Technetium-99m-Sestamibi Imaging before Reoperation for Primary Hyperparathyroidism

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Recent studies have reported high sensitivities for parathyroid localization with ^{99m}Tc-sestamibi and have been performed using either ^{123}I/^{99m}Tc-sestamibi or a double-phase sestamibi scanning technique. These studies have focused primarily on patients undergoing initial surgery. We studied 35 patients prior to reoperative surgery to investigate the relative sensitivities of these two techniques in this patient population. **Methods:** Double-phase sestamibi scanning (early and delayed imaging) was performed in all patients. Evaluable ^{123}I/^{99m}Tc-sestamibi subtraction studies were also obtained in 25 patients. Results were correlated with surgical findings in 32 patients and with clinical outcome in 3 patients in whom mediastinal lesions were radiographically ablated. **Results:** Overall, double-phase sestamibi imaging detected 23 of 39 abnormal parathyroid glands (59%), whereas ^{123}I/^{99m}Tc-sestamibi detected 19 of 27 (70%). Oblique imaging, delayed imaging and ^{123}I subtraction all contributed to sensitivity, and ^{123}I subtraction also proved useful in patients with partial thyroid suppression. Two patients had lesions visible on the early sestamibi images that were not seen at all on the delayed scans. There were four false-positive findings. **Conclusion:** No significant differences between double-phase sestamibi and ^{123}I/^{99m}Tc-sestamibi subtraction scanning were found, although the latter tended to be more sensitive.

Key Words: iodine-123/technetium-99m-sestamibi; subtraction; hyperparathyroidism

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The use of ^{99m}Tc-sestamibi in combination with ^{123}I NaI for thyroid subtraction (*1–5*) and as a single agent in the so-called double-phase technique (*6,7*) for parathyroid localization has been the subject of several recent studies. These studies have reported sensitivities ranging from 88% to 100% for parathyroid adenomas and have led many to believe that sestamibi will prove to be a superior agent in comparison to ^{201}Tl for subtraction scanning in hyperparathyroidism. With the exception of a report by Weber et al. (*3*), however, these studies have been conducted primarily in patients undergoing initial surgery.

In this report, we present the results of our initial experience using ^{123}I/^{99m}Tc-sestamibi subtraction in combination with delayed ^{99m}Tc-sestamibi imaging in a group of patients referred for reoperative surgery. The contribution of the various imaging components of this protocol to the detection of parathyroid lesions is also presented.

MATERIALS AND METHODS

Patients

Thirty-five patients were referred for reoperative surgery for primary hyperparathyroidism, having undergone 1–4 previous surgeries (mean = 1.6). Twenty-four (69%) were women and 11 (31%) were men. The average age of the women was 56 yr (range 28–86 yr) and that of the men was 52 yr (range 17–69 yr). Six patients had multiple endocrine neoplasia type 1 (MEN1). Twelve patients had received recent intravenous contrast and/or were on Synthroid at the time of the study because of a history of prior thyroid resection or thyroid disease.

Imaging Protocol

For ^{123}I/^{99m}Tc-sestamibi imaging, patients were positioned under a gamma camera approximately 4 hr after receiving 300–400 μCi ^{123}I NaI orally. A 5-min image was acquired using a low-energy, all-purpose, parallel-hole collimator with 1.5 magnification and a 15% energy window over the 159-keV photopeak of ^{123}I. Following injection of 20 mCi ^{99m}Tc-sestamibi and using a 15% window over the 140-keV photopeak of ^{99m}Tc, twenty 1-min sequential images were acquired simultaneously with two 10-min analog images. These are followed by 5-min right and left anterior oblique views and an unmagnified image of the anterior chest. Approximately 2–3 hr after injection, repeat 5-min anterior and oblique views of the neck and a chest view were obtained.

A subtraction image was then generated. First, four to five of the early 1-min ^{99m}Tc-sestamibi images were examined and corrected for motion, if necessary. These were then summed to obtain a composite sestamibi image which was then aligned with the ^{123}I image of the thyroid and normalized for equal counts in a region of interest drawn around the thyroid gland. The normalized ^{123}I image was then subtracted from the composite ^{99m}Tc-sestamibi image to obtain a subtraction image.

Patients undergoing double-phase ^{99m}Tc-sestamibi imaging alone underwent the same protocol, minus the ^{123}I imaging. Analog ^{99m}Tc-sestamibi images were used for interpretation of double-phase scans.

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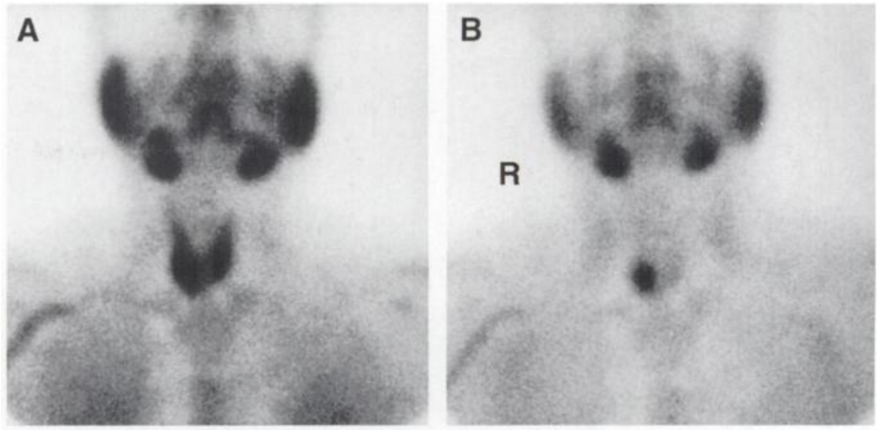

FIGURE 1. Early anterior ^{99m}Tc-sestamibi image (A) shows uptake in the thyroid with prominence of the right lower lobe. A 2-hr delayed image (B) demonstrates retention of ^{99m}Tc-sestamibi in a right lower parathyroid adenoma (5.25 cm^3) compared to surrounding thyroid tissue.

Scan Interpretation

Interpretation of scintigraphic studies was performed by a nuclear medicine physician blinded to the results of other localization studies. Each ^{123}I/^{99m}Tc-sestamibi study was interpreted twice, both with and without the information provided by ^{123}I subtraction. Scans were scored as positive or negative for parathyroid localization. Indeterminate studies were considered negative for the purposes of this report. When using only the early and delayed ^{99m}Tc-sestamibi images for interpretation, a study was read as positive if there was a definite focus of increased or separate sestamibi uptake relative to thyroid tissue on either the early or delayed images, or both (Fig. 1). Relative retention of activity on delayed images was not required for a lesion to be considered positive on the double-phase study.

Iodine-123/^{99m}Tc-sestamibi subtraction studies were considered positive if there was evidence of excess sestamibi uptake compared to ^{123}I (Fig. 2). Studies with complete absence of ^{123}I uptake by the thyroid were considered nonevaluable in the region of the thyroid bed. This was because of the possibility of ^{99m}Tc-sestamibi uptake in suppressed thyroid tissue causing false-positive results on a subtraction image.

The dimensions of the parathyroid lesions found at surgery were used to calculate their size, using the formula for the volume of an ellipse: $4/3\Pi r_a r_b r_c$, where r_{abc} = radii of the three dimensions. For the patients who had tissue removed in more than one piece (due to the location relative to nerve in one case and to the presence of multiple discrete parenchymal implants in two patients), the volumes of the pieces were calculated separately and summed. The volumes of radiographically ablated lesions were determined using measurements obtained by CT.

Statistical Analysis

McNemar's test for paired data was used to calculate a two-sided p value when comparing the results of double-phase ^{99m}Tc-sestamibi versus ^{123}I/^{99m}Tc-sestamibi scanning.

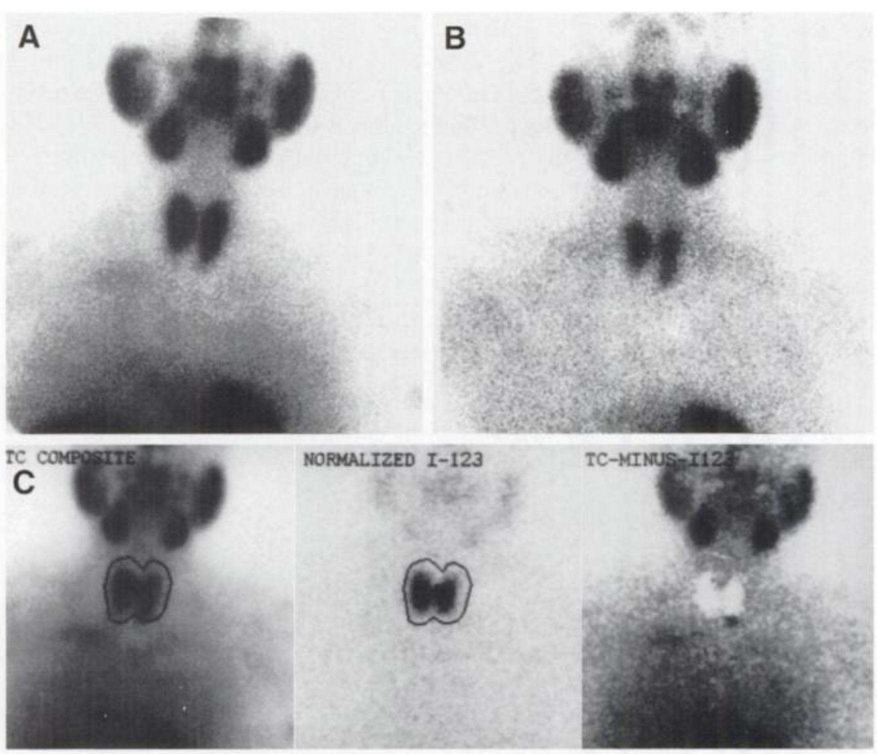

FIGURE 2. Early (A) and delayed (B) anterior ^{99m}Tc-sestamibi images in a patient with MEN1 reveal uptake in the thyroid gland without areas of definite focality or differential retention over time. Subtraction study (C) consists of ^{99m}Tc-sestamibi (left), ^{123}I (middle) and subtraction (right) images. Excess ^{99m}Tc-sestamibi uptake is seen in a left lower hypercellular parathyroid gland (0.35 cm^3). Hypercellular right (0.63 cm^3) and left (0.21 cm^3) upper glands which did not image were also removed at surgery.

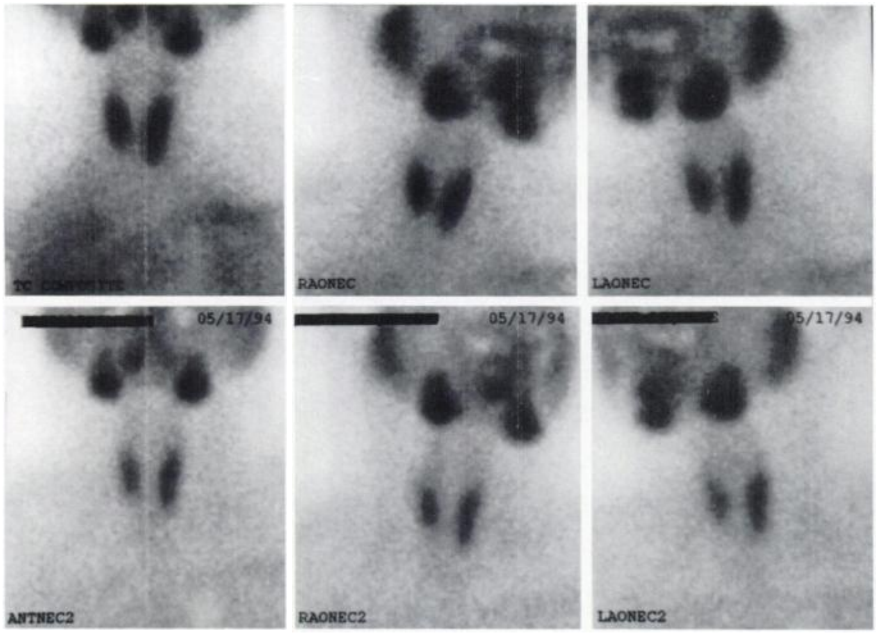

FIGURE 3. Early (top) and delayed (bottom) ^{99m}Tc-sestamibi images demonstrate uptake and washout from the thyroid. A vague area of ^{99m}Tc-sestamibi uptake is seen above the left lobe of the thyroid on the early anterior image (upper left) but not on the delayed images.

RESULTS

Of the 35 patients, 32 eventually underwent reoperation for hyperparathyroidism with resection of 36 histologically abnormal glands, while 3 patients with mediastinal lesions underwent successful ablation of solitary adenomas using hyperosmolar contrast. All patients were biochemically cured. A total of 39 abnormal glands in 35 patients were removed or ablated. Twenty-eight patients had solitary parathyroid adenomas. One non-MEN1 patient was found to have two hypercellular glands, and nine hypercellular glands were found in six MEN1 patients at re-exploration.

Early and delayed (double-phase) ^{99m}Tc-sestamibi imaging was performed in all 35 patients. Iodine-123/^{99m}Tc-sestamibi imaging was performed in 28 of these patients and considered evaluable in 25. During the first several months of performing these scans, ^{123}I imaging was omitted in patients with a history of thyroid suppression (Synthroid or recent intravenous contrast). This was changed, however, when it became apparent that many of these patients were not fully suppressed and that thyroid imaging could still be useful in some. Overall, ^{123}I was omitted in seven patients, four of whom had a history of thyroid suppression, two of whom had had a recent [^{99m}Tc]pertechnetate scan as part of a ^{99m}Tc/^{201}Tl study, and in one because ^{123}I was not available on the day of the study.

In patients with solitary adenomas, double-phase ^{99m}Tc-sestamibi images correctly localized 18 of 28 lesions (64%). In comparison, ^{123}I/^{99m}Tc-sestamibi subtraction (evaluable in 21 cases) correctly identified 16 of 21 lesions (76%). Likewise, of the 11 hypercellular glands found in patients with a history of multiglandular disease (sporadic or MEN1), double-phase ^{99m}Tc-sestamibi scanning successfully identified 5 of 11 glands (45%), whereas ^{123}I/^{99m}Tc-sestamibi imaging (evaluable in 4 patients) detected 3 of 6 glands (50%).

Overall, in the 25 patients in whom both studies were performed and evaluable, double-phase ^{99m}Tc-sestamibi imaging correctly localized 16 of 27 lesions (59%) compared to 19 of 27 (70%) for ^{123}I/^{99m}Tc-sestamibi subtraction scanning ($p2 = 0.25$). In the larger group, double-phase ^{99m}Tc-sestamibi imaging correctly localized 23 of 39 lesions (59%) (Table 1). In three patients, ^{123}I subtraction identified lesions missed or deemed indeterminate by ^{99m}Tc-sestamibi alone (Figs. 2–4). No lesions seen on double-phase scanning were missed by the ^{123}I/^{99m}Tc-sestamibi technique.

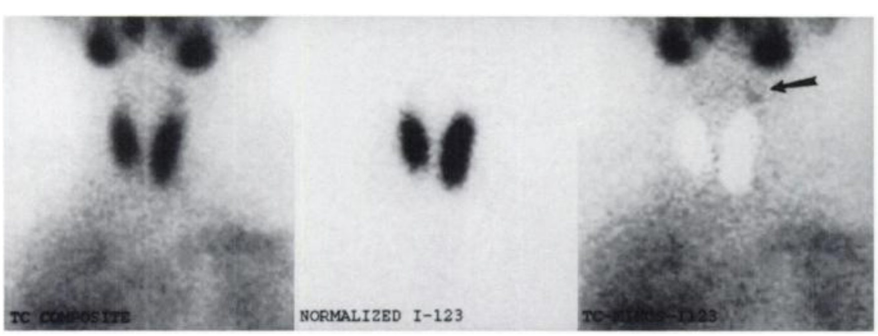

FIGURE 4. Addition of ^{123}I/^{99m}Tc-sestamibi subtraction imaging to the study illustrated in Figure 3 reveals a definite area of excess ^{99m}Tc-sestamibi uptake (arrow) in a parathyroid adenoma (0.25 cm^3).

TABLE 1
Imaging Results

Technique	No. of lesions	TP	FN	Sensitivity (%)
$^{123}I/^{99m}Tc$-sestamibi (evaluable)	27	19	8	70
Double-phase ^{99m}Tc-sestamibi	39	23	16	59
Early anterior (alone)	39	15	24	38
Early anterior + obliques	39	19	20	49

TP = true-positive; FN = false-negative

Of the negative double-phase ^{99m}Tc-sestamibi studies, there were four patients in whom the parathyroid abnormalities were actually well visualized with ^{99m}Tc-sestamibi alone, appearing as solitary foci of activity in the thyroid bed. Unfortunately, because of their location and the absence of normal surrounding thyroid activity, these lesions could not be distinguished from possible residual thyroid tissue on the double-phase ^{99m}Tc-sestamibi scan, and therefore, for the purposes of this report, have been scored as false-negative studies. This occurred in one patient with a positive $^{123}I/^{99m}Tc$-sestamibi study who was on Synthroid and had a history of hemithyroidectomy and Hashimoto's disease. It also occurred in the three patients with $^{123}I/^{99m}Tc$-sestamibi studies that were not evaluable due to total absence of ^{123}I thyroid uptake, although two of these patients had previously undergone total thyroid ablation for thyroid cancer (and therefore should not have had any residual thyroid tissue). The last patient had a history of partial thyroid resection for multinodular goiter, was on Synthroid and had received intravenous contrast 1 day prior to her scan. In all four patients, surgery later identified the visualized foci as parathyroid abnormalities, and all four studies were considered to have been clinically useful. Had these four studies been considered true-positives, overall sensitivity of the double-phase ^{99m}Tc-sestamibi technique in this series would have been raised to 27/39, or 69%. Likewise, had the three nonevaluable $^{123}I/^{99m}Tc$-sestamibi scans been scored as true positives, our sensitivity for subtraction scanning would be 22/30 or 73%.

Analysis of the various components of the double-phase ^{99m}Tc-sestamibi study showed that early anterior images definitively demonstrated only 15 of 39 parathyroid abnormalities, providing a sensitivity of 38% (Table 1). Acquisition of right and left anterior oblique images revealed four additional lesions (Fig. 5), resulting in an overall sensitivity of 49% (19/39) for early imaging (anterior and oblique images combined). Acquisition of delayed images allowed detection of an additional four lesions and increased the sensitivity to 59% (23/39). For the most part though, delayed images merely confirmed the findings seen on the early images or added no additional information. In two patients, however, mild abnormalities visible on the early images (scored as indeterminate in one case and positive in another) demonstrated rapid washout relative to thyroid tissue and were not visible at all on the delayed images (Figs. 3, 4). The subtraction studies in these two patients were both positive, since $^{123}I/^{99m}Tc$-sestamibi subtraction is performed with the early ^{99m}Tc-sestamibi images.

Overall, the mean size of lesions which were correctly localized by $^{123}I/^{99m}Tc$-sestamibi scanning was 1.12 cm^3 (range = 0.13–5.72) compared to 1.29 cm^3 (range = 0.13 to 5.72) for those detected using the double-phase ^{99m}Tc-sestamibi technique. Missed lesions averaged 0.64 cm^3 (range = 0.05 to 1.77) for $^{123}I/^{99m}Tc$-sestamibi and 0.73 cm^3 (range = 0.05 to 3.46) for double-phase scanning.

Four false-positive findings were encountered in this series of patients. The false-positive nature of these lesions, however, was fairly obvious in each case due to their locations and the other ^{99m}Tc-sestamibi scan findings. Two patients with discrete areas of ^{99m}Tc-sestamibi uptake consistent with ectopic parathyroid tissue also had increased uptake in abnormal thyroid tissue—one in a thyroid adenoma and the other in a large substernal goiter. Two other false-positive findings consisted of diffuse ^{99m}Tc-sestamibi

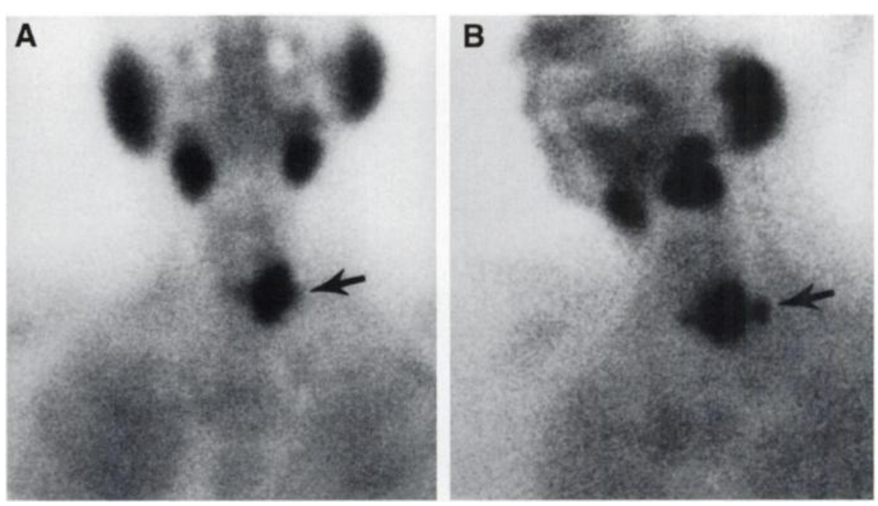

FIGURE 5. Early anterior ^{99m}Tc-sestamibi image (A) demonstrates uptake in the left lobe of the thyroid which appears to have an irregular contour (arrow). Most of the right thyroid lobe has been removed. Left anterior oblique image (B) shows that the contour irregularity is due to a parathyroid adenoma (0.47 cm^3) lying posterior to the thyroid (arrow).

uptake near the midline at the level of the heart. In both cases, it was felt that ^{99m}Tc-sestamibi uptake in this location was unlikely to represent ectopic parathyroid tissue. In one patient, the scan also revealed what later proved to be an undescended parathyroid gland on the left. This patient had had a recent negative chest exploration with median sternotomy. The other patient had an otherwise negative ^{123}I/^{99m}Tc-sestamibi scan. At surgery, a parathyroid adenoma was found in the neck and the patient was biochemically cured. The chest was not explored.

DISCUSSION

Recently, ^{99m}Tc-sestamibi has become a popular substitute for ^{201}Tl in radionuclide parathyroid localization studies. First described by Coakley et al. (*8*), reported sensitivities range from 88% to 100% for parathyroid adenomas (*1,2,4*) and from 53% to 67% in patients with diffuse parathyroid hyperplasia (*1,2*). These studies have been performed primarily in patients prior to initial surgery and in conjunction with ^{123}I thyroid scanning for subtraction. However, both the study by Weber et al. (*3*), which dealt with reoperative patients, and the studies by Taillefer et al. (*6*) and Irvin et al. (*7*), which used a single agent sestamibi (double-phase) technique, also reported sensitivities of 88% and 90%–94%, respectively.

In the current series of patients, overall sensitivities of 70% and 59% were obtained for ^{123}I/^{99m}Tc-sestamibi and double-phase ^{99m}Tc-sestamibi scanning, respectively. The reasons for these lower sensitivities relative to other series are probably related to the patient population studied. Patients with easily identified parathyroid lesions, either by size or location, are generally treated successfully at the initial surgical procedure. For this reason, a population presenting for reoperative surgery tends to have lesions that are smaller and/or more frequently ectopic than those of patients undergoing initial neck exploration. This selection bias may contribute to the lower sensitivities in this study since lesion size contributes to the ability of most imaging modalities, including double-phase and ^{123}I/^{99m}Tc-sestamibi scanning, to localize abnormal parathyroid glands. With scintigraphy, the depth of a lesion is also significant, as deeper lesions are subject to greater attenuation from overlying tissues.

Lastly, many (12/35) of the patients in our study had suppressed or absent thyroid tissue due to a history of thyroid ablation, therapy with Synthroid or recent intravenous contrast. Thyroid suppression, in particular, complicates subtraction scanning, which is dependent on ^{123}I uptake by the thyroid. We generally elect to perform thyroid imaging in these patients despite the fact that their ^{123}I uptake is expected to be decreased, as patients are often not fully suppressed and useful information can be obtained from these scans. One hazard to such an approach, however, is that since suppressed thyroid tissue often retains its ability to take up ^{99m}Tc-sestamibi compared to iodine (*9–11*), a subtraction study could result in false-positive findings. Of the five evaluable ^{123}I/^{99m}Tc-sestamibi studies performed in thyroid-suppressed patients in this series, however, none resulted in false-positive findings. To the contrary, addition of ^{123}I subtraction scanning allowed differentiation of thyroid from parathyroid tissue in some of these patients, which was not apparent from the Sestamibi images alone.

This study shows that the sensitivity of ^{99m}Tc-sestamibi imaging in persistent or recurrent primary hyperparathyroidism may be somewhat lower than what has been reported so far in the literature and highlights the need for further study with this agent. Compared to previously published results from this institution, which found a 37% sensitivity for ^{99m}Tc/^{201}Tl subtraction scanning in reoperative cases (*12*), we believe that ^{99m}Tc-sestamibi will prove to be superior to ^{99m}Tc/^{201}Tl scanning. In patients presenting for reoperative surgery, ^{123}I/^{99m}Tc-sestamibi subtraction scanning should be performed to optimize sensitivity. Many reoperative patients have had their thyroid morphology altered during prior surgery, and the ^{123}I image is useful in defining these abnormalities, as well as in confirming results of double-phase ^{99m}Tc-sestamibi scans. Subjectively, we also believe that ^{123}I subtraction increases the level of certainty with which many lesions are called, and that the additional costs and time involved with ^{123}I scanning are outweighed by the benefits gained.

CONCLUSION

Our current approach to evaluating patients prior to reoperation included: (a) performing ^{123}I/^{99m}Tc-sestamibi subtraction scanning in all patients, even if they are thyroid-suppressed; (b) minimizing the number of thyroid-suppressed patients by scheduling CT scans after the radionuclide study and, when possible, decreasing or stopping Synthroid therapy prior to the study; (c) performing early and delayed double-phase imaging in all patients and (d) performing right and left anterior oblique ^{99m}Tc-sestamibi images in all patients. SPECT imaging is performed as needed. Lastly, one should be aware that with the double-phase technique, differences in washout rates between thyroid and parathyroid tissue are not always obvious. In addition, some parathyroid abnormalities may be visible only on early images due to rapid tracer washout. For this reason, delayed imaging alone is not reliable and early ^{99m}Tc-sestamibi images should be used for ^{123}I/^{99m}Tc-sestamibi subtraction.

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