11 Modern Diagnostic and Therapeutic Approaches in Thyroid Diseases: Theranostics and the Changing Role of Radioactive Isotopes

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It is a great honor and a great pleasure to contribute to a Festschrift for Professor Richard Baum, a very good friend, a brilliant scientist, and one of the leading clinically active physicians in the field of coupling diagnostic and therapeutic approaches using radioactive isotopes—the so-called "theranostics".

Outside nuclear medicine, theranostic represents the tight connection of diagnostic procedures and therapeutic regimens, resulting in personalized medicine. Diagnostic tools on a molecular level are gaining more and more importance with the upcoming development of highly specific drugs such as kinase inhibitors and immunotherapeutic substances. Due to dramatic progresses in radiochemistry and radiopharmacy, molecular imaging with radioactive isotopes coupled with specific treatment options becomes a central issue with respect to the meaning of radioactive isotopes in modern medicine, focused on multimodal treatment regimens. It is not so easy to give an exact definition for the use of isotopes in theranostics: it is related to a substance, that "finds its way" to target tissue (by specific molecular mechanisms) which might be—benign or malignant—the pathologic tissue, e.g., a neuroendocrine tumor, or a (healthy) target for pathological processes like the thyroid gland in Graves' disease for autoantibodies.

Radioactive iodine was the first isotope in history engaged in a theranostic approach, initially used to treat thyroid diseases. The first radioiodine treatments were done in the early 1940s and published in 1946 [1]. The first therapy in Europe was performed by Cuno Winkler in 1948 [2]. Based on the high effectivity of the sodium iodine transporter, highly specific uptake and striking effects could be achieved with radioiodine therapy. I-131 was discovered by Glenn Seaborg and John Livingood at the University of California. Initially, I-128 was used in animal studies, it was substituted by I-130 and finally I-131 with respect to superior physical and logistic characteristics. Iodine-123 for scintigraphic and SPECT imaging and I-124 for PET imaging followed. Like in all other theranostic applications, radioactive iodine isotopes can be used to perform dosimetry with respect to target organs as well as to critical organs to minimize side effects.

It took several decades and overwhelming successes in radiochemistry to copy the observed convincing effects of radioiodine treatment in the

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therapy of other diseases, particularly in cancer. The classic theranostic feature of I-131 with beta- and gamma-radiation can still be addressed as a blueprint for modern treatment regimens with radioactive isotopes. Nevertheless, compared to the time before 2000, the "classic" indications for radioiodine treatments are decreasing worldwide. Several reasons for this issue have to be discussed:

Mazzaferri and his group [3, 4] proved dramatic advantages of therapy regimens to treat differentiated thyroid cancer including radioiodine therapy not only in metastatic disease to destroy radioiodine-positive metastases (Fig. 11.1), but also to ablate remnant tissue in cases without visible remnant or metastatic malignant tissue. Outcome of patients treated with radioiodine improved markedly [3, 4] with respect to progression-free survival as well as overall survival. The reasons for the superiority of remnant ablation are obvious: besides the possible destruction of intrathyroidal micrometastases in tissue remnants, the conditions for an optimal follow-up are based on the absence of scintigraphically detectable (also benign) thyroid tissue and negative serum thyroglobulin as the most important tumor

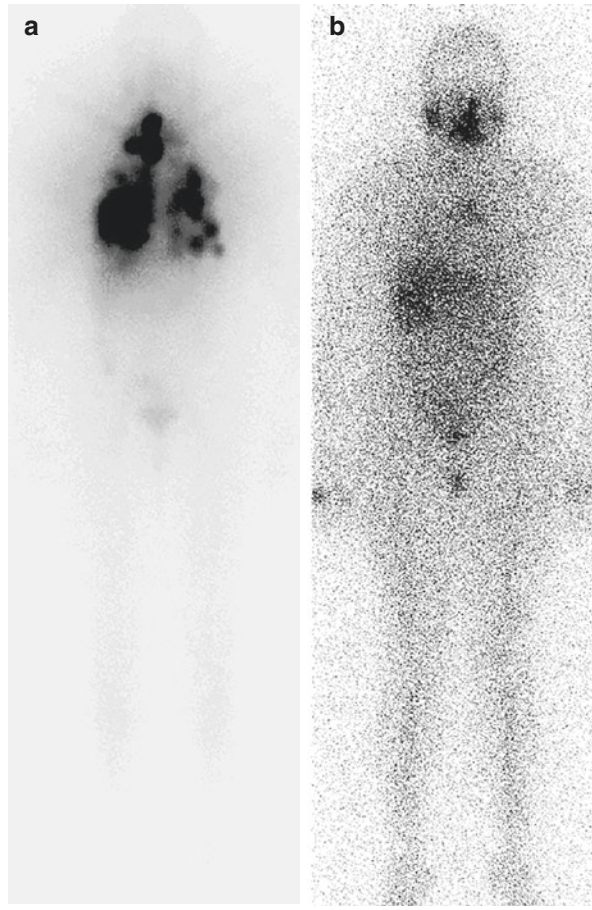

Fig. 11.1 59-year-old female patient after thyroidectomy and central lymph node dissection because of papillary thyroid cancer (pT2m, pN1a (9/42)). (**a**) Whole-body scan after first radioiodine application: multiple radioiodine-positive lung metastases (thyroglobulin: 113 ng/mL). (**b**) Whole-body scan after second radioiodine application, showing the treatment success of the first radioiodine therapy: only faint residual thoracic radioiodine uptake (thyroglobulin: 0.1 ng/mL). (**c**) CT scan before radioiodine treatment: multiple small lung metastases. (**d**) CT scan 6 months after high dose radioiodine treatment: remission of the lung metastases. (**e**) CT scan 1 year after high dose radioiodine treatment: further regression of the lung metastases

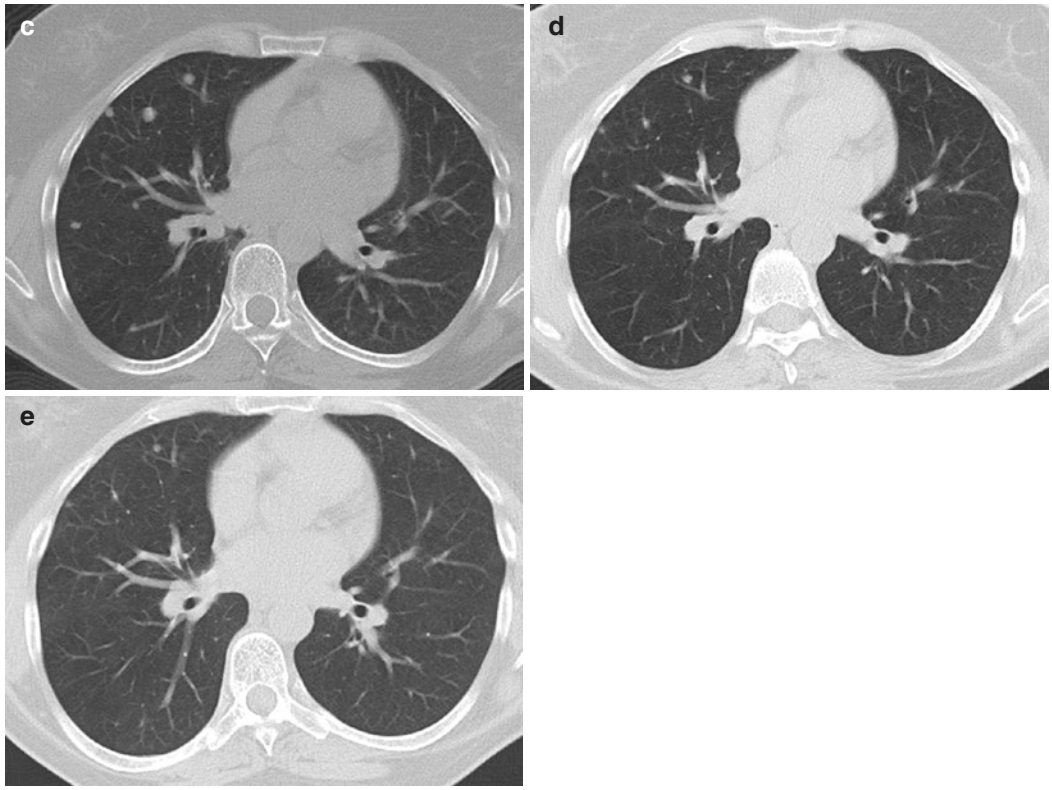

Fig. 11.1 (continued)

marker in differentiated thyroid cancer. Nevertheless, in some guidelines, written during the last years, e.g., published by the American Thyroid Association (ATA) [5] recently, besides restrictions concerning scintigraphy (recommended only, if TSH is suppressed) radioiodine treatment is considered less important and recommended only in higher tumor stages of differentiated thyroid cancer. Moreover, in papillary microcarcinoma, active surveillance is discussed instead of surgery (and ablation radioiodine therapy) [6, 7].

The reasons for these recommendations remain somewhat unclear. Partly, they are based on a number of publications dealing with possible secondary malignancy after radioiodine therapy in thyroid cancer, e.g., by Iyer et al. and other groups [8–11]. Several drawbacks of these papers make it difficult to follow the arguments against the use of treatment regimens, proven to be effective for several decades. Especially the effect of intensified surveillance (subsequently to radioiodine therapy) and resulting changes in early diagnosis in various cancers (addressed as secondary malignancies) were not taken into account. Moreover, cancers diagnosed as early as 6 months after radioiodine application were counted as secondary malignomas, contradicting radiation biology experiences, that it takes several years or even decades to develop stochastic radiation burdens, as described in these papers. In addition, a dose-effect relationship which should be expected in diseases, caused by a distinct factor, was not observed in most of these studies. A well-written paper dealing with some weak arguments concerning secondary malignancies (referring to a paper published by Molenaar et al. [12]) was published by Tulchinsky et al. [13]. A partial harmonization of ATA guidelines with especially European understandings [14] of optimal treatment regimens could be achieved in the "Martinique process" [15] by specialists from

several continents. A second reason for the decreasing number of radioiodine treatment in thyroid cancer worldwide might be the emerging importance of screening programs, including thyroid ultrasound [16]. On one hand, subsequently, thyroid cancers are detected at lower tumor stages with less nodal or distant metastatic involvement [17] and therefore decreased need for ablative radioiodine therapy (besides changes in the guidelines recommendations). On the other hand, higher detection rates could cause more radioiodine treatments (only those cases, in which the tumor would otherwise not be clinically obvious during lifetime). Surgical techniques have been improved, causing lower volumes of remnant tissue after thyroidectomy, resulting in lower numbers of radioiodine treatment cycles and lower amounts of radioiodine needed for complete remnant tissue ablation. Radioiodine uptake and thyroglobulin-guided radioiodine ablation was proven to be superior to fixed doses with respect to efficacy as well as side effects [18]. Risk-adapted treatment schedules are important also in metastatic disease with respect to the known outcome difference between synchronous and metachronous manifestation of distant metastases [19]. Whereas initial data did not show inferiority of low-dose (1.1 GB) radioiodine ablation in low-risk patients [20], in subsequently published papers it was proven that low-risk patients as well as high-risk patients benefit from higher activities [21]. Using I-124, Jentzen et al. [22] reported high success rates in dosimetry-guided therapeutic regimens.

Also in benign thyroid diseases, especially in Plummer's disease, we observe a decreasing number of radioiodine treatments (and also amounts of radioiodine needed), due to earlier detection of subclinical hyperthyreosis by screening programs and TSH measurements in standard clinical work-up. In addition, in former iodine deficiency areas, prevalence of functional autonomy is decreasing with the improvement of nutritional iodine supply [23, 24].

In diagnostic approaches, the use of radioisotopes decreases with respect to thyroid diseases as well since several guidelines recommend scintigraphy only in case of TSH suppression (see above). It is difficult to follow this argumentation since papers dealing with the prevalence of functional autonomy prove the necessity of scintigraphy also in cases with known thyroid nodules and normal TSH, because autonomic foci can be detected in many patients suffering from nodular goiter and presenting with normal TSH [25, 26]. Not only the need for treating functional autonomy, e.g., by radioiodine, can be derived from scan results, but also, with respect to deciding on the malignancy risk of suspicious nodules, it is important to avoid biopsy of hot nodules since these often show up as follicular neoplasia, which in general has to be addressed as an indication for surgery with histological work-up of the lesion, if the nodule is cold but is misleading in case of hot nodules. Other techniques, like elastography or power Doppler, might give some additional information on the tissue characteristics of thyroid nodules but are not able to replace scintigraphy [27, 28]. In addition, the thyroid scan is important to differentiate between thyroiditis with thyroid hormone releasing from destructed follicles and Graves' disease with hyperthyreosis [29].

New fields for the use of radioactive isotopes in malignant thyroid diseases were established within the last two decades and particularly the last few years—especially with respect to interdisciplinary settings. The loss of radioiodine uptake, due to the loss of sodium iodine symporter (or its embedding in the cell membrane) markedly decreases prognosis [30]. In addition to morphological imaging with ultrasound, CT, and MRI, various functional imaging techniques were established to detect malignant tissue within the thyroid gland as well as radioiodine-negative tumor sites after thyroidectomy and ablative therapy.

Besides "functional scintigraphy" with Tc-99 m-pertechnetate or I-123, "metabolic imaging "with Tc-99 m-Hexakis-(2-methoxy-2-methylpropylisonitrile) (MIBI), and—if available—FDG-PET scan have proven to contribute significantly to the characterization of suspicious thyroid nodules [31, 32]. The very high negative predictive value of MIBI scintigraphy (>90%) has brought this technique to clinical routine in the work-up of thyroid nodules. FDG-

PET has its major role in the detection of radioiodine-negative lesions in differentiated thyroid cancer [33, 34] and medullary thyroid cancer [35] and is superior to morphological imaging with CT and MRI. MIBI scintigraphy can be useful during follow-up and recurrence detection when FDG-PET/CT is not available [36, 37]. Radioiodine refractory condition is—according to paper published by Cabanillas et al. [38]—defined as

- Lack of radioiodine uptake on posttherapy scan (>1.1 GB).
- Lack of radioiodine uptake on whole body scan in known structural disease.
- Lack of demonstratable ability of the tumor to concentrate sufficient radioiodine for a tumoricidal effect (<80 Gy in metastatic foci),
- Structural progression 6–12 months after radioiodine therapy.
- Rising Tg levels 6–12 months after radioiodine therapy.
- Continued progression despite cumulative activities of >20 GBq.

In these situations, other treatment options have to be discussed. Conventional chemotherapy (e.g., with doxorubicin or cisplatin) did not show positive effects in most cases and was used in some patients suffering from anaplastic or poorly differentiated thyroid carcinomas [39]. Recently, particularly multikinase inhibitors emerged as promising treatment options. They showed positive effects as to tumor shrinkage and progression-free survival [38]. Sorafenib was approved on the basis of the DECISION trial, which showed a prolonged progression-free survival from 5.8 to 10.8 months [40] with no significant effect on the overall survival. Lenvatinib was approved by the FDA on the basis of the SELECT trial [41]. Progression-free survival was 18.3 months in the verum group and 3.6 months in the placebo group [41]. The response rate was as high as 65%, including 4 complete remissions. Therefore, lenvatinib seems to be the most promising kinase inhibitor (without considering possible effects on radioiodine uptake of other drugs) hitherto.

Former approaches to reinduce radioiodine uptake and therefore engage the radioisotope theranostic principle were done with retinoic acid [42, 43] and rosiglitazine [44]. In about 30% of all cases, radioiodine uptake in initially radioiodine-negative tumor lesions could be achieved by retinoic acid. Nevertheless, there are only few cases with reported clinical success for this kind of redifferentiation therapy.

According to a number of recently published results, molecular profiling could be extremely helpful in radioiodine refractory cancer [45–51] with respect to evaluating individual outcome prognosis as well as choosing optimal targeted therapy [52]. Immune checkpoint inhibitors proved to be effective in various cancer types and can be expected to be helpful also in some patients suffering from thyroid cancer. A new approach was the use of selumetinib [53]. It was effective to increase radioiodine uptake and shrink tumor mass, especially in RAS-mutated tumors. In 12 out of 20 patients, radioiodine uptake was increased significantly, causing partial remission in 5 cases [53]. Recently, dabrafenib was shown to be able to reinduce striking radioiodine uptake in BRAF-positive cases [54]. All these data are leading back to the above-mentioned personalized treatment (also called theranostic), coupled with genetic tumor characterization. Larger series are necessary to evaluate the success rate, the intensity of iodine uptake, and the therapeutical effects of dabrafenib in initially radioiodine-refractory cancer.

In general, increasing importance of mutation analyses can be expected in the near future, e.g., for larotrectinib, a highly selective inhibitor of the three tropomyosin receptor kinase proteins TRKA, TRKB, and TRKC. Larotrectinib is a tissue unspecific kinase inhibitor ("tissue agnostic") and is approved for all cancer types with NTRK fusion. Only around 1% of all malignant tumors are NTRK-positive, but (besides salivary gland cancer and sarcomas) papillary thyroid cancers have the highest likelihood to be NTRK-positive. Only a few cases were reported [55], but this substance might become more important in the therapy of radioiodine-negative/refractory papillary thyroid cancer in the future.

Since all these drugs have remarkable side effects (hypertension, diarrhea, fatigue, weight loss, hand-foot skin reaction), which are in part severe and can be life-threatening, their toxicity has to be kept in mind when weighing advantages against disadvantages of starting kinase inhibitor treatments. Especially in slow-growing thyroid cancers, it is really difficult to find the right time point to start with the treatment when symptoms become more evident and/or progression of the disease accelerates. According to the ATA guidelines, multi-kinase inhibitors should be engaged in case of a diameter increase of more than 20% within 6 months [5]. Other groups [56] recommended to start with kinase inhibitors, when the tumor diameter is >1 cm and progression occurred within less than 12 to 14 months.

But also "classic" isotope theranostics (besides iodine isotopes) which were developed for other cancer types, e.g., somatostatin receptor positive neuroendocrine tumors, proved to be helpful in some cases of differentiated thyroid cancer (Fig. 11.2). Somatostatin receptor overexpression has been demonstrated in normal thyroid as well as thyroid cancer cells [57–62]. A series of 16 patients had been treated with PRRT by the group of Richard Baum. Stable disease was observed in 36%, and partial response in 18% [63]. Since PSMA-positivity could be demonstrated not only in prostate cancer but also in several other tumor types, PSMA-specific ligands were used for diagnosis and therapy in various cancers. PSMA ligand uptake was also seen in differentiated thyroid cancer (by incident as well as in specific work-up of cases with suspected recurrence [64, 65]) and Lu-177 ligands have been used to treat radioiodine-refractory differentiated thyroid cancer [66].

Fibroblast activation protein inhibitor (FAPI) is overexpressed in cancer-associated fibroblasts in many tumors and Ga-68-PET/CT was proven to be a suitable diagnostic tool in various cancers, including differentiated thyroid cancer [67]. Perhaps FAPI can be used as a theranostic substance in the future—labeling with Actinum-225 and Yttrium-90 has been described [68, 69]. Nevertheless, Ga-68-FAPI uptake in poorly differentiated thyroid cancer was rather low [70].

C-X-C chemokine receptor type 4 (CXCR-4)-mediated uptake of radioactive ligands has been used for diagnostic (with Ga-68-Pentixafor) [71] as well as therapeutic (with Lu-177-Pentixather) [72–74] approaches. The chemokine receptor CXCR-4 is overexpressed in various tumors (including solid tumor tissue such as breast cancer, pancreatic adenocarcinoma, hepatocellular carcinoma, lung and colorectal cancer) and is linked to tumor invasiveness and resulting poorer outcome [71]. In addition, CXCR-4 is positive in inflammatory diseases [74]. A meta-analysis, dealing with CXCR-4 expression in thyroid tissue, showed a distinct overexpression in papillary cancer (OR 67!) and a weak overexpression also in thyroiditis (OR 1.7) [75]. Therefore, due to very high overexpression in papillary cancer, this theranostic substance might be a promising solution for iodine refractory cases in the future.

Also in benign thyroid diseases new fields for the use of radioisotopes can be defined: Around 15 years ago, thermal ablation procedures were introduced successfully to clinical routine in the treatment of thyroid nodules [76–79]. Initially addressed as an alternative to radioiodine treatment and therefore a competing technique, it could be proven that it is possible to combine both techniques for optimal treatment of nodular goiter, especially with hot and cold nodules present in one thyroid gland [80]. In Graves' disease, total thyroid ablation (TTA) was proven to be superior to surgery alone with respect to improvement of endocrine orbitopathy. In patients treated by TTA, endocrine orbitopathy could be reduced significantly [81].

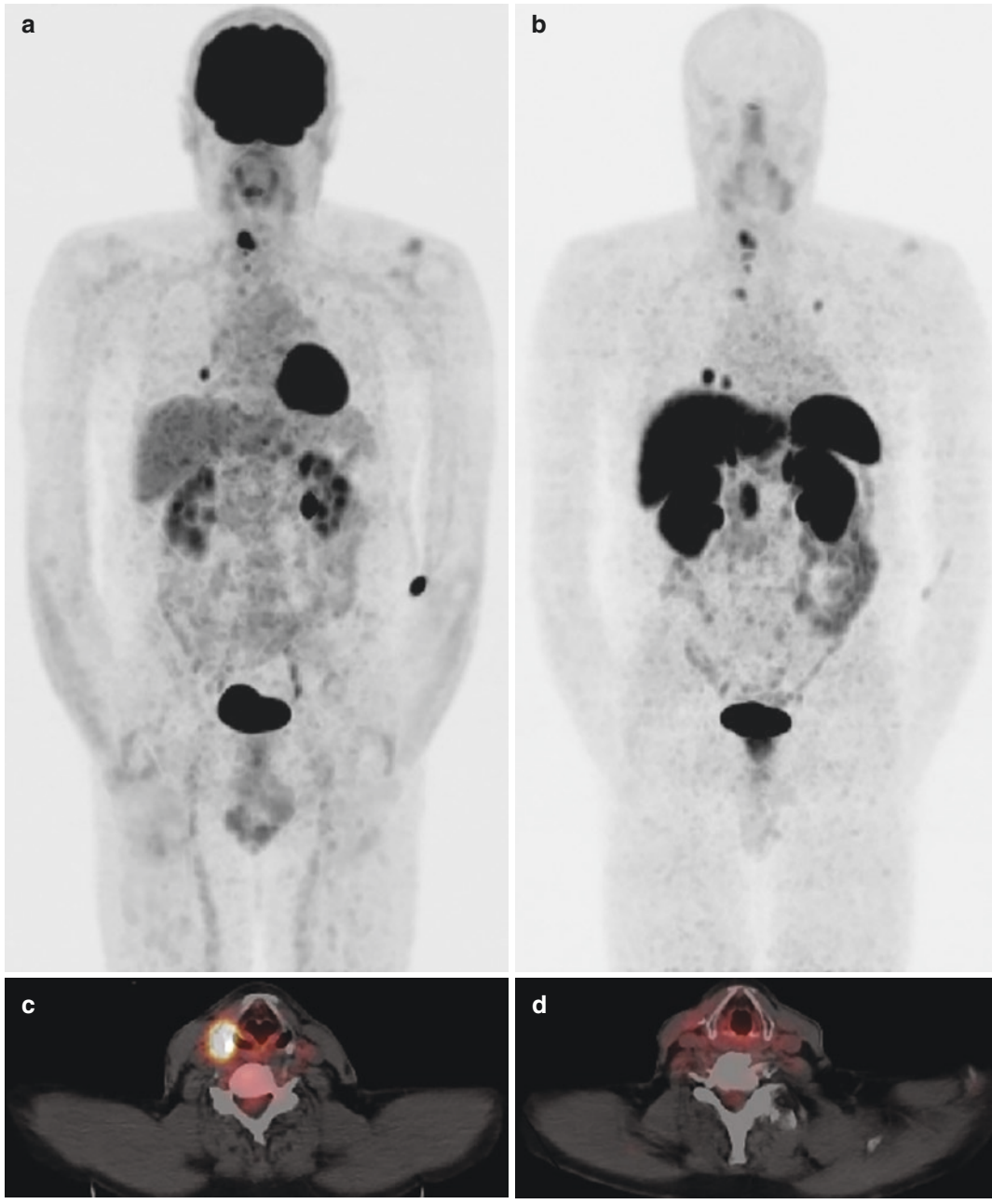

Fig. 11.2 60-year-old male patient after thyroidectomy, several subsequent operations, several radioiodine treatments (including one therapy after retinoic acid pretreatment) because of follicular Hürthle cell carcinoma (pT3m cN1) without significant radioiodine uptake. (**a**) FDG-PET/CT (MIP) showing local recurrence and lung metastases. (**b**) Ga-68-DOTATATE-PET/CT (MIP) showing somatostatin receptor positivity in tumor lesions. (**c**) FDG-PET/CT (transversal slice) before treatment with Lu-177-DOTATATE showing high glucose metabolism in local recurrence (including lymph nodes). (**d**) FDG-PET/CT (transversal slice) after treatment with Lu-177-DOTATATE showing therapeutic success (decreased glucose metabolism)

11.1 Conclusion

Thyroid scintigraphy has to face competition with several other diagnostic procedures, but it has still an undoubtable major role in the functional characterization of thyroid nodules. Although treatment of other diseases, particularly systemic malignant diseases, is more vigorously attracting the nuclear medicine scientific community, the use of radioisotopes in thyroid diseases offers important fields for new developments and optimization besides the classic and well-established techniques of thyroid theranostic, radioiodine, which is the historical origin of all theranostic principles, based on molecular mechanisms in the thyroid gland.

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