PAPER

Reassessment of Parathyroid Hormone Monitoring During Parathyroidectomy for Primary Hyperparathyroidism After 2 Preoperative Localization Studies

Atul A. Gawande, MD, MPH; Jack M. Monchik, MD; Thomas A. Abbruzzese, MD; Jason D. Iannuccilli, MD; Shahrul I. Ibrahim, MD; Francis D. Moore, Jr, MD

Hypothesis: For patients with primary hyperparathyroidism and patients with 2 localization studies showing the same single location of parathyroid disease, use of intraoperative parathyroid hormone (IOPTH) measurement does not significantly increase the success of minimally invasive parathyroidectomy.

Design: Retrospective cohort study.

Setting: Experience of 2 academic centers over 5 years (at Brigham and Women's Hospital, Boston, Mass) and almost 4 years (at Rhode Island Hospital, Providence).

Patients: A total of 569 patients with primary hyperparathyroidism who underwent technetium Tc 99m sestamibi (MIBI) parathyroid imaging and neck ultrasonography (US).

Main Outcome Measures: Incidence of correct prediction of location and extent of disease.

Results: In 322 patients (57%), MIBI and US imaging identified the same single site of disease. In 319 (99%) of these 322 patients, surgical exploration confirmed a parathyroid adenoma at that site, and the IOPTH levels normalized on removal. In 3 (1%) of the 322 patients, IOPTH measurement identified unsuspected additional disease. In 3 (1%) of the remaining 319 patients, IOPTH-guided removal of a single adenoma failed to correct hypercalcemia. Therefore, the failure rate of surgery in patients with positive MIBI and positive US imaging was 1% with IOPTH measurement and 2% without IOPTH measurement ($P=.50$). In 201 (35%) of the 569 patients, only 1 of the 2 studies recognized an abnormality or the studies disagreed on location. In these cases, either MIBI imaging or US imaging (if MIBI imaging was negative) failed to predict the correct site or extent of disease in 76 (38%) of the 201 patients ($P<.001$ vs concordant studies).

Conclusions: In primary hyperparathyroidism, concordant preoperative localization with MIBI and US imaging is highly accurate. Use of IOPTH measurement in these cases adds only marginal benefit. When only 1 of the 2 studies identifies disease or the studies conflict, however, IOPTH measurement remains essential during minimally invasive parathyroidectomy.

Arch Surg. 2006;141:381-384

Author Affiliations: Harvard School of Public Health (Dr Gawande) and Department of Surgery, Brigham and Women's Hospital and Harvard Medical School (Drs Gawande, Abbruzzese, Ibrahim, and Moore), Boston, Mass; and Department of Surgery, Rhode Island Hospital and Brown Medical School, Providence (Drs Monchik and Iannuccilli).

MINIMALLY INVASIVE parathyroidectomy (MIP) (or unilateral parathyroidectomy) for primary hyperparathyroidism (PHPT) has been made successful by the combination of 2 kinds of technologies. Radiologic studies—in particular, technetium Tc 99m sestamibi (MIBI) parathyroid imaging and high-resolution ultrasonography (US)—have allowed surgeons to direct their surgical exploration to the most likely location of a parathyroid adenoma. Rapid intraoperative parathyroid hormone (IOPTH) measurement has allowed surgeons to confirm that removal was curative.[1] Precisely which combination of preoperative and intraoperative technologies is most effective, however, remains unclear. Technetium Tc 99m sestamibi parathyroid scintigraphy has a specificity of 90% to 95% in localizing disease, although the reported sensitivity has varied from 39% to 92% depending on the technique and institution.[2] Neck US can achieve similarly high specificity, and sensitivity is just as variable.[3] Both have particular difficulties with accuracy in patients with multiglandular disease,[4] which can be present in up to 10% of patients.[5]

Some surgeons who perform MIP depend exclusively on MIBI imaging, some accept either MIBI or US imaging, and some require both preoperatively. At least 3 different studies[3,4,6] found improved sensitivity and specificity when both are used. If 1 imaging study suggests a particular location for an adenoma, however, it is unknown whether a second study adds sig-

Table 1. Relationship Between Imaging Findings and Surgical Outcome for Parathyroidectomy in Patients With Primary Hyperparathyroidism

Imaging Findings	Patients, No. (%)	Patients With Correct Localization, No. (%)	Patients With Incorrect Localization, No. (%)	Patients With Surgical Failure, No. (%)*
MIBI and US imaging positive for same site (concordant)	322 (57)	319 (99)†	3 (1)†	3 (1)‡
MIBI and US imaging discordant	201 (35)	125 (62)	76 (38)	6 (3)
MIBI and US imaging negative (no localization)	46 (8)	NA	46 (100)	1 (2)
Total	**569** (**100**)	**444** (**78**)	**125** (**22**)	**10** (**2**)

Abbreviations: MIBI, technetium Tc 99m sestamibi; NA, not applicable; US, ultrasonography.
*Surgical failure indicates persistent hypercalcemia after parathyroidectomy.
†$P<.001$ vs discordant imaging.
‡$P = .08$ vs discordant imaging.

nificant accuracy to that prediction or is unnecessary. Furthermore, if a second imaging study does add accuracy, whether rapid IOPTH measurement provides significant additional benefit is also unknown.

We have routinely obtained both MIBI and US images for preoperative localization in patients with PHPT. We therefore sought to examine our combined institutional experience with MIP to more precisely determine the relationship between imaging and outcome. We hypothesized that 2 studies do indeed provide significantly greater accuracy of preoperative localization than 1 study. We further hypothesized that when both studies predict the same single location for parathyroid disease and when surgical exploration reveals an adenoma at that location, IOPTH measurement does not significantly increase the likelihood of resolution of PHPT following removal of that adenoma.

METHODS

In this retrospective cohort study, we gathered clinical data on all of the patients with PHPT undergoing US imaging, MIBI imaging, and parathyroidectomy at Brigham and Women's Hospital, Boston, Mass, between January 1, 1998, and December 31, 2003, and at Rhode Island Hospital, Providence, between January 1, 2000, and November 1, 2004. Patients with recurrent disease were excluded. Recorded data included the site of localization (if any) in each of the 2 studies, the findings at surgical exploration, and IOPTH measurements.

Imaging by MIBI was performed by administering 16 to 20 mCi of technetium Tc 99m sestamibi intravenously and obtaining early and delayed planar images (at 15 minutes and 2-3 hours) as well as single positron emission computed tomographic images of the neck and thorax. Ultrasonography was performed primarily by dedicated radiologists using color and power Doppler imaging. The radiologists performing either study were not blind to prior imaging results.

If findings for either study were at least suggestive of a possible site for a parathyroid adenoma, we regarded the study as positive for localization. We considered MIBI and US imaging concordant if they both localized a single adenoma on the same side of a patient's neck. They were discordant if one localized an adenoma and the other did not or if they localized disease on opposite sides.

If one or both studies localized a single potential parathyroid adenoma, we performed MIP focused on that site with limited incision and without contralateral exploration. (When the MIBI and US imaging were in conflict, the site identified by MIBI was targeted.) Blood samples for IOPTH measurement were taken prior to exploration (as a baseline) and at 10 minutes following removal of the suspected culprit parathyroid. The preoperative imaging was considered to have made a correct localization if an adenoma was found at the expected location and the IOPTH level dropped at least 50% following resection. Otherwise, the imaging was considered to have made an incorrect localization, and a complete neck exploration was performed.

Calcium and PTH measurements were obtained at postoperative follow-up, generally 2 to 4 weeks following surgery, and we recorded whether these confirmed the resolution of hypercalcemia. (Although we routinely obtain follow-up calcium and PTH measurements at 3 and 6 months following surgery, these were not analyzed for the purposes of this study.) If the patient remains persistently hypercalcemic with an inappropriately elevated PTH level after parathyroidectomy despite correct localization, this was considered a surgical failure.

The data were examined for any relationship between concordance or discordance of imaging findings and the measured surgical outcomes using χ^2 testing. We considered a χ^2 value with a P value less than .05 to be statistically significant.

RESULTS

We identified a total of 569 patients for inclusion in the study. In 322 patients (57%), MIBI and US imaging identified the same single site of disease (imaging was concordant). In 201 patients (35%), the imaging studies were discordant—either the studies identified disease on opposing sides (16 patients) or only 1 of the 2 studies localized an abnormal parathyroid (185 patients). In an additional 46 patients (1%), neither study localized a potential site of disease, and a complete neck exploration was performed.

Table 1 shows the relationship between the imaging findings and the outcome of parathyroidectomy. Among patients with discordant studies, the MIBI imaging (or the US imaging if the MIBI imaging was negative) correctly predicted the site of parathyroid disease in 125 (62%) of 201 patients as determined by both findings at surgical exploration and an appropriate drop in the rapid PTH level. Six (3%) of the 201 patients had persistent hypercalcemia after parathyroidectomy.

Concordant studies were significantly more accurate, correctly predicting the location of the adenoma normalization of IOPTH levels following removal in 319 (99%) of 322 patients ($P<.001$ vs patients with discordant studies). In 3 (1%) of 322 patients, the IOPTH level did not

Table 2. Types of Error in Parathyroid Localization by Classes of Imaging Discordance

Imaging Findings	Patients With Localization at Incorrect Side of Neck, No. (%)	Patients With Missed Multiglandular Disease, No. (%)	Patients With Total Incorrect Localization, No. (%)
MIBI and US imaging positive for same site (concordant) (n = 322)	0*	3 (1)*	3 (1)*
MIBI and US imaging discordant (n = 201)	48 (24)	28 (14)	76 (38)
MIBI and US imaging negative (no localization) (n = 46)	46 (100)	7 (15)	46 (100)
Total (N = 569)	**94 (16)**	**38 (6)**	**125 (22)**

Abbreviations: MIBI, technetium Tc 99m sestamibi; US, ultrasonography.
*$P<.001$ vs discordant imaging in each category of comparison.

Table 3. Accuracy of Imaging Studies

Imaging Study	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive Predictive Value, % (95% CI)
MIBI	69 (66-73)	92 (90-94)	89 (85-92)
US	63 (59-67)	90 (87-92)	89 (86-92)
MIBI and US imaging positive for same site (concordant)	56 (51-60)	60 (56-64)	99 (97-100)

Abbreviations: CI, confidence interval; MIBI, technetium Tc 99m sestamibi; US, ultrasonography.

decrease sufficiently, and further exploration revealed unsuspected additional disease. In an additional 3 (1%) of 319 patients, IOPTH-guided removal of an adenoma failed to correct hypercalcemia. There was a trend toward decreased surgical failure in patients with concordant studies ($P=.08$ vs patients with discordant studies).

The failure rate of surgery in patients with 2 concordant localizing studies was 1% with IOPTH measurement and 2% without IOPTH measurement. This was not a significant difference ($P=.50$). A sample of 2000 patients would be required to detect a difference of this small size.

Three quarters of the imaging errors involved localizing disease on the wrong side of a patient's neck or nowhere at all (**Table 2**). One quarter of the errors involved undetected multiglandular disease. **Table 3** summarizes the accuracy of the imaging studies individually and together. The MIBI and US imaging each had a sensitivity in the 60% to 70% range and a positive predictive value of 89%. When both were concordant for the same site, the positive predictive value increased to 99%.

COMMENT

Our series demonstrates that when US and MIBI parathyroid imaging both localize the same suspicious site for disease in PHPT, the localization is highly accurate. None of our 322 patients undergoing MIP in this circumstance had incorrect lateralization. Furthermore, IOPTH levels failed to normalize following removal of the localized adenoma in only 3 of these 322 patients. This accuracy is significantly higher than that of any single imaging study and higher than that of 2 studies when only 1 localizes a suspicious site of disease.

Previous series have suggested this possibility. Haber et al[3] found that concordant localization by MIBI and US imaging had a positive predictive value of 100% in 47 patients, and Scheiner et al[7] found the same in 31 patients who underwent MIP. Arici et al[6] reported a positive predictive value of 96% in 105 patients who underwent MIP. Miura et al[8] found a positive predictive value of 95% in 39 patients undergoing bilateral neck exploration. Summing these studies, 216 (98%) of 222 patients with concordant imaging findings proved to have correct localization, and the results are very similar to ours. However, in each study, samples were too small to judge the role of IOPTH measurement with statistical confidence.

There are important limitations to our analysis. We did not systematically record calcium levels at 6-month follow-ups in this study. Although early recurrence after initially successful MIP is unusual,[5] our ultimate surgical success rate could prove lower than 99%. Also, MIBI and US imaging can have variable results depending on technique and experience. Our results were based on studies done predominantly by radiologists with a large volume of experience with parathyroid imaging. As a consequence, the sensitivity and perhaps even the positive predictive value of these studies may be lower in settings where such imaging is not routinely done.

Nonetheless, our findings have significant implications for surgeons performing parathyroidectomy. First, the results indicate that routinely obtaining both US and MIBI images in patients with PHPT provides useful information, even if an initial test result is positive. Patients with only 1 of 2 tests localizing disease have a one-third chance of needing a complete neck exploration because of incorrect lateralization or failure to detect multiglandular parathyroid disease. If MIP is attempted in these patients, IOPTH measurement is essential.

Second, the results indicate that IOPTH measurement provides only marginal, if any, benefit in patients with concordant studies. More than half of our patients with PHPT had concordant studies. For them, the likelihood of having an accurately localized, single adenoma is so high—approaching 100%—that we could not find a statistically significant decrease in the surgical failure rate from using IOPTH measurement.

There are some disadvantages to using IOPTH measurement. Patients have their anesthesia and operative time extended while waiting for the IOPTH results. Also, IOPTH measurement itself can be inaccurate. In about 6% of patients with only a single parathyroid adenoma, PTH levels will remain elevated longer than 10 minutes after removal, perhaps prompting unnecessary neck exploration.[9]

Based on the evidence, a reasonable approach could be to reserve IOPTH measurement for patients with discordant imaging studies only. Patients with concordant studies would be informed of the 2% overall risk of early failure of MIP and, at unilateral exploration, must have a normal parathyroid identified and documented in addition to the adenomatous one removed. Extended exploration would then be reserved for those patients documented to have persistent hypercalcemia at follow-up.

Physicians have long sought a means to reliably localize parathyroid disease in patients with PHPT before surgery. In 1991, a National Institutes of Health Consensus Development Conference Panel[10] examined a wide range of imaging options and concluded that routine preoperative localization was not beneficial or recommended. Despite advances in imaging technology since then, no one imaging method has proved accurate enough to be relied on without IOPTH measurement confirmation. With this series, however, we have found that a combination of 2 methods, US and MIBI imaging, can reliably provide that accuracy in more than half of patients with PHPT.

Accepted for Publication: November 18, 2005.
Correspondence: Atul A. Gawande, MD, MPH, Department of Surgery, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115 (agawande@partners.org).
Previous Presentation: This paper was presented at the 86th Annual Meeting of the New England Surgical Society; October 1, 2005; Bretton Woods, NH; and is published after peer review and revision. The discussions that follow this article are based on the originally submitted manuscript and not the revised manuscript.
Acknowledgment: We give special thanks to Stuart Lipsitz, PhD, for his statistical advice.

REFERENCES

1. Irvin GL III, Sfakianakis G, Yeung L, et al. Ambulatory parathyroidectomy for primary hyperparathyroidism. *Arch Surg.* 1996;131:1074-1078.
2. Gotthardt M, Lohmann B, Behr TM, et al. Clinical value of parathyroid scintigraphy with technetium-99m methoxyisobutylisonitrile: discrepancies in clinical data and a systematic metaanalysis of the literature. *World J Surg.* 2004;28:100-107.
3. Haber RS, Kim CK, Inabnet WB. Ultrasonography for preoperative localization of enlarged parathyroid glands in primary hyperparathyroidism: comparison with (99m) technetium sestamibi scintigraphy. *Clin Endocrinol (Oxf).* 2002;57:241-249.
4. Purcell GP, Dirbas FM, Jeffrey RB, et al. Parathyroid localization with high-resolution ultrasound and technetium Tc 99m sestamibi. *Arch Surg.* 1999;134:824-830.
5. Udelsman R. Six hundred fifty-six consecutive explorations for primary hyperparathyroidism. *Ann Surg.* 2002;235:665-672.
6. Arici C, Cheah WK, Ituarte PHG, et al. Can localization studies be used to direct focused parathyroid operations? *Surgery.* 2001;129:720-729.
7. Scheiner JD, Dupuy DE, Monchik JM, Noto RB, Cronan JJ. Pre-operative localization of parathyroid adenomas: a comparison of power and colour Doppler ultrasonography with nuclear medicine scintigraphy. *Clin Radiol.* 2001;56:984-988.
8. Miura D, Wada N, Arici C, Morita E, Duh QY, Clark OH. Does intraoperative quick parathyroid hormone assay improve the results of parathyroidectomy? *World J Surg.* 2002;26:926-930.
9. Irvin GL III, Deriso GT III. A new, practical intraoperative parathyroid hormone assay. *Am J Surg.* 1994;168:466-468.
10. National Institutes of Health Consensus Development Conference Panel. NIH conference: diagnosis and management of asymptomatic primary hyperparathyroidism: Consensus Development Conference statement. *Ann Intern Med.* 1991;114:593-597.

DISCUSSION

Benedict Cosimi, MD, Boston, Mass: What is the cost for a sestamibi scan?

Dr Gawande: The charge for the patient is in the $200 to $400 range.

John Wei, MD, Burlington, Mass: I may seem kind of young but I remember back in the old days, for at least most of the surgeons who trained here, we didn't get localization studies prior to initial parathyroidectomy. In 1990 at the NIH [National Institutes of Health] consensus conference, I believe it was John Doppman, the radiologist, who said the only localization study you need is to locate a good surgeon. For a time in the early 90s, everybody was doing everything—MRI [magnetic resonance imaging] scans, CT [computed tomography] scans. For a while, the Cleveland Clinic was pushing getting PET [positron emission tomography] scans, and all this does is keep adding to the aggravation of treating what we know to be the natural distribution of disease etiology and what surgical intervention can do. By and large, for most surgeons who don't have the localization capabilities but have a good training and a sense as to how to treat parathyroid disease by doing a bilateral neck exploration, you could have a very high success rate with a minimal complication rate. There were some surgeons who advocated uniformly always exploring 1 side, and if you did that without any localization studies, you were lucky 40% of the time doing a unilateral neck exploration alone. I think you have to factor in what the cost-benefit ratio is of obtaining a sestamibi, neck ultrasonography either in radiology or intraoperatively, and the additional cost of intraoperative PTH monitoring. What is the cost to the patient and society, and what benefit does the individual patient gain?

Dr Gawande: Thank you for the question. There is no question that a complete neck exploration for any patient with primary hyperparathyroidism is effective and good therapy for patients. The benefits of being able to offer them minimally invasive approach are simply being able to do this surgery under local anesthesia if desired, having a day surgery instead of an overnight stay, not putting a laryngeal nerve on both sides at risk of injury, and decreased operative time. These are not dramatic benefits, but the public has demonstrated preference for them by choosing to go to surgeons who offer the technique.

Steven Schwaitzberg, MD, Boston: This is an operation that demonstrates that there are many ways to skin a cat. My first question is, what is your definition of minimally invasive parathyroidectomy? When you look at the literature from the *World Journal of Surgery*, one of the criteria was less than 4-cm incision, which I would consider a maximally invasive parathyroidectomy, personally.

I've been using ultrasound and PTH for many years, but I use the ultrasound in the operating room and I have found similar results. If the ultrasound and the sestamibi agree, then it's a pretty straightforward operation and the PTH hasn't been that helpful. The reason why I do ultrasound in the operating room is that the position of the neck in both the sestamibi scan and in the ultrasound and the quality of the operator doing the ultrasound creates great variation in results. So I use a very experienced ultrasonographer in the OR [operating room], and I can make an incision generally 2 cm or less to take out the gland. When do you perform your ultrasound and what do you consider minimally invasive?

Dr Gawande: Thank you for the question. Our definition of minimally invasive is that it is a unilateral exploration. We routinely use a 2-cm incision and, you are correct, the localization by ultrasound allows us to have a very small and targeted exploration. Our ultrasound is done by dedicated radiologists, and so a caveat for our results is that our precision may have benefited. In general, we do not do our ultrasound in the operating room. We have the imaging, reports, and anatomic landmarks available to us in advance, and that has allowed us to plan our operation appropriately. I agree, a routine 4-cm incision would not be considered minimally invasive.