Parathyroid Scintigraphy

A Technologist's Guide

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Foreword
Sylviane Prévot

Today the notion of competence is at the heart of professional development. Technologists' specific professional skills of working efficiently and knowledgeably are essential to ensure high-quality practice in nuclear medicine departments.

Since they were formed, the EANM Technologist Committee and Sub-committee on Education have devoted themselves to the improvement of nuclear medicine technologists' (NMTs) professional skills.

Publications that will assist in the setting of high standards for NMTs' work throughout Europe have been developed. A series of brochures, "technologists' guides", was planned in early 2004. The first of these was dedicated to myocardial perfusion imaging and the current volume, the second in the planned series, addresses parathyroid imaging.

Renowned authors with expertise in the field have been selected to provide an informative and truly comprehensive tool for technologists that will serve as a reference and improve the quality of daily practice.

I am grateful for the hard work of all the contributors, who have played a key role in ensuring the high scientific content and educational value of this booklet. Many thanks are due to Sue Huggett, who coordinated the project, to the members of the EANM Technologist Sub-committee on Education and particularly to Bristol-Myers Squibb Imaging for their confidence and generous sponsorship.

Efforts to image the parathyroid gland date back many years. I hope this brochure will be useful to technologists in the management of patients with hyperparathyroidism and will benefit these patients by optimising care and welfare.

Sylviane Prévot
Chair, EANM Technologist Committee

Introduction

Sue Huggett

The first publication of the EANM Technologist Committee sponsored by Bristol Myers Squibb in 2004 was a book on myocardial perfusion imaging for technologists. We are very grateful that they have sponsored us again this year to produce this book on parathyroid imaging, the second book in what we hope will be a series.

We hope that we have combined the theory and rationale of imaging with the practicalities of patient care and equipment use. I think that certain things I wrote for the last book bear repeating, and so I will do so here for the benefit of those for whom this is their first book.

Knowledge of imaging theory provides a deeper understanding of the techniques that is satisfying for the technologist and can form the basis for wise decision making. It also allows the technologist to communicate accurate information to patients, their carers and other staff. Patient care is always paramount, and being able to explain why certain foods must be avoided or why it is necessary to lie in awkward positions improves compliance as well as satisfaction.

Awareness of the rationales for using certain strategies is needed in order to know when and how various protocol variations should be applied, in acquisition or analysis, e.g. for the patient who cannot lie flat for long enough for subtraction and may need to be imaged with another protocol or when we may need a different filter if the total counts are low.

Protocols will vary between departments, even within the broader terms of the EANM Guidelines. This booklet is not meant to supplant these protocols but will hopefully supplement and explain the rationales behind them, thereby leading to more thoughtful working practices.

The authors are indebted to a number of sources for information, not least local protocols, and references have been given where original authors are identifiable. We apologise if we have inadvertently used material for which credit should have been, but was not, given.

We hope that this booklet will provide helpful information as and when it is needed so that the integration of theory and practice is enabled and encouraged.

Applications of parathyroid imaging

Elif Hindié

Primary hyperparathyroidism

Primary hyperparathyroidism (pHPT) is a surgically correctable disease with the third highest incidence of all endocrine disorders after diabetes mellitus and hyperthyroidism (Al Zahrani and Levine 1997). Through their secretion of parathyroid hormone (PTH), the two pairs of parathyroid glands, located in the neck posterior to the thyroid gland, regulate serum calcium concentration and bone metabolism. PTH promotes the release of calcium from bone, increases absorption of calcium from the intestine and increases reabsorption of calcium in the renal tubules. In turn, the serum calcium concentration regulates PTH secretion, a mechanism mediated via a calcium-sensing receptor on the surface of the parathyroid cells. pHPT is caused by the secretion of excessive amounts of PTH by one or more enlarged diseased parathyroid gland(s). Patients with pHPT may suffer from renal stones, osteoporosis, gastro-intestinal symptoms, cardiovascular disease, muscle weakness and fatigue, and neuropsychological disorders. The highest prevalence of the disease is found in post-menopausal women. A prevalence of 2% was found by screening post-menopausal women (Lundgren).

In the past, pHPT was characterised by severe skeletal and renal complications and apparent mortality. This may still be the case in some developing countries. The introduction of calcium auto-analysers in the early 1970s led to changes in the incidence of pHPT and deeply modified the clinical spectrum of the disease at diagnosis (Heath et al. 1980). Most new cases are now biologically mild without overt symptoms (Al Zahrani and Levine 1997). Parathyroidectomy is the only curative treatment for pHPT. In the recent guidelines of the US National Institute of Health (NIH), surgery is recommended for all young individuals and for all patients with overt symptoms (Bilezikian et al. 2002). For patients who are asymptomatic and are 50 years old or older, surgery is recommended if any of the following signs are present: serum calcium greater than 10 mg/l above the upper limits of normal; 24-h total urine calcium excretion of more than 400 mg; reduction in creatinine clearance by more than 30% compared with age-matched persons; bone density more than 2.5 SDs below peak bone mass: T score < -2.5. Surgery is also recommended when medical surveillance is either not desirable or not possible. After complete baseline evaluation, patients who are not operated on need to be monitored twice yearly for serum calcium concentration and yearly for creatinine concentration; it is also recommended that bone mass measurements are obtained on a yearly basis (Bilezikian et al. 2002). Some authors recommend parathyroidectomy for all patients with a secure diagnosis of pHPT (Utiger 1999).

Successful parathyroidectomy depends on recognition and excision of all hyperfunctioning parathyroid glands. pHPT is typically caused by a solitary parathyroid adenoma, less

frequently (about 15% of cases) by multiple parathyroid gland disease (MGD) and rarely (about 1% of cases) 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 (Marx et al. 2002). Conventional surgery consists in routine bilateral exploration with identification of all four parathyroid glands.

Imaging is mandatory before reoperation

For several decades, preoperative imaging was not used before first-time surgery. Unguided bilateral exploration, dissecting all potential sites in the neck, achieved cure in 90–95% of patients (Russell and Edis 1982). 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 (Levin and Clark 1989). Repeat surgery is associated with a dramatic reduction in the success rate and an increase in surgical complications. Imaging is therefore mandatory before reoperation (Sosa et al. 1998). ^{99m}Tc-sestamibi scanning (Coakley et al. 1989) has been established as the imaging method of choice in reoperation of persistent or recurrent hyperparathyroidism (Weber et al. 1993). In these patients it is necessary to have all information concerning the first intervention, including the number and location of

parathyroid glands that have been seen by the surgeon and the size and histology of resected glands. Whichever ^{99m}Tc-sestamibi scanning protocol is used, it is necessary to provide the surgeon with the best anatomical information by using both anterior and lateral (or oblique) views of the neck, and SPECT whenever useful, especially for a mediastinal focus. It is the author's opinion that ^{99m}Tc-sestamibi results should be confirmed with a second imaging technique (usually ultrasound for a neck focus and CT or MRI for a mediastinal image) before proceeding to reoperation.

Scanning with ^{99m}Tc-sestamibi is increasingly ordered on a routine basis for first-time parathyroidectomy

The first exploration is the best time to cure hyperparathyroidism. Most surgeons would now appreciate having information concerning whereabouts in the neck to start dissection and the possibility of ectopic parathyroid glands (Sosa et al. 1998; Liu et al. 2005). When the rare cases (2-5%) of ectopic parathyroid tumours are recognised preoperatively, the success of bilateral surgery can now reach very close to 100% (Hindié et al. 1997). In the case of a mediastinal gland, the surgeon can proceed directly with first-intention thoracoscopy, avoiding unnecessary initial extensive neck surgery in the search for the elusive gland (Liu et al. 2005). Preoperative imaging would also shorten the duration of bilateral surgery (Hindié et al. 1997). By allowing the surgeon to find the offending gland earlier in

the operation, the time necessary for frozen section examination can be used by the surgeon for inspection of the other parathyroid glands, also reducing surgeon anxiety.

Important points to know when proceeding with parathyroid imaging

- Imaging is not for diagnosis. The increase in plasma levels of calcium (normal value 88–105 mg/l) and PTH (normal value 10–58 ng/l) establishes the diagnosis.

- Imaging does not identify normal parathyroid glands, which are too small (20–50 mg) to be seen.

- Imaging should detect abnormal parathyroid(s) and indicate the approximate size and the precise relationship to the thyroid (the level of the thyroid at which the parathyroid lesion is seen on the anterior view; and whether it is proximal to the thyroid or deeper in the neck on the lateral or oblique view or SPECT) (Fig. 1).

- Imaging should identify ectopic glands (add SPECT in cases of a mediastinal focus, and ask for additional CT or MRI for confirmation and anatomical landmarks) (Fig. 2).

- Imaging should be able to differentiate patients with a single adenoma from those with MGD (Fig. 3).

- Imaging should identify thyroid nodules

that may require concurrent surgical resection.

The choice of imaging technique

The most common preoperative localisation methods are radionuclide scintigraphy and ultrasound. As stated before, the two main reasons for failed surgery are ectopic glands and undetected MGD (Levin and Clark 1989). Because high-resolution ultrasound would, even in skilled hands, fail to detect the majority of these cases, it is not optimal for preoperative imaging as a single technique. In the study by Haber et al. (2002), ultrasound missed six of eight ectopic glands and five of six cases of MGD. Ultrasound may, however, be useful in combination with ^{99m}Tc-sestamibi imaging (Rubello et al. 2003).

[99m]Tc-sestamibi scanning is now considered the most sensitive imaging technique in patients with pHPT (Giordano et al. 2001; Mullan 2004). Whatever the protocol used, ^{99m}Tc-sestamibi scanning will usually meet the requirement of detecting ectopic glands (all eight were detected in the study by Haber et al.). With regard to the recognition of MGD, however, the protocol in use will determine the sensitivity. When ^{99m}Tc-sestamibi is used as a single tracer with planar imaging at two time points -- the "dual-phase" (or washout) method – the sensitivity for primary hyperplasia is very low (Taillefer et al. 1992; Martin et al. 1996). Better results can be obtained by adding SPECT. Subtraction scanning, using either [123]I (Borley

et al. 1996; Hindié et al. 2000; Mullan 2004) or ^{99m}Tc-pertechnetate (Rubello et al. 2003) in addition to ^{99m}Tc-sestamibi, improves the sensitivity for hyperplastic glands. One difficulty with subtraction imaging is keeping the patient still for the time necessary to scan the thyroid, to inject ^{99m}Tc-sestamibi and to record images of this second tracer. Simultaneous recording of ^{123}I and ^{99m}Tc-sestamibi can be a simple answer to these difficulties. It prevents artefacts on subtraction images due to patient motion, and shortens the imaging time (Hindié et al. 1998; Mullan 2004).

Preoperative imaging has opened a new era of minimally invasive parathyroid surgery

Conventional bilateral exploration is still considered the gold standard in parathyroid surgery. However, the introduction of ^{99m}Tc-sestamibi scanning, the availability of intraoperative adjuncts such as the gamma probe and intraoperative monitoring of PTH to help detect MGD have challenged the dogma of routine bilateral exploration. When preoperative imaging points to a single well-defined focus, unequivocally suggesting a "solitary adenoma", the surgeon may now choose focussed surgery instead of bilateral exploration. Focussed excision can be made by open surgery through a mini-incision, possibly under local anaesthesia, or by video-assisted endoscopic surgery under general anaesthesia (Lee and Inabnet 2005). Compared with patients who undergo bilateral surgery, those in whom focussed parathyroid surgery is successfully

completed enjoy a shorter operation time, the possibility of local anaesthesia, a better cosmetic scar, a less painful postoperative course, less profound postoperative "transient" hypocalcaemia and an earlier return to normal activities. The fact that many clinicians now use a lower threshold for surgery is partly due to the perception that parathyroid surgery is easier than in the past (Utiger 1999).

Patients at specific risk of failure of minimal surgery are those with unrecognised MGD. Therefore, when choosing minimal surgery, the surgeon is committed to distinguishing cases of MGD either preoperatively, through an appropriate imaging protocol, or by intraoperative monitoring of PTH plasma levels, or by a combination of both. The true sensitivity of intraoperative PTH for MGD is still under debate. What raises concern is that studies relying solely on intraoperative measurements report a low percentage of MGD, only 3% (Molinari et al. 1996), which is three to four times lower than is generally observed during routine bilateral surgery. Whether this will lead to higher rates of late recurrence is not known. It is thus important that imaging methods used to select patients for focussed surgery have a high sensitivity for detecting MGD.

In this new era of focussed operations, the success of parathyroid surgery depends not only on an experienced surgeon but also on excellent interpretation of images. A localisation study with high accuracy is mandatory to

avoid conversion of the surgery to a bilateral exploration under general anaesthesia after minimal surgery has been started. It is important to avoid confusion with a thyroid nodule, and precise anatomical description is also important. With enlargement and increased density, superior parathyroid adenomas can become pendulous and descend posteriorly. A lateral view (or an 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, because visualisation through the small incision is restricted. Moreover, the surgeon may choose a lateral approach to excise this gland instead of an anterior approach. To achieve a high sensitivity in detecting MGD with subtraction techniques, the degree of subtraction should be monitored carefully. Progressive incremental subtraction with real-time display is a good way to choose the optimal level of subtraction (residual ^{99m}Tc-sestamibi activity in the thyroid area should not be lower than in surrounding neck tissues). Oversubtraction could easily delete additional foci of activity and in some patients provide a false image suggestive of a single adenoma.

Secondary hyperparathyroidism

Secondary hyperparathyroidism is a common complication in patients with chronic renal failure. Hypocalcaemia, accumulation of phosphate and a decrease in the active form of vitamin D lead to increased secretion of PTH. With chronic stimulation, hyperplasia of parathyroid glands accelerates and may develop into autonomous adenomas. The extent of parathyroid growth then becomes a major determinant of PTH hypersecretion. Secondary hyperparathyroidism leads to renal bone disease, the development of soft tissue calcifications, vascular calcifications and increased cardiovascular risk, among other complications. When medical therapy fails, surgery becomes necessary. Surgery can be either subtotal parathyroidectomy, with resection of three glands and partial resection of the fourth gland, or total resection with grafting of some parathyroid tissue into the soft tissues of the forearm in order to avoid permanent hypoparathyroidism.

Preoperative imaging

Surgery of secondary hyperparathyroidism requires routine bilateral identification of all parathyroid tissue. Moreover, early studies based on single-tracer ^{99m}Tc-sestamibi scanning have reported a very low sensitivity of about 40–50% in detecting hyperplastic glands. Inefficiency of single-tracer techniques both in secondary hyperparathyroidism and in primary hyperplasia is possibly due to more rapid washout of tracer from hyperplastic glands than from parathyroid adenomas. For those reasons, preoperative imaging has not yet gained wide acceptance among surgeons. Dual-tracer subtraction imaging, planar or SPECT, provides substantial improvement in the rate of detection of hyperplastic glands in

patients with renal failure (Hindié et al. 1999; Perié et al. 2005)

What information can be obtained?

- The preoperative map may facilitate recognition of the position of aberrant parathyroid glands, also reducing the extent of dissection (Hindié et al. 1999).

- Parathyroid glands with major ectopia would be missed without preoperative imaging.

- Although the usual number of parathyroid glands is four, some individuals (about 10%) have a supernumerary fifth gland (Akerström et al. 1984). When this information is provided by preoperative imaging, it may prevent surgical failure or late recurrence (Hindié et al. 1999).

Imaging findings in patients with persistent or recurrent secondary hyperparathyroidism

Immediate failure and delayed recurrence are not unusual, occurring in 10–30% of patients. Imaging is mandatory before reoperation. Knowledge of all details concerning the initial intervention is necessary for interpretation. As with primary hyperparathyroidism, we recommend that lesions seen on the ^{99m}Tc-sestamibi scan be matched with a second radiological technique (ultrasound or MRI) for confirmation and identification of anatomical landmarks before reoperation.

Some aspects specific to patients reoperated for secondary hyperparathyroidism need to be emphasised:

- Specific views of the forearm should be obtained in patients who have had a parathyroid graft.

- It is not unusual for imaging in these patients to show two foci of activity, one corresponding to recurrent disease at the subtotally resected gland (or grafted tissue) and the other corresponding to an ectopic or fifth parathyroid, missed at initial intervention (unpublished data).

Figure 1

Parathyroid subtraction scintigraphy, with simultaneous acquisition of ^{99m}Tc-sestamibi and ^{123}I in a patient with primary hyperparathyroidism. The anterior view and the lateral view show a solitary adenoma located at the lower right pole of the thyroid. At surgery, an adenoma of 1.9 g was found at the predicted site.
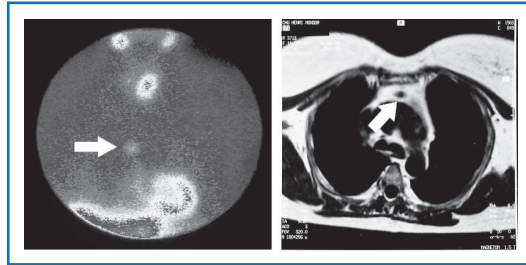
Figure 2

This patient with a previous history of thyroid surgery (right lobectomy) was referred with a recent diagnosis of primary hyperparathyroidism. Ultrasound examination suggested the presence of a parathyroid adenoma at the side of previous thyroid lobectomy, which was a false-positive image. The large field of view ^{99m}Tc-sestamibi acquisition shows a mediastinal focus (arrow). The suspected ectopic parathyroid was confirmed by MRI (arrow). A mediastinal parathyroid adenoma of 0.59 g was resected.

Figure 3

Parathyroid ^{99m}Tc-sestamibi/^{123}I subtraction scintigraphy in a patient with primary hyperpara-thyroidism. The computed subtraction images show two sites of preferential ^{99m}Tc-sestamibi uptake: one at the lower third of the left thyroid lobe and the second lateral to the lower pole of the right thyroid lobe. Two adenomas were excised: a left parathyroid adenoma weighing 2.3 g and a right adenoma weighing 0.07 g.

Radiopharmaceuticals

Linda Tutty

Radiopharmaceuticals used for parathyroid scintigraphy

Details of the photo peak energy, half-life, effective dose and standard dose for radiopharmaceuticals commonly used for parathyroid scintigraphy are shown in Table 1.

[201]Tl-chloride

[201]Tl-chloride has a physical half-life of 73.1 h. Its main photo peak is due to characteristic x-rays of mercury, which have an energy range of 69–83 keV. In addition, gamma rays are produced at 167 keV (8%) and 135 keV (2%). The administered activity is 80 MBq and it is given intravenously. ^{201}Tl-chloride is taken up by abnormal parathyroid tissue and thyroid tissue in proportion to blood flow.

[99m]Tc-pertechnetate

[99m]Tc-pertechnetate has a half-life of 6 h and a gamma energy of 140 keV. ^{99m}Tc-pertechnetate is used to delineate the thyroid gland because functioning thyroid parenchyma traps it. This image is then subtracted from the ^{201}Tl or ^{99m}Tc-sestamibi images, and what remains is potentially a parathyroid adenoma. When utilising ^{201}Tl, the administered activity is usually 75–150 MBq, depending on the administered radioactivity of ^{201}Tl and which of the two radiopharmaceuticals is administered first. If using ^{99m}Tc-sestamibi, the amount of pertechnetate administered is usually 185–370 MBq, because ^{99m}Tc-sestamibi has a higher total activity in the thyroid tissue than [201]Tl.

[99m]Tc-sestamibi

The range of intravenously administered radio-activity is 185-900 MBq; the typical dose is 740 MBq. This radiotracer localises in both parathyroid gland and functioning thyroid tissue, and usually washes out of normal thyroid tissue more rapidly than out of abnormal parathyroid tissue. The exact mechanism of uptake remains unknown (Farley 2004). ^{99m}Tc-sestamibi uptake depends on numerous factors, including perfusion, cell cycle phase and functional activity (Beggs and Hain 2005). The final cellular localisation of ^{99m}Tc-sestamibi is within the mitochondria. It accumulates in the mitochondria of many tissues but particularly in normal cardiac and thyroid cells; it is especially prominent in overactive parathyroid glands and is held there preferentially (Farley 2004).

[123]I-sodium iodide

[123]I has a half-life of 13 h and emits a photon with an energy of 159 keV. It has been used particularly with ^{99m}Tc-sestamibi as a thyroid-imaging agent in subtraction studies. The administered dose, given orally, ranges from 7.5 to 20 MBq.

[99m]Tc-tetrofosmin

[99m]Tc-tetrofosmin use in parathyroid imaging is described in the literature (Smith and Oates 2004). Its manufacturers do not license it for use as a parathyroid scintigraphy agent. ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin have similar imaging characteristics (Smith and Oates 2004). The typical dose of administered activity is 740 MBq.

[11]C-methionine

[11]C-methionine has a half-life of 20 min. It is

cyclotron produced. Its uptake reflects amino acid reflux into stimulated parathyroid tissue (Otto et al. 2004; Beggs and Hain 2005). Uptake in inflammatory conditions may pose a problem and should be considered when interpreting images. The typical radioactivity dose ranges between 240 and 820 MBq, with an average intravenous dose of 400 MBq.

^{18}F-FDG

^{18}F-FDG has a half-life of 110 min and is cyclotron produced. ^{18}F-FDG allows glucose metabolism to be assessed and evaluated using PET. There is differential concentration of FDG in abnormal parathyroid tissue and this difference is used to demonstrate the abnormal gland. FDG also accumulates in other malignant and benign tissues, and in inflamed or infected tissue; this potentially limits its usefulness. The typical intravenous dose is 400 MBq.

Radiopharmaceutical features

Multiple radiopharmaceuticals have been described for the detection of parathyroid lesions. Thallium, sestamibi and tetrofosmin are the three most commonly used (Ahuja et al. 2004). All these agents were originally developed for cardiac scanning. In the 1980s, ^{201}Tl was the most commonly used agent, but it has a longer half-life and delivers a higher radiation dose to the patient (Kettle 2002). Consequently, ^{201}Tl is no longer commonly used, and most recent literature refers to the use of ^{99m}Tc-sestamibi. However, for the subtraction

method it is probable that each radiopharmaceutical would provide the same diagnostic information (Kettle 2002).

Subtraction agents

Thyroid-specific imaging with ^{123}I or ^{99m}Tc-pertechnetate may be employed using a subtraction method to differentiate parathyroid from thyroid activity (Clark 2005).

The two main agents used for imaging the thyroid are [123]I (sodium iodide) and ^{99m}Tc-pertechnetate. There is a slight preference for the use of ^{123}I, as it is organified and therefore provides a stable image. The pertechnetate washes out from the thyroid gland with time, and if there is some delay in imaging there may be a reduction in the quality of the thyroid image (Kettle 2002). However, both agents may be affected if the patient is taking thyroxine or anti-thyroid medications or has recently received iodine contrast agents.

Thyroid-specific radiopharmaceuticals may aid delineation of the thyroid parenchyma if required after dual-phase imaging. This may be helpful as a second-line "visual subtraction" procedure when no parathyroid adenoma is visible on dual-phase parathyroid imaging (Clark 2005).

Activities given for imaging the thyroid and parathyroid glands are as follows: [99m]Tc pertechnetate, 80 MBq; ^{123}I, 40 MBq; ^{201}Tl, 80 MBq; ^{99m}Tc-sestamibi, 900 MBq. If a [99m]Tc-

pertechnetate/^{99m}Tc-sestamibi combination is used then the radiation dose for the combined study is 11.6 mSv. If ^{123}I and ^{201}Tl are used, this rises to 18.3 mSv.

Dual-phase agents

[99m]Tc-sestamibi and ^{99m}Tc-tetrofosmin are commonly used agents for dual-phase parathyroid scintigraphy. The washout technique relies on the fact that while ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin are taken up by both the thyroid gland and the parathyroid at a similar rate, there is a faster rate of washout from the thyroid gland.

These tracers localise in the thyroid gland as well as in parathyroid adenomas. This makes correlation of the adenoma in relation to the thyroid gland possible on planar as well as early SPECT imaging. ^{99m}Tc-sestamibi is released from the thyroid with a half-life of about 30 min but is usually retained by abnormal parathyroid glands (Smith and Oates 2004). ^{99m}Tc-tetrofosmin may clear more slowly from the thyroid gland. This differential washout improves the target-to-background ratio so that abnormal parathyroid tissue should be more visible on delayed images (Smith and Oates 2004; Clark 2005). However, thyroid adenomas and carcinomas can coexist and may retain ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin, resulting in false positive results (Smith and Oates 2004).

[99m]Tc-sestamibi and ^{99m}Tc-tetrofosmin have comparable imaging characteristics. Usually, the choice of imaging agent depends on its availability and the experience of the nuclear medicine radiologist.

The dual-phase subtraction method with adjunctive thyroid-selective imaging (^{99m}Tc or ^{123}I) may be helpful, or even essential, in patients with goitres or other confounding underlying thyroid disease, after thyroid surgery or in those patients with a palpable mass (Smith and Oates 2004).

PET imaging agents

Use of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) and [11]C- methionine PET for parathyroid imaging has been described (Otto et al. 2004; Beggs and Hain 2005). Initial studies with PET have shown conflicting results when using FDG as a tracer to image the parathyroid glands (Beggs and Hain 2005; Otto et al. 2004). It has been shown that ^{11}C-methionine PET holds more promise than FDG PET imaging of the parathyroid localisation (Beggs and Hain 2005). ^{11}C-methionine PET scanning is of value in cases of primary hyperparathyroidism in which conventional imaging techniques have failed to localise the adenoma before proceeding to surgery, or in patients in whom surgery has been performed but has failed to correct the hyperparathyroidism (Beggs and Hain 2005).

Adverse reactions to radiopharmaceuticals

Table 2 shows side-effects and reactions to radiopharmaceuticals used for parathyroid scintigraphy.

Table 1

Radiopharmaceuticals used for parathyroid scintigraphy

	^{201}Tl-chloride	^{99m}Tc sestamibi	^{99m}Tc tetrofosmin	^{11}C methionine	^{18}F fluorodeoxy-glucose
Photo peak energy (keV)	69-80 (98% abundance) 135 (2%) 167 (8%)	140	140	511	511
Half-life	73.1 hours Cyclotron product to be ordered ready for use	6 hours Always available (24-month shelf life at room temperature)	6 hours Always available (6-month shelf life at 2-8°C	20 min Cyclotron produced	110 min Cyclotron produced
Effective dose adult (mSv)	18	11	9	2	10
Standard dose*(MBq)	80	900	900	400	400

*Allowable upper limits of radiotracers may differ from country to country. Please refer to the Summary of Product Characteristics in each European country. Doses given here are quoted from ARSC, December 1998.

Table 2

Adverse reactions to radiopharmaceuticals used for parathyroid scintigraphy (as printed in J Nucl Med 1996;37:185–192, 1064–1067)

Radiopharmaceutical	Side-effects, reactions
^{201}Tl-chloride	Fever, erythema, flushing, diffuse rash, pruritis, hypotension
^{99m}Tc-pertechnetate	Chills, nausea, vomiting, diffuse rash, pruritis, hives/urticaria, chest pain, tightness or heaviness, hypertension, dizziness, vertigo, headache, diaphoresis, anaphylaxis
^{99m}Tc-sestamibi	Nausea, erythema, flushing, diffuse rash, pruritis, seizures, headache, metallic taste, tingling
^{123}I-Sodium iodide	Nausea, vomiting, diffuse rash, pruritus, hives/urticaria, chest pain, tightness or heaviness, respiratory reaction, tachycardia, syncope or faintness and headache, tachypnea, parosmia
^{99m}Tc-tetrofosmin	Angina, hypertension, torsades de pointes (these three probably occurred because of underlying heart disease); vomiting, abdominal discomfort, cutaneous allergy, hypotension, dyspnoea, metallic taste, burning of mouth, unusual odour, mild leucocytosis
^{18}F-FDG	None

Imaging equipment – preparation and use

José Pires Jorge and Regis Lecoultre

Quality control procedures that must be satisfactorily performed before imaging

After acceptance testing, a QC protocol must be set up in each department and followed in accordance with national guidelines. The following routine quality control test schedule is typical:

a) Daily energy peaking

b) Daily flood uniformity tests

c) Daily gamma camera sensitivity measurement

d) Weekly linearity and resolution assessment

e) Weekly centre-of-rotation calibration

A routine quality control programme for a SPECT gamma camera includes quality control procedures appropriate to planar scintillation cameras (a–d) and specific SPECT quality controls (e). Further, more complex tests should be undertaken on a less frequent basis.

Energy peaking

This quality control procedure consists in "peaking" the gamma camera for relevant energies prior to obtaining flood images. It is mandatory that the energy peaking is undertaken on a daily basis and for each radionuclide used.

Checking the peaking is needed to ascertain that:

- The camera automatic peaking circuitry is working properly

- The shape of the spectrum is correct

- The energy peak appears at the correct energy

- There is no accidental contamination of the gamma camera

It is recommended that the spectra obtained during peaking tests are recorded.

Daily flood uniformity tests

After a successful peaking test it is recommended that a uniformity test is performed on a daily basis. Flood fields are acquired and evaluation of camera uniformity can be made on a visual assessment. Quantitative parameters should also be computed regularly and recorded in order both to demonstrate sudden variations from normal and to alert the technologist to progressive deterioration in the equipment. On cameras that have interchangeable uniformity correction maps, it is vital that one is used that is *for the correct nuclide*, accurate and up to date.

Daily gamma camera sensitivity measurement

A practical means of measuring sensitivity is

by recording the time needed to acquire the flood field using the known activity. It should not vary by more than a few percent from one day to another.

Weekly linearity and resolution assessment

Linearity and resolution should be assessed weekly. This may be done using transmission phantoms.

Centre of rotation calibration

The centre of rotation measurement determines the offset between the axis of rotation of the camera and the centre of the matrix used for reconstruction, as these do not correspond automatically.

The calibration of the centre of rotation is made from the reconstruction of a tomographic acquisition of a point source placed slightly offset from the mechanical centre of rotation of the camera. A sinogram is formed from the projections and is used to fit the maximum count locations to a sine wave. Deviations between the actual and fitted curves should not exceed 0.5 pixels.

Collimator

The choice of a collimator for a given study is mainly determined by the tracer activity. This will influence the statistical noise content of the projection images and the spatial resolution. The number of counts needs to be maximised, possibly at the expense of some resolution and taking into account that in parathyroid imaging the difference in tracer activity between $^{99m}TcO_4$ (thyroid only) and any ^{99m}Tc-labelled agent (thyroid and parathyroid) must be significant.

Collimators vary with respect to the relative length and width of the holes. The longer the hole length, the better the spatial resolution obtained, but at the expense of a lower count sensitivity. Conversely, a larger hole gives a better count sensitivity but with a loss of spatial resolution.

When using ^{201}Tl, the available counts are greatly reduced owing to the long half-life of the isotope and the consequent limited dose; so traditionally a low-energy general-purpose collimator is recommended. With ^{99m}Tc-pertechnetate and ^{99m}Tc-labelled agents, count rate is no longer a major limitation, and furthermore, the resolution of a high-resolution collimator decreases less with distance from the source than does that of a general-purpose collimator. Thus a high-resolution collimator is currently recommended for SPECT imaging, despite the lower sensitivity. Although the choice of collimator is crucial, it should be borne in mind that other technical aspects play an important role in determining optimal spatial resolution, such as the matrix size, the number of angles and the time per view.

Matrix and zoom factor

The SPECT images (or projections from the

angles round the patient) create multiple raw data sets containing the representation of the data in one projection. Each of these is stored in the computer in order to process them later on and extract the information.

Matrix
Each projection is collected into a matrix. These are characterised by the number of picture elements or pixels. Pixels are square and organised typically in arrays of 64×64, 128×128 or 256×256.

In fact, the choice of matrix is dependent on two factors:

a) The resolution: The choice should not degrade the intrinsic resolution of the object. The commonly accepted rule for SPECT (Groch and Erwin 2000) is that the pixel size should be one-third of the full-width at half-maximum (FWHM) resolution of the organ, which will depend on its distance from the camera face. The spatial resolution of a SPECT system is of the order of 18–25 mm at the centre of rotation (De Puey et al. 2001). Thus a pixel size of 6-8 mm is sufficient, which, for a typical large field of view camera, leads to a matrix size of 64×64.

b) The noise: This is caused by the statistical fluctuations of radiation decay. The lower the total counts, the more noise is present and, if the matrix size is doubled (128 instead of 64), the number of counts per pixel is reduced by a factor of 4. 128×128 matrices produce approximately three times more noise on the image after reconstruction than do 64 x 64 matrices (Garcia et al. 1990).

The planar images (or static projections) do not have the reconstruction problem and can be acquired over longer times so a 256× 256 matrix is commonly used.

Zoom factor
The pixel size is dependent on the camera field of view (FOV). When a zoom factor of 1.0 is used, the pixel size (mm) is the useful FOV (UFOV, mm) divided by the number of pixels in one line. When a zoom factor is used, the number of pixels per line should first be multiplied by this factor before dividing it into the FOV.

Example:
Acquisition with matrix 128, zoom 1.0 and UFOV 400 mm. Pixel size: 400/128=3.125 mm.

The same acquisition with a zoom factor of 1.5. Pixel size: 400/(1.5×128)=2.08 mm.

It is important to check this parameter before the acquisition, as it is very often used in parathyroid imaging, especially if a subtraction technique is used.

Preferred orbit
Either circular or elliptical orbits can be used in SPECT imaging (Fig. 1). A circular orbit (Fig.

1a) is defined by a fixed distance from the axis of rotation to the centre of the camera surface for all angles. Elliptical orbits (Fig. 1b) follow the body outline more closely.
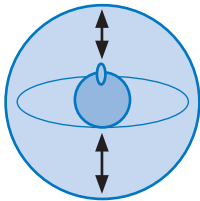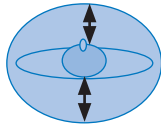

Figure 1a   Figure 1b

Figure 1a circular orbit

Figure 1b elliptical orbit

With a circular orbit, the camera is distant from the body at some angles, causing a reduction in spatial resolution in these projections. This will reduce the resolution of the reconstructed images.

With an elliptical orbit, spatial resolution will be improved as the camera passes closer to the body at all angles. Nevertheless, the distance from the organ to the detector varies more significantly with an elliptical orbit than with a circular orbit. This may generate artefacts simulating small photopenic areas when reconstructing using filtered back projection.

Programmes that allow the camera to learn and closely follow the contours of the body are available and improve resolution, although at the expense of computing power to modify the data before reconstruction.

The loss of spatial resolution with a circular orbit has to be offset against the potential artefacts that may be generated by an elliptical or contoured orbit.

Filtered back projection image reconstruction: some considerations

The main goal of nuclear medicine parathyroid imaging procedures is to identify the site of parathyroid hormone production, usually a single parathyroid adenoma. However, parathyroid adenomas can be found in diverse locations: alongside, beside or within the thyroid, or in anatomical regions distant from thyroid, such as high or low in the neck and mediastinum. The diversity of these anatomical locations makes SPECT a useful tool in parathyroid imaging.

Furthermore, parathyroid adenomas are small structures with increased uptake often close to normal thyroid activity. The choice of an optimum filter when using filtered back projection for reconstruction is crucial (Pires Jorge et al. 1998).

A filter in SPECT is a data processing algorithm that enhances image information, without significantly altering the components of the input data, creating artefacts or losing information. It should produce results that lead to

a correct diagnosis. Incorrect or over-filtering may produce adverse effects by reducing either resolution or contrast, or by increasing noise.

A filter in SPECT, being a processing algorithm, operates in the frequency-amplitude domain, which is obtained from the spatial domain by the Fourier transform. In the spatial domain, the image data obtained can be expressed by profiles of any matrix row or column showing the activity distribution (counts) as a function of distance (pixel location). The Fourier method assumes that this profile is the sum of several sine and cosine functions of different amplitudes and frequencies. The Fourier transform of the activity distribution of a given profile is a function in which the amplitude of the sine or cosine functions is plotted against the corresponding frequency of each. This representation is also called the image frequency-amplitude domain.

In input data, the highest frequency that can be measured is named the "Nyquist frequency", which is determined by the matrix size as well by the scintillation detector size and is expressed by the formula: $f_n=1/(2\times d)$ where f_n is the Nyquist frequency and d is the acquisition pixel size. For example, when using a 64×64 matrix with a 41-cm gamma camera UFOV, the pixel size (d) is 0.64 cm. Therefore the Nyquist frequency is 0.78. This means that any input data where the frequency is higher than 0.78 cannot be measured.

The input data plotted in the image frequency-amplitude domain present three components that are partially superposed: the low-frequency background, useful or target data and the high-frequency noise. Here background does not mean surrounding natural radiation or surrounding non-tissue activity but rather the low-frequency waves generated by the reconstruction process, such as the well-known "star artefact" that appears in an unfiltered back projection. The high-frequency noise is related to background and scatter radiation or statistical count fluctuations during SPECT acquisition, which may induce image distortions.

Usually SPECT filtered back projection couples a ramp filter with an additional filtering (e.g. Hann, Hamming, Parzen). The ramp filter is so called as its shape looks like a ramp and it will eliminate an important portion of the unwanted low-frequency background. However, the ramp filter amplifies the contribution of the high-frequency noise to the image. This is why it is recommended that an additional filter be coupled with the ramp filter in order to smooth an image where some details could appear very noisy. The degree of smoothing for each additional filter is under the control of the user, as s/he has to decide the "cut-off" frequency at which the filter will be applied. The cut-off frequency is the frequency value that defines the maximum frequency acceptable (which may contain useful data) while ignoring the higher frequency noise.

Obviously the maximum value of the cut-off frequency for a given additional filter is the Nyquist frequency.

As parathyroid adenomas appear as small hot spots, frequently within normal thyroid activity, the optimum choice of filter is a "high-pass" type filter with a cut-off frequency value close to the Nyquist frequency. A high-pass type filter will be applied in order to eliminate the background image components (low frequency) and conserve target data, although some noise (high frequency) will have to be tolerated because of the low image smoothing.

Patient preparation

Audrey Taylor and Nish Fernando

Patient identification

To minimise the risk of a misadministration:

- Establish the patient's full name and other relevant details prior to administration of any drug or radiopharmaceutical.

- Corroborate the data with information provided on the diagnostic test referral.

If the information on the referral form does not match the information obtained by the identification process, then the radiopharmaceutical/drug should not be administered to the patient. This should be explained to the patient and clarification sought as soon as possible by contacting the referral source.

The patient/parent/guardian/escort should be asked for the following information, which should then be checked against the request form and ward wristband in the case of an in-patient:

- Full name (check any spellings as appropriate, e.g. Steven vs Stephen)

- Date of birth

- Address

- If there are any known allergies or previous reactions to any drug, radiopharmaceutical, iodine-based contrast media or products such as micropore or Band-Aids

A minimum of **TWO** corroborative details should be requested and confirmed as correct.

The following information should be checked with the patient/parent/guardian/escort where appropriate:

- Referring clinician/GP/hospital

- Any relevant clinical details

- Confirmation that the patient has complied with the dietary and drug restrictions

- Confirmation that the results of correlative imaging (e.g. echocardiography, angiography, etc.) are available prior to the study, and noting of any recent interventions

If in doubt, do not administer the radiopharmaceutical or drug and seek clarification.

Specific patient groups

This is a guide only. Patients who are unable to identify themselves for any of a variety of reasons should wear a wrist identification band.

- Hearing difficulties: Use written questions and ask the patient to supply the information verbally or to write their responses down.

- Speech difficulties: Ask the patient to write down their name, date of birth and address and other relevant details.

- Language difficulties: If an accompanying person is unable to interpret the questions, then the study should be rebooked when a member of staff or relative with the appropriate language skills or an interpreter is available.

- Unconscious patient: Check the patient's ID wristband for the correct name and date of birth. If no wristband is attached, ask the nurse looking after the patient to positively confirm the patient's ID.

- Confused patient: If the patient is an in-patient, check the patient's ID wristband for the correct name and date of birth. If no wristband is attached, ask the nurse looking after the patient to positively confirm the patient's ID. If the patient is an out-patient, ask the person accompanying the patient to positively confirm the patient's ID.

If a relative, friend or interpreter provides information re the patient's name, date of birth etc., it is advisable for them to sign so as to provide written evidence confirming the relevant details.

Patients can be required to send in a list of medications, approximate height, weight and asthma status so that stressing drugs can be chosen in advance. They should be advised to contact the department if they are diabetic so as to ensure that the appropriate guidance is given with regard to eating, medication etc.

A full explanation of the procedure should be given, including, risks, contraindications and side-effects of stress agents used, time taken for scan, the need to remain still etc.

If the patients are phoned prior to appointment, it acts as a reminder of the test and gives the patient an opportunity to discuss any concerns.

Pregnancy

Women of childbearing potential should have their pregnancy status checked using a form such as the example below:

QUESTIONNAIRE FOR ALL FEMALE PATIENTS OF CHILD BEARING AGE (12 – 55 YEARS)

We are legally obliged under The Ionising Radiation (Medical Exposure) Regulations 2000 to ask females of child bearing age who are having a nuclear medicine procedure whether there is any chance they may be pregnant or breastfeeding.

Prior to your test, please answer the following questions in order for us to comply with these regulations:

PATIENT NAME .... D.O.B

1. Have you started your periods? (please tick appropriate box)

Y ☐ What is the date of your last period ....

N ☐ Please sign below and we can then proceed with your test

OR Have you finished your periods / had a hysterectomy (please tick appropriate box)

Y ☐ Please sign below and we can then proceed with your test

N ☐ What is the date of your last period

2. Is there any chance you may be pregnant (please tick appropriate box)

Y ☐ We will need to discuss your test with you before we proceed

Not sure ☐ We will need to discuss your test with you before we proceed

N ☐ Please sign below and we can then proceed with your test

3. Are you breastfeeding? (please tick appropriate box)

Y ☐ We will need to discuss your test with you before we proceed

N ☐ Please sign below and we can then proceed with your test

I have read and understood the questions above and confirm that I am not pregnant or breastfeeding and that I am aware that ionising radiation could damage a developing baby.

Signed: _____ Date: _____

(Patient)

For all patients under 16 years of age

I have read and understood the question above and confirm that the patient named is not pregnant or breastfeeding

Signed: _____ Date: _____

Parent ☐   Guardian ☐   (please tick appropriate box)

THIS FORM WILL BE CHECKED / DISCUSSED PRIOR TO THE START OF THE TEST

The operator administering the radiopharmaceutical should advise the patient on minimising contact with pregnant persons and children. In addition, the operator administering the radiopharmaceutical should check that any accompanying person is not pregnant (e.g. escort nurse)

Parathyroid patient preparation

- If possible, and under guidance from the referring clinician, the patient should be off any thyroid medication for 4–6 weeks prior to imaging.

- Establish whether the patient has had any imaging procedure using iodine contrast

within the last 6 weeks (CT with contrast, IVU etc). Allow a period of 6 weeks between these procedures and thyroid imaging.

- Iodine-containing medications may have to be withdrawn, and the referring clinician's advice should be sought. These medications include: propylthiouracil, meprobamate, phenylbutazone, sulphonamides, corticosteroids, ACTH, perchlorate, antihistamines, enterovioform, iodides, Lugol's solution, vitamin preparations, iodine ointments and amiodarone.

- Before any pharmaceuticals are ordered, check whether the patient has had a total thyroidectomy. If this is the case, then the subtraction technique should not be carried out and consideration should be given to undertaking a dual-phase ^{99m}Tc-sestamibi study.

- Ask the patient whether he or she has any thyroid disorders such as thyrotoxicosis, hypothyroidism, thyroid nodules or thyroid goitre. These conditions can increase instances of false-positive ^{99m}Tc-sestamibi uptake and also affect ^{123}I sodium iodide uptake. In the case of hypothyroidism, do not carry out the subtraction technique and consider undertaking a dual-phase ^{99m}Tc-sestamibi study.

- Ask the patient whether he or she is able to lie supine for the duration of the study and also whether he or she is claustrophobic. Consider another imaging modality if the patient cannot lie still for the duration of the study owing to discomfort or anxiety.

- Although ^{123}I sodium iodide contains little carrier-free iodide, it is important to ask the patient about any adverse reactions to iodide in the form of contrast media or medication. If positive, seek the advice of the lead clinician.

Imaging protocols
Nish Fernando and Sue Huggett

There are many variations in the imaging protocols used. For dual-isotope studies where images are acquired sequentially with the second nuclide being injected after the first set of images, consideration must be given to timing of uptake and downscatter from the higher energy nuclide when considering which nuclide to use first. Of course, simultaneous imaging, although affected by downscatter, obviates problems of image registration.

One subtraction and one washout technique are described, including SPECT imaging, as examples only. Explanations have been given for the choices so that adaptations can be made with knowledge of their effects.

SPECT/CT has been suggested as a suitable technique to increase the sensitivity of detection (Gayed et al. 2005) but is beyond the scope of this booklet.

[123]I sodium iodide/^{99m}Tc-sestamibi subtraction

- Give a full explanation of the procedure to the patient. In particular, stress the importance of keeping still during the acquisition.

- Ensure good venous access. A venflon with a three-way tap system into a vein in the patient's arm or the back of the hand is more convenient than a butterfly needle as veins more frequently collapse around a butterfly needle than around the plastic of a venflon. Also, the patient has more freedom of movement if a venflon is inserted.

- Inject ^{123}I sodium iodide followed by a saline flush of 10 ml. Wrapping a bandage around the arm or hand where the venflon is sited will protect it during the period of delay.

- At 40 min post ^{123}I injection, ask the patient to empty the bladder. Ask the patient whether he or she understands the procedure. Again, stress the importance of keeping still.

- At 50 min post ^{123}I injection, position the patient supine on the gamma camera couch. Ensure the neck is extended by positioning his/her shoulders on a pillow. Use sandbags and a strap to immobilise the head and neck. Ensure the patient is comfortable and understands the need to keep still. A pillow placed underneath the knees can reduce back discomfort.

- Position the patient so that an anterior image of the thyroid and mediastinum can be obtained, allowing any ectopic tissue to be included in the image. Place the patient's arm that has the venflon and three-way system onto an arm rest. Ensure patency of the venflon by flushing through with saline. Re-site the venflon if the vein has collapsed.

- Start acquisition at 60 min post ^{123}I sodium iodide injection using a dual-isotope dynamic acquisition with *non-overlapping*

windows for ^{99m}Tc (-10% to +5% about the peak at 140 keV) and ^{123}I (-5% to +10% about the 159-keV peak).

- Acquire 2-min frames for 20 min using a zoom of 4.0 and a matrix of 128×128. A dynamic acquisition is preferable to a static one as movement correction, provided it is in the x- or y-direction, can be applied to the images. The large zoom is chosen in order to increase spatial resolution. However, this will increase noise in the image and so the acquisition must be of sufficient duration to compensate for this.

- Pure iodide images may be acquired for 10 min. As well as being critical for processing, these pure iodide images can be beneficial in reducing false-positive cases due to thyroid disease.

- Without any patient movement, inject ^{99m}Tc-sestamibi followed by a 10-ml saline flush, between the 11th and 12th minute and continue the acquisition for 30 min.

- As a large zoom has been used, it is advisable at the end of the dynamic acquisition to carry out an unzoomed image to include the salivary glands and the heart. This will ensure the detection of any ectopic parathyroid glands, which can occur in the region of the unzoomed image. Acquire this image on the same dual-isotope settings for 300 s onto a matrix of 256×256.

Processing

In order to detect the increased uptake of ^{99m}Tc-sestamibi in the parathyroid tissue it is necessary to subtract the ^{123}I image from the ^{99m}Tc-sestamibi image.

The precise computer protocol will vary from centre to centre and even from camera system to camera system. However, all protocols will follow the same basic steps.

Movement correction

As the images have been acquired simultaneously, there will be no need to match the positions by shifting either image, but the images should be checked for movement and any correction algorithms applied before commencing. This can be as simple as checking all the frames and rejecting any with blurring before the frames are summed. This will not help if the patient has moved to a different position rather than having coughed or swallowed deeply and returned to the original position.

If overall movement has occurred, the situation may be rescued if the subsequent frames can be shifted by reference to some standard point (sometimes the hottest pixel) or even by eye.

The subtraction

Both sets of frames (corrected if necessary) are summed to make one ^{99m}Tc and one ^{123}I image.

There will be more counts in the thyroid on the ^{123}I image, so it must be matched to the ^{99m}Tc image before subtraction and a scaling factor is used so that the counts in the subtraction image are reduced by this factor, pixel by pixel.

The simplest technique reduces the image to be subtracted to, for example, 30%, 40%, 50%, 60% and 70% of its original values, and these images are subtracted in turn from the ^{99m}Tc-sestamibi image, that which gives the best result for eliminating the thyroid tissue being chosen by eye.

A more automated system will draw a region of interest around the normal thyroid on the ^{123}I image by allowing the operator to choose the count contour line which best represents its edges. The counts in this region are then compared against the counts in the same region on the ^{99m}Tc image. The scaling factor is calculated from the ratio of these two values. This adjusted image is then subtracted from the ^{99m}Tc image and the results displayed as a new image. Again, there are usually two or three options offered for the operator to choose the best result.

SPECT imaging

Additional SPECT imaging gives increased sensitivity and more precise anatomical localisation. Acquiring both early and delayed SPECT can be a useful addition to either the dual-phase ^{99m}Tc-sestamibi method or the dual-isotope ^{123}I/^{99m}Tc-sestamibi subtraction method.

- Early SPECT should be acquired 10–30 min after the ^{99m}Tc-sestamibi injection and delayed SPECT at around 3 h post injection.

- The camera is peaked for both ^{99m}Tc and ^{123}I as before.

- An 180° acquisition optimises the time close to the area of interest and attenuation is not a problem with structures so close to the body surface.

- Acquisition should start with the camera head at 270°; proceed in a clockwise rotation and stop at 90°.

- If the acquisition is carried out on a double-headed camera, a 90° L-Mode SPECT will be useful and more counts will be collected as both heads are used for the acquisition.

- Contouring can be used if available, although the patient should be warned if the camera will move closer during the acquisition.

- It should be ensured that the zoom chosen allows adequate coverage of the mediastinum to locate any ectopic glands there.

- Using a zoom of 2 will ensure better spatial resolution than no zoom, and there should be enough coverage of the mediastinum.

- A 64×64 matrix is sufficient for the expected

resolution and will optimise counts per pixel and hence reduce noise.

- 30× 60-s frames is manageable for the patient and will maximise counts in the image.

- For delayed SPECT, increasing the time per projection to 90 s will restore the total counts.

Processing

- The data may be reconstructed using the methods of filtered back projection or iterative reconstruction. Streak artefacts may be seen in data reconstructed by filtered back projection and these will not occur for the iterative method.

- The raw data can be viewed as a rotating image and the limits for the region to be reconstructed chosen.

- The region should extend from the parotid glands to the mediastinum to locate any ectopic tissue.

- The reconstruction programme with chosen filters is initiated.

- Once the reconstruction is completed, the images are viewed in the transverse, coronal and sagittal planes.

- Datasets can be viewed as volumetric displays as well as tomographic slices.

^{99m}Tc-sestamibi washout technique

If ^{99m}Tc-sestamibi is used alone, the two sets of images (early and delayed) are inspected visually.

740 MBq ^{99m}Tc-sestamibi is injected using the same protocols for patient preparation, i.e. ID and LMP checks/explanation to patient as before and imaging typically at 10 min and 2–3 h

- The camera is peaked for technetium and a low-energy high-resolution collimator can be used as images can be taken for a sufficient time to avoid statistical noise problems and pinhole collimators are used in some centres. Zoom can be used but remember the possibility of ectopic tissue.

- Neck and mediastinum views are taken with patient positioning as before. Again, a single view of 600 s counts can be taken or a series of 10×60-s frames acquired so that movement artefacts can be corrected.

- The same parameters and positioning must be used for the 10-min and late views

- Right and left anterior oblique views can be obtained if required.

- SPECT can be used in this case also.

All films should be correctly annotated with L, R and anatomical markers and labelled.

Technical aspects of probe-guided surgery for parathyroid adenomas

Domenico Rubello

Bilateral neck exploration (BNE) still represents the 'gold standard' approach in patients with primary hyperparathyroidism (pHPT). However, surgical approaches to pHPT patients have altered significantly in many surgical centres during the past decade, with the development of minimally invasive parathyroidectomy using endoscopic surgery or radio-guided surgery (MIRS). This development can be attributed to two main reasons: (a) the consciousness that pHPT is due to a single parathyroid adenoma in the majority of patients (at least 85%), and (b) the technical improvements introduced into surgical practice with the availability of microsurgery instruments, endoscopes, intraoperative measurements of quick parathyroid hormone (QPTH) and gamma probes.

New approaches to minimally invasive parathyroidectomy consisting in the removal of a solitary parathyroid adenoma via a small 1–2 cm skin incision have been widely adopted. Of course, in contrast to BNE, minimally invasive parathyroidectomy always requires accurate preoperative imaging in order (a) to establish whether the parathyroid adenoma is effectively solitary and (b) to locate precisely the enlarged gland. The present chapter focusses mainly on technical aspects of the MIRS technique. Moreover, the MIRS technique developed in our centre is based on the injection of a very low ^{99m}Tc-sestamibi dose – 37 MBq – compared with the traditional MIRS technique, which uses a 'high' ^{99m}Tc-sestamibi dose – 740–925 MBq.

Selection criteria for offering MIRS

When planning MIRS (unlike when performing BNE), strict inclusion criteria need to be followed: (a) evidence at ^{99m}Tc-sestamibi scintigraphy of a solitary parathyroid adenoma; (b) intense ^{99m}Tc-sestamibi uptake in the parathyroid adenoma; (c) absence of concomitant thyroid nodules at ^{99m}Tc-sestamibi scintigraphy and high-resolution (10 MHz) neck ultrasound; (d) no history of familial HPT or multiple endocrine neoplasia; and (e) no history of irradiation to the neck. Of note, previous thyroid or parathyroid surgery is not a contraindication to MIRS. When these inclusion criteria are adopted, approximately 60–70% of pHPT patients can be offered MIRS. The main reason for exclusion is the presence of ^{99m}Tc-sestamibi-avid thyroid nodules, which, by mimicking a parathyroid adenoma, can cause false positive results during surgery. Figure 1 shows a patient scheduled for MIRS while Fig. 2 shows a patient excluded from MIRS.

Preoperative imaging protocol

In our protocol, preoperative imaging procedures include single-session ^{99m}Tc-sestamibi scintigraphy and neck ultrasound (Norman and Chheda 1997; Costello and Norman 1999; Mariani et al. 2003; Rubello et al. 2000). In patients with concordant ^{99m}Tc-sestamibi and ultrasound results (both positive or negative), no further imaging is performed, while in cases with discrepant findings (^{99m}Tc-sestamibi positive and US negative) a tomographic (SPECT) examination is obtained to investi-

gate a possible ectopic or deep position of the parathyroid adenoma. SPECT is obtained just after the completion of planar ^{99m}Tc-sestamibi scintigraphy, thus using the same radiotracer dose; in this way, ^{99m}Tc-sestamibi re-injection is not necessary, thus avoiding additional radiation exposure to the patient and personnel. In other centres, preoperative ^{99m}Tc-sestamibi scintigraphy alone is considered a sufficient tool for the planning of MIRS.

Intra-operative MIRS protocol

Table 1 shows the steps in the MIRS protocol used in our centre.

A collimated gamma probe is recommended with an external diameter of 11–14 mm. A non-collimated probe, which can be used for sentinel lymph node biopsy, is not ideal for parathyroid surgery owing to the relative component of diffuse and scatter radioactivity deriving from the anatomical structures located near to the parathyroid glands, mainly related to the thyroid gland. Probes utilising either a NaI scintillation detector or a semiconductor detector have proved adequate for MIRS.

A learning curve of at least 20–30 MIRS operations is recommended for an endocrine surgeon. During these, the presence in the operating theatre of a nuclear medicine physician is usually considered mandatory. In the opinion of the writer, the presence of a nuclear medicine technician, with expertise in probe utilisation, is very useful in helping the surgeon to become more skilled in the use of the probe.

The probe is usually handled by the surgeon, who should measure radioactivity in different regions of the thyroid bed and neck in an attempt to localise the site with the highest count rate before commencing the operation. This site is likely to correspond to the parathyroid adenoma. Then, during the operation, the surgeon should measure the relative activity levels in the parathyroid adenoma, thyroid bed and background. Moreover, a check of the empty parathyroid bed after removal of the parathyroid adenoma is a very useful parameter to verify the completeness of removal of hyperfunctioning parathyroid tissue. Ex vivo measurement of any removed surgical specimen should be done to verify the total clearance of the parathyroid adenoma. The calculation of tissue ratios – parathyroid to background (P/B) ratio, thyroid to background (T/B) ratio, parathyroid to thyroid (P/T) ratio and the empty parathyroid bed to background (empty-P/B) ratio – can be useful in evaluating the efficacy of MIRS. The tissue ratios obtained in a large series of 355 pHPT patients operated on in our centre are reported in Table 2.

Attention has to be given to avoidance of intra-operative false negative results due to ^{99m}Tc-sestamibi-avid thyroid nodules and to stagnation of the radiotracer within vascular structures of the neck and thoracic inlet: in this regard, the careful acquisition and evaluation

of preoperative scintigraphy is very helpful (mandatory in the opinion of the author).

Technical factors

All these measurements should be in counts per second. An energy window of 10% of the photo peak of ^{99m}Tc is generally preferred.

Quality controls of the probe should include sensitivity, spatial resolution and count linearity and should be performed every 3–6 months. This is an important step in which the nuclear medicine technician should play a major role.

The performance of additional intra-operative QPTH measurement is also recommended by some authors in order to discover possible unknown glandular hyperplasia, while some other authors judge the use of the probe sufficient for the purpose of MIRS. When using QPTH, a fall of 50% or more in PTH levels 10 min after parathyroid adenoma removal in comparison with the baseline pre-excision value is usually considered indicative of successful parathyroidectomy.

The single-day high ^{99m}Tc-sestamibi dose protocol versus the low ^{99m}Tc-sestamibi dose different-day protocol

The first MIRS protocol was developed by Norman in 1997. It consists of a single-day imaging and surgery approach. The patient is injected with a 20–25 or 740–925 MBq dose of ^{99m}Tc-sestamibi, images are obtained by the dual-phase scintigraphic technique and MIRS is performed within 2–3 h after radiotracer administration. Norman's protocol is attractive from a cost-analysis perspective because ^{99m}Tc-sestamibi scintigraphy and MIRS are performed on the same day and a single radiotracer dose is required for both imaging and surgery. However, Norman's protocol also presents some practical disadvantages given the uncertainty of the scintigraphic results and the differences between MIRS and BNE with respect to the need for operating theatre time (BNE > MIRS) and efficient patient scheduling. This problem would be expected to be even greater in areas with a high prevalence of nodular goitre so that a different-day protocol would be preferable. The protocol developed in our centre is a different-day protocol. On the first day, localising images are obtained by means of dual-tracer ^{99m}Tc-pertechnetate/^{99m}Tc-sestamibi subtraction scintigraphy combined with neck ultrasound. On the day of MIRS, usually within 1 week of imaging, a low 37 MBq ^{99m}Tc-sestamibi dose is given directly in the operating theatre a few minutes before surgery. The low ^{99m}Tc-sestamibi dose protocol has two major advantages: (a) less radiation exposure to the patient and operating theatre personnel (Table 3) and (b) fewer false negative results in parathyroid adenoma with rapid ^{99m}Tc-sestamibi washout.

Nevertheless, favourable results have been reported with both Norman's high ^{99m}Tc-sestamibi dose protocol and our low ^{99m}Tc-ses-

Table 1. Steps in minimally invasive radioguided surgery (MIRS) of parathyroid adenomas using the low [99mTc]-sestamibi dose protocol developed in our centre

Blood samples are drawn from a peripheral vein both before commencing surgery and 10 min following the removal of the parathyroid adenoma to measure intra-operative QPTH levels
37 MBq of [99mTc]-sestamibi is injected in the operating theatre 10 min before the start of surgery
Prior to surgical incision, the patient's neck is scanned with an 11-mm collimated probe to localise the site with the highest count rate, corresponding to the cutaneous projection of the parathyroid adenoma
A transverse midline neck access (approximately 1 cm above the sternal notch) is preferred because conversion to BNE is easily obtained if necessary
An 11-mm collimated probe is repeatedly inserted through a 2-cm skin incision, guiding the surgeon to the maximum count rate area corresponding to the parathyroid adenoma
In some patients with a parathyroid adenoma located deep in the neck, ligature of the middle thyroid vein and of the inferior thyroid artery is required
Radioactivity of the parathyroid adenoma, thyroid gland and background is measured with the probe
Radioactivity is measured ex vivo to confirm successful removal of parathyroid tissue
Radioactivity of the empty operation site is checked to evaluate the completeness of parathyroid tissue removal
Tissue ratios are calculated (P/B, P/T etc.)

QPTH, quick parathyroid hormone; BNE, bilateral neck exploration; P/B, parathyroid to background ratio; P/T, parathyroid to thyroid ratio

EANM

tamibi dose protocol, with a success rate in the intra-operative detection of parathyroid adenoma of approximately 96–98%, without major intra-operative surgical complications. It is likely that Norman's single-day protocol will be preferable in patients with a low likelihood of nodular goitre whilst our different-day protocol appears preferable in areas with a higher prevalence of nodular goitre.

Irrespective of the type of MIRS protocol used, the principal advantages of MIRS over traditional BNE can be summarised as: (a) a small skin incision with favourable cosmetic results, (b) a shorter operating time, (c) the possibility of performing MIRS under local anaesthesia, (d) a shorter hospital recovery time, (e) the possibility of same-day hospital discharge, (f) lower post-surgical time and (g) lower costs.

Table 2. Probe tissue ratios calculated during MIRS for parathyroid adenoma removal (n=355 pHPT patients)

• P/B ratio = 1.6–4.8 (mean 2.6±0.5)
• P/T ratio = 1.1–2.8 (mean 1.5±0.4)
• T/B ratio = 1.5–1.8 (mean 1.6±0.1)
• Empty-P bed/B ratio = 0.9–1.1 (mean 1.0±0.03)
• TN/P ratio = 0.5–1.5 (mean 1.0±0.4)

P=parathyroid
T=thyroid
B=background
TN=thyroid nodule

Table 3. Radiation dose to operating theatre personnel during MIRS with the low (37 MBq) ^{99m}Tc-sestamibi dose protocol used in our centre

	µGy/hour	µGy/year*
Surgeon's body	1.2	120
Surgeon's hands	5.0	500
Anaesthesiologist	0.7	70
Instrument nurse	1.1	110
Other nurses	0.1	10

*Estimated for 100 interventions, each lasting 60 min
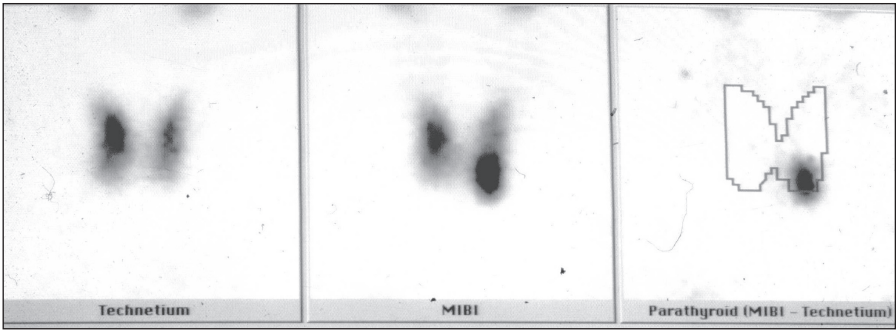
Figure 1. Preoperative dual-tracer parathyroid subtraction scintigraphy. *Left image*: ^{99m}Tc-pertechnetate scan showing a normal thyroid gland. *Middle image*: ^{99m}Tc-sestamibi scan showing an area of radiotracer uptake juxtaposed to the lower pole of the left thyroid lobe. *Right image*: Subtraction (^{99m}Tc-sestamibi–^{99m}Tc-pertechnetate) image, clearly showing a left inferior parathyroid adenoma. This patient was offered MIRS.
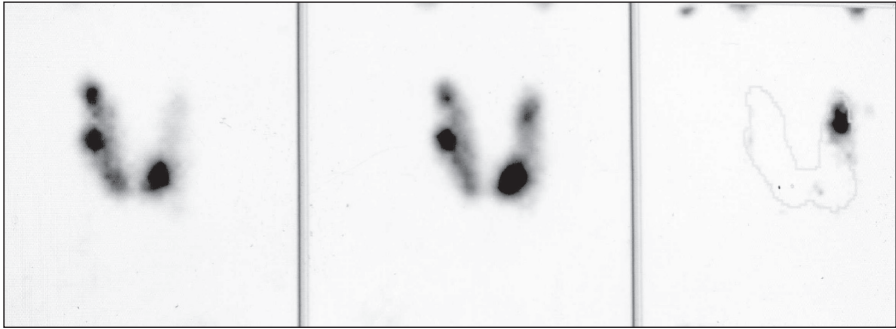
Figure 2. Preoperative dual-tracer parathyroid subtraction scintigraphy. *Left image*: ^{99m}Tc-pertech-netate scan showing a multinodular goitre with some hyperfunctioning nodules (three in the right thyroid lobe, one in the left thyroid lobe). *Middle image*: ^{99m}Tc-sestamibi scan showing a picture similar to the ^{99m}Tc-pertechnetate image plus a left superior area of exclusive ^{99m}Tc-sestamibi uptake. *Right image*: subtraction (^{99m}Tc-sestamibi–[99m]Tc-pertechnetate) image clearly showing a left superior parathyroid adenoma. This patient was excluded from MIRS due to the coexistence of a solitary parathyroid adenoma and multinodular goitre with multiple ^{99m}Tc-sestamibi-avid thyroid nodules in both thyroid lobes

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