# Integrated Imaging of Thyroid Disease

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## Introduction

Since the thyroid and the parathyroid glands can be affected by a variety of different benign and malignant pathologies, both structural and molecular imaging modalities, some of them combined in hybrid modalities, contribute significantly to establish the final diagnosis. Furthermore, they are part of routine follow-up in thyroid disease, especially in differentiated thyroid cancer. However, precise knowledge of the molecular features of the underlying disease is crucial for the correct choice of the imaging modality and the radiopharmaceutical when using molecular imaging such as planar scintigraphy, SPECT/CT, or PET/CT.

## Benign Thyroid Disease

### Ultrasound

After anamnesis, clinical examination, and assessment of blood levels of the most important thyroid parameters (TSH, free T4), ultrasound is the first imaging modality to be performed, independent whether the diagnosis is normothyroid goiter, hypothyroidism, or hyperthyroidism. It allows for morphologic assessment, for volume measurements, and for analysis of vascularization of the whole thyroid gland and of thyroid nodules when present. Solid nodules can furthermore be assessed for presence of echocomplexity, calcifications, pathologic perfusion patterns, and irregular boundaries which are important attributes in discrimination of probably benign from potentially malignant lesions. Depending on the underlying disease, thyroid or nodular tissue may be iso- (e.g., adenoma), hyper- (e.g., adenoma or scar tissue), or hypoechogenous (liquid, inflammation, carcinoma). Diffuse hypervascularization is observed in inflammatory conditions, especially in Graves' disease. Focal hypervascularization can be found in hyperfunctioning adenomas as well as in lesions suspicious for malignancy. Nowadays, the ultrasound findings of normothyroid nodular goiter should be reported according to the TI-RADS (thyroid imaging reporting and data system) criteria [1, 2]. This reporting system also includes measurement of stiffness of thyroid nodules using strain or shearwaves (ultrasound elastography) [3, 4]. Furthermore, the head and neck lymph node basins should be evaluated routinely, especially in case of suspicious thyroid nodules, since ultrasound may detect macroscopically visible lymph node metastases already in early stages of thyroid carcinoma (Table 1).

### Thyroid Scintigraphy

Depending on clinical suspicion, blood samples, ultrasound findings, and potential therapeutic pathways, thyroid scintigraphy is the tool of choice for further functional evaluation of thyroid disease. Due to its excellent sensitivity, in suspected congenital thyroid agenesis, hypothyroidism or ectopic thyroid tissue, thyroid scintigraphy is the exam of first choice, even before ultrasound. In hyperthyroidism, thyroid scintigraphy enables to discriminate between the different

**Table 1** TI-RADS scoring system and risk of malignancy

| TI-RADS score | Description | Risk of malignancy (%) |
|---|---|---|
| 1 | Normal scan | 0 |
| 2 | Benign lesions | 0 |
| 3 | Very probably benign lesions | 0.25 |
| 4A | Low suspicion of malignancy | 6 |
| 4B | High suspicion of malignancy | 69 |
| 5 | Clearly malignant | 100 |

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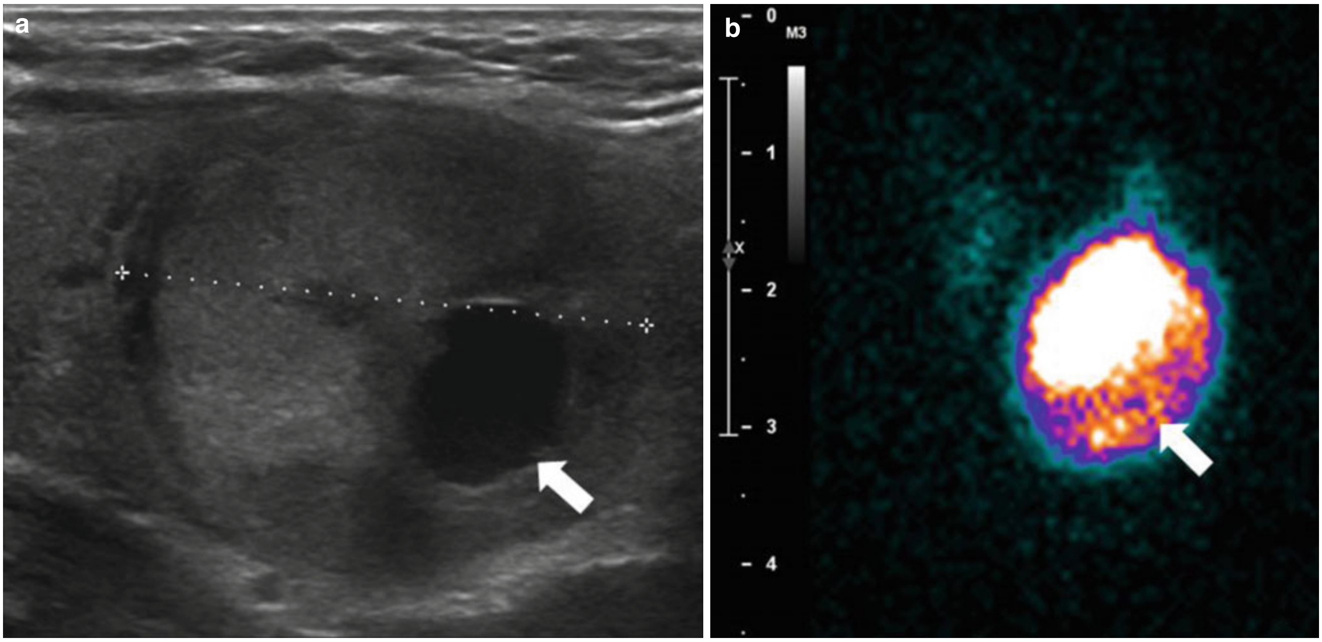


**Fig. 1** Sagittal ultrasound (**a**) and planar anterior $^{123}$I scintigraphy (**b**) of a hyperfunctioning nodule (adenoma) of the left thyroid gland in a patient presenting with hyperthyroidism. Note the nearly complete functional extinction of the normal thyroid tissue. Furthermore, a liquid part (*arrows*) is present in the inferolateral part of the nodule, visible as an echo-free zone in ultrasound and as "cold" zone in the scintigraphic image

**Table 2** Typical scintigraphic patterns of different thyroid conditions

| Globally decreased tracer uptake | Focally decreased tracer uptake | Globally increased tracer uptake | Focally increased tracer uptake |
|---|---|---|---|
| Hypothyroidism<br>Thyroiditis<br>Iodine contamination<br>Hyperthyreosis factitia | Nonfunctioning thyroid nodules<br>Thyroid cysts<br>Suppressed normal thyroid in presence of focal autonomy | Disseminated autonomy<br>Graves' disease<br>Lobar autonomy | Uni- or multifocal thyroid autonomy |

underlying pathologies such as uni- or multifocal autonomy, disseminated autonomy (Fig. 1), or different presentations of thyroid inflammations which may initially present with hyperthyroid conditions. The typical scintigraphic patterns of the various underlying pathologies are summarized in Table 2. In multinodular goiter, thyroid scintigraphy can be helpful in guidance of fine needle aspiration.

In current clinical practice, thyroid scans are performed using $^{99m}$Tc-pertechnetate and $^{123}$iodine as specific markers of thyroid function, whereas $^{99m}$Tc-MIBI may be used additionally as a nonspecific tumor-seeking agent in patients with normothyroid nodular goiter. Depending on thyroid function, both $^{123}$I and $^{99m}$Tc-pertechnetate are internalized in the thyroid cells via the $Na^+/I^-$-symporter. $^{123}$I is then further metabolized and integrated in the thyroid hormones, whereas $^{99m}$Tc-pertechnetate is not metabolized. Usually, images of the thyroid are acquired 20 min after intravenous administration of $^{99m}$Tc-pertechnetate and 2 or 24 h after oral administration of very low activities of $^{123}$iodine. Ideally, the scans are acquired with a dedicated thyroid gamma camera or, if not available, with a conventional large field of view gamma camera using either pinhole collimators or zoomed images. Most frequently, planar anterior views are acquired. Additionally, right and left oblique views may be obtained for better localization of focally decreased or increased uptake.

In addition to the scintigraphic images, semiquantitative parameters, such as technetium (TcTU) or radioiodine uptake, are routinely calculated. Both parameters are helpful in the differential diagnosis of benign thyroid disease. In case of hyperthyroidism, the maximal thyroid radioiodine uptake in percent of the administered dose is one of the parameters needed to define an individually calculated therapeutic activity of $^{131}$I. In case of nodular goiter, nodules presenting with decreased or absent tracer uptake (scintigraphically "cold" nodules), which were classified as solid in ultrasound, can be further evaluated by nonspecific tumor-seeking radiopharmaceuticals (e.g., $^{99m}$Tc-MIBI or $^{99m}$Tc-tetrofosmin) due to their good sensitivities and negative predictive values for discrimination between benign and malignant lesions [5]. With exception of suspected congenital hypothyroidism (especially suspected ectopic thyroid gland), thyroid scintigraphy should not be performed in hypothyroidism.

### PET/CT and SPECT/CT

The value of these hybrid imaging techniques for evaluation of benign thyroid disease is not yet clear and is currently under investigation. First studies showed that PET/CT using $^{18}$F-FDG, targeting increased glucose consumption of potentially malignant thyroid nodules, was helpful to better discriminate between benign and malignant lesions and thus avoided non-necessary diagnostic surgery in a significant proportion of the patients [6]. However, there is no role for FDG PET/CT in the assessment of hyper- or hypothyroidism.

### Hyperparathyroidism

Once hyperparathyroidism is confirmed by elevated blood levels of parathormone, the standard diagnostic procedure consists from ultrasound of the neck region as well as of planar and tomographic parathyroid scintigraphy. This exam can be performed in double-isotope ($^{99m}$Tc-pertechnetate or $^{123}$I in combination with $^{99m}$Tc-MIBI) or single-isotope (dual phase $^{99m}$Tc-MIBI) technique. In general, focal $^{99m}$Tc-MIBI uptake in the absence of $^{99m}$Tc-pertechnetate or $^{123}$iodine uptake is diagnostic for parathyroid adenoma or hyperplasia (Fig. 2). However, diagnosis may be difficult in nodular goiter with hypofunctioning, MIBI-positive thyroid nodules or intrathyroid parathyroid adenomas. Independent of the chosen approach, subtraction of the two scans is helpful for better discrimination between normal thyroid tissue and parathyroid adenoma. The use of hybrid SPECT/CT significantly improves precise localization of parathyroid adenomas or hyperplastic parathyroid glands [7]. Additionally, hybrid imaging facilitates planning of the surgical procedure and allows a minimal invasive approach in most cases [8]. In contrary to ultrasound alone, parathyroid scintigraphy allows also for detection and precise localization of ectopic parathyroid adenomas which accounts for up to 8 % of the cases.

Hybrid PET/CT using $^{18}$F-fluorocholine, a biomarker of cellular phosphatidylcholine metabolism, appears to be a new and promising diagnostic tool for primary and secondary hyperparathyroidism, especially in patients presenting with negative or discordant ultrasound and scintigraphic results [8–10].

## Malignant Thyroid Disease

### Differentiated Thyroid Carcinoma (DTC)

#### Ultrasound

Already in the detection of primary DTC, ultrasound plays an important role. At initial diagnosis, highly suspicious or malignant thyroid nodules typically show the following patterns: the nodules are taller than wide, markedly hypoechogenic, and they present with irregular boundaries, microcalcifications, and a high stiffness in sonoelastography. Besides anamnesis, clinical examination, and determination of blood thyroglobulin levels, ultrasound is an essential part of routine follow-up in DTC. After total thyroidectomy and radioiodine remnant ablation, any vascularized tissue in the thyroid region has to be considered as suspicious for local recurrence. Additionally, any round, hyperechogenic, and hypervascularized lymph node that has lost its typical single sinusoidal vessel has to be considered as suspicious for lymph node metastasis. In doubtful cases, ultrasound-guided fine needle aspiration of suspicious lesions should be performed to confirm the suspicion and initiate adequate treatment (surgery, radioiodine treatment, etc.).

#### Whole Body Scanning ($^{123}$I and $^{131}$I) Including Hybrid SPECT/CT

Pre-ablative diagnostic whole body scans using low activities of $^{123}$I or $^{131}$I allow for detection of significant remnant thyroid tissue and occult locoregional and distant metastases. These findings are subject to significantly changing the further management of the patients, e.g., reoperation in order to diminish the amount of remnant thyroid tissue to treat or increase the $^{131}$I ablative activity in order to sufficiently treat locoregional and distant metastases [11, 12]. In every case, whole body scans including hybrid SPECT/CT are performed between 4 and 7 days after administration of the ablative activity of $^{131}$I. Therefore, $^{131}$I can be considered as a theragnostic agent since it its properties allow for a therapeutic and diagnostic use at one time. The post-therapeutic whole body scans are performed in order to determine the definitive amount of remnant thyroid tissue and/or the presence of locoregional or distant metastases. This post-ablation scan serves also for risk stratification and further risk-adapted follow-up and treatments (depending on tumor type and presence or absence of locoregional or distant metastases). Papillary thyroid carcinoma essentially tends to metastasize towards locoregional lymph nodes, whereas follicular thyroid carcinoma additionally tends to spread to distant organs, especially to the lung and to the skeleton. Hybrid SPECT/CT is particularly helpful in discriminating between remnant thyroid tissue, lymph node metastases, and nonspecific radiotracer uptake or retention in the oral cavity, the salivary glands, and the esophagus. Post-therapy whole body scans are repeated after every new radioiodine therapy of iodine-avid tumor manifestations (Fig. 3).

According to ATA (American Thyroid Association) recommendation no. 67, diagnostic whole body scans with a low activity of $^{131}$I or, alternatively, $^{123}$I may be of value and should be performed 6–12 months after remnant ablation in patients with high or intermediate risk of persistent disease. Furthermore, these diagnostic scans are valuable in patients presenting with antibodies against thyroglobulin or patients who presented extra-thyroid uptake already at the post-ablation whole body scan [13].

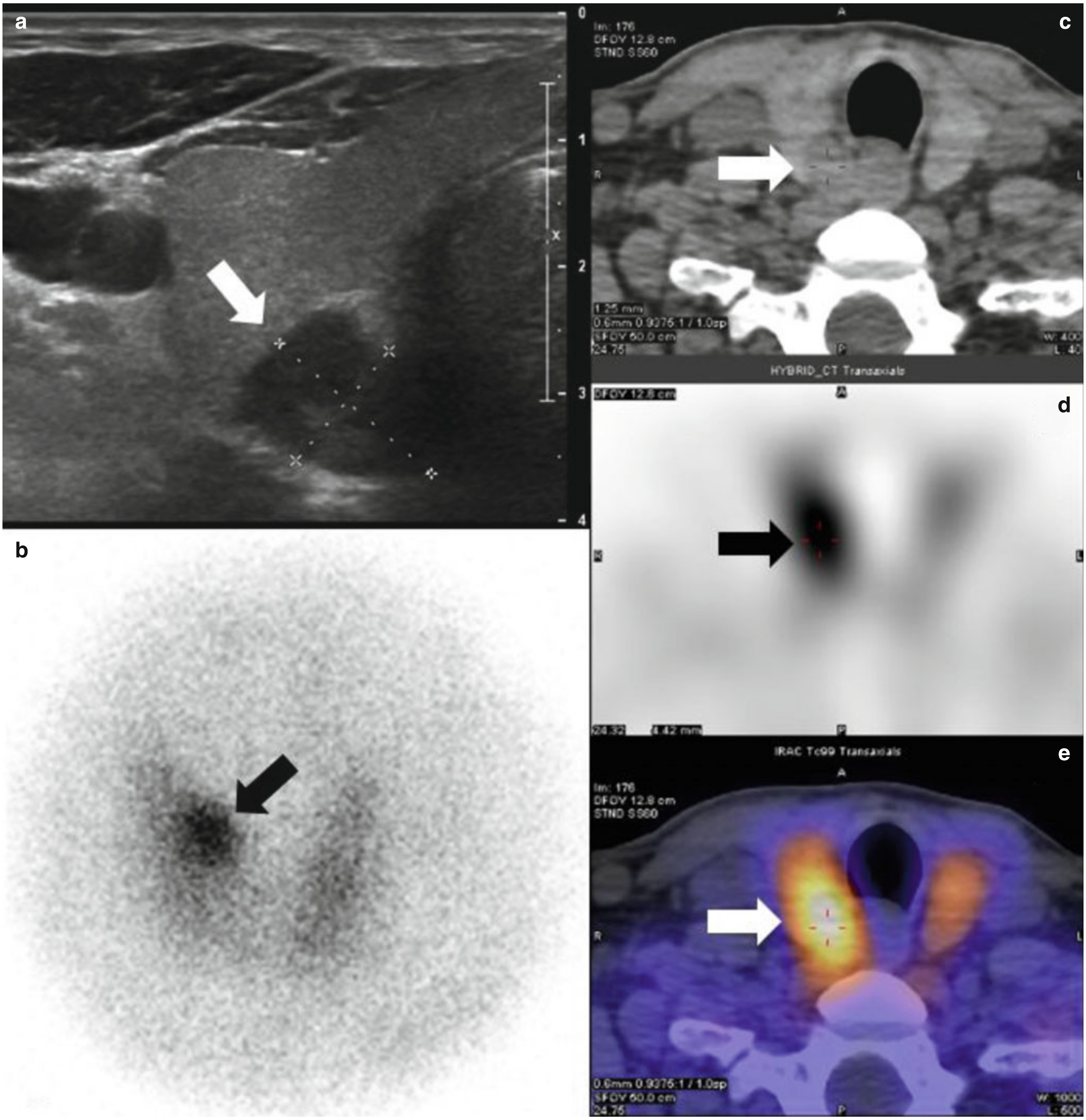


**Fig. 2** Ultrasound (**a**), planar $^{99m}$Tc-MIBI scintigraphy (**b**), and hybrid $^{99m}$Tc-MIBI SPECT/CT (**c**–**e**) of a parathyroid adenoma located behind the right lobe of the thyroid (*arrows*). The transversal ultrasound images demonstrate a hypoechogenous nodular structure; the scintigraphic images show markedly increased tracer uptake in a rather hypodense structure located in between the right thyroid lobe, the trachea, and the esophagus

## PET/CT

$^{18}$F-FDG PET/CT is a very valuable diagnostic tool to assess patients presenting with measurable thyroglobulin, negative neck ultrasound, and negative diagnostic $^{131}$I or $^{123}$I whole body scan including SPECT/CT, indicating dedifferentiated manifestations of the underlying disease (Fig. 4). Especially, the presence of a low thyroglobulin doubling time is highly predictive of positive FDG PET/CT scans [14]. Also the presence of both differentiated and dedifferentiated manifestations of DTC is possible ("flip-flop phenomenon").

First applications of PET/CT using $^{124}$I showed promising results, but due to its limited availability, this tracer is not yet part in the routine workup and follow-up of DTC. The role of PET/MRI in diagnosis and follow-up of thyroid cancer also remains to be investigated.

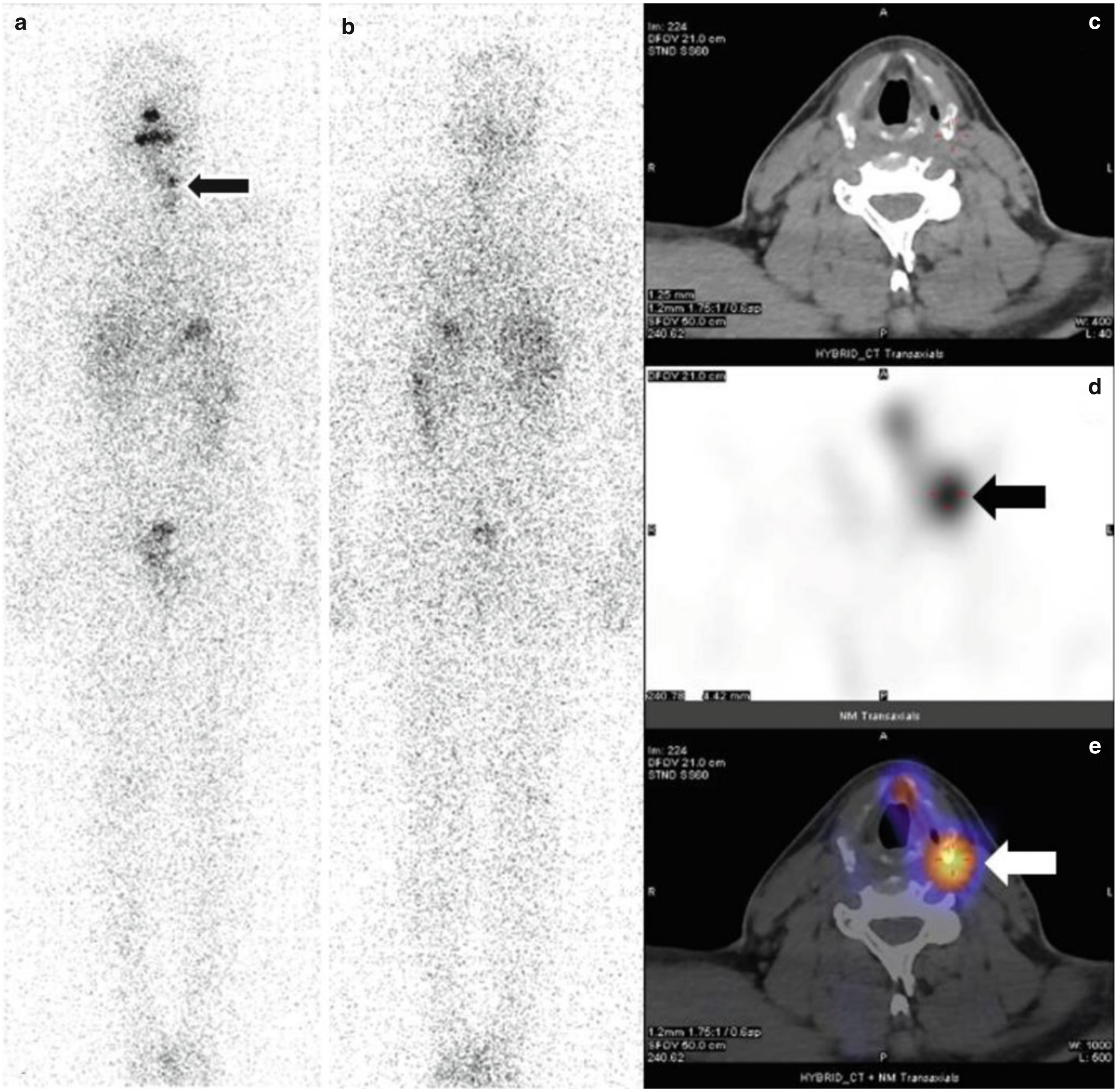


**Fig. 3** Diagnostic planar anterior (**a**) and posterior (**b**) $^{131}$I whole body images and cervical hybrid SPECT/CT (**c**–**e**) showing local recurrence (*arrows*) in a patient presenting with biochemical relapse of papillary thyroid carcinoma. SPECT/CT enables to discriminate pathologic radiotracer uptake from physiological radiotracer retention in salivary glands, the larynx, and the esophagus

### CT and MRI

Since contrast-enhanced CT should not be performed in patients with iodine-avid DTC, native CT does not play a significant role in diagnosis and follow-up. In contrary, native CT is very valuable for attenuation correction and morphologic localization of radiotracer accumulating lesions in hybrid PET/CT and SPECT/CT. In selected cases with nonconclusive findings in hybrid PET/CT and SPECT/CT, the excellent soft tissue contrast of MRI can add valuable additional information. Furthermore, it allows for contrast media administration and thus discrimination of vascular from other structures, especially very small lymph nodes in close proximity of the blood vessels.

## Anaplastic Thyroid Carcinoma

Anaplastic thyroid carcinoma is a very aggressive, dedifferentiated entity with a very poor prognosis. Due to its poor grade of differentiation, there is only a very low or even

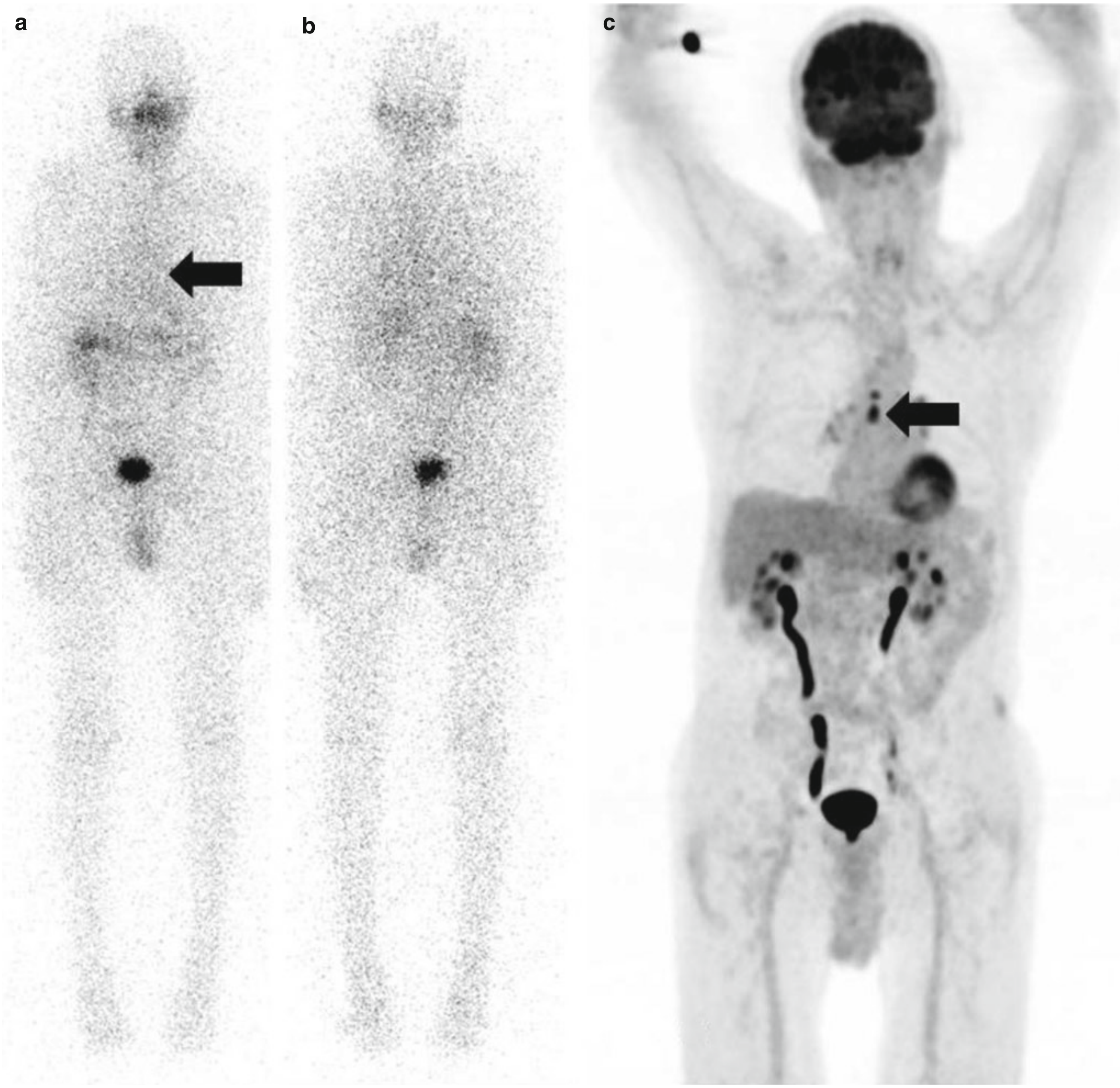


**Fig. 4** Planar anterior (**a**) and posterior (**b**) $^{131}$I whole body scans and $^{18}$F-FDG PET MIP image (**c**) in a patient presenting with biochemical recurrence of papillary thyroid carcinoma. The radioiodine scan is negative, whereas FDG PET shows suspicious tracer uptake in mediastinal lymph nodes (*arrows*)

absent avidity for radioiodine. Remnant ablation using $^{131}$I is routinely performed, taking into account the radioiodine avidity of the remnant thyroid tissue and the so-called bystander effect which means an irradiation of non-iodine-avid cells by surrounding iodine-avid cells. However, in the follow-up, neck ultrasound and FDG PET/CT are the imaging modalities of choice. Due to the very low iodine avidity, of the tumor cells even contrast-enhanced CT may be performed in these patients. Whenever possible, surgery is the therapy of choice, followed by external beam irradiation.

## Medullary Thyroid Carcinoma (MTC)

Medullary thyroid carcinoma is a rare tumor (accounting for 3% of all thyroid tumors) originating from the calcitonin-producing parafollicular cells of the thyroid. In a significant proportion, especially in hereditary MTC, it is associated with other endocrine neoplasms (especially parathyroid adenoma and pheochromocytoma) which is called multiple endocrine neoplasia type 2. In terms of imaging for the initial diagnostic workup, neck ultrasound plays an important role

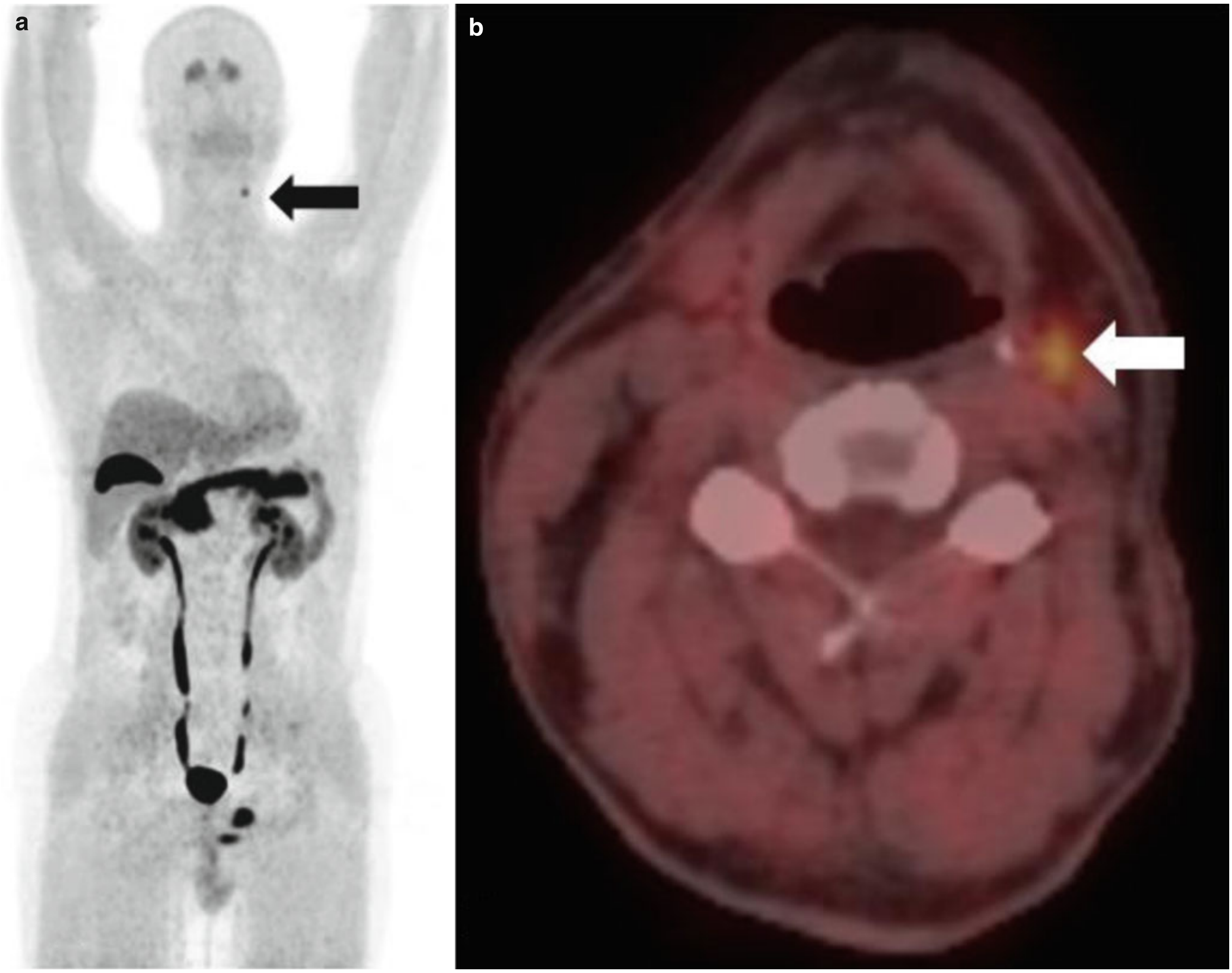


**Fig. 5** MIP (**a**) and fused transversal (**b**) $^{18}$F-DOPA PET/CT images in a patient presenting with biochemical recurrence of medullary thyroid carcinoma. The PET images nicely show intense tracer uptake a single subcentimetric metastasis in the left cervical lymph node area III

for detection of suspicious thyroid nodules and neck lymph nodes. Structural imaging procedures consist of contrast-enhanced CT and MRI, depending on the body region to scan. Molecular targets for radionuclide imaging are the somatostatin receptors and the APUD (amine precursor uptake and decarboxylation) system which can be addressed with rather low diagnostic performance by hybrid SPECT/CT ($^{111}$In-octreotide, a somatostatin analogue) and with high diagnostic performance by hybrid PET/CT using $^{68}$Ga-DOTA-peptides (somatostatin analogues) or $^{18}$F-DOPA (targeting the APUD cell system) [15–17] (Fig. 5). In cases of high-grade tumors, $^{18}$F-FDG PET/CT can be used to detect poorly differentiated tumor manifestations.

## Conclusion

In addition to clinical and laboratory exams, imaging modalities providing structural (ultrasound), molecular (scintigraphy), and hybrid structural and molecular (SPECT/CT and PET/CT) play an important role in the diagnosis and follow-up of benign and malignant thyroid and parathyroid disease. Ultrasound is a basic imaging modality for any kind of thyroid or parathyroid disorder. Thyroid scintigraphy plays an important role in differential diagnosis and determination of the therapeutic activity of $^{131}$I in hyperthyroidism, whereas it is not indicated in most cases of hypothyroidism. In nodular goiter, $^{99m}$Tc-MIBI can add useful information and help to advance in diagnostic stratification. Combination of ultrasound and $^{99m}$Tc-MIBI scintigraphy represents the standard for localization of orthotopic or ectopic parathyroid adenomas or hyperplastic parathyroid glands. Ultrasound and diagnostic or post-therapeutic whole body scans including hybrid SPECT/CT are the imaging modalities of choice in the follow-up of DTC. Hybrid FDG PET/CT plays an important role in the detection of dedifferentiated manifestations of DTC and in anaplastic thyroid cancer. New diagnostic molecules for integrated PET/CT are expected to play an important role in the detection of occult parathyroid adenomas ($^{18}$F-choline) and in the staging and follow-up of medullary thyroid cancer ($^{68}$Ga-DOTA-peptides, $^{18}$F-DOPA). The role of PET/MRI as new integrated imaging modality needs to be investigated. In thyroid ultrasound, the implication of elastography and standardized reporting following the TI-RADS classification are also expected to improve diagnostic accuracy and risk stratification of the patients.

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