Technetium Tc 99m Sestamibi Sensitivity in Oxyphil Cell–Dominant Parathyroid Adenomas

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Objective: A subset of parathyroid adenomas contains a relative overabundance of oxyphil cells that are capable of greater technetium Tc 99m sestamibi tracer uptake and retention than other cell types. We examined whether the presence of oxyphil cells augments the sensitivity of technetium Tc 99m sestamibi preoperative localization and whether the histologic findings of a lesion could be predicted based on the adenoma mass and serum calcium and parathyroid hormone levels.

Design: Retrospective, single-blinded comparison of technetium Tc 99m sensitivity rates, lesion mass, and preoperative serum calcium and parathyroid hormone values of patients with chief and mixed cell–dominant adenomas and those with oxyphil-dominant parathyroid adenomas.

Setting: Tertiary care university hospital.

Patients: Sixty-three patients diagnosed as having a parathyroid adenoma.

Intervention: All patients underwent resection of a parathyroid adenoma following a preoperative technetium Tc 99m sestamibi localization study and serum calcium and parathyroid hormone level analysis.

Main Outcome Measure: Technetium Tc 99m sensitivity rate.

Results: The overall technetium Tc 99m sestamibi sensitivity rate was 76.2%. The sensitivity within the chief and mixed cell–dominant (n=52) and oxyphil cell–dominant groups (n=11) were 71.2% and 100%, respectively (P=.04). There was no correlation between histologic findings of the lesion and its size or serum calcium and parathyroid hormone levels.

Conclusions: Oxyphil cell predominance within an adenoma augments technetium Tc 99m sestamibi scan sensitivity in a statistically significant manner. The use of technetium Tc 99m sestamibi preoperative localization may therefore be differentially greater in patients with these types of lesions.


Primary hyperparathyroidism is a chronic, surgically correctable disease that occurs in 1 of 500 women older than 40 years and in 1 of 2000 men. The majority of primary hyperparathyroidism cases (80%-85%) result from benign adenomas whereas cases of diffuse hyperplasia (8%-15%) and carcinoma (0.5%) compose a small but clinically important minority.1,2

Conventional surgical intervention involves bilateral exploration during first-time surgery for primary hyperparathyroidism. However, the introduction of preoperative localization studies and the 85% to 90% cure rate following the removal of the single enlarged parathyroid gland prompted some surgeons to adopt a unilateral approach in which resection of the diseased gland and identification of normal tissue in an ipsilateral gland were considered adequate. Others have taken this strategy even further by advocating minimally invasive surgery in which the operation is performed through a 1- to 4-cm incision using preoperative and intraoperative localization modalities. There are multiple arguments for unilateral surgery, including reduction of operation and anesthesia time, lower risk of postoperative hypocalcemia and recurrent laryngeal nerve injury, and shorter hospital stays.3

Given the high cure rate and accuracy of available radiologic techniques, the role of preoperative localization in patients undergoing initial neck exploration is controversial. The predictive value of ultrasonography, computed tomography, or magnetic resonance imaging ranges from 40% to 80%.4 Although technetium Tc 99m sestamibi localization is associated with improved sensitivity rates of 70% to 100%,5 the persistence of false-negative findings remains problematic and may be associated with patients with multiglandular disease.6
Some authors have postulated that the wide variability in the efficacy of technetium Tc 99m sestamibi localization results from differences in the abundance of mitochondrial-rich oxyphil cells found within parathyroid adenomas. Hetrakul et al showed that tracer accumulation and retention within oxyphil cells is mediated by mitochondrial activity and could be reversed by an uncoupler of oxidative phosphorylation. It is not currently known whether this difference in tracer uptake is significant enough to alter scan results. In the study described herein, we explored how the presence of oxyphil-dominant lesions has an impact on the sensitivity of preoperative sestamibi localization.

**METHODS**

**PATIENT POPULATION**

Data from 81 patients presenting with hyperparathyroidism from October 1997 to May 2005 were retrospectively collected. Sex, age, and preoperative serum values for calcium and intact parathyroid hormone (PTH) were recorded. Sixty-three patients underwent preoperative technetium Tc 99m sestamibi localization studies (technetium Tc 99m sestamibi–iodine I 123 subtraction imaging, n=41; technetium Tc 99m sestamibi delayed imaging, n=22). A true-positive scan was defined as one that made it possible to identify and lateralize a diseased gland to the correct side of the neck. All patients underwent neck exploration performed by 1 of 2 surgeons (A.A.C. and R.S.W.) at the hospital of the University of Pennsylvania, Philadelphia, and all lesions were histologically identified as parathyroid adenomas (Figure 1 and Figure 2). Two patients had double adenomas in the ipsilateral neck. These patients were included in the study because their scans met our criteria for a true positive. These lesions were subsequently analyzed for their mass and percentage of oxyphil content by a single pathologist (V.A.L.). No concomitant thyroid disease was noted in our patient population.

**STATISTICAL METHODS**

To assess the effect of oxyphil cell dominance on technetium Tc 99m sestamibi scan sensitivity, patients were categorized into oxyphil cell–dominant (n=15) and chief cell– and mixed cell–dominant (n=56) groups by 1 pathologist (V.A.L.) at the University of Pennsylvania. Scan sensitivities for those who tested positive among those whose tests were true positives were calculated for each category and for all patients with a positive diagnosis. We then compared the scan sensitivities using an exact $\chi^2$ test. We used $t$ tests with adjustment for unequal variances to compare continuous variables between tumor types. We used recursive partitioning with 3 variables (lesion mass and preoperative serum calcium and PTH levels) and identified variable-specific cutoff points that defined 2 groups in whom the difference in scan sensitivity was maximized. Multivariate logistic regression analysis was used to determine whether these binary variables were prognostic factors and independent of the cellular composition of the lesion.

**RESULTS**

Our patient population included 22 men and 59 women. We identified 15 patients as oxyphil cell dominant and 56 as chief and mixed cell dominant. The oxyphil cell–dominant group had a significantly higher proportion of women compared with the other group (93.3% and 68.2%, respectively, $P=.05$). Age was not found to be significantly different between the 2 groups ($P=.75$). The range of preoperative serum calcium values was 8.60 to 13.00 mg/dL (2.15-3.25 mmol/L) (mean±SD, 10.84±0.97 mg/dL [2.71±0.24 mmol/L]; n=65). The range of preoperative intact PTH levels was 3.40 to 329.00 pg/mL (mean±SD, 60.66±69.64 pg/mL; n=66; reference range, 12-65 pg/mL). Lesion masses ranged from 0.20 to 15.00 g (1.54±2.03 g; n=80). There was no statistically significant difference in preoperative levels of serum PTH or calcium, or in size between the 2 groups. We calculated an overall technetium Tc 99m sestamibi scan sensitivity of 76.2% (n=63). The sensitivities within the chief cell– and mixed cell–dominant (n=52) and oxyphil cell–dominant (n=11) groups were 71.2% and 100%, respectively, which were statistically different ($P=.04$). We analyzed several clinical variables to assess their effect on technetium Tc 99m sestamibi scan sensitivity. Sensitivity was significantly higher in patients with preoperative serum calcium values exceeding 9.5 mg/dL (2.3mmol/L) compared with those with lower values.
The role of the oxyphil cell in hyperparathyroidism has been investigated extensively over the past 30 years. As recently as 1978, oxyphil cell parathyroid adenomas were considered to be largely nonfunctioning. Along with several other authors, Allen and Thorburn demonstrated that oxyphil cells were, in fact, capable of secreting PTH. Concurrent histopathologic studies also revealed that the percentage of oxyphil cells in parathyroid adenomas was greater than that in normal parathyroid tissue. These reports implied that the oxyphil cell participated in the progression of hyperparathyroidism in a manner that was previously unappreciated. With the advent of technetium Tc 99m sestamibi preoperative localization techniques, it became clear that oxyphil cells were also capable of differentially increased sestamibi uptake and retention relative to chief cells, the other dominant cell type found within these lesions. These findings suggested that technetium Tc 99m sestamibi localization sensitivity may be augmented by the presence of lesions with a high percentage of oxyphil cells.

With current imaging technology, the reported sensitivities of preoperative sestamibi scans have ranged from 72% to 100%, although a recent meta-analysis reported an overall sensitivity and specificity of 91% and 99%, respectively. Despite the apparent success of preoperative localization using technetium Tc 99m sestamibi imaging techniques, Allendorf et al found no significant difference in cure rate or length of stay between patient populations who had and those who had not undergone preoperative scanning. This study concluded that preoperative localization may be appropriate only for less experienced surgeons and in the setting of recurrent disease. McHenry et al reported that the current level of sensitivity of sestamibi scanning obviated its use in lieu of bilateral neck exploration in their study of 124 patients. The evident controversy surrounding the efficacy of preoperative localization underscores the persistent need to optimize sensitivity rates by more fully elucidating the mechanism underlying these imaging studies.

Our study demonstrated that the presence of oxyphil cell–dominant lesions augmented the sensitivity of technetium Tc 99m sestamibi localization in a statistically significant manner. Melloul et al found a correlation between the technetium Tc 99m sestamibi region-of-interest uptake ratio of parathyroid lesions and their oxyphil cell content. This finding supports earlier data presented by Carpentier et al. Several recent studies that were unable to find a significant association between oxyphil cell content and technetium Tc 99m sestamibi uptake may have been limited by qualitative image assessments or reduced sensitivity levels in the setting of oxyphil cell–deficient lesions from patients with secondary hyperparathyroidism. Opinions on whether differential technetium Tc 99m sestamibi uptake in oxyphil cells is significant enough to augment scan sensitivity have been similarly divided within the literature. Pinero et al along with several other authors, found no significant relationship between oxyphil cell content and scan sensitivity. In contrast, Takebayashi et al found that their technetium Tc 99m sestamibi true-positive adenomas had greater mean oxyphil cell areas than their false-negative glands. This relationship, however, was not statistically significant, although their data may have been limited by sample size. Our findings were congruent with those reported by Takebayashi et al; however, to our knowledge, we are among the first to comment on this relationship in a statistically significant manner.

Our results suggest that the sensitivity of technetium Tc 99m sestamibi preoperative localization may be differentially greater in patients with oxyphil cell–rich lesions.

In light of these findings, we examined whether we could preoperatively select for this patient population via lesion mass or serum calcium and PTH values. There are few data in the literature addressing the correlation between oxyphil cell predominance and other clinical variables. In one study, Erickson et al reported that patients with oxyphil cell parathyroid carcinomas were associated with an elevated serum calcium level (15.5 mg/dL [3.9mmol/L]), which was actually higher than in patients with chief cell carcinomas (13.7 mg/dL [3.4mmol/L]). In contrast, our study failed to demonstrate any significant relationship using lesion mass or serum PTH and calcium levels, although we restricted our analysis to patients with parathyroid adenomas. Although lesion mass and preoperative serum calcium and PTH levels did not seem to be predictive of lesion type, it is possible that our data were limited by sample size, and thus further investigation with a larger patient population is warranted.

We also sought to analyze whether these clinical values could predict scan sensitivity in independent logistic findings. Although we did not demonstrate any significant relationship using lesion mass and serum PTH level, we did find that a preoperative calcium level greater than 9.5 mg/dL (2.4mmol/L) significantly correlated with increased scan sensitivity. Although the patients with calcium levels below 9.5 mg/dL (2.4mmol/L) do not fall within the classic presentation of primary hyperparathyroidism, those included in our study had normal renal function, and all were cured with the resection of a single functioning adenoma. Our findings may relate to greater sestamibi uptake in more metabolically active lesions; however, the lack of a similar correlation with serum PTH levels makes the significance of this finding less clear.

Our current understanding of the importance of the oxyphil cell in the treatment of hyperparathyroidism has been enhanced by studies demonstrating its relative abundance in parathyroid adenomas and its ability to differentially absorb and retain technetium Tc 99m sestamibi tracer. To our knowledge, this study is among the first to establish that technetium Tc 99m sestamibi localization sensitivity rates are augmented in patients with oxyphil cells–dominant adenomas in a statistically significant manner. Although our data suggest that serum calcium levels may be used to predict scan sensitivity, additional studies with larger populations are war-
ranted to fully elucidate whether other clinical variables may be similarly efficacious. Through this line of investigation, we hope to develop appropriate criteria to allow us to predict histologic findings of lesions and thereby minimize the failure rate of scan-directed unilateral neck exploration.

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REFERENCES