Hypothesis: High-resolution ultrasound and technetium Tc 99m sestamibi scanning can be used for preoperative localization of abnormal parathyroid glands in patients with hyperparathyroidism.

Design: Ultrasound and sestamibi scanning were performed in patients undergoing neck exploration for hyperparathyroidism. If the 2 scans agreed in identifying a single adenoma, and surgery confirmed the location of a single adenoma and an ipsilateral normal gland, a unilateral exploration was performed.

Setting: University tertiary care center.


Interventions: High-resolution ultrasound was performed in 59 patients and sestamibi scanning in 58 patients; all patients underwent neck exploration by a single surgeon.

Main Outcome Measures: The results of preoperative ultrasound and sestamibi scanning were compared with operative and histological findings.

Results: All patients were cured of hypercalcemia. Specificity of ultrasound and sestamibi scanning was 98% and 99%, respectively; however, their sensitivity was only 57% and 54%, respectively. Both imaging modalities had lower sensitivities in the setting of multigland disease. If both imaging studies were considered as a single test, sensitivity for imaging in patients with primary hyperparathyroidism reached 78%. Our localization protocol allowed a unilateral approach in 43% of patients (23 of 53).

Conclusions: These results confirm the value of preoperative localization in patients with hyperparathyroidism. A unilateral approach can be used with a high degree of success in cases where ultrasound and sestamibi scanning agree in the identification of a single adenoma confirmed by surgical exploration with the identification of a normal ipsilateral gland.

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HYPERPARATHYROIDISM results from the enlargement of 1 or a number of parathyroid glands, either because of alterations in growth regulation intrinsic to the gland (primary hyperparathyroidism) or because of the metabolic consequences of physiological abnormalities extrinsic to the gland, such as renal failure (secondary hyperparathyroidism). Treatment of hyperparathyroidism involves surgical removal of abnormally enlarged parathyroid glands with restoration of a sufficient parathyroid mass to render the patient eucalcemic. The classic surgical approach involves bilateral neck exploration, identification of all 4 parathyroid glands, removal of enlarged parathyroid glands, and biopsy of normal glands to confirm identification. Although the surgical approach to primary hyperparathyroidism is usually straightforward, 15% to 20% of patients can have double adenomas or hyperplasia, which is often asymmetrical. Ectopic parathyroid glands, supernumerary glands, and previous neck exploration can further complicate surgical treatment.

The use of preoperative localization continues to be controversial. Although there is general agreement that preoperative imaging is indicated in the reoperative setting, many endocrine surgeons argue that preoperative localization for the first neck exploration is unnecessary. Others, however, have advocated the use of routine preoperative localization, arguing that it can result in a shorter operation, avoid the need for bilateral neck exploration, and identify rare patients with ectopic glands. A number of imaging modalities are currently used, including...
PATIENTS AND METHODS

PATIENTS

All patients undergoing neck exploration with a diagnosis of hyperparathyroidism between September 1, 1994, and September 30, 1997, were included in the study. We recorded each patient’s age, preoperative diagnosis (primary, secondary, or tertiary hyperparathyroidism), preoperative serum calcium level, preoperative intact parathyroid hormone (PTH) level, creatinine level, phosphate level, ionized calcium level, previous neck surgery, surgical procedure with a description of parathyroid gland location, pathologic findings, and postoperative serum calcium level. In cases with multiple laboratory serum determinations, the most recent values were used for analysis. All patients were operated on by a single surgeon (RJW).

Five patients had a history of previous neck exploration. Three patients with primary hyperparathyroidism had had previous neck surgery; 1 patient had undergone a total thyroidectomy, 1 patient had had 1 previous neck exploration for hyperparathyroidism, and 1 patient had had 2 previous unsuccessful neck explorations for hyperparathyroidism. Two patients with secondary hyperparathyroidism had had previous parathyroid surgery. One patient had undergone a 3-gland resection, with failure to find the fourth gland (subsequently found in this series as an undescended left inferior gland) and 1 patient had had a previous 3½-gland resection with enlargement of the remaining parathyroid gland remnant.

There were no operative complications, including no instances of recurrent laryngeal nerve injury, recurrent or persistent hypercalcemia, or permanent postoperative hypocalcemia. All patients with primary hyperparathyroidism had stopped taking calcium supplementation by 3 weeks after surgery and had normal serum calcium levels.

ULTRASOUND

Fifty-nine of the 61 patients underwent preoperative high-resolution sonography. Two patients who did not have preoperative ultrasound were referred with persistent hyperparathyroidism after neck exploration at another institution. Both patients had successful localization with sestamibi and magnetic resonance imaging, which confirmed the location of an ectopic gland. Both longitudinal and transverse images of the neck were obtained from the level of the angle of the mandible to the sternal notch by means of 7- to 10-MHz transducers. Parathyroid adenomas were identified on gray-scale imaging by the characteristic appearance of a hypoechogenic mass distinct from the thyroid gland. Three patients (3%) had scans performed at outside institutions; all other patients had scans performed at the Department of Radiology, Stanford University, Stanford, Calif. Thirty-nine of the 56 ultrasound studies performed at Stanford were performed by a single radiologist with expertise in parathyroid imaging (RBJ). The remaining 17 scans were performed by various members of the Radiology Department.

Correct localization or a true-positive (TP) result was the radiology report were compared with operative findings. Correct localization or a true-positive (TP) result was the identification of an abnormal parathyroid gland on the same side as reported for the imaging study. Normal glands that were not identified on imaging were considered true negative (TN). In this analysis we assumed that each patient had 4 glands. Since all patients were cured of hypercalcemia, it is likely that all abnormal glands were identified at operation.

Abnormal parathyroid glands that were not identified by an imaging technique were considered false negative (FN). Abnormalities reported by imaging that did not correspond to an abnormal parathyroid gland were considered false positive (FP). Sensitivity was calculated as TP/(TP + FN) and specificity was calculated as TN/(TN + FP). We also determined the sensitivity for combined results considering ultrasound and sestamibi as a single test. In this analysis, the results constituted a TP if either study correctly localized an abnormal gland. Abnormal parathyroid glands not imaged by either technique were recorded as FN, and all scan abnormalities that did not correspond to abnormal parathyroid glands for both tests were recorded as FP. The TNs were not recorded in this analysis because of ambiguity of the definition.

The parathyroid scintigraphic images that were obtained at Stanford University were subsequently reviewed retrospectively and compared with surgical and pathologic information to determine whether the interpretation would have changed with this information. In this later interpretation, precise localization of abnormal parathyroid glands was defined as TP, imperfect localization as FP, failure to identify as FN, and a negative finding where there was no abnormal parathyroid as TN.

PARATHYROID SCINTIGRAPHY

Most patients were injected with 370 MBq of ⁹⁹ᵐTc sestamibi. A minority received 740 MBq. Images were obtained early with serial 5-minute acquisitions for 20 to 30 minutes after the intravenous injection. The field of view extended from the level of the ears to the diaphragm, encompassing all sites where ectopic parathyroid glands might be found. Delayed images were obtained 2 to 4 hours after the injection. The distributions of sestamibi in the early and delayed images were compared. Uptake in the early phase was considered to be attributable to parathyroid as well as thyroid, and in the late phase, only parathyroid. In some patients, pinhole images were made at the time of delayed imaging. Nineteen patients had ⁹⁹ᵐTc pertechnetate scanning to superimpose an additional thyroid image for anatomical localization at the time of the delayed scan.

ANALYSIS

Results of imaging studies as determined from the official radiology report were compared with operative findings. Correct localization or a true-positive (TP) result was the identification of an abnormal parathyroid gland on the same side as reported for the imaging study. Normal glands that were not identified on imaging were considered true negative (TN). In this analysis we assumed that each patient had 4 glands. Since all patients were cured of hypercalcemia, it is likely that all abnormal glands were identified at operation.

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high-resolution ultrasound, technetium Tc ⁹⁹ᵐ (⁹⁹ᵐTc) sestamibi scanning with or without single photon emission computed tomography, magnetic resonance imaging, computed tomography, and positron emission tomography. Each of these imaging techniques has been shown to be successful for preoperative localization of abnormal parathyroid glands, with sensitivities in the range of 50% to 80%.16
To determine the value of parathyroid localization, we routinely obtained ultrasound and sestamibi scans on patients referred for parathyroid surgery at our institution. A number of studies of parathyroid imaging have demonstrated a higher success rate for ultrasound and sestamibi scans in patients with single-gland adenomas. On the basis of this finding, we developed a protocol for unilateral neck exploration. If ultrasound and sestamibi scans both identified a single adenoma and surgical exploration confirmed an abnormal gland and an ipsilateral gland with normal appearance and histological characteristics, then a unilateral neck exploration was performed. We present our results for 61 consecutive patients undergoing neck exploration with a diagnosis of hyperparathyroidism.

RESULTS

Sixty-one consecutive patients (44 women and 17 men) with a diagnosis of hyperparathyroidism underwent neck exploration. Their mean age was 53 years (range, 23-78 years). Fifty-three patients (87%) had primary hyperparathyroidism. Within this group, 44 patients (83%) had a single adenoma and 9 patients (17%) had hyperplasia or double adenomas. The average preoperative serum calcium level for patients with primary hyperparathyroidism was 2.78 mmol/L (11.1 mg/dL) (range, 2.35-3.15 mmol/L [9.4-12.6 mg/dL]), with an average preoperative intact PTH level of 17.9 pmol/L (170 pg/mL) (range, 6.2-102.9 pmol/L [59-977 pg/mL]). Eight patients in this series had secondary or tertiary hyperparathyroidism as a result of chronic renal failure. The average age of patients with secondary or tertiary hyperparathyroidism was 41 years, compared with an average age of 55 years for patients with primary hyperparathyroidism.

All patients in this series were cured of hypercalcemia. There were no cases of recurrent hypercalcemia during an average follow-up of 17 months. A normal calcium value was documented in 50 (82%) of 61 patients with follow-up of 3 months or longer and in 46 (75%) of 61 patients with follow-up of 6 months or longer. When ultrasound and sestamibi scans agreed in the localization of a single adenoma, and exploration disclosed a parathyroid adenoma and a normal ipsilateral gland (confirmed by biopsy and frozen section), a unilateral exploration was performed. For the 53 patients with primary hyperparathyroidism, this surgical protocol allowed unilateral exploration in 23 patients (43%). In cases of discordant imaging, multiple-gland imaging, or evidence of hyperplasia or double adenoma at operation, bilateral neck exploration was performed.

Fifty-nine patients underwent neck ultrasound preoperatively. These results are summarized in Table 1. The sensitivity of high-resolution ultrasound for all patients with hyperparathyroidism was 57%. In patients with primary hyperparathyroidism, the sensitivity of ultrasound for parathyroid localization was 66%. Specificity for parathyroid localization was 98% for all patients and 98% and 100% for patients with primary and secondary or tertiary hyperparathyroidism, respectively.

Fifty-eight patients had parathyroid localization with sestamibi scan (Table 2). Sensitivity of sestamibi scanning for precise localization, the sensitivity was 52% and specificity was slightly better for patients with primary hyperparathyroidism, sensitivity for patients with primary and secondary hyperparathyroidism was 56% and 50%, respectively. Specificity of sestamibi scanning for parathyroid localization for all patients was 99%. In the retrospective evaluation incorporating the requirement for precise localization, the sensitivity was 52% and specificity 93%.

Table 3 presents the analysis of ultrasound and sestamibi scanning as a single localization test. The overall sensitivity of this study was 72% in all patients and 78% in patients with primary hyperparathyroidism. Specificity was not calculated because of the ambiguity of definition of TN tests. These data indicate a significant improvement in sensitivity for parathyroid localization by combining localization results of ultrasound and sestamibi scanning.

The performance characteristics of ultrasound are influenced by the experience of the radiologist. The ultrasound data were further analyzed by comparing results of a single radiologist with the most experience in parathyroid imaging (R.B.J.) with the results for the remaining radiologists.*
Patient with primary hyperparathyroidism who underwent ultrasound examination at Stanford University. Sensitivity improved to 79% from 33% when an experienced radiologist was compared with the remaining staff (P < .01, \( \chi^2 \)). Details of the 9 parathyroid glands missed by the experienced radiologist are shown in Table 5. The majority of parathyroid glands missed by ultrasound occurred in patients with multigland disease. Glands that were not localized by ultrasound were also commonly in ectopic sites or relatively small (<100 mg). It is our practice to remove glands that are 70 mg or greater because they are greater than twice normal size. However, it is possible that these mildly enlarged glands have no physiological consequences. If we consider these 2 glands normal, the sensitivity of ultrasound would be 83%.

The use of routine preoperative localization for patients with primary hyperparathyroidism remains controversial. Preoperative localization can eliminate the need for routine bilateral neck exploration and theoretically decrease operative time. One study failed to demonstrate a decrease in operative time with localization; however, patients had bilateral neck exploration regardless of preoperative localization. Several studies have demonstrated a significant decrease in operative time attributed to preoperative localization. In addition, one study demonstrated that localization can decrease postoperative persistent hyperparathyroidism. Although complications of neck exploration are low, routine bilateral neck exploration may carry an increased risk of recurrent laryngeal nerve injury and postoperative hypoparathyroidism. Previous studies have clearly demonstrated an increased rate of transient hypocalcemia associated with routine bilateral neck exploration with biopsy of all normal glands.

One obvious disadvantage of preoperative localization is increased cost. The cost of combined ultrasound and sestamibi scanning at Stanford is approximately $1500. The current cost of operative time is approximately $25 per minute. Therefore, the cost of preoperative localization is equivalent to 60 minutes of operative time. This time estimate is within the range of published operative time differences for unilateral vs bilateral neck exploration. The cost advantage of preoperative localization could be improved by first performing high-resolution ultrasound and performing sestamibi scanning only in cases in which ultrasound is nondiagnostic.

The success rate for initial neck exploration for primary hyperparathyroidism is reported to be 90% to 95%. A precise preoperative localization test could theoretically allow surgical exploration to be uniformly successful. Although current methods of localization demonstrate 95% to 100% specificity, our findings are in agreement with other studies that report sensitivity of ultrasound of 30% to 70% and sensitivity of sestamibi scanning of 50% to 80%. On the basis of current localization technology, a unilateral approach would result in missing a second enlarged gland in approximately 2% to 5% of patients. This problem could be avoided by using the rapid intraoperative PTH assay. Bilateral neck exploration could be performed in patients with persistent hyperparathyroidism after resection of an enlarged parathyroid gland. However, the rapid intraoperative PTH assay costs $500 to $1000 per patient, depending on how many tests are performed. If the cost of the rapid PTH assay were decreased, this approach may become widely accepted.

Several technical considerations may contribute to FN tests with the use of ultrasound. Glands located in the mediastinum, paraesophageal, and high cervical locations are commonly missed. As demonstrated by our data, experience of the radiologist also affects the ability to locate abnormal glands. The relatively low sensitivity for patients with secondary hyperparathyroidism also suggests that hyperplastic glands are more difficult to locate than single adenomas. The data in Table 5 show that even in the setting of primary hyperparathyroidism, failure to localize abnormal parathyroid glands is likely to occur in patients with multigland disease. Abnormal parathyroid glands occurring in the setting of multigland disease may have different characteristics than single adenomas. Alternatively, the identification of 1 abnormal gland may distract a radiologist from pursuing other abnormalities. Our data support the conclusion that a close working relationship between the surgeon and the radiologist with a particular interest in parathyroid imaging will improve preoperative detection of abnormal glands in patients with primary hyperparathyroidism.

The sensitivity achieved in this series for localization with ultrasound scanning was less than commonly re-

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**Table 4. Results of Single Radiologist Compared With Staff**

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>No. of FNs</th>
<th>Location of FN Finding</th>
<th>Weight of Adenoma Missed, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experienced radiologist</td>
<td>36</td>
<td>34</td>
<td>9</td>
</tr>
<tr>
<td>Staff radiologists</td>
<td>14</td>
<td>6</td>
<td>34</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>40</td>
<td>133</td>
</tr>
</tbody>
</table>

*TP indicates true positive; TN, true negative; FN, false negative; and FP, false positive.

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**Table 5. Data From 8 Patients With False-Negative (FN) Ultrasound Results**

<table>
<thead>
<tr>
<th>Total No. of Abnormal Glands</th>
<th>No. of FNs</th>
<th>Location of FN Finding</th>
<th>Weight of Adenoma Missed, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1</td>
<td>LS</td>
<td>550</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>LS</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>LS</td>
<td>726</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>Ectopic RI</td>
<td>680</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>Ectopic RI</td>
<td>370</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>LS</td>
<td>468</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>RI, RS</td>
<td>322,70</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>Ectopic RI</td>
<td>640</td>
</tr>
</tbody>
</table>

*LS indicates left superior; RI, right inferior; and RS, right superior.*
In addition, there was a lower sensitivity in patients with multigland disease. In this series, all patients with primary hyperparathyroidism who had multigland disease had at least 1 FN result. We did not find that imaging of the thyroid with 99mTc pertechnetate or iodine 123 aided the interpretation. Single photon emission computed tomography was not routinely used in our imaging protocol, and this technique may improve sensitivity. Early in the use of sestamibi scanning, a decision was made to reduce the dose of 99mTc from 740 MBq to 370 MBq; this technical point needs to be reevaluated, since there are data to indicate improved imaging success with higher doses.23 We are currently analyzing the details of our sestamibi localization procedures in an attempt to improve sensitivity for parathyroid localization.

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REFERENCES


DISCUSSION

Orlo H. Clark, MD, San Francisco, Calif: Purcell, Weigel, and colleagues in their paper titled “Parathyroid Localization With High-Resolution Ultrasound and Technetium Tc 99m Sestamibi” report their results using these parathyroid localization studies, and at parathyroidectomy in 61 consecutive patients with hyperparathyroidism during a 3-year period. Among the 61 patients, 53 patients had primary hyperparathyroidectomy, including a few with recurrent or persistent hyperparathyroidism; all were successfully treated and there were no significant complications. This certainly documents their excellent surgical results. Overall, for the 53 patients with primary hyperparathyroidism, 23 (43%) could be treated with a unilateral approach based on the results of 2 preoperative localization studies, as well as by documenting 1 normal and 1 abnormal parathyroid gland during the operation. Fifty-nine of these 61 patients had ultrasound examinations. The 2 who did not have persistent disease and had positive magnetic resonance images that concurred with the results of their sestamibi studies so that ultrasound studies were not done. Overall, ultrasound studies were true positive in 42 of the 59 patients with primary hyperparathyroidism, false positive in 3, and false negative in 22, for a sensitivity of 66% and a specificity of 98%. Ultrasound studies were more accurate when done by one experienced radiologist (79% sensitivity) vs others (33% sensitivity). The majority of abnormal parathyroid glands that were missed by ultrasound examination occurred in the 17% of patients with multiple abnormal parathyroid glands as well as in patients with smaller parathyroid glands and those situated in ectopic positions.

Sestamibi scanning was done in 58 patients. In 35 patients with primary hyperparathyroidism there was a true-positive study, in 2 a false-positive study, and in 28 a false-negative study, for a 56% sensitivity and a 99% specificity. To improve the overall accuracy for parathyroid localization, ultrasound scanning and sestamibi scanning were analyzed as a single localization test by the authors. Using this approach in 35 patients, there were 51 true-positive studies, 3 false-positive studies, and 14 false-negative studies, for a sensitivity of 78%. These findings demonstrate that localization studies are helpful to the surgeon, but are not accurate enough to be recommended for a focal approach such as identification of only 1 gland, since the error rate would be too high. They also only allowed a unilateral approach in 43% of the patients in this series. As Dr Leonard Rosoff, a distinguished member of the PCSA, stated when I presented a paper on parathyroid localization some years ago, “a surgeon with less than an 80% success rate dur-
ing parathyroid operations for patients with primary hyperparathyroidism should consider another career."

Localization studies do, however, allow the surgeon to begin the exploration on the side where a presumed parathyroid tumor has been identified. When an abnormal and a normal gland are observed, the abnormal gland can be removed and either the operation discontinued, with about a 7% failure rate as reported by Dr Quan-Yang Duh and our group, or the other side can be explored and usually the operation completed before the results of the frozen section are reported (World J Surg. 1992;16:791-797).

There is considerable controversy today concerning the most appropriate surgical approach for patients with primary hyperparathyroidism. There is also considerable misinformation on and marketing Web sites regarding the treatment of patients with hyperparathyroidism. Some surgeons suggest that operating on a patient without localization studies “is like an experienced driver driving at night without his lights on.” I suggest that “operating based only on preoperative localization or intraoperative localization has dramatically increased the number of failed parathyroid operations.”

The observations made in this article confirm several important points: (1) Fifteen to 20% of patients with primary hyperparathyroidism have multiple abnormal parathyroid glands. Preoperative localization studies are unfortunately misleading in about 70% of patients with multiple abnormal parathyroid glands. (2) Localization studies are significantly more accurate in patients with a solitary parathyroid tumor and when done by an experienced radiologist in this field (79% vs 33%). (3) Ultrasound is more likely to identify parathyroid glands that are also easy for the surgeon to identify, that is, the larger parathyroid tumors situated in a normal position near the thyroid gland.

I have several questions for the authors: (1) Do you believe a unilateral approach is accurate enough to be used today without using an intraoperative PTH assay, and how accurate is intraoperative PTH in predicting a successful operation? What failure rate is acceptable? (2) Did you identify any abnormal glands in ectopic positions, such as in the superior mediastinum, with sestamibi scanning? (3) Why do you do localization studies in patients with secondary hyperparathyroidism, since bilateral exploration is required? (4) Did any of your patients have coexisting thyroid disease, since thyroid abnormalities can make localization studies less accurate? If any of your patients had coexistent thyroid abnormalities, were your localization studies as accurate in these patients?

We must continue to develop more accurate localization tests and seek less invasive approaches to cure patients with primary hyperparathyroidism. One should remember, however, that, as demonstrated in this paper, more than 95% of patients with primary hyperparathyroidism can be successfully treated with few complications.

Quan-Yang Duh, MD, San Francisco: I have a comment and some questions. My main comment is that the most important issue in localization studies for the first-time operation should be the ability to identify the patient you are going to have trouble with in your operation, that is, those with multiple-gland disease. But these studies are not very good for multiple-gland disease. If you know about these patients preoperatively, you are going to explore all glands regardless of what the sestamibi scan or the ultrasound shows.

The primary hyperparathyroidism patients who have single-gland disease rarely have a failed operation. So it comes down to the group of 9 patients with multiple-gland disease out of the 53 patients with primary hyperparathyroidism. How can we identify this group of patients before the operation? The issue with the preoperative localization study in this group of patients is not sensitivity or specificity. If the scan shows you nothing, you will worry about that patient and you will explore all glands in that patient. If the scan shows 2 glands, you will also explore all glands. The key issue is, how often do you get a misleading localization study? The misleading scan occurs in the group of patients who have multigland disease but the preoperative localization study showed a single-gland disease. These are the only patients who you will potentially help with good studies and potentially hurt with bad studies. In our own series we found that about 20% of our patients have multiple glandular disease just like yours. Of those, one third had no positive scan. One third of the scans showed multiple-gland disease. For these patients you would explore all glands. But one third had misleading scans. If you have similar numbers, 3 out of the 9 patients would have had misleading scans.

Doing a unilateral exploration in these 3 patients, you would have picked up at least 1 and potentially 2 of these patients. So are we talking about the difference of about 1 patient in the whole series that your localization studies potentially could have helped or could have been misleading. That is the biggest problem of your study and other multiple studies in the literature, studying 60 patients but looking for the potential difference of only 1. Statistically, one cannot conclude from a study like this that it is good to do preoperative studies.

These studies are quite expensive and we are talking about potential difference in 1 reoperation. In fact, I disagree with Dr Clark regarding bilateral exploration for all patients in that I think it is perfectly okay to do a unilateral exploration or a focused exploration, as long as we are willing to do more reoperations. When we do limited operations, we subject the patient to a potential increase in the reoperation rate. The current localization studies unfortunately have not solved this problem.

Lawrence A. Danto, MD, Stockton, Calif: I am going to rearrange my comments, because the issue has become confusing. I would like to add the concept of the nonfunctioning adenoma to the discussion. We have found about a 10% incidence of nonfunctioning adenomas in the contralateral neck at the time of initial exploration. These are adenomas that are not picked up by sestamibi that are large enough to be visualized and, if left in place, the patient would be misleadingly eucalcemic at the end of the operation. If you use eucalcemia as your end point for defining success, you are probably picking the wrong end point, at least in the early period, and early here extends out maybe 3 years or so into the postoperative period.

So my questions, then, are these: How often did ultrasound pick up a contralateral lesion not identified by sestamibi? Have you explored the contralateral neck in this set of patients to confirm your imaging findings, or are you simply relying on early postoperative eucalcemia? If you are, I would suggest that maybe this is not the proper end point in this instance.

My final question, and I ask this with only a small amount of innuendo, is it better to reoperate on probably 10% of patients later in life after a failed exploration or perform a directed bilateral exploration on all patients the first time around?

Maria Allo, MD, San Jose, Calif: I want to underscore the importance of the comments by Dr Duh, which I agree with entirely, and would raise the issue of not doing any localization studies at the first operation. Can you comment on reoperation with not preoperative sestamibi but perhaps immediately preoperative sestamibi with a gamma probe–directed exploration at the time of reoperation?

Samuel E. Wilson, MD, Los Angeles, Calif: Dr Weigel, as localizing methods become more accurate, is it too soon to speculate or even envision the role of percutaneous image-guided therapy, for example, a cryoprobe of some sort for treatment of a single adenoma?
Dr Weigel: The first question I want to address is the question concerning the nonfunctioning adenomas, and I think part of the answer to this question relies on what we call nonfunctioning. As I understood your question, it related to imaging with sestamibi scan as an indication of nonfunction. I don't know of anyone who has actually done a study that has identified a large parathyroid adenoma not imaged by sestamibi and then decided to leave it there and follow the patient postoperatively. I don't think that we have the answer to your question, but I am certainly convinced that sestamibi scan does not identify all large parathyroid glands that clearly have metabolic consequences and are causing hyperparathyroidism. I say that because I know of many patients who had nothing imaged by sestamibi scan who had a large adenoma that was removed, and the hyperparathyroidism was cured. So clearly imaging with sestamibi and metabolic function in terms of excess secretion of parathyroid hormone are not the same thing. So I think the answer to part of your question relies on what the definition of nonfunctioning is. My conclusion is that all enlarged parathyroid glands are hyperfunctioning. I don't know of any study that has been done to disprove that.

The question from Dr Allo related to use of the gamma probe. We have not used the gamma probe. I think a large degree of those studies are based on trying to do a more cosmetic operation. There are additional costs and also difficulties in trying to get the patient injected and into the operating room at the right time post injection, and we have not been involved in the gamma probe used today.

Dr Quan Duh's question is very well taken. I think that I would agree with everything that he had to say. Our study shows that the agreement of ultrasound and sestamibi with the identification of what is apparently a solitary adenoma preoperatively is in fact a selection for those patients who have single adenomas. You are absolutely right that when I have a patient who has discordant imaging studies or who has nothing imaged by either technique, that is a case where you are "worried" prior to operation, and it is a good indication that those patients are likely to have hyperplasia or some sort of multigland disease. So, yes, a bilateral approach is used.

Your issue of cost is a good one, and our study did not specifically look at operative times. But in studies where operative times have been examined, the difference between unilateral and bilateral exploration is on the order of about 60 minutes. That number is certainly skewed by those rare patients in whom it takes an hour or longer of additional operative time to find that fourth parathyroid gland that ends up being down in the thymus and is normal. So those kinds of operation can go on for quite a while. Part of what these imaging studies do is to try to cut down on the number of times you find yourself in the operating room looking for a fourth gland that ends up being normal. I know we have all been there. I think that the trade-off in operative times vs the cost for the imaging studies, the breakeven point, is about 1 hour of operative time. So I think the cost issue is close, and certainly if we can bring down the cost of the imaging studies, the largest cost of the 2 studies being sestamibi scan, that we may get into a range where the cost issue is a wash.

I appreciate Dr Clark's comments and I will try to address those. I agreed with all of the initial comments that you had to make dealing with the issues that you made. I agree that localization studies with a radiologist who is not experienced in parathyroid localization are a waste of time, and that is why we always ask for the most experienced radiologist. I also agree that the times when the localization studies are most needed are exactly the times when they are unable to be successful, trying to find ectopic glands, trying to find patients who have multigland disease.

I agree that localization is helpful. It is only a road map. I know that when I take a patient to the operating room and I have a well-localized solitary adenoma, my degree of concern or worry for that patient is much less. I am more likely to schedule multiple other cases following that as opposed to someone who has no imaging or bilateral imaging.

Yes, we do use frozen section for confirmation that we have identified the parathyroid glands, and our pathologists are right almost every time.

The use of the intraoperative PTH assay, I think, still needs to be investigated more clearly. We do not currently have intraoperative PTH capabilities, but we should have those capabilities sometime within the next 6 weeks or so, I am told. I have been working on that for a little over a year and a half now. I think that using ultrasound for a road map and then using the intraoperative PTH assay may be a way to avoid the expense of sestamibi and still decrease operative times in those patients who do not need bilateral neck exploration.

Again, finding abnormal glands in the superior mediastinum or undescended parathyroid glands is an added plus. There were, I think, 2 patients in our series who had parathyroid adenomas that were solitary and were within the superior mediastinum. The operation started with pulling the thymus up, taking out the adenoma. That would not be how I would do a bilateral approach. I would look for more common places for parathyroid adenomas and probably an hour into the operation finally would start pulling up the thymus gland. So clearly it has been helpful in some patients. A number of our patients did have coexisting thyroid disease. We had a number of patients with thyroid nodules, and in several instances that was the cause of our being unable to do a unilateral approach. The patient had a left thyroid nodule in which fine-needle aspiration was suspicious and the adenoma was localized on the contralateral side. So, yes, we had a number of our patients who had concurrent thyroid disease that was managed surgically at the same time.

Finally, Dr Wilson's question about more accurate localization studies and the desire to treat this percutaneously. It is a very provocative question, and it has been addressed a number of times. Dr Jeffrey has asked a number of times about treating patients percutaneously with alcohol injection, especially those who are considered poor risk for surgery. The recurrent laryngeal nerve can pass very close to the adenoma and might be injured by percutaneous treatment.