Radioguided Tumorectomy in the Management of Parathyroid Adenomas

Nikoletta Sidiropoulos, MSII; John Vento, MD; Carl Malchoff, MD; Giles Whalen, MD

Hypothesis: A clearly localizing sestamibi scan predicts a successful minimally invasive radioguided parathyroidectomy that can be performed with a shorter operative time, low morbidity, and decreased duration of hospital stay.


Setting: Hospitalized care.

Patients and Methods: Parathyroidectomy was performed on 55 patients with a secure biochemical diagnosis of hyperparathyroidism and a sestamibi scan performed at the University of Connecticut Health Center. Of the 40 patients with a clearly positive sestamibi scan result, 31 underwent radioguided parathyroidectomy. The results of radioguided parathyroidectomy are compared with those of the standard bilateral exploration performed in the remaining 24 patients.

Main Outcome Measures: Ionized calcium concentration, postoperative complications, and operative time.

Results: All patients were cured of hyperparathyroidism, and no patients experienced recurrent laryngeal nerve damage. Parathyroid adenomas were found at the predicted site in all 40 patients with a clearly localizing sestamibi scan. Of the 31 patients who underwent radioguided parathyroidectomy, a single parathyroid adenoma was identified in 30 patients, and a double adenoma was found in 1 patient. Conversion to a standard procedure was necessary in 1 patient with a large adenoma. The average operating room time was 128 minutes for the radioguided procedure and 224 minutes for the standard exploration. The average incision length for radioguided parathyroidectomy was 3.3±0.7 cm.

Conclusions: A clearly localizing sestamibi scan predicts that 97% of patients can undergo a successful and safe minimally invasive radioguided parathyroidectomy that requires less operative time than the standard exploration.

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We have selectively undertaken a minimally invasive, probe-directed tumorectomy in patients with primary hyperparathyroidism and a solitary adenoma found by sestamibi scanning for whom there were no reasons to suspect multiglandular disease. We review our results and test the hypothesis that a clearly localizing sestamibi scan identifies individuals in whom minimally invasive radioguided parathyroidectomy can be performed successfully. Secondary hypotheses are that radioguided parathyroidectomy will reduce operating room time, can be performed without increased morbidity, and will shorten hospital stay.

METHODS

Sixty-five patients underwent parathyroidectomy at the University of Connecticut Health Center from January 1, 1998, to June 30, 2002. Fifty-five of these underwent sestamibi scanning at this institution and form the basis of the present study. Forty patients had a clearly positive sestamibi scan result, and 31 of these underwent minimally invasive radioguided parathyroidectomy. The remaining 24 underwent standard bilateral neck exploration. Two patients in each group underwent redo operations. The selection of the 2 groups was based on the surgeon's belief that a minimally invasive approach was feasible, the availability of the procedure, and the patient's consent to have the procedure. There were 9 patients with a clearly positive sestamibi scan result in whom a minimally invasive parathyroidectomy was not performed: in 4 patients the surgeon did not have the appropriate expertise, in 1 patient logistic obstacles precluded the procedure, in 1 patient there was a known thyroid abnormality, in 1 patient there was a positive family history that suggested multiglandular disease, and in 2 patients the delay between preoperative sestamibi injection and the operation exceeded 3 hours. In these last 2 patients, the minimally invasive procedure had been planned but was abandoned in favor of a standard approach, because after 3 hours there was no longer increased radioactivity in the parathyroid adenoma. A single surgeon (G.W.) performed 92% of all parathyroid operations during this period.

The criteria used in selecting patients to whom we would offer a minimally invasive radioguided parathyroidectomy were a secure biochemical diagnosis of primary hyperparathyroidism, a clearly localizing sestamibi scan from our institution, and absence of clinical suspicion of multiglandular disease. A secure biochemical diagnosis of primary hyperparathyroidism was defined as an elevated plasma ionized calcium concentration, a nonsuppressed plasma parathyroid hormone concentration, and urinary calcium excretion of more than 100 mg/24 h (2.50 mmol/d) or kidney stones. A clearly localizing sestamibi scan was defined as one that unequivocally identified a solitary focus of technetium Tc 99m sestamibi uptake that was clearly distinguishable from the iodine uptake into the thyroid gland. Cure of hyperparathyroidism was defined as normalization of ionized calcium on the follow-up visits to the surgeon and referring endocrinologists. All patients gave informed consent for the parathyroidectomy procedure. Patients undergoing the minimally invasive procedure understood that conversion to a standard exploration was a possibility.

The 10 additional patients who underwent parathyroidectomy during this period who were not included in this study either did not have sestamibi scans (3 patients) or had scans of varying quality from outside institutions (7 patients), which were not repeated. Nine of the 10 patients underwent a standard operation and 1 underwent a probe-directed tumorectomy. Two patients, both of whom underwent standard exploration, proved to have hyperplasia, and the other 8 patients had single adenomatous disease. The postoperative calcium was normalized in 7 of 10 of these patients, including the patient who underwent minimally invasive surgery.

Sestamibi scanning at the University of Connecticut Health Center is performed via dual simultaneous isotope acquisition and subtraction analysis (Figure). Patients ingested approximately 0.5 mCi (18.5 MBq) of sodium iodide I 123 in the capsule form and then were injected intravenously with approximately 25 mCi (925 MBq) of technetium Tc 99m sestamibi. Four images of the iodine and sestamibi uptake were obtained simultaneously. A pinhole collimator was used to obtain anterior, right anterior oblique, and left anterior oblique images. A low-energy, high-resolution parallel hole collimator was used to obtain a chest view.

Sestamibi scanning does not reliably detect and localize all multiglandular disease.9 We used sestamibi scanning for the sole purpose of correctly identifying the location of a single parathyroid adenoma in patients who had single gland disease. We defined sensitivity and specificity in these terms and not simply whether or not an abnormality was seen on the scan. A true-positive result was defined as a scan that correctly identified the location of a single adenoma when the patient subsequently proved to have a solitary adenoma. A false-negative result was defined as a scan that showed no uptake or more than one area of uptake when the patient subsequently proved to have a solitary adenoma. Conversely, a true-negative result was defined as a scan that showed no uptake or more than one area of uptake when the patient subsequently had multiglandular disease. Lastly, a false-positive result was defined as a scan that misidentified the location of a single parathyroid adenoma or a scan that misidentified the location of a single parathyroid adenoma in a patient with multiglandular disease.

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We aimed to begin the operation 1.5 to 2 hours after a preoperative injection with approximately 25 mCi (925 MBq) of technetium Tc 99m sestamibi. General anesthesia was used for most patients, although local anesthesia was used in 2 cases. Patients were positioned so that the neck was fully extended, and a collar incision was marked. Counts were taken at all 4 poles before incision. Then, a small, midline, horizontal incision was made down the strap muscles, which were split open to enter the deep visceral compartment. In one severely kyphotic individual, the incision and dissection proceeded lateral to the strap muscles. The probe was introduced and aimed toward the hottest spot, which guided blunt dissection to the parathyroid gland. A radioguided tumorectomy was performed in all patients with a review of the outpatient and inpatient medical records and re-review of the scans. The average age of the patients was 62 years (range, 37-88 years). The study group consisted of 45 women (82%) and 10 men (18%). Most patients had more than one symptom or sign (Table 1). Ninety-five percent of the patients had a secure biochemical diagnosis of primary hyperparathyroidism. In the patients who did not have a secure biochemical diagnosis, we were unable in the retrospective review to find a documented 24-hour urinary calcium value. Age, sex, preoperative ionized calcium or parathyroid hormone values, and signs and symptoms were similar in the group that underwent standard exploration and the group that underwent radioguided parathyroidectomy (Table 1).

Of the 31 patients undergoing radioguided parathyroidectomy, 30 successfully completed the procedure without conversion to a standard procedure and with cure of the hyperparathyroidism. One patient’s operation was converted to an open procedure, since the parathyroid adenoma was too large to reach through a small incision. One patient had 2 adenomas at the site of sestamibi uptake. A clearly positive sestamibi scan result predicts that a minimally invasive parathyroidectomy can be completed in 97% of patients. If the 2 patients in whom we did not perform minimally invasive radioguided parathyroidectomy because of the delay between preoperative Tc99m sestamibi injection and incision were considered conversion operations and included in this calculation, the positive predictive value of a sestamibi scan is 91%.

The minimally invasive procedure was safe. Six percent of the patients in this group and 13% of the standard group experienced transient hoarseness. No patients had recurrent laryngeal nerve injury. There were no intraoperative complications in either group.

There were 3 other benefits of minimally invasive radioguided tumorectomy compared with the standard exploration. Patients who underwent the minimally invasive procedure and did not experience any difficulties were discharged from the recovery room. The incisions made in the minimally invasive operation were shorter, averaging 3.3 ± 0.7 cm in length. Lastly, operative times were 41% shorter in minimally invasive vs standard surgery. Average minimally invasive, probe-directed operative time not including the operation that was converted to standard exploration was 75 ± 29 minutes (range, 40-180 minutes) vs 183 ± 82 minutes (range, 40-390 minutes) of standard parathyroidectomy. The average time spent in the operating room for the minimally invasive procedures vs the standard procedures was 128 minutes and 224 minutes, respectively, which is a 57% reduction in the time spent in the operating room (Table 2).

By definition, all of the patients included in this study had a preoperative sestamibi scan at our institution. A total of 73% of the scans were interpreted as suggesting a single adenoma. Five percent of the scans showed more

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**Table 1. Signs and Symptoms Associated With Primary Hyperparathyroidism in Patients Undergoing Radioguided Tumorectomy vs Standard Procedures**

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
<th>Radioguided</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>3 (10)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Renal stones</td>
<td>10 (32)</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (35)</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Decreased bone density</td>
<td>19 (61)</td>
<td>12 (50)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (32)</td>
<td>8 (33)</td>
</tr>
<tr>
<td>Depression</td>
<td>6 (19)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Nervousness</td>
<td>0 (0)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>History of ulcer disease</td>
<td>8 (28)</td>
<td>5 (21)</td>
</tr>
<tr>
<td>Cognitive complaints</td>
<td>6 (19)</td>
<td>5 (21)</td>
</tr>
<tr>
<td>Musculoskeletal complaints</td>
<td>18 (59)</td>
<td>12 (50)</td>
</tr>
</tbody>
</table>

**Table 2. Results of Minimally Invasive Radioguided Tumorectomy Compared With Standard Parathyroidectomy**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Radioguided</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conversions to standard neck exploration, %</td>
<td>3</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Normalized postoperative ionized calcium concentration, %</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Mean operating room time, min</td>
<td>128</td>
<td>224</td>
</tr>
<tr>
<td>Transient hoarseness, %</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Permanent recurrent laryngeal nerve injury, %</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Length of incision, mean ± SD, cm</td>
<td>3.3 ± 0.7</td>
<td>Standard 0.7</td>
</tr>
</tbody>
</table>
than one area of uptake, and 22% of the scans showed no uptake. In the patients with no uptake on the scan, a solitary adenoma was found 83% of the time. Overall sensitivity and specificity were 81% and 86%, respectively. In the 40 patients with a clearly positive sestamibi scan result, 39 (98%) had a single parathyroid adenoma at the site predicted by the scan. One patient had a superior parathyroid adenoma descend behind and immediately adjacent to the lower pole parathyroid that was a second smaller adenoma. Both adenomas in this patient were at the site predicted by the sestamibi scan.

Preoperative injection of technetium Tc 99m sestamibi generally occurred approximately 2 hours before the initial incision (114 ± 32 minutes). At that time, preoperative counts at the 4 pole positions correlated with the scan findings, but the counts were not necessarily dramatically higher in the target area. Timing of injection is important. Surgery was delayed more than 180 minutes following the preoperative sestamibi injection in 2 patients. Consequently, radioguided localization of the adenoma that would have otherwise, given the appropriate timing, exhibited increased radioactive counts did not occur. Although a brief attempt was made at a minimally invasive approach, these 2 cases were quickly converted to a standard procedure.

Successful use of the probe requires aiming for the hottest spot, not the hot spot, and awareness that the count increase over background counts might be subtle compared with expectations. The average bump in counts over the target area was only 20% over background, and this ranged from a low of 7% to a high of 70%. The greater the differential was, the more confidently the probe-directed dissection could proceed. The size of the difference in counts between the target area and background did not correlate with the size of the adenoma, the amount of sestamibi injected, or the time between injection and measurement.

Similarly, when the adenoma was removed, it was not usually as hot as the remaining background. Overall, the ex vivo counts were 73% of their background counts (range, 16%-280%). There were 5 cases in which the ex vivo counts were equal to or higher than the background counts. Excluding these 5 cases, the average ex vivo counts were 57% of the bed in which they resided. In all cases, successful removal of the adenoma led to all counts in the neck and operative field returning to the level of background.

Since the NIH released its consensus statement in 1990 regarding the role of gland localization technology in the management of primary hyperparathyroidism, much has changed. An experienced parathyroid surgeon continues to have an essential role in the effective treatment of this disease, but now reliable technology is available that can improve efficiency in localizing diseased glands, minimize dissection, and probably lessen patient discomfort associated with a collar incision.

The results of our study suggest that a clearly localizing sestamibi scan is a highly reliable preoperative localization tool in patients with a secure biochemical diagnosis of primary hyperparathyroidism and no other reasons to suspect multiglandular disease. A clearly positive sestamibi scan result predicts successful radioguided parathyroidectomy that is performed through a small incision with minimal dissection of tissue. Cure rates are comparable to those of standard bilateral neck exploration. In addition, there is no unexpected or increased frequency of complications, operative time is decreased, and a small incision is used.

In performing radioguided tumorectomy, we have learned 3 important lessons. First, timing is important. After the injection of technetium Tc 99m sestamibi, both the thyroid gland and the parathyroid adenoma will be hot. The counts will decrease in both with the passage of time, but they will wash out the thyroid gland faster than they do from the parathyroid adenoma. Consequently, soon after injection, no distinction can be made between the thyroid gland and the parathyroid adenoma, and later, there is no distinction because the counts will have washed out of both. In this regard, a 3-hour delay between preoperative injection and incision was too long. This was the case for 2 patients who could not undergo scheduled radioguided tumorectomy and instead had to undergo standard neck exploration because the time delay precluded localization of the adenoma with the probe. We aim for the window when more counts have washed out of the thyroid gland than the parathyroid adenoma. The second lesson is that large adenomas in difficult locations remain difficult to remove through small incisions and, therefore, prolong operative times. Our third lesson was to aim at the hottest spot and, within reason, trust the probe. The probe usually localizes where the tumor resides, even when you do not believe it. In one case, as the surgeon was attempting to localize a lower pole parathyroid adenoma, he was aiming the probe toward the heart. Sestamibi is avidly taken up by the myocardium, and since the probe was aimed in that direction and had identified a large dark blue structure as the hot spot, the surgeon dismissed the structure as the jugular vein. A long search for the adenoma ensued before attention was returned to the large, hot blue structure. It was dissected out and proved to be a large parathyroid cyst.

Usually in the minimally invasive radioguided approach, a small incision is made and the surgeon searches for and finds the adenoma in the area indicated by the scan. There have been several other cases in which the probe has proved to be extremely useful. In one instance, an intrathyroidal parathyroid adenoma was discovered immediately as opposed to a default finding after a prolonged negative search, thus minimizing the extent of dissection. Another reassuring moment was the demonstration that the adenoma had not been removed from behind a slightly abnormal gland that had already been removed. In this case, a potentially failed operation was prevented.

We are not suggesting that the probe should be a substitute for a reasonably experienced parathyroid surgeon. It is merely a useful tool to help guide dissection down to a preoperatively localized adenoma. By using it as such, the extent of neck dissection is minimized and the operative times are halved. We are also not suggest-
ing that our data demonstrate superiority of a probe-directed dissection over bilateral neck exploration in curing the patient. Our 2 groups were not randomized. Rather, the patients in whom the probe was used were selected for a high likelihood of success with the technology. The greatest risk of this approach is the possibility that multiglandular disease would be missed at the initial operation. In this study, we attempted to minimize this risk by patient selection and skeptical review of the sestamibi scan.

Our conclusion that we did not miss multiglandular disease in the patients who underwent radioguided tumorectomy was based on postoperative calcium values. We did not use a rapid intraoperative parathyroid hormone assay to conclude that we did not miss multiglandular disease because it was not available at our institution. We believe that it would be a useful additional tool and that it would further minimize the chance of missing multiglandular disease. However, there are extra costs associated with the rapid intraoperative parathyroid hormone assay, albeit ones that are decreasing. We have calculated that the consequences of missing multiglandular disease during minimally invasive, probe-directed surgery do not carry the same increased risk of reoperation as after standard bilateral neck exploration. In a patient who previously underwent radioguided parathyroidectomy, a redo operation should mostly involve undisturbed tissue planes.

The NIH consensus statement of 1990 concluded that there was no cost benefit of preoperative localization studies in the management of primary hyperparathyroidism. Denham and Norman performed a meta-analysis to analyze cost and found that if a minimally invasive approach was used in only 51% of the patients scanned, money will be saved. In our study, scanning revealed single adenomatous disease in 73% of patients scanned, with a true-positive value of 98%. Radioguided tumorectomy was performed on 78% of these patients. This is consistent with the conclusions of Denham and Norman and suggests that there may be a decrease in the overall cost of parathyroid surgery associated with preoperative localization with sestamibi and a probe-directed, minimally invasive dissection.

In the hands of a competent parathyroid surgeon, the use of sestamibi scanning and radioguided parathyroidectomy in appropriately selected patients is a useful technique. We have applied this technique in selected patients and achieved success comparable to what we achieved with contemporaneously performed standard neck exploration. Furthermore, in using the minimally invasive radioguided approach, we essentially halve the operating time, decrease the length of incision, and discharge patients from the recovery room. We conclude that minimally invasive radioguided parathyroidectomy is a safe and effective technique in patients with a secure biochemical diagnosis of primary hyperparathyroidism and a good-quality sestamibi scan that localizes a single adenoma.

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Corresponding author and reprints: Giles Whalen, MD, Department of Surgery, University of Massachusetts Medical School, Joseph Benedict Building, Room A3-1036, Third Floor, 55 Lake Ave N, Worcester, MA 01655 (e-mail: WhalenG@ummhc.org).

REFERENCES