

¹²⁴I PET/CT in Thyroid Cancer

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1. Introduction

Papillary and follicular thyroid cancer (differentiated thyroid carcinoma, DTC) are the most frequent histological types of thyroid cancer (85-90%). Total thyroidectomy with or without lymph node dissection is the initial therapy and is followed by radioactive iodine therapy to remove thyroid remnants and tumour residuals. In most of the differentiated thyroid cancer cells, three important functional features of the normal thyroid cells are preserved. Firstly, the ability to respond to (endogenous or exogenous) TSH, which has led to the use of thyroid hormone therapy to suppress TSH and prevent tumour growth. Secondly, the ability to accumulate iodine through the Na⁺/I⁻ symporter (NIS), which allows post-surgical treatment with ¹³¹I and the use of diagnostic ¹²³I/¹³¹I scanning during follow-up. The presence of the NIS in thyroid cancer cells is well documented. However, expression of the NIS receptor is decreased compared to normal thyroid tissue. Moreover, 20-30% of patients with DTC have lost the ability to concentrate iodine, making treatment with radioiodine impossible. Usually this occurs during follow-up, it is relatively rare at baseline. Thirdly, the ability of differentiated thyroid cancer cells to synthesize and secrete the protein thyroglobulin (Tg), which makes Tg a widely-used and specific tumour marker for persistent, recurrent or metastatic disease.

Although the prognosis of DTC is excellent with a 10-years survival of 80-95%, relapse can occur in up to 20% and has a less favourable prognosis. Measurement of the serum level of thyroglobulin (Tg), under (recombinant human, rh) TSH stimulation or suppression, and ultrasonography have gained a central role in the detection of recurrent thyroid cancer.

Patients with increasing or elevated Tg can be blindly treated with a high dose of ¹³¹I, followed by a post-treatment ¹³¹I scan which also serves as a diagnostic tool. However, with this strategy, there is a risk of giving an unnecessarily high radiation dose (with possible side effects such as sialoadenitis, loss of taste, fertility disorders, long-term risk of secondary malignancies) especially in patients who subsequently have no ¹³¹I uptake on their post-treatment scan. Improvement of diagnostic imaging for the detection of recurrent or metastatic disease and a better (anatomical) localization e.g. using advanced imaging technique such as ¹²⁴I-PET/CT allows more selective application of ¹³¹I therapy and might avoid futile high dose treatments.

¹²⁴I is a positron emitting isotope and therefore suitable for PET imaging. Its half-life is 4,2 days with a very complex decay scheme leading to extra non- or partial annihilation radiation coincidence detection. Approximately 23% of the disintegrations results in positron emissions. ¹²⁴I PET (/CT) may be able to detect recurrent or residual disease in DTC with a higher sensitivity than the conventional (diagnostic) ¹³¹I scans because of the higher spatial resolution. The effective dose of ¹²⁴I is less than a blinded dose ¹³¹I, so there is also considerably less radiation exposure. Thus, ¹²⁴I-PET imaging could possibly

be a useful diagnostic tool during the follow-up of DTC patients. Furthermore, performing dosimetry prior to radioiodine therapy using ¹²⁴I PET(/CT) seems to be feasible and more accurate than dosimetry based on planar gamma camera using ¹³¹I or ¹²³I.

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

Differentiated thyroid carcinoma (papillary/follicular)

- a. (re)staging of recurrent/residual disease in a whole body procedure, before high dose ¹³¹I treatment.
- b. the kinetics of ¹²⁴I are identical to those of ¹³¹I and therefore suitable for dosimetry prior to ¹³¹I therapy, which allows individual assessment of radiation exposure and to optimize treatment. The goal of personalized radioiodine therapy is to eliminate all thyroid remnants and metastatic tissue without exceeding critical blood dose of 2 Gray (Gy), which is considered the threshold for bone marrow toxicity. In phantom and clinical studies ¹²⁴I-PET/CT seems to be a feasible and promising tool to perform dosimetry in therapy planning.

4. Relation to other diagnostic procedures

In patients with elevated or increasing Tg, ultrasonography of the neck and ¹³¹I/¹²³I -whole body scan (WBS) are used to detect recurrent/residual and metastatic disease. Ultrasonography has proven to be a valuable diagnostic tool, but it is limited to the neck region.

Morphological imaging with CT alone (with or without contrast enhancement) has limited value in the follow-up of DTC due to low sensitivity and specificity, hampered by postsurgical changes of the neck anatomy which make it difficult to differentiate between scar and tumour tissue. On the other hand, CT is useful in detecting pulmonary metastases. ¹²⁴I is a highly specific tracer that poorly visualizes the surrounding anatomical structures. ¹²⁴I-PET combined with CT not only accurately localizes foci of highly specific radioiodine uptake but also non-iodine avid tumours with a low radiation dose in a whole body procedure. This is particularly important in the pre-treatment planning of patients with DTC. ¹²⁴I PET(/CT) provides images of higher spatial resolution and a better contrast compared to conventional planar and additional single photon emission tomographic (SPECT) imaging using ¹²³I or ¹³¹I.

In patients with increasing or elevated Tg or Tg antibodies but without iodine accumulation, tumour dedifferentiation, and therefore a poorer outcome, must be suspected. At this stage ¹⁸F-fluorodeoxyglucose (FDG) PET(/CT) has been useful in the detection of recurrent or metastatic disease with good sensitivity and specificity, especially when performed after (rh)TSH stimulation.

5. Medical information necessary for planning

- a. Type of tumour
- b. Date and extent of thyroidectomy and/or lymph node dissection

- c. Findings at surgery and pathological anatomy: tumour size, extension beyond the thyroid capsule, angio-invasion, lymph node metastases, radicality of the resection
- d. Findings on previous diagnostic and/or post therapeutic ¹²³I /¹³¹I whole body scans
- e. Findings on other forms of imaging, e.g. ultrasound, CT, MRI
- f. Use of thyroid hormone medication
- g. Possibility of iodine contamination in the past 4 months: e.g. iodinated contrast medium (contrast enhanced CT) or medication (including homeopathic remedies)
- h. Blood tests: TSH, thyroglobulin, thyroglobulin antibodies in serum
- i. Pregnancy and/or breastfeeding

6. Radiopharmaceutical

Tracer:	¹²⁴ I-sodium iodide
Nuclide:	Iodine-124
Activity:	25-74 MBq
Administration:	intravenously or orally

7. Radiation safety

Absolute contraindications: pregnancy and breastfeeding. Breast feeding should be interrupted for at least 3 weeks according to ICRP 106.

Radiation exposure: the effective dose of ¹²⁴I is of the same order of magnitude as ¹³¹I. The effective dose of ¹²⁴I is 0,095 mSv/MBq with a thyroid uptake of 0% and increases to 15 mSv/MBq with a thyroid uptake of 35%.

8. Patient preparation/essentials for procedure

- a. The following preparations are required for an optimal procedure:
- b. In women of childbearing age pregnancy must be excluded prior to ¹²⁴I administration.
- c. Thyroid hormone medication should be discontinued prior to scintigraphy: 4 weeks for levothyroxine, 2 weeks for triiodothyronine (Cytomel R).
- d. If the patient is to be treated/ assessed under recombinant TSH, 0,9 mg rhTSH is administered intramuscularly at 24 h and 48 h prior to the administration of radioactive iodine. This is an alternative to thyroid hormone withdrawal and can be administered by a general practitioner. Thyroid medication need not be stopped if rhTSH is used.
- e. At the time of maximal TSH stimulation (after thyroid hormone withdrawal or after 2 consecutive rhTSH injection), and just before administration of ¹²⁴I, determine Tg, anti-Tg, as well as TSH and fT4.
- f. Iodinated contrast medium (contrast enhanced CT) and iodinated medication (including homeopathic remedies) must be avoided.
- g. As of 7 days prior to the administration of radioactive iodine, salt-water fish should be avoided. A diet limited in iodine is recommended as of 4 days prior to radioactive iodine administration.
- h. Prior to the scintigraphy allow the patient to urinate and to drink a glass of water. Remove all metal as well as handkerchiefs from pockets.

9. Acquisition and processing

- a. Whole body PET(/CT,) imaging (from upper thigh to the top of the skull) is acquired 24 h after administration of ¹²⁴I. ¹²⁴I is a highly specific PET-tracer. The PET however,

lacks identifiable anatomical references. Therefore combining it with CT (without contrast enhancement due to possible subsequent radioiodine therapy) is needed for accurate localization of lesions. CT data is also used for attenuation correction. PET data is acquired in 2D or 3D mode for 5 minutes over 5-8 bedpositions, depending on the type of PET/CT camera. The images are reconstructed with attenuation-weighted OSEM using 8 subsets and 2 iterations.

- b. Dosimetry using ¹²⁴I PET/CT requires serial whole PET (/CT) scans to determine lesion activity and lesion volume, whole body counting using gamma camera and blood sampling to estimate the critical blood activity up to five consecutive days (4, 24, 48, 72, 96 h and PET/CT 25 h after administration of ¹²⁴I under TSH stimulation). This method has been extensively described in the patient study of Freudenberg et al. (2007) and Jentzen et al. (2008). Although this 5-time-point protocol is the most accurate approach, it is difficult to perform in clinical practice due to logistical and time demands. A more simplified protocol has been proposed using time point 24 and 96 h after administration with reliable results.

10. Interpretation and pitfalls

- a. Physiological uptake is seen in the salivary glands, lacrimal glands, thyroid tissue, oropharynx, nasopharynx, breast tissue, thymus, oesophagus, gastrointestinal tract and genitourinary tract.
- b. Uptake outside these locations is suspected to be tumour tissue.
- c. False-positive uptake can be caused by accumulation of activity resulting from contamination (e.g. tear, saliva, sweat, urine, faeces), cystic lesions (e.g. kidney, breast, ovary), hydronephrosis, inflammatory/infectious disease (e.g. bronchiectasis/pneumonitis, arthritis, skin infection), benign and malignant non-thyroidal tumours (e.g. breast, lung, stomach, ovary). Uptake of ¹²⁴I near the trachea can result in annihilation of the opposite wall of the trachea which incorrectly suggests ¹²⁴I uptake at that location ("shine through").
- d. False-negative outcomes can result from inadequate preparation, (e.g. insufficient TSH stimulation, iodine contamination) or tumour dedifferentiation (no iodine uptake). Iodine-avid diffuse lung micrometastases (which are visible on posttreatment ¹³¹I scan) can be missed on ¹²⁴I PET visually, but can be detected after quantitative analysis using the lung/background (L/B) ratio. Regions of interest (ROI) are drawn in the left and right lung using the left and right shoulder as background.

11. Report

- a. Report the amount of radioactivity administered and time interval between administration and scanning.
- b. Describe locations with physiological and pathological activity.
- c. Describe unexpected findings and give an indication of whether/what further investigation is required.
- d. If dosimetry is performed for pre-therapy planning, describe the dosimetry methods, calculations and results.

12. Literature

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