Radionuclide parathyroid imaging: a concise, updated review

Abstract

The hypercalcemia of hyperparathyroidism (HPT) can cause devastating effects to the patient and only surgical removal of the hyperfunctioning parathyroid tissue can definitely cure the disease. Radionuclide parathyroid imaging has no role in the diagnosis of HPT or in the selection of the type of treatment. However, once surgery is decided ^{99m}Tc-sestamibi scanning can localize abnormal parathyroid glands preoperatively. In primary HPT radionuclide assessment may occasionally be helpful before bilateral neck exploration, it can identify patients suitable for focused surgery and is a prerequisite of the minimally invasive radioguided parathyroidectomy. In secondary and tertiary HPT the clinical value of parathyroid scintigraphy remains debatable, but in persistent or recurrent disease this modality is a first line examination before reoperation. *In conclusion*, ^{99m}Tc-sestamibi assessment has a well defined clinical role in the surgical management of patients with primary HPT and in recurrent disease, but its usefulness in cases of secondary HPT is not clearly established.

Introduction

The parathyroid (PT) glands are key organs in calcium homeostasis and their hyperfunction may lead to hypercalcemia with potentially harmful consequences to the patient, if left untreated. Over the past years the advances in the scintigraphic localization of hyperfunctioning glands have paved the way to focused parathyroid surgery.

There are two superior and two inferior PT glands in humans, adjacent to the poles of the lobes of the thyroid gland and each one weights 30-40mg. They are composed mainly of chief cells (secreting parathormone) and oxyphil cells (packed with mitochondria), surrounded by adipose tissue. If the glands are situated above or below the level of the thyroid gland or are distant from its posterior aspect they are considered ectopic. Parathyroid glands secrete parathormone in order to regulate the maintenance of extracellular calcium concentration within a very narrow range which is crucial for various human functions [1-3].

Hyperparathyroidism

Clinical elements

There are three different clinical types of hyperparathyroidism (HPT): primary, secondary and tertiary. *Primary hyperparathyroidism* affects 0.2%-0.5% of the population and it is the most common cause of hypercalcemia in the outpatient setting. The disease is more prevalent in women than in men (3:1) and it is the third most frequent endocrine disorder, after diabetes mellitus and hypothyroidism [4]. Histopathologically, primary HPT is classified into single adenomas (80%-85%), double adenomas (5%) and diffuse hyperplasia of all glands (10%-15%), whereas parathyroid cancer is very rare (<1%) [3]. Adenomas more often originate from inferior glands and often at diagnosis their size is 1-3cm and their weight >300mg [5]. In primary HPT multigland hyperplasia usually is associated with a syndrome of multiple endocrine neoplasia (MEN).

The classical clinical manifestations of primary HPT (kidney stones, painful bones, abdominal groans, lethargic moans and psychiatric overtones) are not often encountered. With the widespread use of serum autoanalyzers, evidence of hypercalcemia on routine blood analysis leads to the recognition of the disorder in the majority of patients (50%-80%) [5-8]. Although these patients are considered to have *asympto-*

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matic *hyperparathyroidism*, they may suffer from non-specific symptoms (fatigability, musculoskeletal pain, irritability, mood swings, etc), which usually diminish after parathyroidectomy [4, 7, 8].

The diagnosis of primary HPT in a hypercalcemic patient is established by an elevated serum parathormone measurement. Less frequent are the cases of primary HPT with hypercalcemia and a high-normal serum parathormone value, but a substantial number of patients with primary HPT with an increased serum parathormone and high-normal serum calcium levels is realized lately [5, 7, 9, 10].

Secondary hyperparathyroidism is commonly due to chronic kidney disease, in which low serum calcium concentrations stimulate diffuse gland hyperplasia, and it is not a cause of hypercalcemia. However, in those patients PT glands may continue to grow and become overactive, resulting in typical asymmetric hypertrophy and frank hypercalcemia because of autonomous function (*tertiary hyperparathyroidism*) [5, 11].

Treatment of hyperparathyroidism

The definite cure of hypercalcemia caused by primary HPT is accomplished only by surgical removal of the hyperfunctiong parathyroid tissue. Surgical management is warranted in patients with symptoms or complications of HPT. In milder disease medical treatment has been suggested (bisphosphonates, estrogens in postmenopausal women, calcimimetics) and the most recent (2009) guidelines recommend operative management in asymptomatic patients meeting specific criteria [7, 12, 13].

The traditional surgical procedure consists of a collar incision, bilateral neck exploration with direct macroscopic assessment of all 4 parathyroid glands and removal of the abnormal one(s). In cases of hyperplasia, total parathyroidectomy is performed and a small piece of parathyroid tissue is autotransplanted in the brachioradialis or the sternocleidomastoid muscle. Alternatively, subtotal parathyroidectomy may be preferred, leaving a 50-100mg tissue remnant in the gland that appears most normal [2, 4, 8]. Operative success rates of 95%-98% with rare complications of 1%-2% have been reported by experienced surgeons. With the advent of scintigraphic techniques, offering accurate preoperative localization of hyperfunctioning glands, focused and minimally invasive surgical approaches have been developed, endoscopic or radioguided, with high curative rates (>97%) and exceptional cosmetic results (incision of 2-3cm) [4, 14]. Moreover, accurate scintigraphic localization allows thoracoscopic removal of aberrant PT glands from the mediastinum [15].

Radionuclide parathyroid imaging

The rationale of parathyroid imaging

The diagnosis of HPT is established by biochemical criteria and it is not influenced by a positive or negative result of any parathyroid imaging modality. Likewise, medical or surgical management decisions are made according to the severity of the disease, the goal of parathyroidectomy is the restoration of normocalcemia and it should not be postponed if a parathyroid abnormality is not portrayed in imaging tests. However, radionuclide techniques can localize hypersecreting glands preoperatively and identify them intraopera-

tively; hence, they can facilitate focused or minimally invasive surgical procedures. Radioguided parathyroidectomy is based on the concept of the metabolic status of the glands (uptake of radiotracer) as a standard of abnormality, instead of the macroscopic impression of the surgeon. It is broadly accepted that PT scintigraphy is superior to other imaging modalities, which usually are assigned a complementary role [1, 16].

Radiotracers - Techniques

There are no specific radiotracers for PT scintigraphy and those used for this purpose were originally introduced for cardiac imaging and are taken up by both the thyroid and the PT glands. The older clinically used subtraction technique was based on the uptake of ^{201}Thallous chloride (^{201}TlCl) by both the thyroid and the parathyroid glands and the uptake of ^{99m}Tc-pertechnetate (^{99m}TcO$_4^-$) only by thyroid parenchyma. The subtraction of the latter from the former scintigram allowed the visualization of hyperfunctioning PT glands [17, 18]. However, this scintigraphic technique showed no advantage over other imaging modalities, it has an unfavorable dosimetry (>15mSv) and a lower sensitivity than ^{99m}Tc-sestamibi imaging and hence it was replaced by the latter [19, 20].

Hexakis-2-methoxy-isobutyl-isonitrile labeled with technetium-99m (^{99m}Tc-sestamibi) consists of monovalent cationic lipophilic molecules which after intravenous (i.v.) injection distribute according to blood flow [1, 21]. These molecules cross the cell membranes according to the electrochemical gradient and intracellularly accumulate in the mitochondria. The uptake of ^{99m}Tc-sestamibi by PT glands relates with their content in mitochondria-rich oxyphil cells. ^{99m}Tc-sestamibi is also taken up by the thyroid gland, but as it washes out more rapidly from normal thyroid tissue than out of PT glands, 1.5-3h later those glands can be visible. ^{99m}Tc-sestamibi is sequestered also in the myocardium, the salivary glands and in brown fat which often is noted as a mild supraclavicular shade [1, 21]. 1,2-bis [bis(2-ethoxyethyl) phosphino] ethane labeled with technetium-99m (^{99m}Tc-tetrofosmin) shares similar characteristics with ^{99m}Tc-sestamibi. However, although it is taken up by both the thyroid and PT glands, it does not demonstrate differential washout and a separate thyroid scintigraphy is required together with a subtraction technique to visualize hyperfunctioning PT glands [21, 22].

Two-dimensional planar PT scanning has been the standard technique for many years, the three-dimensional single photon emission tomography (SPET) was added later on and more recently the latter is combined with computed tomography (CT). The protocols for ^{99m}Tc-sestamibi PT scans are based on two techniques: (a) the single tracer double phase scintigraphy and (b) the double tracer subtraction scanning.

(a) In the single tracer double phase protocol the first set of images is acquired 10-15min after i.v. injection of 600-800MBq ^{99m}Tc-sestamibi. These images usually are not diagnostic and a second acquisition 1.5-3h later is required to visualize the hyperfunctioning PT glands, as there is little activity left in normal thyroid parenchyma (Fig. 1). However, in a number of cases (10%-20%) the thyroid and the PT glands may demonstrate similar washout rates which averts the recognition of abnormality [23, 24]. Moreover, diagnostic difficulties may arise from retention of ^{99m}Tc-sestamibi in thyroid nodules, a situation of particular concern in areas with endemic nodular goiter.

(b) In the double tracer subtraction scintigraphy ^{99m}Tc-sestamibi is retained by both the thyroid and PT glands and a second tracer (^{123}I -as sodium iodide- or ^{99m}TcO$_4^-$) is used for thyroid imaging. The thyroid scintigram can be subtracted digitally from the ^{99m}Tc-sestamibi scan, while other physicians prefer visual comparison of the pair of images for the assessment of parathyroid abnormalities (Fig. 2) [1, 23, 25]. Three different procedures are used according to the type of tracer for thyroid imaging and the sequence of agent administration [14, 21, 23]:

(i) ^{123}I / ^{99m}Tc-sestamibi technique. ^{123}I (10-12MBq) is administered i.v. (or orally) and after 2-4h ^{99m}Tc-sestamibi (500-700MBq) is injected. Images can be recorded simultaneously using two different energy windows for ^{123}I and ^{99m}Tc; alternatively, ^{99m}Tc-sestamibi imaging may follow ^{123}I scanning. With simultaneous acquisition, motion artifacts are avoided, but cost and availability issues limit the use of ^{123}I.

(ii) ^{99m}TcO$_4^-$ / ^{99m}Tc-sestamibi technique. A low dose of ^{99m}TcO$_4^-$ (40-60MBq) is injected i.v. and 20min later the thyroid is scanned. Subsequently, ^{99m}Tc-sestamibi (600MBq) is administered and an image is obtained from which the thyroid scan is subtracted. Alternatively, before starting thyroid scanning the patient may receive orally 400mg potassium perchlorate which enhances a rapid wash out of ^{99m}TcO$_4^-$, thus diminishing its interference with the ^{99m}Tc-sestamibi image. In this case 150-200MBq of ^{99m}TcO$_4^-$ can be used.

(iii) ^{99m}Tc-sestamibi / ^{99m}TcO$_4^-$ technique. Double phase ^{99m}Tc-sestamibi (500-700MBq) scintigraphy is followed by a ^{99m}TcO$_4^-$ (150MBq) thyroid scan. The latter is corrected for residual activity from previous scintigraphy and it is subtracted from the ^{99m}Tc-sestamibi image.
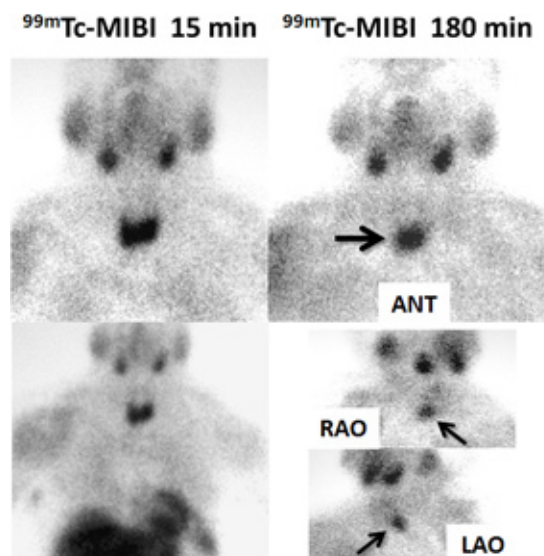

Figure 1. Double phase ^{99m}Tc-sestamibi (^{99m}Tc-MIBI) parathyroid scintigraphy. In delayed imaging focal tracer retention is seen in the lower part of the thyroid gland (arrow). In the right and left anterior oblique views (RAO and LAO, respectively) the abnormal focus "changes its position significantly" relative to the submandibular salivary glands, indicating that it is located in the thyroid area and not deep in the neck.

A matrix size of 256x256 and a 5-10min acquisition is generally recommended for planar images with a parallel hole collimator. In the double tracer subtraction technique the patient should remain immobile between the two successive scans and images should be carefully subtracted to avoid artifacts. In scanning in secondary HPT it is advised to withhold drugs refraining PT hyperfunction, namely calcimimetics for 2 weeks and vitamin D supplements for 1-4 weeks [21]. If a subtraction technique is used, iodine-containing preparations should be avoided for >4 weeks and thyroxine for 3 weeks. If ^{123}I is used for thyroid scanning, thyrostatic drugs should be stopped for 1 week. When thyroid imaging is not feasible (due to thyroidectomy, iodine-containing preparations, etc) ^{99m}Tc-sestamibi washout scintigraphy is the only option.

The radiation exposure in PT scintigraphy depends on the particular protocol used. On average the effective dose is estimated 6-7mSv, but it is higher with hybrid imaging (SPET/CT) [21, 23].
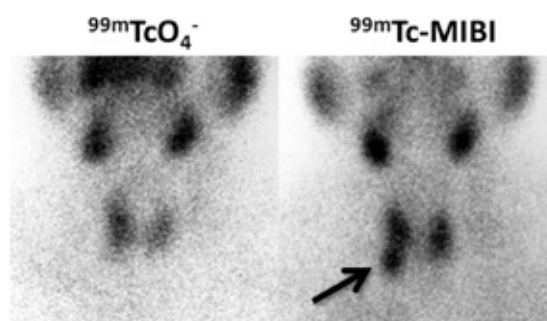
Figure 2. In a patient with primary hyperthyroidism double tracer parathyroid scintigraphy shows a solitary focus adjacent to the lower pole of the right thyroid lobe which takes up ^{99m}Tc-sestamibi but not ^{99m}TcO$_4^-$. It is very likely that this patient suffers from a single adenoma and he is suitable for a targeted surgical treatment.

Diagnostic performance and comparative evaluation of the scintigraphic techniques

The assessment of the diagnostic efficacy of PT scintigraphy is difficult because of the variety of techniques, histopathologic types and location of the disease and also differences in the population, the experience and the interpretation standards in various centers. Although the reported sensitivity in the detection of hyperfunctioning PT glands with ^{99m}Tc-sestamibi varies widely (13%-100%), it is supported that with good quality imaging 85%-95% of PT adenomas can be identified [26, 27].

In the detection of PT adenomas with planar imaging and parallel hole collimation, double phase ^{99m}Tc-sestamibi scanning has a sensitivity of 75%-80% and a specificity of 90%-95%, but in the subtraction technique the sensitivity rises up to 90% with a preserved specificity of 90%-95% [20, 28-31]. When the subtraction technique is used in conjunction with a pinhole collimator and anterior together with anterior oblique views (30^0 left and right), the sensitivity is even higher (95%) [12, 32-34]. The sensitivity for the detection of abnormality in multigland disease is limited with the ^{99m}Tc-sestamibi washout scanning (40%-50%), it is better with a subtraction technique (60%-65%) and further improves when pinhole collimation is used [31, 33-35]. However, in PT hyperplasia 1-2 glands are usually visible and extremely rarely all of them (Fig. 3) [36, 37].

Single photon emission tomography is advantageous in the recognition of pathologic processes in deep body structures and hence it appears attractive for the localization of overproductive PT glands which may reside behind the thyroid gland and also in ectopic sites from the submandibular

space to the lower mediastinum. Double phase ^{99m}Tc-sesta-mibi has demonstrated higher sensitivity with SPET (85%) compared to planar scintigraphy with a parallel hole colli-mator [20, 24, 38-40]. [123]I / ^{99m}Tc-sestamibi subtraction SPET seems to further improve the diagnostic accuracy for over-productive PT glands [29]. However, the subtraction planar imaging technique with pinhole collimation and extra ante-rior oblique views appears to supersede SPET in the thyroid area [31-34]. Conversely, SPET is superior in the accurate lo-calization of abnormal foci primarily in the mediastinum and also posteriorly in the neck (Fig. 4).

Regarding SPET/CT, although it may be considered more effective than SPET alone for diagnostic purposes, published results are variable and no difference in surgical success rates has been reported. A number of authors support improved sensitivity with hybrid imaging, other investigators propose a more accurate localization of hyperfunctioning PT tissue and certain researchers limit the advantage of SPET/CT in the

exact anatomic registration of ectopic PT glands [41-44]. Fur-ther data suggest that in double phase ^{99m}Tc-sestamibi imag-ing, early SPET/CT offers the highest accuracy, irrespective of the type of delayed acquisition (planar, SPET or SPET/CT), with the advantage to avoid radiation exposure from a sec-ond CT [44].

There is limited evidence on PT imaging with positron emission tomography (PET) and the experience with ^{18}F-fluoro-2-deoxy-D-glucose PET is not very encouraging [26]. Conversely, the use of ^{11}C-methionine PET has provided promising results, but the short half-life of [11]C (20min) pre-vents a wide clinical application of this technique [45]. Par-athyroid PET can be a resort when conventional imaging is not informative.

Imaging and interpretation
Parathyroid abnormalities in the vicinity of the thyroid gland can be reliably assessed with planar scintigraphy, preferably
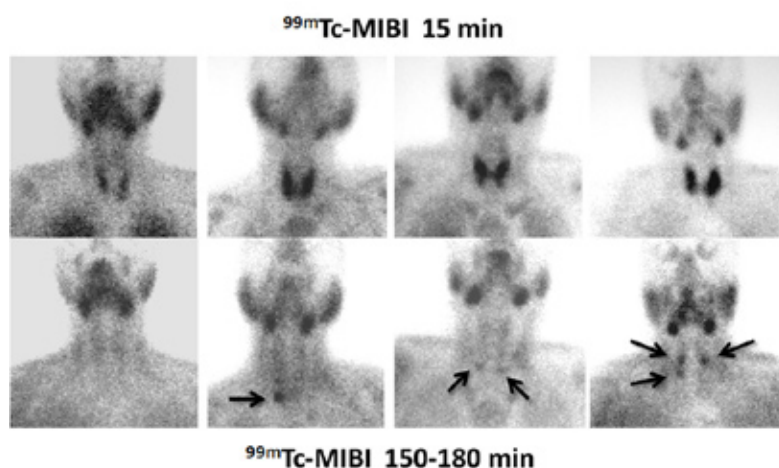
Figure 3. Patients with chronic kidney disease and secondary of tertiary hyperparathyroidism. These patients typically have asymmetric hyperplasia of the parathyroid glands and are can-didates for total or subtotal parathyroidectomy, regardless the number of abnormal foci visualized with ^{99m}Tc-sestamibi wash-out imaging.
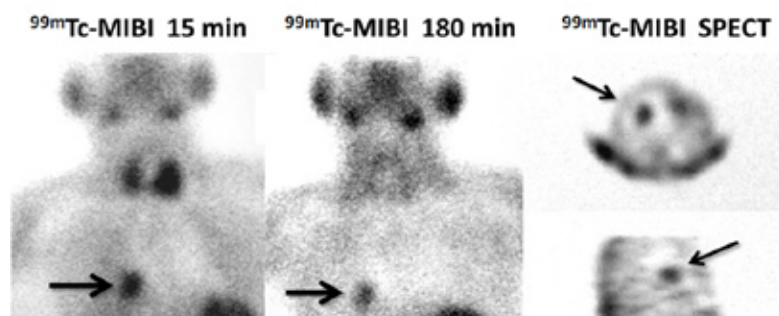
Figure 4. In a patient with primary hyperparathyroidism an ectopic hyperfunctioning parathyroid gland is detected in the lower mediastinum and more accurately localized with SPET. Operation plans were modified accordingly.
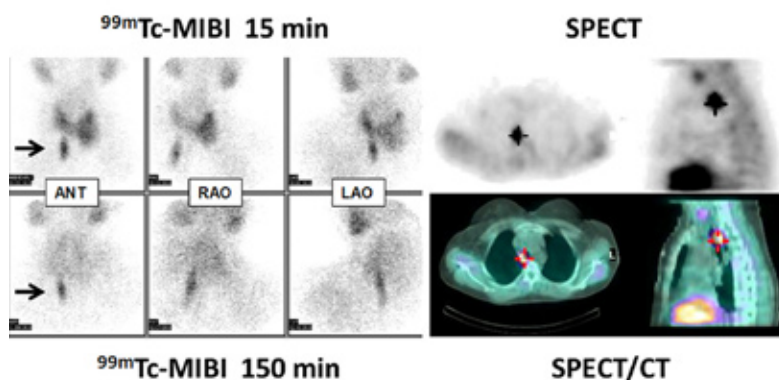
Figure 5. Double phase ^{99m}Tc-sestamibi scanning. In planar im-ages with pinhole collimation, the abnormal focus (arrow) "does not change its position significantly" relative to the salivary glands in the oblique views and it "does not follow" the right thyroid lobe forward in the right anterior oblique view (RAO). These signs suggest a posterior cervical location. Subsequent SPET localizes accurately the abnormality and SPET/CT determines its anatomic associations, with the overproductive parathyroid gland being situated in a right paraesophageal position (courtesy, from the Clini-cal Laboratory of Nuclear Medicine, University of Patras).

with a subtraction technique and ideally with a pinhole colli-mator and anterior together with anterior oblique views [46]. *The procedure should be supplemented invariably by anterior planar images of the neck and the chest with a parallel hole collimator* [16, 47]. *Single photon emission tomography is en-couraged for the identification and accurate localization of ectopic PT foci, particularly in the mediastinum, and SPET/CT ascertains the anatomic relationships of abnormal findings* (Fig. 5) [16, 21, 46].

In primary HPT normal PT glands are not scintigraphically visible because of their small size and a low metabolic state (dormant glands). Enlarged and hypersecreting PT glands typically are visualized in the neck as foci of avid ^{99m}Tc-ses-tamibi uptake either with a subtraction technique or in the delayed images of the double phase scintigraphy (Fig. 1). If the PT abnormalities are distant from the thyroid bed they can be identified without subtraction or in the early ^{99m}Tc-sestamibi scan (Fig. 2, 5).

With good quality scanning, PT glands as small as 100-150mg can be detected, but the efficacy of localization re-lates to the size of the glands and frequently one can discern unequivocal abnormalities when their weight is >500-600mg [14, 23, 31, 38, 48]. Inferior PT abnormalities are more often detected than superior gland pathology and the likelihood of the identification of hypersecreting glands depends on their content in oxyphil cells, the expression of P-glycopro-tein and the cell cycle phase [1, 49, 50]. Multigland disease is more difficult to identify because of the small size of the glands, possibly the lower content in oxyphil cells and the expression of P-glycoprotein which mediates a fast washout of ^{99m}Tc-sestamibi (Fig. 3). It has been proposed also that the probability of detection of abnormal PT glands correlates positively with serum levels of calcium and parathormone, but this correlation is not strong or consistent across studies [48, 51]. Overall, it is obvious that a cut-off point for serum calcium or parathormone above which overproductive PT glands would be visible cannot be set.

In patients with primary HPT a normal ^{99m}Tc-sestamibi scin-tigraphy is a false negative result. In primary disease a single focal abnormality most likely reflects a solitary adenoma, al-though there is a remote probability for double adenomas or very rarely for cancer (Fig. 1, 2, 5). In HPT from chronic kid-ney disease usually all PT glands are hyperplastic, but in scin-tigraphy fewer or none abnormal foci are noticed (Fig. 3).

^{99m}Tc-sestamibi is taken up by benign and malignant thy-roid nodules and in the differentiation from hyperfunction-ing PT glands thyroid scanning and ultrasound or fine nee-dle biopsy may be helpful. False positive results have been associated with lymphoma, sarcoidosis, metastatic or reac-tive cervical lymph nodes, brown tumors, a thymic remnant and bronchial carcinoids. Moreover, diagnostic difficulties have been described with primary carcinomas of the head and neck, breast and lung and their local metastases [1, 47].

Other parathyroid imaging modalities
High resolution ultrasound is a widely available, low-cost and non-ionizing technique. However, this procedure depends highly on the expertise of the operator and also the speci-fications of the equipment used. Moreover, its diagnostic ability is diminished in cases of small PT glands and also in the assessment of ectopic adenomas deep in the neck or the mediastinum [52]. Ultrasound can confirm or register anatomically scintigraphic findings, it can be used for the

assessment of thyroid nodules or reactive lymph nodes and occasionally it provides evidence of disease when ^{99m}Tc-ses-tamibi scintigraphy is normal [53, 54]. In the detection of sol-itary adenomas the sensitivity of high resolution ultrasound is 70%-80% and the specificity is 70%, but with wide vari-ability in different centers and reduced diagnostic efficacy in the other histopathologic types of HPT [8, 26, 55]. In the preoperative localization of PT adenomas the combination of ^{99m}Tc-sestamibi imaging and high resolution sonography raises the sensitivity up to 95% and hence combined assess-ment is widely used before minimally invasive parathyroid-ectomy [8, 56, 57].

Computed tomography is less effective than radionuclide imaging in the preoperative detection of PT glands with a sensitivity of no more than 80%-85%, while *magnetic reso-nance imaging* (MRI) displays a similar diagnostic perform-ance [16, 26]. These modalities are used preferably for the as-sessment of the mediastinum and also in disease recurrence [1]. More recently, by monitoring the temporal changes of the contrast medium in CT (4D-CT) promising results have been reported in the identification of overproductive PT glands, including multinodular disease [58, 59].

Clinical utility of parathyroid scintigraphy

Primary hyperparathyroidism
The usefulness of PT scintigraphy in patients scheduled for bilateral neck exploration has been a controversial issue [23, 36]. Undoubtedly, before parathyroidectomy a major con-cern is "to localize an experienced PT surgeon" which would have success rates equal to or higher than the sensitivity of ^{99m}Tc-sestamibi scanning in the identification of abnormal glands [60]. However, radionuclide imaging may be helpful to less experienced surgeons, it may modify surgical plan-ning in cases of unusual ectopic locations of overproductive PT glands (e.g. in low mediastinum) and it may facilitate sur-gery in distorted neck anatomy (e.g. previous thyroidectomy, obesity, short neck, etc) (Fig. 4). Moreover, as for many sur-geons bilateral neck exploration is no more the procedure of choice in solitary PT adenomas, preoperative localization with ^{99m}Tc-sestamibi may guide decisions for unilateral ap-proaches and it is a prerequisite of the minimally invasive ra-dioguided parathyroidectomy [61, 62]. Published data have demonstrated quicker neck exploration and shorter hospital stay with preoperative PT localization and targeted surgical approaches [63, 64].

Secondary and tertiary hyperparathyroidism
In HPT from chronic kidney disease all glands are usually af-fected, but only 1%-2% of these patients undergo total or subtotal parathyroidectomy, irrespective of the scintigraph-ic results (Fig. 3). Because recurrent disease is more frequent in these patients, preoperative ^{99m}Tc-sestamibi imaging has been advocated to detect ectopic or supernumerary glands [21, 65]. However, the diagnostic ability of this modality is no more than moderate in eutopic gland hyperplasia, whereas many surgeons assert that the identified aberrant glands are usually located in sites that are routinely explored dur-ing surgery [16, 66]. Moreover, it has been reported that an autotransplant from a non-visualized gland is associated with a decreased probability of recurrent disease, as op-posed to implanted PT tissue from a scintigraphically dem-

onstrated abnormal gland, but seemingly this observation has not gained wide clinical acceptance [14]. In addition, it has been shown that ^{99m}Tc-sestamibi PT imaging can assess the response to calcimimetics and the absence of response with scintigraphy has been proposed as a decisive factor for parathyroidectomy [67]. However, it is not clear if imaging is more reliable than clinical and biochemical assessment in determining the response to treatment. Apparently, more data, including cost analyses, could support more convincingly such clinical applications.

Persistent and recurrent hyperparathyroidism

In persistent HPT abnormalities of calcium metabolism continue or relapse within 6 months after parathyroidectomy and surgical failure is usually due to an ectopic or supernumerary gland or to multigland disease. *In recurrent disease* HPT reappears more than six months after PT surgery and the commonest cause is multigland disease [13].

Reoperation is associated with decreased curative rates and an increased probability of complications. Therefore, a detailed preoperative assessment is compelling. Although in reoperative cases ^{99m}Tc-sestamibi has a reduced sensitivity (75%), it is superior to other imaging modalities in the detection of abnormal PT foci and particularly advantageous is the use of SPET or SPET/CT (Fig. 6) [68, 69]. The site of an autotransplant should be checked because implanted PT tissue may be the cause of recurrence. The aid of high resolution imaging modalities is desirable and PET may be used if previous investigation is negative [21]. Selective venous sampling and arteriography are justified when imaging tests are fruitless [13, 70].

Minimally invasive radioguided parathyroidectomy

Parathyroid imaging is used preoperatively and a gamma-probe is used intraoperatively to guide the surgeon. In Europe a protocol of minimally invasive parathyroidectomy has been proposed by Rubello and Mariani [14, 71]. The preoperative assessment includes ^{99m}TcO$_4$-/^{99m}Tc-sestamibi planar imaging of the neck and chest and a high resolution sonographic examination. If ultrasound results deviate from the scintigraphic findings, SPET of the neck and chest is performed. A high probability for a single adenoma is required to proceed with minimally invasive parathyroidectomy. At the day of surgery, 37MBq of ^{99m}Tc-sestamibi are i.v. injected in the operation room and 10min later maximal neck activity is determined with a gamma-probe. After a small transverse neck incision, a gamma-probe is used to identify the area of maximum count rate which corresponds to the PT adenoma. Radioactivity is measured in the removed gland, the empty PT bed and the thyroid gland to judge the completeness of

surgical resection. Frozen section examinations of the PT specimens are obtained routinely and a quick parathormone measurement is used intraoperatively to conclude surgery (a >50% drop from the preoperative serum parathormone levels 5-10min after successful removal of the overproductive PT gland) [72]. In applying strict selection criteria, approximately 65% of patients with primary HPT are eligible for this type of operation [71].

In the United States, Norman has introduced earlier the minimally invasive radioguided parathyroidectomy and he continues to upgrade his surgical protocol [73, 74]. In the latest version, ^{99m}Tc-sestamibi is injected 1.5-2h before the operation and planar imaging of the neck and chest is used to rule out ectopic locations of PT glands rather than to detect solitary adenomas [12, 74]. After patient's sedation and a small transverse suprasternal incision, the neck is explored bilaterally. Macroscopically abnormal PT glands are removed and a gamma-probe is used to confirm their hyperfunction and also to determine the metabolic state of the remaining glands ex vivo from very small resected pieces. The gamma-probe is adjusted to measure how much parathormone any individual gland is producing, while intraoperative parathormone assays and frozen samples are not employed. The operation is carried out on an average of 17min, the patient is discharged 1-2h later and cure rates are excellent (>99%) [14, 74].

Outcome based appraisal

The assessment of the clinical impact of PT imaging relies upon the surgical success as end-point. It is conceivable that in this type of studies surgical approaches often are driven by the scintigraphic findings and the results are based on abnormal glands that were successfully removed and characterized histopathologically. Other PT glands with milder disease, which macroscopically and sctinigraphically may have been deemed normal, may become clinically evident later on as recurrent disease [75]. Moreover, the histopathologic characterization of PT glands is often challenging, especially in hyperplasia, whereas intraoperative parathormone measurements may occasionally fail to document the completeness of surgical resection [14, 20]. Clearly, a more robust assessment of the clinical value of PT scintigraphy would require follow-up data.

In a long-term follow-up study of 15,060 patients having undergone parathyroidectomy for primary disease in Norman's specialized center, a <1% recurrence rate has been reported by bilateral neck exploration [74]. Conversely, failures were 11 times more likely in the unilateral surgical approach and 5% of these patients had recurrent disease the ensuing years. Interestingly, 65% of patients referred from different medical centers had one or more negative scans at presen-
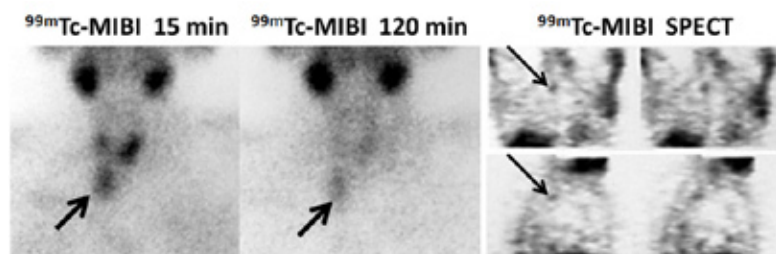
Figure 6. Persistent hyperparathyroidism. The abnormality identified (arrow) is separate from the thyroid parenchyma and it is easily visible despite the similar washout rates between the thyroid and the parathyroid glands. This overproductive parathyroid gland had been detected prior to the unsuccessful operation. Although its position below the thyroid gland frequently reflects a location along the thyrothymic tract, in this case SPET determines an ectopic site close to the spine.

tation, whereas in that specialized institution approximately 80% of patients had abnormal findings in routine preoperative planar scintigraphy. Moreover, in 20% of patients with a ^{99m}Tc-sestamibi scan suggesting unilateral disease, at least one additional overproductive PT gland was removed by bilateral neck exploration. Similar was the impression on unilateral versus bilateral PT surgery from a different institution reporting on 1,158 patients [76]. These results motivated Norman to abandon unilateral approaches in parathyroidectomy and switch to standard bilateral neck exploration with a minimally invasive surgical technique and scintigraphic support, as summarized above [12, 74].

Concluding remarks

The hypercalcemia of HPT can cause unpleasant symptoms and significant complications to the patient and surgical removal of the hyperfunctioning tissue offers the only durable cure. Radionuclide PT imaging has no role in the diagnosis of HPT or in the decision for surgical treatment, but it can localize abnormal PT glands preoperatively. In primary HPT nuclear assessment may occasionally be helpful before bilateral neck exploration, it can identify patients eligible for targeted surgical approaches and it is an irreplaceable component of the minimally invasive radioguided parathyroidectomy. In secondary and tertiary HPT the clinical usefulness of ^{99m}Tc-sestamibi scintigraphy is questionable, but in persistent or recurrent disease it is the examination of choice.

Routine clinical practice does not necessarily replicate the optimal results of certain studies, while a technically advanced imaging system does not guarantee diagnostic infallibility [77]. A reliable and clinically meaningful scintigraphic assessment of the PT glands depends significantly on the competence of the imager, but it cannot replace the skills of an experienced endocrine surgeon [14, 16, 47]. Radionuclide PT assessment, as a tool of preoperative mapping and intraoperative guiding, would interest principally endocrine surgeons rather than endocrinologists.

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