18. THYROID CANCER IMAGING

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INTRODUCTION

Molecular imaging in thyroid cancer using nuclear medicine methods is based on specific cellular characteristics. These characteristics can be derived from common cell features, but can also be based on specific properties of thyroid cancer cells. While in the diagnosis of thyroid cancer these methods have not found great potential, many applications can be found in treatment and follow up of the papillary, follicular and medullary thyroid carcinoma patients. In anaplastic thyroid carcinoma the experience with nuclear imaging is scarce, but the clinical relevance in this aggressive tumor is low.

The broad spectrum of radioactive tracer methods is associated with a great variety in sensitivity and specificity. This variation is partly based on cellular or tumor cell characteristics but also can be explained by the different technical factors and techniques. For example, where radioiodine imaging is among the cornerstones of thyroid cancer treatment, this tracer is of limited value in medullary thyroid cancer. This difference illustrates the importance of the specific cell characteristics that governs uptake of radiotracers. C-cells do not take up radioiodine, while follicular thyroid cells do. Another example can be found in the uptake of the tracer 18 FluoroDeoxyGlucose (FDG), which can be used in conjunction with the Positron Emission Tomography (PET) technique. Uptake of this tracer is based on the glucose metabolism that is present in benign and malignant cells. However, the demand for glucose is considerably higher in malignant cells, which results in higher tracer uptake and adequate

imaging of thyroid cancer lesions. Also other nuclear imaging techniques have their additional value in the diagnosis and sometimes treatment of thyroid cancer. For some tracers the discovery of its value in the diagnosis of thyroid cancer is a matter of serendipity and the mechanisms of action are not always fully understood.

In this chapter nuclear medicine tracers methods, commonly used in thyroid cancer patients, will be reviewed, with a special emphasis on the general uptake mechanism, followed by the method of scanning and the clinical applications.

IODINE

General mechanism

The synthesis of thyroid hormone depends on the supply and metabolism of iodine in the thyroid gland and on the synthesis of thyroglobulin (a receptor protein for iodine). Iodine is taken up by the thyroid follicular cells as inorganic iodide and is transformed through a sequence of metabolic process into thyroid hormones (thyroxine (T4) and triiodothyronine (T3)).

The recommendations of the World Health Organization (WHO) for the iodine intake is 90–200 μg/day (90 μg/day for the newborn, 200 μg/day for the pregnant and lactating women) to maintain growth, development and normal thyroid function (1). The average daily dietary intake of iodide varies greatly per area or country. An average of 190–300 μg iodide per person is ingested daily in the United States. In Europe the average daily intake varies greatly from 50 μg (Belgium) to 430 μg (Great Britain) (2,3). About 60 to 80 μg of iodide is taken up daily by the thyroid from the circulating pool that ranges from 250 to 750 μg. If this extrathyroidal iodide pool is labeled with radioactive iodine (^{131}I or ^{123}I), the percentage of uptake of this tracer in 24 hours (8 to 35%) gives a dynamic index of the thyroid gland activity. The total iodide content of the thyroid gland averages 7500 μg, virtually all of which is in the form of iodothyronines (secretory products of the thyroid gland). In a steady state condition 60 to 80 μg (approximately 1% of the total) iodide is released from the thyroid gland daily. Of this amount 75% is secreted as thyroid hormones, and the remainder is free iodide. The large ratio of iodide stored in the form of hormone to the amount of tuned over daily, can protect the individual from the effects of iodide deficiency for about 2 months (4).

Iodide is actively transported into the thyroid follicular cells against chemical and electrical gradients, the iodide trapping. The site of active iodide transport in thyroid follicular cells is the basolateral membrane. The transport of iodide across this membrane is linked to the transport of sodium (Na+/I symporter (NIS)), generated by Na+/K+-ATPase as the driving force. Iodide trapping is stimulated by the thyroid-stimulating hormone (TSH).

Once in the thyroid follicular cell, iodide moves to the apical surface of the cell and seems to be translocated across the apical membrane by the chloride/iodide transporter molecule pendrin (encoded by PDS-gene) into the lumen (colloid) of the follicle cell (5,6,7). The function of pendrin in the thyroid is currently not precisely determined (5,6,8). Once in the follicular lumen, iodide is immediately incorporated into tyrosine

residues of thyroglobulin (a glycoprotein synthesized on the rough endoplasmatic reticulum). Within the follicle thyroglobulin is iodinated and via monoiodotyrosine (MIT) and diiodotyrosine (DIT) T_4 and T_3 are formed.

Radioactive iodide (^{131}I and ^{123}I) can be used to visualize the thyroid gland and to measure the iodide trapping function. Only the follicular and the papillary variants of thyroid carcinomas, together called differentiated thyroid carcinoma (DTC), have the ability to concentrate radioiodine. Nevertheless, the iodine metabolism is profoundly altered in DTC. Iodine uptake is quantitatively decreased compared with the uptake in normal thyroid tissue. Furthermore, the iodine organification process is defective in thyroid cancer tissue, resulting in shorter biological half-life within the thyroid. Thyroid hormone synthesis is also usually absent. These abnormalities in organification and hormone synthesis are related to decreased NIS-expression and peroxidase genes and the impairment of the pendrin- PDS gene pathway (7). PDS-gene and pendrin expression seems to be dramatically decreased only in DTC (6, 7).

Stimulation of TSH will induce uptake of in tumors that are able to concentrate radioiodine and increase Tg production by all tumor tissues, even in lesions unable to concentrate radioiodine (9). In order to be detectable by gammacamera imaging, lesions must have a critical combination of size and tracer uptake. Thus, the ability to visualize thyroid cancer remnants or metastatic tissue with radioiodine depends on several factors: a critical cell mass; the activity of the iodine trapping and organification mechanisms and incompletely defined mechanism (e.g. pendrin) that export or clear iodine from the cells.

Delivery of radioiodine to the thyroid tissue therefore requires stimulation by high level of endogenous TSH, induced after an adequate period of withdrawal from thyroid hormones causing hypothyroidism.

Iodine isotopes

Several iodine isotopes play an important role in nuclear medicine, as well for in vivo imaging as for in vitro investigations. Radioiodine can be used as a tracer itself, but is also very suitable to label other molecules. Three kinds of iodine isotopes, including iodine-123 (^{123}I), iodine-125 (^{125}I) and iodine-131 (^{131}I), are widely applied in nuclear medicine. ^{123}I and ^{131}I are used for imaging, ^{125}I is unsuitable for imaging, but often used for in in vitro applications and radiolabeling of other substances. Iodine-124 (^{124}I) is a positron emitting isotope, which is suitable for positron emission tomography (PET) imaging. A summary of the properties of these iodine isotopes is presented in Table 1.

Table 1. Characteristics of iodine isotopes

Iodine isotopes	$T^1/_2$	Decay	Energy (keV)	Application
^{123}I	13 hours	EC, γ	159	diagnostic
^{124}I	4.1 days	$\beta+$	511	PET
^{125}I	60 days	EC, γ	28 + 35	radioimmunoassay
^{131}I	8.04 days	β^-	330 (max)	therapeutic
		γ	364	diagnostic

For diagnostic purposes the gamma emissions are important. The distribution of the radiopharmaceutical inside the body can be externally measured through imaging with gamma cameras. For therapeutic purposes the beta energy emission is important because of the destructive character in tissue. The path length of the beta particle depends on the energy and ranges from several mm to 1 cm.

Iodine-131

An important property of ^{131}I is that it can both be used for imaging purposes (high energy gamma ray) as well as for therapeutic purposes (medium-energy beta emission) while most of other radionuclides only have diagnostic utility. ^{131}I has however sub-optimal imaging characteristics, including high energy gamma ray (364 keV), which is not optimal for most gamma cameras. The long half-life (8.04 days) and high beta emission limit the administered dose for diagnostic purpose only. The path length of the beta particle is about 0.5 mm, the toxic effects are limited to the thyroid tissue, with therefore sparing of adjacent normal tissue. The normal biodistribution of iodine includes salivary glands, stomach and renal tract including the bladder.

The long half-life is advantageous in the detection of functioning metastatic thyroid cancer lesions, because imaging can be done for many days after administration. This enables long take up periods in metastatic tissue and adequate clearance of background activity.

The radiation dose delivered by ^{131}I concentrated in a tissue depends on two factors: the radioactive concentration (the ratio between total uptake and the volume of functioning tissue) and the effective half-life (time after which the radioactivity in the tissue has decreased by a factor of 2). The effective half-life is related to the physical half-life and the biological half-life, which is related to the elimination of ^{131}I from the concentrating tissue.

In normal thyroid tissue the concentration is about 1 to 2% of the administered ^{131}I activity per gram and effective half-life is about 8 days. Functional thyroid cancer tissues concentrate under favourable condition about 0.1 to 0.5% of the administered ^{131}I activity per gram and the effective half-life is shorter than 3 days (9).

Iodine-123

Like ^{131}I the chemical behavior of ^{123}I is identical to that of stable iodide. The half-life of ^{123}I is 13.2 hours. ^{123}I decays by electron capture and is a lower energy gamma emitter (159 keV) compared with ^{131}I. Therefore the resulting imaging quality is better than ^{131}I. In addition, ^{123}I delivers a lower radiation dose to the thyroid tissue due to the absence of beta particle emission which may prevent a possible 'stunning' effect (discussed below). The major disadvantages of ^{123}I are the high cost due to the facts that it is produced by cyclotron, the limited availability and furthermore, the short half-life.

Iodine-124

While the radioisotopes ^{123}I and especially ^{131}I are used on a wide scale in diagnosis and treatment of all thyroid disorders, the positron emitting isotope ^{124}I, which is suitable for PET, has received little attention. Chemically identical to non-radioactive iodine, this

isotope would allow thyroid cancer imaging using the high resolution PET technique (10). ^{124}I,however, is difficult to obtain and only available at specific research centers, as it is produced in a cyclotron. The isotope has a relatively low yield ofradiation (positron yield 23%) suitable for imaging, but also emits other high-energy gamma radiation that increases the radiation to the thyroid (when present) almost to the (therapeutic) level of ^{131}I. In addition, the high-energy byproducts may deteriorate image quality. For these reasons clinical use has been minimal. ^{124}I has been used for dosimetric purposes or thyroid volume measurements (11, 12, 13, 14, 15). Recent development of combined PET-CT scanners with a single gantry, may increase clinical application in thyroid cancer patients, as detailed anatomical information is combined with the location of iodine positive tissue (16). The clinical value, for example, as compared to ^{131}I scintigraphy, is currently unknown.

Iodine-125

^{125}I decays by electron capture and gamma emission. The very low energy gamma emission (28–35 keV) and the long half-life (60 days) of ^{125}I make this radionuclide less suitable for in-vivo application. The very low energy gamma ray is to weak to be detected by gamma cameras. However, ^{125}I is extremely suitable for in-vitro application. It is a common agent for use in radioimmunoassay.

Scan method

Patient preparation

Thyroid stimulating hormone (TSH), produced by the pituitary is essential for stimulation of thyroid cells for optimal imaging with radioiodine. There are two ways to prepare a patient for radioiodine imaging: thyroid hormone withdrawal or administration ofrecombinant human TSH (rhTSH) during thyroid hormone therapy. Standard thyroid hormone medication (l -thyroxine, T4) withdrawal is usually 4–6 weeks until the serum TSH is greater than 30 mU/l to permit maximum stimulation of thyroid tissue. L-triiodothyronine (T3, Cytomel) replacement therapy (25 μg BID or TID) can be given the first 4 weeks of a 6 weeks withdrawal due to the short half-life and the immediate effects of L-triiodothyronine. The transient thyroid hormone suppletion withdrawal is associated with morbidity of hypothyroidism and therefore decreases the quality of life and diminishing productivity (17).

Recombinant human TSH (rhTSH) prevents the profound symptoms of hypothyroidism as a consequence ofthyroid hormone withdrawal. rhTSH increases serum TSH concentration sufficiently to stimulate thyroidal ^{131}I uptake and release of thyroglobulin (Tg) while patients are still taking thyroid hormone medication. The recommended protocol of rhTSH is two intramuscular injections of 0.9 mg given on 2 consecutive days followed by 148 MBq (4 mCi) ^{131}I on the third day and a WBS and Tg measurement on the fifth day. Whole body images were acquired after 30 minutes of scanning or after 140,000 counts. This is necessary because 4 mCi ^{131}I after rhTSH has about the same effect as 2 mCi given in the hypothyroid state with reduced renal clearance and raised ^{131}I body retention (18,19).

However, it must be emphasized that there is so far few experience concerning this issue especially on the long term effects on outcome, so the application of rhTSH in the diagnostics still a matter of discussion (20).

Diagnostic ^{131}I WBS

TECHNIQUES OF SCANNING. Imaging is performed using high-energy collimator. The bladder must be emptied before imaging. Supine anterior and posterior images of the neck, chest, abdomen and pelvis are acquired. Anatomic landmark or transmission scans using cobalt marker can be helpful in the interpretation of the images. Additional or delayed images can be obtained in patients with atypical findings on the scans.

INTERPRETATION. The correct interpretation of the radioiodine images is crucial in the therapy management of thyroid cancer. It requires knowledge and understanding of the normal biodistribution of radioiodine. Radioiodine uptake in the choroid plexus, nasal mucosa, salivary glands, mammary glands, gastric mucosa, gastrointestinal tract and urinary tract including bladder should be considered as physiological. These tissues contain like thyroid tissue NIS-transporter. Diffuse iodine uptake in the liver can also be seen on the post-treatment scans when there is functioning thyroid due to the incorporation of radioiodine into thyroid hormones which are degraded in the liver by de-iodination and conjugation. Uptake of radioiodine outside the above mentioned organs should be considered as residual and/or metastatic thyroid tissue (true positive) or as contamination (false positive) (21,22).

Clinical application

Pretherapeutic diagnostic scintigraphy

The goal of the diagnostic scan after total or near-total thyroidectomy is to quantify the residual thyroid and detect metastatic disease. It is also included as part of the follow-up procedures. The ablative or therapeutic dose of ^{131}I used for treatment can be based on the results of the diagnostic scan. The diagnostic WBS is usually acquired 48–72 hours after administration of a diagnostic dose of ^{131}I during hypothyroid state.

Performing diagnostic ^{131}I scans before ablation therapy (23) or during follow-up, up is controversial (24).

The reason to perform no pre-ablative diagnostic ^{131}I scintigraphy is, that it is known that nearly all patients show residual neck uptake after (near) total thyroidectomy. And some believe that low diagnostic dose of ^{131}I may impair the thyroid remnants uptake of the subsequent ablative dose of ^{131}I, the so-called stunning effect. This issue will be discussed further on. Carlisle et al. (22) support performing diagnostic scans prior to therapy for several reasons. First, patients with undectectable Tg and a normal diagnostic scan after total thyroidectomy need not to be treated with ^{131}I. Second, a correct treatment ^{131}I dose can be determined when the extent of the disease is known.

Discussions are continuing concerning performing diagnostic scans before ^{131}I treatment in patients with elevated serum Tg. Cailleux et al. (24) suggest that diagnostic scanning need not to be done when serum Tg is higher than 5 ng/ml and one rather should considered therapy and posttherapeutic scan after thyroid hormone withdrawal.

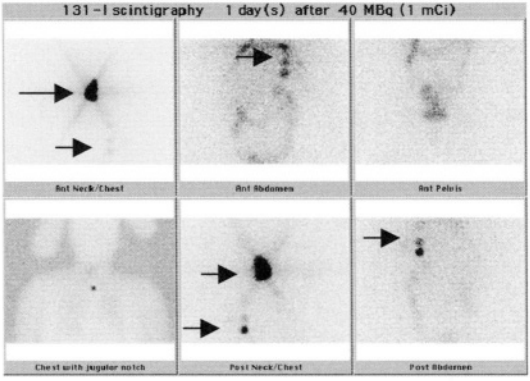

Figure 1.1. Pre-therapeutic diagnostic ^{131}I-WBS 1 day after 40 MBq in a 37-year-old patient with papillary thyroid carcinoma with elevated serum Tg after total thyroidectomy. It shows intense uptake in the neck (arrow) and uptake in the lung (arrow). Normal biodistribution in the gastrointestinal tract and bladder. This patient was subsequently treated with ablative dose of 1850 MBq ^{131}I.

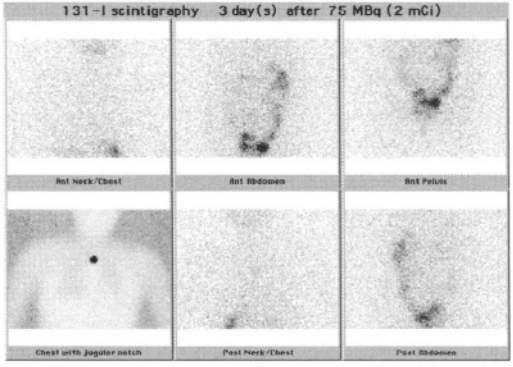

Figure 1.2. Posttherapeutic ^{131}I-WBS 10 days after a treatment dose of 5550 MBq in the same patient with papillary thyroid carcinoma with persistent elevated serum Tg and a negative diagnostic ^{131}I-WBS 3 months after ablative dose of 1850 MBq. This posttherapeutic ^{131}I-WBS was also negative, with only normal biodistribution in the gastrointestinal tract and bladder.

Pacini (25) suggest that diagnostic scanning is of low usefulness when the serum Tg-off T4 is undetectable after initial therapy.

Posttherapeutic (diagnostic) scintigraphy

A consensus for optimal dose of ^{131}I for ablation has not been reached. Some preferred a dosimetric approach by blood and whole-body and quantitative dosimetry to define the ablative dose. The majority use a standard fixed dose, which can range from 1110 MBq to 7400 MBq (30 mCi–200 mCi), depending on tumor characteristics (18,26), because of its simplicity and safety.

The timing of the acquisition of a post-therapy scan can vary widely. The interval varies from 1 day to 10 days after a therapeutic dose. However, shorter time interval allows less time for soft tissue clearance of radioiodine resulting in a relatively higher soft-tissue background which could make ^{131}I foci less visible and difficult to detect (27,28). More lesions are identified on the post-therapy scans than on the diagnostic scans. Carlisle (22) have found a discrepancy of 10% which alter the treatment management in 5% of the cases. These findings were similar with that of Fatourechi (29). The reasons of detecting more disease on the post-treatment scans compared with the diagnostic scans are probably due to the higher therapeutic doses and the longer time delay (22).

Post-therapy scans are most likely to yield important information when the serum Tg is elevated in a patient who is clinically disease-free with negative diagnostic scans or other conventional radiologic imaging (19,30).

Stunning

The timing and the amount of the diagnostic and therapeutic ^{131}I dose are controversial. There has been controversy concerning whether radiation of the diagnostic dose really has a suppressive effect on the uptake of subsequent therapeutic ^{131}I, the so-called stunning-effect (31). For extensive review of stunning see chapter 11.

The issue whether stunning is a real phenomenon and its clinical relevance/consequence is questionable (32). Our retrospective evaluation of 158 patients, who received a high-dose diagnostic scan with 370 MBq (10 mCi) because of a negative low-dose diagnostic scan with 74 MBq (2 mCi) ^{131}I, demonstrates that diagnostic ^{131}I scan with 74 MBq (2 mCi) is sufficient for correct clinical decision making with regards to further radioiodine treatment, when combined with Tg-off measurements. In 98% of the patients a 370 MBq (10 mCi) dose of ^{131}I for diagnostic WBS had no additional value (33).

rhTSH

The yield of ^{131}I scans seems to be slightly lower with rhTSH than following thyroid hormone withdrawal (17), although another study mentioned a similar diagnostic yield (34). ^{131}I scanning itself provides complementary information besides the measurement of Tg after withdrawal (24) or after rhTSH (35). For now it is unclear which specific patient group will have benefit of this follow-up policy with rhTSH (20).

The retrospective review of Robbins (35) showed no significant difference in the rate of complete ablation between a group of patients who were prepared with rhTSH or by thyroid hormone withdrawal. Other reports mention the effectiveness of rhTSH in ablative therapy (26,36). However, in the study of Menzel (37) there is a significant reduction in the effective half-life of ^{131}I in patients after rhTSH-stimulated TSH before radioiodine therapy compared with patients after endogenous stimulated TSH. Although the use of rhTSH in the follow up patients with thyroid cancer is proposed (38,39) proper prospective data concerning rhTSH applications are still very poor or even lacking (40).

Lithium

Lithium has an inhibitory effect on the release of iodine from the thyroid but does not change the uptake. The mechanism by which lithium inhibits the secretion of thyroid hormone is not well understood. In vitro, lithium decreases the droplet formation of the colloid of thyroid follicular cells, which is a reflection of a decreased pinocytosis of colloid from the follicular lumen (41). The efficiency of proteolytic digestion of thyroglobulin may also be impaired. For this feature lithium may be useful as an adjuvant for ^{131}I therapy of thyroid cancer.

However, there are very few experiences concerning the application of lithium in thyroid cancer. Only in one study was shown, that lithium prolonged the biological and effective half-lives and increased the accumulation of ^{131}I by 50% in tumors and 90% in thyroid remnants.

Thus, it is in tumors that are less likely to respond to ^{131}I therapy that lithium may be most useful but further experience is required (42).

Retinoic acid

Retinoic acids are biologically active metabolites of vitamin A. They play an important role in the morphogenesis, differentiation and proliferation of many cells (43,44). Retinoic acid has been used for cancer treatment due to their growth and differentiation effects.

Dedifferentiation changes can occurred in differentiated thyroid cancer. This is accompanied by loss of thyroid-specific function and loss of iodide uptake, which makes the therapy with radioiodine inaccessible. It seems that retinoic acids have the potential for redifferentiating therapy in these advanced stage of thyroid cancer (43,44). Nevertheless, the therapeutic effects of isotretinoin in thyroid cancer is so far very disappointing and further controlled clinical trials are required (45).

Sodium iodide symporter (NIS)

The human NIS gene is localized on chromosome 9p12–13.2. NIS is an integral protein of the basolateral membrane of thyroid gland follicular cells. Uptake of iodide from the interstitium into the cell through the NIS-transporter is an active process.

NIS-expression is inversely related to the degree of differentiation of thyroid cancer cells. NIS is more expressed in differentiated thyroid cancer and often negative in less well-differentiated thyroid cancer. Elucidating of the molecular mechanism of NIS expression in thyroid cancer might have the potential in enhancing the diagnostic and therapeutic management since thyroid cancer tissues with NIS expression take up more ^{131}I and subsequent show a high rate of response to radioiodine therapy than those without NIS expression (46,47) (see also chapter 11).

Blind therapy of ^{131}I

After total thyroidectomy and radioiodine ablation, an elevated serum Tg level as well as positive diagnostic radioiodine scanning, are good indicators of the presence of persistent, recurrent or metastatic thyroid cancer (48,49). However, there is a management

dilemma in case of negative diagnostic radioiodine scanning and an elevated serum Tg. Negative diagnostic radioiodine scanning may be caused by factors such as an insufficient rise in serum TSH or iodine contamination (50). Another explanation for negative diagnostic scanning is dedifferentation of the tumor leading to a loss of its iodine trapping ability while Tg production is still preserved. Finally, the presence of microscopic metastases that are too small to be visualized with a diagnostic ^{131}I dose, which can cause false negative scans. Nowadays in patients with negative diagnostic radioiodine scanning, an empirical therapeutic dose between 100–300 mCi ^{131}I, followed by a posttherapy whole-body scan (WBS) is advocated (24,28,38,51,52). The purpose of this approach is twofold. First, posttherapy radioiodine scanning after high-dose ^{131}I treatment is believed to be the most sensitive tool for localizing residual disease not shown by diagnostic scanning with 2–5 mCi ^{131}I (28,53,54). Thus detected residual disease can be treated with other forms of therapy, such as surgery or radiotherapy. Second, small metastases not seen on diagnostic scanning may accumulate sufficient ^{131}I after high-dose ^{131}I treatment, leading to a relevant reduction in tumor load. Several studies have shown a drop in serum Tg after high-dose ^{131}I treatment in patients with negative diagnostic radio-iodide scanning (54,55). Serum Tg remained the same or Tg increased (28,56). Since patient numbers in these studies are small and follow-up data are scarce, it is still unclear whether such high-dose ^{131}I treatment after negative diagnostic radio-iodide scanning is of benefit for the patient. Recently, several reports were published that show no additional effect of high-dose ^{131}I therapy (52,57,58), except for limited cases as lung metastases (52). High-dose ^{131}I treatment in patients with negative diagnostic ^{131}I WBS and detectable serum Tg during hypothyroidism can be used as a diagnostic and prognostic tool (59).

18 FLUORODEOXYGLUCOSE (FDG)

General mechanism

The glucose analogue FDG is a tracer of glucose metabolism, and enters cells by the same mechanisms both in benign and malignant tissue. However, the energy metabolism of malignant cells is considerably less efficient than the metabolism in their benign counterparts (60). For example anaerobic glycolysis is strongly increased in malignant cells, which is associated with less energy (ATP) production per molecule of glucose as compared to the energy production resulting from the citric acid cycle. Therefore, the need for glucose molecules and FDG is strongly increased in malignancy, which is the basis for the preferential uptake of FDG in malignancy. FDG is intracellularly phosphorylated by a hexokinase into FDG-6-phosphate, which is not further metabolized, in contrast with glucose-6-phosphate. In addition, the FDG-6-phosphate cannot leave the cell again, and the compound is therefore trapped intracellulary. The final accumulation of FDG-6-phosphate is proportional to the glycolytic rate of the involved cell. In some tissues however, the level of phosphatase activity may be variable, and FDG accumulation in liver, kidney, intestine, muscle and some tumor cells may be lower. Apart from the increased glycolysis, it has been demonstrated that levels of

transmembrane glucose transporters (e.g. the GLUT-1 transporter) and possibly also of some hexokinase isoenzymes are also increased in malignancy and relate to FDG uptake (61,62,63,64). On the one hand, the uptake mechanism of FDG with selective irreversible trapping of the tracer in malignant tissue is ideal for Positron Emission Tomography (PET) imaging, which has generated the increasing clinical application in oncology. On the other hand, it can be understood that FDG uptake does not exclusively occur in malignant tissues, as also benign tissue requires glucose. Especially activated macrophages, as present in infection and inflammation, are known to accumulate much FDG, sometimes to a degree that interferes with oncological image interpretation (65,66).

Scan method

In PET imaging radioactive tracers are used that emit positrons. After positron emission, the positron annihilates with a ubiquitous electron, which causes emission of two 511 KeV photons, precisely under an 180 degree angle. These photons are simultaneously detected by a ring of detectors, which are the main component of the PET camera.

FDG uptake occurs rapidly after administration, and due to the uptake mechanism, the amount of FDG that is taken up in tumor tissue, increases over time. Due to excretion of FDG, which causes clearance of 'background' uptake, and the decay of the radioactivity ($T^1/_2$ = 110 min) the optimal moment for imaging is generally considered to be 60–90 min after tracer administration.

For precise patient preparation and image protocols we refer to dedicated PET papers or books (67). Briefly, patients are generally injected with FDG in a fasting condition and after oral prehydration. The injected dose varies between 2-8MBq/kg. The scan duration for a whole body scan varies largely, but is in general 30–60 min.

Clinical application

Papillary and follicular thyroid carcinoma

FDG PET is not considered to be a useful method in the primary diagnosis of thyroid cancer. Although this issue has not received much study, the uptake of FDG in thyroid cancer in general appears to be low, and image interpretation may suffer from interfering uptake in benign tumors, such as follicular adenoma. In addition, the diagnosis can nearly always be obtained by other diagnostic methods.

Much more data are available to underscore the value of PET in the follow-up of thyroid cancer patients, such as to detect recurrences or metastases, especially in cases where metastases do not trap radioiodine. Interestingly, there appears to be a complementary uptake of FDG and radioiodine, which has been termed the 'flip-flop' phenomen. This means that some metastases within the same patient that do not trap radioiodine may accumulate FDG, and metastases that do not trap FDG, accumulate radioiodine. Some lesions accumulate both tracers. This observation was first described by Joensuu (68). It might be explained by the different degree of tissue

differentiation. Well-differentiated thyroid cancer tissue has retained its iodine trapping capabilities, but is metabolically inactive, causing uptake of radioiodine and no or minimal FDG accumulation. Less differentiated thyroid cancer tissue, as may develop during treatment, loses its iodine trapping capability and becomes metabolically more active. This results in FDG positivity and iodine negativity. For this reason, most PET research has focussed on detection of thyroid cancer metastases in radioiodine negative patients with increased thyroglobulin levels, which currently seems to be the best clinical application.

In a recent meta-analysis the value of FDG PET in papillary and follicular thyroid cancer both in patients with negative radioiodine scans and in patients with known neoplastic foci was determined (69). They selected 14 studies that met quality criteria as described by the Cochrane Methods Group on Screening and Diagnostic Tests. Although general evidence levels appeared to be low, precluding quantitative summary, all these studies claimed a positive role for PET, especially in the group of patients with negative radioiodine scans. Sensitivity for finding tumor locations of PET varied between 70 and 95%, and specificity was between 77 and 100%. Considerable heterogeneity existed, however, in the pre-PET data risk profile, such as patient selection criteria concerning variations in TNM stage, Tg levels, radioactive radioiodine dose and levels of TSH. Although troubled by severe methodological problems, the performance of FDG PET appeared to be superior to 99mTc-Sestamibi or Tc99m-furifosmin, and probably Tl-201 scintigraphy. Also the impact on overall clinical outcome of PET was difficult to assess, but, due to the general slow disease progression, that may be true for many diagnostic studies in thyroid cancer.

A frequently observed issue whether PET should be performed during the hypothyroid state (e.g. after thyroid hormone withdrawal) or in euthyroid state (during thyroxine treatment). In a study van Tol (70) better performance of PET in hypothyroid state was found, but the issue is not clearly settled.

Furthermore, it has been hypothesized that exogenous TSH stimulation with rhTSH increases FDG uptake by differentiated thyroid cancer and seems apparently more accurate than FDG-PET under suppression, in terms of number of detected lesions and tumor/background contrast (71). In a small study this hypothesis has been confirmed (18).

Medullary thyroid cancer

Nearly all imaging modalities (Ultrasonography, CT, MRI, scintigraphy using In-111-octreotide, Tc99m-DMSA-V, MIBG) have limited sensitivities (40–70%) compared to the apparently very high sensitivity of the calcitonin tumor marker (72). Although the clinical course of metastatic medullary thyroid cancer can be mild in some patients, others develop clinically relevant metastases (in liver, bone, lungs) that remain undetected until a relatively late stage. Earlier detection of metastases during follow up after primary treatment might therefore have relevant therapeutic implications. Results of FDG PET studies in MTC demonstrate slightly better performance (sensitivity around 75%—specificity 79%) as compared to other imaging modalities, but patient selection probably influences these results (73,74).

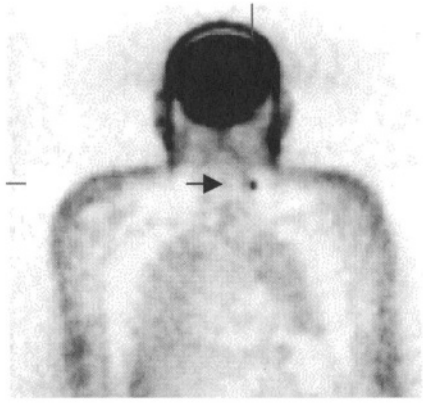

Figure 2. 50-year-old patient with papillar thyroid carcinoma, negative posttherapeutic ^{131}I-WBS 10 days after a treatment dose of 5550 MBq, thyroglobulin 25 ng/ml. FDG PET coronal slice showing a small lesion in the right neck (arrow) that proved to be a small metastasis of papillary thyroid cancer.

Other PET tracers

Similar to other neuroendocrine tumors as described above, uptake of FDG appears to be low, and theoretically radiolabeled amino acids might perform better in these calcitonin producing tumors (75). Preliminary experience using C11-methionine does not seem to confirm this expectation (76). Recent experience with the catecholamine precursor amino acid ^{18}F-DOPA and PET appears to be more promising. In a small group Hoegerle found more lymph node metastases of MTC using ^{18}F-DOPA PET than with any other modality (77). Also ^{18}F-DOPA PET was reported to be able to detect a medullary thyroid cancer lesion in a MEN2a patient (78).

THALLIUM-201 CHLORIDE

General mechanism

Thallium-201 (Tl-201) is a potassium analogue. This positively charged ion is actively transported over the cell membrane by an ATP-dependant sodium/potassium transport system and localizes non-specifically in thyroid cells, as well as in other tissues with high cellularity and high perfusion. Additional mechanisms ofentry have not been excluded. Originally Tl-201 has been developed for myocardial perfusion imaging, for which it is still routinely used, but it also accumulates in kidney, stomach, liver, spleen, testes, salivary glands, large bowel and in thyroid tissue (79). Several reports have suggested that comparison between early and delayed Tl-201 images could distinguish between benign and malignant thyroid diseases, but usually results in benign and malignant tissues overlap and have not lead to sound clinical application (80,81).

Isotope characteristic

Tl-201 is an isotope that decays by electron capture to Mercury-201. Mercury 201 emits characteristic gamma rays of 68–90 keV and much smaller amount of gamma

rays of 135 keV and 167 keV. The half-life of Tl-201 is 73.1 hours. Tl-201 is normally administered as thallium chloride and rapidly disappears from the blood with a half-life between 30 seconds and 3 minutes. Peak uptake in the thyroid occurs 5–10 minutes after injection.

The relative long half-life and the poor physical characteristic of the radiopharmaceutical limit the injected dose (3–5 mCi). The low photon energy causes a relatively large radiation burden and is also less suitable for imaging, because of scattered and absorbed radiation. This results in low image quality.

Scan method

Techniques of scanning

Tl-201 imaging for thyroid cancer does not require withdrawal of thyroid hormones or restriction of iodine intake. Imaging, using a low-energy collimator, is usually performed 10–20 minutes after intravenous injection of Tl-201, because at that time tumor/background ratio is highest. The accumulation in tumoral tissues remains constant between 20–60 minutes. Supine anterior and posterior whole-body scans are acquired. Additional or delayed images can be obtained 3–4 hours postinjection to differentiate malignant tissues (slower washout) from benign tissues (82).

Clinical application

Papillary and follicullar thyroid carcinoma

The primary value of Tl-201 is the analysis of patients with a negative ^{131}I scan and elevated thyroglobulin levels. Several studies discuss the usefulness of Tl-201 in the localization of metastatic disease (83,84,85,86). The combination of ^{131}I with Tl-201 scintigraphy resulted in a sensitivity for recurrent tumor of 90–100% at a specificity of 95%–100%. Adding also the information from thyroglobulin measurements even further increases diagnostic yield. Tl-201 alone generally depicts approximately half of all thyroid cancer lesions. Few reports have specifically addressed the value of Tl-201 scintigraphy in patients with negative ^{131}I scans.

Tl-201 scintigraphy seems to be most value in the localization of local metastases and in mediastinal lymph nodes. Sensitivity has been reported between 55–94%, specificity between 82–97% (85,86,87). The large variety in sensitivity can be attributed to the different methods of disease confirmation, the variability in location of metastases and the different selection of the patients.

Although most published studies were performed with planar images, SPECT imaging shows a 25% increase in sensitivity, especially for chest, neck and micronodular pulmonary metastases (88).

In the small study of Shiga et al. (89) Tl-201 scintigraphy seems to provide similar information in the detection of metastatic lesions after total thyroidectomy compared with FDG-PET.

Medullary thyroid carcinoma

There have been several studies of Tl-201 uptake in medullary thyroid carcinoma, most of them with a limited number of patients and in comparison with DMSA-V or

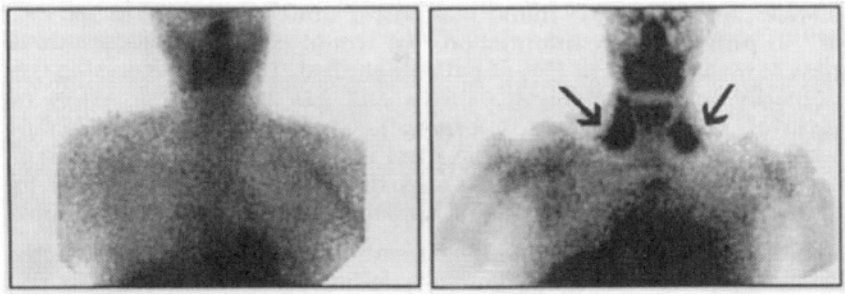

Figure 3. ^{201}Tl neck and chest scans. Normal scan taken when Tg was 4 ng/mL and ^{131}I scan was negative. Repeat ^{201}Tl scan when Tg was 75 ng/mL. Note uptake in the apices of the lungs (arrows). Iodine scan remained negative.

MIBG. The non-specific uptake of this tracer in background tissues and low tumoral uptake probably cause the relatively low sensitivity. DMSA-V scintigraphy has shown to be clearly superior to Tl-201 (90). Another study showed Tl-201 superior to MIBG. Although non-specific, Tl-201 may be be useful in individual clinical setting.

Although only limited comparison data of FDG PET and Tl-201 scintigraphy are available, but FDG PET is considered to be clearly superior.

TECHNETIUM-99M-SESTAMIBI (METHOXY-ISOBUTYL-ISONITRILE)

General mechanism

Technetium-99m-sestamibi (Tc-99m-sestamibi) is a lipophilic cationic agent that primary localizes in the mitochondria.Tc-99m-sestamibi accumulates in the mitochondria secondary to a negative potential of the mitochondria. Tc-99m-sestamibi uptake is driven by a negative transmembrane potential and up to 90% of the intracellular tracer is found in the mitochondria. The uptake is an energy dependant process. Tc-99m-sestamibi is also a substrate for the transmembrane P-glycoprotein drug efflux pump (91).

The affinity for mitochondria probably generates the specific uptake in Hürthle cell carcinoma, which is often poorly iodine concentrating, but rich in mitochondria. Similar to Tl-201, Tc-99m-sestamibi uptake in thyroid cancer cell is independent of TSH stimulation, although one report mentioned a TSH dependent uptake (92).

Isotope characteristic

Tc-99m-sestamibi is obtained by elution from a Tc generator, which contains the parent isotope molybdenum-99 (Mo-99). Mo-99 is a radionuclide with a half-life of 66 hours. The isolated 140 keV gamma emission of Tc-99m is ideally suited for gamma camera imaging. The 6 hr half life is very convenient for radiopharmaceutical production on a day to day basis. The commercial production of generators, which can be eluted up to 1 week, make Tc99m very easily available. These factors make Tc-99m the most used radioisotope in nuclear imaging in general. A kit preparation for radiolabeling of Tc-99m to sestamibi is commercially widely available.

Scan method

Tc-99m-sestamibi scintigraphy does not require any patient preparation and no thyroid hormone withdrawal. The favorable scan characteristics and the relative short half-life of Tc-99m (6 hours) in comparison to 131I (8 days) enable the use of relatively larger doses which increases image quality. This is a clear advantage over Tl-201.

Imaging is usually performed early, 10–30 minutes after tracer administration, and repeated 3 hours later. Others only image 60 minutes p.i., which might be less sensitive.

Clinical application

Tc-99m-sestamibi is only applied in papillary and follicular thyroid carcinoma.

The application of Tc-99m-sestamibi scanning is in patients with a negative 131-scan and an elevated thyroglobulin. In many instances Tc-99m-sestamibi has shown predilection to concentrate in the same abnormal sites as Tl-201.

Tc-99m-sestamibi scanning is particularly sensitive for the detection of nodal metastases. One study reported more sensitivity than high doses ^{131}I (93), another found the lowest sensitivity for lung metastases (94). Especially in high risk patient with a negative ^{131}I scan a combination of MIBI and ultrasound may be useful in detecting lymph node metastases (95).

Other Tc-99m based tracers

The data about the clinical application in thyroid cancer and value of Tc-99m Tetrofosmin, Tc-99m Pertechnate, Tc-99m Furifosmin is very limited and the results are conflicting. All three tracers are characterized by accumulation in the mitochondria by a different and not clearly understood mechanism.

Of the limited published data on Tc-99m tetrofosmin high sensitivities are mentioned (>85%) (96,97) in papillary and follicular thyroid carcinoma. No additional value is found in medullary thyroid carcinoma (90).

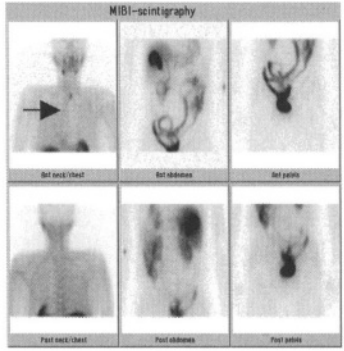

Figure 4. Technetium-99m-sestamibi scan 15 minutes after injection of 730 MBq in a 85-year-old patient with recurrent papillary thyroid carcinoma. It shows uptake in the neck (arrow). The ^{131}I-WBS was negative.

INDIUM-111 DTPA—PHE-1-OCTREOTIDE

General mechanism

Somatostatin receptors are present on many neuroendocrine tissues, both benign and malignant, also including normal thyroid cells and thyroid carcinoma cells. These receptors are the basis of scintigraphy using the radiolabelled somatostatin analogue, In-111-octreotide, which is an important diagnostic tool in neuroendocrine tumors in general. Five somatostatin receptors subtypes have been isolated. Somatostatin and its synthetic analogues act through specific binding to these receptors subtypes. Each subtype has its own tissue distribution pattern, and has specific pharmacological properties. After ligand—receptor interaction signals are transmitted (using G-proteins) to adenylate cyclase pathway, resulting in inhibitory effects on cell growth and proliferation. Normal thyroid tissue shows expression of all somatostatin receptor subtypes except somatostatin receptor subtype (SST) 2 in one study (98), while others found a high expression of SST3 and SST5, and only a weak expression of SST1 and SST2 (99). Thyroid cancer tissue shows a different SST expression. Papillar and follicular tumours have high expression of SST3, 4 and 5, while in Hürthle cell and medullary thyroid tumours SST2 expression is present.

Apart from different tissue distribution, ligand affinity also varies. The well-known somatostatin analogue, octreotide, has the highest affinity for SST2 and lower affinities for SST3 and SST5 and no affinity for SST1 and SST4. The lack or the low density of SST2 receptor is presumably the reason that only half of all thyroid cancers can be visualized by scintigraphy using radiolabelled octreotide (100).

Isotope characteristic

Indium-111 (In-111) has a half-life of 67.5 hours and is cyclotron-produced. It predominantly emits gamma photons with gamma-energy of 171 keV and 247 keV. Indium is coupled to the octreotid peptide using DTPA as a chelator (In-111-DTPA), and the ready-to-inject compound is commercially available. The tracer is also called In-111-pentreotide.

Scan method

Thyroid hormone suppression can be continued during scanning, although one study has shown a small increase in detection of positive lesions after thyroid hormone withdrawal (101). Whole-body imaging is performed 24 hours after intravenous injection of 200 MBq of In-111-octreotide, using a medium energy collimator. Laxation of patients is often performed to facilitate intestinal clearance. Normal distribution consists of intense uptake in kidneys and spleen, minor uptake in liver and intestine. Endocrine organs such as the thyroid and pituitary gland can also often be seen. Minor non-specific uptake can be observed in inflammatory lesions. Additional images, lateral views and/or SPECT, of the neck and upper abdomen improve the detection of smaller or equivocal lesions in those areas. Delayed images can be obtained 48 hours postinjection, mostly because of interfering accumulation of radioactivity in the bowel to differentiate pathological from physiological uptake.

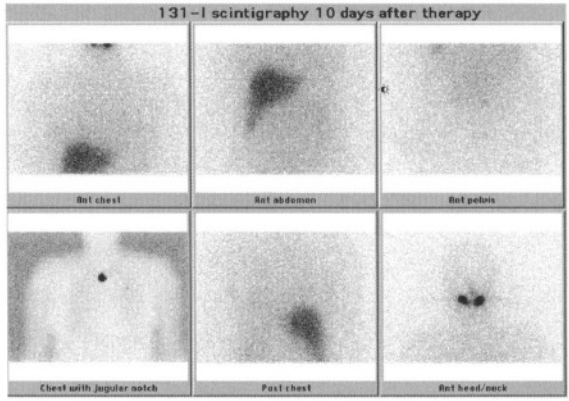

Figure 5.1. Negative posttherapeutic ^{131}I-WBS 10 days after a treatment dose of 5550 MBq in a 63-year-old patient with DTC with persistent elevated serum Tg and negative diagnostic ^{131}I-WBS 3 months after the ablative dose of 5550 MBq. Normal biodistribution in the liver and salivary glands. This patient showed on the first pre-ablative diagnostic ^{131}I-WBS, 6 weeks after total thyroidectomy, uptake in the neck and was subsequently treated with an ablative dose of 5550 MBq; the posttherapeutic ^{131}I-WBS 10 days after the ablative dose also showed uptake in the neck.

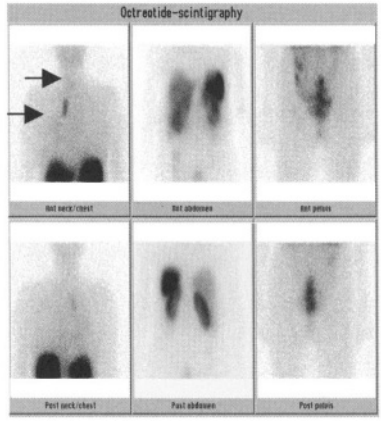

Figure 5.2. Indium-111-octreotide scan 24 hours after injection of 185 MBq in the same patient with DTC with persistent elevated serun Tg and negative ^{131}I-WBS. The indium-111-octreotide scan clearly shows uptake in the right lung (arrow) and faintly uptake in the neck (arrow).

Clinical application

Papillary and follicular thyroid carcinoma

In-111-Octreotide scintigraphy is especially useful in patients with 131-I negative scans and clinical suspicion on persistent tumor activity, as confirmed with recent studies (101,102,103). The uptake of In-111-Octreotide broadens the ability of the application of radiolabeled somatostatin analogues in general. High doses of Yttrium-90 (beta

emitting) or the In-111 (gamma emitting) DOTA chelated somatostatin analogues have been applied in both patients with papillary and follicular thyroid cancer and with medullary thyroid cancer for therapeutic reasons. Currently response rates are around 35%. (104).

Medullary thyroid carcinoma

In medullary thyroid carcinoma In-111-octreotide scintigraphy can have a complementary value in individual cases. However, the somatostatin receptor density and the number of receptors appears to be lower in medullary thyroid carcinoma in comparison to other neuro-endocrine tumors. Also some medullary thyroid tumors can produce somatostatin which may be competitive in the receptor binding (105). However, In-111-octreotide can be a useful radiotracer for the detection of metastatic or recurrent medullary thyroid carcinoma. Especially in cases with minimal residual disease, as can be found by persistently elevated calcitonin levels, In-111-octreotide scintigraphy showed more tumor localisation than conventional techniques (106,107). Liver metastases are slightly less more difficult to visualise (108) because of the non specific background uptake in the liver. In-111 octreotide has the similar sensitivity (±80%) to CT and MRI for the detection of recurrent or metastatic medullary thyroid carcinoma (109).

META-IODOBENZYLGUANIDINE (MIBG)

General mechanism

Metaiodobenzylguanidine (MIBG) is a norepinephrine analogue that can be radiolabeled with ^{131}I or ^{123}I. MIBG is an aralkylguanidine, with combines the benzylgroup of bretylium and the guanidinegroup of guanethudine with an idione on the meta place. By competition with the energy dependent transport mechanism of norepinephrine MIBG is taken up in cells (110). Evidence has been found that probably a sodium-dependent and a sodium-independent uptake system is present. Differential expression of the uptake systems, may be responsible for the variations of the kinetic parameters for both norepinephrine and MIBG in different tumor cells. (111). It is especially sensitive in (nor)epinephrine producing tumors, such as pheochromocytoma, neuroblastoma or paraganglioma. In vitro experiments have shown that MIBG may act as a substrate for chromaffin granules. The vesicular mono-amine transporter (VMAT) type 2, that has extensively been expressed in pheochromocytomas seems to be responsible for MIBG transport and tumor visualization (112,113).

Scan method

MIBG can be radiolabeled with both ^{123}I or ^{131}I. Because of the unfavorable imaging characteristics and the higher radiotion dose, ^{123}I-MIBG is mostly used, although the ^{131}I labeled variant allows imaging up to several days after administration. In general thyroid uptake of (in small quantities liberated from the tracer) free iodine is blocked by administering non radioactive iodine or perchlorate at the time of injection. Imaging is generally performed 24 hrs after tracer administration. A large variety of medications

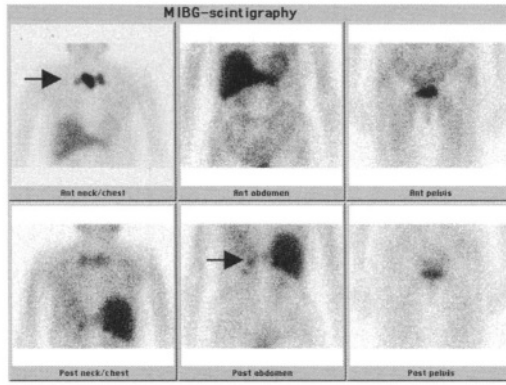

Figure 6. I-123 MIBG whole body scan 24 hours after injection of 185 MBq in a 78-year-old patient known with MTC, hyperparathyroidism and suspected of pheochromocytoma (MEN-2a). It shows intense uptake in the neck with bilateral paratracheal expansion (arrow); it also shows uptake in the left adrenal region (arrow).

may have some impact on tumoral uptake (e.g. alpha receptor blocking agents). Whole body and spot imaging may be supplemented by SPECT imaging.

Application

There is no place for MIBG scintigraphy in patients with differentiated thyroid cancer, but in medullary cancer the method may be helpful.

In medullary thyroid cancer, MIBG scans are positive in only a limited number of patients with medullary thyroid carcinoma with mentioned sensitivities of 12–30% (114,115).

A pitfall in imaging arises when liberated free iodine localizes in thyroid remnants (in the rare patients that were not ablated after thyroidectomy), but this can usually be differentiated from uptake in medullary thyroid cancer metastases. In cases of doubt Tc-pertechnetate imaging can be helpful.

A number of patients with medullary thyroid cancer have been treated with 131I-MIBG and a palliative response has been reported in 50% of the patients (116). Pentavalent 99m Technetium Dimercaptosuccinic Acid (99mTc (V)DMSA).

General mechanism

Pentevalent Tc-DMSA (called DMSA-V) is derived from DMSA, but includes the Tc99m label in a 5+ molecular charge, instead of 7+, as is the common chemical form of Tc99m. 99mTc(V) DMSA is not taken up by the normal thyroid gland, but can be applied in the diagnosis of medullary thyroid cancer due to an increased turnover of calcium and phosphate ions.The compound localizes in a number of tumours. The precise mechanism is not well known, uptake may be related to the intracellular phosphate concentration (117). 99mTc(V) DMSA exists in three isomeric forms and the biodistribution of the individual isomers differs from the whole radiopharmaceutical.

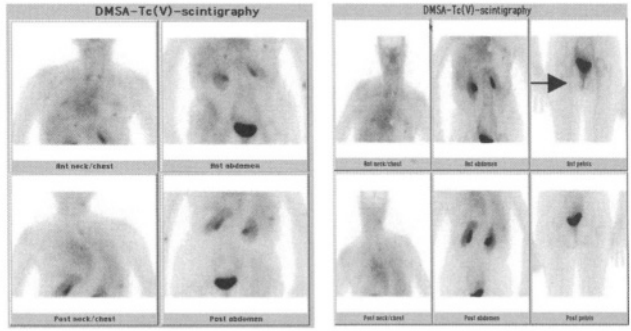

Figure 7. Tc-99m(V)-DMSA scan 2 hours after injection of 290 MBq in a patient known with MTC (MEN-2a) with persistent elevated serum calcitonin. The scan shows uptake in the neck, chest and in the right proximal femur (arrow). This patient also has severe scoliosis of the thoracal spine.

Scan method

Images are acquired 2–3 hours after injection. SPECT imaging of suspected areas may be helpful to improve the sensitivity of tumour detection.

The normal biodistribution is seen after 2 hours in the nasal mucosa and faintly in the skeleton, with breast uptake in women. Excretion is through the kidneys, liver uptake is not prominent. Some blood pool activity may also be present.

Clinical application

99mTc(v) DMSA is not commercially available in the United States but is well used in other countries. Tumor lesion sensitivity is reported to be between 50 and 95% (118,119).

RADIOLABELED ANTI CARCINOEMBRYONIC ANTIGEN ANTIBODY

General mechanism

Serum calcitonin and carcinoembryonic antigen (CEA) are used as tumormarkers in medullary thyroid carcinoma (MTC).

The specific positive immuno-histochemical property of a positive staining for calcitonin and carcinoembryonic antigen (CEA) and the expression of CEA levels at the surface of the cells were the basis for the development of specific anti-CEA monoclonal antibodies, the so-called radioimmunoscintigraphy, to image patients with MTC. Various anti-CEA antigen antibodies can be labeled with 99m-Tc, 111-In, ^{123}I or ^{131}I. The disadvantages of using monoclonal antibodies include the low tumor-background ratio and the forming of human anti-mouse antibodies (HAMA) making repeated studies difficult.

Scan method

The injected dose depends on the radionuclide the antibodies are labeled with, just like the timing of scanning and the choice of collimator (120,121,122). Injected activity

are 555–1110 MBq (15–30 mCi) for 99m-Tc labeled antibodies, 74–370 MBq (2-10 mCi) for ^{131}I labeled antibodies and 111–185 MBq (3–5 mCi) for 111-In labeled antibodies. With the 99m-Tc labeled anti-CEA antibodies planar and SPECT imaging of the neck/chest, abdomen and pelvis can be acquired 4 and 24 hours postinjection with an LEHR-collimator. With the 111-In labeled anti-CEA antibodies imaging can be performed up to 72 hours postinjection with a medium energy collimator. Imaging of ^{131}I labeled anti-CEA antibodies can be performed 4 hours and up to 7 days postinjection. Blood pool activity may be prominent, kidney and bone marrow uptake can be seen.

Clinical application

Reported lesion based sensitivity of various anti-CEA antibodies in medullary thyroid carcinoma is around 70–100%, for both known and occult disease (121,122,123). However, only a limited number of groups have published about these results. Apart from the limited application in medullary thyroid cancer, the anti-CEA antibodies scan has been extensively used in the detection of metastatic colon cancer, where it appears to have a sensitivity of 50–70% and provides clinically relevant information, especially in combination with CT scanning.

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