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Editorial

Is there an ideal algorithm in preoperative localisation of primary hyperparathyroidism?

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Introduction

Parathyroid adenomas represent the most common cause of hyperparathyroidism, and represent a significant health problem that can be treated efficiently with surgical excision. Historically, bilateral neck exploration was used to identify all four glands, and the enlarged gland was removed with or without biopsy of the remaining glands. This often involved a relatively long operative time and complications such as neck fibrosis resulting from the large neck wound. A major development has been the introduction of the 'minimally invasive technique' that does not require general anaesthesia, thereby reducing morbidity and hospital stay, optimising overall cost and providing better cosmetic results. However, an essential prerequisite for the success of minimally invasive surgery is the accurate localisation of the abnormal gland(s), and this relies heavily on a variety of imaging techniques, including anatomical and functional imaging or a combination of both.

Anatomical imaging

Ultrasound (US) has a reported sensitivity of 65 to 85% in the detection of parathyroid adenomas [1]. The typical ultrasound appearance is of a round or oval homogenous, hypoechoic, hypervascular nodule with an echogenic capsule. Larger adenomas may demonstrate cystic change, hyperechoic component(s) and calcification [2]. The sensitivity of US is operator-dependent [3], and is limited in the presence of a multinodular goitre, which can mimic or mask a parathyroid adenoma. In addition, some areas are inaccessible to ultrasound examination such as the mediastinum and the retro-oesophageal region; therefore, an ectopic adenoma cannot be excluded on ultrasound examination alone. The diagnostic yield, however, is increased when US is combined with scintigraphy (see below).

Computed tomography (CT), using post-contrast thin collimation images, has a sensitivity that varies from 46% to 87%, with adenomas usually demonstrating avid enhancement [1]. The major advantage of CT over ultrasound is the ability to detect ectopic adenomas in the mediastinum, but has disadvantages that include movement artefact (respiration and swallowing), the use of iodinated intravenous contrast and exposure to ionizing radiation.

Magnetic resonance imaging (MRI) has sensitivity of 65% to 80% in detecting adenomas. The most useful sequence is the fat-suppressed T2-weighted in the axial plane with the addition of intravenous gadolinium [1, 4, 5]. The main disadvantage of MRI is its limited availability, high cost and long scan times. Computed tomography and MRI are therefore useful in patients with recurrent or persistent hyperparathyroidism when the probability of ectopic glands is high.

Selective venous sampling (SVS) is an invasive procedure which involves puncture of the femoral vein followed by catheterization of cervical and mediastinal veins. Approximately 20–30 blood samples are obtained, numbered and analysed for parathyroid hormone (PTH) levels. SVS is defined as positive when a 1.5-fold increase in PTH concentration compared with the femoral vein is found, followed by a decreasing gradient in consecutive samples [6]. Due to the invasive nature of the procedure, SVS is often only used when non-invasive imaging modalities are inconclusive or in cases of recurrent or persistent hyperparathyroidism following surgery.

Functional imaging

Earlier nuclear medicine procedures benefited from the different uptake mechanisms of radiotracers such as selenium-75-methionin or thallium-201-chloride (taken up by the thyroid and

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parathyroid glands) and various iodine isotopes or technetium-99m-pertechnetate (taken up by the thyroid only) to obtain a 'subtraction image' that represents uptake in the parathyroid only. Subtraction scans required accurate determination of regions of interest and physics input, necessitating continuous search for a more practical and reliable method.

The introduction of Technetium-99m Sestamibi (^{99m}Tc-MIBI) scintigraphy in clinical practice in 1989 by Coakley and co-workers [7] substantially improved the role of preoperative scintigraphic imaging in hyperparathyroid patients. The original technique developed by Coakley consisted of dual tracer subtraction scintigraphy. In the following years, some variations of the techniques were proposed. Taillefer et al. [8] proposed the modified and practical scintigraphic approach of dual phase, or wash out, technique based on the observation that ^{99m}Tc-MIBI retention by parathyroid adenomas was prolonged in comparison with the normal thyroid tissue. As a consequence, imaging performed 2 to 3 hours after the injection of ^{99m}Tc-MIBI was expected to show a relatively rapid radiotracer wash out from the thyroid gland with well visualized residual or retained tracer in the parathyroid adenomas (differential wash out) [9].

This technique was adopted by centres interested in parathyroid imaging due to the simplicity of the acquisition protocol. However, increasing experience with the planar dual phase technique has clearly shown some limitations including:

- the difficulty in distinguishing ^{99m}Tc-MIBI-avid thyroid nodules from parathyroid adenomas, with consequent possible false positive results. This poses a significant limitation in areas where the prevalence of coexisting thyroid nodular disease is high, such as in parts of central and south Europe and Asia, where the prevalence can be as high as 30–50%;
- the relatively low sensitivity in parathyroid adenomas with a rapid ^{99m}Tc-MIBI wash out that accounts for at least 20–30% of cases in our experience and is even greater in secondary hyperparathyroidism due to the relative paucity of oxyphilic mitochondria-rich cells.

These limitations have been, at least in part, overcome by the introduction of single photon emission computed tomography (SPECT) acquisition in addition to the planar acquisition. Several protocols have been proposed such as:

- the routine acquisition of SPECT during ^{99m}Tc-MIBI dual phase scintigraphy both following early (15–20 minutes after radiotracer injection) and delayed (2–3 hours after radiotracer injection) planar imaging. This protocol is time-consuming but has shown improved sensitivity [10];
- the acquisition of SPECT only after early or delayed planar ^{99m}Tc-MIBI images have failed to show a well defined area of tracer retention, thus reducing the overall acquisition time [9].

With either of these protocols, an improvement on scintigraphic sensitivity and accuracy has been reported. The reported higher sensitivity using early rather than delayed SPECT is probably related to the fact that a proportion of parathyroid adenomas are characterized by relatively rapid radiotracer wash out [11, 12]. Another reason for choosing early SPECT is related to the Sestamibi kinetics. This was demonstrated by O'Doherty and colleagues [13], showing the peak of maximum Sestamibi uptake in parathyroid adenomas to take place within a few minutes of radiotracer injection. It is therefore expected that, in the absence of significant thyroid disease, the "maximum information" of Sestamibi uptake in parathyroid adenomas is obtainable earlier rather than later in the study. This applies to both planar and SPECT acquisition, during a dual phase single tracer ^{99m}Tc-MIBI scintigraphy or during a dual tracer ^{99m}Tc-Pertechnetate/^{99m}Tc-MIBI subtraction scintigraphy.

^{99m}Tc-Pertechnetate/^{99m}Tc-MIBI subtraction scintigraphy is based on obtaining a thyroid pertechnetate scan following the delayed Sestamibi image acquisition in order to investigate possible concurrent thyroid abnormalities [9], and early SPECT acquisition (approximately 20–40 minutes after ^{99m}Tc-MIBI injection) has been shown to give good results [12, 14]. Other modifications have been suggested to improve the performance of this technique such as the addition of dynamic imaging, pinhole SPECT [15] and hybrid SPECT/CT imaging [16].

^{99m}Tc-Tetrofosmin shares some qualities with ^{99m}Tc-MIBI though its mechanism of uptake is different from that of ^{99m}Tc-MIBI being retained primarily in the cytosol rather than the mitochondria. When used for parathyroid imaging, it has shown a slow washout from the thyroid making it unsuitable for the single-tracer dual-phase procedure [17]. However, its sensitivity is substantially improved when used in a dual-tracer subtraction protocol with SPECT [18].

Other functional imaging has been used in the detection of parathyroid adenomas. Positron emission tomography (PET) using fluorine-18 deoxyglucose (^{18}F-FDG) was investigated as a marker of increased metabolic activity in adenomas and showed conflicting results. Neumann and co-workers compared ^{18}F-FDG PET and ^{99m}Tc-MIBI in preoperative assessment of 21 patients suspected of having parathyroid adenomas and found it to be more sensitive but less specific than ^{99m}Tc-MIBI SPECT [19], while others reported a very low sensitivity of 29% [20].

Amino acid influx into abnormally stimulated parathyroid tissue can be detected by another PET radiotracer, L-[methyl-11 C]methionine (^{11}C- methionine). A high detection rate was shown by Sundin et al in 34 patients with primary or recurrent adenomas. Using semi-quantitative standard uptake values (SUV) and transport rate constant, their true positive detection rate was 85% compared to 59% and 57% for CT and US [21]. Beggs and Hain used ^{11}C- methionine in the assessment of 51 patients with suspected adenomas who had negative or equivocal conventional imaging, including CT, MRI, venous sampling and ^{99m}Tc-MIBI scans. They showed ^{11}C- methionine to have a sensitivity of 83%, a specificity of 100% and an accuracy of 88% in successfully locating parathyroid adenomas. False negative results were found to be due to adenomas in the lower mediastinum not included in the area of scanning [22].

However, PET imaging in general is still limited in availability worldwide, while the major drawback of using ^{11}C is its extremely short half-life of 20 minutes that limits its use to centres in close proximity to cyclotrons. In practical terms, ^{99m}Tc-MIBI SPECT remains the standard functional imaging technique due to its availability and cost.

Combined scintigraphy and US

The experience of the first author in S. Maria della Misericordia Hospital in Rovigo is to use a dual tracer ^{99m}Tc-Pertecnetate/

/^{99m}Tc-MIBI scintigraphy combined with US performed by the same operator in the same session of scintigraphy [12, 23]. Using this protocol in more than 400 consecutive primary hyperparathyroid patients, a successful localization rate of approximately 95% was obtained [24]. The main reasons for the development of these integrated scintigraphic/US protocols were the following:

- to select patients with a solitary parathyroid adenoma characterized by a clearly positive ^{99m}Tc-MIBI scan, with the aim to offer the patient minimally invasive radioguided parathyroidectomy. This has been achieved in two-thirds of cases;
- to exclude patients with concomitant nodular thyroid disease, especially those with ^{99m}Tc-MIBI avid thyroid nodules, thus avoiding intraoperative false positive results;
- to separate solitary parathyroid adenoma from glandular hyperplasia, allowing the surgeon to perform a traditional bilateral neck exploration instead of minimally invasive radio-guided parathyroidectomy.

The addition of US plays an important role in confirming the presence and location of solitary parathyroid adenomas, particularly those with relatively low ^{99m}Tc-MIBI uptake. In addition, typical adenomas can also be distinguished from a ^{99m}Tc-MIBI avid thyroid nodule, all of which is vital information for planning further surgical intervention. Ultrasound can also be helpful in diagnosing glandular hyperplasia, which is a contraindication to the minimally invasive approach. In patients who have positive planar scintigraphy but negative US, a parathyroid adenoma may be located deep in the para-tracheal/para-oesophageal space or in ectopic sites such as the mediastinum, and this is a strong indication for SPECT. The SPECT images are acquired approximately 30–40 minutes after planar dual tracer subtraction scintigraphy. Another benefit of SPECT is that it allows for the precise calculation of the parathyroid to background ratio which is an important parameter to plan a radioguided parathyroidectomy as this calculation in planar images would underestimate parathyroid adenomas located deeply in the neck or mediastinum [25].

In conclusion, the introduction of ^{99m}Tc-MIBI scintigraphy into clinical practice has significantly improved preoperative parathyroid localisation and, consequently, parathyroid surgery planning. Many procedural improvements have been proposed to further refine this technique, particularly the addition of SPECT. The current practice of dual tracer ^{99m}Tc-MIBI/^{99m}Tc-pertechnetate combined with early SPECT and US should be recommended as the "gold standard" in preoperative imaging.

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