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The role of nuclear medicine in differentiated thyroid cancer

Susanne Kohlfürst

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Die Rolle der Nuklearmedizin beim differenzierten Schilddrüsenkarzinom

Zusammenfassung Bei Patienten mit Schilddrüsenkarzinom deckt die Nuklearmedizin wie bei kaum einer anderen Tumorentität das breite Spektrum von Diagnostik, Therapie und Nachsorge ab. Da die Klinik dieses Tumors oftmals unspezifisch ist und andererseits Schilddrüsenknoten durch Routineuntersuchungen häufig diagnostiziert werden, spielen neben der klinischen Untersuchung die Sonographie, Feinnadelbiopsie und Szintigraphie, die in nuklearmedizinischen Einrichtungen gemeinsam angeboten werden, zur Früherkennung eine wichtige Rolle. Auch wird nach erfolgter chirurgischer Thyreoidektomie bei histologisch verifiziertem differenziertem Schilddrüsenkarzinom in der Mehrzahl der Fälle eine aktinische Therapie mit Jod-131 an einer nuklearmedizinischen Therapiestation zur Restelimination oder gegebenenfalls zur Metastasentherapie angeschlossen. Die posttherapeutische und diagnostische ^{131}J Ganzkörperszintigraphie haben neben der Halssonographie und der Tumormarkerbestimmung im Follow Up von Schilddrüsenkarzinompatienten einen etablierten Stellenwert. Durch die Entwicklung der dualen Bildgebung wie SPECT/CT und PET/CT mit der Möglichkeit auch entdifferenzierte Schilddrüsenkarzinome funktionell (^{18}F-FDG, ^{68}Ga-Rezeptor PET) und morphologisch (CT) darzustellen hat sich das Spektrum der nuklearmedizinischen Diagnostik noch erweitert.

Schlüsselwörter: Schilddrüsenkarzinom-Diagnostik, Schilddrüsenkarzinom-Therapie, Schilddrüsenkarzinom-Nachsorge

S. Kohlfürst, MD (✉)
Department of Nuclear Medicine and Endocrinology, PET-CT Center Klagenfurt, Klinikum Klagenfurt am Wörthersee, Feschnigstraße 11, 9020 Klagenfurt, Austria
e-mail: susanne.kohlfuerst@kabeg.at

Summary In differentiated thyroid cancer (DTC) nuclear medicine is able to cover the spectrum from diagnosis and treatment to follow up keeping patient's management in one institution. Nowadays, DTC is often diagnosed per chance, presenting as small indolent nodule diagnosed on routinely performed ultrasound. Ultrasound and ultrasonography-guided fine-needle aspiration biopsy together with scintigraphy are probably the most adequate tools for diagnosis. After thyroidectomy, treatment with iodine-131 is routinely performed in a nuclear medicine therapy institution as a standard procedure in most of the cases with regard to histology. In case of iodine positive metastases, repeated therapies can be performed in order to reduce tumour burden. In the follow up of DTC thyroglobulin (tumour marker), ultrasound and diagnostic whole body scan are established procedures. With the development of SPECT/CT and PET/CT (^{18}F-FDG, ^{68}Ga-somatostatin receptor) combining functional and anatomic imaging the nuclear medicine spectrum has further increased.

Keywords: Diagnosis of differentiated thyroid cancer, Therapy of differentiated thyroid cancer, Follow up of differentiated thyroid cancer

Introduction

In thyroid cancer, nuclear medicine is able to cover the broad spectrum from diagnosis and treatment to follow up keeping patient's management in one institution. Thyroid cancer is a rare malignancy and incidence rates vary from 4 to 9 per 100,000 per year. In Austria, a former iodine-deficient and due to salt iodination now iodine-sufficient country, an increasing incidence rate of 8.5 per 100,000 per year is reported by "Statistik Austria" in 2009. Papillary thyroid cancer is the dominant histopathologic form and accounts for more than two thirds of differentiated thyroid cancer (DTC) [1–3], followed by follicular DTC and a mixed form that have different incidence and prognosis. These subtypes have a favourable prognosis

with high cure rates, especially when diagnosed at an early stage. Medullary thyroid cancer, a completely different form originating from the C-cells of the thyroid gland and the non iodine storing forms of Hurthle cell carcinoma and anaplastic carcinoma are less frequent and have a poorer prognosis.

This article will highlight the role of nuclear medicine in diagnosis as well as treatment and follow up of patients with differentiated thyroid cancer.

Nuclear medicine and diagnosis of differentiated thyroid cancer

Ultrasound and ultrasonography-guided fine-needle aspiration biopsy

According to the AACE/AME/ETA guidelines, published in 2010, *ultrasound* and ultrasonography-guided fine-needle aspiration biopsy (US-FNAB) are the most adequate tools to diagnose DTC. The clinical presentation of patients with thyroid cancer varies. Thyroid nodules are quite common and the objective is to exclude malignancy in the majority of cases. Most thyroid cancer nowadays are diagnosed at an early stage, presenting as small indolent nodules incidentally diagnosed on routinely performed ultrasound of the neck. Only in rare cases, the thyroid cancer is diagnosed as large cervical mass, often growing fast, sometimes involving the recurrent laryngeal nerve followed by hoarseness of voice and often associated with a poorly differentiated histopathologic pattern and poor prognosis. Many studies have been performed to evaluate sonographic features of benign and malignant thyroid nodules in order to define those patients that require US-FNAB. Most studies [4–10] showed that nodules that present as solid, hypoechogenic, irregular and taller-than-wide shape, with micro and macrocalcifications, blurred and ill-defined margins, with intranodular dominant flow are more likely to be malignant. Furthermore, growth beyond the thyroid capsule and the detection of suspicious lymph nodes are associated with malignancy. Benign nodules are described as hyper or isoechoic, solid or cystic. Recently, a few studies have been published evaluating elastography in the setting of differential diagnosis of benign and malignant thyroid nodules using hardness of tissue as an indicator for malignancy [11, 12]. All mentioned criteria, however, are not fully reliable and different studies show different results regarding sensitivity and specificity rates when combining the different ultrasonographic features. Besides high specificity of ultrasound malignancy criteria sensitivity is quite low. In addition, the previously reported ultrasonography findings of thyroid malignancies are in conformity with most of the papillary but not with follicular carcinomas. Therefore, cytologic criteria should be carefully applied and other diagnostic tools should be implemented in the diagnostic work-up of thyroid nodules.

US-FNAB is an excellent tool to assess thyroid nodules that are suspicious with regard to ultrasonographic features. In the hands of an experienced physician it is highly effective (representative results up to 95 %) [13], easy to perform and of low complication rate. Mikosch et al. [14] reported a sensitivity of 87.84 % per specificity of 78.50 % per negative predictive value of 98.13 % per positive predictive value of 33.51 % and accuracy of 79.53 % when cytology indicated suspicion of thyroid malignancy. Other studies [15, 5] showed similar results. Especially in papillary thyroid cancer, cytology is highly predictive. In follicular DTC, cytologic analysis remains controversial and often only histological work-up after surgery can establish a definitive diagnosis of follicular adenoma or carcinoma.

In order to improve diagnostic management of thyroid nodules, nuclear medicine imaging procedures using radionuclides with affinity to malignancy have been evaluated.

Diagnostic nuclear medicine imaging

Planar scintigraphy with Tc^{99m}-pertechnetate and iodine-123 is commonly used in clinical routine in order to discriminate hypofunctional nodules in the thyroid gland. Scintigraphy, however, is of limited value in small thyroid nodules. Although it has been proven by various studies that hypofunctionality of a thyroid nodule is associated with malignancy, only 3–5 % of nodules in iodine-sufficient areas (10 % in iodine-deficient areas) are malignant in definitive histology [16–18). In patients with multinodular goiter, scintigraphy may add information and guide the clinician which nodule should be further evaluated by US-FNAB (Figs. 1, 2).

Other nuclear medicine imaging procedures have been investigated in the diagnostic management of thyroid nodules, especially when cytology is inconclusive.

Several studies have been performed to assess malignancy by using ^{201}Tl chloride, Tc^{99m} sestamibi, Tc^{99m}

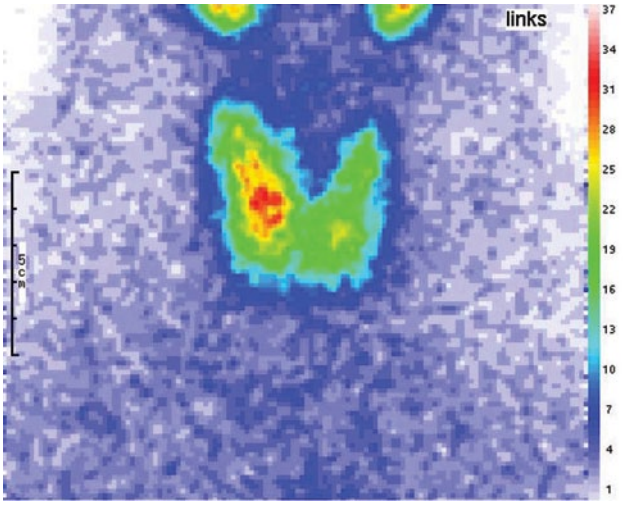

Fig. 1 Tc^{99m} pertechnetate scintigraphy in a 40-year-old female patient with a suspicious nodule (Fig. 2) in the left thyroid lobe showing a hypofunctioning area

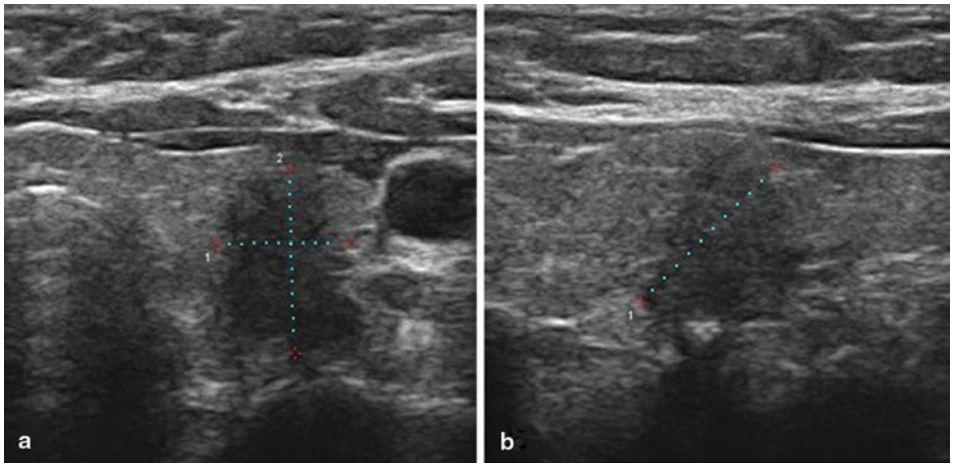

Fig. 2 Transverse and longitudinal ultrasonography show a suspicious hypoechoic, solid thyroid nodule with poorly defined margins and taller than wide shape presenting hypofunctional on scintigraphy (Fig. 1). Ultrasound-guided fine-needle aspiration biopsy indicated papillary thyroid cancer

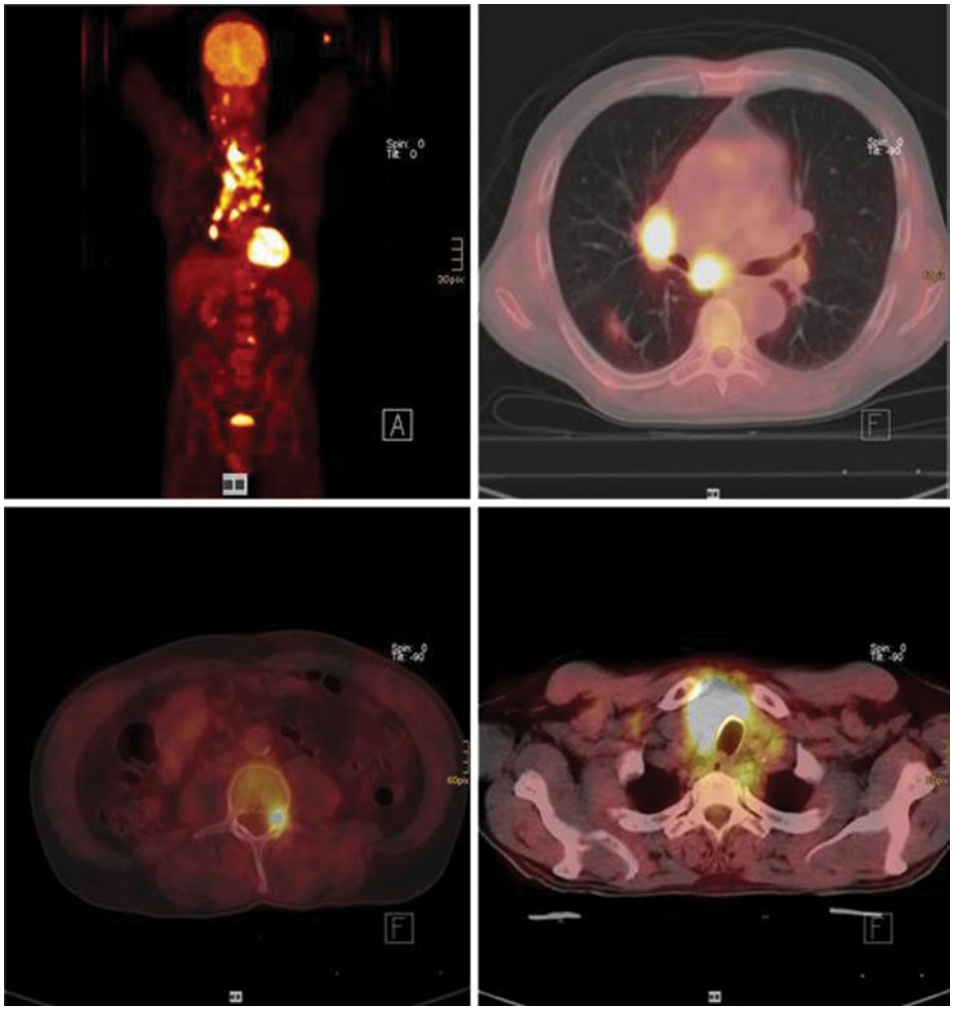

Fig. 3 ^{18}F-FDG PET-CT of a 53-year-old man with a fast growing thyroid mass, US-FNAB indicated dedifferentiated thyroid cancer. ^{18}F MIP and transaxial fused images show the extent of disease with additional multiple lymph node metastases, lung and bone metastases. The patient died 3 months after diagnosis despite systemic chemotherapy because of progressive tumour disease

tetrofosmin, but results showed low specificity [19, 20]. ^{18}F-FDG positron emission tomography (PET) is a well-established method in the follow up of DTC patients with elevated tumour marker (Thyroglobulin (Tg)) and negative ^{131}I scintigraphy. More recently the diagnostic role of ^{18}F-FDG PET-CT was studied, but these data also showed that a clear differentiation between benign and malignant nodules is not possible. Adding ^{18}F-FDG PET-CT findings especially to neck ultrasound provided no diagnostic benefit [21–23]. In anaplastic or poorly differentiated thyroid cancer, preoperative ^{18}F-FDG PET-CT may play a role in order to assess the full extent of disease to plan a patient-tailored regimen (Fig. 3).

Nuclear medicine and therapy of differentiated thyroid cancer

^{131}I therapy-remnant ablation

Differentiated thyroid cancer is known to have an excellent prognosis after initial treatment with surgery and ^{131}I systemic therapy. After successful treatment thyroglobulin (Tg, tumour marker) should not be detectable and diagnostic imaging with ^{131}I whole body scintigraphy (WBS) should be negative [24]. Thus, systemic radioiodine treatment is routinely performed as a standard procedure in DTC patients with the exception of unifocal papillary DTC ≤ 1 cm confined to the thyroid gland. TSH serum levels > 30 mU/l are required to optimise radioiodine intake into thyroid tissue. These levels are achieved either through endogenous TSH elevation with thyroid hormone withdrawal over 3–5 weeks or through exogenous TSH stimulation (recombinant TSH, Thyrogen® intramuscularly on two following days) [25, 26]. In anaplastic thyroid cancer, due to dedifferentiation and inability of iodine intake as well as in medullary thyroid cancer (originating from the parafollicular C-cells that do not store iodine), radioiodine treatment is not recommended [27–30]. The rationale for radioiodine-remnant ablation is to eliminate residual thyroid tissue in order to facilitate follow up and to destroy possible microscopic thyroid cancer cells after surgery. Furthermore, highly sensitive posttherapeutic whole body scans can be acquired in order to detect iodine positive metastases previously not diagnosed. In suitably equipped centres, the administered ^{131}I activities vary and range between 1,100 MBq and 3,700 MBq or even higher, e.g. in case of known distant metastases. Recently, studies with lower activities of ^{131}I under exogen TSH stimulation for initial treatment have been published. A prospective randomized study by Pilli et al. [31] showed that patients under exogenous TSH stimulation receiving an activity of 1,850 MBq (50 mCi) ^{131}I differed not significantly with regard to successful ablation compared with those receiving higher activities of 3,700 MBq (100 mCi). They even found no difference in the presence of cervical lymph node metastases. Further studies, however, and maybe longer follow up intervals are needed towards a possible direction to lower activities in initial treatment under recombinant TSH.

In recent time, the need of subsequent radioiodine ablation therapy in patients with minimally invasive follicular thyroid cancer (MIFTC) has been a matter of debate. With respect to an estimated low malignant potential and a very favourable prognosis, a less radical surgery approach is discussed. In case of MIFTC with capsular invasion only and maybe also in case of limited vascular invasion (≤3, examination of at least 10 tissue blocks of the entire tumour mandatory), based on the criteria of Rosai 2005, a hemithyroidectomy without systemic lymphadenectomy with a lower postsurgical complication rate is maybe sufficient without subsequent radioiodine treatment concluded Hermann et al. [32]. The difficulty, however, is that data from literature are not homogeneous because of inconsistent histopathological classification and amount of obtained tissue blocks in case of MIFTC. Thompson et al. [33] published a study in 2001 where the histopathologic records of 130 patients with diagnosed MIFTC were re-evaluated and complete clinical follow up was mandatory for study inclusion. According to their classification with regard to capsular and vascular invasion, 95 patients were confirmed to have MIFTC and the remaining 35 patients showing tumours with large vessel invasion or other features were classified as "not low grade." The authors could show that despite the extensive heterogenous treatment approaches in the two groups (lobectomy followed by complete thyroidectomy, lobectomy alone, subtotal thyroidectomy, subsequent or no subsequent radioiodine therapy), the prognosis was generally excellent. Taking all arguments into account, there is the need to perform prospective studies with clearly defined histopathologic criteria comparing patient outcome of hemithyroidectomy alone in case of MIFTC or total thyroidectomy with subsequent radioiodine ablation. However, there is also the need for a long follow up period, because it is known that in DTC, the recurrences or distant metastases may occur years after initial treatment.

Nuclear medicine treatment in metastatic differentiated thyroid cancer

The various national and international recommendations and guidelines from different medicine specialities with regard to metastatic thyroid cancer disease show quite similar treatment approaches. In case of local tumour recurrence, lymph node or distant metastases, the whole armamentarium of possible treatment options should be taken into account. If limited disease is diagnosed, surgery should be considered. In case of single or few small, not resectable or multiple iodine positive metastases, subsequent circles of iodine treatment with activities up to 7,400 MBq (200 mCi) should be performed as long as iodine avidity is present and disease regression is documented by decrease of iodine uptake on posttherapeutic WBS and decline in serum Tg levels. Also external radiation therapy, e.g. in symptomatic bone metastases for pain control and additional treatment options with bisphosphonates or Denosumab should be considered. Other parameters, however, considering patient age, health status, tumour burden, quality of life and disease symptoms should be also taken into account. Especially in presence of additionally FDG positive metastases, an individual patient approach is mandatory.

Posttherapeutic ^{131}I whole body scintigraphy and SPECT/CT

After first radioiodine-remnant ablation, whole body scintigraphy is performed 5–7 days after treatment. This nuclear medicine imaging procedure offers the opportu-

nity not only to judge effectiveness of treatment but also allows a whole body staging [34, 35]. The precise anatomical localization of pathological lesions and the diagnosis of physiological iodine uptake are sometimes difficult on conventional planar imaging. With the growing availability of integrated SPECT-CT, a precise anatomical localization of foci with increased iodine uptake is possible. SPECT-CT, a dual imaging modality combines functional information from the scintigraphic data (SPECT) and anatomic information (CT) in a single examination. In a prospective study [36], we evaluated the diagnostic impact and influence on patient management of posttherapeutic ^{131}I SPECT-CT findings when they were inconclusive on planar images. Regarding neck lesions, the SPECT-CT provided a diagnostic impact in 28.9 %, on a patient basis SPECT-CT changed N-status in 36.4 % and led to a treatment change in 24.2 %. Regarding lesions distant from the neck, SPECT-CT had a diagnostic impact in 12.7 %. Considering all patients together, SPECT-CT led to a treatment change in 24.4 %. Also other studies showed the superiority of SPECT-CT over planar scintigraphy in case of inconclusive lesions [37, 38] and confirmed its usefulness in daily clinical routine (Fig. 4).

Nuclear medicine and follow up of differentiated thyroid cancer

Thyroglobulin and ultrasound

Thyroglobulin and ultrasound are highly effective tools in the follow up of patients with DTC. Because it is not the main topic of the article, only a short overview is given.

Thyroglobulin (*Tg*) is the tumour marker of DTC after total thyroidectomy and radioiodine ablation. Thyroglobulin measured with sensitive and ultrasensitive immuno-radiometric assays offering also recovery rates of Tg and in the absence of antibodies should be undetectable in case of complete remission [39–42]. Elevated or rising Tg levels in the follow up most likely indicate DTC local recurrence, lymphnode or distant metastases. Besides ultrasonography of the neck imaging procedures with iodine or other tracers, favourable ^{18}F-FDG PET-CT are recommended in those cases. Thyroglobulin measurement, however, is most reliable under TSH elevation >30 mU/l (either through thyroid hormone withdrawal over 4–5 weeks or with the use of recombinant TSH). Under thyroid hormone medication, thyroglobulin has been found falsely negative in up to 20 %, thus a negative stimulated Tg is highly predictive for absence of disease [35, 42]. Only in rare cases, e.g. in dedifferentiated or anaplastic thyroid cancer, Tg may remain in lower ranges under huge tumour burden due to dedifferentiation of cells.

Ultrasound of the neck is a highly accurate imaging technique for the detection of thyroid local recurrence and lymph node metastases and is therefore mandatory at any visit in follow up [34]. Especially papillary thyroid cancer has a high propensity to spread to lymph nodes in the neck, less common in follicular thyroid cancer. A round shape, loss of the nodal hilum, peripheral hypervascularity, necrosis, cystic appearance, calcifications, sometimes also increased echogenecity are signs of thyroid lymphnode metastases [43, 44]. There are, however, rare false negative stimulated serum Tg levels in presence of especially small lymph node metastases [45, 46]. US-

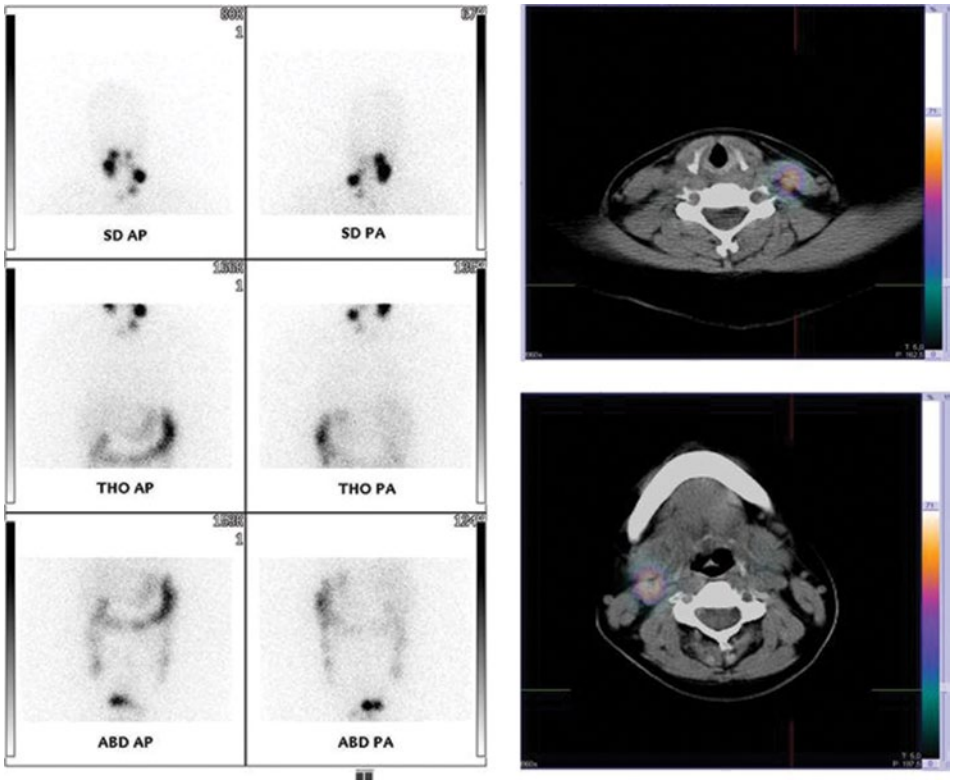

Fig. 4 Additional information and exact lesion localisation in case of multiple foci of iodine uptake in the neck. SPECT-CT demonstrates ^{131}I-positive lymphnode metastases. Because of the size and patient's age, surgery was performed with precise anatomical information provided to the surgeons preoperatively

FNAB is recommended in suspicious lymphnodes to improve accuracy of ultrasound [34].

Diagnostic ^{131}I whole body scintigraphy (WBS) and SPECT/CT

Iodine-131 WBS is still performed in many institutions as part of the posttherapeutic assessment to state a patient free of disease. In a European consensus paper by Pacini et al. [34], a successful ablation is defined as an undetectable serum Tg level following endogenous or exogenous TSH stimulation and a normal ultrasound of the neck. The authors argue that diagnostic WBS according to low sensitivity ranging from 45 to 75 % adds no additional information. Lubin et al. [47] showed that in 261 patients, there were no instances of diagnostic whole body scans and negative stimulated TSH. The role of routine diagnostic radioiodine whole body scintigraphy has been recently evaluated by de Meer et al. [48] in patients with high-risk differentiated thyroid cancer. The authors concluded in case of undetectable stimulated Tg levels diagnostic WBS added no additional information. On the other hand, it is well known that a negative diagnostic scan in case of elevated serum Tg does not necessarily indicate a negative posttherapeutic scan in presence of iodine positive metastases due to the higher activities administered [49, 50]. With the increasing availability of SPECT-CT devices, the value of diagnostic WBS has been re-evaluated by several studies. Barwick et al. [51] showed in a study that SPECT-CT significantly improved the diagnostic information over conventional ^{123}I WBS and SPECT alone. Spanu et al. [52] found in 108 patients who underwent diagnostic imaging for DTC, a clear superiority compared to planar imaging with regard to precise localisation and additional lesions diagnosed.

PET/CT in the follow up of differentiated thyroid cancer

The performance of *^{18}F-FDG PET-CT* in patients with suspected iodine negative metastases in case of elevated serum Tg and iodine negative posttherapeutic WBS is quite established. Due to dedifferentiation of tumour cells and because of high proliferation index, the tumour glucose metabolism is significantly increased, indicating a poorer prognosis of DTC. The superiority of PET-CT combining functional (PET) and morphological (CT) information in a single device has been evaluated in multiple studies [53]. Other tracers such as ^{201}Tl, Tc^{99m}-tetrofosmin and Tc^{99m}-sestamibi have been replaced in case of availability of PET or better PET-CT. As discussed earlier, ^{18}F-FDG PET-CT in a preoperative setting of suspicious nodules is still a matter of debate, in case of elevated Tg levels and negative posttherapeutic ^{131}I scans it is classified as I A indication. It is also known that in DTC patients, iodine positive and negative metastases may be present in one patient. In case of markedly elevated Tg levels and only minor pathology on iodine WBS, FDG positive metastases have to be suspected (Fig. 5).

Several studies evaluated sensitivity, specificity and accuracy of ^{18}F-FDG PET-CT with respect to serum thyroglobulin levels in patients with negative ^{131}I scans. Bannas et al. [54] investigated 30 patients with elevated serum Tg and negative I^{131} WBS for diagnostic accuracy of ^{18}F-FDG PET-CT for two subgroups below and above 10 ng/ml, respectively. They reported overall sensitivity,

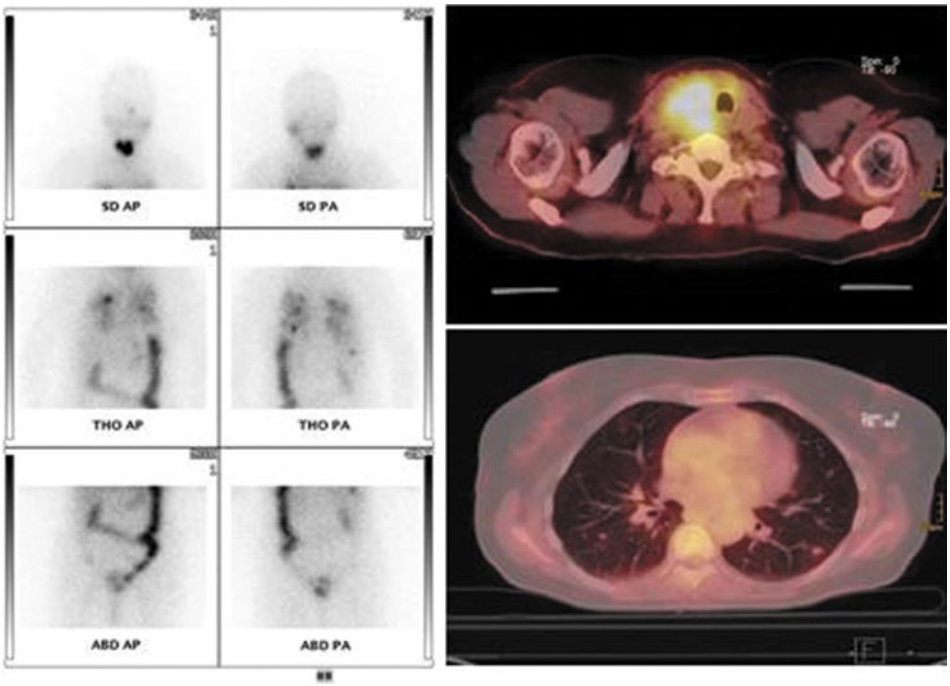

Fig. 5 ^{131}I posttherapeutic WBS 5 days after administration of 3,700 MBq ^{131}I showing a thyroid remnant in the neck and multiple iodine positive lung metastases. ^{18}F FDG PET-CT shows intense FDG uptake in the thyroid bed and faint uptake in lung metastases—indicating both iodine positive and negative lesions in one patient

specificity and accuracy of 68.0, 60.0 and 66.7 %, respectively. In the group with Tg levels above 10 ng/ml ($n=21$), the sensitivity, specificity and accuracy reached 70.0, 100.0 and 71.4 %, respectively. Shammas et al. [55] evaluated 61 patients in a similar setting using cut off serum Tg levels less than 5, 5–10 and more than 10 ng/ml. They found an overall sensitivity, specificity and accuracy of ^{18}F-FDG PET-CT of 68.4, 82.4 and 73.8 %, respectively. Regarding sensitivities of Tg less than 5.0, 5–10 and above 10 ng/ml they reported 60, 63 and 72 %, respectively, showing similar results for the >10 ng/ml group as Bannas et al. [54]. A study by Giovanella et al. [56], however, reported higher sensitivity, specificity and accuracy for serum Tg levels ≥4.6 ng/ml of 93, 84 and 90 %, respectively. Other studies reported an increased sensitivity of ^{18}F-FDG PET-CT when performed under TSH stimulation, especially in presence of low serum Tg levels [57, 58].

The positron emitter isotope ^{124}I with a long half life of 5 days is also used for diagnostic and dosimetry purposes in patients with thyroid cancer. The performance of ^{124}I PET-CT therefore allows not only a precise visualisation of iodine positive lesions from DTC—because of the higher sensitivity and spatial resolution of PET compared to gamma scintigraphy—it can also be used for patient specific radioiodine therapy dosimetry for a tailored patient treatment protocol [59, 60].

There are only few studies published using *^{68}Ga-somatostatin receptor (SRS) PET-CT* in dedifferentiated thyroid cancer. Middendorp et al. [61] reported about 17 patients who underwent both ^{18}F-FDG PET-CT and ^{68}Ga-DOTATOC PET-CT. They concluded that ^{18}F-FDG PET-CT was superior to ^{68}Ga-SRS PET-CT in the detection of iodine negative lesions. Gabriel et al. [62] showed results in patients with radioiodine negative metastases where ^{68}Ga-SRS PET/CT guided towards somatostatin receptor (SRS) mediated radionuclide therapy.

Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Gomez-Segovia I, Gallowitsch HJ, Kresnik E, et al. Descriptive epidemiology of thyroid carcinoma in Carinthia, Austria: 1984–2001. Histopathologic features and tumor classification of 734 cases under elevated general iodination of table salt since 1990: population based age stratified analysis on thyroid carcinoma incidence. Thyroid. 2004;14(4):277–86.
2. Lind P, Kumnig G, Heinisch M, et al. Iodine supplementation in Austria: methods and results. Thyroid. 2002;12:903–7.
3. Colonna M, Guizard AV, Schvartz C, et al. A time trend analysis of papillary and follicular cancers as a function of tumour size: a study of data from six cancer registries in France (1983–2000). Eur J Cancer. 2007;43(5):891–900.
4. Gharib H, Papini E, Paschke R, et al. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. Endocr Pract. 2010;16 Suppl 1:1–43.
5. Hambly NM, Gonen M, Gerst SR, et al. Implementation of evidence-based guidelines for thyroid nodule biopsy: a model for establishment of practice standards. AJR AM J Roentgenol. 2011;196(3):655–60.
6. Chan BK, Desser TS, Mc Dougall IR, et al. Common and uncommon sonographic features of papillary thyroid carcinoma. J Ultrasound Med. 2003;22:1083–90.
7. Mikosch P, Gallowitsch HJ, Kresnik E, et al. Präoperative Dignitätsabklärung von Schilddrüsenknoten im Strumaendemiegebiet: Möglichkeiten und Limitationen. Wien Med Wochenschr. 2000;150:278–287.
8. Wong KT, Ahuja AT. Ultrasound of thyroid cancer. Cancer Imaging. 2005;5:157–66.
9. De Nicola H, Szejnfeld J, Logullo AF, et al. Flow pattern and vascular resistive index as predictors of malignancy risk in thyroid follicular neoplasm. J Ultrasoun Med. 2005;24(7):897–904.
10. Bianek-Bodzak A, Zaleski K, Studniarek M, et al. Color Doppler sonography in malignancy of thyroid nodules. J Ultrasoun Med. 2003;22:758.
11. Rago T, Santini F, Scutari M. Elastography: new developments in ultrasound for predecting malignancy in thyroid nodules. J Clin Endocrinol Metab. 2007;92:2917–22.
12. Rago T, Scutari M, Scartini F, et al. Real-time elastosonography: useful tool for refining the presurgical diagnosis in thyroid nodules with indeterminate or non diagnostic cytology. J Clin Endocrinol Metab. 2010;95(12):5274–80.
13. Rorive S, D'Hene N, Fossion C, et al. Ultrasound-guided fine-needle aspiration of thyroid nodules: stratification of malignancy risk using follicular proliferation grading, clinical and ultrasonographic features. Eur J Endocrinol. 2010;162:1107–15.
14. Mikosch P, Gallowitsch HJ, Kresnik E, et al. Value of ultrasound-guided fine-needle aspiration biopsy of thyroid nodules in an endemic goitre area. Eur J Nuc Med. 2000;27(1):62–9.
15. Carmeci C, Jeffrey RB, Mc Dougall IR, et al. Ultrasound-guided fine-needle aspiration biopsy of thyroid masses. Thyroid. 1998,8(4):283–289.
16. Kresnik E, Gallowitsch HJ, Mikosch P, et al. Scintigraphic and ultrasonographic appearance in different tumor stages of thyroid carcinoma. Acta Med Austraca. 2000;27(1):32–5.
17. Kusic Z, Becker DV, Saenger EL, et al. Comparison of technetium-99m and iodine-123 imaging of thyroid nodules: correlation with pathologic findings. J Nucl Med. 1990;31(4):393–9.
18. Beierwalters WH. Comparison of technetium-99m and iodine-123 nodules: correlation with pathologic findings. J Nucl Med. 1990;31(4):400–2.
19. Kresnik E, Gallowitsch HJ, Mikosch P, et al. Evaluation of thyroid nodules with Tc-99m tetrofosmin dual phase scintigraphy. Eur J Nucl Med. 1997;24:716–21.
20. Lind P. Multi-tracer imaging of thyroid: is there a role in the preoperative assessment of nodular goiter? Eur J Nucl Med. 1999;26:795–7.
21. Kim BS, Kim SJ, Kim IJ, et al. Factors associated with positive F-18 Fluorodeoxyglucose positron emission tomography before thyroidectomy in patients with papillary thyroid carcinoma. Thyroid. 2012 Mar 5 Epub ahead of print.

22. Deandreis D, Al Ghuzlan A, Auperin A, et al. Is (18)F-fluorodeoxyglucose-PET/CT useful for the presurgical characterization of thyroid nodules with indeterminate fine needle aspiration cytology? Thyroid. 2012;22(2):165–72.
23. Joensuu H, Ahonen A, Klemi PJ. 18F-fluorodeoxyglucose imaging in the preoperative diagnosis of thyroid malignancy. Eur J Nucl Med. 1988;13:502–506.
24. Verburg FA, Stockel MP, Düren C, et al. No survival difference after successful I131 ablation between patients with initially low risk and high risk differentiated thyroid cancer. Nucl Med Mol Imaging. 2010;37(2):276-83.
25. Pacini F, Ladenson PW, Schlumberger M, et al. Radioiodine ablation of thyroid remnants after preparation with recombinant human thyrotropin in differentiated thyroid carcinoma: results of an international randomized, controlled study. J Clin Endocrinol Metab. 2006;91:926–32.
26. Luster M, Sherman SI, Skarulis MC, et al. Comparison of radioiodine biokinetics following the administration of recombinant human thyroid stimulating hormone and after thyroid hormone withdrawal in thyroid carcinoma. Eur J Nucl Med Mol Imaging. 2003;30:1371–7.
27. Coopers DS, Doberty GM, Haugen BR, et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2006;16:109–42.
28. Luster M, Clarke SE, Dietlein M; et al. Guidelines on radioiodine treatment of differentiated thyroid cancer. Eur J Nucl Med Mol Imaging. 2008;35(10):1941–59.
29. Pacini F, Castagna MG, Brilli L, et al. Differentiated thyroid cancer: ESMO Clinical recommendations for diagnosis, treatment and follow up. Ann Oncol 2010;21 Suppl 5:214–9.
30. Hackshaw A, Hasmer C, Mallick U, et al. 131 I activity for remnant ablation in patients with differentiated thyroid cancer: A systematic review. J Clin Endocrinol Metab. 2007;92:28–38.
31. Pilli T, Brianzoni E, Capocetti F, et al. A comparison of 1850 (50 mCi) and 3700 MBq (100 mCi) 131-iodine administration doses for recombinant thyrotropin-stimulated postoperative thyroid remnant ablation in differentiated thyroid cancer. JCEM. 2007;92(9):3542.
32. Hermann M, Tonninger K, Kober F. Minimal invasive follicular thyroid carcinoma. Not always total thyroidectomy. Chirurg. 2010;81:627–635.
33. Thompson LD, Wieneke JA, Paal E, et al. A clinopathologic study of minimally invasive follicular carcinoma of the thyroid gland with a review of the English literature. Cancer. 2001;91(3):505-24.
34. Pacini F, Schlumberger M, Dralle H, et al. European thyroid cancer taskforce. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol. 2006;154:787–803.
35. Fatourechi V, Hay ID, Mullan BP, et al. Are posttherapy radioiodine scans informative and do they influence subsequent therapy of patients with differentiated thyroid cancer? Thyroid. 2000;10:573–7.
36. Kohlfuerst S, Igerc I, Lobnig M, et al. Posttherapeutic 131I SPECT-CT offers high diagnostic accuracy when the findings on conventional planar imaging are inconclusive and allows a tailored patient treatment regimen. Eur J Nucl Med Mol Imaging. 2009;36:886–893.
37. Schmidt D, Szikszai A, Linke R, et al. Impact of 131I SPECT/spiral CT on nodal staging of differentiated thyroid carcinoma at the first radioablation. J Nucl Med. 2009;50:18–23.
38. Grewal RK, Tuttle RM, Fox J, et al. The effect of posttherapy 131 SPECT/CT on risk classification and management of patients with differentiated thyroid cancer. J Nucl Med. 2010;51(9):1361–7.
39. Van Herle AJ, Uller RP. Elevated thyroglobulin: a marker of metastases in differentiated thyroid carcinoma. J Clin Invest. 1975;56:272–6.
40. Cherk MH, Francis P, Topliss DJ, et al. Incidence and implications of negative serum thyroglobulin but positive I-131 whole body scans in patients with well differentiated thyroid cancer prepared with rhTSH or thyroid hormone withdrawal. Clin Endocrinol (Oxf) 2012;76(5):734–40.
41. Lind P, Kohlfürst S. Respective roles of thyroglobulin, radioiodine imaging, and positron emission tomography in the assessment of thyroid cancer. Semin Nucl Med. 2006;36(3):194–205.
42. Pacini F. Follow up of differentiated thyroid cancer. Eur J Nucl Med. 2002;29 Suppl 2:492–496.
43. Haber RS. Role of ultrasonography in the diagnosis and management of thyroid cancer. Endocr Pract. 2000;6:396–400.
44. Rosario PW, de Faria S, Bicalho L, et al. Ultrasonographic differentiation between metastatic and benign lymph nodes in patients with papillary thyroid carcinoma. J Ultrasound Med. 2005;24(10):1385–9.
45. Pacini F, Molinaro E, Castagna MG, et al. Recombinant human thyrotropin-stimulated serum thyroglobulin combined with neck ultrasonography has the highest sensitivity in monitoring differentiated thyroid carcinoma. J Clin Endocrinol Metab. 2003;88:3668–3673.
46. Torlontano M, Attard M, Crocetti U, et al. Follow-up of low risk patients with papillary thyroid cancer: role of neck ultrasonography in detecting lymph node metastases. J Clin Endocrinol Metab. 2004;89:3402–3407.
47. Lubin E, Mechlis-Frish S, Zatz S et al. Serum thyroglobulin and iodine-131 whole body scan in the diagnosis and assessment of treatment for metastatic differentiated thyroid carcinoma. J Nucl Med. 1994;35(2):257–262.
48. De Meer SG, Vriens MR, Zelissen PM, et al. The role of routine-diagnostic radioiodine whole-body scintigraphy in patients with high-risk differentiated thyroid cancer.J Nucl Med. 2011;52(1):56–9.
49. Pineda JD, Lee T, Ain K, et al. Iodine-131 therapy for thyroid cancer patients with elevated thyroglobulin and negative diagnostic scan. J Clin Endocrinol Metab. 1995;80(5):1488–92.
50. Lind P. Should high hTg levels in the absence of iodine uptake be treated. Eur J Nucl Med. 2003;30:157–160.
51. Barwick T, Murray I, Megadmi H et al. Single photon emission computed tomography (SPECT)/computed tomography using Iodine-123 in patients with differentiated thyroid cancer: additional value over whole body planar imaging and SPECT. Eur J Endocrinol. 2010;162(6):1131–9.
52. Spanu A, Solinas ME, Chessa F, et al. 131 I SPECT/CT in the follow up of differentiated thyroid carcinoma: incremental value versus planar imaging. J Nucl Med. 2009;50(2):184–90.
53. Zoller M, Kohlfuerst S, Igerc I, et al. Combined PET/CT in the follow-up of differentiated thyroid carcinoma: what is the impact of each modality? Eur J Nucl Med Mol Imaging. 2007;34(4):487–95.
54. Bannas P, Derlin T, Groth M, et al. Can (18)F-FDG-PET/CT be generally recommended in patients with differentiated thyroid carcinoma and elevated thyroglobulin levels but negative I-131 whole body scan? Ann Nucl Med. 2012;26(1):77–5.
55. Shammas A, Degirmenci B, Mountz JM, et al. 18F-FDG PET/CT in patients with suspected recurrent or metastatic well-differentiated thyroid cancer. J Nucl Med. 2007;48(2):221–6.

56. Giovanella L, Ceriani L, De Palma D, et al. Relationship between serum thyroglobulin and (18) FDG PET/CT in (131) I-negative differentiated thyroid carcinomas. Head Neck 2012;34(5):626–31.
57. Leboulleux S, Schroeder PR, Busaidy NL. Assessment of the incremental value of recombinant TSH stimulation before FDG PET/CT imaging to localize residual differentiated thyroid cancer. J Clin Endocrinol Metab. 2009;94:1310–1316.
58. Petrich T, Börner AR, Otho D. Influence of rhTSH on ((18) F) fluorodeoxyglucose uptake by differentiated thyroid carcinoma. Eur J Nucl Med Mol Imaging. 2002;29(5):641–7.
59. Jentzen W, Freudenberg L, Bockisch A, et al. Quantitative imaging of (124)I with PET/CT in pretherapy lesion dosimetry. Effects impairing image quantification and their corrections. Q J Nucl Med Mol Imaging. 2011;55(1):21–43.
60. Freudenberg LS, Jentzen W, Stahl A, et al. Clinical applications of 124I-PET/CT in patients with differentiated thyroid cancer. Eur J Nucl Med Mol Imaging. 2011;38 Suppl 1:S48–56.
61. Middendorp M, Selkinski I, Happel C, et al. Comparison of positron emission tomography with 18F FDG and 68 Ga DOTATOC in recurrent differentiated thyroid cancer. Preliminary data. Q J Nucl med Mol Imaging. 2010;54(1):76–83.
62. Gabriel M, Andergassen U, Putzer D, et al. Individualized peptide-related-radionuclide-therapy concept using different radiolabelled somatostatin analogs in advanced cancer patients. Q J Nucl Med Mol Imaging. 2010;54(1):92–9.