Chapter 6

FDG PET in Thyroid Cancer

Irina Wimmer and Robert Pichler

Additional information is available at the end of the chapter

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Abstract

Thyroid malignancies are relatively rare cancer types but have a substantially high incidence in the group of all endocrine malignancies. Most thyroid cancer patients have differentiated thyroid cancer and prognosis is generally favourable. Tumour growth tends to be slow and radioiodine therapy is successful in differentiated cell tumour type with the ability to accumulate iodine. So, where can ^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET) imaging be applied? The role of FDG PET in differentiated thyroid cancer starts with the development of metastatic diseases, which are not responsive to radioiodine therapy anymore. FDG accumulates in tumour lesions that are missed by iodine scintigraphy. FDG PET is more sensitive in patients with an aggressive histological subtype, including Hürthle cell. Thyroid cancer is definitely not the role model indication for FDG PET imaging, but for the management of differentiated thyroid cancer with metastases and more aggressive types of malignancies of the thyroid, FDG PET proves to be clinically useful. Incidental detection of malignancy in FDG-avid thyroid nodules has to be taken into consideration when FDG PET examinations have been conducted for reasons unrelated to the thyroid.

Keywords: thyroid cancer, FDG PET, incidentaloma, iodine, DOPA PET

1. Introduction

1.1. Thyroid cancer

Thyroid malignancies are relatively rare cancer types but have a substantially high incidence in the group of all endocrine malignancies [1]. Most thyroid cancer patients have differentiated thyroid cancer (i.e. the papillary and the follicular type), and prognosis is generally favourable [1]. Tumour growth tends to be slow and radioiodine therapy is successful in differentiated

cell tumour type with the ability to accumulate iodine. Therefore, where can ^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET) imaging be applied?

2. FDG PET in thyroid cancer

In the last two decades, PET and PET/CT have proven to show a substantial diagnostic role in most human cancer entities. The development was related to FDG, a glucose derivate labelled with F18, showing avidity in cancer types with high tumour-related metabolism and upregulation of the glucose transporter system [2]. Imaging with positron emitting isotopes has the advantage of higher spatial resolution compared to gamma cameras. That enables quantification and hybrid imaging with CT, which provides precise morphological data. However, what appears to be useful for patients with melanoma or high-grade lymphoma must not be useful in the case of thyroid cancer. Here, nuclear medicine provides the possibility of specific gamma camera imaging with iodine 131 (^{131}I) or 123 (^{123}I) and recently also by PET with iodine 124 (^{124}I).

2.1. FDG PET in differentiated thyroid cancer

There exists a consensus that FDG PET has no objective in the primary evaluation of differentiated thyroid cancer—routine preoperative FDG PET scanning is not recommended by the American Thyroid Association (ATA) Management Guidelines [3]. A primary cancer lesion of the thyroid can easily be missed by FDG PET [1, 4]. In general, the suspicion of thyroid malignancy leads to thyroidectomy and by this to histologically based diagnosis, including eventually some form of cervical lymph node surgery. If there is some indication, the next step is to perform radioiodine ablation, which results additionally in providing post-therapeutic iodine scan images. For the follow-up examinations, thyroglobulin (Tg) is considered a strong marker of persistent or recurrent disease [5]. The role of FDG PET starts with the development of metastatic diseases, which are not responsive to radioiodine therapy any more. FDG accumulates in tumour lesions that are missed by iodine scintigraphy [1, 4]. A German group of Tübingen explained these findings as early as 1995 [6]. Highly differentiated thyroid cancer (DTC) cells still express the sodium-iodide symporter (NIS), which enables iodine uptake in the thyroid. This ability gets lost when cells become less differentiated. On the contrary, FDG is internalised to the cell by a transporter protein (glut-1), which is overexpressed in malignant cell types. Inverse alterations of either iodine or FDG uptake in metastases are called the flip-flop phenomenon. Feine et al. presented a group of 34 patients showing FDG and/or ^{131}I uptake, 30 of whom exhibited the flip-flop phenomenon. Five per cent of the metastases had both FDG and ^{131}I uptake [4]. Since then, there has been knowledge of the coexistence of functionally more differentiated tumour cells with retained iodine trapping mechanism and low glucose metabolism, and more undifferentiated carcinoma cells that have lost their iodine trapping mechanism and have a high glucose uptake [7].

A meta-analysis by Dong et al. in 2009 covered 571 patients who had recurrent or metastatic DTC and a radioiodine-negative whole-body scan (WBS) [8]. FDG-PET was proven to be especially effective in detecting metastases in patients with elevated Tg levels and normal

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radioiodine WBS. A pooled patient-based sensitivity and specificity of about 84% each was found for FDG PET.

Optimal initial therapy is mandatory for favourable patient outcome, but can only be performed if all non-avid tumour lesions are known before treatment planning. Rosenbaum-Krumme et al. found that the TNM stage was changed due to the FDG PET results in 21% of the patients. The authors concluded that FDG PET in high-risk patients with DTC nowadays has been established as an initial-staging modality [7] (**Figure 1**).

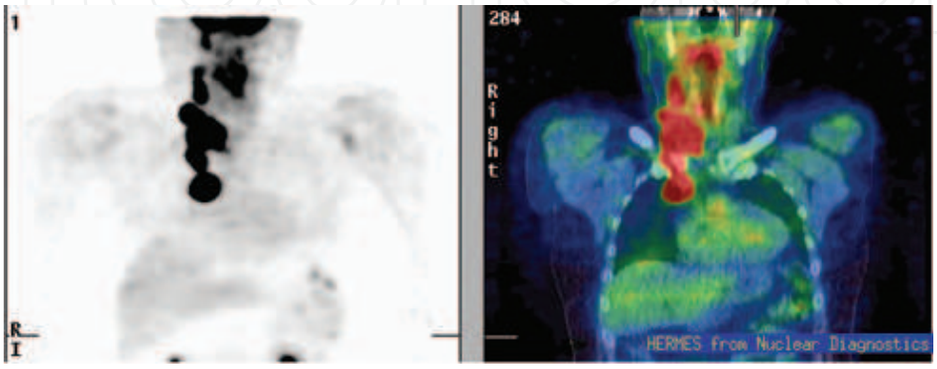

Figure 1. A 47-year-old man presented with sensomotoric deficit of the left arm at the Neurological Clinic in Linz (Austria). Further diagnosis revealed a thyroid malignoma infiltrating the cervical vertebral column and adjacent soft tissue (as can be seen FDG-avid on FDG PET/CT images). The next step was a combined operation of the malignant goiter and the tumour masses infiltrating to the bone. As histology still presented papillary differentiation (Ki-67 was 4%), the patient was sent to radioiodine therapy further on.

FDG PET has a high negative-predictive value (NPV) about 90% in DTC patients regarding recurrence-free follow-up after 3 years. FDG PET should be performed in all high-risk DTC patients—after the first radioiodine therapy—to improve patient management and risk stratification [9]. A prognostic relevance of FDG imaging is therefore presumed. Also, the volume of FDG-positive malignant tissue is of relevance, Wang et al. showed that volumes of ≤125 ml were associated with a 3-year survival of 96% compared to 18% of patients with higher volumes [10].

Elevated Tg levels are an indicator for FDG-positive lesions [11], but it has been demonstrated that high Tg levels are not related to FDG positivity alone, but also to iodine positivity [7]. It was recognised that about 10–15% of patients have elevated serum Tg levels despite negative iodine WBS [12]. In respect to the clinical value of Tg measurement, it has to be considered that Tg autoantibodies interfere with the measurement and may mask the presence of recurrent or metastatic disease [13]. In this condition, patient surveillance is complicated and some of the restrictions might be overcome with routinely practised FDG PET in this patient group, additionally to neck ultrasound and other diagnostic modalities provided by nuclear medicine.

In total, ATA guidelines strongly recommend considering FDG PET scanning in high-risk DTC patients with elevated serum Tg (generally >10 ng/ml) when negative radioiodine imaging is expressed [3]. As the availability of PET/CT scanners and cyclotrons has become satisfactory at least in central Europe, we advocate combined imaging with iodine and FDG whenever

thyroid hormone withdrawal or stimulation with recombinant human thyroid stimulating hormone (TSH) has been conducted. Although there have been conflicting reports regarding the additional advantage for FDG PET imaging, a possible modest benefit due to TSH stimulation can be assumed [11]. Such a procedure has been successfully introduced in our institutions located in Austria.

2.2. FDG PET in subtypes of DTC and anaplastic thyroid cancer

Aggressive histologic subtypes of thyroid cancer carry a worse prognosis [14]. The clinical usefulness for FDG-PET may be more robust for Hürthle cell thyroid cancer (3–4% of DTC) as opposed to papillary and follicular DTC [15]. Generally, FDG PET is more sensitive in patients with an aggressive histological subtype, including Hürthle cell, but also poorly differentiated

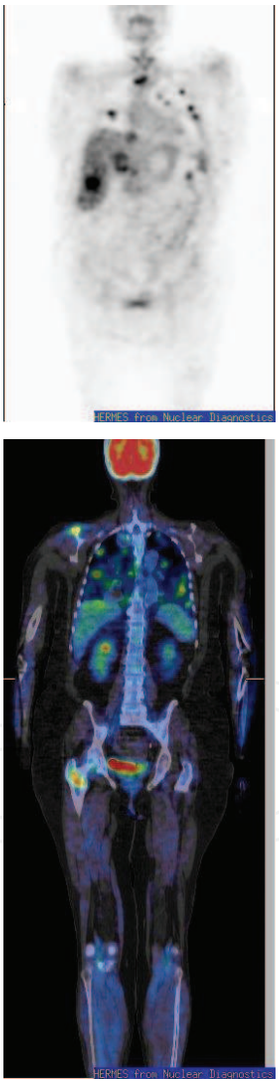

Figure 2. This 72-year-old woman originally presented with multiple lung metastases incidentally detected at the Hospital of Wels (Austria). The primary tumour was localised in the thyroid gland and histology revealed poorly differentiated thyroid carcinoma (Ki67 25%, TTF-1 and Tg positive). For post-operative restaging, FDG PET was arranged and presented multiple metastases of lung, liver and bone.

carcinoma, tall cell [3] and insular cell variants. Accurate localisation of disease is essential in Hürthle cell thyroid cancer because surgery and external beam radiation therapy may be beneficial. Hürthle cell thyroid cancer tends to be FDG-avid and all patients should undergo FDG PET in the post-operative setting onwards [15].

Poorly differentiated thyroid carcinoma represents a distinct stage in the progression from well-differentiated to anaplastic carcinoma [14]. When primary dedifferentiation with high Ki67 values can be observed and especially in the case of anaplastic thyroid cancer (which represents about 1.5% of all thyroid malignancies), the usefulness of iodine scanning tends to be low. This emphasises the importance of FDG PET in this setting (**Figure 2**). Approximately 20–50% of patients with early tumour dissemination are positive for distant metastases [16]. Unfortunately, the relevance for monitoring the disease is limited because of the bad prognosis of anaplastic thyroid cancer. Anaplastic carcinoma usually shows intense FDG uptake, and in selected cases FDG PET may be helpful in directing or evaluating treatment [14]. Here, nuclear medicine can provide somatostatin receptor imaging as well (to evaluate therapeutic options as radiopeptide therapy [17]), but monitoring the disease would still be the task of FDG PET.

It is worth noting that the role for FDG PET in staging and restaging of primary lymphoma of the thyroid gland is evidentially present [18].

2.3. FDG PET in medullary thyroid cancer

Medullary thyroid cancer (MTC) is a rare form of thyroid cancer (about 4–5%), descending from calcitonin-producing C-cells not related to iodine-capture processes and thyroid hormone production. Ultrasound, serum calcitonin screening, genetics of multiple endocrine neoplasia (MEN) syndromes, cytology and histology with immunohistochemistry for calcitonin, and various diagnostic tools of radiology play an important role for diagnosis and disease monitoring.

In regard to nuclear medicine, the impact of FDG and DOPA PET as well as somatostatin receptor imaging—and the order in which those methods should be applied—is still a matter of debate.

A PET study may be requested in patients with high serum calcitonin and/or carcinoembryonic antigen (CEA) levels after surgery. FDG PET is not a meaningful test in patients with low to moderate calcitonin levels and can occasionally be negative even at very high calcitonin levels of >1000 pg/ml [14]. Archier et al. recently reported experiences with a relatively large group of 86 MTC patients. DOPA PET/CT was positive in 65 patients (sensitivity of 76%), and distant metastatic disease was observed in 29 patients [19]. Beheshti et al. compared FDG and DOPA PET in the same patients with MTC and showed superiority of DOPA to detect metastases. However, lymph node metastases, which were only seen on FDG PET, were also described [20]. We suggest to use DOPA PET on the first run and to save FDG PET imaging for inconclusive or DOPA PET-negative cases. An illustrative case can be seen in **Figure 3**.

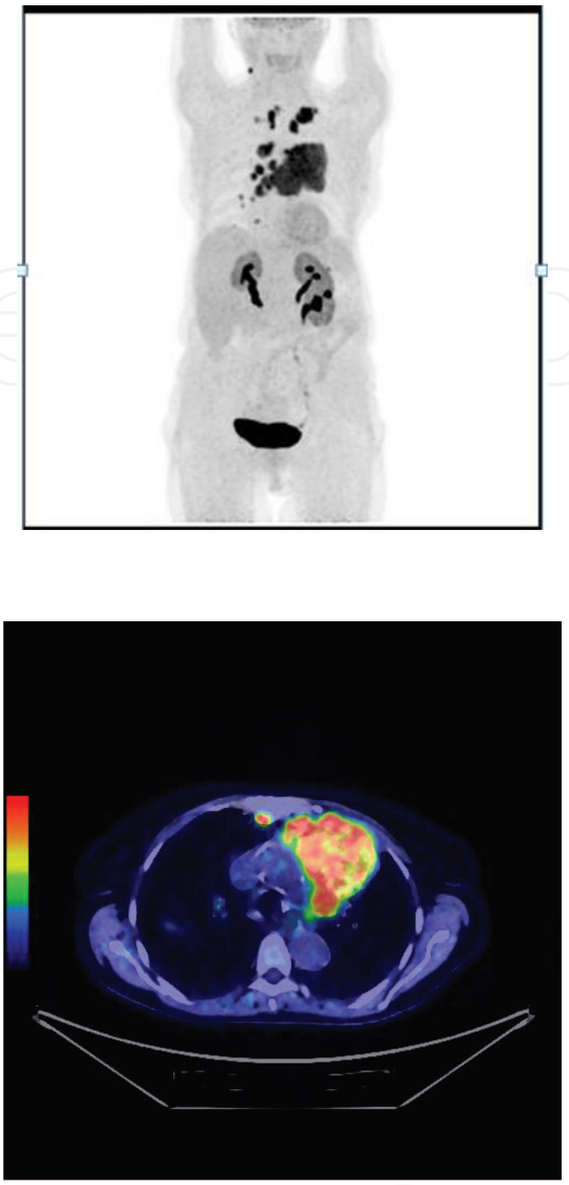

Figure 3. Medullary thyroid carcinoma was identified in 2008 at a metastatic stage yet. In 2015, the 74-year-old patient was sent to the University Hospital St. Pölten (Austria) for restaging by L-3,4-Dihydroxyphenylalanin (is an amino acid) (DOPA) PET (serum calcitonin of >3000 ng/dl). She also presented with diarrhoea as an associated endocrine symptom. The DOPA PET images revealed inoperability with cervical tumour masses and extensive thoracic lymph node metastases. The endocrine clinic ameliorated by the use of somatostatin analogues.

3. FDG PET in thyroid incidentalomas

Meanwhile, there are abundant data consisting of patients who underwent FDG PET/CT for (mostly oncological) reasons unrelated to pathologies. Then, the finding of a focal FDG uptake in a thyroid nodule generally merits further examination, and thyroid surgery with histological verification is necessary in many cases. The intensity of FDG uptake measured by SUV

(standard uptake value) cannot discriminate with certainty benign and malignant thyroid nodules. The risk to find a malignant entity can be estimated at 25–50%. Of course, these data depend upon the characteristics of the patient group as age and iodine supply of the home country are contributing factors. Diffuse-elevated FDG uptake in the thyroid can be found when Hashimoto´s thyroiditis is present. Focal uptake is limited to nodules of the thyroid. A prevalence of 1.5–3% for FDG-avid incidentaloma can be expected [21–23].

4. Conclusion

Thyroid cancer is definitely not the role model indication for FDG PET imaging, but for the management of differentiated thyroid cancer with metastases and more aggressive types of malignancies of the thyroid, FDG PET proves to be clinically useful. Incidental detection of malignancy in FDG-avid thyroid nodules has to be taken into consideration when FDG PET examinations have been conducted for reasons unrelated to the thyroid.

Author details

Irina Wimmer[1] and Robert Pichler[2,3,4*]

*Address all correspondence to: Robert.Pichler@gespag.at

1 Department of Internal Medicine and Institute of Nuclear Medicine, Karl Landsteiner Medical University, University Hospital St. Pölten, St. Pölten, Austria

2 Institute of Nuclear Medicine, Kepler University Hospital, Neuromed Campus, Linz, Austria

3 Institute of Nuclear Medicine, LKH Steyr, Steyr, Austria

4 Department of Radiology, Institute of Nuclear Medicine, Medical University Graz, Graz, Austria

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