid gland was still present. After positive scan by the technique described, surgeons can have a high level of confidence that a hyperplastic gland can be found and removed through a limited incision but not the same level of confidence that the outcome will be successful. However, surgery was also unsuccessful in 2 of 6 operations in which both sides of the neck were carefully reexplored (patients 5 and 6) and on one occasion when bilateral neck exploration and mediastinotomy were performed after a negative, early postoperative scan (patient 5).

Statistically, it could be expected that half of any supernumerary glands undetected by sestamibi scanning would be on the same side of the neck as the preserved remnant and that unilateral reexploration would be successful in more than 80% of patients. Contralateral and mediastinal exploration cannot be guaranteed to increase this to 100%, whereas our experience suggests that, despite failure at first reexploration, this figure is approachable in even the most difficult cases by repeating scanning in a few weeks’ time. If surgery is performed immediately after the scan, a directional isotope probe facilitates location through a minimal incision. We have never encountered parathyroidosis with large numbers of tiny islands of parathyroid scattered throughout the tissues in patients with MEN 1, although this has been seen in sporadic hyperplasia. The unhappy era for surgeons and patients of unsuccessful blind chest exploration is, it is hoped, ending. It would seem appropriate to discuss the comparative success rates and morbidity of limited access or comprehensive reexploration with informed patients before surgery.

CONCLUSIONS

Radioisotope scanning with sestamibi and SPECT imaging achieved 100% sensitivity and 92% specificity in localizing a single site of recurrent parathyroid hyperplasia but was unsuccessful in locating more than 1 residual gland. It does not distinguish between thyroid adenoma and parathyroid adenoma or hyperplasia.

Immediate additional scans after surgical removal of 1 localized lesion were unsuccessful in locating additional glands. Additional scans after 3 months’ delay were successful.

Most patients with MEN 1 and recurrent hypercalcemia after removal of 3½ glands have hyperplasia of the half gland preserved and no supernumerary glands.
Statistical considerations indicate that reexploration of the side of the remnant with removal or reduction of this and excision of any supernumerary tissue on that side should be successful in 80% or more of recurrences. In this series, minimal or unilateral surgery was successful in 8 of 10 operations. Exploration of both sides cannot guarantee 100% success and in this series was unsuccessful in 2 of 6 operations plus 1 in which it accompanied mediastinotomy. Phased-later (later removal of accurately targeted supernumerary glands one at a time) minimally invasive procedures based on an understanding of the limitations and appropriate timing of isotope scanning are an alternative option for discussion with informed patients before surgery.

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REFERENCES


ARCHIVES OF INTERNAL MEDICINE

Physicians’ Ethical Beliefs About Cost-Control Arrangements
Daniel P. Sulmasy, OFM, MD, PhD; M. Gregg Bloche, MD, JD; Jean M. Mitchell, PhD; Jack Hadley, PhD

Background: Although much has been written about the ethics of new methods of health care financing, little is known about the extent to which physicians experience these cost-control arrangements as ethical problems.

Method: A cross-sectional telephone survey of 1549 physicians, 8 to 17 years after residency, randomly selected from 75 US metropolitan service areas (response rate, 74.0%).

Results: Only 17.0% believed that financial incentives to limit services are ethically acceptable. Although 52.9% thought that physicians should try to abide by guidelines discouraging the use of interventions with possible but unproven benefit, only 14.5% thought such guidelines should be enforced by payers. Only 5.7% thought that it was morally acceptable for payers to discourage physicians from telling patients about their personal financial incentives, and only 9.1% found compliance with such restrictions morally acceptable. Changes in the health care system in the past 5 years were believed to have had a negative impact on their own patients’ trust in them by 50.6%, and 80.8% believed that changes in the health care system in the past decade have diminished physicians’ commitment to an ethic of undivided loyalty to patients. In multiple regression analysis, physicians who reported that the overall personal financial incentives in their practices encouraged them to reduce services were significantly more likely to have ethical objections to such incentives, to believe their own patients’ trust in them had diminished, and to believe that the ethic of undivided loyalty to patients had diminished.

Conclusions: Many of the methods now commonly used to influence medical decision making are considered ethically objectionable by most midcareer physicians. Whether their ethical disquiet about these arrangements is justified cannot be answered from these data. (2000;160:649-657)

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