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GUIDELINES

2009 EANM parathyroid guidelines

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Abstract The present guidelines were issued by the Parathyroid Task Group of the European Association of Nuclear Medicine. The main focus was imaging of primary hyperparathyroidism. Dual-tracer and single-tracer parathyroid scintigraphy protocols were discussed as well as the various modalities of image acquisition. Primary hyperparathyroidism is an endocrine disorder with high prevalence, typically caused by a solitary parathyroid adenoma, less frequently (about 15%) by multiple parathyroid gland disease (MGD) and rarely (1%) by parathyroid carcinoma. Patients with MGD may have a double adenoma or hyperplasia of three or all four parathyroid glands. Conventional surgery has consisted in routine bilateral neck exploration. The current trend is toward minimally invasive surgery. In this new era, the success of targeted parathyroid surgery depends not only on an experienced surgeon, but also on a sensitive and accurate imaging technique. Recognizing MGD is the major challenge for preoperative imaging, in order to not direct a patient towards inappropriate minimal surgery. Scintigraphy should also report on thyroid nodules that may cause confusion with a parathyroid adenoma or require concurrent surgical resection. The two main reasons for failed surgery are ectopic glands and undetected MGD. Imaging is mandatory before re-operation, and scintigraphy results should be confirmed with a second imaging technique (usually US for a neck focus, CT or MRI for a mediastinal focus). Hybrid SPECT/CT instruments should be most helpful in this setting. SPECT/CT has a major role for obtaining anatomical details on ectopic foci. However, its use as a routine procedure before target surgery is still investigational. Preliminary data suggest that SPECT/CT has lower

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sensitivity in the neck area compared to pinhole imaging. Additional radiation to the patient should also be considered. The guidelines also discuss aspects related to radio-guided surgery of hyperparathyroidism and imaging of chronic kidney disease patients with secondary hyperparathyroidism.

Keywords Hyperparathyroidism · Primary hyperparathyroidism · Secondary hyperparathyroidism · Parathyroid surgery · ^{99m}Tc-sestamibi · Localization studies · Scintigraphy · Subtraction scanning · Parathyroid adenoma · Parathyroid hyperplasia · Minimally invasive surgery · Gamma probe

Anatomy, physiology and pathophysiology of parathyroid glands

Anatomy

Parathyroid glands are derived from the third and fourth pharyngeal pouches and are generally four in number, subdivided into two upper and two lower. Their most probable location is behind the thyroid gland, in particular, the upper parathyroid glands (also called P4) that take origin from the endoderm of the fourth pouch are located behind the superior third of the two thyroid lobes; the lower parathyroid glands (also called P3) that originate from the third pouch are generally located behind the inferior third of the two thyroid lobes. The parathyroid glands are found in the peri-thyroid sheath but outside the thyroid capsule or, rarely so, in the subcapsular site [1–5].

It is very important to note that the location of parathyroid glands can vary, especially the site of the lower glands. This is due to the longer pathway and more difficult migration process that the lower glands have to follow after their origin from the third pharyngeal pouch. So they can be intrathyroidal, within the thyrothymic ligament, within the thymus and in the mediastinum, or fail to migrate and remain very high in the neck [1].

Although there are normally four parathyroid glands, not infrequently, five or more parathyroid glands can be present. These supernumerary and accessory glands derive from the numerous dorsal and ventral wings of the pouches and can be variously located from the cricoid cartilage down into the mediastinum. The most probable location of accessory glands is the thymic region [1, 3].

The normal parathyroid glands vary considerably in shape and size between individuals and within the same individual. Usually they are ovoid or bean-shaped but may be elongated, leaf-like or multilobulated. Their diameter is variable, although it should not be larger than 7 mm, and their individual weight ranges from 20 to 45 mg [1, 3]. On some occasions lesser than four parathyroid glands can be present, even the complete absence of parathyroid glands is possible as in case of the genetic abnormalities in some genes encoding for transcription factors required for the parathyroid tissue development such as Gcm2 gene, or in DiGeorge syndrome.

Within the parathyroid glands there are two main glandular components: parenchymal cells and fat cells. The proportions of these two kinds of cells vary with age: in young people, there are only a few sparse fat cells, which increase gradually and about the age of 30 years fat cells constitute 10–25% of the glandular volume [1, 3, 5]. After this age the proportion of fat cells remain relatively constant. The parenchymal cells are mainly chief cells, the functional part of the glands. The chief cells, as active endocrine cells that produce the parathyroid hormone (PTH), have slightly eosinophilic cytoplasm and few mitochondria. The other parenchymal cells are oxyphilic cells, which may be able to produce PTH, transitional oxyphilic cells, a variant of oxyphilic cell, and clear cells with unknown function, fundamentally inactive [1]. Vascular and nervous cells are also present in the parathyroid tissue.

Physiology

The parathyroid glands produce PTH, which is a key molecule important for maintaining calcium, phosphate and vitamin D homeostasis, and ultimately bone health. PTH is produced by chief cells in the form of pre-pro-PTH (115 amino acids), in a second step it is converted into pro-PTH (90 amino acids) and at the end into PTH; the final form is stored in cytosolic granules that, after suitable stimulus, are secreted in the blood flow [1, 2, 5]. When the final entire molecule (84 amino acids, molecular weight 9500 [5]) passes through the liver and the kidney it is cut into N-terminal fragment and C-terminal fragment. The full-length (1–84) molecule and the N-terminal fragment (1–34) possess most of the biological activity. Biological activity of N-terminal truncated fragments (3–84, 7–84) and of C-terminal fragments is currently the subject of intense investigation. The main function of PTH is to keep the blood calcium level stable: a decrease of blood calcium level, in particular the ionized form, stimulates PTH production and secretion. In fact the parathyroid cell surface is equipped with a cation-sensitive receptor mechanism through which the cytosolic calcium concentration and PTH secretion are regulated [1–3].

PTH preserves the calcium, phosphate and vitamin D homeostasis through several main actions: (a) stimulating renal tubular calcium reabsorption, (b) stimulating urinary phosphate excretion through the inhibition of the sodium-phosphate cotransporter NPT2a, (c) stimulating the activity of the 1α-hydroxylases and the synthesis of calcitriol, (d) increasing calcium absorption from the gastrointestinal tract via the stimulation of calcitriol production and (e) stimu-

lating osteoclastic and osteoblastic activity in the bone (bone remodelling) that results in the release of calcium and phosphate from bone [1, 3, 5].

The major part of PTH actions on the target organs are mediated by the binding of PTH to a specific PTH type I receptor and the stimulation of cyclic adenosine monophosphate (cAMP), a second messenger that, in the case of primary hyperparathyroidism (PHPT), can be found increased at the urinary level. PTH functions, especially so at the intestinal site, are also mediated by active vitamin D, whose formation is stimulated by PTH at the kidney level, again mediated by cAMP. Moreover, vitamin D increases the skeletal effects of PTH [5].

Pathophysiology

Hyperparathyroidism exists in three different forms: primary, secondary and tertiary [1–3].

Primary hyperparathyroidism PHPT is the most frequent pathological condition of the parathyroid glands and one of the most frequent endocrine disorders overall. It is characterized by increased production and secretion of PTH. The consequent biochemical changes are the result of a lack of calcium homeostasis: increased blood and urine calcium levels, decrease in blood phosphate level and increase in urine phosphate level [1–3]. Clinically, this condition causes nephrocalcinosis, urolithiasis, bone disease, neuropsychiatric disorders (from mild behavioural changes to coma), gastrointestinal disturbances (from mild abdominal pain to acute pancreatitis) and neuromuscular manifestation (weakness, cramps and muscle pain) [2]. It has become unusual for patients to present with florid symptoms since the increased use of laboratory tests encompassing routine chemistry screening. Most new cases of PHPT are indeed diagnosed in a subclinical state [1, 3, 4, 6].

PHPT can be due to a hyperplastic or neoplastic disease of parathyroid gland(s), more frequently adenomas, most rarely carcinomas [1, 3, 7, 8]. About 85% of PHPT is caused by a solitary adenoma of the parathyroid glands [1–3, 7]. This is a benign tumour that can vary in weight from less then 100 mg to more than 100 g (there is some correlation between adenoma size and the degree of hypercalcaemia) [1, 3]. Microscopically, the adenoma is surrounded by a rim of normal parathyroid tissue outside the capsule. It is formed predominantly of chief cells that are usually enlarged with nuclei larger and more variable in size compared to normal parathyroid tissue [1]. The nuclear pleomorphism is not a sign of malignancy, but it is considered a criterion to differentiate adenoma from hyperplasia. In patients with solitary adenoma, the remaining parathyroid glands are generally smaller than normal glands and show signs of secretory inactivity on electron microscopy [1]. In about 5% of cases typical adenomas affect more than one gland, "double adenomas".

Parathyroid hyperplasia causes less than 15% of PHPT [1, 3]. Chief cell hyperplasia is the most common type and it is characterized by a mixture of chief cells and to a lesser extent oxyphil cells. The cells are arranged in a diffuse pattern or in nodules; sometimes there is a mixture of both patterns. In PHPT hyperplasia affects the glands asymmetrically, to varying degrees, and commonly one or two glands may be of normal size although they show microscopic signs of endocrine hyperfunction [1].

Carcinoma of parathyroid glands represents less than 1% of cases of PHPT and can arise in any gland, usually in patients between the age of 30 and 60 years and it is generally accompanied by clinical signs of hyperparathyroidism. Unlike an adenoma it is not capsulated, it is larger and appears lobulated, firm and often adherent to the surrounding structures [1, 8].

PHPT can be sporadic or familial. The familial form can affect parathyroid glands exclusively or, more often, be part of a multiple endocrine syndrome (MEN): in particular MEN1, which includes hyperparathyroidism, pituitary tumours and pancreatic neuroendocrine tumours, and MEN2A, characterized by hyperparathyroidism, medullary thyroid cancer and pheochromocytoma. In multiple endocrine syndrome with hyperparathyroidism the disease usually involves more than one parathyroid gland (parathyroid hyperplasia). It is worth noting that in the case of recurrent hyperparathyroidism a MEN syndrome must be suspected.

Secondary hyperparathyroidism Secondary hyperparathyroidism is consequent to a chronic hypocalcaemic condition that can be caused by renal failure, gastrointestinal malabsorption, dietary rickets and ingestion of drugs, like phenytoin, phenobarbital and laxative, which generate a decreased intestinal absorption of calcium. The continuous stimulus to produce and to secrete PTH results in parathyroid gland hyperplasia [1, 3]. Secondary hyperparathyroidism is a frequent and serious complication in haemodialysis patients. Because all parathyroid tissue is stimulated, the presence of unsuspected supernumerary glands has major impact in terms of surgical failure.

Tertiary hyperparathyroidism Tertiary hyperparathyroidism is a condition where parathyroid hyperplasia, secondary to chronic hypocalcaemia, becomes autonomous with development of hypercalcaemia. This condition generally does not regress after the correction of the underlying cause that generated chronic hypocalcaemia. Usually, in tertiary hyperparathyroidism, we find asymmetrical parathyroid gland hyperplasia [1, 3]. Tertiary hyperparathyroidism is also used to designate hyperparathyroidism that persists or develops after renal transplantation.

Complementary methods to parathyroid scintigraphy

Parathyroid glands can be imaged with multiple modalities, including scintigraphy, high-resolution (7.0–10.0 MHz) ultrasonography (US), thin-section CT and MRI [9]. US and parathyroid scintigraphy with methoxyisobutylisonitrile (sestamibi) [59] are the dominant imaging techniques used in the setting of PHPT. CT and MRI are generally useful additional imaging modalities in the case of ectopic mediastinal parathyroid adenomas since they provide detailed anatomical localization of ectopic mediastinal lesions for surgical planning. Evaluation of patients with combined modalities is gaining clinical importance. Correlative metabolic imaging with anatomical methods such as SPECT/CT and PET/CT and combined interpretation has a great impact on diagnosis in oncology. Combined interpretation of scintigraphy and US, or scintigraphy and CT, can improve the diagnostic interpretation of parathyroid scintigraphy and clinical decision making.

Ultrasonography

Although US is an advantageous modality as a non-radiation emitting, and widely available technique, it has some limitations mainly due to its highly operator-dependent nature and high subjectivity in interpretation being a real-time imaging modality. Parathyroid adenoma usually present on US as a homogeneous well-demarcated mass, hypoechoic in contrast to the hyperechoic thyroid tissue. Enlarged inferior parathyroid adenomas are usually found immediately adjacent to the inferior pole of the thyroid lobes. They could also be located in the thyrothymic ligament or in the upper cervical portion of the thymus. Enlarged superior parathyroid adenomas are usually found adjacent to the posterior aspect of the thyroid lobe and tend to migrate posteriorly and in a downward direction.

Several studies have shown a lower sensitivity and accuracy of US compared with scintigraphy for showing parathyroid neoplasms. However, when US is used together with scintigraphy findings, it can provide vital information for the diagnosis of parathyroid diseases [10–12]. The pitfalls of US in which it has lower success rates include intrathyroidal parathyroid lesions, deeply located lesions, ectopic and especially mediastinal parathyroid lesions, where it has no practical use [13]. US is often used in combination with other imaging procedures for the pre-operative localization of parathyroid adenomas, before unilateral neck exploration. In particular, combination of US with thyroid scintigraphy is useful to differentiate enlarged parathyroid glands from thyroid nodules, in geographic areas where the prevalence of nodular goitre is high. US-guided aspiration biopsy is also suggested for the differential diagnosis of intrathyroidal parathyroid adenoma from a thyroid nodule [14]. Combined interpretation of scintigraphy and US by the same physician can be superior to separate interpretation. Combined interpretation of morphological US imaging with scintigraphy in the same session is especially useful to confirm the presence of a scintigraphy-positive solitary parathyroid adenoma and exclusion of thyroid nodule.

SPECT/CT

Despite CT being a more successful imaging modality than US for retrotracheal, retro-oesophageal and mediastinal adenomas, its lesion detection sensitivity is very low for ectopic lesions located in the lower neck at the level of the shoulders and lesions close to or within the thyroid gland. To increase sensitivity and accuracy, digital fusion imaging of separate CT and SPECT devices could not provide the desired impact. After the development and marketing of SPECT/CT systems, combining a dual-head gamma camera with an integrated X-ray transmission system mounted on the same gantry, a new era began in diagnostic nuclear medicine. More recently, SPECT/CT systems combining state-of-the-art multidetector CT and state-of-the-art gamma cameras are being produced and guidelines for image acquisition, interpretation and reporting have been published [15]. Subsequently, studies exploring the role of SPECT/CT in parathyroid and other clinical applications were published. These studies are mainly investigating whether the information obtained by SPECT/CT is more accurate than SPECT or CT alone [16, 17]. Use of integrated SPECT/CT with a high spatial resolution, spiral CT used for anatomical localization, improves accuracy and reporter confidence in clinical practice [18]. Interestingly enough, these studies did not demonstrate a clear superiority or clinical impact of SPECT/CT over SPECT when the end-point is success of surgery [19]. On the other hand, for major ectopic lesions and distorted neck anatomy SPECT/CT is more informative by giving the exact anatomical localization of the lesion [20].

Parathyroid imaging agents: biodistribution and dosimetry

Introduction

Parathyroid imaging has involved a number of different radiotracers that were used in many different ways. The major imaging methods have used ^{201}Tl, ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin for parathyroid localization, ^{99m}Tc-pertechnetate and ^{123}I for thyroid scan, and in the parathyroid PET field ^{11}C-methionine or ^{18}F-fluorodeoxyglucose.

^{201}Thallous chloride was the first agent used to successfully image parathyroid glands in the 1980s [21]. Previous attempts to image with ^{75}Se-selenomethionine were not clinically reliable. ^{99m}Tc-sestamibi imaging was first described for parathyroid localization involving the subtraction technique using ^{123}I to outline the thyroid [22]. ^{123}I has the advantage of being a compound that is both trapped and organified by the thyroid and it is stable within the thyroid for a long period, thus providing images of good quality [23]. However, it is expensive and normally requires a delay of some hours between administration and imaging, with a lengthening of the entire procedure. The biodistribution of sestamibi within the thyroid and parathyroid was demonstrated by O'Doherty et al. [23]. This paper demonstrated that sestamibi was distributed into the thyroid and the parathyroid tissues like thallium. The uptake of sestamibi per gram of parathyroid tissue was lower than for thallium, but the ratio between the parathyroid and thyroid tissue was higher. The kinetics of sestamibi were also different in the two tissues such that the uptake of sestamibi remained constant (possibly due to mitochondrial binding or reduced PgP expression) whereas there was washout from the thyroid. This feature is the mainstay of the dual-phase technique (see dedicated section).

^{99m}Tc-tetrofosmin has also been investigated for imaging parathyroid tissue since it is a similar class of radiopharmaceutical as ^{99m}Tc-sestamibi. The kinetic data are different from those of sestamibi in that the uptake in the thyroid and parathyroid do not demonstrate differential washout [24].

Positron emission tomography (PET) tracers have met variable success. 18-fluoro-2-deoxy-D-glucose (FDG) has been found useful by some authors for the identification of parathyroid adenomas [25–27], although others have not had this success. ^{11}C-methionine seems promising although there is still limited experience. Nevertheless, it is useful when there are problems in identification of a parathyroid site with conventional scintigraphy [28–30].

Biodistribution and dosimetry

The biodistribution and dosimetry have been evaluated predominantly within the framework of studies where these radiotracers were used for other disease processes. Thallium, sestamibi and tetrofosmin are all cardiac imaging agents. In the neck they are taken up by salivary tissue as well as the thyroid and parathyroid glands. In the chest the heart is clearly visualized but the mediastinum should be clear of focal uptake with only a low-grade blood pool depending on the imaging time. For the PET tracers, FDG has low-grade uptake in the mediastinum as a result of blood pool and can have low-grade focal uptake in lymph nodes of benign cause. The uptake in the neck may be complicated by the normal variants that are seen, e.g. brown fat, benign thyroid uptake, uptake in the salivary glands, etc. Methionine has low-grade uptake in the thyroid and in salivary tissue; there also is low-grade uptake in the mediastinum, predominantly blood pool.

The dosimetry for each of the tracers is shown in Table 1. It should be noted that the effective dose estimates for women could be 20–30% higher than in men [31].

Parathyroid paediatric procedures are rare. Administered activity can be adapted with the help of the "EANM Paediatric Dosage Card" [32].

Double-tracer parathyroid scintigraphy "subtraction scanning"

Introduction

The peculiarity of double-tracer parathyroid scintigraphy derived from the fact that a specific tracer for parathyroid tissue does not exist. In fact, the tracers utilized in routine parathyroid nuclear medicine imaging, like ^{201}Tl-chloride, but above all ^{99m}Tc-sestamibi, and also ^{99m}Tc-tetrofosmin, are myocardial perfusion tracers and are taken up not only by the hyperfunctioning parathyroid glands but also by

Table 1 Dosimetry

Radiopharmaceutical	Effective dose (mSv/MBq)	Typical administered activity (MBq)	Effective dose (mSv)	Dosimetry reference
^{123}I-iodide (thyroid uptake 35%)	2.2×10^{-1}	10–20	2.2–4.4	ICRP 80
^{99m}Tc-pertechnetate	1.3×10^{-2}	75–150	1.0–2.0	ICRP 80
^{99m}Tc-sestamibi	9.0×10^{-3}	200–740	1.8–6.7	ICRP 80
^{99m}Tc-tetrofosmin	7.6×10^{-3}	200–740	1.5–5.6	ICRP 80
^{201}Tl-chloride	1.7×10^{-1}	80	13.6	Addendum 4 to ICRP 53
^{11}C-methionine	7.4×10^{-3}	400–800	3–5.9	Addendum 5 to ICRP 53
^{18}F-FDG	1.9×10^{-2}	400	7.6	ICRP 80

In the UK The Administration of Radioactive Substances Advisory Committee, ARSAC, have at the request of practioners increased the diagnostic reference level to 900 MBq for 99mTc-sestamibi.

thyroid tissue. Hence, the necessity of comparison with a second tracer, which is taken up by the thyroid gland only, such as ^{99m}Tc-pertechnetate ($^{99m}TcO_4^-$) or ^{123}I. The distributions of the two tracers can be visually compared and, afterwards, the thyroid scan can be digitally subtracted from the parathyroid scan to remove the thyroid activity and enhance the visualization of parathyroid tissue.

A double-tracer protocol involving sestamibi was first described by Coakley and colleagues, who used sequential acquisition of ^{99m}Tc-sestamibi and ^{123}I followed by image realignment and image subtraction [22, 23]. Prospective evaluation confirmed superiority of this method over the thallium-technetium subtraction scan [33], the first subtraction technique introduced by Ferlin and co-workers in the 1980s [21]. Lower sensitivity of ^{201}Tl, together with higher radiation dose compared to ^{99m}Tc-sestamibi, made its use for parathyroid scanning substantially obsolete.

^{99m}Tc-tetrofosmin is an alternative to sestamibi for parathyroid subtraction scanning. Absence of differential washout in the thyroid and parathyroid has not allowed its use as a single agent for double-phase study (see dedicated section in the text). However, because only early imaging is required with subtraction imaging, ^{99m}Tc-tetrofosmin can be an appropriate tracer [24].

There are two thyroid tracers that can be combined with sestamibi (and also with ^{99m}Tc-tetrofosmin even if the experience is smaller), either ^{123}I or ^{99m}Tc-pertechnetate. They can be used in many different ways [34]. As general rule, we can say that ^{123}I requires at least 2 h for adequate uptake by the thyroid and is more expensive than ^{99m}Tc-pertechnetate. The cost can be optimized if the nuclear medicine department has a routine use of ^{123}I for thyroid scans or if multiple parathyroid scans are done the same day (37 MBq ^{123}I cost approximately 125 euros in Europe and allow imaging for three patients). However, ^{123}I has a selective advantage: images of ^{99m}Tc-sestamibi and of ^{123}I can be recorded simultaneously [35, 36]. This is a substantial gain in gamma camera imaging time. Moreover, because both images are acquired simultaneously, there is no necessity for image realignment and there are no motion artefacts on the subtraction image.

Applications

Subtraction scanning has been applied successfully in many clinical situations in patients with hyperparathyroidism:

1. To detect recurrent or persistent disease both in PHPT and secondary hyperparathyroidism [37].
2. To improve results of initial surgery in PHPT [38]. There is still debate, however, regarding the routine use of localization studies in the case of conventional parathyroidectomy.
3. To select patients with PHPT for unilateral surgery or focused surgery, instead of the conventional bilateral neck exploration [39]. Many authors (but not all) have reported high sensitivity of subtraction imaging in detecting patients with multiple parathyroid gland disease (MGD) [39–42]. Depicting hyperplasia or double adenoma is essential to avoid directing the patient toward inappropriate focused surgery. Among recommendations to improve detection of MGD is to avoid over-subtraction. Progressive visually controlled subtraction should leave an activity in the thyroid area that is similar to the background of adjacent neck tissues. Over-subtraction that generates a "hole" in the thyroid area can easily delete (remove) a second focus of lesser activity than the main one [42]. The single-tracer sestamibi imaging technique is reported to have lower sensitivity in detecting MGD, whether it by planar, SPECT or SPECT/CT techniques [16, 19, 43, 44]. The sensitivity of ultrasound for MGD is also low [45].
4. The use of sestamibi scanning before initial surgery of secondary hyperparathyroidism is controversial. High sensitivity was reported by some teams using subtraction scanning [46–49].

Patient preparation

The investigation should be done in the absence of iodine saturation. Radiological studies with iodine-containing contrast media should be avoided during 4–6 weeks prior to the subtraction parathyroid imaging. When subtraction scintigraphy is to be performed in a patient on thyroid hormone replacement, this treatment should be withheld for 2-3 weeks before the investigation. Alternatively, one can use single-tracer sestamibi washout techniques. Treatment with methimazole or propylthiouracil should be stopped for 1 week. Vitamin D therapy might reduce sestamibi uptake, although this point has not been fully investigated.

When imaging secondary hyperparathyroidism, drugs used to refrain parathyroid hyperfunction should also be temporarily withheld. Active vitamin D therapy should be withheld for at least 1 week, and at least 4 weeks if supplementation with native vitamin D. Calcimimetics should be interrupted for at least 2 weeks before the parathyroid imaging.

Radiopharmaceuticals

The average activity of ^{99m}Tc-2-methoxyisobutylisonitrile (sestamibi) is 600 MBq (500–700 MBq) injected intravenously.

^{99m}Tc-1,2-bis [bis (2-ethoxyethyl) phosphino] ethane (tetrofosmin) can also be used in place of sestamibi, but only for subtraction imaging.

^{123}I (as sodium iodide) can be administered intravenously or orally. The average activity is 12 MBq (10–20 MBq).

The activity of ^{99m}Tc-pertechnetate that is used depends on the protocol: about 60-100 MBq are used if the protocol starts by thyroid imaging, and 150 MBq are given if thyroid imaging is done at the end of the procedure (after ^{99m}Tc-sestamibi imaging).

Procedure for simultaneous dual-tracer ^{99m}Tc-sestamibi and ^{123}I scanning (planar)

^{123}I is given. Two hours later, the patient is placed under the gamma camera and ^{99m}Tc-sestamibi is injected. Images are acquired simultaneously using appropriate windows without energy overlap. Symmetric windows with 10% total width are one option (140 keV±5% and 159 keV±5%). Hindié et al. used a 14% energy window centred over the 140-keV photopeak of ^{99m}Tc and an asymmetric window of 14% for ^{123}I (159 keV −4%; +10%). This procedure increases count rates, while keeping cross-talk between isotopes to less than 5%, which does not require correction [36].

Imaging can start 3–5 min after ^{99m}Tc-sestamibi injection with a broad field of view of the neck and mediastinum extending from the submandibular salivary glands to the upper part of the myocardium to ensure detection of ectopic glands [50]. Digital data are acquired in a 256×256 matrix using a low-energy, high-resolution, parallel hole collimator (5 min).

Then a magnified image of the thyroid/parathyroid bed area is obtained using a pinhole collimator (10–15 min). The pinhole increases count efficiency and allows better resolution [51]. It can thus differentiate between two adjacent parathyroid lesions.

Image processing An image analysis computer program is used to subtract a progressively increasing percentage of the ^{123}I image from the ^{99m}Tc-sestamibi image. Progressive subtraction is controlled visually and is considered optimal when residual ^{99m}Tc-sestamibi activity in the thyroid area becomes similar to that in the neighbouring neck tissues [42]. At this time, any focus (or foci) of increased ^{99m}Tc-sestamibi uptake is (are) suspicious of abnormal parathyroid gland(s). Delayed images (2 h post-injection) are not useful and do not add to the sensitivity of the subtraction protocol.

Additional views Additional image acquisition can be useful in the following situations:

When the anterior view images show a single focus suggesting an inferior parathyroid adenoma, an additional view is useful to determine whether this is a true inferior adenoma (close to the thyroid) or a superior parathyroid gland adenoma that has moved caudally and lies in the tracheo-oesophageal groove or even behind the oesophagus. This information can be obtained using either a lateral pinhole view with the detector tilted caudally to avoid the shoulder [42], or with an anterior oblique view or by SPECT acquisition [52].

When ectopic uptake is seen (mediastinal or submandibular), an additional SPECT acquisition is useful. It is also useful as we said above for deeply seated cervical para-oesophageal or retro-oesophageal locations [52]. Based on the location of the suspected focus, SPECT acquisition can be run as dual-isotope or as single-isotope (^{99m}Tc-sestamibi). Optimal anatomical information can be obtained with SPECT/CT [19].

Procedure for double-tracer ^{99m}Tc-pertechnetate and ^{99m}Tc-sestamibi with successive acquisition

A subtraction scan based on sequential image acquisition of these two tracers can be carried out in many different ways [41, 53, 54]:

1. $^{99m}TcO_4^-$/^{99m}Tc-sestamibi: the patient is injected i.v. with 185 MBq $^{99m}TcO_4^-$ and after 20 min the thyroid image is acquired. At the end, keeping the patient in the same position, 300 MBq of ^{99m}Tc-sestamibi are administrated i.v. and a 20-min dynamic acquisition is performed. This protocol has good sensitivity and specificity, but it has a drawback: high count rates from the thyroid gland do not allow, after the subtraction, identification of a small parathyroid hyperfunctioning gland located behind the thyroid [3, 55].
2. $^{99m}TcO_4^-$/^{99m}Tc-sestamibi modified by Geatti and coworkers [54]: they reduced the $^{99m}TcO_4^-$ activity and increased the ^{99m}Tc-sestamibi dose: 20 min after injection of 40–60 MBq of ^{99m}Tc-pertechnetate, a 10-min pinhole (or parallel hole collimator) image of the neck is obtained. Then, without moving the patient, 600 MBq of ^{99m}Tc-sestamibi are injected. Five minutes after injection, a pinhole image of the neck is recorded for 15 min (or a 20/35-min dynamic acquisition).
3. $^{99m}TcO_4^-$ + potassium perchlorate ($KClO_4^-$)/^{99m}Tc-sestamibi: this is a variant of the technique described above and it was suggested by Rubello and colleagues. This procedure consists in administering orally 400 mg potassium perchlorate immediately before starting acquisition of the thyroid scan, with the aim of inducing rapid $^{99m}TcO_4^-$ washout from the thyroid and reducing its interference on the ^{99m}Tc-sestamibi image [53]. In this protocol 150–200 MBq of $^{99m}TcO_4^-$ and 550–600 MBq of sestamibi are injected.

If imaging starts with a pinhole view over the thyroid, it is advised to leave a small safety margin above and below the visualized thyroid gland in order not to miss a parathyroid tumour slightly outside the thyroid bed area. A matrix size of 128×128 is adequate. A large field of view image with parallel hole collimator is always necessary to detect aberrant parathyroids and should include the submandibular salivary glands and the upper part of the myocardium. For this planar image is recommended a matrix size of 128×128 or 256×256 and a suitable zoom.

Image processing for all the previously methods described Computer subtraction of the pinhole (or parallel hole collimator) ^{99m}Tc-pertechnetate image from the pinhole (or parallel hole collimator) ^{99m}Tc-sestamibi image is performed. Realignment of images is sometimes needed to correct for patient motion between the two sets of images (an insert intravenous cannula is useful to avoid motion during sestamibi injection). Progressive incremental subtraction with real-time display is a good way to choose the optimal level of subtraction (following subtraction, residual activity in the thyroid area should not be lower than in surrounding neck tissues).

Interpretation criteria for subtraction scanning

The sets of images corresponding to each isotope are inspected visually and compared. Focal areas that persist following subtraction are suspicious of parathyroid tumours, as well as any focal uptake outside the usual area of physiological distribution of sestamibi.

In this new era of focused operations, the success of parathyroid surgery requires optimal interpretation of images. The thyroid scan can be very helpful in differentiating a thyroid nodule from a parathyroid tumour. Precise anatomical description is also important. With enlargement and increased density, superior parathyroid adenomas can become pendulous and descend posteriorly. A lateral view (or oblique view, or SPECT) should indicate whether the adenoma is close to the thyroid or deeper in the neck (tracheo-oesophageal groove or retro-oesophageal). This information is useful to the surgeon, because the visualization through the small incision is restricted. Moreover, the surgeon may choose a lateral approach to excise this gland instead of an anterior approach. For the same reason, and in particular distinguishing sestamibi-avid thyroid nodules from parathyroid adenoma positioned near to the thyroid tissue, an ultrasound may be also very useful (see the specific section in the text). To reach a high sensitivity in detecting MGD with subtraction techniques, the degree of subtraction should be monitored carefully. Over-subtraction can easily delete additional foci and provide a wrong image suggestive of a single adenoma.

Report

Besides information related to suspicious parathyroid tumours (number and location) and the presence or absence of thyroid abnormalities, the report should include the kind of radiopharmaceuticals used and their respective activity, the timing and the modality of image acquisition. Planar images must be labelled to show the type of projection and the region imaged. SPECT should include reconstruction images in the three axes.

Double-tracer subtraction scintigraphy SPECT

Favourable results with ^{99m}Tc-sestamibi planar and SPECT in PHPT have been reported by Rubello et al. especially regarding parathyroid adenomas located deep in the neck or in ectopic sites.

Simultaneous acquisition of ^{99m}Tc-sestamibi and ^{123}I should be possible using pinhole SPECT. However, at present, most modern cameras are not supplied with an approved algorithm for reconstruction of pinhole SPECT data.

Subtraction scintigraphy based on simultaneous acquisition of ^{99m}Tc-sestamibi and ^{123}I SPECT data using a parallel hole collimator has been reported successfully by Neumann and colleagues, but has not gained wide use in clinical practice [49]. Based on a recent report [56], dual-tracer ^{99m}Tc-sestamibi and ^{123}I subtraction SPECT has disappointingly low sensitivity (71%) and specificity (48%), despite the use of a large ^{99m}Tc-sestamibi activity (average 1,200 MBq). The use of SPECT/CT improved specificity, but unfortunately could not improve sensitivity [56]. The role of dual-tracer SPECT/CT should be investigated in recurrent hyperparathyroidism as it allows correlation with morphological information, but clearly, low sensitivity in the thyroid bed area compared to pinhole subtraction imaging precludes its routine use before first operation.

Dual-phase or washout parathyroid scintigraphy both with planar and SPECT acquisition

Introduction

Dual-phase parathyroid scintigraphy exploits the different washout timing that some radiotracers show in thyroid and parathyroid tissues: to find parathyroid hyperfunctioning tissue, washout timing of radiotracer from the parathyroid must be slower than from thyroid tissue.

This kind of parathyroid scintigraphy is a simplification of double-tracer scan and it was introduced for the first time by Taillefer and colleagues [43].

Applications

Dual-phase parathyroid scintigraphy is useful in patients with primary and secondary hyperparathyroidism who could benefit from parathyroid surgery [57]. It is used:

1. To localize hyperfunctioning parathyroid gland(s) before first surgery [44, 58]
2. To detect recurrent or persistent disease both in case of primary and secondary hyperparathyroidism

Patient preparation

No special preparation is necessary.

Radiopharmaceuticals

For dual-phase parathyroid scintigraphy ^{99m}Tc-sestamibi is the agent of choice, recommended dose is 600–900 MBq (16–24 mCi) injected intravenously. Sestamibi is taken up in both normal thyroid tissue and in hyperfunctioning parathyroid glands but washout from normal thyroid tissue is faster.

^{99m}Tc-tetrofosmin has a slower washout at the thyroid level [2, 24]; an effective differential washout does not exist [2]. Based on evidence in the literature, we can say that the use of tetrofosmin for dual-phase scintigraphy is not advised, and sestamibi is the tracer of choice. The case is different for double-tracer subtraction scintigraphy [24] where the two radiopharmaceuticals are interchangeable (see the double-tracer parathyroid scintigraphy section).

In some patients, especially in the case of nodular thyroid disease, after the dual-phase scan a thyroid scan with $^{99m}TcO_4^-$ may be helpful to differentiate between thyroid nodules and pathological parathyroid tissue; in fact, a thyroid nodule can take up sestamibi like hyperfunctioning parathyroid. This "hybrid technique" is recommended above all in endemic goitre areas. Before deciding to carry out the thyroid scan it is necessary to be sure that the patient is in absence of iodine saturation and is not receiving thyroid hormones, methimazole or propylthiouracil therapy.

It is worth noting that, anyhow, dual-phase scintigraphy with the subsequent association of thyroid scan is less sensitive and specific than double-tracer parathyroid scintigraphy.

Image acquisition

Various acquisition protocols have been reported to perform dual-phase parathyroid scintigraphy in order to improve the image quality and accuracy of the technique.

For this purpose, SPECT, SPECT/CT and pinhole SPECT have been used and have the ability to more precisely locate the sites of the hyperfunctioning parathyroid than simple planar imaging and allow the detection of smaller lesions.

Planar images Digital data should be acquired in a 128×128 or larger matrix using a low-energy, high-resolution, parallel hole collimator (pinhole or converging collimators such as cone beam may increase count efficiency). A single-head gamma camera can be used for planar images which must include anterior views of the neck and the upper thorax in all cases (oblique views are optional). The patient must be in the supine position with arms down. Early (10–15 min post-injection) and delayed (1.5–2.5 h post-injection) high count images (at least 600 s/per image) are obtained. Further delayed images (4 h post-injection) can be obtained if thyroid washout is poor.

SPECT SPECT imaging has been shown to offer increased sensitivity and provide a more precise localization of abnormal parathyroid glands with a better anatomical demarcation of ectopic lesions [60–62]. SPECT study should be acquired immediately following early planar acquisitions (to avoid false-negative results due to parathyroid adenomas with rapid washout) [61] with the patient in the same position, using a matrix of 128×128 for 120 projections every 3° (360° rotation) and with an imaging time of 15–25 s/per projection and suitable zoom factor.

SPECT/CT SPECT/CT provides fused images of functional and anatomical modalities which considerably improve the interpretation of findings of individual procedures [16, 17, 63]. This innovation might improve the relatively poor results obtained in the detection of multiglandular hyperplastic disease, but further data are needed to establish its role in the field.

Pinhole SPECT The use of a pinhole collimator instead of a parallel hole collimator improves the sensitivity of planar scintigraphy, especially for small or not very active parathyroid adenomas [64, 65]. Pinhole SPECT study should be acquired immediately following early planar acquisitions with the patient in the same position with 32 projections over 180° with a circular orbit. The acquisition time per step may be set to 40 s. The main characteristics of the pinhole collimator are a 3-mm aperture and an inner focal length of 205 mm. The pinhole collimator should be tilted to 15.7±5.8°, ensuring that the thyroid is always in the field of view.

No special processing for planar images is needed.

For SPECT processing transaxial tomograms are reconstructed by filtered back-projection using a low pass filter without attenuation correction. Attenuation correction can be useful when using SPECT/CT.

Considering pinhole SPECT, most modern cameras are not supplied with an approved algorithm for reconstruction of pinhole SPECT data.

Interpretation criteria

The two sets of planar images (early and delayed) are inspected visually. Focal areas of increased uptake, which show either a relative progressive increase over time or a fixed uptake which persisted on delayed imaging, must be considered pathological hyperfunctioning parathyroid glands.

SPECT or SPECT/CT images give information about the correct position of the hyperfunctioning gland, especially if deep in the neck or ectopic. The use of volume rendering of parathyroid SPECT images might be helpful for visualization. Cine view of projections can reveal a parathyroid lesion hidden by the thyroid gland or other structures.

Report

The report should include timing of acquisition of images. Planar images must be labelled to show the type of projection and the region imaged. SPECT should include reconstruction images in the three axes (coronal, sagittal and transaxial).

Radio-guided surgery of hyperparathyroidism

Introduction

Minimally invasive parathyroidectomy is a surgical technique to perform parathyroidectomy through a shorter incision (length less than 2–3 cm) which became popular after successful pre-operative imaging, particularly sestamibi scintigraphy and US [66]. The success of minimally invasive parathyroidectomy can be improved with the use of an intra-operative gamma probe which facilitates the surgical exploration and provides a line of sight for the surgeon.

Background and definitions

There have been significant changes in the management of PHPT in the last decade. Current widely accepted surgical methods for parathyroid surgery are bilateral neck exploration, unilateral neck exploration, limited dissection under local anaesthesia, endoscopic (video-assisted) parathyroidectomy and minimally invasive surgery [67]. Bilateral neck exploration, which was first described in 1925, has remained the standard surgical treatment method for many years [68]. Success with this approach, measured by return to normal calcium levels, depends primarily on the experience and judgment of the surgeon in recognizing the difference between enlarged and normal sized glands. Although bilateral neck exploration without prior imaging is accepted as a successful surgical approach in the NIH 1991 consensus report [69], failure rates exceeding 10% have also been reported [70]. Ectopic parathyroid tumours and unrecognized multiglandular parathyroid disease are major causes of surgical failure. Re-operation is always a more risky and technically difficult procedure due to fibrosis and deformed normal anatomy. Considering the low sensitivity of previously available diagnostic imaging modalities and the argument that in expert hands the cure rate of standard four gland parathyroid exploration parathyroidectomy is over 95%, the NIH consensus statement on the treatment of PHPT in 1990 stated that “pre-operative localization in patients without prior neck surgery was rarely indicated and not proven to be cost effective”. The approach to parathyroid surgery dramatically changed after the use of sestamibi for pre-operative imaging of PHPT. After the original report of Coakley, many investigators reported the successful localization of abnormal parathyroid glands in patients with PHPT [22, 71]. With the introduction of sestamibi parathyroid scintigraphy and the identification of parathyroid adenoma location, the time of focused exploration or minimally invasive parathyroidectomy began. Radio-guided minimally invasive surgery for hyperparathyroidism using a gamma probe facilitates the surgical exploration and several papers were published about its usefulness after the initial reports [72]. Alternative arguments have also been reported in the following years arguing that radio guidance was unnecessary [73, 74]. The cost-effectiveness of the image-guided minimally invasive approach and the expense of the imaging with the equipment required has been questioned. However, the potential savings from decreased operating time and hospital stay were found to be comparable and in favour of the minimally invasive approach in many analyses [75, 76]. A survey of the members of the International Association of Endocrine Surgeons indicated that minimally invasive parathyroidectomy based on sestamibi scintigraphy has been adopted by 59% of surgeons [77]. The most popular surgical technique (92%) is the focused approach with a small incision, followed by a video-assisted technique (22%) and a true endoscopic technique with gas insufflations (12%). Techniques used to ensure completeness of resection include intra-operative PTH measurements (68%) and gamma probe (14%).

Gamma detecting intra-operative probe

The gamma detecting intra-operative probe is a hand-held radiation detector device which gives both auditory signals and digital counts to guide the surgeon to dissect the radioactive target tissue. From a technical point of view, some aspects of the physical characteristics of the probes

used for the radio-guided parathyroidectomy need to be pointed out: (a) for the purpose of minimally invasive surgery it is obviously recommended to use the smallest sized probe, that is the 11 mm diameter; (b) other probes such as the 14–15 mm diameters can be useful in cases of only a mild uptake of sestamibi in parathyroid adenoma in which a higher sensitivity is advisable. As regards commercially available probes, scintillation probes seem to provide better sensitivity in comparison with the semiconductor probes, but the latter have higher spatial resolution. Despite these considerations, no significant differences between the two types of probes have been reported in clinical practice. Instead, a very important point for the purpose of a parathyroid radio-guided surgery is that a well "collimated" probe is mandatory, mainly because the background activity (i.e. thyroid gland) is significantly higher in parathyroid surgery in respect to other types of radio-guided surgery than in axillary sentinel node biopsy.

Indications Radio-guided minimally invasive parathyroidectomy is recommended in patients in whom sestamibi scintigraphy suggests a high probability of a solitary parathyroid adenoma with a significant uptake, no concomitant thyroid nodules showing sestamibi uptake, no history of familial hyperparathyroidism or MEN and no history of previous neck irradiation [4]. Radio-guided parathyroidectomy is also indicated in re-operation for persistent or recurrent hyperparathyroidism and ectopic adenomas. In patients with multinodular goitre dual-phase sestamibi scintigraphy combined with US examination or double-tracer subtraction protocols is recommended before planning the surgery to demonstrate sestamibi-avid thyroid nodules [78]. As the gamma probe is much more sensitive than a gamma camera, gamma probe-guided surgery may also be used in patients undergoing bilateral neck exploration with a negative pre-operative scintigraphy because it decreases operation time and gives more guarantee about the pathological parathyroid tissue removal [10].

Advantages Advantages of the gamma probe-guided surgery of hyperparathyroidism are:

1. An easier surgical approach and shorter operation time since the gamma probe guides the surgeon to the pathologic tissue
2. Verification of the correct excision of the pathological tissue and success of surgery since the gamma probe measures counts of the removed specimen ex vivo

Timing of surgery after sestamibi injection The success of radio-guided surgery is dependent on the differential kinetics of sestamibi in thyroid and parathyroid glands [79]. The gamma probe is most helpful when there is a significant difference between the thyroid and parathyroid count rates. This difference usually occurs within a window of 2–3 h after injection.

To optimize the parathyroid-thyroid count ratio, different protocols have been introduced. Norman and Chheda's protocol consists of dual-phase sestamibi scintigraphy on the day of surgery and gamma probe-guided surgery begins at the end of scintigraphy, about 2.5–3 h after the injection of radioactivity [80]. According to this protocol the standard activity of dual-phase scintigraphy that must be used is about 740 MBq (see the dedicated section).

Casara et al. performed gamma probe-guided surgery using a separate day protocol: sestamibi diagnostic imaging is performed some days before the surgery, preferably with double-tracer protocol. On the day of surgery, a smaller activity of sestamibi is injected in the operating room just before the operation, about 37 MBq [81]. This protocol reduces the radiation dose to the surgery team and allows localization of parathyroid tissue with rapid washout timing (less than 2.5–3 h). Moreover, if doubt remains about the correct localization of the hyperfunctioning gland(s) after the double-tracer scintigraphy, there is time to acquire SPECT (or SPECT/CT) imaging and to perform further exploration by neck ultrasound.

Bozkurt et al. performed a patient-specific optimal time to surgery method [10]. In their protocol, double-phase MIBI scintigraphy was performed on a separate day before surgery including a dynamic sestamibi acquisition to obtain a time-activity curve showing differential parathyroid to thyroid ratio to determine the optimum time to surgery. They reported a different optimal time to surgery for each patient with a mean time of 136±43 min.

Different protocols have their own advantages and disadvantages like scheduling of the operating room for the surgery and cooperation between nuclear medicine and surgery departments. A different day protocol is probably preferable in iodine-deficient geographic areas with a high prevalence of nodular goitre in order to better select the patient for gamma probe-guided surgery [82]. On the basis of a specific protocol adapted by the institute, gamma probe-guided surgery can be started 30 min to 3 h after injection.

Injected radioactivity As already mentioned, injected activity differs according to the protocol chosen. If a same day protocol including double-phase imaging followed by surgery is planned, 740 MBq are usually administrated. In a separate day protocol, in order to decrease the dose to the patient and surgical staff in the operating room, a lower dose of sestamibi (37 MBq) can be used with satisfactory results [82].

Several other groups use a modified separate day protocol in which a higher sestamibi activity (370 MBq) is injected to reach a higher target to background ratio. This procedure is useful to identify ectopic parathyroid adenomas [4].

Ex vivo radioactivity counting "20% rule" Measurement of the radioactivity in the excised tissue allows the physician to distinguish parathyroid adenoma from normal parathyroid tissue and other neck structures in order to make the appropriate operative decisions. This method which is also called the "20% rule" implicates that any excised tissue containing more than 20% of background radioactivity at the operative basin is a parathyroid adenoma and additional frozen section is not required [83]. According to Murphy et al., the hyperplastic glands will not accumulate more than 18% of background radioactivity whatever their size. However, other investigators reported that although the ex vivo count method clearly identifies hyperactive tissue from other neck tissues like lymph node, thymus or thyroid, larger parathyroid hyperplastic glands may behave like parathyroid adenoma in their total counts [84, 85]. Also, as stated earlier, the technique should not be used in patients with concomitant thyroid nodules because some nodules may show high sestamibi uptake.

High ex vivo radioactivity counts clearly represent that excised tissue is a pathological parathyroid tissue. However, as there is a direct correlation between the mass of the excised hyperactive parathyroid tissue and gamma probe counts, no definitive conclusions can be made to differentiate single gland disease from MGD (parathyroid hyperplasia or multiple adenomas). With its good ability to identify hyperactive parathyroid tissue (hyperplasia/adenoma) gamma probe-guided surgery can replace frozen section, but for the confirmation of complete parathyroid removal gamma probe-guided surgery should be used in association with intra-operative PTH measurements.

Gamma probe-guided operation technique

1. Minimally invasive approach: After the induction of the chosen anaesthesia (local/general), a gamma probe survey is done over the skin to locate the hot spot and make a mark over the skin (skin marking can also be done in the nuclear medicine department under the gamma camera by using a cobalt pen during scintigraphy). Then, a small incision (less then 2 cm) is done through this point and, after dissection of strap muscles, the underlying space is explored using the gamma probe. The gamma probe's auditory and digital signals guide the surgeon to find the hyperactive gland. An in vivo parathyroid to thyroid ratio greater than 1.5 and parathyroid to background ratio greater than 2.5–4.5 strongly suggest the presence of parathyroid adenoma. After the excision of the radioactive suspected tissue, ex vivo counts are obtained and the 20% rule is applied, with the limitations cited previously.
2. Bilateral cervical exploration: Radio-guided surgery is also useful when performing a standard bilateral approach. If bilateral cervical exploration is going to be performed, before skin incision counts over four quadrants in the neck as well as over the mediastinum are obtained with the gamma probe. A standard collar incision and a bilateral cervical exploration are performed. Suspected tissues with high in vivo gamma probe counts compared with background counts are excised and ex vivo counts are recorded. Exploration of the neck is terminated after a post-resection gamma probe survey of all four quadrants.

Radiation safety considerations

In order to decrease the radiation dose to operating room personnel, the lowest dose of sestamibi that is necessary to effectively remove the pathological parathyroid tissue should be given. Surgeons and operating room personnel are accepted as non-radiation workers and are allowed 1 mSv annual dose limit. Norman et al. calculated 0.05 mSv dose per patient to the surgeon for their above-mentioned single day protocol (injection of 740 MBq Sestamibi 2.5–3 h before surgery). They calculated that 20 patients/year are needed to reach the limit. Instead, with the 2-day protocol (injection of 37 MBq on the day of operation), the radiation exposure to the surgeon is less: 400 patients/year are needed to reach the limit [86]. The radiation dose rates from excised specimens are quite low and would not result in significant radiation exposure to pathology personnel [87].

Discussion and conclusion

Imaging is not for diagnosis. Calcium and PTH plasma levels establish the diagnosis of hyperparathyroidism. Imaging is a localization technique for abnormal parathyroid glands and does not identify normal parathyroid glands, which are too small (20–50 mg) to be seen.

Successful parathyroidectomy depends on the recognition and excision of all hyperfunctioning parathyroid glands.

Primary hyperparathyroidism Primary hyperparathyroidism is an endocrine disorder with high prevalence [88, 89], typically caused by a solitary parathyroid adenoma, less frequently (about 15%) by MGD and rarely (about 1%) by parathyroid carcinoma. Patients with MGD have either double adenomas or hyperplasia of three or all four parathyroid glands. Most cases of MGD are sporadic, while a small number are associated with hereditary disorders such as multiple endocrine neoplasia type 1 or type 2A, or familial hyperparathyroidism [90]. The two main reasons for failed surgery are ectopic glands and undetected MGD [91]. Conventional surgery has consisted in routine bilateral exploration with identification of all four parathyroid glands [92]. The current trend is toward minimally invasive focused surgery, whenever this strategy appears appropriate.

In this new era of minimally invasive surgery, the success of parathyroid surgery not only depends on an experienced surgeon but also on a sensitive and accurate imaging technique. When scintigraphy and US are concordant, the positive predictive value is very high. Recognizing MGD is important to avoid inappropriate one-gland surgery. Imaging should detect all abnormal parathyroid(s) and indicate their precise location (at what level of the thyroid is the parathyroid lesion seen on anterior view and whether it is proximal to the thyroid or deeper in the neck on the lateral or oblique view or SPECT). Reporting on thyroid nodules that may require concurrent surgical resection is useful. The use of imaging protocols with low overall detection sensitivity and inability to detect MGD may threaten all the efforts and progress made in minimally invasive parathyroid surgery [93]

Imaging is mandatory when re-operation is required. The two main reasons for failed surgery are ectopic glands (retro-oesophageal, mediastinal, intrathyroid, in the sheath of the carotid artery or undescended) and undetected MGD [91]. Repeat surgery is associated with a dramatic reduction in the success rate and an increase in surgical complications. In these patients it is necessary to have all information concerning the initial surgery, including the number and location of parathyroid glands that have been seen by the surgeon and the size and histology of resected glands. Whatever sestamibi scanning protocol is used, it is necessary to provide the surgeon with the best anatomical information using both anterior and lateral (or oblique) views of the neck, and SPECT whenever useful, especially so for a mediastinal focus. Sestamibi results should be confirmed with a second imaging technique (usually US for a neck focus, CT or MRI for a mediastinal image) before proceeding to re-operation [30]. The new SPECT/CT technique may prove very useful in this setting [16, 19]. ^{11}C-methionine, a PET tracer, may be useful before re-operation when sestamibi scan is negative [3].

Secondary hyperparathyroidism Secondary hyperparathyroidism is a common complication in patients with chronic renal failure on maintenance dialysis and is associated with significant morbidity and mortality [94]. Pre-operative imaging in secondary hyperparathyroidism has not gained wide acceptance. Early studies based on single-tracer sestamibi scanning have reported low sensitivity of about 40–50% in detecting hyperplastic glands. However, many authors have reported improved sensitivity with subtraction imaging [46–49].

What information can be obtained in secondary hyperparathyroidism?

1. A pre-operative map may detect ectopic gland(s), thus avoiding surgical failure or reducing the extent of dissection [48, 58].
2. Some individuals (about 10%) may have a supernumerary fifth gland [50]. When this information is provided by pre-operative imaging it may avoid surgical failure [48].
3. The use of the parathyroid gland that has the lowest sestamibi uptake intensity as remnant tissue may reduce the risk of recurrent disease [48, 58].

In secondary hyperparathyroidism, immediate failure after surgery and delayed recurrence are not unusual, occurring in 10–30% of patients. Imaging is mandatory before re-operation. Knowledge of all details concerning the initial intervention is necessary for interpretation. Specific views of the forearm should be obtained in patients who had a parathyroid graft. It is not unusual that imaging in these patients shows more than one focus of activity, one corresponding to recurrent disease on the subtotally resected gland (or on grafted tissue) and the other corresponding to an ectopic or fifth parathyroid that was missed at initial intervention.

Guidelines for each diagnostic modality are in constant and periodic upgrade and need to be adapted to each specific patient case. Current data suggest that nuclear medicine parathyroid imaging, possibly associated with conventional imaging methods (especially ultrasound for the neck and CT and MRI for the mediastinum), is an invaluable tool to decide the correct treatment. The functional information that can be obtained by nuclear medicine increases the diagnostic capability over conventional imaging.

After the clinical and biochemical diagnosis of hyperparathyroidism, double-tracer subtraction parathyroid scintigraphy is probably to be preferred to correctly localize the parathyroid hyperfunctioning gland(s). This protocol has better sensitivity for MGD than the others and is more likely to distinguish thyroid nodules that take up sestamibi from parathyroid tumour(s). Moreover, to have the thyroid scan enables the decision as to whether thyroid surgery may be required in addition to the parathyroid surgery on the same day. It is worth noting that it is always necessary to also obtain images of the mediastinum not to miss ectopic foci. SPECT images are strongly recommended to better define the position of an ectopic focus. Hybrid SPECT/CT instruments are most helpful in this regard. In the case of dual-phase scintigraphy, it is better to perform SPECT images after the early phase in order not to miss parathyroid hyperfunctioning gland(s) with rapid washout. Although SPECT and SPECT/CT imaging are becoming very helpful, they cannot replace the standard planar and “pinhole” protocols that are still essential for optimal resolution in the thyroid bed region and for a correct diagnosis.

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