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Early-phase technetium-99m sestamibi scintigraphy can improve preoperative localization in primary hyperparathyroidism

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Abstract

BACKGROUND—In hyperparathyroidism, dual-phase technetium-99m sestamibi scintigraphy is important for parathyroid adenoma localization. We hypothesized that reviewing early-phase scans can increase localization in patients with primary hyperparathyroidism (PHPT).

METHODS—We reviewed our prospectively maintained database for patients with sestamibi scans before parathyroidectomy for PHPT from 2001 to 2011. Early-phase scans were read and compared with the location of the gland(s) removed at operation.

RESULTS—Of 902 patients identified, radiologists read 693 scans as positive. Of 209 negative scans, 141 (67%) were positive in the early phase; 135 (96%) correctly identified the side of the adenoma. Using radiologist reads, 35% of patients with negative scans and 41% of patients with falsely localized glands required bilateral exploration compared with 5% of patients with correctly localized glands.

CONCLUSIONS—A review of early scans in patients with negative imaging increases accurate adenoma localization and allows for minimally invasive operations in more patients.

Keywords

Early-phase sestamibi; Minimally invasive parathyroidectomy; Primary hyperparathyroidism; Technetium-99m sestamibi

Primary hyperparathyroidism (PHPT) is a common disease causing hypercalcemia, with 100,000 new cases in the United States each year.¹ Cases are predominantly (80% to 85%) caused by sporadic, benign, single parathyroid adenomas.¹ Surgical treatment for this disease has shifted over the past 2 decades from bilateral neck exploration with visualization of all 4 parathyroid glands to unilateral exploration for patients with PHPT caused by a single adenoma.¹ Minimally invasive parathyroidectomy (MIP) became the operation of choice because studies found that MIP resulted in a decreased operative time, lower hospital costs, shorter lengths of hospital stay, and fewer events of postoperative hypocalcemia with cure rates equal to bilateral neck exploration.^{2,3}

Dual-phase technetium-99m sestamibi scintigraphy (“sestamibi scans”) became an integral part of preoperative localization for MIP.⁴ When sestamibi scans were used in conjunction

with other preoperative imaging studies and intraoperative adjuncts including ultrasound, rapid parathyroid hormone (PTH) testing, and radioguidance, MIPs could be performed for an increasing number of patients.^{1,2,5,6} At many large centers, MIP is now the most common parathyroid operation^{2,7}; thus, it is important to understand the full usefulness a sestamibi scan offers in the localization of parathyroid disease.

Two techniques exist for parathyroid imaging with technetium scintigraphy: dual-radionuclide, which uses subtraction imaging between sestamibi and a second radiotracer with high thyroid affinity, and dual phase, which uses an early- and late-phase scan with sestamibi alone.⁴ Both techniques seek to define parathyroid from thyroid pathology. The dual-phase technique relies on the faster washout time of sestamibi from thyroid tissue compared with parathyroid tissue. A scan at 15 minutes after radiotracer injection (“early phase”) is compared with a scan at 2 to 3 hours after injection (“late phase”). Although dual-phase scans are simpler to perform, thyroid pathologies such as nodules, thyroiditis, and adenomas can retain sestamibi longer than normal tissue and thus potentially lead to false-positive scans. On the other hand, rapid parathyroid washout with focal uptake in the early phase but not in the late phase is often misinterpreted as thyroid uptake, leading to false-negative scans.⁴

Previous studies have sought to determine the accuracy of sestamibi scans for parathyroid adenomas in comparison with and in combination with other imaging modalities.^{8,9} These studies present a range of disease detection accuracy from 71% to 85% alone to 95% in combination with single-photon emission computed tomography/computed tomography (SPECT/CT) scans and a sensitivity of 89% to 93.4%. Other studies identify factors that are more likely to result in negative sestamibi scan detection. Patients with multigland disease or hyperplasia,¹⁰ lower preoperative serum calcium and PTH levels,⁷ and smaller adenomas¹⁰ have higher negative localization rates. However, few studies have examined the usefulness of early-phase sestamibi scans in localizing adenomas. The purpose of this study was to explore whether a review of the early-phase scan in dual-phase sestamibi imaging could increase preoperative localization of parathyroid adenomas, making MIPs possible for more patients.

Methods

We conducted a retrospective review of a prospectively recorded database of individuals who underwent a sestamibi scan before parathyroidectomy for PHPT caused by a single parathyroid adenoma at the University of Wisconsin, Madison, WI, between January 2001 and January 2011. Patients with secondary or tertiary hyperparathyroidism, familial disease, or hyperplasia were excluded. We identified patients from this population who had sestamibi images available for review. Although all patients at our institution with PHPT undergo a sestamibi scan preoperatively, patients with scans from a referring institution did not always have available images.

Some patients were also evaluated with a neck ultrasound and/or computed tomography (CT) scan, and then all underwent parathyroidectomy. Patients with a positive localization study and no contraindications were offered MIP. Radioguidance and intraoperative PTH monitoring were used to determine the extent of every operation as well as the need for conversion to bilateral exploration as previously described.⁶ Operative cure was determined by a 50% drop in PTH measured at 5, 10, or 15 minutes after excision from the peak pre-excision PTH level.⁵ The locations of the gland(s) removed were recorded and compared with preoperative localization studies to determine the accuracy of the findings. Operative and postoperative findings and complications were recorded.

Our study focused on sestamibi scans as preoperative localization studies. A single endocrinology fellow was trained to read sestamibi scans by the endocrine surgery team. She was uninvolved in the operations and blinded from nuclear medicine and surgical findings. She reviewed all early-phase scans for increased radiotracer uptake indicating a parathyroid adenoma and then compared these findings with the glands removed at operation to determine their accuracy. Scans were considered accurate if they localized an abnormal gland on the ipsilateral side of the gland removed at operation. We compared patients' demographics, pre- and postoperative laboratory values, operative findings, and rates of cure and recurrence based on the findings of early- or late-phase sestamibi scans. Because PTH levels will remain elevated postoperatively in 20% to 25% of patients with successful parathyroidectomy, disease persistence was defined as a serum calcium level >10.2 mg/dL within 6 months of surgery. Recurrence was determined by a rise in calcium levels above 10.2 mg/dL more than 6 months postoperatively.

Data were analyzed using Microsoft Excel 2007 (Microsoft, Redmond, WA) and R for Windows version 2.13.1 (Vienna, Austria). Comparisons were made using the Student *t* test, chi-square test, or Fisher exact test where appropriate, and a *P* value $\leq .05$ was considered significant. This study was conducted with approval of the Institutional Review Board of the University of Wisconsin.

Results

Patient characteristics

We identified 1,062 patients who underwent parathyroidectomy for PHPT because of parathyroid adenoma at the University of Wisconsin between January 2001 and January 2011 who also had a sestamibi scan in their preoperative workup. Of these, 902 had scans available for review, so this population was further analyzed. The patients' mean age was 62 years (range 10 to 90 years), and 77% were female. Their mean preoperative serum calcium and parathyroid hormone levels were elevated at 11.1 ± 0.3 mg/dL and 130 ± 3 pg/mL, respectively. Preoperative serum phosphate levels were within normal range at 2.9 ± 0.0 mg/dL.

Sestamibi imaging

Of these 902 patients, nuclear medicine specialists read 693 of their sestamibi scans as positive ("positive late phase") and 209 as negative ("negative late phase"). Of the positive late-phase scan reads, 596 (86%) correctly and 97 (14%) incorrectly localized the side of parathyroid adenoma removed at operation. On review of the early-phase sestamibi scans, we read 616 scans as positive and accurately localizing the side of the abnormal gland. Of the negative late-phase scans, 141 (67%) were positive and 68 (33%) were negative in the early scan. Of the 141 positive early scans, 135 (96%) correctly and 6 (4%) incorrectly localized the abnormal gland(s) removed at operation (Fig. 1). Although this represents only 16% of the entire population, this would increase the positive sestamibi rate from 77% to 92% and the accuracy of sestamibi detection from 66% to 81%.

Preoperative data

We compared patients who only correctly localized in the late-phase scans ($n = 170$) with those who only correctly localized in the early-phase scans ($n = 190$) (Table 1). Patients with accurate late-phase scans had significantly higher preoperative serum calcium levels. We further targeted the group of patients with negative late-phase scans. We compared the patients in this group with positive early-phase scans ($n = 141$) with those with negative early-phase scans ($n = 68$) and found no differences in age, sex, or laboratory values.

Perioperative data

No significant difference was noted in operative findings or gland weight between the 2 groups with negative late scans. In positive late scan only and positive early scan only groups, the patients with positive early scans had significantly smaller adenomas removed at operation (533 ± 55 mg vs. 902 ± 131 mg, $P = .009$, Table 1).

Operative and postoperative outcomes

Postoperative PTH values were compared and were not significantly different in any group (Table 1). Postoperative maintenance of eucalcemia lasting at least 6 months was achieved in 892 of 902 patients (99%), and cure rates were similar across all groups (Table 1). Overall, 16 (1.8%) patients showed recurrence of disease later than 6 months postoperatively. Again, this rate was not significantly different in any group (Table 1). We calculated the number of patients who required bilateral neck explorations based on the initial nuclear medicine specialist reads of their sestamibi scans. Interestingly, 73 of 209 (35%) patients with negative late-phase scans and 40 of 97 (41%) with falsely localized late-phase scans required bilateral exploration. Only 31 of 596 (5%) of patients with positive, accurate late-phase scans required bilateral exploration.

Comments

When many high-volume endocrine surgery centers began to show that parathyroidectomy could be accomplished with a minimally invasive operation with similar cure and recurrence rates with open procedures, MIPs were adopted as the preferred option in patients with positive preoperative localization studies.⁴ Multiple studies have shown MIPs lead to lower hospital costs, shorter durations of stay, a lower incidence of hypocalcemia, and equally high cure rates with low complication rates.^{2,3,10} Sestamibi scans are an essential modality in the preoperative localization of parathyroid adenomas. However, questions remain as to the interpretation of the dual-phase scan, especially in scans read as negative by nuclear medicine specialists.

This report examines the preoperative sestamibi scans of over 900 patients treated with parathyroidectomy for PHPT at a single high-volume tertiary care center. With review of the early-phase scans, we substantially increase preoperative localization of parathyroid adenomas. Of the 209 sestamibi scans read as negative by nuclear medicine specialists, 67% had localized gland uptake in the early-phase scans. These findings were highly accurate, with 96% of early-phase scans read as positive by our physician correctly localizing the abnormal glands removed at operation. Had these early-phase scans been read preoperatively, it would have increased the positive sestamibi rate from 77% to 92% and the accuracy of sestamibi detection from 66% to 81%. The focal disease identified on early-phase scans alone was biochemically milder and associated with smaller adenomas. Importantly, this high accuracy rate indicates that local sestamibi uptake visualized only in early-phase scans does not usually correspond with thyroid disease but, in fact, represents parathyroid adenomas.

In previous series examining the role of sestamibi scans in MIP, some focus on negative scans and causes for their lack of localization.^{8,9} Udelsman et al's large series² of 1,650 patients notes that one of the common reasons for their patients to undergo a bilateral exploration is negative preoperative imaging. These studies confirm our findings that sestamibi scans are more likely to be nonlocalizing in mild disease, with smaller glands and lower preoperative calcium.⁹ Our results suggest that a preoperative review of the early-phase scan would increase adenoma localization in mild disease, which would allow for more MIPs in this population.

Our study is novel in comparison with these and other recent studies that address the usefulness of surgeon review of sestamibi scans^{11,12} in that it focuses on the information available in the early-phase scans. Zia et al¹¹ evaluated a series of 763 sestamibi scans read by either high- or low-volume radiologists and then independently read by an endocrine surgeon. The sensitivity for sestamibi interpretation was higher by surgeons (93%) than by either the high-volume radiologists (83%) or low-volume radiologists (72%).¹¹ Similarly, Neychev et al¹² showed that on review of 126 negative or indeterminate sestamibi scans, an endocrine surgeon read 80 (63%) as positive, with MIP completed in 91% of these patients. A third study of 80 patients evaluated the difference between early-phase and dual-phase reads, with an outcome indicating that the difference between dual-phase scans and early-phase scans alone is not significant.⁹ These authors concluded that a review of the late phase scan is unnecessary. However, our data show that a review of the early-phase scans in conjunction with late-phase scans provides a higher localization rate than early-phase scans alone (731 [81%] vs 616 [68%]) (Fig. 1) and thus should be used together.

In the end, sestamibi scans are one of many techniques used by a successful surgeon to complete parathyroidectomy. The localization provided by sestamibi scans is carried through to resection for cure with the adjuncts of intraoperative radioguidance and intraoperative PTH levels.^{5,6} By using these tools together, including an early-phase sestamibi review, we can effectively treat PHPT with minimally invasive procedures in more patients than when relying on the late-phase read alone.

Our results are limited by the retrospective nature of this study. This most directly affects our measurement of long-term recurrence of disease. Fortunately, our data are recorded prospectively, with continuing follow-up data monitored through electronic medical records. Our study also deals with a selected group of patients. Because sestamibi scans are less sensitive and specific for detecting abnormal glands in multigland disease,¹⁰ we focused our study on patients with PHPT caused by single or double adenomas. Our purpose was to determine the number of adenomas detectable in the early-phase scan, not necessarily to determine the accuracy of early-phase scans alone for all comers with PHPT. A retrospective reading of examinations can be biased by known operative findings. We attempted to limit this bias by having a single physician who was not involved in the operative care of patients read all of the examinations. She also remained blinded to operative results until all films were read. The process of reading sestamibi films enters some variation into the study. Both hard copies from referring hospitals and scans in an electronic imaging system were included in the study, and the ease of reading these modalities differs. Having a single physician read the studies limited the variation this could introduce.

Accurate localization studies are essential to minimally invasive parathyroidectomies. Dual-phase sestamibi scans are an important part of the preoperative localization workup. In patients with sestamibi scans, we advocate a routine review of all scans, with specific attention paid to early-phase scans because this can help increase accurate parathyroid adenoma localization, especially in patients with milder disease who might not otherwise be offered the option to undergo a minimally invasive procedure.

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Figure 1.

A flowchart of sestamibi scan results for the studied patient population. Late-phase scans correspond to sestamibi scan readings completed by nuclear medicine specialists. Early-phase scan readings were completed by a single physician on our endocrine surgery team who did not participate in care of the patients and was blinded to operative results. PTX = parathyroidectomy.

Table 1

Comparison between accurate scans positive in the early phase only versus the late phase only

Variable	Late positive only (n = 170)	Early positive only (n = 190)	P value
Age, y (range)	60 (10–89)	63 (19–89)	.028
Females (%)	126 (74)	150 (79)	.34
Preop Ca (mg/dL)	11.1 ± 0.1	11.0 ± 0.1	.03
Preop PTH (pg/mL)	137 ± 9	117 ± 7	.07
Preop phosphate (mg/dL)	3.1 ± 0.2	2.9 ± 0.0	.45
Postop Ca (mg/dL)	9.4 ± 0.0	9.4 ± 0.0	.22
Postop PTH (pg/mL)	48 ± 63	45 ± 2	.47
Gland weight (mg)	902 ± 131	533 ± 55	.009
Cure (%)	169 (99%)	187 (98%)	.63
Recurrence (%)	2 (1.2%)	4 (2.1%)	.69

Continuous variables are represented as the mean ± standard error of the mean unless otherwise indicated.

Ca = calcium; Preop = preoperative; Postop = postoperative; PTH = parathyroid hormone.