PAPER

The Effectiveness of Radioguided Parathyroidectomy in Patients With Negative Technetium Tc 99m–Sestamibi Scans

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Background: Many surgeons have shown that radioguided resection of parathyroid glands can facilitate intraoperative localization in selected patients with primary hyperparathyroidism, especially in the reoperative setting. However, in patients with negative technetium Tc 99m–sestamibi (hereafter referred to as "sestamibi") scans, the usefulness of the gamma probe is unclear. Thus, we were interested in determining the role of radioguided techniques in patients with primary hyperparathyroidism and negative or nonlocalizing sestamibi scans.

Design: Retrospective analysis of a prospective parathyroid database.

Setting: Academic medical center.

Patients: Seven hundred sixty-nine patients with primary hyperparathyroidism who had a sestamibi scan and underwent surgical invention by a single surgeon. All patients had radioguided parathyroidectomy using a handheld gamma probe.

Main Outcome Measures: Radioactive counts, eucalcemia rate, and complications were compared between patients with positive and patients with negative sestamibi scans.

Results: All enlarged parathyroid glands were localized with the gamma probe in patients with a negative or with a positive sestamibi scan with similar sensitivities. This occurred despite the fact that smaller parathryoid glands were present, on average, in patients with negative sestamibi scans (428 mg vs 828 mg, $P = .001$). Equivalent high postoperative eucalcemia rates (>98%) and low complication rates (0.5%) were achieved with radioguided techniques in both patient populations.

Conclusions: Radioguided techniques are equally effective in patients with negative (nonlocalizing) sestamibi scans undergoing parathyroidectomy for primary hyperparathyroidism. Moreover, use of the gamma probe led to the detection of all parathyroid glands, including ectopically located ones. These data suggest that the gamma probe has an important role for localization of parathyroid glands in patients with negative preoperative sestamibi scans.

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THE SURGICAL APPROACH FOR the treatment of primary hyperparathyroidism (1HPT) has dramatically changed over the last decade. For many years, parathyroidectomy was performed without the use of preoperative imaging or intraoperative adjuncts. In the past, surgical bilateral neck exploration with resection of enlarged parathyroid gland(s) was the standard operation performed for virtually all patients with 1HPT. This approach is associated with a greater than 95% cure rate and minimal morbidity in the hands of an experienced endocrine surgeon.[1] However, with the development of accurate preoperative imaging and intraoperative localizing technologies, focused parathyroid gland resection, often termed "minimally invasive parathyroidectomy," has become the most common method for operative management of 1HPT.[2-5] As a result, most patients who are biochemically diagnosed as having 1HPT undergo preoperative imaging with technetium Tc 99m–sestamibi (hereafter referred to as "sestamibi") scanning to localize the offending parathyroid adenoma. Sestamibi scans have been shown to detect parathyroid adenomas in approximately 70% to 80% of the cases.

Because parathyroid adenoma can generally be imaged by sestamibi scanning, surgeons have exploited this property to intraoperatively localize parathyroid adenomas using radioguided surgery.[6-9] Patients undergoing radioguided parathy-

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Table 1. Preoperative Data

Variable	Result of Technetium Tc 99m–Sestamibi Scan: Negative (n=134)	Positive (n=635)	*P* Value
Age, mean (SEM), y	60 (1)	61 (1)	.97
Sex, No. (%)			
Female	105 (78)	497 (78)	.98
Male	29 (22)	38 (22)	
Previous neck surgery, No. (%)	18 (13)	88 (14)	.75
Preoperative calcium, mean (SEM), mg/dL	11.0 (0.1)	11.2 (0.02)	.01
Preoperative intact PTH, mean (SEM), pg/mL	110 (6)	132 (4)	.01
Preoperative phosphorus, mean (SEM), mg/dL	2.9 (0.1)	2.9 (0.10)	.69

Abbreviation: PTH, parathyroid hormone.

SI conversion factors: To convert calcium to millimoles per liter, multiply by 0.25; parathyroid hormone to nanograms per liter, multiply by 1; phosphorus to millimoles per liter, multiply by 0.323.

roidectomy are injected with Tc 99m-sestamibi on the day of surgery. In the operating room, a handheld gamma probe is used to guide the operative dissection to the parathyroid adenoma, which should have higher radioactive counts than surrounding tissues. Many surgeons have shown that radioguided resection of parathyroid glands can facilitate intraoperative localization in selected patients with hyperparathyroidism (HPT), especially in the reoperative setting.[5,10,11] Nevertheless, there is conflicting information regarding the feasibility and utility of radioguided surgery in all patients with HPT. In patients with positive sestamibi scans showing a single parathyroid adenoma, it is apparent that the gamma probe would effectively detect the "hot" parathyroid gland intraoperatively since the adenoma has demonstrated its ability to take up the radiotracer. However, in patients with negative sestamibi scans, the usefulness of the gamma probe is unclear. In fact, many surgeons believe that a negative sestamibi scan suggests that the abnormal parathyroid gland must not take up sestamibi and, therefore, would not be detected with the gamma probe during surgical exploration. Thus, we were interested in determining the role of radioguided techniques in a patient with 1HPT who had a negative or nonlocalizing sestamibi scan.

METHODS

Nine hundred thirty-nine consecutive patients with HPT underwent parathyroidectomy by one of us (H.C.) at the University of Wisconsin, Madison. Of these, 828 patients had 1HPT, of which 769 underwent preoperative sestamibi scanning and form the cohort for this study. Although most patients at our institution with 1HPT have sestamibi scans preoperatively, patients with suggested multiple endocrine neoplasia type 1 or those who need standard open surgery for a concomitant procedure such as thyroidectomy generally do not undergo preoperative imaging.

All 769 patients had preoperative sestamibi scans. We routinely use radioguided techniques for all patients undergoing surgery for primary, secondary, or tertiary HPT. All patients in this series underwent radioguided surgery with an 11-mm collimated gamma probe. We have previously described our technique for radioguided parathyroidectomy.[8,12] Briefly, patients are injected with 10 mCi (to convert millicuries to becquerels, multiply by 3.7×10^{10}) of technetium Tc 99m-sestamibi 1 to 2 hours before surgery. In the operating room, background counts are obtained by placing an 11-mm collimated gamma probe (Neoprobe 2000; Ethicon Endo-Surgery Breast-Care, Cincinnati, Ohio) on the thyroid isthmus through the skin. After incision, intraoperative scanning is performed seeking radionuclide counts greater than the background counts to localize abnormal parathyroid glands. The counts obtained by scanning on the identified enlarged parathyroid gland in situ were recorded as in vivo. After excision of the enlarged parathyroid gland, the tissue is placed on top of the gamma probe (directed away from the patient) to determine ex vivo counts. Ex vivo counts are expressed as a percentage of the background counts. An ex vivo parathyroid count greater than 20% of the background count is definitive for parathyroid tissue. The estimated cost for the use of the gamma probe was calculated at less than $200. Since the institution already owns several gamma probes that are reusable, the only added expense is that of the technetium Tc 99m–sestamibi injection. During the initial establishment of the protocol for radioguided parathyroid surgery, there were occasional delays due to the timing of the technetium Tc 99m–sestamibi injection. However, we have had a solid protocol in place for more than 7 years. The circulating nurse coordinates with the preoperative area and radiology at least 30 minutes before the planned procedure to ensure that the patient has received the technetium Tc 99m–sestamibi injection. If the patient has not received the technetium Tc 99m–sestamibi injection, then there is enough time to provide the injection and maintain the scheduled operating room start time.

All data were recorded prospectively in this instutional review board–approved database. Eucalcemia was defined as a serum calcium level less than 10.2 mg/dL (to convert to millimoles per liter, multiply by 0.25) at least 6 months after surgery. Recurrence was defined as a serum calcium level exceeding 10.2 mg/dL in consecutive samples 6 months after surgery. Persistent disease was defined as a serum calcium level greater than 10.2 mg/dL within 6 months of surgery. Data were recorded as mean (SEM). Statistical analysis was performed with commercially available SPSS software (version 10.0, SPSS Inc; Chicago, Illinois) Statistical significance, as determined by analysis of variance and χ^2 tests, was defined as $P<.05$.

RESULTS

PREOPERATIVE DATA

The mean age of all 769 patients was 61 (1) year. Mean preoperative laboratory values included serum calcium levels of 11.2 (0.03) mg/dL and serum phosphorus levels of 2.9 (0.04) mg/dL (to convert phosphorus to millimoles per liter, multiply by 0.323). The mean preoperative serum intact parathyroid hormone (PTH) level was 129 (3) pg/mL (to convert PTH to nanograms per liter, multiply by 1). Of the 769 patients, 134 had negative sestamibi scans while 635 had positive sestamibi scans. We then compared the preoperative data between the patients with negative sestamibi scans with patients with positive sestamibi scans. As listed in **Table 1**, no significant differences were noted between the 2 groups in age, sex, or number of patients who had had previous

Table 2. Pathology Data

Variable	Result of Technetium Tc 99m–Sestamibi Scan: Negative (n=134)	Positive (n=635)	*P* Value
Cause, No. (%)			
Single adenoma	90 (67)	518 (82)	.01
Multiglandular disease	44 (33)	117 (18)	
Parathyroid gland weight, mean (SEM), mg	428 (35)	828 (55)	.001
Ectopic location, No, (%)	29 (22)	175 (28)	.71

neck surgery. Patients with positive sestamibi scans had higher preoperative serum calcium and PTH levels.

PATHOLOGY DATA

Overall, 608 patients (79%) had a single parathyroid adenoma as the cause of their 1HPT while the remaining 161 patients (21%) had multiglandular disease including double adenomas and hyperplasia. **Table 2** summarizes the comparison of the pathology data between the 2 groups. Not surprisingly, a patient who had a positive sestamibi scan had a higher incidence of single adenomas. The mean weight of all resected parathyroid glands was 759 (46) mg. As one would expect, patients who had a positive sestamibi scan had larger parathyroid glands (Table 2). The incidence of ectopically located parathyroid glands was similar between the 2 groups. Ectopic locations included the carotid sheath, thymus, thyroid, retroesophageal, undescended, and superior mediastinal.

INTRAOPERATIVE RADIOACTIVE COUNTS

To determine the role of the gamma probe in patients with negative sestamibi scans, we compared the radioactive counts obtained intraoperatively in both patient groups. The mean background radioactive counts from the thyroid gland in patients with negative sestamibi scans were 194 (9) which was identical to the background counts in patients with positive sestamibi scans (**Figure 1**). In both groups, the in vivo counts of the abnormal parathyroid glands were significantly higher than the background counts (Figure 1). In patients with negative sestamibi scans, the mean in vivo counts were 258 (13) while in the patients with positive sestamibi scans, the mean in vivo counts were 301 (8) ($P<.01$). Given that the in vivo counts were always higher than the background counts in both patient groups, these data illustrate that the gamma probe is equally effective in detection of hyperfunctioning parathyroid glands. We and others have demonstrated that an ex vivo count of greater than 20% of the background count is diagnostic for hyperfunctioning parathyroid tissue.[7,8] All abnormal parathyroid glands in both groups had ex vivo counts greater than 20%. However, patients with positive sestamibi scans, on average, had higher ex vivo counts than patients with negative sestamibi scans (90 [0.3] vs 47 [0.4], $P<.001$; **Figure 2**).

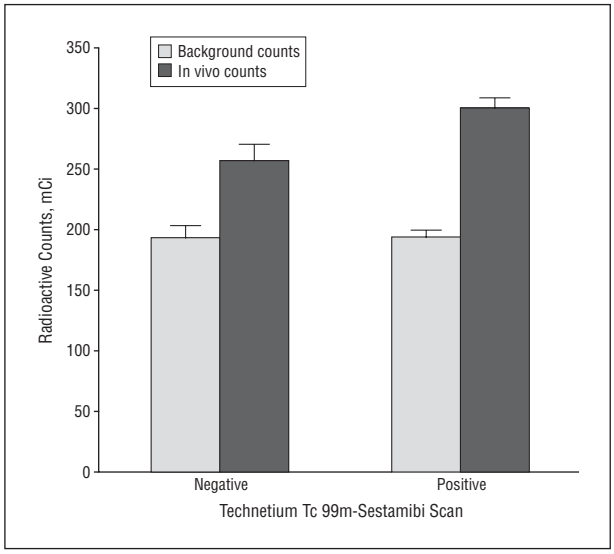

Figure 1. Background and in vivo radioactive counts in patients with technetium Tc 99m–sestamibi negative and positive scans. In both groups, the in vivo counts were significantly higher than the background counts. Values are given as mean (SEM).

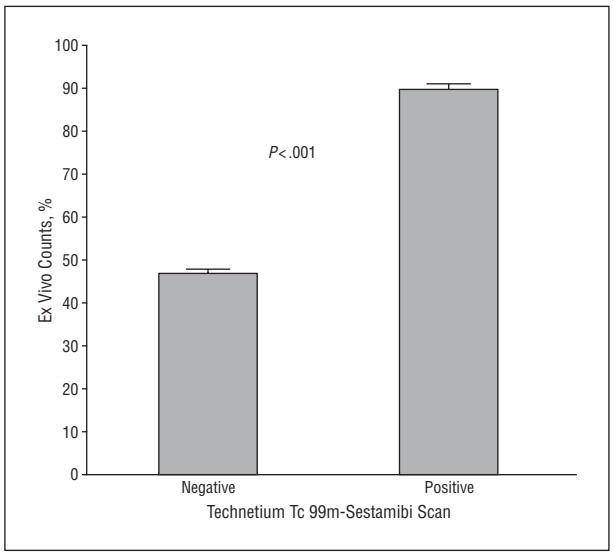

Figure 2. Ex vivo radioactive counts (expressed as a percentage of the background counts) in patients with technetium Tc 99m–sestamibi negative and positive scans. Values are given as mean (SEM).

POSTOPERATIVE OUTCOMES

Postoperative eucalcemia lasting at least 6 months was achieved in 757 of 769 patients (98%) after parathyroid surgery. These cure rates were equivalent between both patient groups (**Table 3**). The mean postoperative serum calcium and PTH levels were also similar between the 2 groups (Table 3). Only 3 patients (0.4%) experienced a major postoperative complication (ie, recurrent nerve injury [n=1], hematoma requiring operative evacuation [n=1], and cellulitis [n=1]). Seventy percent of patients were discharged from the outpatient surgery center on the day of surgery. Patients with a positive sestamibi scan had a significantly shorter hospital length of stay ($P=.01$) (Table 3) compared with patients with a negative scan.

Table 3. Postoperative Outcomes

Variable	Result of Technetium Tc 99m–Sestamibi Scan: Negative (n=134)	Positive (n=635)	*P* Value
Eucalcemia, No. (%)	133 (99)	624 (98)	.89
Postoperative calcium, mean (SEM), mg/dL	9.4 (0.1)	9.6 (0.1)	.09
Postoperative intact PTH, mean (SEM), pg/mL	44 (3)	49 (2)	.11
Major complications, No. (%)	0	3 (0.5)	.79
Hospital length of stay, mean (SEM), d	0.4 (0.03)	0.3 (0.02)	.01

Abbreviation: PTH, parathyroid hormone.
SI conversion factors: To convert calcium to millimoles per liter, multiply by 0.25; parathyroid hormone to nanograms per liter, multiply by 1.

COMMENT

Directed or minimally invasive parathyroidectomy is the most common approach for patients undergoing operative management of 1HPT.[4,13,14] Sestamibi scanning has become an important component to determine which patients with 1HPT are candidates for a focused procedure. Many intraoperative adjuncts such as intraoperative PTH testing, recurrent nerve monitoring, and radioguided techniques have been shown to facilitate minimally invasive parathyroidectomy. The role of these technologies in patients undergoing bilateral surgical exploration for 1HPT is not as well characterized.

In this article, we describe a series of patients with 1HPT undergoing radioguided parathyroidectomy. We and others have shown that radioguided resection of the parathyroid glands can facilitate intraoperative localization in selected patients with HPT.[5,6,12] Radioguided techniques provide several advantages during parathyroid surgery including facilitating parathyroid localization with in vivo counts, confirming resection of parathyroid tissue with ex vivo counts, minimizing operative dissection, and identification of ectopically located parathyroid glands even in the undescended locations and superior mediastinum.[15] These advantages have not been universally recognized.[16] In fact, there is often confusion regarding the feasibility of using radioguided technology in certain patients with HPT. In patients with positive sestamibi scans showing a single parathyroid adenoma, it is apparent that the gamma probe would effectively detect the hot parathyroid gland intraoperatively. But, in patients with negative sestamibi scans, the usefulness of the gamma probe is unclear. In fact, many surgeons believe that a negative sestamibi scan suggests that the abnormal parathyroid gland must not take up technetium Tc 99m–sestamibi and, therefore, would not be detected with the gamma probe during surgical exploration. Thus, we pursued this study to determine the role of radioguided techniques in patients with 1HPT and negative or nonlocalizing sestamibi scans.

We found that radioguided techniques are equally effective in patients with negative sestamibi scans. All enlarged parathyroid glands were localized with the gamma probe in both patients with negative and positive sestamibi scans with similar sensitivities. The in vivo counts in both patient groups were significantly higher than the background counts on the thyroid. This occurred despite the fact that smaller glands were present, on average, in patients with negative sestamibi scans (428 vs 828 mg, $P=.001$). The ex vivo counts in both patient groups were higher than greater than 20%, indicating successful resection of hyperfunctioning parathyroid tissue. Ectopic parathyroid glands were found with the gamma probe in 22% of the patients with negative sestamibi scans and 28% in the patients with positive sestamibi scans. Equivalent high postoperative eucalcemia rates (>98%) and low complication rates (0.5%) were achieved with radioguided techniques in both patient groups.

Overall sestamibi scans in this series localized single parathyroid glands in 79% of the patients. This is consistent with other articles that generally cite the sensitivity of sestamibi scanning between 65% and 85%.[5,17,18] As a result, a significant number of patients with 1HPT will have a negative sestamibi scan. These patients are more likely to have multiglandular disease and smaller hyperfunctioning parathyroid glands.[19] Therefore, operative management of this group of patients can be more challenging than those with apparent single-gland disease. Thus, technologies such as radioguided surgery have the potential to aid surgeons in these potentially difficult cases. We have shown in this research that radioguided techniques are clearly effective in patients with negative sestamibi scans.

Many other investigators have studied the factors that predict the likelihood that a patient with 1HPT will have a positive sestamibi scan showing a single parathyroid adenoma. Calva-Cerqueira et al[20] reported the outcomes of 263 patients undergoing parathyroidectomy for 1HPT. They found that a higher preoperative PTH level ($P=.003$) and heavier adenoma weight ($P<.001$) were associated with positive sestamibi scans imaging a single parathyroid adenoma. Kebebew et al[21] developed a scoring system based on a retrospective review of surgical outcomes of 238 patients who underwent parathyroidectomy. Similar to our results, Kebebew et al found that preoperative calcium and PTH levels were significantly higher in patients with a single parathyroid adenoma. The authors proposed a dichotomous scoring model based on preoperative total calcium level (>12 mg/dL), intact PTH level (>2 times the upper limit of normal levels), positive ultrasonography and sestamibi scans for 1 enlarged parathyroid gland, and concordant ultrasonography and sestamibi scans that reliably distinguished single-gland vs multiglandular cases. In our population, patients with positive sestamibi scans had higher preoperative serum calcium and PTH levels, and they also had heavier parathyroid glands than those patients with negative sestamibi scans.

In conclusion, radioguided techniques are equally effective in patients with normal sestamibi scans undergoing parathyroidectomy for 1HPT. Moreover, use of the gamma probe led to the detection of all parathyroid glands including ectopically located ones. These data suggest that the gamma probe has an important role for localization

of parathyroid glands in patients with 1HTP and negative preoperative sestamibi scans.

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DISCUSSION

Shelby Holt, Dallas, Texas: I commend you, Dr Chen, on an exemplary series. You are a leader in the field of endocrine surgery, and your results set the bar for all of us. I think you know my bias regarding the "divining rod," but having read your article and having experienced an elusive parathyroid recently, I may be willing to take it off the shelf.

That being said, I am curious why everyone is not using the probe. On the one hand we have your group's excellent cure rate with radioguided parathyroidectomy and on the other hand we have similar results from a number of groups, including Mayo [Clinic], Michigan [Ann Arbor], and Miami [Florida], who do not routinely use the probe. So, in my mind, the probe is not the key to success, and I would caution that its use does not make the occasional parathyroid surgeon as successful as you. I do not think it is making you and your group successful either, Dr Chen. Like other leaders in this field, you are successful because you have been there almost 1000 times, and you have an in-depth knowledge of parathyroid gland anatomy. My first question is: when did the gamma probe actually help you find a parathyroid gland that you would not have found otherwise?

I think that most would agree that with or without the probe, the easy cases are still easy. More important, are the hard cases still hard? One challenge we face is recognition and complete resection of multiglandular disease. Your reported incidence of multiglandular disease is higher at 21% than that reported by others who likewise routinely use preoperative imaging and intraoperative PTH level monitoring to obviate the need for full-neck surgical exploration. My second question is: how [do] you define multiglandular disease and how does the probe help you recognize it?

Last, the benefits of minimally invasive parathyroidectomy are widely publicized and, I dare say, advertised. We are always looking to maximize the number of patients who are candidates for a minimally invasive approach, and that largely centers on our localization techniques. Dissatisfied with sestamibi scanning, many groups have used anatomical imaging such as sonography and 4-dimensional computed tomography. My third question is: do you find the probe better than anatomical imaging and does the probe, in fact, allow you to do more minimally invasive parathyroidectomies since you found it worked even in patients with a negative sestamibi scan?

Dr Chen: To answer Dr Holt's first question about why more people do not use the gamma probe, I think people develop

different practice patterns for parathyroidectomy. Some use intraoperative PTH level testing, some use video-assisted techniques, and some use the gamma probe. I think it is based on how you have trained or the experience you have with each technology. I have spoken about radioguided technology during parathyroid gland surgery on different occasions. There are many surgeons who will come up to me from the back of the room and say, "Well, you know, I don't really say I use it, but I do use it once in awhile." So if you poll surgeons, you will find that surgeons will say that they use it occasionally. They may not use it for every case as we do at the University of Wisconsin.

In your second question you asked when did the probe actually help me find a parathyroid gland that I would not have found. That is a difficult question to answer because there are clearly parathyroid glands that I have not found, and the probe did not bail me out in those situations. One case comes to mind though. In this patient, I had to go back in the neck for the seventh time to take out a parathyroid gland. In that situation, the gamma probe really helped me because I do not know if I would have found the abnormal parathyroid gland without it. In Wisconsin, we have a high incidence of obesity, and I believe the probe helps in those patients.

Your third question focused on the definition of multiglandular disease. We define that as the situation when 2 or more parathyroid glands are hypersecreting based on the results of intraoperative PTH level testing. We have had some instances in which I go in, take one gland out, and I see the other gland that looks enlarged. I put the gamma probe on it, it is "hot," and then sometimes I will resect that gland based on the gamma probe reading. However, most of the time, the presence of an additional hyperfunctioning gland is based on the results of PTH level testing.

Last, you alluded to the increased number of patients who are having a focused approach and the increased use of imaging for patients with 1HTP. What is the role of the gamma probe for localization of an adenoma? In looking at our series of minimally invasive parathyroidectomies, about 87% of those cases are done based on a positive sestamibi scan. Now 2% of those patients had a negative scan, and we were able to localize a parathyroid gland with the gamma probe allowing a minimally invasive procedure. So it is uncommon that the gamma probe helps convert a normal operation to a minimally invasive [one], but it does happen.

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