

IMAGING OF PARATHYROID LESIONS WITH RADIONUCLIDES - IS IT WORTH DOING?

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ABSTRACT

Parathyroid adenomas, or hyperplasia may be present in patients with hypercalcemia. Treatment is by surgical excision, but about 10% of the lesions may be in ectopic locations. Pre-operative localization of the lesions with non-invasive imaging, using radionuclides, ultrasound, CT, or MRI, may simplify surgery, and reduce patient morbidity. However, the reports of the accuracy of the currently available techniques have shown wide variations. This problem is reviewed, with emphasis on the radionuclide methods of dual radiopharmaceutical thallium-pertechnetate subtraction, and sestamibi delayed imaging protocols. The author recommends the routine use of sestamibi, with additional non-invasive imaging techniques to be added if the original scan is negative.

Key words: parathyroid imaging; sestamibi; hyperparathyroidism

INTRODUCTION

Hyperparathyroidism may occur in the primary form, due to the presence of a PTH secreting neoplasm, or in the secondary form, due to glandular hyperplasia, associated with medical conditions causing disturbed calcium metabolism, such as chronic renal failure, or intestinal disorders. Except in florid cases, where there is significant bone resorption, causing skeletal pain, or with the development of renal calculi, the clinical presentation of hyperparathyroidism is usually silent, or vague. Most often, the incidental finding of elevated

serum calcium is the first clue to this disorder. However, there are numerous causes of hypercalcemia which are not related to parathyroid disease (1).

In patients with hypercalcemia, the non-invasive diagnosis of a secretory parathyroid lesion should be an effective tool to detect the lesion prior to surgery. As parathyroid adenomas may occur in ectopic locations, such as the mediastinum, they may be missed at routine exploration. Non-invasive methods used include radionuclides, ultrasound, CT, and MRI. However, because

of the wide variation in reports of the sensitivity of detection of abnormalities, some controversy exists in the surgical literature about the value of pre-operative localization methods.

Dual-isotope subtraction scanning

Until recently, the dual radiopharmaceutical subtraction imaging technique, using Tc-99m pertechnetate to image the thyroid gland, and Tl-201 to image both the thyroid and abnormal parathyroid tissue, was the method of choice (1,2). Computer subtraction of the two images left only the abnormal parathyroid tissue displayed.

This technique was originally described by Ferlin et al. (3), and was reported to have a sensitivity of 92%. Gupta et al. (4), and Basarab et al. (5), also reported similar results, but most users have not achieved this degree of accuracy. Gimlette and Taylor (6) reported 64% sensitivity, and Pearl et al. (7) reported 60% sensitivity for correctly localized adenomas. Extensive review of the literature shows a wide range of accuracy reported, from a high of 100% by Jenkins et al. (8), to a low of 42% by Sandrock et al. (9), in a series of 214 patients. Gallacher et al. (10) also had 42% rate, but with a specificity of 97%. The common range for adenoma detection is approximately 65 to 85%. Price (11) totalled 1,785 patients, from 60 publications, and reported 72% sensitivity, with 11% false positive rate for adenomas.

In a previously unpublished review of our experience in 18 patients with surgical confirmation, using the thallium-pertechnetate subtraction technique, we found 10 true positive adenomas, 4 true negatives, and 4 false negative adenomas, ranging in size from 0.21 to 1.5 gm. The overall accuracy was 14/18 (78%), with the sensitivity of 10/14, or 71%, which corresponds to the general experience with this method.

Hyperplastic nodules, associated with secondary hyperthyroidism are generally not well detected with thallium subtraction techniques. Suehiro and Fukuchi (12) achieved 96.2% sensitivity for adenomas, but detected only 48.5% of hyperplastic lesions. Percival et al. (13) found only 41% of hyperplastic lesions, compared with 89% detection of adenomas. Price's summary of 140 patients, from 20 publications yielded 43% sensitivity, and 8% false positive results in hyperplasia (11). Nobin et al. (14) detected 86% of adenomas, but only 13% of hyperplastic glands.

Disparity of published results

The disparity of results from center to center may be due to wide variations in patient selection criteria, (i.e., the frequency of symptomatic patients, vs. asymptomatic with incidental hypercalcemia. This could alter the size of the nodules at initial presentation.), the non-uniformity of the quality of imaging techniques from center to center, and skill of interpretation. When using dual isotope imaging, there may be problems associated with patient motion, and computer subtraction methods.

Subtraction techniques require image manipulation, including background correction, normalization to the hottest pixel, and image registration to correct for patient motion. Ewin et al. (15) reported an initial sensitivity of detection of 44%, which improved to 100% when a better computer algorithm was used.

Tc-99m-sestamibi imaging

As Tc-99m labelled sestamibi (Cardiolite, The DuPont Merck Pharmaceutical Co., Billerica, Mass., USA) became available as a replacement for thallium, Coakley et al. (16) demonstrated that sestamibi was also able to localize in parathyroid adenomas. Numerous reports of sestamibi parathyroid imaging,

using pertechnetate (17), or I-123 (18,19) to subtract the thyroid followed. These publications generally found improvement in the imaging quality, and sensitivity, compared with thallium. O'Doherty et al. (20) reported a higher concentration of thallium, in the parathyroids and in the thyroid, compared with sestamibi. However, the ratio of parathyroid to thyroid was higher with sestamibi, giving a better target to background ratio, and improved image quality. They had better overall results with sestamibi in patients scanned using both radiopharmaceutical techniques.

Taillefer et al. (21) noted that a dual radiopharmaceutical subtraction technique was not necessary following injection of sestamibi. While both the normal thyroid, and parathyroid adenomas may accumulate sestamibi in the early images, there is a differential washout rate between these

tissues. Thus, the delayed scan shows retention in abnormal areas, after the thyroid has cleared, obviating the need for computer subtraction techniques (Figs. 1-5). The "self subtraction" properties of sestamibi eliminates artifacts due to patient motion, and the study requires only a single injection, with two sets of images, at 10 minutes, and approximately 3 hours. Taillefer obtained 90% sensitivity using this "double-phase" method, including one patient who was positive with sestamibi, but negative with thallium.

Sandrock et al. (22) reported that the uptake of thallium in adenomas is related to the number of oxyphil cells, which contain abundant mitochondria. Sestamibi localization in the heart, is related to blood flow, and in vitro binding of the radiopharmaceutical is in cells which have an increased concentration of viable mitochondria (23). Tissues taking up sestamibi show an increase in

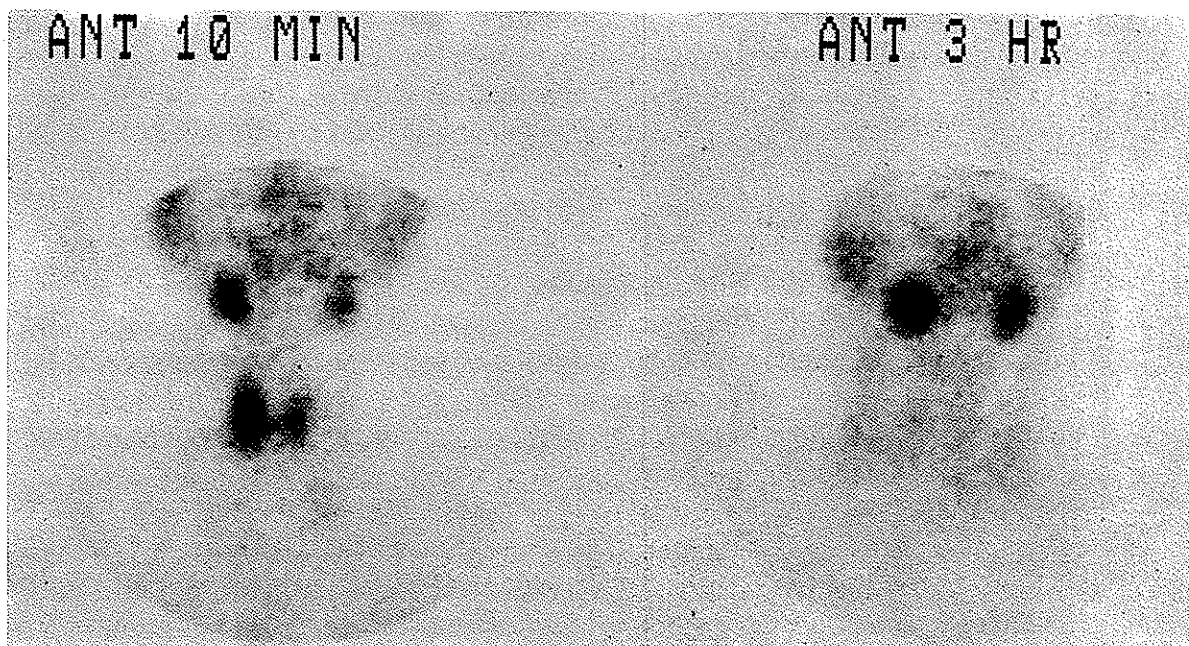


Figure 1. Normal double-phase sestamibi images. At 10 minutes, the thyroid gland and salivary glands are well seen. At 3 hours, the normal thyroid activity has washed out, but some salivary activity normally persists. There is no retained focal activity in the neck or mediastinum.

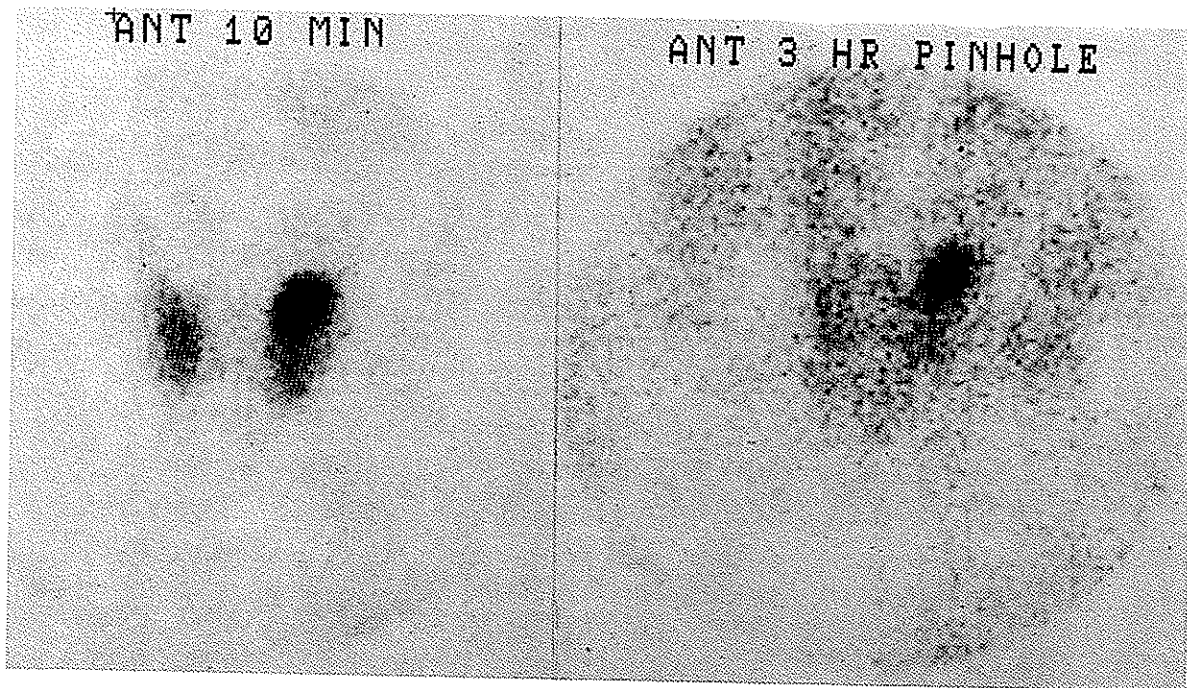


Figure 2. Left upper pole adenoma. A sestamibi pinhole image at 10 minutes shows uptake in the thyroid, with greater uptake in the left upper pole. At 3 hours, the thyroid has substantially washed out, emphasizing the visualization of the adenoma.

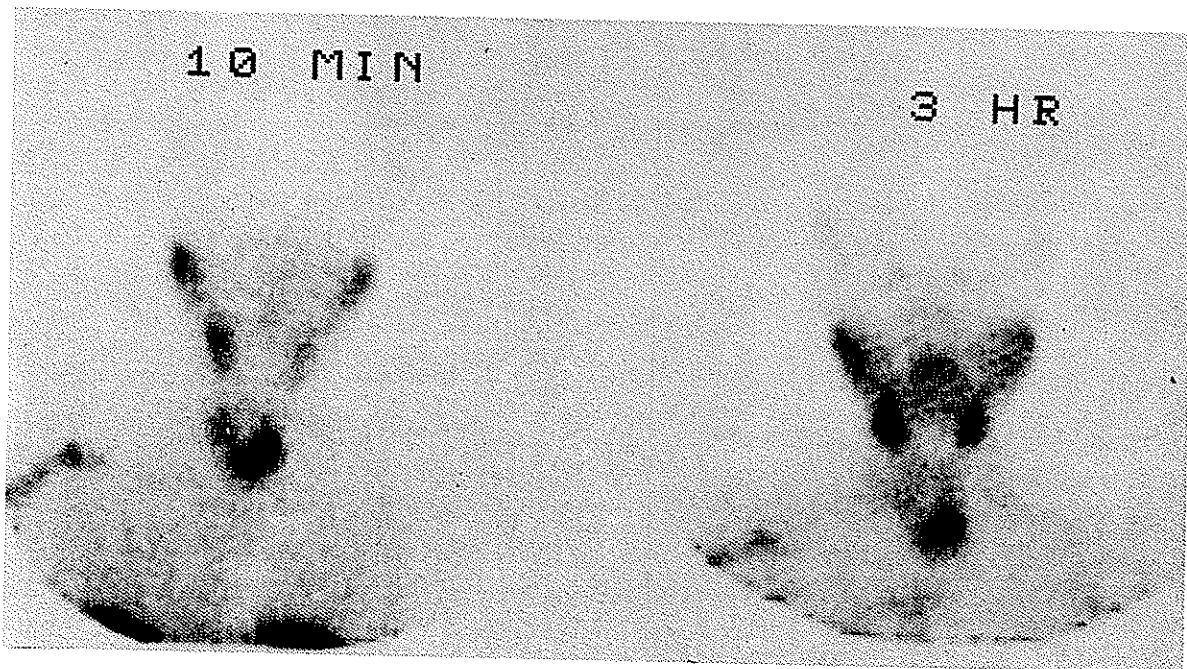


Figure 3. Large left lower pole adenoma. A parallel collimator image at 10 minutes shows sestamibi uptake in the thyroid, salivary glands, and in a large left lower pole nodule, which does not wash out at 3 hours.

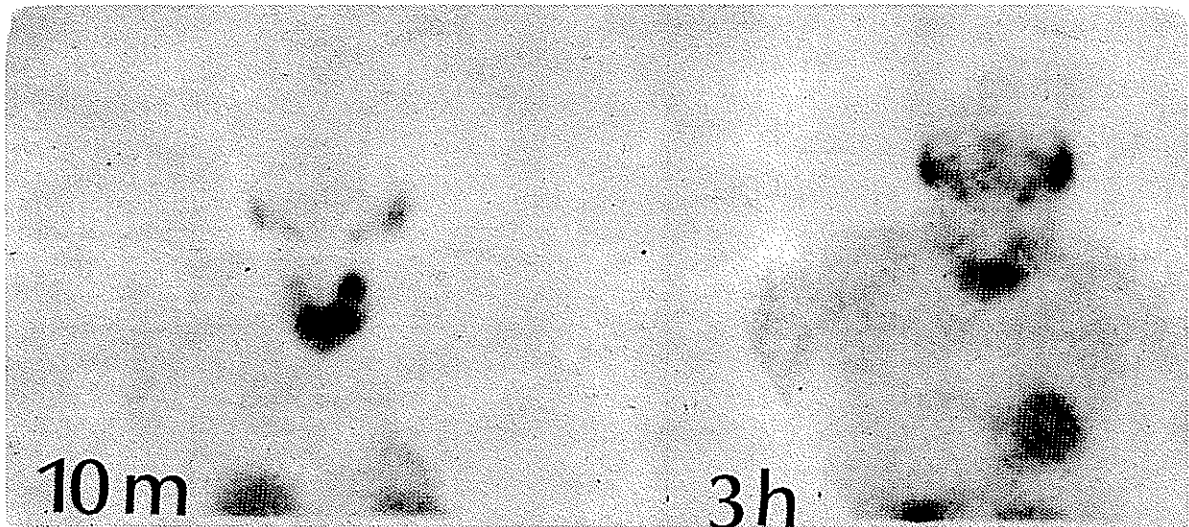


Figure 4. Ectopic parathyroid adenoma. A large active mass below the isthmus of the thyroid retains sestamibi activity in the 3 hour image. The use of the parallel hole collimator permits assessment of the mediastinum, which shows normal cardiac uptake, but no additional lesions.

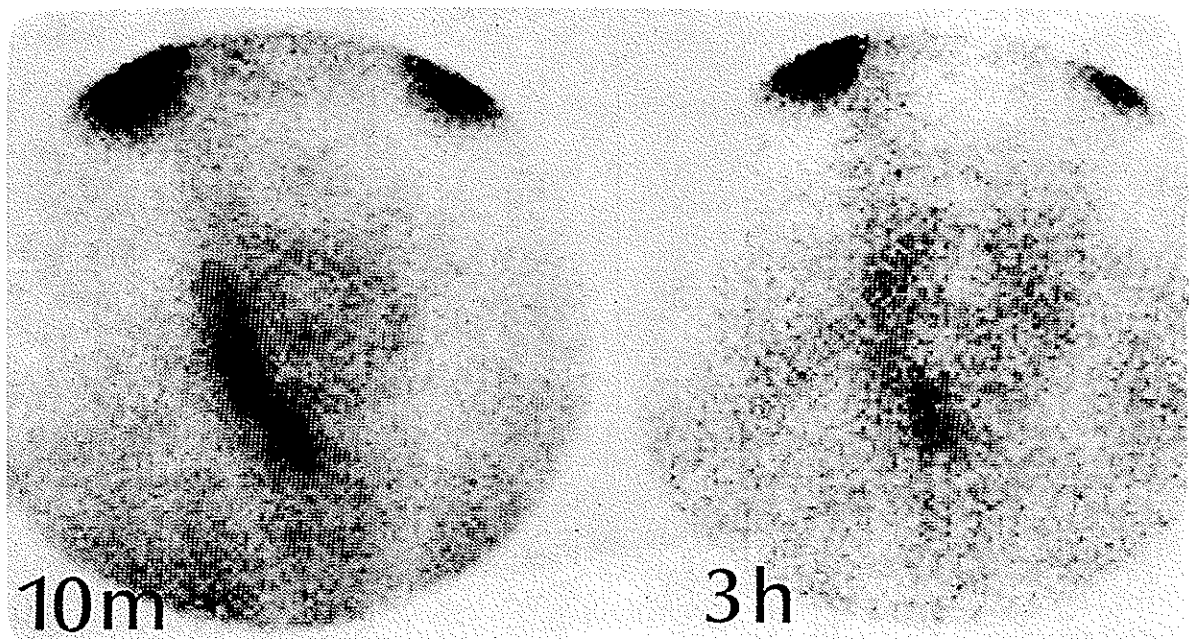


Figure 5. Parathyroid adenoma in a postoperative neck. This patient had a previous left partial thyroidectomy. The focus in the left lower pole retains activity in the 3 hour sestamibi pinhole image.

mitochondrial membrane potentials (24). Thus, the localization in tissues for both of these radiopharmaceuticals is dependent on the presence of mitochondrial activity. This may explain their differential retention in parathyroid lesions, compared to the normal thyroid. It is known that both thallium and sestamibi may localize in various tumours, including thyroid carcinomas, and some adenomas. This may produce the occasional false positive study. However, the possibility of misinterpretation is reduced by selecting only those patients with suspected parathyroid lesions for this technique.

Sestamibi double phase imaging protocol

- a) A planar gamma camera equipped with a parallel hole, high resolution collimator to image the neck and mediastinum (to detect ectopic foci), and a pinhole collimator for a magnified image of the neck;
- b) Intravenous dose of 500 MB_q of Tc-99m sestamibi;
- c) A "flow study" of 2 second/frame images for 30 frames may be obtained, although little additional information is obtained from this part of the study;
- d) 10 minutes after injection, planar images with the parallel hole collimator centered

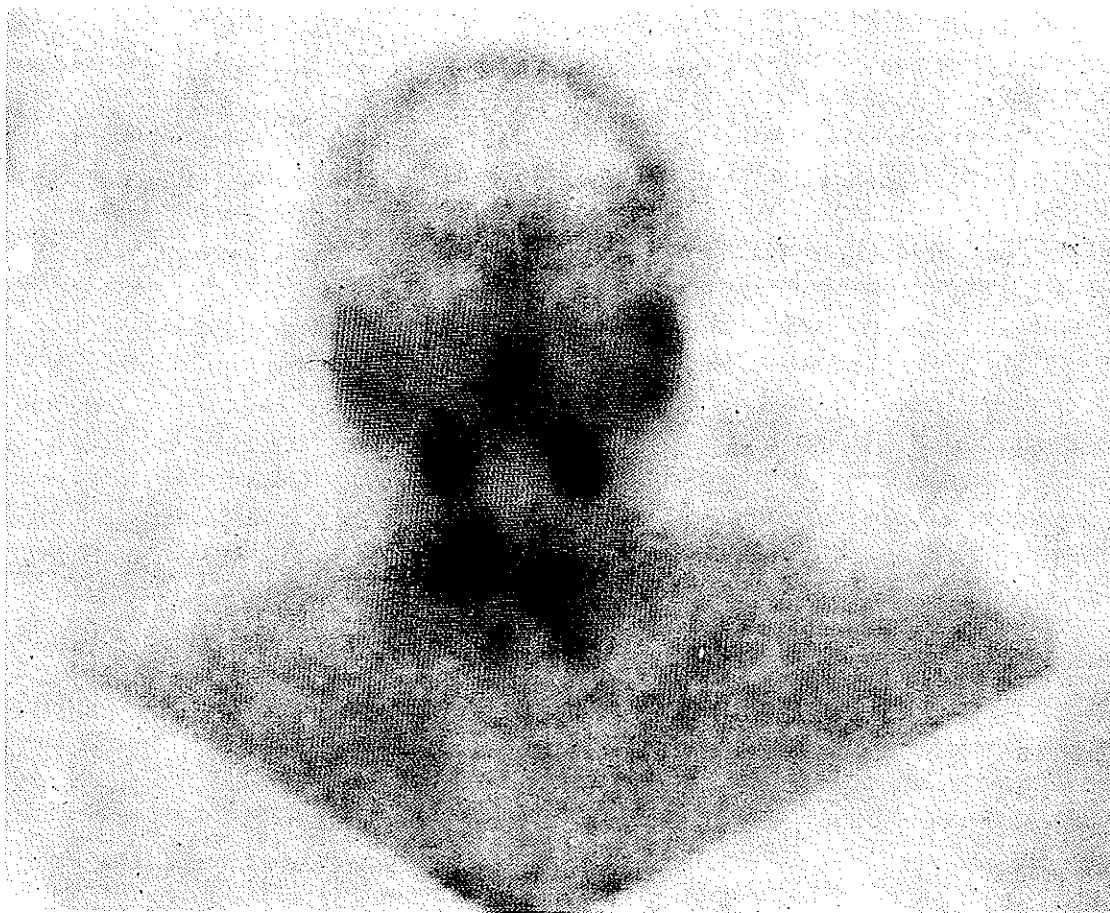


Figure 6. Multiple hyperplastic nodules. A 3 hour delayed sestamibi image in a patient with hypercalcemia, and chronic renal failure. At least 4 (or 5?) foci of retained activity can be noted below the salivary glands. At surgery, this patient had 7 discrete large and tiny hyperplastic nodules.

over the mediastinum, acquiring 500,000 counts, and then pinhole views over the neck for 10 minutes. (These demonstrate uptake in the thyroid, and also in any abnormal parathyroid tissue);

e) 3 hours after injection, the planar images are repeated using both collimators (These show abnormal parathyroid tissues, after the thyroid has "washed-out").

RESULTS

We recently reviewed 25 patients who had sestamibi scans for suspected hyperparathyroidism. Seven patients who had no surgical follow-up, all had negative scans. Eighteen patients with positive scans underwent surgery. Adenomas were found in 14 patients, and hyperplasia in 4. Eleven of 14 of the adenomas found at surgery were correctly detected by scans (a positive scan had focal retained activity at 3 hours, correlating with a lesion found in the same location). Of the 3 false negative scans, one was a lipo-adenoma, one adenoma was very small, but one 2.0 gram adenoma was missed.

Of the four patients with 1 or more hyperplastic nodules (up to 7 in one patient), all had positive scans, but not all of the smaller nodules were demonstrated on the scan (Fig 6). Multiple foci of increased uptake generally indicate hyperplasia, but occasionally multiple primary adenomas may be found (25).

Thus, in all patients with a positive scan, either adenomas, or hyperplastic nodules were found in the correct location (100% positive predictive value per patient). With 3 known false negative scans, the sensitivity was 15/18 or 83.3%. There were no false positives in this series.

DISCUSSION

The advantages of sestamibi

The 140 keV photon of Tc-99m is better suited for gamma camera detection, than the low energy of Tl-201. The shorter half life also permits larger doses of Tc-99m to be injected, while still retaining a lower radiation exposure to the patient. The faster imaging time, and higher count rate available, and better lesion to background ratio should make sestamibi imaging superior to thallium. With the physiological washout of the thyroid, subtraction techniques are not necessary and potential artifacts are avoided. Patient motion between the sets of images is not a problem. O'Doherty et al. (20) obtained slightly better results in patients having sestamibi scans, than in the same patients scanned with thallium.

At this time, sestamibi is not yet released, in the USA, for routine, clinical parathyroid imaging. Thus, the number of published studies with sestamibi is limited.

Other non-invasive techniques

As seen with thallium subtraction imaging, a wide range of sensitivities is also reported in the use of other imaging modalities used for parathyroid lesions. Using ultrasound, Basarab, et al (5) quoted various authors with sensitivities ranging from 44 to 88%, while Kang et al. (26) detected only 12% of abnormal glands. Murchison et al. (27) reported 92% sensitivity, using high resolution, real time ultrasound. Stein and Wexler (28) detected 53% of nodules with ultrasound, but only 36% with thallium imaging. Gooding (29) reported an overall combined sensitivity of 76% after reviewing several studies from numerous centers, while Price (11) quoted a 63% true positive, and an 18% false positive rate in his summary of 1,724 patients reported in 42 publications using ultrasound.

Ultrasound detects less than 50% of hyperplastic glands, and it is not useful in the mediastinum. CT sensitivity ranges from 29 to 88% (5), and MRI from 36% (30), to 88% (26).

Rational for the use of pre-operative imaging

Surgeons claim a 90 to 95% cure rate in the surgical removal of parathyroid lesions. Some have disputed the need for any pre-operative localizing studies, because of the generally poorer sensitivity of non-invasive imaging, compared to direct observation at surgery (31-33). However, almost all of the imaging modalities have a high positive predictive value with a low false positive rate. The addition of multiple non-invasive techniques will give very accurate localization, particularly if the lesion is seen in the same location, on more than one study (34,35). Many failed surgical approaches are the result of missing lesions in ectopic locations (36,37), which occur in about 10% of patients (1). These ectopic foci may be easily detected with nuclear imaging (38). McCall et al. (39) reviewed 9 patients with failed surgery, and obtained 77% true positive results in scanning these patients with thallium. Eighty percent of those lesions were in an ectopic location, either mediastinal, intra-thyroidal, or in the carotid sheath.

A negative exploration has put the patient at an unnecessary risk, produced no benefit, but has wasted time and the resources of the medical system. The operating time is reduced in patients whose surgery is directed to the site of a pre-operatively detected nodule, and there are fewer negative explorations (7,40-42). Re-exploration of a previously operated neck is technically more difficult, and a more hazardous procedure.

CONCLUSIONS

Although far from a perfect test, radionuclide imaging of the parathyroid gland produces satisfactory images of most lesions greater than 0.5 g in size, and frequently in those much smaller. There are few false positives, and thus the positive predictive value of the technique is high (43). Additional non-invasive techniques can be added to the protocol for patients having a negative scan, but in whom there is a high clinical suspicion. One or more of these tests should find all but the smallest nodules (less than 250 mg). As different techniques detect the lesion through different aspects of its structure or function, it is unlikely that they would all be falsely negative (44).

The author proposes that all patients with suspected hyperparathyroidism undergo a radionuclide scan, preferably using the double-phase sestamibi technique, to include visualization of the neck and the mediastinum. A positive scan is usually sufficient to guide the surgeon. If the scan is negative, a second technique, either ultrasound of the neck, or CT or MRI of the neck and mediastinum should be performed. Only a very small percentage of patients with a focal parathyroid lesion will be falsely negative on two tests. If the second test is also negative, another cause of hypercalcemia should be considered prior to surgical exploration.

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