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Review

Nuclear medicine in the diagnosis of benign thyroid diseases

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Abstract

Thyroid gland has the unique ability to concentrate iodine. This phenomenon offers a perfect background for a wide range of diagnostic tests utilizing radioactive iodine nuclides of iodine and technetium. Despite the very good availability of ultrasonography and other imaging modalities, radionuclide methods are still inevitable in a various cases of thyroid disease. In this article, a comprehensive review of all these methods used in the diagnosis of benign thyroid diseases is presented. Iodine and technetium uptake tests are briefly described. Indications to thyroid scan in the context of iodine supply are also presented. Finally, the significance of thyroid findings in PET images is pointed out. The article is illustrated by some typical patterns of radionuclide thyroid images.

KEY words: iodine uptake, goitre, Graves' disease, thyroid nodule

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Introduction

Thyroid gland has the unique ability to take up iodine — an essential component of its hormones. The phenomenon of accumulation of iodine in the thyroid gland allowed for the use of iodine isotopes in the diagnosis of thyroid disease as early as about 70 years ago, although the mechanism of iodine uptake at the molecular level has been carefully examined until the late twentieth century. In 1939, a group of scientists from the University of Berkeley documented the uptake of radioactive iodine in human thyroid for the first time. This gave rise to first therapeutic radioiodine applications in patients with hyperthyroidism and thyroid cancer [1, 2].

Nowadays, we know that the uptake of iodine in the thyroid gland is attributed to the sodium-iodide symporter (NIS), described in 1993 by Kaminsky et al [3]. The uptake of iodine by the thyroid cells is still widely used in the evaluation of thyroid function by means of radioiodine uptake test and thyroid scintigraphy [4].

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Measurement of iodine uptake

Iodine uptake test is mainly used in patients planned for the radioiodine treatment due to hyperthyroidism. The test is performed using a gamma camera or a gamma probe positioned at a certain distance from the patient's neck. In different centres, measurements are performed at various intervals after oral administration of 1–3.7 MBq (30–100 μCi) ^{131}I. Measurements made during the first day are essential for the assessment of iodine accumulation in the thyroid. Therefore, for practical reasons, measurements are often performed 3–6 h and 24 h after administration of the diagnostic dose of ^{131}I. In centres using sophisticated techniques for dosimetry, measurements are performed on several consecutive days [5].

^{131}I uptake in the thyroid is calculated using the formula:

$$IU\ [\%] = 100 \cdot (c_t - c_{bkg})/c_0$$

where: IU — iodine uptake
c_t — number of counts registered over thyroid gland
c_{bkg} — number of background counts in the room
c_0 — number of counts in the diagnostic dose registered before oral administration

Iodine uptake is a parameter with a relatively high variability. On average, in euthyroid patients 24 h after administration of diagnostic activity the uptake is ca. 25–50%. It may be higher in hyperthyroidism and lower in hypothyroidism (Figure 1). Apart from the thyroid functional status, many other, mostly iatrogenic factors may influence the level of thyroid iodine uptake. They are listed in Table 1.

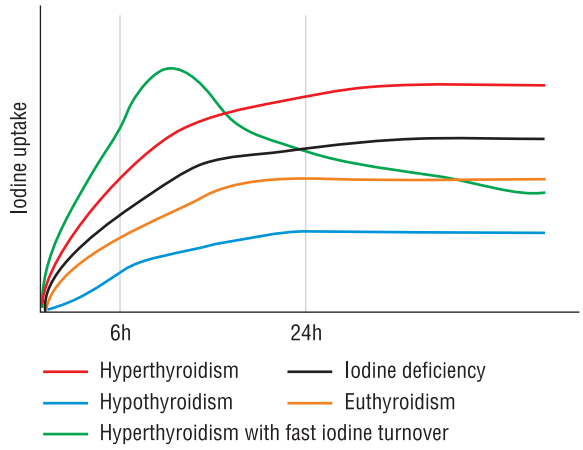

Figure 1. Kinetics of iodine uptake by the thyroid gland in different conditions. In patients with Graves' disease with significant hyperthyroidism (green line) the result of an early measurement (after 6 h) may be higher or close to the late measurement (after 24 h), due to the acceleration of iodine turnover in the gland

Measurement of technetium uptake

In some centres, great attention is attached to the evaluation of technetium-99m uptake in the thyroid. The concept of this measurement is based on the assumption that the uptake of ^{99m}Tc by thyrocytes takes place using the same mechanism as the iodine and in the first 15 minutes after i.v. injection, the curves of ^{99m}Tc and ^{123}I run in parallel (see below). Under the conditions of euthyroidism, with normal iodine intake, uptake of ^{99m}Tc is 0.5–2.0%. As in the case of iodine uptake, this percentage decreases in hypothyroidism and in iodine contamination, and increases in Graves' disease and iodine deficiency. This measurement is simple and is performed as a supplement of thyroid scintigraphy by comparing the number of counts in the regions of interest located over the thyroid with the number of counts above the syringe containing the ^{99m}Tc-pertechnetate prior to injection [5–7].

Thyroid scintigraphy

In addition to the morphological information obtained on the basis of ultrasonography, thyroid scintigraphy visualizes the distribution of active thyroid tissue [5]. Therefore, the general indications for scintigraphy are quite wide and include both single thyroid nodule, and multinodular goitre. The test is also used to evaluate the extent of retrosternal goitre (when ultrasound is not able to visualize the lower pole of the thyroid gland) and in suspected ectopic thyroid. In the case of goitre without clear dominance of one of the nodules, scintigraphy is used to select the biopsy site. Thyroid scintigraphy should be performed in all patients with nodular goitre undergoing treatment with radioiodine, since it allows to assess the anatomical distribution of active thyroid tissue, which may be important in the selection of therapeutic ^{131}I activity [6–8].

In view of the very good availability of ultrasound and biopsy, a tendency to limit the indications to thyroid scintigraphy may be observed. In 2009–2010 American Thyroid Association (ATA) and the Polish Group of Endocrine Cancer published their recommendations suggesting that the thyroid scintigraphy is useful only in patients with nodule diameter greater than 1 cm, provided that TSH concentration is subnormal. The role of scintigraphy in this case is to show whether a nodule, that is manifested in ultrasound, is a focus of excessive hormonal activity (hot nodule) or accumulates the radiotracer at a level similar to or lower than the rest of the gland (warm or cold nodule). Because the hot nodules are rarely malignant, according to ATA guidelines fine-needle biopsy is not necessary in such a case. At the same time, performing scintigraphy in all patients with nodular goitre is not recommended by experts, since adequate assessment obtained with ultrasound and cytology is sufficient in most cases [9, 10].

Table 1. Factors affecting the level of iodine uptake are shown below

Factors decreasing iodine uptake	Pathological conditions: — hypothyroidism — subacute thyroiditis — chronic thyroiditis
	Iodine-containing diet: — seafood, fish — iodinated salt
	Iodine-containing drugs: — amiodarone — potassium iodide (e.g. Jodid) — Lugol's solution — some eye-drops — vitamin preparations (e.g. Feminatal)
	Thyroid hormone preparations: — L-thyroxin (Euthyrox, Letrox) — L-triiodothyronin (Thybon, Cytomel, Novothyral)
	Anti-thyroid drugs (methimazole, propylthiouracil)
	Iodine-containing i.v. contrast agents
	Potassium and natrium perchlorate (Irenat)
Factors increasing iodine uptake:	Pathological conditions: — hyperthyroidism — renal failure
	Iodine-deficient diet
	Hormonal preparations: — recombinant thyrotropin (rhTSH, Genotropin)

Planar images are recorded in patients in a sitting or laying position. Anatomical reference is obtained by placing a marker over sternal notch. Imaging of the thyroid gland may be performed using several radionuclides: ^{99m}Tc, ^{131}I and ^{123}I. Technetium-99m (^{99m}Tc) is administered intravenously in the form of pertechnetate, obtained from a molybdenum-technetium generator. The permanent availability of ^{99m}Tc in nuclear medicine departments, made it the most widely used nuclide in the routine endocrine diagnosis (Figure 2).

^{99m}Tc-pertechnetate as an analogue of iodine is transported to thyroid cells in a similar way as the isotopes of iodine, i.e. by the means of NIS. The maximal accumulation of ^{99m}Tc-pertechnetate is obtained 15–20 minutes after i.v. administration. In this initial phase, the increase of ^{99m}Tc activity in thyroid runs parallel to the increase of activity of intravenous ^{123}I. The percentage of ^{99m}Tc accumulated in thyrocytes reflects the dynamics of absorption of iodine to the thyroid tissue. After 15–30 min, however, the curve of the thyroid ^{99m}Tc activity reaches a plateau and then decreases, while the uptake of iodine is still increasing. This results from the

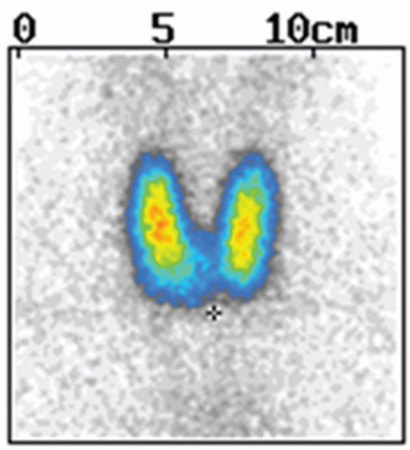

Figure 2. Thyroid scan — normal image

fact that the ^{99m}Tc-pertechnetate is not subject to the organification (as in case of iodine), and is washed-out from the thyrocytes.

In the interpretation of scintigraphic images obtained with ^{99m}Tc, it should be noted that the uptake of ^{99m}Tc is not limited strictly to the thyroid tissue. There is some physiological uptake of ^{99m}Tc-pertechnetate in the salivary glands, gastric mucosa, as well as a relatively high background activity from the vessels.

High availability is not the only advantage of ^{99m}Tc. From the physical point of view ^{99m}Tc is preferred due to low energy of the gamma photons (140 keV) and relatively short half-life (6 h). Thus, it is possible to use much higher activity than ^{131}I and to register more accurate images in a shorter acquisition time. Moreover, despite 20-fold higher activity of ^{99m}Tc, the absorbed dose is about 300 times lower than with the diagnostic dose of ^{131}I [5, 7].

The iodine isotopes: ^{123}I and ^{131}I are also used for thyroid scintigraphy. In terms of physical properties, ^{123}I is similar to ^{99m}Tc – is a pure gamma-emitter, and its gamma photons are also characterized by relatively low energy (159 keV) and short half-life (13 h). The advantage of ^{123}I is the higher specificity and persistence of accumulation in the thyroid caused by the organification. Due to these properties, later acquisitions can be performed and accurate kinetics of iodine in the thyroid tissue may be evaluated. Long-term and higher accumulation of radionuclide in the thyroid in comparison to ^{99m}Tc, result in even more detailed images, with a clearer demarcation of thyroid tissue from the surrounding structures. It is believed that ^{123}I is an ideal radionuclide for the assessment of thyroid - both in benign diseases and in cancer. Unfortunately, due to its low availability (it is produced in cyclotron) and high cost, it is not used routinely in all institutions. In Polish conditions, ^{123}I is used occasionally [7, 9, 11].

^{131}I, often called radioiodine, is the most commonly used radioactive isotope of iodine. This nuclide emits both, beta and gamma radiation with a half-life of 8.1 d. The energy of gamma rays used for diagnostic purposes, is 364 keV. Because of these disadvantages in comparison to ^{99m}Tc and ^{123}I, the use of ^{131}I scintigraphy should be limited to the monitoring of treatment in patients with differentiated thyroid cancer. In case of benign thyroid disease, scintigraphy with ^{131}I is justified if ^{123}I is unavailable, in following indications:

— evaluation of retrosternal and mediastinal goitre;
— differentiation of mediastinal tumour and goitre;
— detection of ectopic thyroid tissue (sublingual or ovarian goitre);
— congenital hypothyroidism in differential diagnosis of thyroid agenesis and ectopy [5, 7].

The characteristics of various nuclides used for the visualization of the thyroid gland are shown in Table 2 [6, 8, 9, 12].

Images of the thyroid obtained using ^{99m}Tc, and one of the isotopes of iodine do not differ significantly. Only a few cases of differentiated thyroid cancer with accumulation of ^{99m}Tc and no uptake of ^{131}I were reported. This phenomenon occurred when registration of ^{99m}Tc images was started too early, when the accumulation of radiotracer in the tumour corresponded to significantly increased perfusion [11].

While interpreting results of thyroid scintigraphy, the physician should be aware of the current situation of the patient:

— history of thyroid disease;
— ultrasound image or report (optimally, the doctor performs ultrasound on his own);
— current TSH;
— used drugs, in particular thyroid hormones, antithyroid drugs and iodine-containing agents (amiodarone, disinfectant and expectorant drugs) (Figure 3).

Table 2. Comparison of nuclides used for thyroid scintigraphy

	99mTc	123I	131I
Uptake mechanism	NIS, then washout	NIS + organification	NIS + organification
Background activity	Rather high	Low	Low
Photon energy	Gamma 140 keV	Gamma 159 keV	Gamma 364 keV + beta
Recommended activity for adults	20–74 MBq* (0,6–2 mCi)	7,4–25 MBq (0,2–0,6 mCi)	1,85–7,4 MBq (0,05–0,2 mCi)
Recommended activity for children	1–5 MBq/kg (0,015–0,07 mCi/kg)	0,1–0,3 MBq/kg (0,003–0,01 mCi/kg)	0,025–0,1 MBq/kg (0,0004–0,0016 mCi/kg)
Ddministration	i.v.	p.o. or i.v.	p.o. or i.v.
Start of acquisition	15–30 min	6–8 h	24 h
Recommended collimators	Low-energy, pinhole	Low-energy, pinhole	High-energy, pinhole
Average effective dose equivalent	0,013 mSv	1,9 mSv	6,6 mSv

*SNM recommends a higher activity of ^{99m}Tc –75–370 MBq (2–10 mCi)

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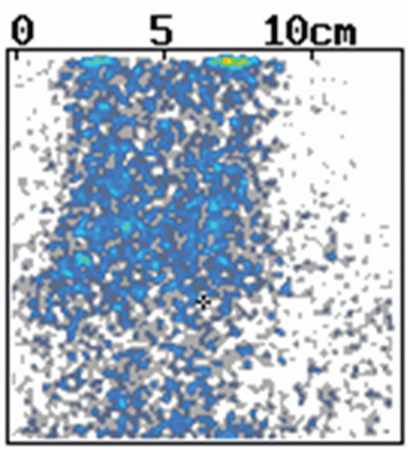

Figure 3. Thyroid scintigraphy in case of low iodine uptake, the patient with hyperthyroidism previously treated with amiodarone

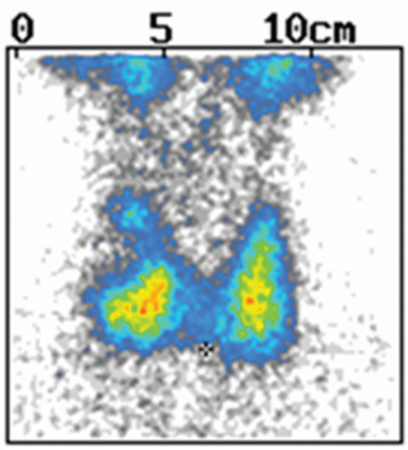

Figure 4. Cold nodule in the upper part of the right thyroid lobe

The report of the thyroid scan should contain:

— the location of thyroid tissue (normal, ectopic, retrosternal goitre);
— structure and size of the gland (symmetry of the lobes, pyramidal lobe); it should be noted that scintigraphy is not able to accurately determine the diameters of the thyroid lobes, especially in the sagittal axis (thickness); therefore, the description of size should be limited to reporting clear deviation from normal size;
— the tracer distribution in the thyroid, foci of increased or decreased tracer accumulation (warm, hot or cold nodules).

Assessment of uptake in a thyroid focus is important in terms of malignancy risk-stratification. The highest probability of malignancy is found in nodules with reduced tracer uptake, so called cold nodules (Figure 4). The probability is mainly dependant on iodine supply in the population: in countries with relatively low iodine intake the risk ranges from 5 to 10% (Austria 5.5%, Italy 8.2%), while in countries with a high supply — more than 10% (UK 11.4%, U.S. 20.5%) [13–15]. Of course, this statistics does not indicate that the iodine supply increases the risk of thyroid cancer — on the contrary, in populations with high iodine supply focal lesions occur less frequently, hence the relative occurrence of thyroid cancer among all cases of nodular disease is higher than in populations with a high incidence of nodular goitre (Figure 5).

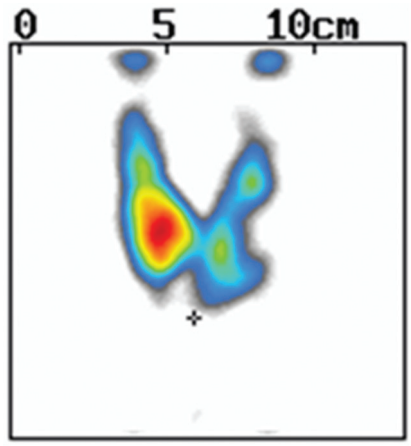

Figure 5. Toxic nodular goitre — a patient admitted for a radioiodine therapy of hyperthyroidism. In the right lobe, an area of increased tracer accumulation, i.e. warm nodule is found. In the left lobe an area with no tracer uptake is visible. In hyperthyroidism, this area does not have to represent a cyst or malignancy and may correspond to normal thyroid tissue, with deficient hormonal activity caused by TSH suppression

In Poland, it may be presumed that about 10% of cold solid nodules are malignant. Among other solid lesions manifested as a cold focus, benign nodules such as non-secreting thyroid adenomas are most frequent. It should be noted that the areas of fluid, i.e. colloid and posthemorrhagic cysts by definition do not show tracer uptake. Therefore presence of a cold area consistent with an anechoic focus in the ultrasound practically excludes the diagnosis of malignancy.

The presence of tracer uptake in a focal lesion (Figure 6, 7) does not exclude thyroid cancer, but the negative predictive value of a hot nodule image is very high [11]. It should be stressed that spatial resolution of scintigraphy is relatively low (ca. 1–2 cm). Therefore, smaller changes showing no tracer uptake may not be visualized, especially when they are surrounded by a thick layer of normal tissue. Such changes may be falsely classified as warm nodules. In some cases, it may be possible to image smaller lesions, but only if they are located at the anterior surface of the gland, and the lobe is not very thick (Figure 8, 9) [7].

There have been reports about the utility of thyroid imaging using methoxyisobutylisonitrile (^{99m}Tc-MIBI). Uptake of this tracer in the mitochondria of cancer cells is associated with an increased number and activity of mitochondria, as well as with increased perfusion of the lesion. It has been suggested that the ^{99m}Tc-MIBI scan should be used in case of inconclusive biopsy and/or cold nodule (Figure 10). Clinical trials have not yielded conclusive results and therefore this method was not included in the guidelines of the management of thyroid nodular disease [16, 17]. There are, however data that indicate that a negative scintigraphy using ^{99m}Tc-MIBI practically excludes malignancy [18]. Recently, possible benefits of SPECT/CT technology in image registration performed using ^{99m}Tc-MIBI have been discussed [19].

Increased but homogenous tracer uptake in the thyroid is characteristic of Graves' disease. Thyroid gland is often enlarged, but may also have a normal size.

The diagnosis of Graves' disease does not exclude the presence of thyroid nodules. Hyperthyroidism of autoimmune origin with the presence of focal lesions in the thyroid is known

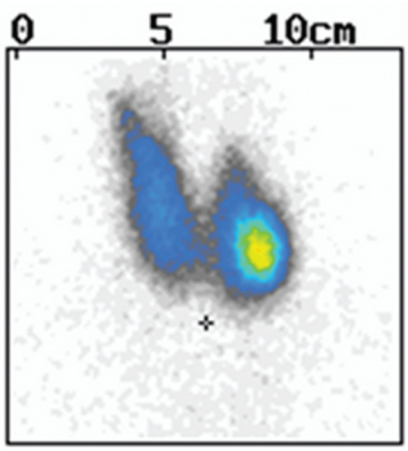

Figure 6. Warm nodule of the left lobe

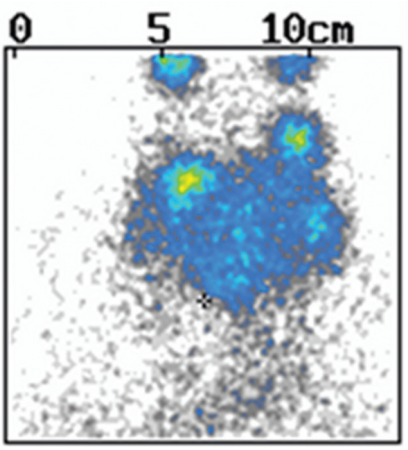

Figure 8. Multinodular goitre with several warm nodules

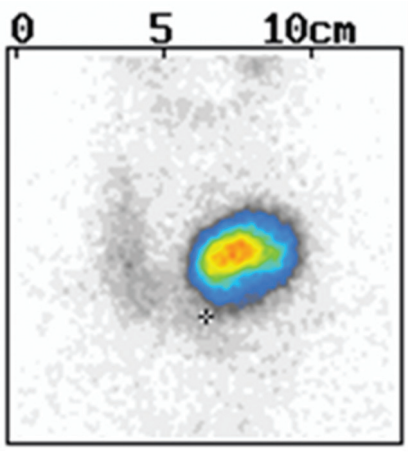

Figure 7. Hot nodule of the left lobe. Autonomous adenoma causes complete suppression of TSH. At the same time, normal thyroid tissue is inactive and does not accumulate the tracer

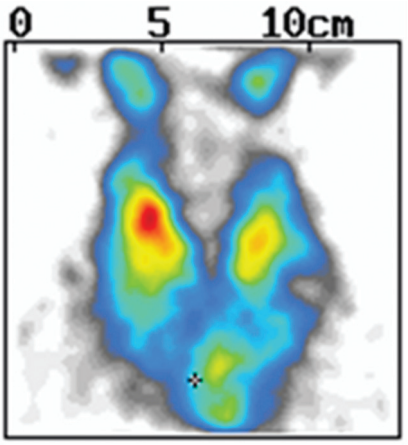

Figure 9. Large multinodular goitre with warm and cold areas. The lower portion of the gland penetrates into the superior mediastinum

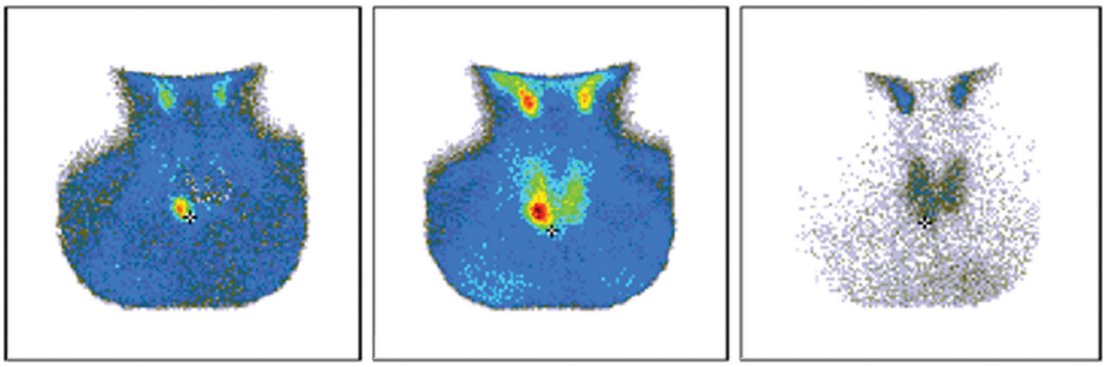

Figure 10. Scintigraphy with ^{99m}Tc-MIBI. A nodule at inferior pole of the right thyroid lobe shows normal uptake of ^{99m}Tc (right image), and increased uptake of ^{99m}Tc-MIBI (middle image). Subtraction image (left) shows activity only in the nodule. Uptake of ^{99m}Tc-MIBI in a thyroid lesion indicates relatively high probability of malignancy

as Marine-Lenhart syndrome (Figure 11). Thyroid scintigraphy in this syndrome is of particular value since the risk of thyroid cancer in a cold nodule in Graves' disease is higher than in a cold nodule without autoimmune thyroid disease and is estimated for 15–19% [20, 21]. In addition, thyroid cancer coexisting with Graves' disease is clinically more aggressive, that is attributed to the stimulating effect of the thyroid antibodies [22].

The initial phase of de Quervaine thyroiditis may be accompanied by painful swelling of the thyroid and elevated levels of fT3 and fT4. The thyroid image is characterized by reduced and

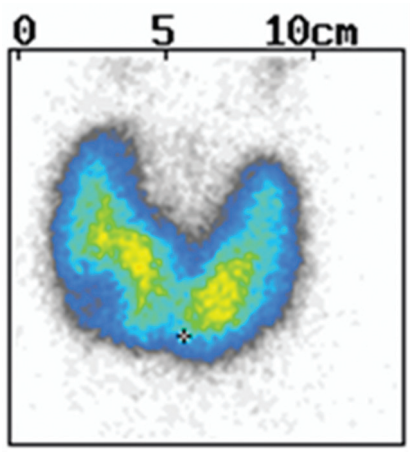

Figure 11. Marine-Lenhart syndrome. A cold nodule in a diffuse goitre caused by Graves' disease

very inhomogenous tracer distribution, especially in the area of inflammatory process.

Suppression thyroid scintigraphy

The aim of a suppression scan is to visualize autonomous thyroid tissue, i.e. functioning independently of the hypothalamic-pituitary-thyroid axis. It involves the performance of thyroid scintigraphy with a radioiodine uptake measurement before and after administration of triiodothyronine or thyroxine preparation for 7–14 days. The recommended daily dose is 80 mcg L-triiodothyronine or 150 mcg of levothyroxine. In a normal gland, thyroid hormone decreases the radioactive iodine accumulation by at least 50%. No change or reduction of iodine uptake less than 30% indicates the autoimmune process. This test can also be done by measuring ^{99m}Tc uptake instead of iodine. An autonomous nodule that is warm at baseline image converts to a hot nodule as the surrounding normal tissue becomes suppressed. Therefore in some centres, suppression test is also used for preparation to radioiodine treatment of a non-toxic nodular goitre [5, 7].

Potassium perchlorate test

Potassium perchlorate test is used to evaluate disorders of iodine organification. In normal conditions after the influx into the cell via NIS, the iodide ions are rapidly oxidized by thyroid peroxidase, and are subsequently incorporated into tyrosyl residues of thyroglobulin. This process takes no more than 2–3 h [7]. In the case of an organification defect (peroxidase defect in Pendred syndrome), free iodine, which has not been organified, is washed out of the cell. Potassium perchlorate inhibits the NIS activity, reducing the flow of iodide into the cell. Thus, in case of deficient peroxidase the content of iodine in the thyroid gland is reduced after administration of perchlorate because of iodine wash-out. The test consists of iodine uptake measurement 2-3 h after intravenous injection of ^{123}I or oral administration of ^{131}I, followed by a next measurement 2 h after oral administration of potassium or sodium perchlorate (0.6–1.0 g of Irenat). Decrease in iodine uptake by 20% confirms the organification defect. In healthy subjects, iodine uptake after administration of perchlorate should not be reduced [5].

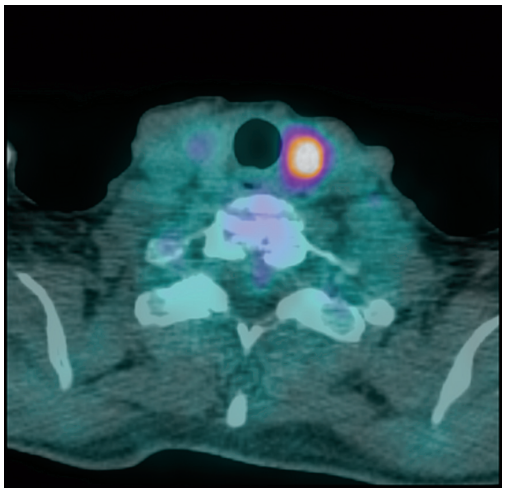

Figure 12. Focal activity of ^{18}F-FDG in the left lobe of the thyroid in PET / CT performed in a patient with lymphoma. The patient was treated surgically — papillary thyroid cancer was diagnosed

Positron emission tomography (PET)

PET using ^{18}F-FDG is widely used in the diagnosis of differentiated thyroid carcinoma. As this paper is limited to the diagnosis of benign thyroid disease, the use of PET in thyroid cancer will not be discussed here. The diagnosis of benign thyroid disease using PET is not recommended, but there are clinical situations in which a thyroid problem is detected incidentally in a PET/CT scan.

In oncology, PET/CT using ^{18}F-FDG is used to differentiate between benign and malignant lesions, e.g. in case of a single pulmonary nodule. In thyroid practice, a common problem is to determine the indications for surgery in case of an inconclusive biopsy or in case of a follicular neoplasm. In these situations, the role of PET is not clear. In several prospective studies image of a metabolically active thyroid nodule was characterized by relatively low positive predictive value (PPV from 33 to 50%). ^{18}F-FDG uptake may occur also in a number of benign lesions. Moreover, the level of glucose metabolism expressed by the standardized uptake value (SUV) in the focal lesion did not improve the diagnostic performance of PET [23–25]. What is of particular interest, the negative predictive value is close to 100% caused by a very low number of false-negative results, i.e. thyroid malignancy almost always shows some metabolic activity. Therefore, the role of PET might rely on reducing the number of thyroidectomy in patients with equivocal biopsy results, although certainly the use of this study to evaluate thyroid nodules is not economically justified [25, 26].

Another problem is the occurrence of abnormal thyroid ^{18}F-FDG activity in patients undergoing PET/CT for other reasons. Normal thyroid does not utilize glucose. ^{18}F-FDG uptake in the thyroid gland is observed in approximately 2% of PET studies [23, 24]. It can be either focal or diffuse. Retrospective studies performed on thousands of PET and PET/CT images, showed that the probability of thyroid cancer in case of incidentally detected focal metabolic activity in the thyroid (so-called incidentalomas, Figure 12) varies from 27 to 47% [27–29].

On the other hand, diffuse, moderate accumulation of ^{18}F-FDG in the entire gland indicates inflammatory process, usually associated with chronic Hashimoto thyroiditis (Figure 13).

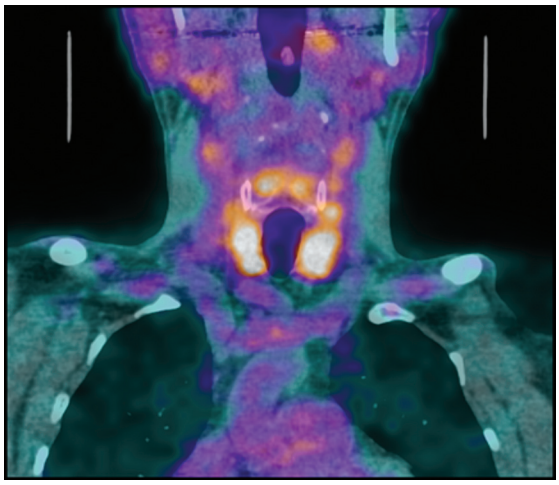

Figure 13. Diffuse ^{18}F-FDG activity in both lobes of the thyroid in PET/CT performed due to a lung tumour. Hashimoto disease with subclinical hypothyroidism was diagnosed after laboratory tests

In conclusion, incidental detection of metabolically active thyroid nodule should be followed by biopsy to exclude thyroid carcinoma, while in case of diffuse ^{18}F-FDG uptake, TSH and thyroid antibodies (aTPO, aTg) measurements should be recommended.

In some centres positron-emitting iodine isotope ^{124}I is available. Its half-life is 4.2 d. The PET/CT with ^{124}I allows for more precise images than routine ^{131}I scintigraphy, with the advantage of no effect on the thyroid stunning [30]. This method is useful only in the diagnosis of differentiated thyroid carcinoma.

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