Parathyroid Adenoma Localization: Surgeon-Performed Ultrasound Versus Sestamibi

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Objectives: Compare surgeon-performed ultrasound versus sestamibi for preoperative parathyroid adenoma localization. Study Design: Single-institutional cohort. Methods: One hundred six consecutive patients undergoing parathyroidectomy at an academic institution between 2004 to 2005 were included. Of those, 103 underwent both surgeon-performed ultrasound and sestamibi-Tc99m localization preoperatively. Primary outcome is sensitivity for adenoma localization to correct quadrant (right vs. left, superior vs. inferior). Results: Hypercalcemia resolved in 97% of patients. Sensitivities for correct quadrant localization for ultrasound versus sestamibi were 87% versus 58% (P < .001). Specificities were 95%. Positive and negative predictive values were 85% versus 78% and 96% versus 87%, respectively. Combined sensitivity was 93%. Sensitivities for correct side localization were 91% and 74% (P = .002). Conclusions: Ultrasound appears more sensitive than sestamibi for localization to correct quadrant or side when performed in-office by the author in this cohort. Key Words: Ultrasound, parathyroid, sestamibi, sensitivity, primary hyperparathyroidism, hypercalcemia, parathyroidectomy, minimally invasive parathyroidectomy.

INTRODUCTION

Primary hyperparathyroidism is a common endocrine disorder that affects 1 in 700 people. The vast majority of patients with excess parathyroid hormone (PTH) secretion have solitary parathyroid adenomas.1 Since the 1960s, when serum autoanalyzers were available to reliably di-agnose hyperparathyroidism, the gold standard for surgical cure has been bilateral neck exploration and evaluation of all four glands. This technique has achieved cure rates of greater than 95%, with minimal morbidity and mortality (<1%).2

During the last decade, in an effort to reduce operative time, provide better cosmesis, and reduce complications (i.e., recurrent nerve damage and postoperative hypocalcemia), minimally invasive parathyroidectomy has been gaining popularity. This focused approach is possible because preoperative imaging can accurately identify the location of solitary parathyroid adenomas and allow the surgeon to perform a unilateral or focused exploration with similar rates of surgical cure, morbidity, and mortality to bilateral neck exploration.3

The most commonly used imaging techniques for preoperative parathyroid adenoma localization include high-resolution sonography, computed tomography, magnetic resonance imaging, and radionucleotide scintigraphy. Currently, the most consistently accurate tests have been Technetium-99m-sestamibi scintigraphy (sensitivities of 54–93%) and ultrasonography (sensitivities of 57–93%), traditionally performed and interpreted by radiologists.4–8

In this study, we wanted to investigate surgeon-performed, in-office, high-resolution ultrasound in comparison with sestamibi scanning for the preoperative localization of parathyroid adenomas. We hypothesize that in-office ultrasound may be an effective localization adjunct for surgeons performing focused parathyroidectomy because it provides greater anatomic detail than radionuclide scans.

MATERIALS AND METHODS

Study Objective and Design

The primary objective of this study is to review a single-institution cohort and compare the sensitivity of surgeon-performed, high-resolution ultrasound to dual-phase technetium 99m sestamibi for preoperative localization of parathyroid adenomas.

Patients

After receiving approval from the local institutional review board, Current Procedural Terminology codes 60500 and 60502 were used to identify patients from departmental databases who underwent parathyroidectomy by the senior author over the pe-
rior from 2004 to 2005. Their medical charts, pathology reports, operative reports, nuclear medicine reports, office ultrasound reports, and laboratory results were reviewed. The objective results of these reports were recorded by two otolaryngology residents (G.D. and C.A.), who were not part of the initial ultrasound or sestamibi interpretation. During this period, 106 patients with biochemically diagnosed primary hyperparathyroidism underwent parathyroid exploration by the senior author in a university-based, tertiary care center. Of these, 103 patients had both preoperative sestamibi and office-based ultrasound performed by the attending surgeon, and the other 3 only had ultrasound, which correctly localized all three cases including two superior mediastinal. These patients were studied to compare the sensitivity of surgeon-performed, high-resolution ultrasound with sestamibi for preoperative localization of parathyroid adenomas. Patients with hyperparathyroidism caused by hyperplasia (1 multiple endocrine neoplasia type 1, 2 multiple endocrine neoplasia type 2a, and 2 sporadic) or failed exploration were excluded from analysis of sensitivity for adenoma localization.

**Ultrasound**

Cervical ultrasound for parathyroid adenoma localization was performed by the primary author after completing a course and receiving accreditation by the American College of Surgeons in Head and Neck ultrasound. This author also had at least 1 year of clinical experience with in-office ultrasound of the thyroid before performing sonographic parathyroid localization. All high-resolution ultrasounds were performed with a 7.5 to 12 MHz transducer using a portable ultrasound, either SonoSite Titan or MicroMax (Bothell, WA). Transverse and longitudinal planes were used to identify the characteristic extrathyroidal hypoechoic mass in B mode (gray scale). Color Doppler was used as an adjuvant to assess vascularity of and blood supply to the mass. Presence or absence along with size and quadrant of the adenomas were recorded in a dictated report. Adenomas sonographically located at or above the level of the cricoid, or completely posterior to the posterior surface of the common carotid or inferior thyroid artery (used as a surrogate marker for the plane of the recurrent laryngeal nerve), were designated as superior.

**Parathyroid Scintigraphy**

The Sestamibi scans were performed within the department of nuclear medicine at any of our regional hospitals and interpreted by one of the attending radiologists and reviewed by the attending surgeon. The scintigraphic technique used the radio-nucleotide Technitium-99m according to a parathyroid localization protocol with imaging of the head, neck, and chest, both with and without anatomic markers (sternal and thyroid notches). Both early (10–20 min postinfusion) and delayed (2–3 hr postinfusion) images were obtained. Most subjects also underwent single-photon emission computed tomography with the delayed imaging. Some subjects also underwent thyroid subtraction technique in cases of side to side asymmetry on initial images without persistence on delayed images.

**Surgery**

Minimally invasive parathyroidectomy was attempted if at least one study was localizing and thyroidectomy was not planned concomitantly. The location of the adenoma was noted (right vs. left, inferior vs. superior), and the excised specimen was sent to pathology for weight and histopathologic confirmation. Adenomas dorsal to the recurrent laryngeal nerve were deemed superior, those ventral deemed inferior. Another ipsilateral gland was also identified unless intraoperative PTH monitoring was used to exclude multiglandular disease. The two contralateral glands were not routinely identified. If the adenoma was not localized through this approach, bilateral neck exploration was performed. Adenoma resection and resolution of primary hyperparathyroidism was confirmed with frozen and permanent histology and an intraoperative or recovery room PTH level and postoperative calcium levels.

**Statistical Analysis**

The primary outcome measure was chosen a priori as sensitivity for preoperative parathyroid adenoma location to correct quadrant (right vs. left and superior vs. inferior) between surgeon-performed ultrasound and sestamibi. Surgical findings were used as the reference standard. Sensitivity is defined as (true-positives)/ (true-positives + false-negatives). Hypothesis testing was done with McNemar testing to compare sensitivity in discordant cases (after exclusion of cases with both tests in agreement), with P < 0.05 defined as significant. Secondary outcomes included other measures of preoperative localization accuracy including specificity and positive and negative predictive values. Surgically confirmed normal parathyroid glands were defined as true-negatives or false-positives. In cases of minimally invasive or unilateral parathyroidectomy wherein all four glands were not explored, an assumption was made that each patient had a total of four parathyroid glands. This assumption was made to calculate specificity for both ultrasound and sestamibi and appears justified given that 80% of subjects have four parathyroid glands and the assumption was made for both ultrasound and sestamibi. Secondary analysis was also calculated for sensitivity of parathyroid adenoma location to correct side (left vs. right). The Center for Biostatistical Services at the University of Cincinnati was consulted for analyses.

**RESULTS**

Of the 106 patients diagnosed with primary hyperparathyroidism by biochemical testing and undergoing parathyroidectomy, 103 had both preoperative surgeon-performed ultrasound and sestamibi. Of these, 97 patients had a histopathologic confirmation of parathyroid adenoma with postoperative resolution of hypercalcemia and primary hyperparathyroidism, one of whom developed recurrence after 6 months (minimum follow-up 4 mo, median follow-up 15 mo). One patient has persistent disease after exploration failed to reveal abnormal parathyroid tissue. The other five patients had primary hyperplasia three diagnosed preoperatively (1 MEN1, 2 MEN2a), and two discovered at surgery, one of which has persistent disease despite 3.5 gland parathyroidectomy (MEN1). The majority of adenomas were inferior (65%) and orthotopic (90%). Of the 10 ectopic glands, 6 were intrathyroidal, 2 within the carotid sheath, and 2 retroesophageal. Of the excluded patients, another four had enlarged anterior superior mediastinal glands, one identified on sestamibi missed by ultrasound (MEN2a), one identified by ultrasound but missed on sestamibi (MEN1), and two others identified on ultrasound but not studied with sestamibi (solitary adenoma).

The mean preoperative serum calcium level was 11.1 (range, 10.1–12.5) mg/dL, and the mean simultaneous intact PTH level was 194 (range 66–657) pg/mL. Mean calcium decreased to 8.9 (range 8.0–10.2) mg/dL postoperatively either with or without oral calcium supplementation. The intraoperative or immediate postoperative intact PTH level also decreased to a mean of 28 (range, 3–98) pg/mL. The reference ranges for calcium at University of Cincinnati is 8.4 to 10.2 mg/dL, with PTH norms of 3–98 pg/mL.
sensitive than sestamibi for both inferior (91% vs. 77%, a significant difference with 48–67%) for exact quadrant (56 of 97 adenomas). This was a significant difference with \( P < .0001 \). Of the 40 discordant cases, ultrasound correctly localized 34 adenomas missed or incorrectly localized by sestamibi, and sestamibi correctly localized 6 adenomas missed or incorrectly localized by ultrasound. When ultrasound and sestamibi were combined, sensitivity was 93% (95% CI = 86–96%) for correct quadrant localization.

Specificity for localization to correct quadrant was 95% for both ultrasound and sestamibi (Table I). Positive predictive value for localization to correct quadrant for ultrasound and sestamibi were 85% versus 78%, respectively. Negative predictive values were 96% versus 87%, respectively.

When analysis was performed for correct side of localization, sensitivity of ultrasound was 91% (88 of 97 adenomas) with a 95% CI of 83 to 95%. In comparison, sestamibi had a sensitivity of 74% (72 of 97 adenomas) with a 95% CI of 65 to 82%. This was significantly different \( (P = .002) \).

Univariate analysis was performed to assess impact of adenoma location (superior vs. inferior, ectopic vs. orthotopic) and size (mass or volume) on preoperative sensitivity for correct quadrant localization of ultrasound and sestamibi. Sensitivity was significantly correlated with superior versus inferior location for sestamibi (77% inferior vs. 27% superior, \( P < .0001 \)) but not ultrasound (91% inferior vs. 81% superior, \( P = .20 \)). Ultrasound was more sensitive than sestamibi for both inferior (91% vs. 77%, \( P = .03 \)) and superior locations (81% vs. 27%, \( P < .0001 \)). Sensitivity was significantly correlated with ectopic versus orthotopic location for ultrasound (70% ectopic vs. 89% orthotopic, \( P = .01 \)) and sestamibi (30% ectopic vs. 61% orthotopic, \( P < .01 \)). No significant difference was noted between sensitivity for ectopic location between ultrasound versus sestamibi (70% vs. 30%, \( P = .09 \)). Sensitivity was not significantly correlated with adenoma size (mass or volume) for ultrasound or sestamibi.

**DISCUSSION**

The results of this study suggest that surgeon-performed, office-based, high-resolution ultrasound was more accurate for preoperative localization of parathyroid adenomas than sestamibi Tc99m in this cohort of subjects. This is consistent with the results of a recent, smaller \( (n = 52) \) study of surgeon-performed ultrasound, which demonstrated greater sensitivity of surgeon-performed ultrasound (82%) than sestamibi (44%) or radiology-performed ultrasound (42%) for preoperative localization to correct side. A recent, larger series \( (n = 226) \) demonstrated similar sensitivities for sestamibi and surgeon-performed ultrasound to side (77%) but concluded that surgeon-performed ultrasound should be the initial and only preoperative localization study if positive because of its high positive predictive value, patient convenience, and greater cost effectiveness. A more recent, smaller \( (n = 43) \) study of office-based ultrasound demonstrated greater sensitivity of ultrasound (79%) versus sestamibi (53%) to correct quadrant and 84% versus 67%, respectively, to correct side \( (both \ P = .03) \). Other comparable studies involving institutions with radiology staff experienced in neck ultrasound have documented higher sensitivities for high-resolution ultrasound than sestamibi.

The primary advantage of ultrasound over sestamibi is the significantly greater anatomic detail provided by sonography. The advantage of the surgeon performing the imaging in “real time” is that it provides additional information compared with reliance on “static” images obtained by a radiologist or a radiology technician. Furthermore, the parathyroid surgeon is likely to have far greater experience with surgical localization of parathyroid glands and the surrounding anatomy than a radiologist or technician. And if planning a minimally invasive or focused approach, the surgeon will have greater motiva-
tion to identify the adenoma and precisely localize it preoperatively, potentially minimizing the time for surgical exploration.\textsuperscript{13} Thus, is the importance of accuracy of localization to correct quadrant (right vs. left and superior vs. inferior), which is often neglected in the studies reporting high sensitivity of sestamibi scans.\textsuperscript{5,9}

In our study, the adenoma mass was relatively small, with a median mass of 600 mg and 25% quartile of 400 mg. Because the degree of sestamibi uptake is positively associated with the volume of hypersecreting tissue, adenomas with a median mass of 165 to 410 mg often demonstrate no uptake on imaging.\textsuperscript{14} This could account for many of our false-negatives and relatively low sestamibi sensitivity to correct side because a fourth of the adenomas were smaller than 400 mg. Our sestamibi results are similar to\textsuperscript{9,11} or better than\textsuperscript{10} other contemporary studies. Because routine renal panels now include calcium measurement, hypercalcemia and primary hyperparathyroidism are increasingly being diagnosed and surgically treated at an earlier stage of disease. As such, surgeons may increasingly desire accurate localization techniques for smaller adenomas.

The primary limitation of ultrasound appears to be technician experience. This is supported by Purell et al.,\textsuperscript{5} who demonstrated that sensitivity of ultrasound can vary from 33\% to 79\% depending on the experience of the radiologist with parathyroid imaging. It is expected that the same would be true for surgeons performing ultrasound, and those with higher volumes of parathyroid surgery may have a steeper learning curve than those performing parathyroidectomy less often. Experience with thyroid ultrasound is likely to be beneficial, although parathyroid localization is generally more difficult than identification of thyroid nodules.

Another distinct advantage of ultrasound is the ability to preoperatively identify thyroid nodules, perform a fine needle aspiration (FNA), and, depending on cytology, allow appropriate thyroid surgery at the time of parathyroidectomy while minimizing unnecessary surgery.\textsuperscript{15} In this series, two patients where diagnosed with thyroid carcinoma preoperatively because of ultrasound FNA of incidentally noted nodules, one of whom had medullary carcinoma. As a result, this patient was diagnosed with MEN2a before neck exploration, which allowed for appropriate surgical planning and biochemical screening for pheochromocytoma preoperatively.

CONCLUSIONS

High-resolution ultrasound appears more sensitive for parathyroid adenoma localization to correct quadrant than sestamibi Tc99m when performed by the attending surgeon in this cohort of subjects. Ultrasound was significantly more sensitive than sestamibi for superior or inferior adenomas, but the difference was most marked for superior locations. Further prospective study is needed, but these results suggest that in-office ultrasound may be an effective localization tool for surgeons performing focused or minimally invasive parathyroidectomy. Complementing with sestamibi further improves localization sensitivity in cases where ultrasound is nonlocalizing and adds confidence to the likelihood of true-positive when the two studies localize to the same quadrant or side. Experience of the ultrasonographer may be the primary limitation of this imaging modality.

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BIBLIOGRAPHY