Functional Imaging of Differentiated Thyroid Cancer

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14.1 Introduction

Due to their relatively unaggressive biological behavior, most differentiated thyroid carcinomas have a good prognosis [7, 33]. This holds true even for patients with lung metastases, particularly in cases with disseminated metastatic sites that are radioiodine-positive. Therefore, thyroid cancer is overall a rare cause of cancer-associated death. Serum thyroglobulin measurement is the most sensitive method to detect recurrence of differentiated thyroid carcinoma during follow-up [46]. Radioiodine scintigraphy can be used as a highly specific method to visualize tumor tissue. But in many cases, particularly in poorly differentiated cancer and in Hürthle cell carcinoma, radioiodine uptake is decreased or absent, owing to several mechanisms. Particularly DNA changes, encoding the Na^+/I^- symporter, have to be considered. Therefore, the sensitivity of radioiodine scintigraphy is decreased from about 70% to less than 50% during the clinical course [44, 54]. Although therapeutic options are often limited to some extent in patients with radioiodine-negative metastases, correct staging is very important to plan further diagnostic and therapeutic steps. But also in cases with known radioiodine-positive tumor tissue, other functional techniques are clinically useful to prove or exclude additional radioiodine-negative tumor sites, which cannot be influenced by further radioiodine treatments. In some cases, recurrence or metastases are suspected during follow-up, even if no increased thyroglobulin values are observed. The reason might be pathological thyroglobulin recovery values or the existence of very poorly differentiated cell lines which have lost the capability to synthesise Tg. Tumor-specific functional imaging techniques are necessary to evaluate equivocal morphological alterations in these patients.

14.2 Tracers

14.2.1 Thallium Chloride

^{201}Tl was initially used to image myocardial viability and blood flow. Thallium is a monovalent cationic isotope and has a high affinity to the Na^+/K^+ pump, but

it does not behave exactly like potassium because the affinity of thallium to the pump is even higher than that of potassium itself and there are two binding sites at the ATPase enzyme system for thallium – in contrast to potassium. ^{201}Tl has been used for tumor imaging for more than 20 years. The uptake of this tracer depends mainly on blood flow and metabolic demand. Several factors can influence the metabolic demand of tumor cells. The most important factors are viability and malignancy grade; the latter correlates with tumor growth. Therefore, ^{201}Tl scintigraphy can be used for tumor detection, therapy control, and in vivo grading of several tumor types. The clinical use of ^{201}Tl for tumor imaging has decreased because of its low gamma energy and the increasing importance of the ^{99m}Tc-labeled tracers hexakis 2-methoxyisobutylisonitrile (MIBI) and 1,2-bis [bis(2-ethoxyethyl)phosphino] ethane (tetrofosmin), as well as the increasing availability of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET).

14.2.2 MIBI and Other ^{99m}Tc-Labeled Tracers

Like ^{201}Tl, MIBI was initially developed as a myocardial tracer. The uptake of this radiopharmaceutical depends mainly on the mitochondrial potential. More than 90% of the tracer is accumulated in the inner mitochondrial matrix [42]. The mitochondrial content of the tumor and the mitochondrial potential have a major influence on the tracer uptake in malignant tissue. The mitochondrial content does not change during the clinical course in most cases, whereas the potential is influenced by several factors. The most important factor is the metabolic demand, depending on the tumor growth. Hürthle cell tumors (which are frequently radioiodine-negative) are known to have a high mitochondrial content and can be detected with a high sensitivity using MIBI (Fig. 14.1) [3]. Since uptake values of ^{201}Tl and MIBI do not differ significantly in most thyroid tumors [10], MIBI is preferred mainly because of its favorable physical characteristics with respect to imaging [particularly single-photon emission computed tomography (SPECT)] and radiation exposure. Other ^{99m}Tc-labeled cationic complexes such as tetrofosmin or ^{99m}Tc-furifosmin (Q12), which have been developed as myocardial tracers also [4], have been used less frequently for thyroid carcinoma imaging. The specific uptake mechanisms of these substances – particularly in tumor cells – are partly unclear; the uptake of tetrofosmin (like that of MIBI) depends at least partially on the mitochondrial potential.

14.2.3 ^{18}F-Fluorodeoxyglucose

Glucose consumption is known to be increased in tumor cells [54]. Malignant tissue can metabolize glucose by oxidation or to lactic acid, even if saturated with oxygen. In addition to this increased use of glucose, trapped in the tumor cells, changes in glucose transporter systems and hexokinase activity influence glucose uptake [38]. Thus, the overexpression of glucose transporter genes

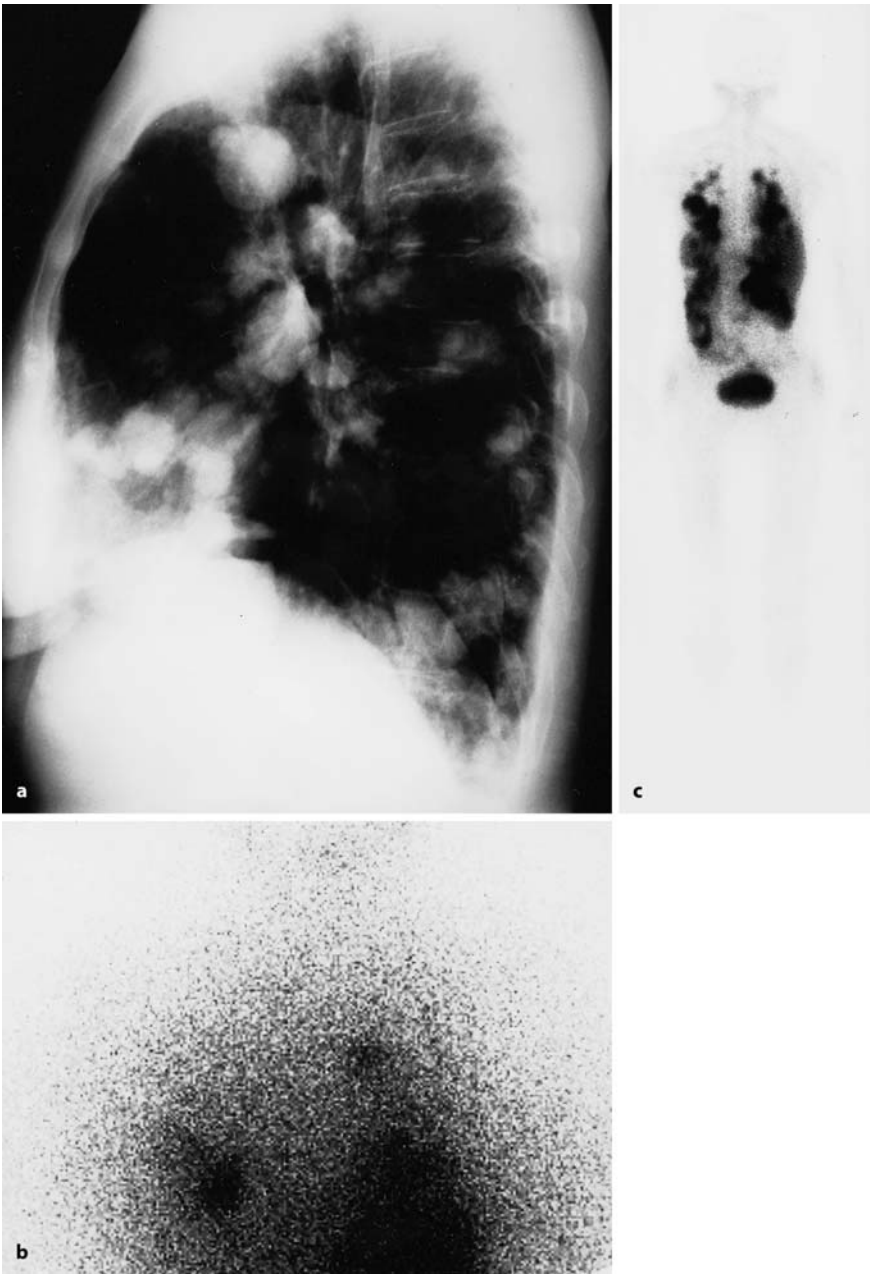

Fig. 14.1 a–d A 71-year-old female patient with Hürthle cell thyroid cancer and multiple lung metastases. The X-ray appearance is shown in **a**. Whole-body scintigraphy with radioiodine (dorsal view) shows faint uptake at one pulmonary site (**b**). Whole-body MIBI scintigraphy (dorsal view) (**c**) and SPECT imaging with MIBI (**d**) show high tracer uptake in the pulmonary metastases

(*GLUT*), particularly *GLUT1* and *GLUT3*, and the increased activity of hexokinase in cancer cells are also responsible for the high glucose transport rate into the cells. Besides being accumulated in the tumor cells themselves, FDG is accumulated in tumor-associated macrophages [31]. Therefore, fast-growing tumors are detectable with a higher sensitivity by FDG-PET. In most tumors, tracer uptake correlates with malignancy grade. Yoshioka et al. [55] showed that FDG uptake increases in pancreatic, gastric, and colonic cancer cells with loss of differentiation. Most differentiated thyroid carcinomas, particularly G1 tumors, are relatively slow growing and are therefore expected to be frequently FDG-negative. These highly differentiated tumors are radioiodine-positive in most cases, since the Na^+/I^- symporter can be expected still to be active in such tumors. Arturi et al. [2] reported a lack of the Na^+/I^- symporter gene expression in the primary tumor in 50% of patients suffering from whole body scintigraphy-negative metastases. In contrast, an increased expression of the symporter in papillary thyroid carcinomas has been described recently [45]. The clinical significance of these observations still remains to be evaluated.

With respect to thyroid carcinoma, some specific mechanisms concerning the FDG uptake have to be considered. Sisson et al. [48] reported on sequential FDG-PET studies with and without thyroxine replacement therapy in one patient, suggesting higher FDG uptake under TSH stimulation. In contrast, in the German multicenter study [26] a lower sensitivity of FDG-PET was observed in cases with high TSH levels (67%). In patients in whom FDG-PET was done under thyroid hormone therapy, sensitivity was 91%. No relation between TSH levels and PET results were observed by Wang et al. [53]. Several influences of thyroid hormone and TSH levels on FDG uptake in differentiated thyroid cancer cells have to be considered. An increased uptake of FDG and MIBI under TSH stimulation was initially expected, related to a higher metabolic demand of thyroid cells, specifically stimulated. But also the overall decreased metabolic activity, which includes tumor cells, during hypothyroidism has to be considered. Whereas the activity of glucose transporters is increased in hypothyroidism, the total number of transporters is decreased [35]. The decreased number of glucose transporters might be another reason for the decreased sensitivity of FDG-PET during thyroid hormone withdrawal, besides the influence of hypothyroidism on tumor growth. Recently published data [13, 41] show that TSH is able to increase FDG uptake in human thyroid cells in vitro and in thyroid carcinoma tissue in vivo. Tumor grading can be expected to affect TSH influence on tracer uptake since well-differentiated cancer cells can be expected to be more TSH dependent. In the German multicenter study on a large patient group, no major differences between tumor types (papillary versus follicular) with respect to sensitivity of any functional imaging technique were observed.

14.2.4 ^{111}In-Octreotide

Somatostatin receptor scintigraphy has predominantly been used for imaging of medullary thyroid cancer, rather than for DTC. Recently, reports on the use of

^{111}In-octreotide in DTC have been published [19, 21, 22, 27, 49, 51]. Somatostatin receptors mediate the antiproliferative effects of somatostatin and are present in normal tissue as well as in a variety of endocrine tumors such as medullary thyroid cancer. In tumor tissue, somatostatin receptor density is usually higher than in nontumoral tissue. In order to visualize somatostatin receptor-containing tumors, a long-acting somatostatin analog was required, because the half-life of native somatostatin in the circulation is extremely short (about 3 min) due to rapid enzymatic degradation [32]. The synthetic peptide (somatostatin analog) octreotide, which was developed by Bauer et al. [5], meets these requirements. However, the labeling procedure for octreotide is not suited for routine use. Therefore, a diethylenetriaminepentaacetic acid (DTPA)-conjugated derivative of octreotide labeled with ^{111}In has been developed for clinical routine use. ^{99m}Tc-labeled octreotide derivatives have been introduced in the clinical routine for some applications [18], with some limitations concerning the abdomen, but can be expected to be comparable in neck and mediastinum.

14.3 Clinical Use of Functional Imaging

14.3.1 Presurgical Evaluation

Several studies have dealt with the clinical significance of ^{201}Tl and MIBI scintigraphy for the evaluation of thyroid nodules. Although no clear-cut differentiation between malignant and benign nodules is possible, particularly MIBI is frequently used for presurgical imaging. The risk that a circumscribed lesion will be malignant seems to be distinctly higher if the lesion is cold on pertechnetate scintigraphy and hot on MIBI scintigraphy [37]. Nevertheless, since thyroid adenomas frequently show increased MIBI uptake, the specificity of MIBI scintigraphy with respect to the detection of malignancy is limited [17, 30, 34]. The specificity of FDG-PET is too low – especially in iodine-deficiency areas with a high incidence of (mostly benign) thyroid nodules – for preoperative use in nodular thyroid diseases. Like MIBI, FDG is taken up by benign adenomas in most cases. In papillary carcinoma, the sensitivity of FDG-PET is lower [29]. Using semiquantitative techniques, Adler and Bloom [1] observed a better differentiation between benign thyroid nodules and thyroid cancer. In summary, the large variety of metabolic rates of malignant and benign thyroid nodules prevents routine clinical use of FDG-PET prior to surgery. Nevertheless, in cases with preoperatively known carcinoma, particularly in medullary thyroid cancer, preoperative scintigraphy with MIBI or FDG-PET can be useful for staging to allow optimized surgical planning. In cases of circumscribed increased FDG uptake in the thyroid gland during a PET study performed for other reasons, particularly malignant melanoma, further evaluation is necessary to exclude malignancy [36]. Scott et al. [47] reported successful preoperative staging of the diffuse sclerosing variant of papillary carcinoma and of cervical lymph node metastases using FDG-PET. But especially in iodine-deficiency areas with a high incidence of nodular

goiter and a high rate of surgical procedures concerning the thyroid gland, the definitive diagnosis of DTC is not known before histological evaluation in the majority of cases.

14.3.2 Postsurgical Treatment and Follow-up

It is sometimes difficult to distinguish remnant tissue from local recurrence, particularly during the initial weeks after the first ablative radioiodine therapy, since radiothyroiditis in the remnant tissue can show up with an increase in glucose utilization or MIBI uptake. Therefore it is recommended that FDG-PET and MIBI scintigraphy be used no earlier than 6 weeks after the first radioiodine treatment. Besides problems due to increased tracer uptake in inflammatory remnant tissue, imaging with single-photon emitters cannot be done earlier than about 6 weeks after radioiodine administration since even small amounts of radioiodine can interfere with imaging using ^{99m}Tc or ^{201}Tl owing to the long half-life and the high gamma energy of radioiodine. PET imaging is not affected by single-photon emitters (including radioiodine), although ^{99m}Tc-labeled tracers and ^{201}Tl should not be used on the same day after FDG administration. Exogenic TSH stimulation (rTSH injection) is known to increase PET sensitivity [41], in contrast to TSH stimulation after thyroid hormone withdrawal. The accuracy of ^{201}Tl or tetrofosmin imaging has been described to be independent of thyroid hormone replacement therapy [50]. No data have been published concerning the sensitivity and specificity of MIBI scintigraphy in relation to TSH levels. Morphological techniques such as ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI) have the disadvantage that the identification of radioiodine-negative tumor masses is often limited because of their inferior specificity, particularly in cases with altered anatomy (e.g., after neck dissection). Therefore, especially in radioiodine-negative cases with recurrence or metastatic disease, additional functional imaging techniques are necessary. The differentiation of scar tissue from local recurrence and of unspecific lymph node enlargement (cervical or mediastinal) from lymph node metastases is often very difficult using CT and MRI. In addition, the use of CT is limited, because this method can only be applied without contrast enhancement in view of further radioiodine administration. Moreover, all morphological imaging techniques lack sensitivity to some extent owing to their limited field of view.

Therapeutic strategies in cases with radioiodine-negative tumor tissue – which is detected by functional imaging – can include surgery, radiation therapy, chemotherapy, or redifferentiation therapy [8, 15, 25, 43]. Radioiodine treatments might be useless if radioiodine-negative tumor sites exist in addition to radioiodine-positive sites because of a variety of less differentiated tumor cell lines, which are more frequently radioiodine-negative.

In radioiodine-negative cases, the sensitivity of FDG-PET is as high as 85% (Fig. 14.2), whereas it is about 75% in the whole group of differentiated thyroid carcinomas [14, 16, 23, 24, 26]. The phenomenon that thyroid tumor cells take up either radioiodine or FDG was called “flip-flop” by Feine et al. [16]. The com-

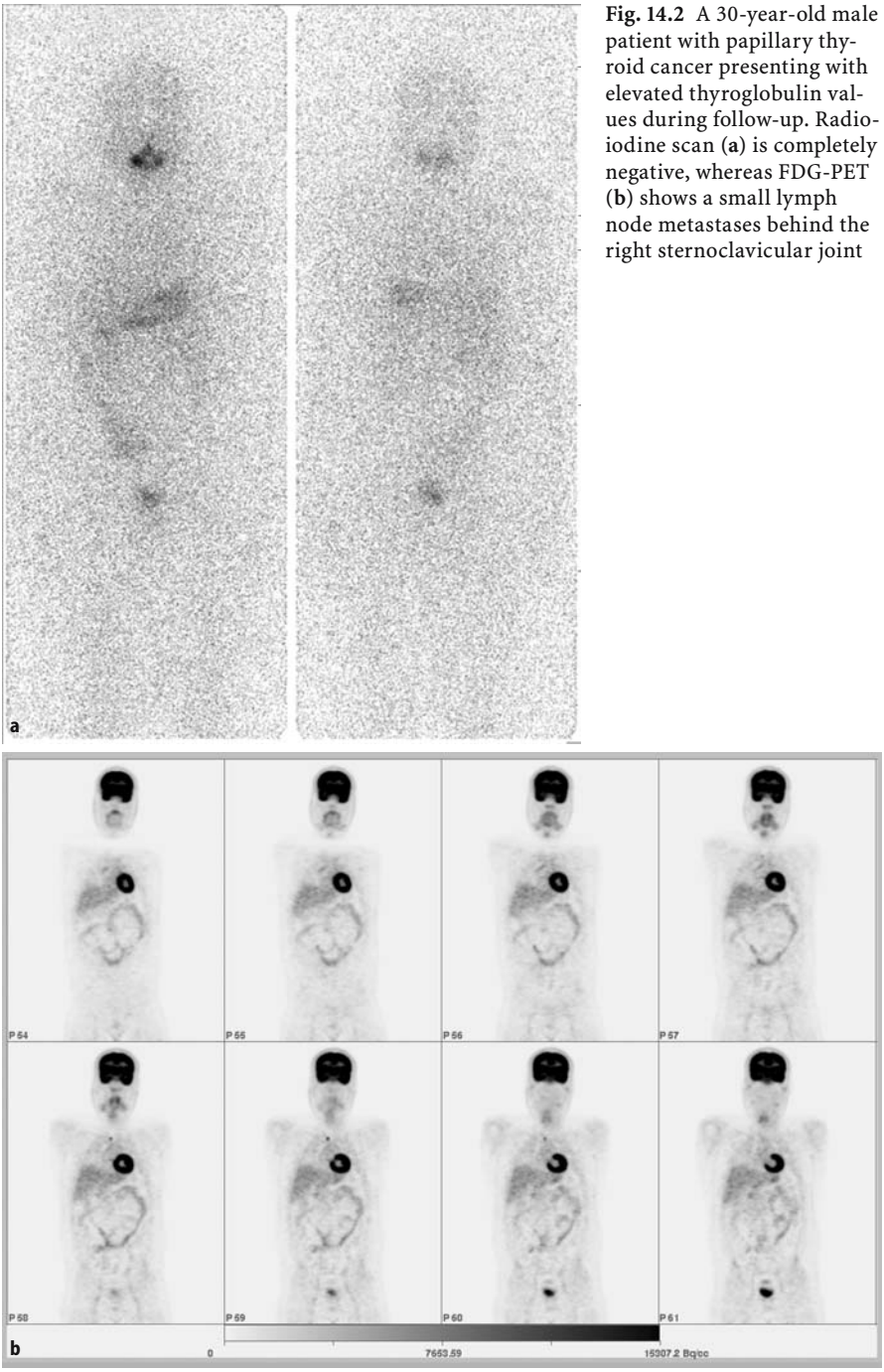

Fig. 14.2 A 30-year-old male patient with papillary thyroid cancer presenting with elevated thyroglobulin values during follow-up. Radioiodine scan (**a**) is completely negative, whereas FDG-PET (**b**) shows a small lymph node metastases behind the right sternoclavicular joint

bination of FDG-PET and posttherapeutic radioiodine scintigraphy gave a sensitivity of 93% in the German multicenter study [26]. In a group of 37 patients with negative radioiodine scan, Wang et al. [53] were able to localize tumor sites in 71% of all cases with elevated thyroglobulin values. The overall specificity of FDG-PET is inferior to that of radioiodine scintigraphy, because increased FDG uptake in nontumor tissue can occur for several reasons. For example in the lung, nontumor-associated FDG uptake can be caused by sarcoidosis, tuberculosis, aspergillosis, or pneumonia [10]. Activation of cervical muscles after tracer injection, which frequently occurs if the patients are not able to relax after tracer injection, can cause significant cervical FDG uptake which can resemble cervical lymph node metastases. In the mediastinum, false-positive results can be due to thymus tissue.

^{201}Tl was used initially for nonradioiodine scintigraphy in thyroid cancer with promising results [28], but its sensitivity is too low for routine clinical use, especially in comparison with MIBI and tetrofosmin, mainly due to inferior physical characteristics of the isotope. Ohnishi et al. [40] reported a false-negative rate of 53%, while MRI was false-negative in only 23% in the same group. In the first years of clinical use, a sensitivity of about 70–90% was reported for MIBI [10, 12, 39]. Recent studies on tetrofosmin [20] have yielded promising results, suggesting this tracer to be comparable with MIBI, as was expected due to comparable tracer uptake mechanisms. Gallowitsch et al. [20] reported sensitivity values up to 100% in small groups, depending on the site of the metastases, but further studies are necessary to confirm these preliminary data. A recently published paper, comparing furifosmin and FDG-PET, gave poor results for this ^{99m}Tc-labeled tracer [9]. Only a few studies have dealt with the causes of false-positive results with single-photon emitters, but these have to be considered as well. Since all radiopharmaceuticals are myocardial tracers, they are taken up by myocytes and can cause false-positive results in cervical muscles. In addition, sometimes scar tissue can take up MIBI or tetrofosmin. In a direct comparison of MIBI (or ^{201}Tl in a few cases) and FDG-PET, an inferior sensitivity of single-photon emitters was observed [26]. The lower sensitivity of MIBI and ^{201}Tl in direct comparison with FDG-PET is probably caused by the inferior spatial resolution (about 5 mm for PET imaging and about 10 mm for SPECT imaging). In all regions which have to be evaluated with tomographic imaging (e.g., the mediastinum), a higher spatial resolution – and therefore higher sensitivity of PET – can be expected. Planar imaging might be superior for superficial sites in the neck in some cases, but is significantly inferior with regard to other regions. Moreover, differences of tracer uptake mechanisms have to be considered. The lower sensitivity of MIBI/^{201}Tl scintigraphy in the German multicenter study on FDG-PET, compared with earlier studies on MIBI imaging, might have been caused by the selection criteria, since at least a few FDG-PET studies were done after negative results of scintigraphy using radioiodine, MIBI, or ^{201}Tl.

In addition, more complicated cases with small tumor sites have to be considered. Hürthle cell carcinomas are radioiodine-negative in most cases. Therefore, in these patients, functional imaging with other tracers is particularly necessary. In patients with Hürthle cell carcinomas, the sensitivity of FDG-PET is as high as 85% [26], whereas it is very low for radioiodine, as might be expected. Since

Hürthle cell carcinomas are known to have a high mitochondria content, they were expected to take up high amounts of all tracers which are accumulated in accordance with the mitochondrial potential and content (MIBI, tetrofosmin). However, the sensitivity of imaging using MIBI in Hürthle cell carcinoma was not observed to be higher than that of FDG-PET.

Somatostatin receptor expression in thyroid tissue (particularly in endemic goiter) was observed by Becker et al. [6]. Recently, somatostatin receptor expression has been described in three patients with Hürthle cell carcinoma using ^{111}In-octreotide [27]. Compared with conventional radiologic procedures, Valli et al. [51] found somatostatin receptor imaging to be inferior with respect to the obtained clinical information. In only one case did somatostatin receptor imaging detect mediastinal lymph node metastases not seen with morphological techniques [51]. Görges et al. [21] reported a good correlation of somatostatin receptor scintigraphy with the autoradiographically measured receptor status. They studied 24 cases of differentiated thyroid cancer and found a higher sensitivity of somatostatin receptor scintigraphy, compared with MIBI and ^{201}Tl. The highest sensitivity was achieved by FDG-PET in this group [21]. As well as for tumor detection, this method can be used to evaluate subsequent therapeutic options with somatostatin analogs. But no correlation between therapeutic effects of cold octreotide and receptor scintigraphy could be proven by Görges et al. [21].

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