ORIGINAL ARTICLE

Surgery for Hyperparathyroidism in Image-Negative Patients

Rodney K. Chan, MD; Daniel T. Ruan, MD; Atul A. Gawande, MD, MPH; Francis D. Moore Jr, MD

Hypothesis: Patients with primary hyperparathyroidism and negative preoperative localization imaging have a different outcome than patients with positive imaging.

Design: Prospective single-surgeon case series.

Setting: Referral center.

Patients: Forty-two patients with primary hyperparathyroidism, indications for surgery, and both cervical ultrasonographic results and technetium Tc 99m sestamibi nuclear images that were nonlocalizing over a 5-year span.

Main Outcome Measures: Extent of surgery required to produce cure; operative findings.

Results: Of 430 patients undergoing surgery for primary hyperparathyroidism, 351 underwent both ultrasonographic and sestamibi imaging. Among 351 patients, the imaging results of 42 patients did not show an adenoma, and these patients underwent cervical exploratory surgery. Of 42 patients, 41 were cured at a mean follow-up of 90 days; 1 patient underwent surgical reexploration and was cured by removal of a mediastinal adenoma. To achieve initial cure, 12 of 42 patients (28.6%) required partial thyroidectomy, 9 (21.4%) required partial thymectomy, 17 (40.5%) required paratracheal dissection to access or devascularize an obscure adenoma. Pathologic examination disclosed single adenoma in 26 of 42 patients (61.9%), parathyroid hyperplasia in 14 (33.3%), and double adenoma in 2 (4.8%).

Conclusions: Patients whose preoperative localization studies fail to localize solitary adenoma commonly require extensive surgery to cure hyperparathyroidism. Lack of localization may be a reasonable criterion on which to base referral of the patient to a high-volume medical center.

Arch Surg. 2008;143(4):335-337

ACCURATE PREOPERATIVE localization is important to successful focused parathyroidectomy. In the past, intraoperative parathyroid hormone (PTH) level monitoring has complemented preoperative radiographic testing, allowing surgeons to observe a physiologic drop in the PTH level after resection of the affected adenoma. Although technetium Tc 99m sestamibi imaging and ultrasonography (US) are highly specific for localization of the affected gland when used together, neither technique is very sensitive. In the Mayo Clinic experience of almost 1400 patients, sestamibi imaging has a sensitivity of 86%, whereas US has a sensitivity of 61%.[1] In a recent review of the experience at our institution, sestamibi imaging has a sensitivity of 69%, whereas US has a sensitivity of 63%.[2] Therefore, failure of either or both techniques to localize an affected adenoma is possible.

Our research group previously showed that the positive predictive value in localizing an affected adenoma can be increased with the use of US and sestamibi imaging together and that concordant localization might negate the need for intraoperative PTH level monitoring.[2] For that reason, we adopted the technique of obtaining both preoperative imaging modalities whenever feasible. Despite this, a subset exists of patients who otherwise have clinical primary hyperparathyroidism and in whom both techniques will fail to localize an affected gland.

The characteristics and outcomes of these image-negative parathyroidectomies in patients with nonlocalizing sestamibi images are not well characterized, and it is the intent of this study to further define these lesions. It has been speculated that parathyroid glands with negative imaging carry a higher incidence of multiglandular disease, although there have been only sporadic reports in the literature specifically studying this issue.[3]

Author Affiliations:
Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.

METHODS

In this prospective, single-surgeon case series, we gathered clinical data on all patients who underwent surgery for primary hyperparathyroidism at Brigham and Women's Hospital, Boston, Massachusetts, between January 2000 and June 2005, performed by one of us (F.D.M.). We excluded all patients with renal failure and patients who had recurrent disease. Data recorded included operative findings, basic demographics, preoperative indications, findings of the 2 imaging modalities, preoperative calcium and PTH levels, rapid PTH assay measurements (if any), and final pathologic diagnosis and follow-up data, including calcium level at 3½ months after surgery.

The study was approved by the institutional review board at Brigham and Women's Hospital; all data collection was performed in accord with regulations defined in the study protocol. All identifying information about specific patients was removed.

All patients with negative imaging went to the operating room with the intent to undergo a 4-gland exploratory procedure. Surgical exploration commenced on the right side, and a blood sample for baseline PTH level measurement was drawn from the internal jugular vein before any significant dissection or retraction was performed. If a clinically evident adenoma was identified and resected with an associated greater than 50% drop in PTH level in a second blood sample 10 minutes later, contralateral exploration was abandoned. If no adenoma was found on the right side, contralateral exploration was pursued until adenoma or hyperplasia was identified with certainty. We found that the intraoperative PTH level measurement was helpful when only a single side was surgically explored and an adenoma was immediately found, and the assay helped exclude a second adenoma without further exploration. The technique used for rapid intraoperative PTH assay has been previously described.[4] Further dissection is ceased during the 10-minute wait time until the postresection sample PTH level is analyzed.

In cases in which all 4 glands were enlarged (parathyroid hyperplasia), biopsy specimens were obtained of all 4 parathyroid glands to confirm their identity as parathyroid tissue. All 4 were then resected except for a portion of 1 gland approximating the mass of a single normal parathyroid gland.

Failure to identify an adenoma led to further surgical exploration on the side of the missing parathyroid gland, consisting of unilateral cervical thymectomy, retroesophageal exploration, jugular sheath exploration, and division of the thyroid upper pole vessels to enhance visualization of the region of the recurrent nerve insertion into the larynx. When this maneuver failed to identify the missing adenoma, partial thyroidectomy was performed on the side of the missing parathyroid gland. If the missing parathyroid gland was definitively identified as in the lower position, this thyroid resection included only the inferior 50% of the thyroid. If the missing parathyroid gland was thought to be in the upper or lower position, complete partial thyroidectomy was performed.

Failure of the partial thyroidectomy specimen to contain the abnormal parathyroid, per immediate pathologic examination, led to paratracheal dissection to remove or devascularize any occult parathyroid tissue. Paratracheal dissection includes resection of unilateral paratracheal soft tissue consisting of fat, lymph nodes, and any missing parathyroid tissue from the space defined by the trachea and esophagus medially, the pretracheal fascia posteriorly, and the carotid artery laterally. The upper parathyroid gland, if normal, is preserved on a vascular pedicle extending to the inferior thyroid artery. The dissection extends from the level of the insertion of the recurrent laryngeal nerve into the larynx down to the upper mediastinum. The recurrent nerve is preserved.

Statistical analysis was performed using commercially available software (Sigmaplot; SPSS Inc, Chicago, Illinois). Results are given as mean (SE) unless otherwise indicated. If needed, comparison groups were subjected to 1-way analysis of variance, and a *t* test was applied when statistical significance was found.

RESULTS

During 5 years, 430 patients underwent surgery for primary hyperparathyroidism. Of these, 351 underwent both US and sestamibi imaging. Among these, 174 had concordant findings, 135 had discordant findings, and 42 did not show an adenoma by either modality.

All 42 patients underwent cervical exploratory surgery, which commenced on the right side (our usual practice). In 11 patients, an obviously abnormal right parathyroid gland was found and was resected with an associated drop in the rapid intraoperative PTH assay, consistent with cure. The remaining 31 patients went on to undergo a contralateral exploratory procedure. Among our 42 patients, no complications, including bleeding, hypocalcemia, and vocal cord paralysis or paresis occurred.

Of 42 patients, 41 required no further surgery at a mean follow-up of 90 days. One patient underwent surgical reexploration and was cured by removal of a mediastinal adenoma, through a median sternotomy, located on the aortic arch. Among the patients with negative imaging, 12 of 42 (28.6%) required partial thyroidectomy, 9 (21.4%) required partial thymectomy, 17 (40.5%) required paratracheal dissection to access or devascularize an obscure adenoma. A mean of 4 (range, 1-11) frozen sections per patient were sent for pathologic examination. Among 42 patients with negative imaging, final pathologic examination disclosed single adenoma in 26 (61.9%), parathyroid hyperplasia in 14 (33.3%), and double adenoma in 2 (4.8%). Of 12 resected thyroid specimens, 8 contained intrathyroidal parathyroid tissue. Resection of affected glands was performed in the cases of single and double adenomas, and subtotal parathyroidectomy, as already described, was performed in the case of parathyroid hyperplasia. Twenty-six single adenomas were found. Thirteen (6 right upper and 7 right lower adenomas) were on the right side, and 13 (7 left upper and 6 left lower adenomas) were on the left side.

COMMENT

Patients with negative imaging represent an important subset of patients with primary hyperparathyroidism in whom traditional 4-gland operative exploratory surgery remains the optimal management because of the increased frequency of multiglandular disease (38% vs 15% in patients with positive imaging[5-7]). Based on the findings of this study, these patients perform well with long-term cure of their disease after undergoing an appropriate surgical procedure. Because of the higher incidence of multiglandular disease in these patients, surgery needs to be conducted with a level of suspicion that multiglandular disease exists to ensure that all diseased glands are resected during the operation.[2] If an adenoma is found immediately and is resected with an associated greater

than 50% drop in PTH level at 10 minutes after the resection, contralateral exploratory surgery in theory can be abandoned, as was done in several of these cases. However, the positive predictive value of a fall in intraoperative PTH level is highest in patients with positive imaging, among whom the incidence of solitary adenoma exceeds 90%. In the setting of patients having negative imaging, with a much higher incidence of multiglandular disease, changes in intraoperative PTH levels have lower positive predictive value, and interpretations should be made with care. Therefore, the wiser strategy in the case of a rapidly discovered parathyroid adenoma in a patient with negative imaging might be to continue the surgical exploration to ensure that further abnormal tissue is not present.

The incidence of patients with negative imaging is significant. Based on a review[8] published in 1980, the mean annual incidence of primary hyperparathyroidism is 51 cases per 100 000. In review of our experience, 14% of these do not have an adenoma that can be found using sestamibi imaging or US. Other centers at which both of these preoperative imaging modalities are used report a similar rate of negative imaging, ranging from 12% to 18%.[3,9] Findings from another study[10] suggest that sestamibi imaging–negative cases have histologic findings that are different from those associated with hyperparathyroidism. This nuclear medicine study histologically compared parathyroid specimens from patients with negative preoperative nuclear imaging with those from patients with positive imaging, and the authors conclude that patients with negative imaging have a higher preponderance of chief cells than do patients with positive imaging, who had a higher incidence of oxyphilic cells. Others report that sestamibi imaging–negative hyperparathyroidism is associated with smaller adenomas than are positive-imaging cases.[11] The PTH levels associated with these small adenomas were also less than the PTH levels from positive-imaging cases. This group previously reported a direct relationship between serum PTH levels and adenomatous gland weight.[12] We did not address this issue. However, the common need for extensive surgical exploration, including paratracheal dissections and thyroid resections, indicates (at the least) that the frequency of occult parathyroid adenomas and difficult explorations is increased in patients with negative imaging. Our data do not support this finding.

The length of patient follow-up after surgery that is necessary to determine whether a patient is cured is a major ambiguity in the parathyroid surgery literature. To our knowledge, other than the already-mentioned single patient with the adenoma on the aortic arch, there has not been persistent or recurrent disease in the patients described herein.

Although solitary adenomas account for most abnormalities in this subset of patients with negative imaging, parathyroid exploratory surgery often and unpredictably requires more extensive neck exploration, including paratracheal dissection, thymectomy, and partial thyroidectomy. The immediate availability of intraoperative rapid PTH monitoring and of expert frozen section analysis is important to accomplish successful cures. This suggests the need for referral of these patients to high-volume medical centers for parathyroid surgery.

Accepted for Publication: March 12, 2007.
Correspondence: Francis D. Moore Jr, MD, Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, 75 Francis St, Boston, MA 02115 (fmoore@partners.org).
Author Contributions: *Study concept and design:* Chan, Gawande, and Moore. *Acquisition of data:* Chan and Ruan. *Analysis and interpretation of data:* Chan and Moore. *Drafting of the manuscript:* Chan and Moore. *Critical revision of the manuscript for important intellectual content:* Chan, Ruan, Gawande, and Moore. *Statistical analysis:* Gawande and Moore. *Obtained funding:* Moore. *Administrative, technical, and material support:* Chan and Moore. *Study supervision:* Gawande and Moore.
Financial Disclosure: None reported.
Previous Presentation: This study was presented in part at the 87th Annual Meeting of the New England Surgical Society; September 15, 2006; Groton, Connecticut.

REFERENCES

1. Grant CS, Thompson G, Farley D, van Heerden J. Primary hyperparathyroidism surgical management since the introduction of minimally invasive parathyroidectomy: Mayo Clinic experience. *Arch Surg.* 2005;140(5):472-479.
2. Gawande AA, Monchik JM, Abbruzzese TA, Iannuccilli JD, Ibrahim SI, Moore FD Jr. Reassessment of parathyroid hormone monitoring during parathyroidectomy for primary hyperparathyroidism after 2 preoperative localization studies. *Arch Surg.* 2006;141(4):381-384.
3. Sebag F, Hubbard JG, Maweja S, Misso C, Tardivet L, Henry JF. Negative preoperative localization studies are highly predictive of multiglandular disease in sporadic primary hyperparathyroidism. *Surgery.* 2003;134(6):1038-1041.
4. Chan RK, Ibrahim SI, Pil P, Tanasijevic M, Moore FD. Validation of a method to replace frozen section during parathyroid exploration by using the rapid parathyroid hormone assay on parathyroid aspirates. *Arch Surg.* 2005;140(4):371-373.
5. Moore FD Jr, Mannting F, Tanasijevic M. Intrinsic limitations to unilateral parathyroid exploration. *Ann Surg.* 1999;230(3):382-391.
6. Rasmussen K, Larsen LP, Arveschoug A, et al. Predictive value of parathyroid scintigraphy in the preoperative evaluation of patients with primary hyperparathyroidism. *Scand J Surg.* 2006;95(3):199-204.
7. Lo CY, Lang BH, Chan WF, Kung AW, Lam KS. A prospective evaluation of preoperative localization by technetium-99m sestamibi scintigraphy and ultrasonography in primary hyperparathyroidism. *Am J Surg.* 2007;193(2):155-159.
8. Heath H III, Hodgson SF, Kennedy MA. Primary hyperparathyroidism: incidence, morbidity, and potential economic impact in a community. *N Engl J Med.* 1980;302(4):189-193.
9. Sugg SL, Krzywda EA, Demeure MJ, Wilson SD. Detection of multiple gland primary hyperparathyroidism in the era of minimally invasive parathyroidectomy. *Surgery.* 2004;136(6):1303-1309.
10. Mihai R, Gleeson F, Buley ID, Roskell DE, Sadler GP. Negative imaging studies for primary hyperparathyroidism are unavoidable: correlation of sestamibi and high-resolution ultrasound scanning with histological analysis in 150 patients. *World J Surg.* 2006;30(5):697-704.
11. Goldstein RE, Carter WM II, Fleming M, et al. Unilateral cervical surgical exploration aided by intraoperative parathyroid hormone monitoring in patients with primary hyperparathyroidism and equivocal sestamibi scan results. *Arch Surg.* 2006;141(6):552-559.
12. Goldstein RE, Billheimer D, Martin WH, Richards K. Sestamibi scanning and minimally invasive radioguided parathyroidectomy without intraoperative parathyroid hormone measurement. *Ann Surg.* 2003;237(5):722-731.