Unilateral Cervical Surgical Exploration Aided by Intraoperative Parathyroid Hormone Monitoring in Patients With Primary Hyperparathyroidism and Equivocal Sestamibi Scan Results

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Hypothesis: Equivocal parathyroid technetium Tc 99m sestamibi scan results are likely to demonstrate the correct location for parathyroid adenomas.

Design: Patients with primary hyperparathyroidism prospectively consented to participate in an institutional review board–approved study. The parathyroid technetium Tc 99m sestamibi scan results were classified as positive, negative, or equivocal.

Setting: A tertiary private hospital in which university faculty practice.

Patients: Technetium Tc 99m sestamibi imaging was performed for 464 patients with primary hyperparathyroidism. Eighty-four of these patients had scan results considered equivocal for unilateral adenomas. The algorithm for this group of patients specified that they should receive an injection with technetium Tc 99m sestamibi prior to parathyroidectomy and that an intraoperative parathyroid hormone (iPTH) level decrease of more than 50% be used to define intraoperative success. Seventy-two patients had postoperative calcium levels measured at least 2 weeks after their surgical procedure and defined the study group. The mean follow-up was more than 6 months.

Intervention: Parathyroidectomy.

Main Outcome Measure: Correlation of equivocal scan interpretation with operative findings and biochemical cure of hyperparathyroidism.

Results: Of the 72 patients, 39 underwent unilateral surgical explorations and 33 underwent bilateral surgical explorations; 67 (93%) of the patients were initially cured and 68 (94%) were ultimately cured. In the unilateral group, 38 (97%) of the patients were cured. The 1 failure was associated with a false-positive iPTH level decrease. In the bilateral group, 29 (88%) of the patients were initially cured and 30 (91%) were ultimately cured. Two failures were associated with a false-positive iPTH level decrease and 2 with failure to find the adenoma. Of the 33 patients in the bilateral group, surgical exploration of the opposite side was purely by surgeon choice in 11 cases. Of the other 22 patients, in addition to the 3 failures, 7 had 4-gland hyperplasia, 4 had double adenomas, and 6 had false-negative iPTH level results with iPTH level decreases of less than 50%.

Conclusion: Overall, between 48 (67%) and 54 (75%) of the 72 patients would have been cured with unilateral surgical exploration alone.

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This last decade has been witness to a significant change in the paradigm for the surgical treatment of primary hyperparathyroidism (PHPT). Prior to this past decade, surgical management of PHPT included careful bilateral surgical exploration of the neck with the intent of identifying all of the 4 parathyroid glands. Surgical judgment and experience were significant factors, and skilled endocrine surgeons reported cure rates of 97% to 99% using this approach. In the past decade, 3 developments that have allowed the paradigm of unilateral neck surgical exploration to take hold in the field of parathyroid surgery have occurred. This is often performed in a minimally invasive, highly directed manner. These developments include parathyroid imaging, the miniaturized handheld gamma probe, and the quick intraoperative parathyroid hormone (iPTH) assay. Dual-phase technetium Tc 99m sestamibi (MIBI) parathyroid scintigraphy (MIBI scanning) has been reported to have a sensitivity for detecting parathyroid adenomas of up to 91% with a specificity of 98.8%. The development of the MIBI scan combined with the introduction and subsequent miniaturization of the handheld gamma probes led to the technique known as minimally invasive radioguided parathyroidectomy (MIRP). Two of the more

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METHODS

Four hundred sixty-four patients with a diagnosis of PHPT gave consent for an institutional review board–approved prospective protocol and subsequently underwent parathyroidectomy by 1 of 4 surgeons (R.E.G., J.B., E.L., and M. Flynn) between May 1, 1998, and July 1, 2004. A diagnosis of HPT was based on hypercalcemia and an elevated intact PTH level. Most subjects also had 24-hour urine collections to assess calcium excretion. All of the patients with PHPT underwent dual-phase MIBI imaging consisting of at least the acquisition of anterior planar images 15 minutes after intravenous injection of 740 to 1000 MBq of MIBI (11 MBq/kg for patients with obesity).7 Similarly obtained at 15-minute and 2-hour intervals in a parallel-hole collimator, a 256×256 matrix with a ×1.6 zoom, and an energy window of 140 keV±10% (Figure 1). Using a pinhole collimator over the neck, 10-minute acquisitions were similarly obtained at 15-minute and 2-hour intervals in a 256×256 matrix format.13 Single-photon emission computed tomography imaging was rarely performed. The attending nuclear radiologist and the patient’s surgeon reviewed all of the MIBI scans.

Three hundred ten patients had a MIBI scan interpreted by the radiologist and surgeon to demonstrate a single focus of pathologically increased activity in the neck, which was thus considered a positive scan result (Figure 1). These patients subsequently underwent MIRP and served as the control group for this study.

Eighty-four patients had a MIBI scan result interpreted as equivocal by the radiologist and the surgeon. An equivocal scan result was one that was thought to suggest the presence of a single adenoma in the neck yet was not sufficiently defined to allow for a positive reading or a planned directed unilateral surgical approach (Figure 2). Only those patients whose scan results were read as equivocal by both the radiologist and the surgeon are included in this article. Patients whose family history suggested multiple endocrine neoplasia type 1 or familial HPT and patients with renal disease were excluded from this analysis. Of the 84 patients with equivocal MIBI scan results, follow-up information including calcium and PTH levels at least 2 weeks after surgery was available for 72 patients. These patients formed the basis for this study.

At the start of the study period, an algorithm was created to define surgical management (Figure 3). If patients had a positive MIBI scan result, they underwent a MIRP, and an intraoperative measurement of the PTH level was not routinely performed. If the MIBI scan result was negative, bilateral neck surgical exploration was performed, and it was aided by the iPTH assay. If the scan result was equivocal, the patient was reinserted with MIBI as if a MIRP was going to be performed, with a plan to first examine the side of the neck where the scan sug-
gested an adenoma. If an enlarged parathyroid adenoma was located, the iPTH assay was performed to help guide the decision about whether to surgically explore the contralateral side. Based on the results of the iPTH assay and clinical judgment, the surgeon made a decision about whether to surgically explore both sides of the neck or to only perform a unilateral procedure.

The quick iPTH assay was performed using the immuno-chemiluminescence iPTH assay (Nichols Institute Diagnostics, San Juan Capistrano, Calif). A preincision PTH sample was drawn from a peripheral vein. A preexcision PTH sample was drawn from the ipsilateral internal jugular vein as soon as the potential adenoma was identified. Following resection of the adenoma, a PTH sample was again drawn from the same location at 5 and 10 minutes after excision. A single parathyroid adenoma was considered to have been successfully resected if the PTH level in the 5- or 10-minute sample was 50% or less of the preexcision PTH level.

When performing a MIRP, the patient was reinjected with 740 MBq of MIBI 30 to 60 minutes prior to the procedure but was not reimaged. Unless contraindicated, patients had a choice of intravenous sedation (monitored anesthesia care) or general endotracheal anesthesia. Intravenous sedation consisted of midazolam and propofol plus local application of lidocaine hydrochloride with epinephrine with the addition of 10% sodium bicarbonate into the subcutaneous tissue of the anterior neck below the level of the thyroid notch. An incision of 2.5 to 4.5 cm was made in a transverse direction 2 fingerbreadths above the sternal notch. It was weighted toward the side of the expected adenoma.

Minimal subplatysmal planes were created; the strap muscles were divided in the midline and then dissected off of the inferior aspect of the thyroid lobe on the side of the parathyroid adenoma. The dissection from this point on was guided by the handheld gamma probe with a 14-mm head (Neoprobe Corp). Care was taken to be aware of the recurrent laryngeal nerve; however, given the limited dissection, the nerve was identified less than half of the time.

Once the targeted gland was removed, the radioactivity of the presumed adenoma was measured ex vivo with the probe directed away from the patient and was compared with those counts obtained by slowly tracking the probe over the central neck. If the ex vivo radioactivity totaled at least 20% of the remaining background counts and there was no significant step-up of counts in any quadrant of the neck, the dissection was terminated and the incision was closed without a drain.

Data were collected from a prospective database maintained on all of the patients enrolled in the study. Equivocal and positive MIBI scan results were compared using t tests (SPSS, Inc, Chicago, Ill), with P = .05 needed to reach statistical significance. Data are presented as mean ± SE.

RESULTS

Of the 72 patients who were able to be evaluated, 39 underwent unilateral surgical explorations guided by the handheld gamma probe combined with the iPTH assay. The other 33 patients underwent bilateral procedures (Figure 4).

UNILATERAL PROCEDURES

Of the 39 patients who underwent unilateral procedures, all but 3 had decreases of 50% or more in the iPTH level by 10 minutes after excision. In 1 of these 3 pa-
patients, the trend was decreasing and the surgeon drew a third postexcision sample at 20 minutes; this sample did demonstrate a decrease of 50% or more. In the other 2 cases, the preexcision levels of iPTH were less than 7.15 pmol/L (3.96 and 5.17 pmol/L), and there was concern regarding the validity of the assay.

Of these 39 patients, 38 (97%) remain cured. The 1 failure occurred in a woman whose iPTH levels decreased from 87 pmol/L before excision to 14 pmol/L at 10 minutes after excision, and she was subsequently found to have a second adenoma on the contralateral side during a second procedure.

**BILATERAL PROCEDURES**

Of the 33 patients in whom surgical exploration was performed bilaterally, 11 had an enlarged parathyroid gland identified that corresponded to what was shown with the equivocal MIBI scan result, and the iPTH level decreased by at least 50% after the excision of the parathyroid gland (Figure 5). In these 11 patients, it was the surgeon’s choice to surgically explore the second side. Ten of these patients would have been cured if the surgeon had stopped the procedure after only surgically exploring the first side. The 11th patient had multiglandular disease, and the iPTH level result was a false positive.

Of the remaining 22 patients, 7 had 4-gland hyperplasia and 3 had double adenomas, all of whom had iPTH levels that did not decrease by 50% after the initial gland was resected. A fourth double adenoma was associated with a false-positive decrease of greater than 50% in the iPTH level, resulting in a missed second adenoma that was resected with a second procedure. In 6 additional patients, the iPTH level did not decrease by 50% after resection of an apparent adenoma; however, surgical exploration of the contralateral side demonstrated 2 normal parathyroids and subsequent PTH and calcium level determinations have been in the normal range, suggesting that these represented false negatives. In 3 of the remaining 5 patients, 2 normal parathyroids were identified on the side of the equivocal image but the true adenoma was located on the contralateral side. In the other 2 remaining patients, a parathyroid adenoma was never identified. Overall, 30 (91%) of the 33 patients remain cured. Potentially, 16 of these patients could have undergone a successful unilateral procedure. Ten of them had operative findings and iPTH assay results that would have allowed for a unilateral approach; an additional 6 had operative findings consistent with a single adenoma but underwent contralateral surgical exploration owing to a false-negative iPTH assay result.

**COMPARISON WITH CONTROL GROUP**

In the positive MIBI scan result control group (n=310), 23% were male and the mean±SE age of the group was 59±1 years. The mean±SE PTH and calcium levels were 19.0±1.0 pmol/L and 2.74±0.01 mmol/L, respectively (Table). The mean±SE adenoma gland weight was 1420±117 mg. Adenomas ranged in weight from 70 to 16400 mg. In the equivocal MIBI scan result group, 12 (20%) of 59 patients with equivocal scan results who subsequently shown to have single adenomas were male (P>.05), and the mean±SE age was 65±2 years (P<.05). The mean±SE PTH and calcium levels were 15.3±1.2 pmol/L (P<.05) and 2.76±0.02 mmol/L (P>.05), respectively. The mean±SE adenoma gland weight was 732±117 mg (P<.01). Adenomas ranged in weight from 53 to 3000 mg.

The principal finding of this prospective study is that even when a patient with PHPT has an equivocal MIBI scan result, there is anywhere from a 67% to 75% chance that they can undergo a unilateral highly directed cervical surgical exploration and be cured. Such a unilateral approach allows for shorter operative times, decreased hospital charges, and a decreased hospital stay.3

There have been 3 primary technological developments over the past decade that have allowed unilateral paradigm to become accepted. The most significant of these has been dual-phase MIBI parathyroid scintigraphy, commonly known as the parathyroid scan. In 1998, Denham and Norman1 reported that the scan had a sensitivity for detecting parathyroid adenomas of up to 91% with a specificity of 98.8%. Merlino et al16 reported an overall scan sensitivity for detecting and localizing abnormal parathyroid tissue of 77% with a positive predictive value of 99%. Sensitivity increased to 84% with a 99% predictive value when only adenomas were considered. Grant et al17 reported that the MIBI scan had a sensitivity of 86% with a positive predictive value of 93%. The technetium Tc 99m isotope used for parathyroid scans can be detected by the new generation of miniaturized, handheld gamma probes marketed as the Navigator and the Neoprobe. This technology represents the second technological advance, and it was originally applied to sentinel-node mapping for melanoma and breast cancer but was adapted to parathyroid surgery in 1997 in the article by Norman and Chheda.4 The third major advance in technology that altered parathyroid surgery is the iPTH assay.9

With these technologies available, 2 new general paradigms have emerged for unilateral scan-directed parathy-
patients. Udelsman and colleagues reported excellent cure rates of 99% using this approach. Udelsman also compared these cure rates using the MIP approach with that of standard bilateral surgical exploration and found no significant difference, with cure rates of 99% and 97%, suggesting that good preoperative imaging combined with a scan-directed surgical approach that used the iPTH assay to confirm biochemical cure compared favorably with careful bilateral surgical exploration. Grant et al recently reported a 97% cure rate using MIP in 601 patients. Siperstein et al, however, have questioned unilateral approaches and suggested in a recent study that failure to surgically explore the contralateral side would have led to a 15% failure rate in their series, a finding at odds with the previously mentioned studies. They also reported significant discordance between MIBI scanning and ultrasonography for adenoma localization, a finding somewhat contrary to that by Solorzano et al. The other unilateral paradigm, MIRP, relies heavily on the MIBI radiopharmaceutical and the handheld gamma probe to provide both a targeted approach to the parathyroid adenoma and functional confirmation of completeness. Using this technique, Murphy and Norman recently reported a 100% cure rate in a large series of MIRPs performed at a single institution. Using the MIRP technique in 112 patients, Goldstein et al reported a long-term cure rate of 98%, with no patient having persistent HPT. As with MIP, more than half of the procedures were able to be completed with less than general endotracheal anesthesia.

What is common to virtually all of these unilateral approaches is the necessity for a positive preoperative parathyroid scan result. Conversely, given a clearly positive parathyroid scan result, whether a patient undergoes a MIP, a MIRP, or a limited parathyroidectomy with an iPTH assay, the probability of cure is likely in the range of 97% to 99%. Factors that are likely to effect scan positivity include gland weight and serum PTH concentration. In addition, Goldstein et al found that for any given PTH level, women were more likely than men to have a positive parathyroid scan result. Thus, sex may play a role in scan sensitivity. Efforts to further improve the sensitivity of parathyroid scanning are ongoing and have included thyroxine suppression and the addition of calcium channel blockers.

One remaining issue is the likelihood of whether a patient with an equivocal parathyroid scan result is still a candidate for a unilateral procedure, and if so, what the probability is of a successful unilateral procedure. This is the question that the current study addresses. Irvin et
al14 have reported success using limited parathyroidectomy with the iPTH assay for patients with equivocal scan results but have not specifically described this subgroup. The data from the current study support the algorithm where patients with an equivocal MIBI scan result undergo MIRP and the iPTH assay is used as an adjunct to confirm completeness. Upwards of 75% of the patients with equivocal scan results would have been cured if a unilateral procedure had been performed. Six (8%) of the 72 patients had the contralateral side nontherapeutically surgically explored owing to a false-negative iPTH result. Grant et al17 reported false-negative and false-positive results to occur with a frequency of 2% and 1%, respectively. Although the false-negative rate in the current study is somewhat high, it also reflects a specific subgroup of patients and may not be representative of the entire group of patients in which the iPTH assay was used.

In the current study, adenomas associated with equivocal MIBI scan results were, as a group, smaller than adenomas associated with positive scan results, and the PTH levels associated with these adenomas were less than the serum PTH levels associated with positive scan results. This is not surprising given the previously noted relationship between PTH levels, gland weight, and scan positivity.1 It is interesting that parathyroid adenomas weighing up to 3000 mg were associated with equivocal scan results, reinforcing the lack of understanding of exactly why some very large adenomas fail to take up or retain the isotope.

Overall, 18% of the patients in our study had multiglandular disease in the setting of equivocal scan results and no family history of parathyroid disease. Previously published studies have not tended to break out an equivocal MIBI scan result group, so direct comparisons are difficult.18 Merlino et al19 reported that a positive MIBI scan result was associated with 83% of patients with a single adenoma but only 38% of patients with multiglandular disease. Of 89 total patients in the series, 76 (85%) had single adenomas and 13 (15%) had multiglandular disease. Irvin et al20 reported a 3% rate of multiglandular disease in 890 patients with sporadic PHTP. Grant et al17 reported a 13% rate of multiglandular disease in their recent description of 1361 patients. Standing separate is the study by Siperstein et al,20 who reported an unusually high 31% incidence of multiglandular disease in 350 patients. Overall, the rate of multiglandular disease in our study is likely within the wide range of multiglandular disease associated with the majority of these other studies.

In summary, while one might argue as to whether a particular MIBI scan result is truly positive or equivocal, the data from the current study suggest that these patients with PHPT can be successfully managed, in many cases with a unilateral surgical procedure, using an algorithm that incorporates MIRP with the iPTH assay.

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REFERENCES

tion for curative parathyroidectomy. Intraoperative PTH monitoring as initially promoted by Dr Irvin appears to be a natural fit. Dr Goldstein has shown that potentially two thirds to three fourths of patients with sporadic primary hyperparathyroidism can successfully be managed in this manner to accomplish unilateral cervical exploration.

However, some concerning aspects of their study are: first, the short postoperative follow-up used to define a cure. Many authors have suggested a 6-month follow-up. Second, only 67% of all patients had a clearly positive sestamibi scan when other studies report closer to 80%. Third, 3 false positives, 7 false negatives at 10 minutes, and 2 technical failures for a total failure of intraoperative PTH to properly guide surgical management in 12 patients. That is 16.7%, when Dr Irvin (Oper Tech Gen Surg. 1999;1:18-27) and Dr Grant (Arch Surg. 2005;140:472-479) report closer to 3%. Good preoperative localization studies are paramount to increasing the likelihood of unilateral cervical exploration. At many institutions, the preferred parathyroid scan is subtraction imaging with SPECT [single-photon emission computed tomography] localization. Ultrasound can clarify an equivocal scan and pinpoint abnormal parathyroid glands. Our preference is for surgeon-performed ultrasound examinations preoperatively. Dr Goldstein, were ultrasound examinations a part of the preoperative evaluation of your studied patients, and if so, did they influence surgical management in any patients?

Dr Goldstein: Ultrasound findings, which is very similar to your results. We are finding similar, if not better, results with surgeon-performed ultrasound. We have published what ultrasound performed by our radiologists can add to sestamibi scanning. Between 10% to 15% more patients were able to have minimally invasive parathyroidectomy because of the ultrasound findings, which is very similar to your results. We are finding similar, if not better, results with surgeon-performed ultrasound.

Minimally invasive parathyroidectomy is done by many surgeons without the use of a radioguided probe. Maybe you could comment on what benefits you see from using that approach. Follow-up is difficult for all of us but is critical for evaluating our results. Two weeks is certainly too short, so can you tell us more about the follow-up of these patients? Can you give us information on the postoperative parathyroid levels in your patients? Have they all returned to normal or do you have many that are still elevated?

You asked about any specific reasons why some surgeons in our group would look on both sides whether or not the iPTH fell by 50%. I think it was clearly surgeon dependent. I don't think that there were other factors. I personally feel that if one is going to make use of the quick PTH assay, then one should use the data. And if it is not worth using, then the assay shouldn't be used. So, I continue to base what I would do in terms of the opposite side on what the parathyroid looked like and the result of the quick PTH assay.

Richard A. Prinz, MD, Chicago, Ill: Your study is based on equivocal sestamibi scans. One person's equivocal scan may not be another's. So, I wonder if you would define that term to us. Second, Dr Snyder brought up the issue of doing SPECT sestamibi scans. Were your scans SPECT scans? Were all the scans done in your hospital or did you rely on studies done outside and brought to you by the patients? Did the surgeons read all of the scans or just rely on the readings?

We like to underscore that Dr Snyder said about surgeon performed ultrasound. We have published what ultrasound performed by our radiologists can add to sestamibi scanning. Between 10% to 15% more patients were able to have minimally invasive parathyroidectomy because of the ultrasound findings, which is very similar to your results. We are finding similar, if not better, results with surgeon-performed ultrasound.

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Dr Goldstein: You asked how one actually defines equivocal scans. In our study, it was defined at the time of the initial workup as an equivocal scan if both the surgeon and the nuclear radiologist felt that it was not a clearly positive scan. That is why I tried to give you some typical examples of what defines the scans in this presentation. But, I think that if you polled 10 different surgeons on 72 studies, not all would be in complete agreement on what exactly is an equivocal scan.

The point I was trying to make is that currently in the world of endocrine surgery, different institutions might say that at their hospital, 90% of scans are positive and hence if you come to their institution, you will be more likely to have a unilateral same-day procedure when compared to another institution. We are trying to say that if there are scans where it is not clearly positive, you could very readily and very realistically offer those patients a unilateral procedure or set it up with the expectation that it is very likely to be cured using a single-sided procedure if they have an equivocal scan. I hope that answers the question. I think one purpose of this study is that all of us have scans that are not clearly positive, and what do we do with those scans?

SPECT imaging. No, we don't routinely use SPECT imaging, only rarely. We looked at this issue when I was at Vanderbilt and have not found it to be particularly helpful. We have had some success using pinhole collimators, and one of these equivocal scan images I put up there was obtained using a pinhole. This has been particularly helpful in some of these.
The probe. I think that is always an issue. Does using the handheld gamma probe help? I personally think that it can make the procedure faster in certain patients. I have not been able to think of a good way to actually collect that data. I think it is particularly helpful in fairly obese patients where many times, particularly in the setting of a positive scan, we can do a much quicker procedure through a smaller incision. I don’t know an easy way to design a study to answer that question, but I have thought about it.

Minimal follow-up was 2 weeks. That consisted of at least seeing the patient back and getting a calcium and a PTH level. Our average follow-up was well over 6 months. All these patients are prospectively consented into this protocol. We really aggressively collect data on them. A lot of our population lives several hours away and it can be very difficult to get 1-year and 2-year data. Our cut-off on this study was about a year and a half ago. And if any of our patients appear to be a failure, it is highly likely they will be sent back to us. But, 2-week follow-up was the minimum, and average follow-up was well over 6 months.

Peter Angelos, MD, Chicago: At your institution, what is the difference for the patient between the unilateral exploration and a bilateral exploration? Is it a difference in just the incision length, or the time of the operation, or does one group go home and the other group not go home?

Dr Goldstein: There will be differences in the incision length, in the length of the operation. We have not yet sent this group of patients home on the same day. I think the results of this certainly bring up the potential to send those patients home 3 to 4 hours later, which would cut down on hospital costs.

Quan-Yang Duh, MD, San Francisco, Calif: Since most of us don’t use radioguidance to do parathyroidectomy and you have more experience than most of us here, can you tell me what you do when you decide that the patient may have multigland disease? Do you continue to use a probe? Have you found a second one with a probe? What do they look like by the radioguided study?

Dr Goldstein: I think that in general, when there is multigland disease, you will tend not to have a lot of uptake in the hyperplastic glands. If it looks like we are dealing with a multigland disease, I tend to then stop using the probe.

Fiemu Nwariaku, MD, Dallas, Tex: In those sestamibi scans which were equivocal, your intraoperative use of the radioguided probe was successful. I am wondering how to reconcile the fact that you are injecting the same isotope during the preoperative scan that is negative but the use of the intraoperative probe is positive. The second question is, some have used bisphosphonates to improve the sensitivity of sestamibi. I wonder if you have any experience with that.

Dr Goldstein: To answer the second one first, I don’t have any personal experience with using bisphosphonates to increase scan sensitivity. We have had a few patients where we have tried thyrhoxine suppression. I haven’t analyzed that data, but there definitely have been a few patients where that has yielded a more positive scan that correlated with an adenoma, but there have also been some patients where it hasn’t worked at all. I know that Martha Zeiger had a paper on calcium channel blockers and increased scan sensitivity. So, I think there are definitely groups out there looking at ways to improve scan sensitivity.

You asked about the probe. The current probes are fairly heavily collimated. There are cases where the scan is equivocal, yet when you explore that area of the neck, the probe identifies the adenoma quite well.

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**Announcement**

In concert with the International Committee of Medical Journal Editors (ICMJE), Archives of Surgery will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as http://ClinicalTrials.gov). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after March 1, 2005. For trials that began enrollment before this date, registration will be required by June 1, 2005, before considering the trial for publication. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorials by DeAngelis et al in the September 8, 2004 (2004;292:1363-1364) and June 15, 2005 (2005;293:2927-2929) issues of JAMA. Also see the Instructions to Authors on our Web site: www.archsurg.com.