Objective: To investigate why some patients with single parathyroid adenomas have negative preoperative sestamibi scans.

Design: Retrospective review.

Setting: Tertiary care center.

Patients: Twenty-one patients with false-negative (FN) scans were compared with 22 patients with true-positive (TP) scans. All patients had single parathyroid adenomas.


Main Outcome Measures: Age; sex; preoperative serum calcium and parathyroid hormone levels; gland weight; location; and pathologic features.

Results: There was no significant difference in age or preoperative serum calcium or parathyroid hormone levels. Gland weight was greater in the TP group compared with the FN group (mean±SD, 1336±1603 mg vs 475±365 mg; \( P = .04 \)); 13 (62%) of the 21 glands in the FN group were located in the upper position, compared with 6 (27%) of the 22 glands in the TP group (\( P = .03 \)). Ten of the 22 glands in the TP group consisted predominantly of oxyphil cells, compared with 2 of the 21 glands in the FN group (\( P = .02 \)). A multivariate logistic regression model yielded the following factors that predicted an accurate scan: higher percentage of oxyphil cells (\( P = .03 \)), heavier gland (\( P = .03 \)), female sex (\( P = .04 \)), and gland location in the lower position (\( P = .04 \)).

Conclusions: Smaller-volume parathyroid adenomas and those in the upper position are less likely to be localized with sestamibi scans. A TP scan correlates with oxyphil cell predominance, supporting a role for the mitochondrial-rich cell in sestamibi uptake and retention.

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The last decade has witnessed dramatic changes in the surgical treatment of primary hyperparathyroidism (HPT). The introduction of highly accurate localization studies coupled with rapid intraoperative parathyroid hormone (PTH) assays has facilitated the development of focused parathyroid explorations. The widespread success of limited parathyroid explorations is based on the fact that the vast majority of cases of primary HPT are caused by enlargement of a single parathyroid gland. Consistently over the last 70 years at the Massachusetts General Hospital, 80% to 85% of the patients with primary HPT have had a single adenoma.\(^1\,^2\) An essential component of the focused approach is the preoperative localization of the enlarged parathyroid. At present, the most commonly used preoperative localization study is the technetium Tc 99m sestamibi scan.

In the recent literature, sestamibi scintigraphy has been documented to have a high sensitivity, in the range of 95%, in patients with single-gland disease.\(^3\,^4\) It has also been documented that in patients with double adenomas and 4-gland parathyroid hyperplasia, as well as in patients with thyroid nodules and thyroiditis, preoperative sestamibi scintigraphy is less accurate and often does not detect the abnormal parathyroid gland(s). Despite the fact that sestamibi scintigraphy is highly accurate in patients with single-gland disease and normal thyroid glands, there is a small but significant number of pa-
Patients who have negative preoperative sestamibi study results but at exploration are found to have a single adenoma causing their HPT. Recent studies have investigated potential causes of false-negative (FN) sestamibi scintigraphy results in patients with documented single-gland disease. For example, smaller-volume parathyroid adenomas with a relatively low proportion of oxyphil cells have been associated with a high incidence of FN scans.\(^5,6\)

In the current study, we identified 21 patients with a negative preoperative sestamibi scan and no thyroid abnormality who were documented at surgery to have a single parathyroid adenoma. These 21 patients were compared with 22 patients with true-positive (TP) scans with regard to age, sex, preoperative serum calcium and PTH levels, and gland weight. In addition, pathologic analysis was performed on the glands in each group to define differences in the cellular composition of glands with and without sestamibi uptake.

**METHODS**

Patients with FN sestamibi scans were identified by a retrospective search of the medical records of all patients who underwent sestamibi scans at our institution from 2000 to 2005. Beginning in 2004, it became standard practice at our institution to obtain sestamibi scans on all patients undergoing parathyroid exploration. Prior to 2004, sestamibi scans were obtained at the discretion of the individual surgeon. During the period from 2000 to 2005, a total of 506 sestamibi scans were performed for parathyroid localization and 92 were read as negative (no parathyroid adenoma seen). Of these 92 patients with negative scans, 21 had no history of thyroid disease, a normal preoperative thyroid ultrasound, and a single parathyroid adenoma removed at surgery, with resolution of HPT.

Sestamibi scintigraphy was performed with the intravenous injection of 740 MBq of technetium Tc 99m–sestamibi, and images were obtained with a large-field-of-view camera with a high-resolution parallel hole collimator and interfaced computer. Initial images were obtained immediately after injection and delayed images, 1.5 hours after injection. Image acquisition was done with the patient in the supine position with the neck extended. Immediate anterior planar images of the neck and upper chest were performed with left and right anterior oblique images at a 30° angle. Single-photon emission computed tomographic imaging of the neck and upper chest was done and each of these images was repeated at the time of delayed imaging. Images were then reconstructed in the transaxial, coronal, and sagittal planes.

An FN scan was defined as a patient without a parathyroid adenoma seen on sestamibi scan, but with a single, enlarged parathyroid gland identified and removed at exploration, with resolution of elevated serum calcium and PTH levels. Selected at random were 22 patients with TP sestamibi scans (preoperative scan indicating a single parathyroid adenoma, location confirmed at exploration, with resolution of elevated calcium and PTH levels). The sestamibi scans were reviewed by an experienced nuclear medicine physician who was blinded to the operative and pathologic findings. An example of a TP sestamibi scan performed on a patient in our study is shown in Figure 1. The surgical approach and extent of exploration was determined by the operating surgeon.

All patients included in the study underwent preoperative ultrasonography to localize the parathyroid adenoma and examine the thyroid gland. To eliminate the possibility of thyroid interference in the sestamibi study, all patients included in the study had normal preoperative thyroid ultrasounds. In addition, patients with multigland parathyroid disease or a history of thyroid or parathyroid surgery were excluded from the study.

The 2 groups were compared with regard to age, sex, preoperative serum calcium and PTH levels, and gland weight and...
The mean age of the patients in the FN group was 59 years (range, 33-85 years), compared with 60 years (range, 25-87 years) in the TP group; this was not significantly different. The mean preoperative calcium and PTH levels in the FN group were 10.8 mg/dL (2.7 mmol/L) (range, 9.5-12.0 mg/dL [2.4-3 mmol/L]) and 130.5 pg/mL (range, 83-343 pg/mL) compared with 11.2 mg/dL (2.8 mmol/L) (range, 10-13.9 mg/dL [2.5-3.5 mmol/L]) and 151.9 pg/mL (range, 83-343 pg/mL) in the TP group; again, these differences in calcium and PTH levels did not reach statistical significance. Gland weight in the TP group was significantly greater than in the FN group (mean ± SD, 1336 ± 1603 mg vs 475 ± 365 mg; \( P = .04 \)). Thirteen (62%) of the 21 glands in the FN group were located in the upper position, compared with 6 (27%) of the 22 glands in the TP group (\( P = .03 \)). Ten of the 22 glands in the TP group consisted predominantly of oxyphil cells, compared with 2 of the 21 glands in the FN group (\( P = .02 \) (Figure 2 and Figure 3)). These results are summarized in Table 1.

With regard to the ultrasonography findings, in the 21 patients with FN sestamibi scans, 12 had a normal preoperative ultrasound (no parathyroid adenoma seen), 2 had an ultrasound that incorrectly identified the location of the parathyroid adenoma, and 7 had correct localization. In the 22 patients with a TP scan, 6 had a normal preoperative ultrasound, 3 had an ultrasound that incorrectly identified the location of the parathyroid adenoma, and 13 had correct localization.

A multivariate logistic regression model analyzing various demographic, clinical, and pathologic covariates on sestamibi scan result yielded the following factors, which independently significantly predict an accurate scan: higher percentage of tumor comprising oxyphil cells (\( P = .03 \)), heavier gland (\( P = .03 \)), female sex (\( P = .04 \)), and gland location in the lower position (\( P = .04 \)).

### RESULTS

The original pathologic slides were evaluated for the distribution and proportion of cell types, with glands classified as predominantly chief cells, predominantly oxyphil cells, or mixed. The pathologic features were reviewed by an experienced parathyroid pathologist who was blinded to the clinical, radiologic, and operative findings.

The univariate comparison of the gland weight of the TP and FN groups was tested using a Wilcoxon rank sum test with a continuity correction. The univariate comparisons of the groups with regard to the proportion of glands in the upper position and the proportion of adenomas consisting primarily of oxyphil cells were done using Fisher exact tests. All statistical tests were 2-sided using a significance level of 5%. A stepwise variable selection procedure was used to determine the significant independent predictors of sestamibi scan result using multivariate logistic regression.

This study was conducted with the approval of our institutional review board (protocol P-001200/1).

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**Figure 2.** Photomicrograph of a parathyroid adenoma composed predominantly of mitochondrial-rich oxyphil cells with a granular, eosinophilic cytoplasm. The nuclei are dense and moderately pleomorphic. The sestamibi scan correctly localized the adenoma to the left lower location (hematoxylin-eosin, original magnification \( \times 20 \)).

**Figure 3.** Photomicrograph of a parathyroid adenoma composed entirely of vacuolated glycogen-rich chief cells. The sestamibi scan failed to locate the adenoma. At exploration, a 440-mg parathyroid adenoma was removed from the left upper location (hematoxylin-eosin, original magnification \( \times 20 \)).

### Table 1. Comparison of 21 Patients With False-Negative Sestamibi Scans and 22 Patients With True-Positive Sestamibi Scans*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>False-Negative (n = 21)</th>
<th>True-Positive (n = 22)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (range)</td>
<td>59 (33-85)</td>
<td>60 (25-87)</td>
<td>.79</td>
</tr>
<tr>
<td>Female, No./total No. (%)</td>
<td>16/21 (76)</td>
<td>18/22 (82)</td>
<td>.72</td>
</tr>
<tr>
<td>Preoperative calcium level, mg/dL, mean (range)</td>
<td>10.8 (9.3-12)</td>
<td>11.2 (10-13.9)</td>
<td>.18</td>
</tr>
<tr>
<td>Preoperative PTH level, pg/dL, mean (range)</td>
<td>130.5 (48-262)</td>
<td>151.9 (83-343)</td>
<td>.22</td>
</tr>
<tr>
<td>Gland weight, mg, mean ± SD</td>
<td>475 ± 365</td>
<td>1336 ± 1603</td>
<td>.04</td>
</tr>
<tr>
<td>Gland in upper location, No./total No. (%)</td>
<td>13/21 (62)</td>
<td>6/22 (27)</td>
<td>.03</td>
</tr>
<tr>
<td>Oxyphil cell predominance, No./total No. (%)</td>
<td>2/21 (10)</td>
<td>10/22 (45)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviation: PTH, parathyroid hormone.

SI conversion factor: To convert calcium to millimoles per liter, multiply by 0.25.

*All 43 patients were found to have a single adenoma and had normal preoperative thyroid ultrasound results.
Until a decade ago, the surgical procedure of choice for patients undergoing an initial operation for primary HPT was a bilateral cervical exploration under general anesthesia. In the past several years, parathyroid surgery has changed dramatically. With the introduction of highly accurate localization studies and rapid PTH assays, limited parathyroid explorations are now far more common. The approach to a “minimally invasive” parathyroidectomy varies from center to center but generally involves all or some of the following: smaller incision, focal or unilateral parathyroid exploration, regional anesthesia, and same day hospital discharge.

Although there is still ongoing debate regarding the appropriateness of such widespread use of focused explorations and minimally invasive surgical approaches, there is no question that it is currently the procedure of choice for the vast majority of patients with primary HPT. An essential component of a focused exploration is the accurate and reliable preoperative localization of the parathyroid adenoma. Both sestamibi scintigraphy and high-resolution cervical ultrasonography have been used to localize parathyroid adenomas. Although ultrasonography is being used with increasing frequency as technology improves and radiologists and surgeons are gaining experience with head and neck ultrasonography, at present, sestamibi scintigraphy is the most widely used preoperative localization study and has been demonstrated in several studies to be highly accurate in the preoperative detection of parathyroid adenomas.

Despite the sensitivity of sestamibi scintigraphy, there remains a small but significant number of parathyroid adenomas that are not detected. The reason for this is not entirely clear, and a number of potential causes for FN scans have been investigated. It is well documented that patients with multigland parathyroid enlargement are more likely to have a nonlocalizing scan. Abnormal thyroid glands (multiple thyroid nodules, thyrotoxicosis) in patients with HPT can lead to either a false-positive or an FN result on sestamibi scan.

Perhaps most troublesome are the FN sestamibi scans in patients with single-gland parathyroid disease and normal thyroid glands. The reason why a single parathyroid adenoma is not detected on sestamibi scintigraphy is not entirely clear. In this present study, the primary associations with a TP scan, as noted on multivariate analysis, were female sex, gland location in the lower position, heavier gland weight, and a higher percentage of oxyphil cells in the removed gland. We found no difference in preoperative serum calcium and PTH levels in patients with TP vs FN sestamibi scans. The finding on multivariate analysis that female sex was predictive of a positive scan is unlikely to be meaningful clinically; the difference in the sex composition of the 2 groups was not found to be significant on univariate analysis. The fact that parathyroid adenomas located in the upper position were missed on sestamibi scan more often than those in the lower position may be explained by the more posterior location of the upper glands. Upper parathyroid adenomas tend to be less variable in location and are often situated behind the thyroid quite posterior in the neck. This suggests that interference from the thyroid gland, even when normal, could obscure accurate parathyroid localization. Our findings are in agreement with Rodriguez-Carranza et al. who also noted that lesions in the upper neck were missed more frequently than those in the lower neck. It has been hypothesized that smaller parathyroid adenomas are less likely to yield a positive sestamibi result; this would intuitively make sense as well. Recent studies comparing gland weight in patients with FN and TP sestamibi scans have noted that patients with TP sestamibi scans have, on average, heavier parathyroid adenomas than those with FN scans. Other studies, however, have not detected a difference in gland weight when comparing patients with positive and negative sestamibi scans. Higher preoperative serum calcium and PTH levels have also correlated with TP scans in some studies, but not in others.

In this study, parathyroid adenomas with a high percentage of oxyphil cells were more likely to have a TP sestamibi result. Normal parathyroid glands comprise 2 cell types: chief cells and oxyphil cells. The chief cell is responsible for PTH production, and oxyphil cells are eosinophilic cells whose cytoplasm is composed almost entirely of mitochondria. While the normal oxyphil cell does not synthesize and secrete PTH, the oxyphil cells of pathologic parathyroid glands do secrete the hormone. Several studies have investigated the association of oxyphil cell content of adenomas and sestamibi results, and the findings consistently support those in this present study: a predominance of oxyphil cells within an adenoma is more likely to lead to a positive scan. The association of FN scans with lower concentrations of oxyphil cells and a higher percentage of chief cells, clear cells, and fat was first noted soon after the introduction of sestamibi scan for parathyroid localization and has been confirmed in more recent studies. Although the mechanism of sestamibi uptake and retention specifically and selectively in parathyroid adenomas is not fully elucidated, the lipophilic sestamibi molecule is thought to be concentrated by mitochondria. This explains why adenomas with an abundance of mitochondrial-rich oxyphil cells preferentially retain sestamibi and also why there was no significant association of sestamibi result with PTH (produced by the chief cells) and serum calcium levels. A summary of the recent literature investigating the associations and possible causes of FN sestamibi scans is provided in Table 2.

An understanding of the mechanism of sestamibi uptake and the factors that increase the possibility of an FN scan may lead to future improvements in sestamibi scanning techniques. Even with refinements in sestamibi scanning, the fact that all parathyroid adenomas are not created equal on a cellular level may inevitably lead to FN scans in a certain number of cases. In many centers, a minimally invasive parathyroid exploration is offered only to patients with a positive preoperative sestamibi scan definitively indicating a single parathyroid adenoma, the rationale being that (1) the surgeon would not know where to initiate the exploration without preoperative localization and (2) patients with a negative scan have a high rate of multigland disease. This emphasizes the need to complement sestamibi localization with preoperative...
localization studies such as high-resolution cervical ultrasonography. In our study, 13 of the 22 patients with a TP sestamibi scan and 7 of the 21 patients with an FN sestamibi scan had correct localization of the parathyroid adenoma on ultrasound. The fact that a higher percentage of patients in the TP sestamibi scan group had correct ultrasound localization is likely related to the larger size of the adenomas in that group. Regardless, approximately one third of the patients with an FN sestamibi scan had a correctly localizing ultrasonography study and were therefore eligible for a focal exploration. In centers with expertise in ultrasonography for parathyroid localization, a focal approach can be guided by the ultrasonography findings and surgical success confirmed with intraoperative PTH levels. With regard to the possibility of multigland disease in patients with a negative scan, although a negative scan may indicate a higher probability of multigland disease than a positive scan, a patient with a negative scan is still more likely to have a single parathyroid adenoma. A recent study noted that the majority (76%) of patients with a nonlocalizing sestamibi scan did indeed have single-gland disease.

Of particular concern is that there may be the misconception that patients with a negative sestamibi scan are less likely to have a successful surgical outcome and therefore may not be referred for potentially curative exploration. A recent study compared the outcomes of patients with primary HPT and a negative sestamibi scan who underwent surgery versus medical therapy and noted that surgical therapy was superior in terms of quality-of-life measures. Furthermore, Chiu et al noted that a negative sestamibi scan did not predict a higher probability of hypercalcemia 6 months postoperatively and suggested that in patients with a nonlocalizing scan, a unilateral approach with removal of an adenoma, inspection of the ipsilateral normal gland, and intraoperative PTH monitoring is acceptable and eliminates the need for a 4-gland exploration in many patients with a nonlocalizing scan. These findings support the routine referral of patients with primary HPT regardless of sestamibi scan results.

In summary, a patient with primary HPT and a negative preoperative sestamibi scan is most likely to have a single parathyroid adenoma. If the thyroid gland is normal on ultrasonography, the reason for the negative preoperative scan may be an upper gland positioned posterior to the thyroid, a relatively small-volume gland, or a paucity of oxyphil cells. In some cases, high-resolution ultrasonography can be used to guide a focal exploration, with intraoperative PTH levels indicating a successful exploration. Preoperative ultrasonography and the surgical approach in such patients should focus attention on the upper locations.

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Author Contributions: Dr Stephen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Stephen, Gaz, and Hodin. Acquisition of data: Stephen, Roth, Randolph, Gaz, and Hodin. Analysis and interpretation of data: Stephen, Fardo, Finkelstein, Gaz, and Hodin. Drafting of the manuscript: Stephen, Fardo, and Hodin. Critical revision of the manuscript for important intellectual content: Stephen, Roth, Finkelstein, Randolph, Gaz, and Hodin. Statistical analysis: Fardo and Finkelstein. Administrative, technical, and material support: Stephen, Gaz, and Hodin. Study supervision: Randolph, Gaz, and Hodin.

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REFERENCES


Table 2. Summary of Recent Publications Investigating the Factors Associated With TP and FN Sestamibi Scans

<table>
<thead>
<tr>
<th>Source, Year</th>
<th>Findings</th>
</tr>
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<tbody>
<tr>
<td>Pineró et al. 2003</td>
<td>Higher cell proliferation index in TP group; no difference in patient age, sex, gland weight, or preoperative PTH and calcium levels</td>
</tr>
<tr>
<td>Westreich et al., 2003</td>
<td>Higher percentage of oxyphil cells in TP group</td>
</tr>
<tr>
<td>Parikh et al. 2003</td>
<td>Higher preoperative PTH and calcium levels in TP group</td>
</tr>
<tr>
<td>Mehta et al. 2005</td>
<td>Heavier gland weight and higher percentage of oxyphil cells in TP group</td>
</tr>
<tr>
<td>Rodriguez-Carranza et al., 2004</td>
<td>FN scan associated with upper gland location</td>
</tr>
<tr>
<td>Mihai et al. 2006</td>
<td>Heavier gland weight and higher percentage of oxyphil cells in TP group; higher percentage of chief cells in FN group</td>
</tr>
<tr>
<td>Chiu et al. 2006</td>
<td>Heavier gland weight in TP group</td>
</tr>
</tbody>
</table>

Abbreviations: FN, false-negative; PTH, parathyroid hormone; TP, true-positive.


