Parathyroid Scintigraphy

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Scintigraphy of the parathyroid glands continues to be controversial from several standpoints, including radiopharmaceutical choice, imaging protocol, results, and utility in clinical situations. This article reviews: the anatomy, physiology and pathology of the parathyroid glands; mechanisms of radiopharmaceutical localization; commonly accepted imaging protocols; image results; and the appropriate use of parathyroid scintigraphy.
Key Words: parathyroid imaging; thallium-201-chloride; technetium-99m-pertechnetate; technetium-99m-sestamibi; iodine-123-sodium iodide

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Abnormalities of the parathyroid glands are being found with increasing frequency, due to improved methods for measuring serum calcium levels. The treatment of choice for parathyroid abnormalities is usually surgery, but surgery without prior localization will be unsuccessful 5%–10% of the time (*1*). All of the imaging modalities have been studied for their ability to localize abnormal parathyroid glands. Nuclear medicine techniques, in particular, have been examined extensively since ^{201}Tl/^{99m}Tc-pertechnetate subtraction scintigraphy was first proposed by Ferlin et al. in 1983 (*2*). This article discusses parathyroid anatomy, physiology and pathophysiology; offers a survey of scintigraphic techniques; and demonstrates the range of parathyroid abnormalities that can be seen scintigraphically.

ANATOMY, PHYSIOLOGY, AND PATHOLOGY OF THE PARATHYROID GLANDS

The fetal development of the parathyroid glands is the main determinant of their location, both normally and ectopically (*3*). Ovoid in shape, the parathyroids are normally very small (30–50 mg in weight, and 2 × 3 × 3 mm in dimensions). The two upper glands originate in the fourth pharyngeal pouch and migrate with the thyroid gland to the neck. They are normally located in the region of the upper poles of the thyroid, although large parathyroid adenomas may "droop" into the lower pole region. The two lower glands form in the third pharyngeal pouch and migrate inferiorly in conjunction with thymic tissue. Their normal anatomic location is behind the lower poles of the thyroid gland, but they may also be located in the thymic tongue or elsewhere in the mediastinum. There is considerable variation in the location of both normal parathyroid glands and parathyroid adenomas, and even in the number of glands in a particular individual (*1*).

The parathyroid glands produce parathyroid hormone (or parathormone), which is a principal controller of blood levels of calcium and phosphorus. Its mechanisms of action include: (a) increasing bone resorption rates, (b) decreasing calcium excretion and increasing phosphate excretion by the kidneys and (c) increasing the absorption of calcium in the gastrointestinal tract (*4*). An increase in the circulating parathyroid hormone level causes an increase in the calcium level and a decrease in the phosphate level in the plasma. Under normal feedback mechanisms, the rise in the blood calcium level causes a decrease in the secretion of parathyroid hormone. Pathological conditions involving the parathyroid glands override the normal negative feedback, producing a high level of calcium in the blood and concomitant damage most evident in the bones and kidneys, but also affecting the gastrointestinal and nervous systems. The medical school canard for hyperparathyroidism is "renal stones, bad bones, abdominal groans, fatigue overtones and psychic moans."

Primary hyperparathyroidism has four major causes. The most common cause is a solitary parathyroid adenoma (85% of all cases) followed by four-gland hyperplasia (10%), multiple adenomas (4%), and parathyroid carcinoma (1%) (*5*). Clinically, the diagnosis of primary hyperparathyroidism is based on elevated blood calcium and parathyroid hormone levels. The consequences of hyperparathyroidism include osteoporosis, kidney stones, renal failure, peptic ulcer disease, pancreatitis and emotional disorders. In addition, hyperparathyroidism can complicate other illnesses. The seriousness of these consequences leads to the need for treatment of even asymptomatic patients. The treatment of choice is surgical resection of the offending gland or glands.

MECHANISMS OF RADIOPHARMACEUTICAL LOCALIZATION

The small size of the normal parathyroid glands makes them difficult or impossible to visualize with any of the imaging modalities. Solitary adenomas, due to their larger size (0.5–2 cm and up to 500 mg or larger), have been successfully imaged using anatomic methods such as ultrasound or MRI. Nuclear medicine imaging techniques, in contrast, rely on preferential accumulation of radiopharmaceuticals in the organ of interest based on physiology and are less dependent on size. In parathyroid scintigraphy, preferential accumulation is based on increased vascularity and cellularity of the parathyroid glands (6). The agents that have been used for imaging the parathyroids, namely ^{201}Tl chloride and ^{99m}Tc-sestamibi, are good blood flow agents that image well immediately after injection.

In the neck, the only other structure with high vascularity is the thyroid gland. It is therefore necessary to either subtract out the activity in the thyroid gland or to wait some length of time to allow for differential washout of the radiopharmaceutical from the thyroid. The original technique for parathyroid scintigraphy (2) used the former method by injecting a second radiopharmaceutical (^{99m}Tc pertechnetate) and subtracting the two images. More recently, the latter method has been used after ^{99m}Tc-sestamibi injection. These protocols are reviewed below.

The reliance on increased vascularity for preferential accumulation leads to some predictable false-positives, namely reactive lymph nodes and thyroid adenomas (1). Additionally, patients with suppressed thyroid uptake (by exogenous thyroid hormone, large iodine load or previous thyroid surgery) are difficult to image using subtraction techniques (3). These difficulties have contributed to the wide range of reported sensitivities for parathyroid scintigraphy (6). An additional confounding factor in evaluating the efficacy of parathyroid scintigraphy is the wide variety of imaging protocols.

IMAGING PROTOCOLS

Thallium-201-Chloride/Technetium-99m-Pertechnetate Subtraction Protocol

Most protocols for dual-isotope imaging have followed the technique of Ferlin et al. (2). Thallium-201-chloride is injected, and after a few minutes delay, an anterior survey image (large field of view) of the neck and chest is acquired to look for ectopic parathyroid adenomas. Immediately thereafter an anterior pinhole image of the thyroid is acquired. Technetium-99m as pertechnetate is then injected and a second pinhole image is acquired after a 5–10-min delay to allow blood-pool activity to clear. The patient must remain very still between the images to facilitate image subtraction. Some authors have injected [^{99m}Tc]pertechnetate before [^{201}Tl]thallous chloride in order to decrease the time required for patient immobilization (see ref. 1 and 7 for examples). This, however, creates a need for correcting the ^{201}Tl image for ^{99m}Tc downscatter. Others have acquired a dynamic series of images so that any demonstrating motion can be eliminated (7). We have published a technique that seems to be tolerable to patients and gives good results (8).

Technetium-99m-Sestamibi Double-Phase Protocol

O'Doherty et al. (9) and Taillefer et al. (10) proposed the use of ^{99m}Tc as sestamibi to image abnormal parathyroid glands. Taillefer's protocol imaged the head and neck 10–15 min (thyroid phase) and 2–3 hr (parathyroid phase) after injection of 20–25 mCi ^{99m}Tc-sestamibi. Taillefer obtained planar images using a parallel-hole collimator, but pinhole and/or SPECT imaging can also be used. These may be with parallel-hole, converging or pinhole collimators. An area of focally increased uptake that shows either fixed or increasing activity over time is interpreted as parathyroid adenoma. One difficulty with this technique is that computer subtraction of the initial and delayed images is made much more difficult by the changes in patient position. Another difficulty is that the differential rate of washout between the thyroid and parathyroids may vary from individual to individual (11,12).

Technetium-99m-Sestamibi/Iodine-123-Sodium Iodide Subtraction Protocol

O'Doherty's protocol used [^{123}I]sodium iodide to obtain a thyroid image, which is subtracted from the ^{99m}Tc-sestamibi image (9). Four hours after administration of 200 μCi ^{123}I, a pinhole or converging collimator is used to image the thyroid bed. Without moving the patient, ^{99m}Tc-sestamibi is injected, and a repeat image is obtained 10 min later. Downscatter correction of the ^{99m}Tc image may not be required due to the 100-fold difference in administered activity between the two radiopharmaceuticals. Technetium-99m-pertechnetate can also be used to obtain a thyroid image to subtract from the sestamibi. This technique has the added possibility of performing delayed ^{99m}Tc-sestamibi images in 2–3 hr, thus being "convertible" to a double-phase protocol (12).

In summary, a representative protocol of each of these three methods is given in Table 1. The reader should consult the references given here and elsewhere for additional details and more complex protocols.

SENSITIVITY

A brief word about specificity of parathyroid scintigraphy: most patients referred for parathyroid scintigraphy have been identified with certainty as having hyperparathyroidism, based on measurement of serum calcium and parathyroid hormone levels. Thus, there are few, if any, true-negatives in most series. Additionally, patients with true-negative findings would be those surgically proven to have no adenomatous or hyperplastic parathyroid glands, and these patients may not be operated on if localization techniques do not demonstrate an abnormality. Therefore, the most meaningful value for parathyroid imaging techniques is sensitivity.

Reported sensitivities for ^{201}Tl-chloride/[^{99m}Tc]pertechnetate vary from 26% to greater than 90% (6). We believe that this variability is due to differences in protocols and in interpretation [for example, an upper pole adenoma that has descended to the region of the lower pole may be interpreted as

TABLE 1
Suggested Protocols for Parathyroid Scintigraphy

	Protocol		
	^{201}Tl-chloride/ [^{99m}Tc]pertechnetate	^{99m}Tc-sestamibi double-phase	[^{123}I]NaI/^{99m}Tc-sestamibi
Initial radiopharmaceutical	^{201}Tl-chloride	^{99m}Tc-sestamibi	^{123}I-NaI
Delay	2–3 min	10–15 min	4 hrs
Collimator(s)	Parallel-hole (survey image); pinhole	Parallel-hole	Pinhole
Matrix	64 × 64	128 × 128	not given
Counts or time per image	100 K cts	10 min	100 K cts
Second radiopharmaceutical	[^{99m}Tc]-pertechnetate	none	^{99m}Tc-sestamibi
Delay	5–10 min	2–3 hr	10 min
Collimator	Pinhole	Parallel-hole	Parallel-hole
Counts or time per image	100 K cts	10 min (neck)	100 K cts (neck); 800 K cts (mediastinum)
References	8	10	28

false-positive and/or a false-negative in some studies (13)]. Reported sensitivities for double-phase sestamibi imaging range from 83 (14) to 100% (15), but are these values are based on small numbers of patients and may decrease as more patients are evaluated with this technique. Likewise, there are only a few reported sensitivities for ^{99m}Tc-sestamibi/[^{123}I]sodium iodide subtraction, and so far they are all very good. Our in-house sensitivity using ^{201}Tl-chloride/[^{99m}Tc]pertechnetate has been in the 90% range over several years. We believe that our success is due to careful technique, a computer subtraction method that increases our certainty, and a hardware zoom that increases the camera resolution rather than just magnifying it. We are, however, quick to recommend ^{99m}Tc-sestamibi imaging in all equivocal cases.

Some clinicians have claimed that preoperative imaging is unnecessary, because 90% or more of all parathyroid adenomas can be found a priori. However, others have noted shortened operative time and/or greater operative success when preoperative localization is performed (15,16). Our parathyroid surgeon notes a 78% greater operative time if bilateral exploration is required, compared to unilateral exploration based on preoperative localization. When hyperparathyroidism persists after an initial operation and reoperation is considered, the likelihood of success decreases so much because of scarring that any and all localization techniques are recommended (17). Technetium-99m-sestamibi may be especially helpful in this scenario (18).

The most difficult parathyroid abnormality to diagnose preoperatively is four-gland hyperplasia. This disease entity is invoked when surgical specimens of all four parathyroid glands show hypercellularity with or without enlargement (19). Because the glands are often not enlarged, they are difficult to image with nuclear medicine techniques. Some authors have suggested that ^{99m}Tc-sestamibi shows diffuse or nonfocal uptake (14), while others have found it unhelpful (20). The dual-isotope subtraction technique with ^{99m}Tc-sestamibi and ^{123}I correctly predicted multiglandular involvement in two of three patients with hyperplasia in one series (21).

Secondary hyperparathyroidism is seen in renal failure (and other diseases) in which excessive production of parathyroid hormone occurs due to chronic hypocalcemia and skeletal resistance to the metabolic actions of the hormone. Hyperplasia and enlargement of all four glands occurs as a result of the body's need for more parathyroid hormone rather than being the cause of the increased level of parathyroid hormone, as in primary hyperparathyroidism (22). Surgery may be recommended in these patients, and preoperative localization using scintigraphic techniques has been used with less-than-stellar results (23,24). It is important to remember that a solitary adenoma seen scintigraphically does not rule out multigland disease or even hyperplasia, in either primary or secondary hyperparathyroidism.

RESULTS OF PARATHYROID SCINTIGRAPHY

The majority of parathyroid adenomas can be seen on camera images only without subtraction. Because our experience is primarily with the ^{201}Tl-chloride/[^{99m}Tc]pertechnetate subtraction technique, the majority of the cases will be of this type, but similar cases can be demonstrated using the alternative protocols. In Figure 1, the parathyroid adenoma stands out below the right lower pole of the thyroid. A slightly more difficult case in Figure 2 is still easily detected by eye only. The lack of concordance between the thyroid gland outline on ^{201}Tl-chloride versus [^{99m}Tc]pertechnetate indicates the presence of a parathyroid adenoma in the right lower pole. Figure 3 shows a subtle parathyroid adenoma in the left lower pole, an impression strengthened by computer subtraction and ultimately confirmed at surgery. If we were to review this case today, we would recommend ^{99m}Tc-sestamibi imaging to confirm the finding.

Figure 4 shows a classic false-positive. The area of increased activity superior to the left lobe of the thyroid is a lymph node. Its position, which would be highly unusual for a parathyroid adenoma, gives it away.
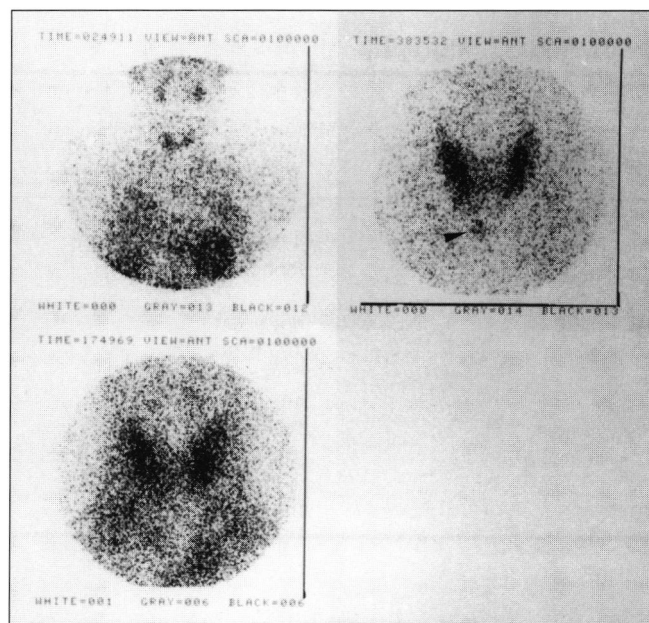
FIGURE 1. Parathyroid adenoma is seen on the ²⁰¹Tl image (upper right) below the right lower pole of the thyroid (arrowhead). There is no corresponding activity on the [⁹⁹ᵐTc]pertechnetate image (lower left).

Parathyroid scintigraphy is made difficult by thyroid abnormalities. Since parathyroid abnormalities are referenced to the lobes of the thyroid, loss or alteration of the normal thyroid anatomy makes localization of parathyroid adenomas that much more difficult. Figure 5 shows a patient with a surgically removed right lobe. Figure 6 shows a parathyroid adenoma in
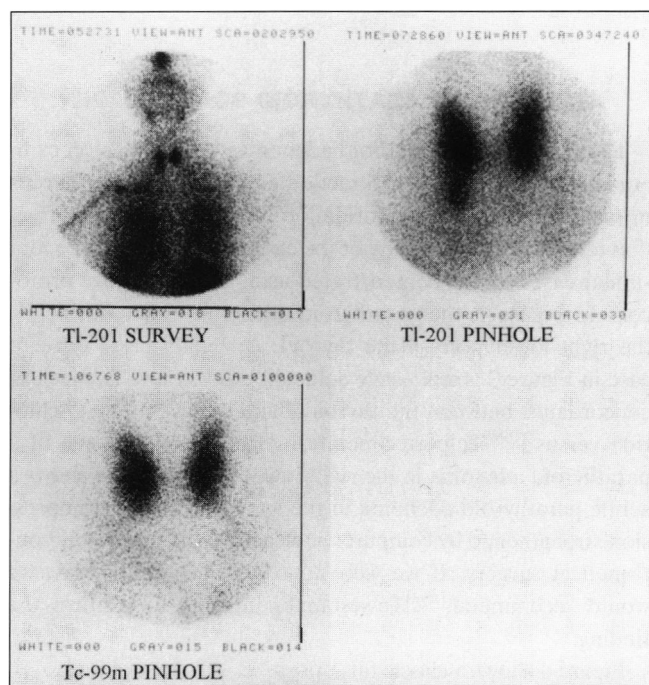
FIGURE 2. This parathyroid adenoma in the region of the right lower pole can be seen by comparing the thyroid gland outline in the ²⁰¹Tl and [⁹⁹ᵐTc]pertechnetate images.
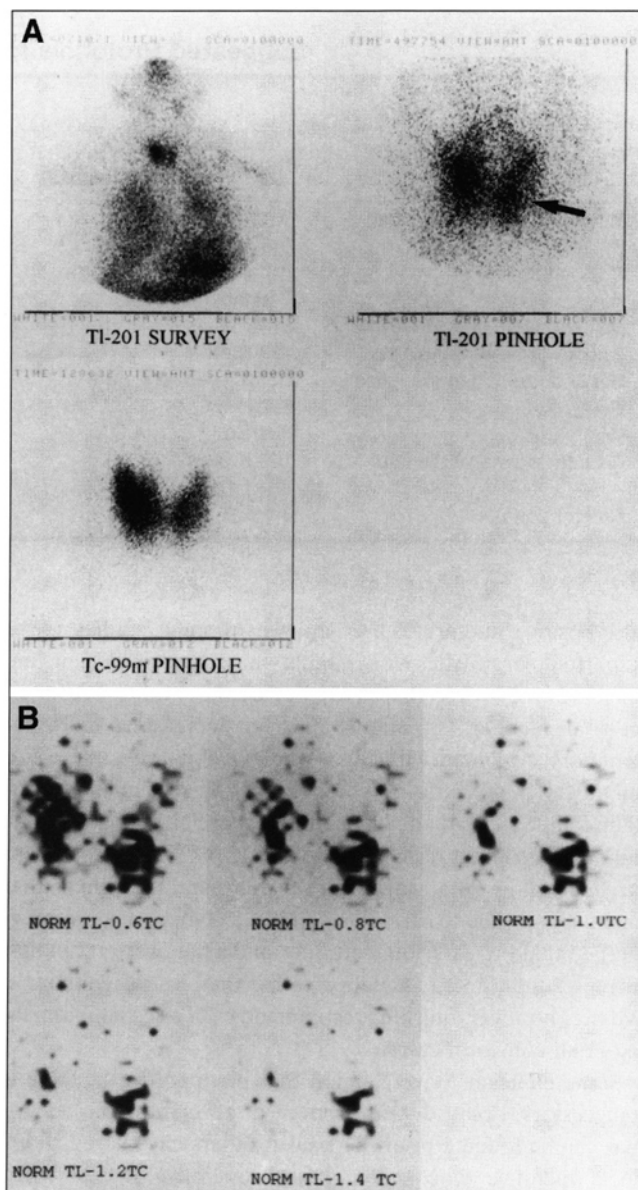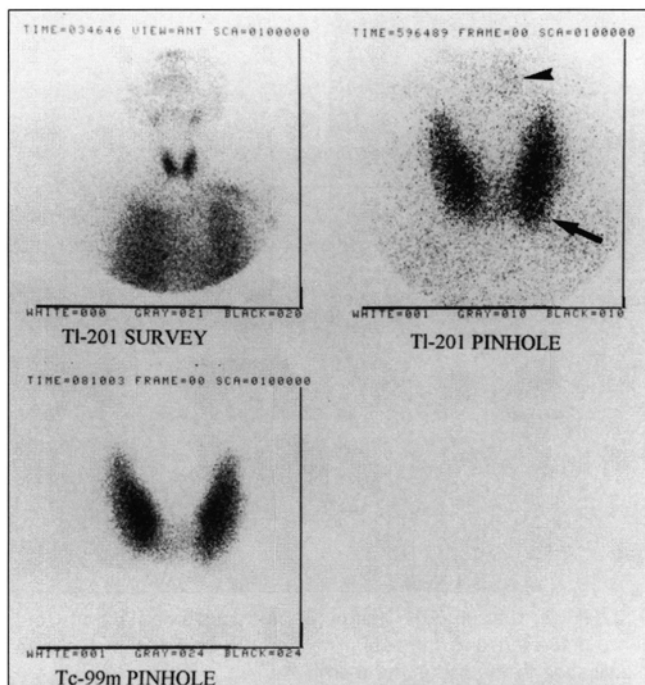

FIGURE 3. A left lower pole parathyroid adenoma was equivocally called in the left lower pole and is better visualized on computer subtraction (B) than on camera images (A, arrow).

the presence of a total thyroidectomy. A similar image would be obtained in a patient on thyroid suppression.

Thyroid adenomas may show increased activity with ²⁰¹Tl, [⁹⁹ᵐTc]pertechnetate, and/or ⁹⁹ᵐTc-sestamibi. Figure 7 shows a left lower pole parathyroid adenoma with a concomitant right lower pole thyroid adenoma. Figure 8 shows ⁹⁹ᵐTc-sestamibi images (immediate and delayed) that apparently demonstrate an intense left lobe parathyroid adenoma and a less intense right lower lobe adenoma. On surgery, however, the parathyroid adenoma was found in the region of the right lower lobe and a large thyroid adenoma in the left lobe.

A small percentage of parathyroid adenomas will be found in the mediastinum. Most are in the superior posterior mediastinum, but a few are in the region of the aortic arch, necessitating a different surgical approach (25). It is for these few

FIGURE 4. A parathyroid adenoma is present in the area of the left lower pole (arrow). Faint activity above the left upper pole (arrowhead) is a reactive lymph node.

cases that the survey image of the chest is so important. The ability of ^{201}Tl to image parathyroid adenomas through the sternum has been questioned, even though it has been used for many yr to image the heart. A recent article demonstrated
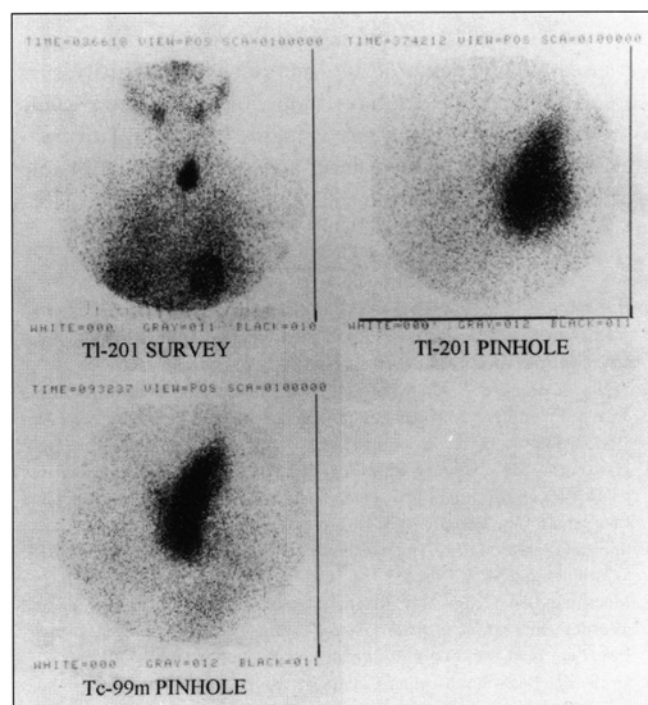
FIGURE 5. In this patient with a surgically absent right thyroid lobe, a parathyroid adenoma can be seen in the lateral aspect of the left lobe.
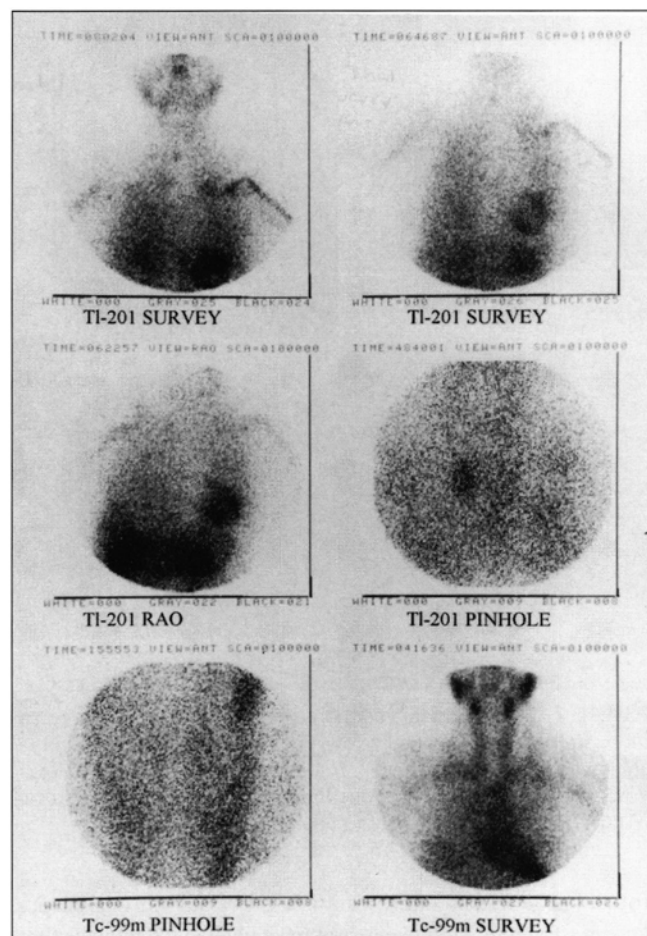
FIGURE 6. This patient had had a total thyroidectomy, so there is no thyroid to subtract. The parathyroid adenoma is seen in the region of the right thyroid bed, with no corresponding ^{99m}Tc activity.

three low mediastinal parathyroid adenomas using ^{99m}Tc-sestamibi (26). In our experience with over 100 patients, we have easily located parathyroid adenomas in the superior mediastinum, and have not missed any in the low mediastinum.

Finally, we present a case of a transplanted parathyroid gland in the left forearm (Fig. 9). In patients with intractable hyperparathyroidism, all four parathyroid glands may be removed, followed by an auto-transplant of a part of one of the glands into the tissue of the neck or forearm. The auto-transplanted gland may be imaged with ^{201}Tl or ^{99m}Tc-sestamibi.

CONCLUSIONS

The parathyroid glands can be imaged scintigraphically using a variety or protocols. While reported sensitivities vary, parathyroid scintigraphy does appear to have a role in the localization of abnormal parathyroid glands, especially when reoperation is being considered. Careful consideration of the technical aspects of this procedure are necessary to obtain good results.

We believe that either a subtraction protocol or a double-phase protocol can, in most cases, give good results. However, we encourage the use of an alternate protocol if one's standard

TI-201 SURVEY

TI-201 PINHOLE

Tc-99m PINHOLE
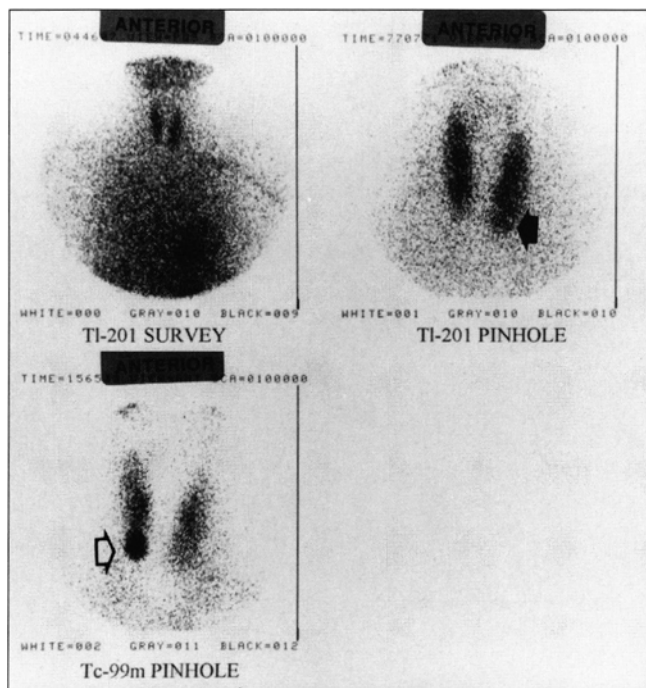
FIGURE 7. The parathyroid adenoma in this patient is in the region of the left lower pole (closed arrow). The thyroid adenoma is in the right lower pole, seen on the [^{99m}Tc]pertechnetate image only (open arrow). This is the "classic" appearance of a thyroid adenoma on ^{201}TI /[^{99m}Tc]pertechnetate subtraction scintigraphy.

protocol produces an equivocal or negative answer in a particular case. Each technique can add to or change a diagnosis that is based on the alternate technique.

The goal of preoperative parathyroid scintigraphy is to guide the surgeon to a specific site to begin his or her search for abnormal parathyroid glands. Thus, it is important to indicate all areas of the thyroid bed where imaging suggests an adenoma. Likewise, a dictated report suggesting an adenoma "in the region of the right lower pole," for example, tells the surgeon where to look without indicating the origin of the adenoma, which may have "drooped" from another area.

Finally, a combination of imaging modalities may be required to diagnose all parathyroid abnormalities. In our institution, ultrasonography is used to identify parathyroid adeno-
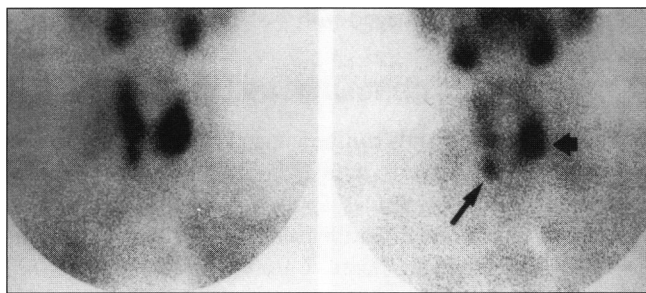
FIGURE 8. Technetium-99m-sestamibi scan of this patient shows a large abnormality in the left lower pole (wide arrow) and a faint area of increased activity in the right lower pole (narrow arrow). The left lower pole lesion was found to be a thyroid adenoma, and the parathyroid adenoma was confirmed on the right.
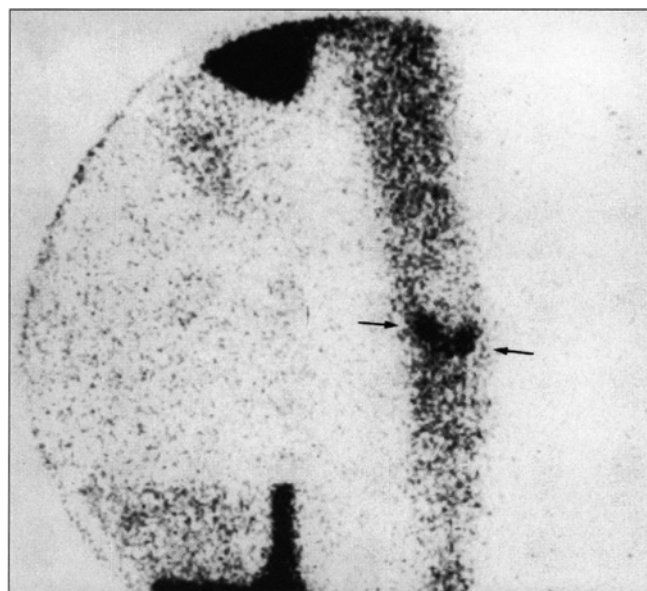
FIGURE 9. Thallium-201 image of a transplanted parathyroid gland in the left arm (arrows). The body is shielded to facilitate visualization to the gland in the arm.

mas that are below the resolution of modern gamma cameras. Nuclear medicine images are used to confirm the sonographic lesions as parathyroid and to localize mediastinal and retroesophageal adenomas that cannot be seen by ultrasound. MRI of the neck and chest can be helpful in reoperative patients in whom localization before surgery is paramount.

The importance of early diagnosis and treatment of hyperparathyroidism cannot be over-emphasized. Long-term follow-up studies have shown an increase in deaths from cardiovascular disease and cancer in patients with hyperparathyroidism (27). Conversely, early parathyroid surgery decreases blood calcium levels, increases bone density, and decreases symptoms of fatigue, bone/joint pain and psychic disorders. Parathyroid surgery is highly beneficial and cost-effective, and parathyroid scintigraphy can play a major role in preoperative localization.

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