ELSEVIER

Radionuclide Imaging of the Parathyroid Glands

Christopher J. Palestro, MD,*,† Maria B. Tomas, MD,*,† and Gene G. Tronco, MD†

The parathyroid glands, which usually are situated behind the thyroid gland, secrete parathyroid hormone, or PTH, which helps maintain calcium homeostasis. Primary hyperparathyroidism results from excess parathyroid hormone secretion. In secondary hyperparathyroidism, the normal PTH effect on bone calcium release is lost. Serum PTH rises, causing generalized hyperplasia. In tertiary hyperparathyroidism, a complication of secondary hyperparathyroidism, normal feedback mechanisms governing PTH secretion are lost, parathyroid gland sensitivity to PTH decreases, and the threshold for inhibiting PTH secretion increases. ^{99m}Tc sestamibi, or MIBI, the current radionuclide study of choice for preoperative parathyroid localization, can be performed in various ways. The "single-isotope, double-phase technique" is based on the fact that MIBI washes out more rapidly from the thyroid than from abnormal parathyroid tissue. However, not all parathyroid lesions retain MIBI and not all thyroid tissue washes out quickly, and subtraction imaging is helpful. Many MIBI avid thyroid lesions also accumulate pertechnetate and iodine, and subtraction reduces false positives. Single-photon emission computed tomography provides information for localizing parathyroid lesions, differentiating thyroid from parathyroid lesions, and detecting and localizing ectopic parathyroid lesions. The most frequent cause of false-positive MIBI results is the solid thyroid nodule. Other causes include thyroid carcinoma, lymphoma, and lymphadenopathy. False-negative results occur because of several factors. Lesion size is important. Cellular function also may be important. Parathyroid tissue that expresses P-glycoprotein does not accumulate MIBI. Parathyroid adenomas that express either P-glycoprotein or the multidrug resistance related protein MRP are less likely to accumulate MIBI. MIBI scintigraphy is less sensitive for detecting hyperplastic parathyroid glands. In secondary hyperparathyroidism, MIBI uptake is more closely related to cell cycle than to gland size. Mitochondria-rich oxyphil cells presumably account for MIBI uptake in parathyroid lesions. Fewer oxyphil cells, and hence fewer mitochondria, may explain both lower uptake and rapid washout of MIBI from some lesions. MIBI is also less sensitive for detecting multigland disease than solitary gland disease.
Semin Nucl Med 35:266-276 © 2005 Elsevier Inc. All rights reserved.

The parathyroid glands, small ellipsoid-shaped structures generally located immediately dorsal, or posterior, to the thyroid gland, were first recognized as distinct endocrine glands in the mid-nineteenth century and were not identified in humans until the late nineteenth century. The current understanding of the relationship between the parathyroid glands and calcium homeostasis is the result of extensive metabolic studies performed at the Renal Stone Clinic of the Massachusetts General Hospital.

Embryology, Anatomy, and Histology

The normal parathyroid gland measures approximately 5 to 7 mm in length and 3 to 4 mm in breadth and weighs approximately 40 to 60 mg.[1,2] The parathyroid glands usually are 4 in number and are derived from the dorsal endoderm of the third and the fourth pharyngeal pouches. They undergo differentiation in the fifth week of gestation and lose their pharyngeal connections by the seventh gestational week.[3] The superior glands, sometimes referred to as "parathyroid IV" because they arise from the fourth pharyngeal pouch, descend from the base of the tongue together with the superior pole of the thyroid gland, eventually coming to lie midway along the posterior borders of the thyroid.[4] The location of the superior parathyroid glands is fairly constant. In approximately 75% of the population, they are found at the junction

*Department of Nuclear Medicine and Radiology, Albert Einstein College of Medicine, Bronx, NY.
†Division of Nuclear Medicine, Long Island Jewish Medical Center, New Hyde Park, NY.
Address reprint requests to Christopher J. Palestro, MD, Division of Nuclear Medicine, Long Island Jewish Medical Center, 270-05 76th Avenue, New Hyde Park, NY 11040. E-mail: palestro@lij.edu

of the upper and middle third of the thyroid gland, postero-lateral to the cricothyroid junction. In approximately 20% of the population, they are immediately posterior to the upper poles of the thyroid gland. In as much as 5% of the population, the glands are intrathyroidal, and in approximately 1%, they are retroesophageal in location.[5]

The location of the inferior glands, "or parathyroid III," which arise from the third pharyngeal pouch and migrate caudally along with the thymus, is more variable than that of the superior glands. The inferior glands can be found anywhere from above the carotid bifurcation to the mediastinum. In approximately 40% of the population, these glands are situated near the lower poles of the thyroid gland. In another 40% of the population, they are found near the thymic tongue. In 20% of the population, they may be in any of several locations: at the angle of the mandible, in the retroesophageal and pretracheal regions, along the tracheoesophageal groove, and even in the pericardium.[5]

Histologically, the normal parathyroid gland is comprised of equal amounts of parenchyma, which consists of interconnecting columns of cells, and stroma. The stroma, which is made up of adipose tissue with an abundant vascular supply, provides support for the parenchyma. The chief, or principal, cells constitute the majority of the parenchymal cells, and are responsible for most of the hormonal secretion. Oxyphil cells are usually not present until 5 to 7 years of age and gradually increase in number after puberty. These cells contain abundant mitochondria, but do not possess a significant secretory function. The number of oxyphil cells and the amount of adipose tissue increase with age.

Hyperparathyroidism

The parathyroid glands secrete parathyroid hormone, or PTH, which together with calcitonin and 1,25-hydroxycholecalciferol, acts to maintain calcium homeostasis. PTH is a polypeptide that consists of an 84-amino acid sequence with a molecular weight of 95,000 Daltons. The 34 amino acids at the amino terminal are the active part of the hormone. PTH increases serum calcium by acting at several sites in the body. In bone, in the presence of 1,25-hydroxycholecalciferol, PTH stimulates both osteoclasts and osteoblasts, even though the net effect is osteolysis. In the kidneys, it acts on the renal tubules, promoting calcium retention, and increasing excretion of phosphate, sodium, and potassium. PTH also facilitates calcium absorption by the small bowel. The normal fasting serum level of PTH is less than 100 pg/mL.[6] Oversecretion of PTH results in hyperparathyroidism, which is classified as primary, secondary, or tertiary.

Primary hyperparathyroidism is a generalized disorder of calcium, phosphate, and bone metabolism caused by excess PTH secretion that results from loss of normal feedback control of PTH by extracellular calcium. The elevation of circulating hormone usually leads to the cardinal features of elevated serum calcium concentrations (hypercalcemia) with an elevated (or inappropriately normal) PTH concentration and resultant hypercalciuria and hypophosphatemia. In the United States, approximately 100,000 people are diagnosed annually with primary hyperparathyroidism, which is 3 times more common in women than in men.[7] The risk of developing the disease increases with age, with a peak incidence between 50 and 60 years. Although unusual, primary hyperparathyroidism is occasionally diagnosed in children.[8]

Approximately 85% of all cases of primary hyperparathyroidism are caused by parathyroid adenomas. Ten to 15% are caused by parathyroid hyperplasia, and parathyroid carcinoma accounts for approximately 3% to 4% of cases of primary disease.[6]

Secondary hyperparathyroidism typically results from chronic renal failure, although it is occasionally associated with intestinal malabsorption. Calcium reabsorption by the small intestine is impaired, there is phosphate retention, and because of a lack of 1,25-hydroxycholecalciferol, the normal effect of PTH on bone calcium release is lost. In a futile attempt to maintain calcium homeostasis, the serum PTH level increases, causing generalized hyperplasia of the parathyroid glands.[6]

Tertiary hyperparathyroidism is a complication of secondary hyperparathyroidism. In the patient with long-standing secondary hyperparathyroidism, the normal autoregulatory feedback mechanism governing PTH secretion is lost, with resultant uncontrolled hormone secretion. The sensitivity of the parathyroid glands to PTH output decreases, and consequently the threshold for inhibiting PTH output increases. The parathyroid glands exhibit gross hyperplasia and focal adenomas may develop.[6]

Parathyroid Localization

Although hyperparathyroidism can be managed conservatively if the patient's condition is stable, surgical removal of the offending gland(s) is the only cure. The conventional surgical approach to primary hyperparathyroidism has, until recently, consisted of bilateral neck exploration, identification of all 4 glands, excision of the grossly enlarged gland(s), and biopsy, with intraoperative frozen section, of the remaining glands. When all 4 glands are diseased, 3.5 glands are removed, leaving sufficient parathyroid tissue for adequate function.[9] The reported success rate of this traditional approach, for skilled surgeons, is in excess of 90%.[10] Consequently, preoperative parathyroid localization has been reserved for cases of recurrent disease or after failed parathyroidectomies. The development of simple, noninvasive, imaging tests and the growth of the increasingly popular surgical technique known as minimally invasive parathyroidectomy, the success of which depends on accurate preoperative parathyroid lesion localization, have greatly expanded the role of preoperative localization procedures.[11-14] These studies are useful to identify multiple adenomas in primary hyperparathyroidism, which occur in up to 10 to 15% of cases, to identify ectopic lesions, and to evaluate function of parathyroid transplants.

Anatomic Modalities

Diagnostic ultrasound of the neck is a useful procedure for localizing parathyroid abnormalities (Fig. 1). The resolution
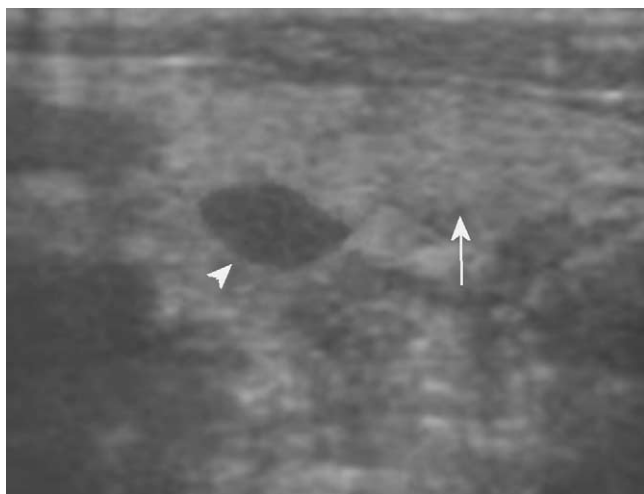
Figure 1 There is a 13 × 7 × 7-mm hypoechoic focus (arrowhead) posterior to the left lobe of the thyroid gland (arrow) on this sagittal ultrasound image. At surgery a 700-mg adenoma involving the left inferior parathyroid gland was resected.

of this technique actually exceeds that of computed tomography and magnetic resonance imaging when a high-frequency probe (10 MHz) is used.[15] Structures can be visualized in a variety of projections, and ultrasound can be used as a guide to biopsy and fine-needle aspiration. Finally, the patient is not subjected to ionizing radiation. Ultrasound is limited in its ability to identify ectopic parathyroid glands in the retrotracheal and retroesophageal spaces as well as in the mediastinum. False-positive results are usually the result of thyroid nodules or lymph nodes. Krusback and coworkers[15] reviewed the results of ultrasound in 100 patients with primary hyperparathyroidism and found that the sensitivity and specificity of neck ultrasound were 55% and 95%, respectively. For lesions located below the level of the thyroid gland, the sensitivity fell to 44%. Clark and coworkers,[16] in a study of 36 patients with recurrent or persistent hyperparathyroidism, reported that the sensitivity of ultrasound was 50%. Eight of the patients in this series had parathyroid lesions below the level of the sternal notch.

Computed tomography occasionally is used to identify enlarged parathyroid glands (Fig. 2). In contrast to ultrasound, both the neck and mediastinum can be examined with this technique. Nonopacifying vessels, lymph nodes, and thyroid nodules can all cause false-positive results, and intrathyroidal parathyroid glands easily can be overlooked. The use of contrast media offers little benefit because the enhancement patterns of the parathyroid glands are variable. The overall sensitivity of computed tomography in primary hyperparathyroidism is approximately 68%.[15]

Magnetic resonance imaging possesses no significant risks and can be used to examine both the neck and the mediastinum. Images can be reconstructed in multiple planes. In general, parathyroid adenomas have a longer relaxation time than thyroid tissue and exhibit higher signal intensity on T2-weighted images. The reported sensitivity of this technique, using surface coils, is about 75%.[6]

With the development of accurate noninvasive localizing tests, the role of more invasive procedures such as angiography and parathyroid venous sampling which are time consuming, costly, and highly dependent on operator skill, has diminished. These tests are reserved for those situations in which noninvasive modalities have failed to localize the offending gland(s), and even then they are rarely used.

Radionuclide Procedures

The parathyroid glands are able to concentrate a variety of chemical substances, including vital dyes and radiopharmaceuticals, and this ability has been exploited for localization purposes. Over the last 4 decades, several radiopharmaceuticals have been used for localizing the parathyroid glands.[17,18] Although a modest degree of success was obtained with selenomethionine-75, the first radionuclide technique to gain widespread acceptance for parathyroid localization was ^{201}Tl-$^{99m}TcO_4^-$, or thallium/pertechnetate, subtraction imaging, which was introduced in the early 1980s.[19] Originally used for myocardial perfusion imaging, ^{201}Tl is an inorganic cationic analog of potassium. This agent is cyclotron produced, has a half-life of 73 hours, emits a spectrum of 68 to 80 keV mercury x-rays, as well as 135 keV and 167 keV gamma rays, and with the aid of the sodium-potassium-ATP pump, is actively transported into the cell, where it is rapidly integrated into the intracellular potassium pool. Thallium accumulates not only in parathyroid tissue, but in thyroid tissue as well, and consequently removal of thyroid activity is required to identify parathyroid activity. This is usually accomplished by administering ^{99m}Tc-pertechnetate, which accumulates in the thyroid gland but not in the parathyroid glands.[201]Tl and ^{99m}Tc-pertechnetate images are obtained in a single session without moving the patient. The ^{99m}Tc-pertechnetate, or thyroid, image is digitally subtracted from the ^{201}Tl, or parathyroid, image. Residual activ-
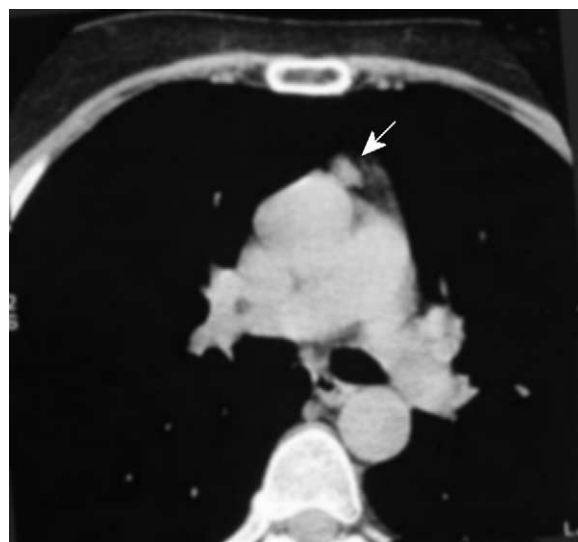

Figure 2 On this image from a CT scan of the chest, there is a 10 mm × 6-mm ovoid shaped soft tissue density (arrow) anterior to the ascending aorta. At surgery a 1080-mg adenoma of the left inferior parathyroid gland was removed.

Figure 3 There is focally increased activity just below the lower pole of the left thyroid lobe on the thallium image (left), but not on the pertechnetate image (middle). This focus is obvious on the subtraction image (right). A 50-mg left inferior parathyroid adenoma was subsequently resected.

ity in the "subtraction" image represents activity in abnormal parathyroid tissue (Fig. 3).

There are disadvantages to this test. The principal photon energy spectrum, 69 to 80 keV, of ^{201}Tl is suboptimal for gamma camera imaging, and the relatively high radiation absorbed dose imparted by this tracer, limits the amount of ^{201}Tl that can be administered. Consequently, the quality of the images generated suffers. The sensitivity of the test has varied from as low as 44% to as high as 95%. Basso and coworkers[20] reported a sensitivity of 20% for adenomas less than 300 mg in weight and 76% for adenomas weighing more than 1250 mg. Sandrock and coworkers,[21] in contrast, found no correlation between lesion size and sensitivity of the test.

In a retrospective review of 49 preoperative thallium/technetium parathyroid scans, Hauty and coworkers[22] reported a sensitivity of 78% and an overall accuracy of 73% compared with the 82% sensitivity and 78% accuracy in an extensive review of 14 previous series of a total of 317 scans. Regardless of the variations in the overall sensitivity of the test, ^{201}Tl/^{99m}Tc-pertechnetate imaging consistently has been reported to be less sensitive for hyperplastic glands than for adenomas.

Coakley and coworkers[23] reported on the use of ^{99m}Tc sestamibi for parathyroid imaging in 1989, and several larger series soon followed. Because of superior image quality, more favorable dosimetry, and improved accuracy, ^{99m}Tc sestamibi
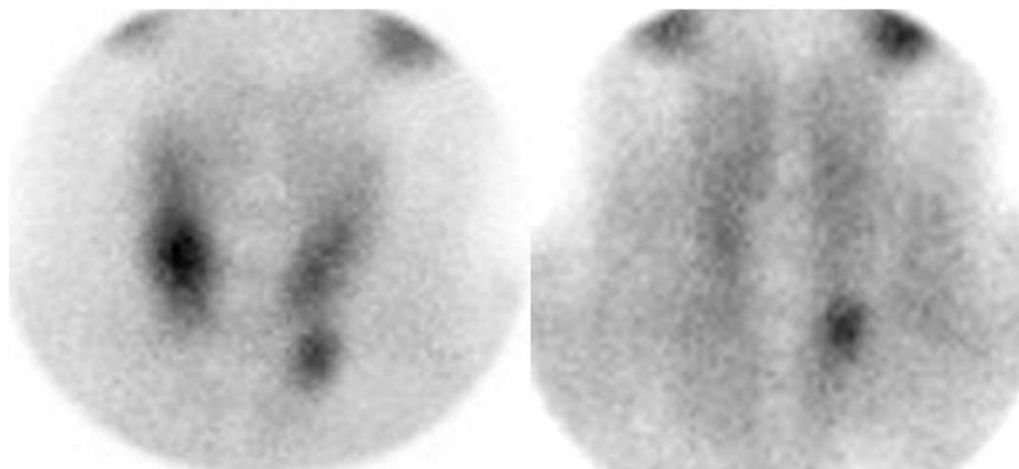

Figure 4 There are areas of focally increased MIBI activity in the lower pole of the right thyroid lobe and just below the lower pole of the left thyroid lobe on the early MIBI image (left). On the late MIBI image (right), the right thyroid focus has nearly disappeared, while the left sided focus persists. At surgery, a 700-mg left inferior parathyroid adenoma and an adenoma of the right thyroid lobe were removed.
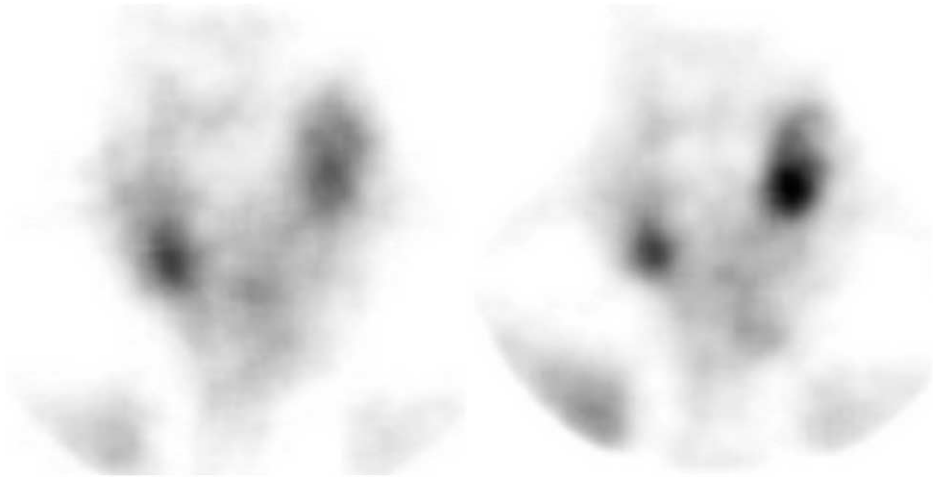
Figure 5 A left upper pole thyroid adenoma increases in intensity from the early (left) to the late (right) MIBI images, whereas a 390-mg right inferior parathyroid adenoma shows little change in intensity form early to late images.

rapidly replaced ^{201}Tl as the radiopharmaceutical of choice for parathyroid imaging. Sestamibi (hexakis 2-methoxy-isobutyl isonitrile) is a lipophilic, monovalent cationic isonitrile compound that passively diffuses across the cell membrane. Because of the large negative transmembrane potential, it is primarily sequestered in the mitochondria and trapped intracellularly.[24,25] The primary route of excretion (33%) is hepatobiliary, with approximately 25%, excreted through the kidneys. The critical organ is the large bowel, which receives approximately 5.4-rads/30 mCi. The total

body dose is approximately 500 mrads. Over the years, numerous methods of performing parathyroid imaging with sestamibi, or MIBI, have been suggested.

Taillefer and coworkers[26] introduced the concept of the
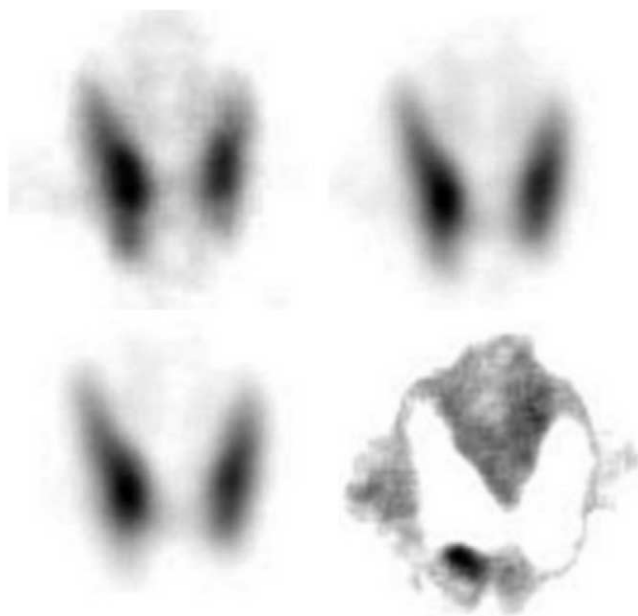

Figure 6 Early (upper left) and late (upper right) MIBI images, and pertechnetate (lower left) images are unremarkable. A focus of activity at the lower pole of the right thyroid lobe is present on the subtraction image (lower right). A 700-mg right inferior parathyroid lesion was subsequently removed.
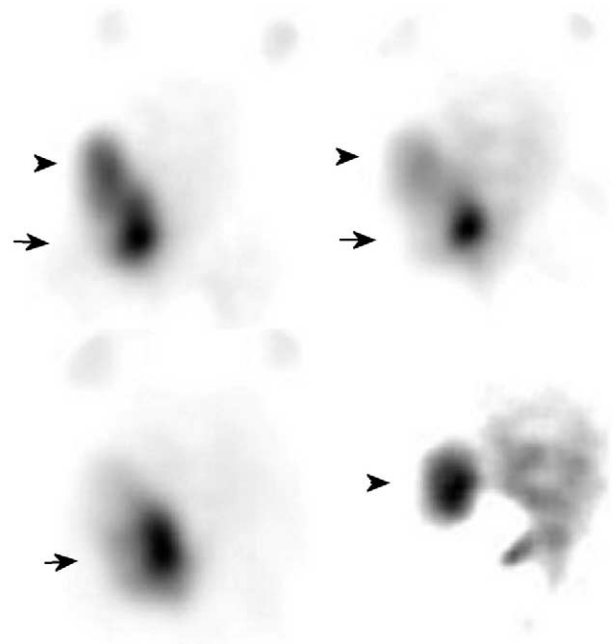

Figure 7 A thyroid adenoma (arrow) in the lower pole of the right thyroid lobe is equally well seen on early (upper left) and late (upper right) MIBI images as well as on the pertechnetate image (lower left). A 225-mg right superior parathyroid adenoma (arrowhead) clearly seen on the early MIBI image has washed out on the late image. Careful comparison of the late MIBI and pertechnetate images does show a subtle mismatch in the right upper pole of the thyroid gland. The subtraction image (lower right) confirms the presence of a parathyroid lesion in the right upper pole. (The patient was status post left thyroid lobectomy).
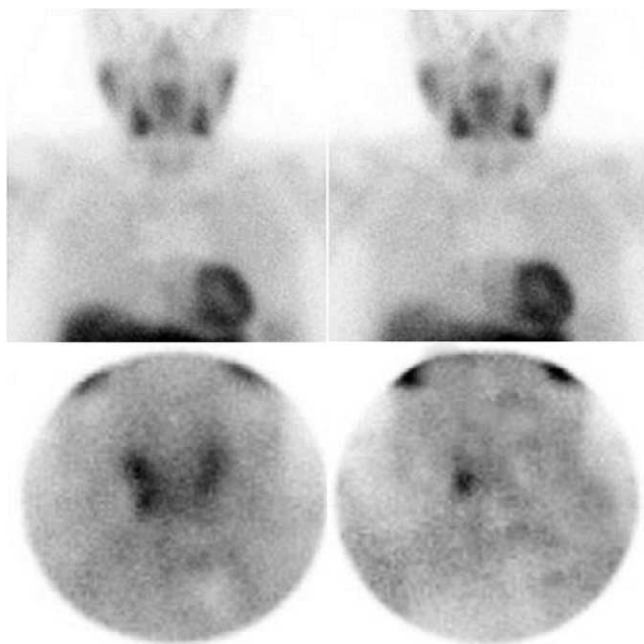
Figure 8 Early (upper left), and late (upper right) parallel hole MIBI images are unremarkable. A 980-mg parathyroid adenoma at the lower pole of the right thyroid lobe is seen on early (lower left) and late (lower right) pinhole images.

"single isotope, double phase technique," which takes advantage of the differential washout rates of MIBI from the thyroid and the parathyroid glands. This technique is based on the observation that MIBI washes out more rapidly from the thyroid than from abnormal parathyroid tissue, where it is retained for a longer period of time. The retention of this tracer in parathyroid lesions is presumably related to the presence of oxyphil cells in these lesions.[27] Oxyphil cells are rich in mitochondria, which are the site of intracellular MIBI sequestration. The single-isotope double-phase technique is simple and easy to perform. It requires only a single injection of MIBI followed by imaging approximately 15 minutes and 1.5 to 3 hours later. A persistent focus of activity, on delayed images, relative to the thyroid gland activity, is indicative of a parathyroid lesion (Fig. 4). Unfortunately, some parathyroid lesions do not retain MIBI, whereas some thyroid lesions, and even cervical lymph nodes, accumulate and retain sestamibi, resulting in both false-negative and false-positive studies (Fig. 5).

Subtraction imaging, especially in patients with thyroid abnormalities, often is helpful. Many thyroid lesions that accumulate MIBI also accumulate pertechnetate and iodine, and subtraction imaging can reduce the number of false positives.[28] In addition to MIBI, the subtraction method requires administration of ^{123}I or ^{99m}Tc-pertechnetate to obtain a thyroid image. When using ^{123}I, the thyroid image is acquired before injection of MIBI. When using ^{99m}Tc-pertechnetate, the thyroid image can be acquired either before or after the completion of the MIBI acquisition. We prefer to use ^{99m}Tc-pertechnetate, which we inject after the late MIBI acquisition. This allows us to perform both early and late MIBI images as

well as SPECT, in addition to subtraction imaging, without any interference from ^{99m}Tc-pertechnetate. Regardless of which tracer is used for the thyroid component of the test, with the aid of a computer, the MIBI and thyroid images are normalized and the thyroid image is "subtracted" from the MIBI image. Residual activity on the subtraction image indicates the location of the parathyroid lesion (Figs. 6 and 7). Simple visual comparison of the two images, without the aid of computer manipulation, also can reveal differences in tracer distribution, facilitating localization of the parathyroid lesion.

The subtraction technique, though useful, has certain limitations. Patient motion during data acquisition may lead to misregistration of the MIBI and pertechnetate images, resulting in a false-positive study. We try to minimize this problem by placing an intravenous line in the patient's arm at the very beginning of the test. The line can be accessed for pertechnetate injection without disturbing the patient or interrupting the imaging. Rather than acquiring two separate pinhole images of the neck for the late MIBI and thyroid images, we perform a dynamic pinhole acquisition consisting of 25 two-minute images, with pertechnetate being injected after the tenth frame. Frames with excessive movement can be eliminated without discarding the entire data set. With computer manipulation, the parathyroid and thyroid images are separated, group-added, pixel reregistered and normalized for proper digital subtraction.

Another pitfall of the subtraction technique is decreased or absent thyroid uptake of pertechnetate, or iodine, which may render the subtraction image invalid. Obtaining a detailed thyroid history and checking the dynamic imaging after per-
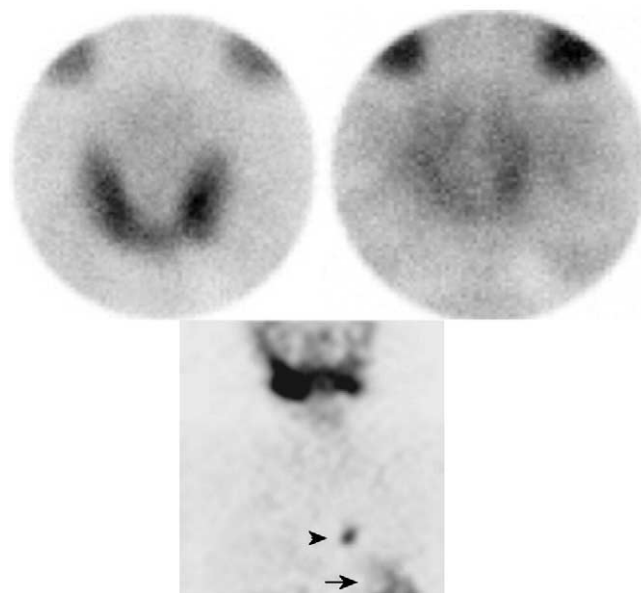

Figure 9 Early (upper left) and late (upper right) MIBI pinhole images are unremarkable. A 700-mg parathyroid adenoma (arrowhead) in the anterior mediastinal region just above the base of the heart (arrow) is identified on the coronal SPECT image. Because as much as 2% of parathyroid lesions are located outside the neck, imaging of the chest should be performed routinely.
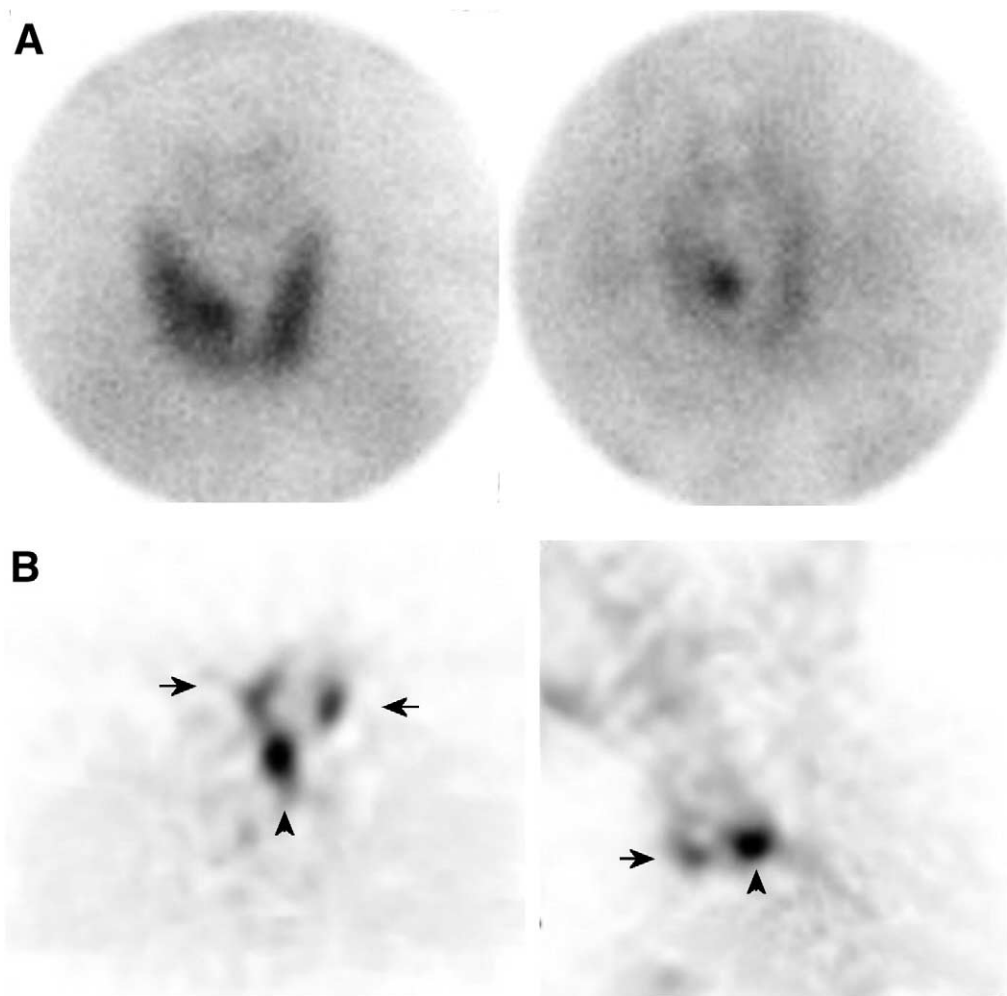
Figure 10 A, A focus of increased activity along the medial aspect of the lower pole of the right thyroid lobe is present on early (upper left) and late (upper right) pinhole MIBI images. B, Transverse (left) and sagittal (right) SPECT images demonstrate that this 700-mg parathyroid adenoma (arrowhead) is well posterior to the thyroid gland (arrow), in the retroesophageal region. The information that SPECT provides about the location of a parathyroid lesion can be useful for surgical planning.

technetate injection to observe uptake by the thyroid gland, facilitates identification of this problem. Very intense MIBI uptake by a parathyroid lesion may occasionally "shine through" on the pertechnetate image and be erroneously interpreted as a "thyroid nodule." Sometimes a parathyroid lesion is situated immediately behind a thyroid lesion and is eliminated with the subtraction technique.

The type of collimator used also affects the sensitivity of the test. Using a parallel hole collimator permits simultaneous imaging of both the neck and the chest. Unfortunately, parathyroid lesions, even when markedly enlarged, are relatively small structures, and may go unrecognized. The pinhole collimator provides the highest resolution of all the collimators used in nuclear medicine, and also magnifies the structures being imaged. Its conical shape fits perfectly in the neck, which is recessed in between the head and the chest when the patient is supine, making it ideally suited for imaging the small structures in this region. Studies have shown that although larger parathyroid lesions are equally well detected with both parallel hole and pinhole collimation, the

use of pinhole collimation significantly improves the sensitivity of the test for smaller lesions (Fig. 8).[29] Because as much as 2% of parathyroid lesions are outside the neck, additional imaging of the chest should be performed routinely, when performing the study with a pinhole collimator.

Single-photon emission computed tomography (SPECT) is a useful complement to planar imaging. Although this method may provide only marginal improvement in sensitivity in comparison to planar imaging, SPECT provides information, not readily available on planar imaging, about the location of a particular abnormality.[30-33] This information is useful not only for localizing a parathyroid lesion but for differentiating a thyroid lesion from a parathyroid lesion. The parathyroid glands are usually located posterior to the thyroid gland, and occasionally a parathyroid lesion lies directly behind a thyroid lesion. It may not be possible, with planar imaging alone, to distinguish an anteriorly located thyroid lesion from a posteriorly located parathyroid lesion. By determining the precise location of the lesion, tomography, can differentiate a thyroid lesion from a parathyroid lesion, and
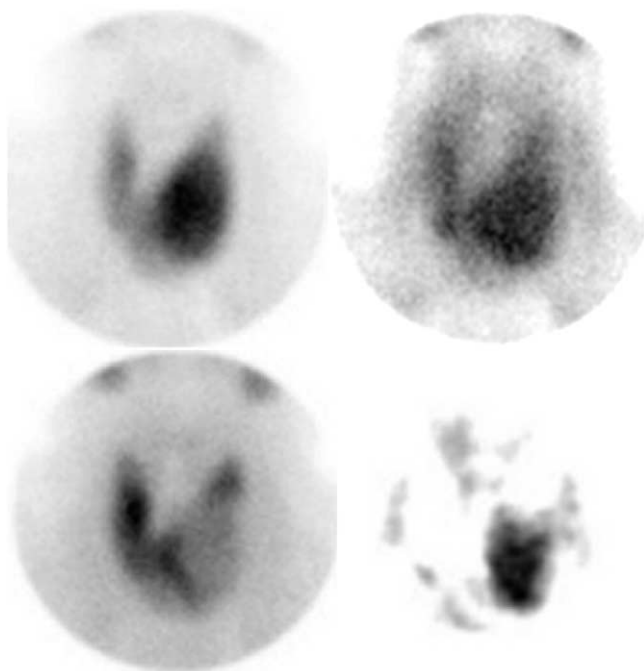
Figure 11 A large MIBI-avid thyroid lesion is seen on both the early (upper left) and late (upper right) images. This lesion does not, however, concentrate pertechnetate (lower left), resulting in a false positive subtraction image (lower right).

can identify the parathyroid lesion located behind a thyroid lesion.

SPECT also is useful for detecting and localizing ectopic parathyroid lesions, which occur in as many as 25% of cases (Figs. 9 and 10).[33] Although mediastinal lesions may be detected on planar imaging, tomography provides more detailed topographic information about the lesion including its relation to various structures such as the sternum, spine, and heart.

Although addition of SPECT only marginally improved the sensitivity from 86% to 90.5% (79.5% to 87% in patients who underwent reoperation) in a study by Billotey and co-workers,[30] lesions in the lower mediastinal area were better localized with SPECT than with planar imaging. There were also no false positives with SPECT in this series. In a recent publication, Gayed and coworkers[34] reported that SPECT imaging alone identified the parathyroid lesion in 89% of the patients. Using SPECT with CT fusion identified one additional lesion and more precisely localized lesions in 4 patients.

There are no well-established criteria regarding the timing of SPECT imaging in relation to the injection of MIBI. Our preference is to perform SPECT soon after completing the early imaging sequence, approximately 30 to 45 minutes after tracer injection. There is sufficient activity remaining in surrounding structures, such as the thyroid gland, at this time to generate the anatomic information necessary to localize the lesion. Furthermore, some parathyroid lesions demonstrate rapid washout and may go undetected if tomography is performed later.

False-Positive Results

The most frequent cause of false-positive results in MIBI parathyroid imaging is the solid thyroid nodule, either solitary or in a multinodular gland (Fig. 11). Other causes of false-positive results include MIBI accumulation in thyroid carcinoma, lymphoma, and other causes of lymphadenopathy, including metastatic disease, inflammation, and even sarcoidosis. MIBI uptake in the brown tumors of hyperparathyroidism has also been described.[6]
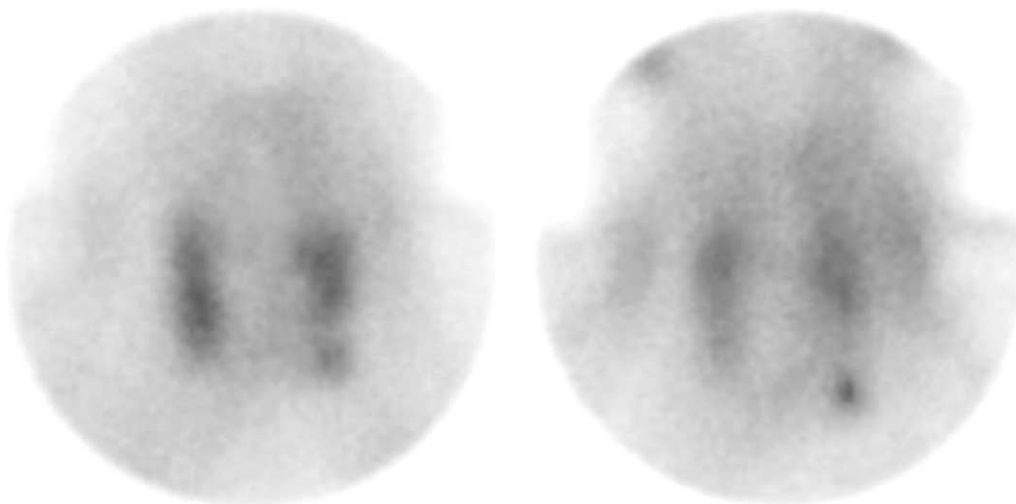

Figure 12 Early (left) and late (right) MIBI images demonstrate a single parathyroid lesion just below the lower pole of the left thyroid lobe. At surgery, in addition to this 260-mg parathyroid adenoma, a 410-mg right superior parathyroid adenoma, and a 130-mg left superior parathyroid adenoma, not seen on the MIBI study, also were removed. MIBI is less sensitive for multigland disease than for the solitary lesion, and consequently preoperative MIBI imaging should not be the sole basis on which the decision to perform limited cervical exploration is made.
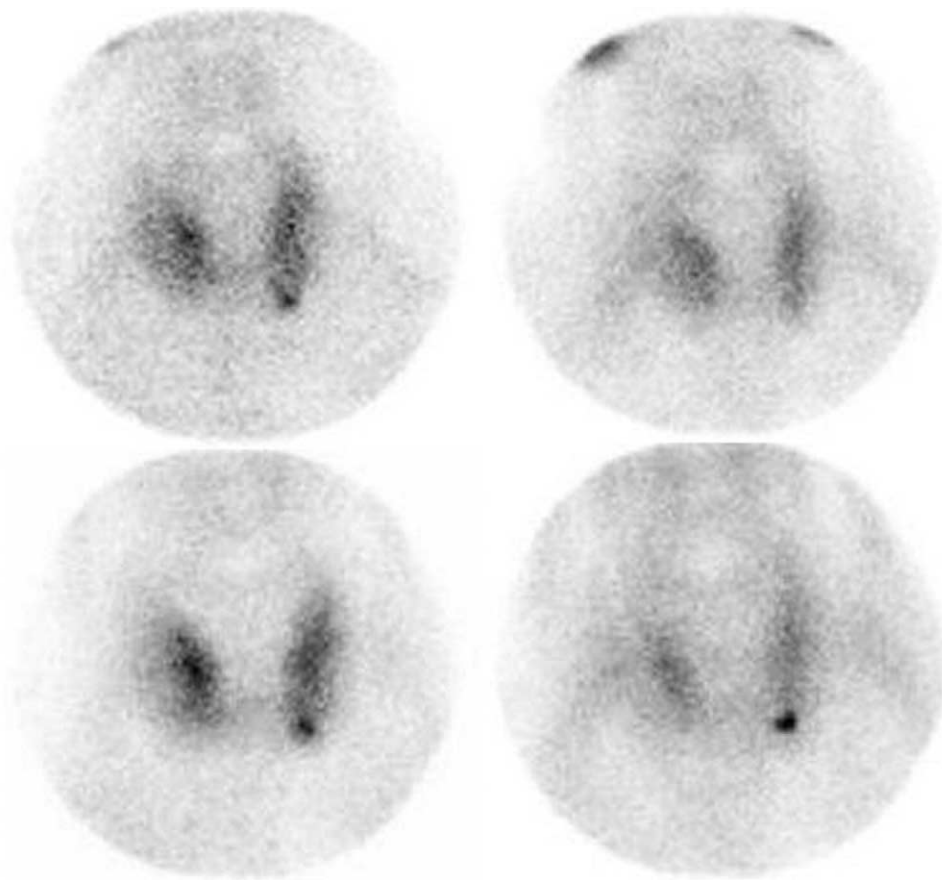
Figure 13 Early and late tetrofosmin images (upper left and upper right, respectively) and early and late MIBI images (lower left and lower right, respectively) from studies performed on a patient with a 500-mg parathyroid lesion at the lower pole of the left thyroid lobe. In the tetrofosmin study, the lesion is seen only on the early image, whereas in the MIBI study, the lesion is present on both the early and late images.

False-Negative Results

The failure of MIBI imaging to identify some parathyroid lesions is likely the result of several factors. Certainly, lesion size is important, both as it relates to system resolution and to the amount of tracer uptake by the parathyroid tissue. Recent investigations have found that parathyroid MIBI uptake may be related to cellular function. Sun and coworkers[35] reported that parathyroid tissue that expresses P-glycoprotein does not accumulate MIBI. They observed that normal parathyroid glands, in addition to some parathyroid adenomas, express this glycoprotein. They found that large parathyroid adenomas that express either P-glycoprotein or the multidrug resistance-related protein, MRP, failed to accumulate MIBI, whereas all those adenomas without either of these 2 proteins accumulated the tracer.

MIBI is less sensitive for detecting hyperplastic parathyroid glands than for detecting adenomatous ones. Part of the explanation is that hyperplastic glands are usually smaller than adenomatous glands. Recent investigations have found that, at least in secondary hyperparathyroidism, MIBI uptake is more closely related to cell cycle than to gland size. Torregrosa and coworkers[36] reported that higher MIBI uptake correlated with the active growth phase of the cells.

The presence of mitochondria-rich oxyphil cells presum-

ably accounts for MIBI uptake in parathyroid lesions, and glands with fewer oxyphil cells, and hence fewer mitochondria, may account for both lower uptake and rapid washout of MIBI from the parathyroid lesion.[25,27,37]

In 10% to 15% of patients, more than one parathyroid lesion is the cause of sporadic primary hyperparathyroidism, and there are data that suggest that MIBI is less sensitive for detecting multigland disease (MGD)[38-41] (Fig. 12). Pattou and coworkers,[39] in a review of several series reported that the sensivity of MIBI for detecting solitary adenomas was 87%, whereas its sensitivity for detecting MGD was only 55%. Bergson and coworkers[40] found that the sensitivity of MIBI imaging in 44 patients with MGD, by patient, was only 23%. Katz and coworkers[41] reported that MIBI imaging, among 15 patients with MGD, failed to identify the presence of bilateral lesions in all 13 patients with bilateral disease. Exactly why the test is less sensitive for MGD than for the solitary lesion is uncertain. This fact does indicate, however, that in the era of the minimally invasive parathyroidectomy, properative MIBI imaging cannot be the sole basis on which the decision to perform limited cervical exploration is made.

[99m]Tc-tetrofosmin is a lipophilic cationic diphosphine introduced by Ishibashi and coworkers for parathyroid imaging in 1997.[42] Like sestamibi, it is used for myocardial per-

fusion imaging, and is actively transported across the cell membrane. Unlike the intracellular retention of MIBI, which depends primarily on the mitochondrial membrane potential, the intracellular retention of tetrofosmin is also dependent on the cell membrane potential.[43] This dissimilarity may be one of the explanations for the different washout rates of these two tracers from the thyroid gland. In the study of Fjeld and coworkers[44] this differential washout rate for parathyroid and thyroid tissues, though not consistently demonstrated with MIBI, was never observed with tetrofosmin. The sensitivity of tetrofosmin for detecting parathyroid adenomas (75%) was, nevertheless, the same as the sensitivity of MIBI (Fig. 13). Despite results comparable with those reported for MIBI, tetrofosmin has never enjoyed widespread use for parathyroid localization.[45]

Summary

MIBI is the current radionuclide procedure of choice for parathyroid localization. Although reasonably good results can be obtained with planar imaging, the use of pinhole collimation, the performance of subtraction imaging, and SPECT improve the accuracy of the test. The parathyroid glands can be found anywhere from the angle of the mandible to the base of the heart, and therefore this entire region should be included in the field of view. MIBI is most sensitive for detecting parathyroid adenomas and therefore is less useful in patients with secondary hyperparathyroidism, where the predominant lesion is hyperplasia. Finally and most importantly, parathyroid scintigraphy is a *localizing* procedure, not a diagnostic procedure. It should, therefore, be reserved primarily for patients with documented primary hyperparathyroidism.

References

1. Parfitt AM: Parathyroid growth: Normal and abnormal, in Bilezikian JP (ed): The Parathyroids: Basic and Clinical Concepts (ed 2), New York, Raven Press, 2001, pp 293-329
2. Yao K, Singer FR, Roth SI, et al: Weight of normal parathyroid glands in patients with parathyroid adenomas. J Clin Endorinol Metab 89:3208-3213, 2004
3. Bannister LH, Berry MM, Collins P, et al (eds): Gray's Anatomy New York, Churchill Livingston, 1995, p 17
4. Mansberger AR Jr, Wei JP: Surgical embryology and anatomy of the thyroid and parathyroid glands. Surg Clin North Am 73:727-746, 1993
5. Wang C: The anatomic basis of parathyroid surgery. Ann Surg 183:271-275, 1976
6. Garvie NW: Imaging the parathyroids, in Peters AM (ed): Nuclear Medicine in Radiologic Diagnosis. London, Martin Dunitz, 2003, pp 681-694
7. US Census Bureau, Population Estimates, 2004
8. Pyra LN, Hodgkinson A, Anderson CK: Primary hyperparathyroidism. Br J Surg 53:245-316, 1966
9. Niederle B, Roka R, Woloszczuk W, Klaushofer K, et al: Successful parathyroidectomy in primary hyperparathyroidism: A clinical follow up study of 212 consecutive patients. Surgery 102:903-909, 1987
10. Mariani G, Gulec SA, Rubello D, et al: Preoperative localization and radioguided parathyroid surgery. J Nucl Med 44:1443-1458, 2003
11. Sofferman RA, Nathan MH, Fairbank JT, et al: Preoperative technetium 99m sestamibi imaging: Paving the way to minimal-access parathyroid surgery. Arch Otolaryngol Head Neck Surg 122:369-374, 1996
12. Bilezikian JP, Marcus R, Levine MA (eds): The Surgical Management of Hyperparathyroidism. The Parathyroids (ed 2), San Diego, Academic Press, 2001, pp 487-498
13. Sackett WR, Barraclough B, Reeve TS, et al: Worldwide trends in the surgical treatment of primary hyperparathyroidism in the era of minimally invasive parathyroidectomy. Arch Surg 137:1055-1059, 2002
14. Udelsman R, Donovan PI, Sokoll LJ: One hundred consecutive minimally invasive parathyroid explorations. Arch Surg 31:1074-1078, 2000
15. Krusback AJ, Wilson SD, Lawson TL, et al: Prospective comparison of radionuclide, computed tomographic, sonographic, and magnetic resonance localization of parathyroid tumors. Surgery 106:639-646, 1989
16. Clark OH, Okerlund MD, Moss AA: Localization studies in patients with persistent or recurrent hyperparathyroidism. Surgery 98:1083-1094, 1985
17. Czerniak A, Zwas ST, Shustik O, et al: The use of radioiodinated toluidine blue for preoperative localization of parathyroid pathology. Surgery 110:832-838, 1991
18. DiGuilo W, Beierwalters WH: Parathyroid scanning with selenium-75 labeled methionine. J Nucl Med 5:417, 1964
19. Ferlin G, Borsato N, Camerani M, et al: New perspectives in localizing enlarged parathyroids by technetium-thallium subtraction scan. J Nucl Med 24:438-441, 1983
20. Basso LV, Keeling C, Goris ML: Parathyroid imaging: use of dual isotope scintigraphy for the localization of adenoma before surgery. Clin Nucl Med 17:380-383, 1992
21. Sandrock D, Merino MJ, Norton JA, et al: Parathyroid imaging by Tc/Tl scintigraphy. Eur J Nucl Med 16:607-613, 1990
22. Hauty M, Swartz K, McClung M, et al: Technetium-thallium scintiscanning for localization of parathyroid adenoma and hyperplasia. Am J Surgery 153:479-486, 1987
23. Coakley AJ, Kettle AG, Wells CP, et al: 99mTc-sestamibi—a new agent for parathyroid imaging. Nucl Med Commun 10:791-794, 1989
24. Chiu ML, Kronauge JF, Piwnica WD: Effect of mitochondrial and plasma membrane potential on accumulation of Hexakis (2-Methoxy isobutyl isonitrile) Technetium in cultured mouse fibroblasts. J Nucl Med 31:1646-1653, 1990
25. Hetrakul N, Civelek AC, Stagg CA, et al: In-vitro accumulation of technetium 99m sestamibi in human parathyroid mitochondria. Surgery 130:1011-1018, 2001
26. Taillefer R, Boucher Y, Potvin C, et al: Detection and localization of parathyroid adenomas in patients with hyperparathyroidism using a single radionuclide imaging procedure with technetium-99m-sestamibi (double-phase study). J Nucl Med 33:1801-1807, 1992
27. Melloul M, Paz A, Koren R, et al: 99m Tc-MIBI scintigraphy of parathyroid adenomas and its relation to tumour size and oxyphil cell abundance. Eur J Nucl Med 28:209-213, 2001
28. Hindie E, Melliere D, Jeanguillaume C, et al: Parathyroid imaging using simultaneous double-window recording of technetium-99m-sestamibi and iodine-123. J Nucl Med 39:1100-1105, 1998
29. Kipper MS, LaBarbera JJ, Krohn LD, et al: Localization of a parathyroid adenoma by the addition of pinhole imaging to Tc-99m sestamibi dual-phase scintigraphy. Report of a case and review of experience. Clin Nucl Med 22:73-75, 1992
30. Billotey C, Sarfati E, Aurengo A, et al: Advantages of SPECT in technetium-99m sestamibi parathyroid scintigraphy. J Nucl Med 37:1773-1778, 1996
31. Sfakianakis GN, Irvin GL 3rd, Foss J et al: Efficient parathyroid guided by SPECT-MIBI and hormonal measurements. J Nucl Med 37:798-804, 1996
32. Lorberboym ML, Minski I, Macadziob S, et al: Incremental diagnostic value of preoperative 99m Tc-MIBI SPECT in patients with a parathyroid adenoma. J Nucl Med 44:904-908, 2003
33. Clark PB, Perrier ND, Morton KA: Detection of an intrathymic parathyroid adenoma using single-photon emission CT 99mTc sestamibi scintigraphy and CT. AJR Am J Roentgenol 184:S16-S18, 2005
34. Gayed IW, Kim EE, Broussard WF, et al: The value of 99mTc-Sestamibi SPECT/CT over conventional SPECT in the evaluation of parathyroid adenomas or hyperplasia. J Nucl Med 46:248-252, 2005
35. Sun SS, Shiau YC, Lin CC, et al: Correlation between P-glycoprotein

(P-gp) expression in parathyroid and Tc-99m MIBI parathyroid image findings. Nucl Med Biol 28:929-933, 2001

36. Torregrossa JV, Fernandez-Cruz L, Canalupo A, et al: ^{99m}Tc-Sestamibi scintigraphy and cell cycle in parathyroid glands of secondary hyperparathyroidism. World J Surg 24:1386-1390, 2000
37. Bhatnagar A, Vezza PR, Bryan JA, et al: Technetium-99m-sestamibi parathyroid scintigraphy: Effect of P-glycoprotein, histology and tumor size on detectability. J Nucl Med 39:1617-1620, 1998
38. Heller KS, Attie JN, Dubner S: Parathyroid localization: inability to predict multiple gland involvement. Am J Surg 166:357-359, 1993
39. Pattou F, Huglo D, Proye C: Radionuclide scanning in parathyroid diseases. Br J Surg 85:1605-1616, 1998
40. Bergson EJ, Snyter LA, Dubner S, et al: Sestamibi scans and intraoperative PTH measurement in the treatment of primary hyperparathyroidism due to multiple gland disease. Arch Otolaryngol Head Neck Surg 130:87-91, 2004
41. Katz SC, Wang GJ, Kramer EL et al: Limitations of technetium 99m sestamibi scintigraphic localization for primary hyperparathyroidism associated with multiglandular disease. Am Surg 69:170-175, 2003
42. Ishibashi M, Nishida H, Kumabe T, et al: Tc99m tetrofosmin. A new diagnostic tracer for parathyroid imaging. Clin Nucl Med 20:902-905, 1995
43. Arbab AS, Koizumi K, Arki T: Uptake of technetium-99m tetrofosmin, technetium-99m MIBI and thallium 201 in tumor cell lines. J Nucl Med 37:551-556, 1996
44. Fjeld JG, Erichsen K, Pfeffer PF, et al: Technetium-99m-tetrofosmin for parathyroid scintigraphy: a comparison with sestamibi. J Nucl Med 38:831-834, 1998
45. Vallejos V, Martin-Comin J, Gonzalez MT, et al: The usefulness of Tc-99m tetrofosmin scintigraphy in the diagnosis and localization of hyperfunctioning parathyroid glands. Clin Nucl Med 24:959-964, 1999