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Parathyroid Imaging: How Good Is It and How Should It Be Done?

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Hypersecretion of parathormone in primary hyperparathyroidism is common, occurring in approximately 1 in 500 women and 1 in 2,000 men per year in their fifth to seventh decades of life. This has been suggested from the literature to be primarily the result of a parathyroid adenoma (80-85% of cases), hyperplasia involving more than 1 gland, usually with all 4 glands being involved (10-15% of cases), or the result, albeit rarely, of parathyroid carcinoma (0.5-1% of cases). Surgical removal of the hypersecreting gland is the primary treatment; this procedure is best performed by a skilled surgeon who would normally find the abnormality in 95% of cases. Imaging, however, should be used to identify the site of abnormality, potentially reducing inpatient stay and improving the patient experience. Functional imaging of parathyroid tissue using thallium was introduced in the 1980s but has largely been superceded by the use of ^{99m}Tc-labeled isonitriles. The optimum techniques have used ^{99m}Tc-sestamibi with subtraction imaging or washout imaging. A recent systematic review reported the percentage sensitivity (95% confidence intervals) for sestamibi in the identification of solitary adenomas as 88.44 (87.48-89.40), multigland hyperplasia 44.46 (41.13-47.8), double adenomas 29.95 (−2.19 to 62.09), and carcinoma 33 (33). This review does not separate the washout and subtraction techniques. The subtraction technique using ^{99m}Tc-sestamibi and ^{123}I is the optimal technique enabling the site to be related to the thyroid tissue when the parathyroid gland is in the neck in a normal position. If there is an equivocal scan then confirmation with high resolution ultrasound should be used. With ectopic glands, the combined use of single-photon emission computed tomography may then provide anatomical information to enable localization of the functional abnormality. In patients who have had surgical exploration by an experienced parathyroid surgeon in a unit with an experienced nuclear medicine team and negative sestamibi imaging, it is reasonable to image the patient with ^{11}C methionine. It is debatable whether patients with a high likelihood of secondary hyperparathyroidism should be imaged. The only possible justification for this is to exclude an ectopic site. There is no substitute for an experienced surgeon and an experienced imaging unit to provide a parathyroid service.
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Hyperparathyroidism may present as an incidental finding or because of the serious consequences of hypercalcaemia or as an incidental discovery as part of a biochemical screen for other conditions. The current primary curative treatment is by the surgical removal of abnormal parathyroid glands, wherever they are located, and requires a dedicated parathyroid surgeon.[1] This step is probably the key in the management of parathyroid disease because an experienced parathyroid surgeon is capable of localizing 95% of abnormal parathyroid glands without imaging assistance. However, there can be no doubt that imaging provides an improvement to global exploration of the thyroid bed and beyond and thus potentially preventing a large number of bilateral neck explorations and promoting unilateral neck exploration or minimally invasive parathyroidectomy.[2] The adoption of minimally invasive surgery has been refined and improved by imaging methods both preoperative and intraoperatively, and these techniques will be discussed in this review. During recent years the use of radionuclide probes, endoscopy, or video-assisted techniques has increased the selective removal of individual glands such that minimally invasive surgery has been performed enhancing patient experience and reducing cost of in patient stay.

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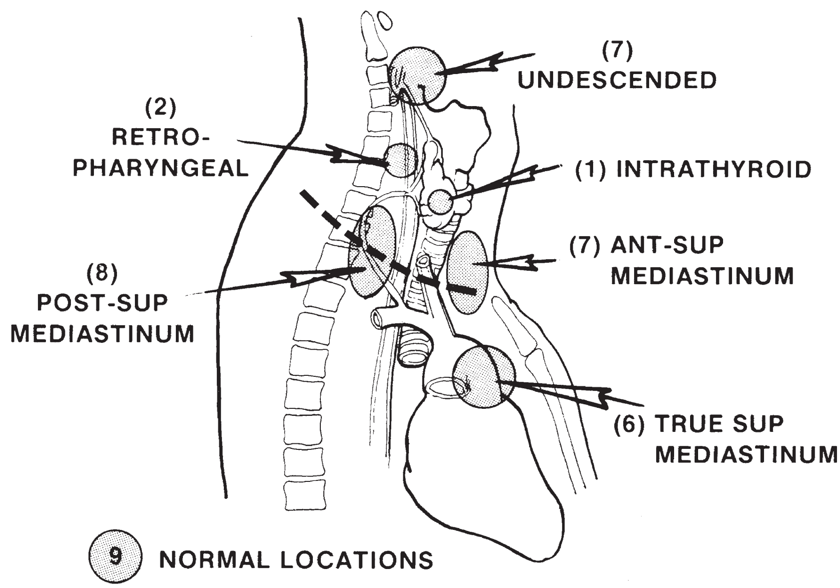

Figure 1 Distribution of the ectopic sites of parathyroid adenomas. (Adapted with permission from Edis et al.[3])

The variable anatomic location of parathyroid tissue supports the need for preoperative localization. This also supports the need for an experienced team to be developed, which includes the presence of experienced imaging unit and the need for an experienced parathyroid surgeon with specialized training and experience in the procedure.[1] There are a variety of imaging techniques to identify the site of a parathyroid adenoma, and this review will discuss the techniques found to be most useful.

Sites of Parathyroid Glands

There can be 2 to 6 parathyroid glands (normally 4). The normal sites are posterior to the thyroid, related to the upper and lower poles of the right and left lobes. A small number of patients, approximately 5%, have more than 4 glands, and a further 5% have only 3 glands.[2,3] The parathyroid glands may be found in a number of ectopic sites in the neck or upper mediastinum. The upper glands may be found posterior to the esophagus or occasionally in the carotid sheath, and the lower glands may be found in the thymus but are usually found within a centimeter or two below the lower pole if ectopic (Fig. 1). Primary and secondary hyperparathyroidism may be identified. Hypersecretion of parathormone in primary hyperparathyroidism is common, occurring in approximately 1 in 500 women and 1 in 2000 men per year, usually presenting in their fifth to seventh decades of life,[4] primarily, as suggested in the literature, the result of a parathyroid adenoma (80-85% of cases), hyperplasia involving more than 1 gland, usually with all 4 glands being involved (10-15% of cases) or, albeit rarely, the result ofparathyroid carcinoma (1% of cases). A recent systematic review of the literature suggests that these estimates may be inaccurate.[4] A review of publications between 1995 and 2003 (20,225 cases) suggests the causes of primary hyperparathyroidism are solitary adenomas (88.9%), multiple gland hyperplasia (5.74%), double adenomas (4.14%), and parathyroid carcinomas (0.74%).[4] Secondary hyperparathyroidism results from any medical condition that tends to produce hypocalcaemia, resulting in stimulation of parathyroid glands, most common cause is renal failure, resulting in hyperplastic changes in the parathyroid glands. Occasionally one or more of the glands can become autonomous, resulting in tertiary hyperparathyroidism.

Preoperative Localizing Techniques

There are a variety of anatomical and functional methods for localizing abnormal parathyroid tissue that have developed over a number of years and have been improved on with the technological developments occurring over the same time period. Functional techniques have included ^{75}Se-selenomethionine, ^{57}Co-vitamin B_{12}, ^{131}I-toluidine blue, ^{123}I-methylene blue, which have been used with little success[5] although the use of methylene blue or toluidine blue peroperatively, without radiolabeling, still creates good localization when the surgeon has direct visualization.

An important development was the identification of the value of ^{201}Tl-thallous chloride and a subtraction technique in combination with pertechnetate.[6] Visualization of primary parathyroid adenomas of between 42% and 96%, with a mean of 72%[7] was achieved with this technique and was far superior to any previous imaging methods. A lower detection rate was found with secondary hyperparathyroidism varying from 32% to 81% with a mean of 43%. ^{99m}Tc-sestamibi imaging was the next major development when it was demonstrated to have uptake in abnormal parathyroid tissue and had a differential washout compared with underlying thyroid.[8,9] A variety of scanning protocols were developed following these observations with subtraction imaging, delayed imaging, and combination imaging protocols developed, which will be discussed here. A recent systematic review did not separate the different imaging methods used with ^{99m}Tc-sestamibi; even so, the reported percentage sensitivities (95%

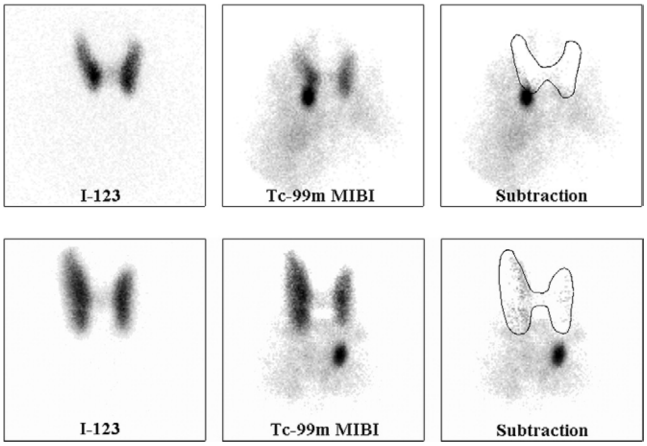

Figure 2 Two patient studies using subtraction imaging and pinhole collimator. The first patient (A) has a normal iodine scan. The sestamibi scan demonstrates an abnormal area of accumulation at the lower pole of the right lobe of the thyroid, without the need for subtraction. The subtraction scan confirms this site of abnormality. The second patient (B) has an ectopic gland below the left lobe of the thyroid.

confidence intervals) for solitary adenomas were 88.44 (87.48-89.40), multigland hyperplasia 44.46 (41.13-47.8), double adenomas 29.95 (−2.19 to 62.09), and carcinoma 33 (33). These results combine delayed imaging and subtraction methods and may therefore underestimate the value of either technique.[4] ^{99m}Tc-tetrofosmin, another isonitrile, also has been used to image the parathyroid but, unlike sestamibi, there is little washout from the thyroid and therefore delayed imaging relying on the differential washout from the thyroid and parathyroid tissue cannot be used.[10-12] The combined use of functional imaging with sestamibi and high-resolution ultrasound imaging also has been explored with probable improvement in identification of site of disease. There also are early reports of improved localization with single-proton emission computed tomography (SPECT) and SPECT/CT imaging with sestamibi. Positron emission tomography has a more limited role with both ^{18}F-fluorodeoxyglucose and ^{11}C-methionine, having been used with varying success.[13-16]

CT, magnetic resonance imaging (MRI), arteriography, and high-resolution ultrasound[17-19] have all been used with varying success. As with most anatomical techniques, they have the greatest accuracy when performed before any surgery. CT has been shown to have sensitivities for the localization of adenomas between 43% and 92%.[19-21] Similar limitations are found with MRI, with sensitivities found of 50% to 93%.[20,22-24] High-resolution ultrasound is a technique that does need further exploration the question is who should perform the test – surgeon or imaging specialist.[25,26] High-resolution ultrasound has reported percentage sensitivity (95% confidence intervals) for solitary adenomas 78.55 (77.15-79.96), multigland hyperplasia 34.86 (29.86-39.86), double adenomas 16.2 (4.16-28.25), and carcinoma 100 (100).[4]

^{99m}Tc-sestamibi is now the imaging agent of choice. The uptake of sestamibi or tetrofosmin may be influenced by a variety of biological factors. These include the size of the adenoma, the cell type (oxyphil cells rather than chief cells), the P-glycoprotein expression, and the mitochondrial structure (oxyphil cells have larger numbers of mitochondria that concentrate sestamibi uptake).[27] Concentration of sestamibi uptake in secondary hyperparathyroidism has been found to be highest in the growth phase and not the resting phase of the parathyroid tissue.[28] Multidrug resistance proteins or P-glycoprotein expression tends to work in the opposite direction in that these proteins increase the efflux of sestamibi from the tumor hampering the visualization of tumors such that false negative scans may occur.

There are therefore a number of radiopharmaceuticals that can be used to image the thyroid and parathyroid tissue, the question is which technique should be used when they are adequately optimized. Consideration has to be given to whether dual phase or subtraction techniques are used, what collimation–parallel hole or pinhole, planar imaging or tomography (parallel hole or pinhole) or the combined use of gamma camera–CT imaging.

Imaging Methodology

Ideally, we would use a tracer that was specific to the parathyroid alone and provide an anatomic image to localize it. Unfortunately, at the present time no such tracer exists and, therefore, a number of methods have been used, each purporting to have advantages over other techniques.

Subtraction Methods

This method requires the visualization the thyroid gland with either ^{99m}Tc-pertechnate or ^{123}I and then subtracting this image from an image of the ^{99m}Tc-sestamibi (or ^{99m}Tc-tetrofosmin) uptake within the thyroid and parathyroid gland(s) (Figs. 2-5). If ^{123}I is used, correction for crosstalk between the ^{123}I and ^{99m}Tc windows is required. Although it is possible to perform an image subtraction based on normalization of the images, it is diagnostically more useful to create a subtraction loop. This process involves subtracting an incremental amount of the thyroid image from the ^{99m}Tc-sestamibi distribution until the point of over subtraction.

To obtain high diagnostic quality, sestamibi images imaging times are long—up to 20 minutes in our own experience. Patient movement during image acquisition may therefore need to be corrected for by acquiring a dynamic acquisition. With the later generation of gamma camera which supports

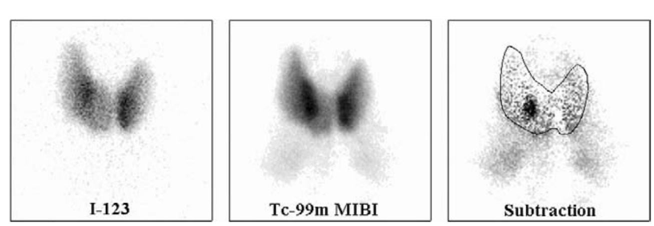

Figure 3 The patient has a normal iodine scan. The subtraction image allows the localization of the parathyroid adenoma to be made with greater confidence than on the sestamibi scan alone.

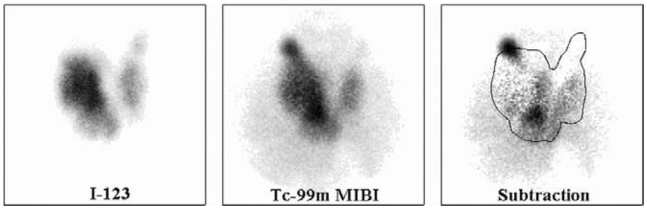

Figure 4 The iodine scan demonstrates a multinodular thyroid. The subtraction scan shows increased uptake of sestamibi in the right lobe of the thyroid within the upper and lower poles, corresponding to 2 adenomas.

overlapping isotope windows, movement correction may be further improved by obtaining the correction required on the ^{123}I thyroid image.

Washout Method

^{99m}Tc-sestamibi uptake in thyroid tissue cleared more quickly than that in parathyroid tissue.[9] Taillefer and coworkers[29] proposed a washout method, dual phase imaging, to exploit this finding. An image of the distribution of ^{99m}Tc-sestamibi within the neck is obtained within a few minutes of its administration and then a delayed image obtained 1 to 2 hours later (Fig. 6). The method is simple to perform and involves only one administration of tracer; however, the technique has limitations of high washout in parathyroid tissue resulting in false negative findings.

In both of these planar imaging methods, pinhole views of the neck are preferred for optimum spatial resolution[30] and an additional full field of view image of the anterior neck and thorax to exclude an ectopic site in the chest. Pinhole imaging also can be acquired as an oblique image to further improve sensitivity.[31]

Tomographic Imaging

Tomographic imaging using either dual isotope, ^{123}I/ ^{99m}Tc-sestamibi SPECT or dual-phase imaging potentially can give improved localization of adenomas in terms of depth and proximity to neighboring structures.[32,33] The additional value of combined gamma camera-CT imaging can enhance the anatomical detail and therefore potentially improve minimally invasive surgery.

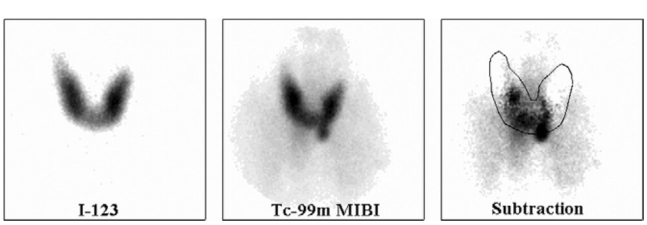

Figure 5 The iodine scan has a normal appearance. The sestamibi subtraction scan demonstrates 3 abnormal areas of uptake, 2 in the right lobe of the thyroid and 1 below the left lobe. The patient had four gland hyperplasia, the upper pole of the left lobe was missed.

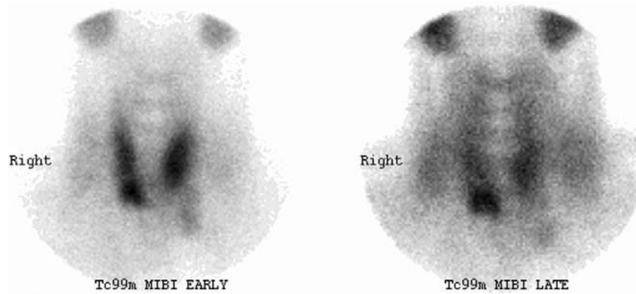

Figure 6 ^{99m}Tc-sestamibi images viewed at 20 minutes and 2 hours after injection of sestamibi (dual-phase technique) using pinhole collimation. The early image on the left shows the distribution of sestamibi in the thyroid and parathyroid tissue, with a small area of slight increased uptake seen at the lower pole of the right lobe of the thyroid. This is seen more clearly at 2 hours when the thyroid activity has "washed out."

Other Imaging Techniques

Ultrasound evaluation of parathyroid glands is extremely operator dependent and can be affected by thyroid enlargement such that posteriorly placed parathyroid glands are more difficult to identify, with nodular glands increasing this difficulty. This perhaps explains why the reported sensitivity and specificity are so varied, ie, sensitivities of 38% to 92% and a specificity of 60% to 80% for adenomas in the neck. Ultrasound also has difficulty in identifying sites of disease when there has been previous surgery or if there is an ectopic gland in the mediastinum. The combined use of ultrasound and sestamibi scanning is likely to be the optimal method in that confirmation of a single gland could be enhanced by this

The high-resolution techniques of CT and MRI generally have been disappointing. The sensitivity of MRI generally is better than that of CT (CT 40-80% and MRI 64-88%), and the specificities are comparable (CT 85-98% and MRI 88-95%), although the use of MRI has not yet been fully explored. Both are able to identify abnormalities in the mediastinum, but the application of T1, T2, and short tau-wave inversion recovery (STIR) images improve the recognition of adenomas and the separation of scar tissue and, therefore, MRI has the possible advantage over CT in patients undergoing additional surgery.[24] However, the combined role of SPECT/CT may improve the role of CT in parathyroid imaging. Gayed and coworkers[34] showed, in 48 patients, no additional clinical value to conventional SPECT imaging in a dual-phase technique and suggested that patients may be spared "additional time, radiation exposure and expense" by not adopting this technique routinely. However, they did find it was helpful in 2 ectopic glands in localizing the site.[34] It may therefore be worth considering as an adjunct if ectopic sites are found to enable the surgical exploration.

If there are continuing difficulties with localization, then the role of selective venous sampling, with or without prior arteriography, has to be considered. Although this may not give an exact position, the test can confirm the general site of an adenoma and can allow parathyroid glands to be distinguished from thyroid nodules.[20] The value is highest in reoperative cases in which imaging does not localize abnormal tissue.

When Should Parathyroid Localization Be Used?

Currently, surgical management of primary hyperparathyroidism is the most effective treatment, although it is possible that other techniques, such as direct injection of the parathyroid adenoma with alcohol to destroy the gland, may gradually increase in their acceptance. The general approach to surgical management of patients is to reduce the time spent in hospital,l thus reducing the cost of management and potentially reducing hospital-acquired infections. To achieve minimum time in hospital for patients with parathyroid disease, it is essential to identify the site of an adenoma and distinguish this from multigland hyperplasia or multiple adenomata. This preoperative identification should allow a change in operative practice. Although the approach to surgery should have changed, there are still many surgeons who use the bilateral neck exploration, which has a success rate of 95% and a complication rate of 1% to 2%.[2] This approach needs to come under increasing scrutiny because 85% of patients will have single-gland disease, and sestamibi scanning has a specificity of 90.7% and a sensitivity of 98.9%.

The use of minimally invasive parathyroidectomy (MIP) with or without the use of aids such as a radionuclide probe, an endoscope, or a video-assisted technique should be the norm rather than the exception. This would particularly be the case if the suggested incidence of solitary adenomas is 88.9%, as suggested by Ruda and coworkers.[4] The minimally invasive technique can be performed as a day case because this normally involves a small lateral incision in the neck while the patient is prepared either using a general anesthetic or cervical block. If the operative removal is combined with intraoperative PTH assays, then a 100% success rate can be obtained, although this utility has been questioned.[35] Ruda and coworkers,[4] in their systematic review, suggest that intraoperative PTH gave true positive test results in 98.4%; however, if declines of greater than 50% were judged as the cutoff, there were 3.37% false-positive results and 1.94% false-negatives rates, suggesting unresected disease still present.[4] The use of a probe to localize the parathyroid tissue requires the injection of the radiotracer approximately 2 hours before the surgery. The value of the probe at surgery is to localize the parathyroid adenoma and confirm the removal of the correct gland by measuring the radioactivity within the adenoma and over the remaining surgical bed after adenoma removal.[36] The selection of patients is therefore crucial before embarking on surgery.

There would appear to be little value in the assessment of patients with secondary hyperparathyroidism when preoperative tests have lower sensitivity and there is a requirement to explore all four glands. If primary hyperparathyroidism is the most likely diagnosis, then the most accurate technique should be used to identify the site of the adenoma.

Which Technique Should Be Used?

Naive Neck

A subtraction technique appears to have a slight advantage over dual-phase imaging[33,37-39] in most situations. Clear exceptions to this would be patients in whom the thyroid is unlikely to be visualized either because of previous surgery, recent administration of iodine contrast, thyroiditis, or concurrent administration of thyroxine. In these situations, a dual-phase technique should be used. The minimum imaging that should be performed is planar imaging of the thyroid region and the mediastinum. The use of pinhole imaging of the thyroid either as an anterior view and additional oblique views may improve the discrimination of abnormal parathyroid tissue.[40] In most situations SPECT imaging is not required although this can give additional anatomic localization particularly if the adenoma is ectopic. The present evidence does not suggest SPECT/CT will have additional value with the exception of ectopic glands where the additional anatomic information may be useful. This image acquisition can be performed using dual energy if ^{123}I and ^{99m}Tc-sestamibi are used. If the radionuclide parathyroid imaging study is equivocal then additional imaging with high resolution ultrasonography may enhance the confidence by identifying a parathyroid gland at the equivocal site. At present the added value of injecting sestamibi intraoperatively or immediately preoperatively to allow probe localization of the glands remains to be seen.

Redo Neck

Patients undergoing additional surgery have a higher morbidity and a lower chance of establishing normocalcaemia. These patients must undergo preoperative localization. Reoperation may be the result of a failed primary operation; in these cases, the parathyroid abnormality is often in a normal position within the neck rather than an ectopic site, or this may be due to recurrence of hyperparathyroidism. This group of patients should have at least 2 tests defining the site of abnormality. The role of ^{11}C-methionine positron emission tomography in these cases should be considered, but a sestamibi scan should be performed initially as described previously and, if abnormal, confirmation with ultrasound or the most appropriate alternative technique considered.

Conclusion

The recent summary statement by a consensus panel on asymptomatic primary hyperparthyroidism states "preoperative localization testing is mandatory when the MIP procedure is used. Preoperative localization tests should not be used to make, confirm, or exclude the diagnosis of primary hyperparathyroidism."[1] It also concludes that the key elements are an experienced parathyroid surgeon and an experienced imaging unit result in the highest success in identifying and removing abnormal parathyroid tissue.[1] There can be no doubt that the value of preoperative localization is cost effective by reducing in patient stay and reducing the incidence of complications.[41] It is also likely that this will improve the patient experience for this procedure. We favor subtraction imaging with the support of high-resolution ultrasound for optimum preoperative localization.

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