Chapter 5

PET Imaging in thyroid carcinoma

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Chapter 5

Introduction

Thyroid cancer is the most common endocrine malignancy. It is divided in several types with papillary, follicular, and Hürthecell cancer (also called differentiated thyroid cancer) originating from the follicular epithelial cells as the most common types (>90%). Other types are medullary thyroid carcinoma (a neuroendocrine tumour originating from the calcitonin producing C-cells) (3%-10%) and anaplastic carcinoma (often a dedifferentiated form of the other types) (2%-10%).

There is a different treatment for each of these types of thyroid cancer. In differentiated thyroid cancer the initial therapy is total thyroidectomy with or without lymph node dissection, followed by adjuvant radioactive iodine therapy. Radioactive iodine therapy with $^{131}$I can be used successfully due to the active uptake of iodine in tumour cells of thyroid origin. However, this property can be lost during dedifferentiation, which limits the use of this therapy in anaplastic carcinoma. Medullary thyroid tumour cells show no iodine uptake at all and curative options are therefore mainly limited to surgical resection of primary tumour and metastases.

The prognosis for differentiated thyroid cancer is good, with an average 10-years survival between 80% and 95%. However, these tumours can dedifferentiate, which results in limited therapeutic options, leading to a much poorer prognosis with a 5-years survival of 30%. Medullary thyroid carcinoma has a 10-years survival of 20%-70%, and for anaplastic thyroid carcinoma the median survival is 2-6 months.

Imaging is especially important in determining the right therapeutic approach for patients with differentiated and medullary thyroid carcinoma. Different imaging techniques are available such as computed tomography (CT), magnetic resonance imaging (MRI), conventional nuclear scintigraphy, positron emission tomography (PET), etc.. While MRI and CT are imaging techniques which show morphologic structures, PET imaging depicts pathophysiological processes and is described as functional imaging. The value of PET imaging is emerging mainly in the follow-up of thyroid cancer. Several PET imaging techniques are available for different types of thyroid cancer and these techniques and their applications are discussed in this chapter.
Positron Emission Tomography

Positron emission tomography imaging is a technique used in nuclear medicine which is based on the use of positron emitting isotopes in specific molecules which are relevant for specific metabolic pathways. The PET technique yields a high resolution and the capability to quantify the amount of radioactivity measured in a specific region.

Positrons, emitted by an unstable atom nucleus, are the antiparticles of electrons and have the same mass, but an opposite charge. Positrons are not detected by a PET camera, but photons, which are formed when a positron fuses with an electron, are detected. This means that the positron binds with an electron to form a positronium which annihilates. In this annihilation process all the mass is converted into energy by which two photons are formed. These photons, always carrying an energy of 511 keV, are emitted in opposite directions under an angle of 180º and are detected by the PET camera.⁶

Radioisotopes used in PET imaging usually have a short half life, such as carbon-11(¹¹C; half-life (T₁/₂) 20 min), nitrogen-13 (¹³N; T₁/₂ 10 min), oxygen-15(¹⁵O; T₁/₂ 2 min) and fluorin-18(¹⁸F; T₁/₂ 110 min). Positron emitting radionuclides are in most cases produced by bombarding the target material with highly accelerated particles (deuterons or protons) using a cyclotron and inducing a nuclear reaction. Centres which use isotopes with a very short half-life, such as ¹⁵O, ¹³N, and ¹¹C, need to have an on-site cyclotron. Other longer living isotopes can be made elsewhere and then transported to the PET imaging facility.⁷

A cyclotron is a type of particle accelerator which accelerates charged particles using a high-frequency, alternating voltage. A perpendicular magnetic field causes the particles to assume a circular orbit so that they reencounter the accelerating voltage many times. When the particles are accelerated fast enough they are bombarded on to specific atoms and radionuclides are formed. These radionuclides are trapped and transported to the laboratory where they can be processed for clinical use. The resulting end-products are called radiotracers. The most commonly used tracers are precursors for metabolic pathways, although many other tracer types exist. After preparation and careful quality monitoring, tracers can be injected.

The imaging device used is the PET camera. Most PET cameras consist of a ring of special detectors which are well suited for the detection of 511 keV gamma rays. Software registers only simultaneously entering photonpairs on different detectors. This is called coincidence detection. Coincidence detection removes the need for a lead collimator such that the
sensitivity of the PET imaging system is much higher than for the conventional Anger camera that is used in planar nuclear imaging or single photon emission computed tomography (SPECT). Both the specific block detector structure and the absence of a collimator contribute to a higher resolution as compared with SPECT. Another advantage of PET is that the amount of radioactivity injected in the body can be quantitatively determined. PET is a non-invasive, sensitive imaging tool for depicting of molecular and biochemical processes without changing its physical properties.\textsuperscript{6}

In contrast to radiologic imaging which shows the morphologic structures, nuclear medicine techniques depict pathophysiological processes and are also described as functional imaging methods. The imaging with PET is considered to be an useful diagnostic tool for the detection of cancer, brain diseases, and coronary artery diseases.

**Combined PET/CT**

The combination of PET and CT scanning is a new promising imaging technique. The integrated PET/CT scanner allows acquisition of CT and PET images in one session. The combination of morphologic and functional imaging leads to more precise anatomical localization of tumour lesions. The localization of tumour foci is important for initiating the appropriate treatment such as surgery. Especially in patients with a negative radioiodine scan where surgery is the only therapeutic option, the integrated PET/CT scan can be helpful in guiding therapeutic management.

**\textsuperscript{18}Fluorine-fluorodeoxyglucose (\textsuperscript{18}F-FDG) PET**

**Mechanism**

Fluorodeoxyglucose (FDG) is a glucose analogue and is used as a precursor for glucose metabolism. In both benign and malignant tissue it enters the cell by the same glucose transporters. However, the need for glucose in malignant cells is strongly increased because these cells have a considerably less efficient energy metabolism.\textsuperscript{8} For example, the energy production per molecule of glucose in malignant cells is decreased because anaerobic glycolysis is strongly increased instead of the much more efficient energy production from the citric acid cycle. This inefficient use of glucose is the basis for the preferential uptake of glucose or an offered glucose analogue as FDG in malignant cells.
In the cell FDG is phosphorylated by a hexokinase enzyme into FDG-6 phosphate which, in contrast to glucose-6-phosphate, cannot be further metabolized. Therefore, the FDG-6-phosphate does not leave the cell and becomes trapped intracellularly. The final quantity of FDG-6-phosphate is proportional to the glycolytic rate of the cell. Besides the increased glycolysis, it has been demonstrated that in malignant cells levels of transmembrane glucose transporters (e.g., the GLUT-1 transporter) and possibly some hexokinase isoenzymes are also increased, also resulting in increased FDG uptake.\textsuperscript{9}

However, in all metabolically active tissues, such as brain cells, active muscles, and activated macrophages, increased glucose metabolism leads to an increased FDG uptake.\textsuperscript{18} F-FDG PET is, therefore, a marker for glucose metabolism in general. In most normal tissues (e.g., liver, kidney, intestine, muscle and some tumour cells) the level of phosphate activity is variable; nevertheless, FDG-6-phosphate accumulation is lower than in malignant tissues. In addition, some benign tissues require more glucose.\textsuperscript{10,11} So, the uptake mechanism of FDG with irreversible trapping in malignant tissue is ideal for PET imaging and has been applied widely in oncology. However, it is important to make a correct interpretation of these PET images, for non-malignant tissue also has FDG uptake.

**Scan method**

Uptake of $^{18}$F-FDG occurs rapidly after administration and the amount taken up increases with time. The most applied imaging moment is 60-90 min after tracer administration. The reason is that the excretion of $^{18}$F-FDG via the kidneys reduces $^{18}$F-FDG in the blood, which causes clearance of ‘background’ uptake and the decay of fluorin-18 ($T_{1/2}$ 110 min). Generally the patient preparation consists of an $^{18}$F-FDG injection in a fasting condition and after or al prehydration. The injected dose varies between 2-8 MBq/kg.

**Clinical application**

**Thyroid nodules**

The value of $^{18}$F-FDG PET in the distinction between malignant and benign thyroid nodules before surgery is unclear. Several studies reported that $^{18}$F-FDG PET is useful in the preoperative evaluation of cytologically inconclusive nodules with a high negative predictive value.\textsuperscript{12-14} De Geus-Oei et al. observed that the probability for thyroid cancer increased from 14% (pre-PET) to 32% (post-PET) in case the nodule was positive on $^{18}$F-FDG PET.\textsuperscript{12} In this study $^{18}$F-FDG PET could reduce the number of futile hemithyroidectomies by 66%. 
Figure 1 These are the images of a 68-year old male known with follicular thyroid cancer. This patient showed increased serum Tg level (14 ng/ml) suspected for recurrent or metastatic disease. Blind treatment with $^{131}$I was given followed by a post-treatment whole body scan (WBS) after 10 days which was negative. $^{18}$F-FDG PET (A) showed a focal lesion in the lower lobe of the left lung (arrow), confirmed by CT (B, arrow). Picture C showed the fusion image of $^{18}$F-FDG PET and CT for the lesion in the left lung (arrow).

However, recent studies by Kim et al. and Bogsrud et al., demonstrated that $^{18}$F-FDG PET is not helpful in differentiating between malignant and benign nodules, and therefore has only limited value in preoperative evaluation of indeterminate thyroid nodules.\textsuperscript{15,16} So, conflicting results are reported on the usefulness of $^{18}$F-FDG PET in the prediction of malignancy in thyroid nodules in case of inconclusive cytology, and therefore further research is needed. Meanwhile histopathological examination remains the gold standard.

Differentiated thyroid cancer (DTC): follow-up

More information is available regarding the value of $^{18}$F-FDG PET in the follow-up of thyroid cancer such as the detection of recurrences or metastases, especially in patients with a negative radioiodine scan or in patients who has lost the ability to accumulate iodine. A
complementary uptake of $^{18}$F-FDG and radioiodine can be present, which is known as the ‘flip-flop’ phenomenon and was first described by Joensuu and Ahonen. This phenomenon might be explained by the degree of tissue differentiation. Well differentiated thyroid tissue has the capability to take up iodine but is metabolically inactive while less differentiated thyroid cancer tissue loses its capability to trap iodine and becomes metabolically more active. This makes $^{18}$F-FDG PET scanning the method of choice for the detection of $^{131}$I negative metastases of differentiated thyroid carcinoma.

Performance of $^{18}$F-FDG PET during thyrotropin (TSH) stimulation improves the results in comparison to the scanning during the euthyroid state (during thyroxin treatment) as was shown by van Tol et al.. In vitro studies have shown a stimulating effect of TSH on Glut 1 expression and glucose transport. This increase in glucose carriers results in a higher uptake of glucose and also $^{18}$F-FDG in thyroid cancer cells, which improves the result of the PET-scan. Stimulation with exogenous TSH (recombinant human(rh) TSH) also increases $^{18}$F-FDG uptake by differentiated thyroid cancer, and therefore more lesions can be detected and tumour/background contrast is enhanced. The influence of rhTSH on the background is not well-known, but there is evidence that rhTSH increases $^{18}$F-FDG uptake in the tumour lesion itself.

Several studies have been performed to assess the value of $^{18}$F-FDG PET imaging in the follow up of thyroid cancer. Hooft et al. performed a meta-analysis of studies that investigated the role of $^{18}$F-FDG PET in patients with thyroid cancer after negative radioiodine scintigraphy and elevated serum thyroglobulin. The diagnostic accuracy of these studies was assessed. Observed sensitivity and specificity in these studies were ranging from 70%-95% and 77%-100%, respectively. Furthermore, they observed that there are methodological problems in these studies such as small sample size, validity of reference tests, and short follow-up. Nonetheless, $^{18}$F-FDG PET is now considered a valuable diagnostic imaging tool in the follow-up of $^{131}$I-negative patients for the detection of recurrences or metastases.

However, it is not known whether PET is superior to bone scintigraphy in the detection of bone metastases in thyroid cancer. Comparative studies of bone scans and $^{18}$F-FDG PET are lacking. In a retrospective study, 24 patients had undergone both $^{18}$F-FDG PET and bone scans within six months because of suspected bone metastases. This study shows that bone scintigraphy is still valuable in differentiated thyroid cancer, as it was found that 38% of bone metastases could be missed on $^{18}$F-FDG PET. Further prospective studies in a higher number of patients are required to define the exact role of bone scan and $^{18}$F-FDG PET in the detection of bone metastases in patients with differentiated thyroid cancer (DTC).
Combined or integrated $^{18}$F-FDG PET/CT in patients with negative $^{131}$I scans and elevated thyroglobulin (Tg) showed that the diagnostic accuracy can be improved compared to $^{18}$F-FDG PET or CT alone. The combination of these imaging techniques has also led to a change in patient management and therapy, e.g., extension of surgery by providing precise anatomical localization of the recurrent or metastatic disease.\(^{26}\)

**Medullary thyroid cancer (MTC)**

The detection of recurrence or metastases in MTC is difficult and there is no single method sensitive enough to reveal all MTC recurrences or metastases. In comparison with the calcitonin tumour marker nearly all imaging modalities (Ultrasonography, CT, MRI, and scintigraphy) have limited sensitivities. The clinical role of $^{18}$F-FDG PET in the diagnosis and staging of recurrent and metastatic MTC seems promising.\(^{27}\)

The sensitivity and specificity of $^{18}$F-FDG PET ranges between 73%-88% and 76%-80%, respectively. In a study by de Groot et al., $^{18}$F-FDG PET was performed in patients with elevated serum tumour markers after total thyroidectomy.\(^{28}\) Compared with $^{111}$In-octreotide imaging (lesion based sensitivity: 41%), $^{99m}$Tc(V)DMSA scintigraphy (57%) and morphological imaging (87%), $^{18}$F-FDG PET (96%) was superior. However, morphological imaging will always be needed because $^{18}$F-FDG PET only yields functional data and no morphological information, which is necessary to assess resectability.

The combination of $^{18}$F-FDG PET/CT can have a useful role in medullary thyroid cancer. Because surgery only can cure the disease, precise anatomical localization and the extent of the recurrent or metastatic disease is mandatory. However, little data and case reports have shown an increased diagnostic accuracy so further studies are needed.\(^{27}\)

**$^{18}$Fluorine-dihydroxyphenylalanine ($^{18}$F-DOPA)**

**Mechanism**

The mechanism responsible for uptake of $^{18}$Fluorine-dihydroxyphenylalanine ($^{18}$F-DOPA) in medullary thyroid carcinoma is probably the strongly upregulated transmembrane transport of amino acids via the large amino acid transporters in medullary thyroid carcinoma cells. It is not yet clear whether the increased uptake of $^{18}$F-DOPA PET is the result of the increased transporter capabilities or the increased metabolic activity of the catecholamine pathway.
After transmembrane transport, $^{18}$F-DOPA is intracytoplasmically converted into dopamine by the enzyme aromatic acid decarboxylase (AADC). The formed $^{18}$F-dopamine is transported into secretory vesicles via the vesicular mono amino acid transporters (VMAT) in which it can be further metabolized to $^{18}$F-noradrenalin and $^{18}$F-adrenalin. Although the $^{18}$F atom influences the metabolism of $^{18}$F-DOPA there is no or little effect on the transport into the intracellular environment. In the kidneys, $^{18}$F-DOPA is rapidly converted into $^{18}$F-dopamine which is than excreted actively in urine. This conversion can be inhibited by oral administration of carbidopa prior to tracer administration.

Carbidopa also lowers the physiological uptake of $^{18}$F-DOPA in the pancreas, but it is yet unknown which mechanism is responsible for this decrease in pancreatic uptake. The reduction in renal and urinary activity leads to a better image quality in the surroundings of the urinary system. Also, the reduced uptake in the pancreas makes the identification of lesions in the pancreatic region easier. It can be speculated that by reducing the excretion of $^{18}$F-DOPA, more $^{18}$F-DOPA is available for neuroendocrine tumour lesions; thereby, increasing the tumour to background ratio, leading to a better discrimination of neuroendocrine lesions.

**Scan method**

In most centres, patients are prepared with oral administration of carbidopa, either in a fixed dose or in a dose calibrated to body weight. Patients are scanned in a fasting condition for 4-6 h. In most centres a whole body study will be performed ranging from the skull to the upper femora. The average injected dose is 200 MBq, the radiation burden ~ 4 mSv. Attenuation correction is applied, either by using a CT in a PET-CT machine or by using camera-specific attenuation protocols.

**Clinical application**

**Medullary thyroid cancer**

Although $^{18}$F-DOPA PET is not yet in widespread use, it is a promising new functional imaging procedure for imaging neuroendocrine tumours. More and more centres gain access to this tracer either via on-site production or production elsewhere. Hoegerle et al. were the first to describe the use of $^{18}$F-DOPA PET in medullary thyroid cancer. In this study $^{18}$F-DOPA PET was compared with $^{18}$F-FDG PET, SRS, and CT/MRI. A high precision of $^{18}$F-DOPA PET was observed in the diagnosis of lymph node metastases (sensitivity 88%), while
organ metastases were better detected with conventional imaging (sensitivity 13%). In the recently published study by Koopmans et al. diagnostic accuracy was assessed for $^{18}$F-DOPA PET in patients with carcinoid tumours which are, like medullary thyroid carcinoma, neuroendocrine tumors.\textsuperscript{32} Compared to conventional somotostatine receptor scintigraphy (SRS) they showed improved sensitivity of $^{18}$F-DOPA PET in staging and identify carcinoid tumours.

![Figure 2](image)

**Figure 2** These are the images of a patient known with medullary thyroid cancer. In this patient $^{18}$F-FDG PET (A) and $^{18}$F-DOPA PET (B) were performed. The $^{18}$F-DOPA PET (B) showed multiple lesions in the liver and several lesions in the spinal column (arrows) while the $^{18}$F-FDG PET showed hardly any lesions.

The value of $^{18}$F-DOPA PET for the detection of recurrent or residual disease in 21 patients with postsurgically elevated calcitonin or CEA was assessed by Koopmans et al.\textsuperscript{33} They compared $^{18}$F-DOPA PET with $^{18}$F-FDG PET, $^{99m}$T(V)DMSA, and CT/MRI. $^{18}$F-DOPA PET was superior to conventional imaging for the detection of MTC on patient (sensitivity 87%) and regional (89%) level. On lesional level $^{18}$F-DOPA PET (sensitivity 71%) was equal to morphological imaging (64%) but superior to $^{18}$F-FDG PET (30%) and $^{99m}$T(V)DMSA (19%).

In the recent study by Beuthien-Baumann et al., $^{18}$F-DOPA-PET also seems to be more specific than $^{18}$F-FDG PET for the detection of metastases of MTC.\textsuperscript{34} Thus, compared with $^{18}$F-FDG PET and conventional imaging techniques, $^{18}$F-DOPA PET provides better results in the imaging of medullary thyroid cancer. However, it is still unclear if this improved imaging results in different therapeutic approaches, and so further research is needed.
**11C-Methionine (MET) PET**

**Mechanism**

Proteins play an important role in virtually all biological processes. Proteins are built from a set of 20 amino acids. Amino acid transport across the cell membranes into the cells occurs primarily via carrier-mediated processes. Amino acid transport is generally increased in malignant transformation.\(^{35-37}\) This increased protein metabolism in cancer cells is important for metabolic tumour imaging, for which radiolabeled amino acids can be applied. These amino acid tracers could help in imaging areas where \(^{18}\)F-FDG is limited such as the interference of high (physiologic) \(^{18}\)F-FDG uptake in the brain. Another reason is that amino acid imaging is less influenced by inflammatory disease. The most frequently used radiolabeled amino acid is L-[methyl-\(^{11}\)C]-methionine. Normal biodistribution of radiolabeled methionine occurs in the pancreas, liver, spleen, kidney, and salivary glands.

**Scan method**

\(^{11}\)C-MET PET scanning can be performed 10 to 20 min after intravenous injection of a fixed dose or a dose calibrated on body weight (suggested range is 70 MBq to 1100 MBq), in a fasting condition for 2-6 h. Images are corrected, either by using a CT in a PET/CT machine or by using camera-specific attenuation protocols.

**Clinical application**

**Differentiated thyroid cancer**

The need for new tracers and improvement of diagnostic tools in thyroid cancer is growing. So far, no data on the application of methionine (MET) PET in thyroid cancer are available. The general feasibility of amino acid imaging in many tumour types has been sufficiently shown.\(^{37}\)

It is imaginable that thyroid cancer could sufficiently concentrate amino acids due to its metabolically inert nature and high protein synthesis (e.g., thyroglobulin). In a feasibility study by Phan et al., \(^{11}\)C-MET PET has been compared with \(^{18}\)F-FDG PET in the detection of recurrent or metastatic disease in 20 patients with negative \(^{131}\)I scans and elevated Tg.\(^{38}\) Six of the 20 patients showed uptake on both PET scans, but the abnormalities were more \(^{18}\)F-FDG-avid and more extensive on the \(^{18}\)F-FDG PET in 3 patients. In four of the 20 patients uptake
was only observed on the $\text{^{11}C}$-MET PET; however, no anatomical localization could be confirmed. Presently, the significance of the MET uptake in these four patients is unclear, so the clinical value of $\text{^{11}C}$-MET PET in the detection of recurrent DTC disease still has to be proven in the (long-term) follow-up.

**Figure 3** These are the images of a 68-yr old female known with papillary thyroid cancer. This patient had unreliable Tg due to the presence of Tg antibodies (which were increasing in the course of the follow-up). The post-treatment $\text{^{131}I}$ whole body scan (WBS) was negative. Due to suspicion of dedifferentiated, metastatic disease $\text{^{11}C}$-MET PET (A) and $\text{^{18}F}$-FDG PET (B) were performed. $\text{^{11}C}$-MET PET (A) showed lesions in the mediastinum with slightly to moderate $\text{^{11}C}$-MET uptake. $\text{^{18}F}$-FDG PET (B) also showed multiple lesions in the mediastinum, but the lesions showed clearly higher $\text{^{18}F}$-FDG uptake and the abnormalities were more extensive.

### $\text{^{124}I}$odine-PET

**Mechanism**

Iodine-124 is a positron emitting isotope, which is suitable for PET imaging, with a half-life of 4.2 days. This isotope has been used for dosimetric purposes or thyroid volume measurements. While the radioisotopes $\text{^{123}I}$ and especially $\text{^{131}I}$ are used on a wide scale in diagnosis and treatment of many thyroid disorders, $\text{^{124}I}$ has received little attention. Chemically identical to nonradioactive iodine, this radioisotope allows thyroid cancer imaging with the high resolution PET technique.
Scan method

The $^{124}$I-PET scan can be obtained 24 h to 6 days after administration of 74-100 MBq of $^{124}$I. A whole body PET scan (from the upper thigh up until the top of the skull) can be performed in 2D or 3D mode, using standard energy window setting of 350-650 keV (or energy window setting 425-650 keV or 460-562 keV in case of the presence of high amounts of $^{131}$I.

Clinical application

Differentiated thyroid cancer

Accumulation of iodine is a highly specific characteristic for differentiated thyroid cancer (DTC) cells. In patients with increasing or recurrent detectable Tg a blind treatment (meaning after a negative diagnostic $^{131}$I scan) with high dose $^{131}$I followed by a post-treatment $^{131}$I scan is used as a diagnostic tool. However, this strategy with (unnecessary) high radiation exposure must be taken into account in patients without $^{131}$I uptake in their metastases. Besides the high radiation exposure, there is a high TSH level which potentially stimulates thyroid cancer cell growth.

Based on the higher spatial resolution, $^{124}$I-PET is potentially able to detect recurrent disease in DTC with a higher sensitivity than (diagnostic) $^{131}$I scans. With this higher sensitivity and the possibility to combine the $^{124}$I-PET scan with morphologic imaging, such as CT data, an appropriate therapeutic decision in terms of surgery and/or additional high dose $^{131}$I can be made. $^{124}$I-PET imaging might, therefore, become the diagnostic tool of choice in the follow-up of DTC. In the study by Freudenberg et al., $^{124}$I-PET (/CT) modalities were compared with the high dose $^{131}$I-WBS in 12 patients with DTC. They showed an overall lesion detectability of 87 %, 83%, and 100% for $^{124}$I, $^{131}$I-WBS and combined $^{124}$I-PET/CT respectively. So, these $^{124}$I-PET (/CT) modalities are promising diagnostic tools and are suitable alternative to the high dose $^{131}$I-WBS in the follow-up of DTC patients.

In a prospective, feasibility study by Phan et al., 20 patients with advanced DTC (T4, extranodal tumour growth, distant metastasis) underwent a low-dose diagnostic $^{131}$I scan, a $^{124}$I PET scan, and a high-dose (posttreatment) $^{131}$I scan. The $^{131}$I images were compared to the $^{124}$I-PET images. $^{124}$I-PET proved to be a superior diagnostic tool as compared to low dose diagnostic $^{131}$I scans, and showed comparable findings with the post-treatment $^{131}$I-WBS which was in agreement with the study by Freudenberg et al. and Abdul Fatah et al.. Therefore, $^{124}$I-PET could be used as a diagnostic tool in the follow-up of patients with DTC for the favourable radiation exposure burden compared to the high dose diagnostic $^{131}$I-WBS.
and the superior diagnostic accuracy compared to low dose diagnostic $^{131}$I-WBS and the fusion possibility with CT which improves clinical decision making.

A. Post-treatment $^{131}$I-WBS

B. $^{124}$I-PET

C. $^{18}$F-FDG PET

Figure 4 These are the images of a 68-year old male known with follicular thyroid cancer. This patient showed increased serum Tg level (14 ng/ml) suspected for recurrent or metastatic disease. Blind treatment with $^{131}$I was given followed by a post-treatment whole body scan (WBS) after 10 days (A), which was negative. The $^{124}$I-PET (B) was also negative, besides physiological uptake in the salivary glands, oesophagus, gastro-intestinal tract, kidney and bladder. $^{18}$F-FDG PET (C) showed a focal lesion in the lower lobe of the left lung (arrow), confirmed by CT. This complementary uptake of radioiodine and $^{18}$F-FDG is known as the flip-flop phenomenon.

Conclusion

This chapter on PET imaging in thyroid cancer gives an overview of the different PET techniques available in thyroid cancer. PET imaging is based on two principles: the ability of unstable atom nucleus to emit positrons and the labelling of organic molecules, which are used in specific metabolic pathways.
For differentiated thyroid cancer the most frequently used PET technique is $^{18}$F-FDG PET imaging, which is based on the use of a glucose analogue. Although its application in the preoperative assessment of thyroid nodules is still unclear, it is considered an useful tool in the follow up of differentiated thyroid cancer. The use of PET/CT scanning which combines functional imaging with morphological imaging is promising, providing more accurate localization of tumour sites, which is important for further treatment.

Other PET radiotracers have been developed: the clinical value of amino acid tumour imaging with $^{11}$C-MET PET is unclear and still has to be proven in the follow-up of differentiated thyroid cancer. Another relative new PET imaging technique is the iodine isotope $^{124}$I. Compared with the high dose diagnostic $^{131}$I whole body scan, $^{124}$I-PET showed similar findings and can therefore be used as a diagnostic tool in the follow-up of differentiated thyroid cancer.

For the follow-up of medullary thyroid cancer $^{18}$F-FDG PET is also the most employed imaging technique. However, $^{18}$F-DOPA PET, which is based on a precursor of dopamine, seems to be superior compared to $^{18}$F-FDG PET in the follow up of medullary thyroid cancer. A potential new tracer is $^{11}$C-5-HTP, which is based on a precursor of serotonin and already has been applied in neuroendocrine tumours. The value of this technique has to be further assessed in medullary thyroid cancer.

The need for new tracers and advanced PET imaging to improve the diagnostic sensitivities and accuracy in detection, staging, and follow-up of thyroid cancer patients is growing. Knowledge of the pathogenesis, the molecular characteristics and the behaviour of the tumour cell is crucial for developing of specific tracers and techniques, e.g., radiolabeled Tg, (rh) TSH. Although new tracers are developed and applied in patients, little data are available on the changes in therapeutic management these new PET-techniques give. While PET-imaging is still in development, more research is needed to assess the effects on therapy of these new developments. In conclusion, PET imaging is a useful diagnostic tool in thyroid cancer and new promising techniques are developed which could further improve the diagnostic accuracy and therapeutic approaches.
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