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Multimodality imaging of the parathyroid glands in primary hyperparathyroidism

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Primary hyperparathyroidism is a common endocrine disorder, affecting approximately 1 in 500 women and 1 in 2 000 men. Surgical removal of the hyperfunctioning parathyroid gland is the primary curative treatment. The last decade has witnessed the development of minimally invasive parathyroidectomy, which is based on the fact that the vast majority of cases are caused by single adenomas. However, the success of this technique relies on accurate preoperative localisation of the parathyroid lesions. The imaging modalities used vary at different institutions according to local expertise and availability, but include high resolution ultrasound, radionuclide studies, computed tomography (CT) and magnetic resonance imaging (MRI). Ultrasound and 99mTc sestamibi scintigraphy, particularly when complemented by single photon emission computed tomography (SPECT), are currently the imaging techniques of choice for preoperative localisation of parathyroid adenomas; a combination of the two methods further improves the sensitivity and accuracy of detection. CT is less commonly used for preoperative localisation and usually reserved for cases of failed parathyroidectomy, for the detection of suspected ectopic glands. MRI appears to be useful in patients with persistent or recurrent hyperparathyroidism, who have previously undergone surgery. Cross-sectional imaging is also useful in cases where the findings at sonography and scintigraphy are discordant.

SPECT/CT appears promising, but further studies are needed to evaluate its role in preoperative localisation.

Key words: Parathyroid diseases - Hyperparathyroidism, primary - Surgical procedures, minimally invasive - Radionuclide imaging - Technetium Tc 99m sestamibi.

The parathyroid glands were first recognised as distinct endocrine glands in the mid-nineteenth century.1 The principal function of the glands is to maintain calcium homeostasis via the secretion of parathyroid hormone (PTH). Oversecretion of PTH results in hyperparathyroidism, which may be classified as primary, secondary or tertiary.

Primary hyperparathyroidism (HPT) is a common endocrine disorder affecting approximately 1 in 500 women and 1 in 2 000 men, most commonly presenting in the fifth to seventh decades of life.2 4 The incidence increased in the 1970s, primarily as a result of increased biochemical screening of asym-
tomatic patients. Although HPT can be managed conservatively, surgical treatment is the only cure.

The vast majority of cases of HPT are caused by a single parathyroid adenoma (89%). This has allowed the development of minimally invasive parathyroidectomy over the last decade, which has been reported to have success rates equal to that of the conventional surgical approach of bilateral neck dissection. Additional benefits of this approach include avoidance of general anesthesia, reduced morbidity, length of stay and cost, and improved cosmetic results.

However, the success of minimally invasive parathyroidectomy depends on accurate preoperative localisation of the parathyroid lesion. The preferred imaging modalities vary at different institutions according to local expertise and availability, but consist of a combination of high resolution ultrasound, radionuclide studies, computed tomography (CT) and magnetic resonance imaging (MRI). Although extensive information exists in the medical literature on the pros and cons of various techniques, especially radionuclide imaging, the aim of this article is to provide a concise overview of the available imaging options, and provide a practical framework for the approach to parathyroid localisation.

**Embryology and anatomy**

There are usually four parathyroid glands, two superior and two inferior. Approximately 5% of patients have more than four glands, with up to 3% having fewer than four. The superior glands are derived from the fourth branchial pouch, along with the lateral lobes of the thyroid, and the inferior glands from the third branchial pouch, along with the thymus. This helps to explain the normal and variant patterns of their anatomic location.

The superior glands tend to be more consistent in location with most glands (75%) located deep in relation to the mid portion of the superior pole of the thyroid near the cricothyroid junction. In approximately 20% of the population, they are immediately posterior to the upper poles of the thyroid gland. Rarely, the superior glands can be found in the retropharyngeal (1%) or retroesophageal (1%) spaces or in the thyroid gland itself.

The inferior parathyroid glands are more variable in location. The most common anatomic location of inferior glands is behind the lower pole of thyroid gland (50%). The next most common location (15%) encompasses an area 1 cm below the lower pole of thyroid. The position of the remaining one third is variable along the thymopharyngeal tract, being present anywhere from the angle of mandible to the lower mediastinum. The variable anatomic location of parathyroid tissue supports the need for preoperative localization.

The normal parathyroid gland is approximately 5x3x1 mm in size and weights between 40 and 50 mg. They are therefore infrequently identified at imaging. Adenomas, on the other hand, are considerably larger, having a mean mass of greater than 10 times the normal parathyroid gland, and are often identified at cross-sectional imaging. Hyperplastic glands can be quite variable in size, but they tend to have a total gland volume comparable to that of single adenomas.

Histologically, the normal parathyroid gland is comprised of equal amounts of parenchyma and supporting stroma. The majority of the parenchyma is comprised of chief cells, which are responsible for most of the hormonal secretion. The other parenchymal cells, known as oxyphils cells, contain abundant mitochondria but do not possess a significant secretory function.

**Pathophysiology**

The parathyroid glands secrete PTH, a polypeptide which consists of an 84-amino acid sequence. The major determinant of PTH secretion is ionised calcium; small reductions in extracellular concentrations result in increased PTH secretion with reciprocal effects to restore normocalcemia.

This is achieved by the action of PTH on several sites in the body. In bone, PTH stimulates osteoclasts, and to a lesser extent osteoblasts, and calcium increases renal tubular reabsorption, and increases intestinal absorption. HPT is often detected by increased serum calcemia and increases from loss of PTH control. It is often detected in patients with clinical manifestations of parathyroid hyperplasia and highly variable fatigue, hyporeflexia, and muscle weakness.

Most cases of parathyroidism and multiple endocrine neoplasia type 1 or 2A and 2B and 2C include parathyroid cyst. The parathyroid tissues such as multiple endocrine neoplasia type 1 (MEN1) and II and IIa and IIc.

**Imaging**

**Radionuclide technique**

Multiple parathyroid adenomas can be evaluated for their activity using the set technique to evaluate the thyroid and parathyroid glands. The radionuclide technetium-99m Tc shows high uptake in the thyroid and parathyroid tissues and can show more accurate localization.

**Tc-99m**

The Tc-99m scan can be used to detect hyperfunctioning adenomas. The scan is performed after injection of the isotope into the bloodstream. The scan is then repeated after injection of a radioactive substance that is preferentially taken up by the parathyroid glands. The scan is then compared to the normal gland to identify any abnormalities.

**CT and MRI**

Computed tomography (CT) and magnetic resonance imaging (MRI) are also used to locate parathyroid adenomas. Both are highly accurate but can be more invasive than other imaging techniques.

**Ultrasound**

Ultrasound is a non-invasive imaging technique that uses high-frequency sound waves to create images of internal structures. It is often used to locate parathyroid adenomas, especially if they are located near the thyroid gland.

**Angiography**

Angiography is a type of imaging that involves the injection of a contrast dye into an artery. It is used to visualize blood vessels and can be used to locate parathyroid adenomas.

**Surgical techniques**

Surgical techniques for parathyroidectomy include open neck surgery and cervical neck dissection. The open neck surgery involves an incision in the neck to access the parathyroid glands. The cervical neck dissection involves a larger incision in the neck that allows for access to the parathyroid glands as well as other neck structures.

**Results**

The success rate of parathyroidectomy for hyperparathyroidism varies depending on the technique used. Open neck surgery has a success rate of about 90%, while cervical neck dissection has a success rate of about 95%. The choice of technique depends on the location and size of the adenoma, as well as the experience of the surgeon.
PARATHYROIDISM

Parathyroid glands can be found in the neck, behind the esophagopharyngeal constrictor muscle and thyroid gland itself.\textsuperscript{11-13} Parathyroid glands are more frequently encountered in the lower pole of the thyroid gland (50%). The upper poles (15%) encompass the lower pole of the inferior lobe, and the remaining one (30%) is posterior to the sternum.\textsuperscript{11} The average weight of a parathyroid tissue is 0.12 g, and the operative localisation is approximated.

Parathyroid weights and sizes are therefore variable in the population. Adenomas, while usually larger, can be 10 times smaller than normal glands and are often discovered by accidental imaging.\textsuperscript{4} The size of the gland is a variable in detecting parathyroid volume, with multiple adenomas.\textsuperscript{15} Hyperplasia of parathyroid glands can lead to multiple amounts of parathyroid hyperplasia. The size of the gland is used in comprised of the thyroid gland, but do not distinguish parathyroid function.

OSTEOBLOASTS

Osteoblasts, with a net effect of osteolysis and calcium mobilization. In the kidneys, it increases renal tubular reabsorption of calcium, and increases excretion of phosphate. In addition, PTH stimulates the production of osteoclasts, which, in turn, promotes absorption of calcium by the gastrointestinal tract.

HPT is considered to be present when serum calcium is elevated and PTH is increased or appropriately normal, resulting from loss of the normal feedback control of PTH by extracellular calcium. Although often detected before symptoms arise, the clinical manifestations of hypercalcemia are highly variable and non-specific, and include fatigue, hypertension, bone pain, proximal muscle weakness, and psychiatric illness.

Most cases of HPT are caused by a single parathyroid adenoma (89%), with hyperplasia and multiple adenomas accounting for 6% and 4% respectively.\textsuperscript{5} Other rare causes include parathyroid carcinoma and parathyroid cyst. There is an increased incidence of parathyroid hyperplasia in familial syndromes such as multiple endocrine neoplasia types I and IIa and familial hypocalcemic hypercalcemia.\textsuperscript{16}

Imaging modalities for parathyroid localization

Radioisotope imaging

Technique

Multiple radiopharmaceuticals have been evaluated for imaging the parathyroid glands in the setting of HPT. The first radionuclide technique to gain widespread acceptance for parathyroid localization was thallium-201 and technetium-99m pertechnetate (Tc-99m) subtraction imaging. However, \textsuperscript{99m}Tc sestamibi has become the radiopharmaceutical of choice as a result of superior image quality, more favourable dosimetry and improved accuracy.\textsuperscript{1,17}

\textsuperscript{99m}Tc sestamibi is taken up by both the thyroid and parathyroid glands, but adenomatous and hyperplastic parathyroid tissue shows more avid uptake of the radiotracer and longer retention than adjacent thyroid tissue,\textsuperscript{18} which is likely to be due to sequestration within mitochondria-rich oxyphil cells.\textsuperscript{18} The single tracer, dual phase technique takes advantage of these differential washout rates.\textsuperscript{19} Images are obtained 10-15 min after intravenous administration of a bolus containing 10 mCi (370 MBq) radiotracer, with delayed images obtained approximately 90 to 120 minutes after the injection of the radiopharmaceutical. The method is simple to perform and involves only one administration of tracer.

However, many thyroid lesions also retain \textsuperscript{99m}Tc sestamibi leading to false positive results, and subtraction techniques are often helpful in these cases.\textsuperscript{20} In addition to \textsuperscript{99m}Tc sestamibi, the subtraction method requires administration of iodine-123 or Tc-99m pertechnetate to obtain a thyroid image. Regardless of which tracer is used for the thyroid component of the test, the sestamibi and thyroid images are normalized and the thyroid image is "subtracted" from the sestamibi image.

In both of these methods, planar images are acquired from the retromastoid region cranially to the xiphisternum caudally. Pinhole views of the neck are preferred for optimum spatial resolution and an additional full field of view image of the anterior neck and mediastinum to exclude an ectopic site in the chest. Single-photon emission tomography (SPECT) is a useful complement to planar imaging as it provides 3-dimensional information about the location of a particular abnormality. Multiple 2-dimensional projections are acquired from multiple angles. Computational analysis is then used to apply a tomographic reconstruction algorithm to the multiple projections, yielding a 3-dimensional image.

Imaging findings

In the single tracer, multi-phase technique, the planar images obtained shortly after the administration of radiotracer will show uptake by both thyroid and parathyroid tissue. However, asymmetric focal of increased radiotracer uptake representing abnormal parathyroid.
about the location of a particular abnormality, in terms of depth and proximity to neighbouring structures.

ADVANTAGES AND LIMITATIONS

One of the primary advantages of sestamibi scintigraphy is its ability to detect ectopic parathyroid adenomas with an accuracy of over 90%.

In addition, by providing more precise topographic information, SPECT can differentiate parathyroid lesions from thyroid lesions, and improve localisation of ectopic lesions. The relative disadvantages of radionuclide imaging are the need to administer a radiopharmaceutical and the requirement of sophisticated scanning equipment and well-trained operators.

The multi-phase technique is limited by rapid sestamibi washout from some parathyroid adenomas, resulting in false negative findings. False positive results also occur due to sestamibi uptake by thyroid nodules, lymph nodes and Brown tumours. The subtraction technique is often helpful in some false positive cases, as many thyroid lesions also accumulate pertechnetate and iodine, and this method can reduce the number of false positives.

However, the subtraction technique has its own limitations of patient motion during data acquisition leading to misregistration of the sestamibi and pertechnetate images, resulting in a false-positive study. This can be minimised using dynamic acquisition, which allows removal of frames with excessive movement without discarding the entire data set. Another pitfall of the subtraction technique is decreased or absent thyroid uptake of pertechnetate, or iodine, resulting in a false positive subtraction image.

Both techniques are limited in cases of small adenomas and hyperplastic parathyroid glands, which may not be detected as a result of the low system resolution and relative lack of tracer uptake and retention by the parathyroid tissue in these cases.

EFFECTIVENESS IN LOCALISATION

The recent literature reports sensitivities between 68% and 88% for the detection of solitary adenomas using SPECT/CT. A similar accuracy of up to 85% has been reported for neck exploration.

Ultrasound

Ultrasound imaging technique is increasingly used in conjunction with other modalities such as MRI and CT. Ultrasound is a cheap and widely available imaging technique that can provide additional information about the anatomy of the neck and head. It is particularly useful for visualising small lesions and lesions that are located close to the skin. Ultrasound can also be used to guide biopsy procedures.

In conclusion, the use of multimodality imaging in primary hyperparathyroidism is becoming increasingly common. It is important to consider the advantages and disadvantages of each imaging modality, as well as the patient's individual circumstances, when deciding on the most appropriate imaging approach.

References


solitary adenomas with \(^{99m}\)Tc sestamibi scintigraphy.\(^5\), \(^6\), \(^7\) These figures appear similar for both the multi-phase and subtraction methods, and no statistical advantage of one method over another has been convincingly demonstrated.\(^8\) SPECT further improves sensitivity compared to planar imaging, especially if acquired early, with reported sensitivities of up to 95%, as well as improved accuracy of localisation.\(^24\), \(^29\)-\(^32\) However, it should be noted that in many of these studies, the difference is not statistically significant.

The combination of SPECT with CT (SPECT/CT) has the potential to improve preoperative localisation even further by combining anatomic and functional information. However, there have been relatively few investigations evaluating hybrid imaging, and results from these initial studies are conflicting in their conclusions about the added usefulness of CT.\(^26\), \(^33\)-\(^35\)

**Ultrasound**

**TECHNIQUE**

Ultrasound is one of the commonest imaging techniques used for evaluating the neck, and at many institutions is the first imaging modality used for investigation of HPT, along with parathyroid scintigraphy.

The patient should be examined in the supine position with the neck slightly hyperextended, and the use of a high-frequency linear transducer (10-12.5 MHz) provides optimal spatial resolution. The study should be performed in transverse and longitudinal planes extending from the carotid artery to midline and from the hyoid bone superiorly to the thoracic inlet inferiorly, with attention focused behind the thyroid gland. Gray-scale imaging is supplemented by colour and power doppler imaging to look for feeding vessels and vascularity of suspected adenomas shown at initial grey-scale imaging.

**IMAGING FINDINGS**

The typical appearance of a parathyroid adenoma is a well circumscribed round or oval nodule which is homogeneously hypoechogenic to the overlying thyroid gland on grey-scale imaging \(^36\), \(^37\) (Figure 2A). Large adenomas may have more variable appearances, including multilobulations, cystic change and calcification.\(^38\) On color-Doppler imaging, 90% of parathyroid adenomas demonstrate an intra-parenchymal hypervascular pattern.\(^39\) This is commonly seen as a peripheral arc of vascularity, as the feeding artery, having entered the gland at one pole, tends to branch around the periphery of the gland before penetrating deeper.\(^10\), \(^40\), \(^41\) (Figure 2B). This feature can help distinguish parathyroid adenomas from cervical lymph nodes, as lymph nodes are supplied by small vessels which enter the node at the echogenic central fatty hilum.
sound,\textsuperscript{5, 27, 44} and accuracy of localisation improves considerably when a feeding vessel is identified on color-Doppler.\textsuperscript{5} Advances in technology have improved the ability of sonography to detect very small structures with specific vascular patterns, such as adenomas, and the sensitivity and accuracy is constantly improving.\textsuperscript{22} Such advances include the use of microbubble intravenous contrast agents, which may be of value in patients with equivocal color-Doppler findings.\textsuperscript{46}

**Computed tomography**

**TECHNIQUE**

CT examination of the neck and mediastinum has also been used for the localisation of parathyroid adenomas. The patient is examined in the supine position and requested to refrain from swallowing during the examination to minimise movement artefact. The data is acquired following injection of intravenous contrast medium with thin collimation, both of which are required for accurate detection. The axial images can be reconstructed to provide sagittal, coronal, and oblique projections.

**IMAGING FINDINGS:**

Identification of an intensely enhancing nodule in characteristic locations for parathyroid tissue, for example posterior to the thyroid gland, is required for CT diagnosis of a parathyroid adenoma\textsuperscript{22} (Figure 3).

**ADVANTAGES AND LIMITATIONS:**

Examination of both the neck and mediastinum is one of the primary advantages of CT, as it improves detection of ectopic glands.\textsuperscript{16} Disadvantages include exposure of the patient to ionising radiation and iodinated contrast medium. The main disadvantage is differential enhancement of adjacent thyroid tissue, which is very similar to that of a parathyroid adenoma, and therefore masks the presence of the closely related parathyroid adenoma (Figure 3). This is not usually a problem with ectopic parathyroid adenomas.

**Effectiveness in localisation:**

The recent literature reports sensitivities between 72\% and 89\% for the detection of solitary adenomas with preoperative ultrasound.\textsuperscript{6, 15, 27, 44} In addition, adenomas are localised using visual cues, and the identification of the feeding vessel is confirmed using other modalities such as CT or MR imaging.
In addition, the ability of CT to detect small adenomas is limited by artefacts from surgical clips, respiration and swallowing. False positive results may occur due to tortuous vessels, lymph nodes and thyroid nodules.\(^1\)\(^2\)

**EFFECTIVENESS IN LOCALISATION**

The reported sensitivities of CT for the localisation of parathyroid adenomas range from 46% to 87\(^{\%}\)\(^{42},^{47},^{48}\) and largely depends on whether the adenoma is intimately related to thyroid tissue or is in close proximity or in an ectopic location. With the advent of multi-detector CT, ultra-fast imaging is possible with better spatial resolution and minimal artefacts, but nevertheless, in the clinical setting, the role of CT is limited to the localisation of ectopic tissue.

**Magnetic resonance imaging**

**TECHNIQUE**

MRI of the neck and mediastinum has been used in recent years for the evaluation of parathyroid pathology, although it has not yet been extensively evaluated. Images of the neck are generally obtained with an anterior neck surface coil, and electrocardiogram gating is used for mediastinal images. Fat-suppressed T2-weighted MRI in the axial plane is the most sensitive imaging sequence for detection of parathyroid adenoma,\(^{49},^{50}\) and images can be reconstructed in multiple planes.

**IMAGING FINDINGS**

Parathyroid adenomas have a longer relaxation time than thyroid tissue. Therefore, the most common appearance is intermediate to low signal intensity on T1-weighted imaging (Figure 4), and high signal intensity on T2 weighted imaging. Haemorrhagic components cause high signal intensity on both T1- and T2-weighted images.\(^{52}\) Less commonly, fibrosis or old hemorrhage can cause low signal intensity on both sequences, and the administration of intravenous gadolinium can help to increase lesion conspicuity in these cases.\(^{49},^{50},^{53}\) As with CT, knowledge of the characteristic locations for parathyroid tissue is required for accurate diagnosis.

**ADVANTAGES AND LIMITATIONS**

The advantages of MRI include its ability to examine both the neck and mediastinum with excellent anatomic detail with multiplanar capability. In addition, it does not expose the patient to ionising radiation. Minimal artefact from surgical clips and sequences which allow separation of scar tissue improve detection in patients who have undergone surgery.\(^{21}\) The disadvantages include movement artefact due to long examination times, relatively limited availability in most countries, and higher cost.

**EFFECTIVENESS IN LOCALISATION**

The reported sensitivities of MRI range from 46% to 87\(^{\%}\).\(^{50}\) Many of these studies were performed in patients who had already undergone surgery. Refinements in MR tech-
nology and techniques, as well as increased investigator experience, are likely to be responsible for the improved sensitivities in recent studies.

**Approach to parathyroid localisation**

99mTc sestamibi scintigraphy, particularly when complemented with SPECT, and ultrasonography are currently the imaging techniques of choice for preoperative localisation of parathyroid adenomas. Studies comparing these techniques suggest similar sensitivities and specificities for solitary adenoma detection. Both techniques remain similarly insensitive for the detection of multiglandular disease and double adenomas.

However, it can be seen that using the two methods in combination may offset some of the limitations of each individual method. Indeed, there is evidence that a combination of the two methods improves the sensitivity and accuracy of preoperative detection and localisation by compared to either technique alone.

Contrast-enhanced CT can also locate parathyroid adenomas but combined studies of ultrasonography and CT suggest that supplemental CT will detect only a few additional adenomas over sonography alone. Thus, it is less commonly used for preoperative localisation and usually reserved for cases of failed hyperparathyroidectomy or recurrent hyperparathyroidism respectively, or to provide supplementary information if ultrasound or radionuclide imaging findings are negative or discordant or if an ectopic adenoma is detected. SPECT/CT appears promising in theory, but further studies are needed to evaluate its role in preoperative localisation.

**Conclusions**

The success of minimally invasive parathyroidectomy in the treatment of HPT relies on accurate localisation of parathyroid lesions. Radionuclide scintigraphy using 99mTc sestamibi and ultrasound are the current imaging modalities of choice for preoperative localisation, especially when used in combination. CT and MRI may be useful in cases of failed parathyroidectomy or recurrent hyperparathyroidism respectively, or to provide supplementary information if ultrasound or radionuclide imaging findings are negative or discordant or if an ectopic adenoma is detected. SPECT/CT appears promising in theory, but further studies are needed to evaluate its role in preoperative localisation.

**Riassunto**

Imaging multimodale delle paratiroidei nell’iperparatiroidismo primitivo

L’iperparatiroidismo primitivo è una comune patologia endocrina, che colpisce circa 1 su 500 donne e 1 su 2 000 uomini. Il principale approccio terapeutico consiste nella rimozione chirurgica della ghiandola paratiroide iperfunzionante. Nell’ultimo decennio si è andata sviluppando la paratiroidectomia chirurgica minimamente invasive, basata sul fatto che la maggioranza dei casi è causata dalla presenza di un singolo adenoma. Tuttavia, il successo dell’intervento chirurgico dipende strettamente dalla localizzazione preoperatoria della lesione iperfunzionante. Le diverse tecniche utilizzate variano a seconda dell’esperienza locale e della disponibilità strumentale e includono ecografia ad alta risoluzione, studi di medicina nucleare con radionuclidi, tomografia computerizzata (TC) e risonanza magnetica (RM). L’ecografia...
e la scintigrafia con 99mTc sestamibi, specialmente se associata a tomografia a emissione di positroni (SPECT), sono attualmente gli strumenti diagnostici di scelta per la localizzazione preoperatoria degli adenomi paratiroidi. L’associazione dei due metodi migliora la sensibilità e l’accuratezza della localizzazione. La TC è più raramente utilizzata per la localizzazione preoperatoria e viene riservata generalmente ai casi di paratiroidectomia fallita e per la dete-
zione di sospette ghiandole ectopiche. La RM sembra utile nei casi di iperparatiroidismo persistente o ricor- nente già precedentemente sottoposti ad intervento chirurgico. L’imaging con sezioni trasverse è utile nelle lesioni in cui l’ecografia e la scintigrafia forniscano dati contrastanti. L’uso di SPECT/TC sembra promettente, ma sono necessari ulteriori studi per stabilire il valore nella localizzazione preoperatoria.

Parole chiave: Tiroide, malattie - Iperparatiroidismo primario - Chirurgia mini-invasiva - Imaging multimodale - Tecnevol 99m sestamibi.

Referenze


