# Parathyroid Scintigraphy

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## 1. Introduction

The diagnosis of hyperthyroidism is made by biochemical testing, not by parathyroid scintigraphy. Parathyroid gland scintigraphy aims to detect parathyroid adenomas (primary hyperparathyroidism, pHPT) or hyperplastic parathyroid glands (secondary hyperparathyroidism, sHPT). The sensitivity of the later is slightly lower. Based on the findings on parathyroid scintigraphy, the surgical approach to the disease can be determined (minimally invasive surgery, unilateral or bilateral exploration).

*Anatomy and physiology*

There are 4 parathyroid glands, two upper and two lower glands, which are normally located behind the thyroid gland. The two upper parathyroid glands are found behind the upper one third of either thyroid lobe. The lower glands are usually behind the lower one third of either thyroid lobe. However, the location varies significantly. Parathyroid glands are often found intra-thyroidally, in the mediastinum, in the thymus or even high in the neck if they do not migrate properly during embryological development. The shape of parathyroid glands (and therefore adenomas) also varies considerably (round, multi-lobulated, leaf like). Single parathyroid glands may be missing. Additional glands are mostly found in the thymus. The parathyroid glands are responsible for the production of parathyroid hormone (PTH) which plays a major role in calcium metabolism of the human body, as well as influencing vitamin D and phosphate levels.

Primary hyperparathyroidism is usually caused by the presence of a hyper functioning parathyroid adenoma, though in 10-15% of cases two parathyroid adenomas are present. Parathyroid carcinoma is found in fewer than 1% of cases. Elevated PTH levels lead to changes in calcium homeostasis with increased calcium levels in urine and blood while phosphate is elevated in urine and low in blood. Patients may present with nephrocalcinosis, urolithiasis, bone disease, gastrointestinal and neuromuscular symptoms. or even neuropsychiatric disorders (ranging from mild behavioural changes to coma). However, due to easier access to biochemical tests, patients are nowadays often diagnosed with subclinical hyperparathyroidism.

Primary hyperparathyroidism also occurs as part of multiple neuroendocrine neoplasia (MEN) syndrome (MEN1 or MEN2A). Secondary hyperparathyroidism results from chronically low calcium levels (such as in renal failure, gastrointestinal calcium malabsorption etc.) but can also be due to the use of certain drugs. Tertiary hyperparathyroidism (tHPT) results from autonomous function as a consequence of hyperplastic parathyroid glands (secondary hyperparathyroidism).

## 2. Methodology

This guideline is based on available scientific literature on the subject, the previous guideline (Aanbevelingen Nucleaire Geneeskunde 2007), international guidelines from EANM and/or SNMMI if available and applicable to the Dutch situation.

### 3. Indications

As stated above, the diagnosis of hyperparathyroidism is based on biochemical parameters. Parathyroid scintigraphy should be used to determine the anatomical localisation of the diseased gland(s). This means, the diagnosis of HPT is based on high PTH levels in the presence of elevated Ca levels – it should be kept in mind, however, that patients with HPT may also have PTH or Ca levels in the upper normal range.

The use of parathyroid scintigraphy and the combination with other imaging procedures may vary between different hospitals. It is also dependent on the preferences of the surgeon as well as the experience of the nuclear medicine physician. The added value of parathyroid imaging was controversial at a time when bilateral neck explorations were the standard surgical procedure for HPT. However, the use of minimally invasive surgery as standard approach nowadays and the need to reduce operation times has led to general acceptance of preoperative imaging in HPT. Also, patients with persistent or recurrent HPT have mostly been operated upon previously, thereby increasing the level of complexity of further operations. In such cases exact preoperative localisation of the lesion is essential in order to reduce operation time and avoid complications which might arise with extensive exploration of the neck.

Thus, parathyroid scintigraphy should be performed in all patients undergoing first minimally invasive or unilateral neck exploration in pHPT and in all patients undergoing reoperation for persistent or recurrent pHPT[3]. Also, parathyroid scintigraphy may help to distinguish between patients who are suitable for minimally invasive surgery and those who require bilateral neck exploration. In sHPT (or tHPT), the lower sensitivity means the case for scintigraphy is not as strong and may depend on the surgeon's preferences. If bilateral neck exploration is performed as primary operation, imaging may not contribute significantly as the lower sensitivity requires exploration of all parathyroid glands during surgery. Instead, an intraoperative PTH assay may help to determine the success of the operation. In case of reoperation, however, imaging may help to better guide the surgeon.

### 4. Relation to other diagnostic procedures

Other diagnostic imaging procedures performed for (suspected) HPT include PET imaging with various radiotracers (FDG, ^{11}C-Methionine and other radio labelled amino acids), CT, MR imaging and, most importantly, high resolution ultrasonography.

<u>PET:</u> Successful localisation of parathyroid adenomas has been described with FDG PET. However, FDG imaging of parathyroid adenomas does not seem to be an appropriate procedure for standard parathyroid imaging due to the unpredictable nature of the results. However, ^{11}C-methionine imaging may be a promising technique for localisation of adenomas not identified by parathyroid scintigraphy and ultrasound. The use of ^{11}C is limited to centres that have a cyclotron available and produce this tracer regularly. As an alternative to ^{11}C methionine, ^{18}F-choline has recently shown promising results for the detection of parathyroid adnomas.

<u>Ultrasound (US):</u> US is an imaging technique which relies on the reflection of sound waves. The reflected waves vary depending on tissue density. US does not require radiation exposure but is highly dependent on the operator. In addition, it is a dynamic investigation so static images taken during US are difficult to interpret by another person. For parathyroid US, the result is highly dependent on the experience of the operator. An ultrasound probe of 12,5 MHz or higher should be used. Parathyroid adenomas

are frequently found if they are in the usual locations, detection of ectopic adenomas, however, can be difficult. If the patient is able to extend the neck with the shoulders on a cushion, it is sometimes possible to detect ectopic parathyroid adenomas retrosternally. US can also detect ectopic adenomas behind the oesophagus. Parathyroid adenomas vary greatly in their appearance on US. While they are usually hypoechogenic, round or oval structures, they can also be inhomogeneous with hyperechogenic parts. The shape can be irregular or lobulated. Intrathyroidal localisation can occur making differentiation from thyroid nodules difficult, as thyroid nodules may show the same characteristics as parathyroid adenomas.

CT and MRI: High resolution CT and MRI may help to localise parathyroid adenomas previously not detected by parathyroid scintigraphy or US. Also, ectopic adenomas which do not show radiotracer uptake and are undetectable by parathyroid US because of their ectopic location may be detected by CT and MRI.

## 5. Medical information necessary for planning

In preparation for parathyroid scintigraphy it is important to know about the thyroid function as well as the presence of thyroid nodules or nodular goitre. This information is essential as both autonomous and normally functioning thyroid adenomas can show radiotracer uptake similar to that of parathyroid adenomas. In addition, patients with a nodular goitre may show inhomogeneous uptake in the thyroid gland thereby blurring the margins of the thyroid.

Iodine containing CT contrast media must not be used 3-4 weeks prior to parathyroid scintigraphy. Iodine containing contrast will significantly reduce the sensitivity of dual tracer imaging by reducing or blocking the uptake of $^{99m}$Tc or $^{123}$I.

## 6. Radiopharmaceuticals

For parathyroid scintigraphy, $^{99m}$Tc labelled sestamibi or tetrofosmin can be used. Both radiotracers accumulate in thyroid tissue as well as in parathyroid adenomas. Sestamibi shows a more rapid washout from thyroid tissue as compared to parathyroid adenomas. This is not the case for tetrofosmin which has a slow washout from both thyroid tissue and parathyroid adenomas. Therefore, while sestamibi can be used for dual tracer as well as dual phase imaging, tetrofosmin should be used for dual tracer imaging only[1]. Hyperplastic parathyroid glands (sHPT) usually show a quicker washout than parathyroid adenomas. However, it should be kept in mind that parathyroid adenomas can show a rapid washout similar to that from thyroid tissue. The activity administered intravenously ranges from circa 500 MBq to 1100 MBq, with higher doses recommended in the US as compared to Europe. European guidelines recommend not exceeding 700MBq.

For dual tracer imaging, the thyroid can be imaged using either $^{99m}$Tc or $^{123}$I. $^{99m}$Tc is taken up by thyroid tissue (but not organified) so the image obtained can be used for subtraction from sestamibi or tetrofosmin images. The remaining activity may then represent a parathyroid adenoma. The recommended doses of activity for intravenous administration is 40-370 MBq. In clinical practice, 35-75 MBq will usually suffice for delineation of the thyroid and the background activity is comparably low. $^{123}$I is taken up by functioning thyroid tissue and organified. The organ to background ratio is higher than for $^{99m}$Tc. Administration of 7,5-22 MBq $^{123}$I is recommended, either orally or intravenously.

### 7. Radiation safety

Sestamibi and tetrofosmin are primarily used as radiotracers for cardiac imaging. Radiation exposure has therefore been determined in cardiac imaging studies. The effective dose for sestamibi is slightly higher than for tetrofosmin ($9\times10^{-3}$ mSv/MBq and $8\times10^{-3}$ mSv/MBq, respectively). The effective dose for 500 MBq is therefore 4,5 mSv and 3,8 mSv. Keep in mind that the effective dose for females may exceed that for males by 20-30%. The effective doses for ^{123}I and ^{99m}Tc are $2,2\times10^{-1}$ mSv/MBq and $1,3\times10^{-2}$ mSv/MBq, resulting in clinical effective doses of 2,2 mSv for 10 MBq of ^{123}I and approximately 0,5 mSv for 37 MBq [99m]Tc. According to ICRP 106 there is no need to interrupt breastfeeding, but due to possible free ^{99m}Tc pertechnetate it is advisable to interrupt the feeding for 4 h.

### 8. Patient preparation/essentials for procedure

Discontinuation of thyrostatic drugs (thiamazol, methimazole or propylthiouracil) is recommended if dual isotope protocols are used, as thyrostatic medication may reduce uptake into the thyroid gland. Discontinuation for 3 days is sufficient, also for propylthiouracil.  The same is true for iodine-containing contrast media for dual tracer imaging, which should be avoided for at least 3-4 weeks. Patients who are unable to lie still for the procedure may require sedation. All patients should be informed of the requirement to remain immobile during the investigation.

It has been suggested that vitamin D should be discontinued prior to scintigraphy in sHPT: active vitamine D for 1 week; native vitamine D for 3-4 weeks; calcimimetics for 2 weeks. In addition, consider discontinuing drugs that suppress parathyroid (hyper)function, for a few days before scintigraphy.

No other specific patient preparation is required.

### 9. Acquisition and processing

Dual phase scintigraphy: early and late planar images should be obtained (5-15 and 120 min post injection of 500MBq ^{99m}Tc-sestamibi/tetrofosmin) with the patient in supine position using a low energy, high resolution parallel hole collimator with a 128x128 or 256x256 matrix (cone beam collimators may increase count efficiency). The field of view should include the salivary glands at the cranial edge and the myocardium at the caudal edge. After the early planar images, preferably starting no later than 1 h p.i., SPECT images should be obtained from the salivary glands as far caudally as possible. A low energy, high resolution parallel hole collimator should be used with a 128x128 matrix (higher matrix sizes may not be supported by currently available reconstruction software packages). Acquisition of 120 views of 20-30 sec each, is recommended. SPECT/CT is recommended for optimal anatomical localisation.

Subtraction scintigraphy: combined ^{123}I/^{99m}Tc-sestamibi/tetrofosmin scintigraphy can be performed as simultaneous planar imaging procedure. 2-3 h after administration of the ^{123}I, ^{99m}Tc-sestamibi/tetrofosmin is injected and the patient is placed in supine position on the camera bed. Five minutes after ^{99m}Tc-sestamibi/tetrofosmin injection, planar images of the head and neck (beginning at the level of the salivary glands) and the thorax (down to the level of the myocardium) are acquired with symmetrical 10% energy windows (140 keV±5% for ^{99m}Tc and 159 keV±5% for ^{123}I). As an alternative, a 14% energy window has been proposed (140 keV-10%/+4% for ^{99m}Tc and 159 keV+10%/-4% for ^{123}I) for reduction of cross-talk between the two isotopes. A low energy, high resolution parallel

hole collimator should be used and the images should be acquired with a 256x256 matrix. Pinhole images may also be acquired for improving the spatial resolution. SPECT images are advised for the detection of parathyroid adenomas located deeply in the neck in the paraoesophageal or retrooesophageal area.

Combined $^{99m}$Tc pertechnetate/$^{99m}$Tc-sestamibi/tetrofosmin scintigraphy cannot be performed as a simultaneous planar imaging procedure but only as a sequential procedure. Several different protocols have been proposed; these differ mainly in the amount of activity recommended. Here, a compromise is suggested between obtaining optimal image quality and reducing radiation exposure. The patient is given 40 MBq $^{99m}$TcO$_4^-$ i.v. and 20 min later, a planar image is obtained. 400 mg of potassium chloride is administered p.o. either right before or after the image is acquired in order to induce more rapid wash-out of the $^{99m}$TcO$_4^-$ from the thyroid thereby reducing interference with following images. The patient remains in the same position and $^{99m}$Tc-sestamibi/tetrofosmin is injected intravenously. Planar images are acquired for 15 min, starting 5-15 min p.i.. As an alternative, dynamic images may be acquired for 20 min starting immediately after $^{99m}$Tc-sestamibi/tetrofosmin administration.

Processing: no specific requirements of processing of planar images have been proposed. When using the dual tracer method, over-subtraction leading to a white field in the area of the thyroid reduces sensitivity and should therefore be avoided. SPECT image reconstruction should be performed using an iterative algorithm that is offered by all camera vendors and some other software packages. Filtered back projection can no longer be recommended. One should be aware that the settings used for reconstruction as well as the choice of the reconstruction software may significantly influence the sensitivity of parathyroid scintigraphy.

## 10. Interpretation

The interpretation of parathyroid scintigraphy should aim at high sensitivity. If combined with US, improved specificity can be achieved by visualization of diseased parathyroid glands by US. The correct interpretation of parathyroid scintigraphy is more dependent on expertise than is the case for many other types of scintigraphic images. Frequent interpretation of parathyroid scintigraphy will help to build up the expertise required. Independent of the imaging technique used (dual phase or dual tracer) and the time point of imaging after iv injection, all sites of sestamibi/tetrofosmin uptake in unusual locations are suspicious for parathyroid adenoma, especially if located in areas where ectopic adenomas can be found. However, focal areas of activity retention located intravenously or in tumours (such as head and neck or breast carcinoma) can lead to false positive findings; these can nevertheless be clinically relevant.

On planar images parathyroid adenomas can be projected over salivary glands and are thus easily missed despite the asymmetry caused. This emphasizes the importance of standard SPECT scanning.

Dual phase scintigraphy: parathyroid adenomas may be detected on early planar images as inconsistencies in the uptake pattern of the thyroid. On the late images, parathyroid adenomas may be represented by areas with retention of radioactivity. However, it should be kept in mind that parathyroid adenomas can show the same washout as thyroid tissue. Thus, proper evaluation of the early images in comparison to the late images is required. Parathyroid adenomas are mostly located behind the thyroid gland. They often appear

as slightly darker areas on either early, late or both images but they do not necessarily change the contours of the thyroid. Any slight increase in uptake in the upper or lower part of a thyroid lobe can potentially represent a parathyroid adenoma.

Due to the quick washout of most parathyroid adenomas, early SPECT images are advised. However, this means the detection of parathyroid adenomas be complicated by the activity present in the thyroid gland. Therefore, inconsistencies in the contour of the thyroid gland can represent suspicious lesions, especially if located dorsal to the upper or lower third of the respective thyroid lobe. Parathyroid adenomas can be represented by protrusions from the upper or lower part of a thyroid lobe may, they can also be located dorsal to the middle part of a thyroid lobe or located ectopically. Changing the scaling several times during interpretation of the images is advised in order to increase sensitivity.

Dual tracer scintigraphy: the thyroid-specific ($^{99m}$Tc or $^{123}$I) scan is compared to the thyroid/parathyroid-specific scan (tetrofosmin or sestamibi). This comparison may be based on fused subtraction images or the fusion may be done visually. Discrepancies indicate the presence of a parathyroid adenoma. Slightly elevated uptake of $^{99m}$Tc or $^{123}$I may also be found at the location of the parathyroid adenoma, although it is less intense than with sestamibi/terofosmin. Another potential pitfall is suboptimal fusion of the $^{99m}$Tc/$^{123}$I and sestamibi/tetrofosmin images resulting in false positive or false negative findings. In particular, the fused images should result in activity in the thyroid area which is comparable to neck background as over correction of the thyroid area may reduce sensitivity and lead to false negative results. Therefore, critical evaluation of the quality of the image fusion is essential.

Comparison to US imaging: in the optimal situation, the scans are evaluated by a physician with extensive experience of parathyroid scintigraphy evaluation but who is also highly skilled in parathyroid US. In this case, the same physician can optimally correlate parathyroid scintigraphy and US in a time-efficient manner. If no such person is available, it may be useful to perform parathyroid US with the nuclear medicine physician present. Thus allowing for review of the parathyroid scintigraph during US imaging. In this manner, suspicious findings on parathyroid scans can be verified by US, which helps an experienced surgeon to plan and conduct the operation optimally. However, this approach only delivers optimal results if the US operator is highly experienced and the necessary amount of time is invested in order to correlate scintigraphy and US with sufficient precision.

## 11. Report

A parathyroid scintigraph report should include all relevant information about the imaging protocols used (including radiopharmaceuticals, activity doses, imaging time points, etc.) and the findings observed (location and number of suspicious lesions, potential differential diagnosis, certainty of diagnosis).

## 12. Literature

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