IMAGING IN ENDOCRINOLOGY

2-[¹⁸F]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography in differentiated thyroid carcinoma: clinical indications and controversies in diagnosis and follow-up

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Abstract

In recent years, 2-[¹⁸F]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) has emerged as an important tool for the postoperative management of patients with differentiated thyroid cancer (DTC) and it is widely used in selected clinical situations. The most valuable role that FDG-PET/CT plays in clinical practice is that it can be used to obtain prognostic information in patients with increasing thyroglobulin (Tg) levels and negative ¹³¹I whole-body scan post-thyroidectomy and radioiodine (RAI) ablation. FDG-PET/CT may also have a potential role in the initial staging and follow-up of high-risk patients with aggressive histological subtypes, in the identification of patients who are at the highest risk of disease-specific mortality, in the management of patients with RAI-refractory disease, in clinical trials of novel targeted therapies in patients with advanced metastatic disease, and in the evaluation of thyroid nodules with indeterminate fine-needle aspiration for cytology. However, several controversies remain to be resolved, namely: the cutoff value of Tg in the selection of DTC patients for FDG-PET/CT, whether FDG-PET/CT scanning should be performed under thyrotropin stimulation or suppression, and the clinical significance of thyroid FDG-PET/CT incidentalomas. The aim of the present article is to provide an overview of the data about the molecular basis for, clinical indications of, and controversies related to the use of FDG-PET/CT in patients with DTC.

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Introduction

The role of 2-[¹⁸F]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) in oncology is rapidly expanding in clinical

practice worldwide, and it is gaining acceptance as a valuable clinical tool for the detection, staging, and management of several malignant tumors. The strength

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of FDG-PET/CT lies in its ability to evaluate specific metabolic pathways, which is greatly enhanced by its ability to combine metabolic images provided by PET with anatomic images obtained by CT in order to achieve greater specificity and accuracy than either PET or CT alone (1).

Despite the availability of numerous new tracers, FDG remains the most widely used PET radiopharmaceutical in clinical oncology. The application of FDG in both basic science and clinical practice has fundamentally changed our understanding of cancer, and there is a relevant body of evidence-based information to support its role in the management of a wide variety of malignancies, namely, lymphoma, melanoma, and metastatic gastro-intestinal, lung, head, and neck cancer (2).

Since the first report of FDG-PET in patients with differentiated thyroid cancer (DTC) in 1987 (3), FDG-PET alone (i.e., without concurrent CT scanning) and FDG-PET/CT have emerged as important tools for the management of patients affected by DTC with suspected or documented radioiodine (RAI)-negative recurrences (4). Although FDG-PET/CT is most valuable in patients with increasing Tg levels, a negative ^{131}I whole-body scan (WBS) post-thyroidectomy, and RAI ablation, new uses of FDG-PET/CT for DTC patients have recently been recognized (5).

In the present article, we provide an overview of the data available about the molecular basis for, clinical indications of, and controversies related to the use of FDG-PET/CT in the management of patients with DTC and of patients with thyroid PET, referring to selected recent references for PET tracers other than FDG (6,7,8).

Molecular basis

PET/CT was the first 'molecular imaging' technique to be validated in the basic sciences as well as in a clinical setting, and FDG is the PET tracer that is most widely used to image malignant tumors (9). An accelerated rate of glucose metabolism mediated by the overexpression of key regulatory glycolytic enzymes and transporters is one of the phenotypic and functional changes that have been observed in malignant transformed cells, and it was first recognized more than 80 years ago (10).

In thyroid tumors, however, an increased uptake of FDG is restricted to more aggressive and high-grade tumors, and no significant tracer uptake occurs in well-differentiated tumors (11). In 1996, Feine *et al.* (12) reported an inverse relationship between RAI and FDG uptake in thyroid carcinoma (the so-called 'flip-flop phenomenon'), which was thought to be the result of a loss in RAI concentration capacity during dedifferentiation combined with an increased demand of tumor cells for glucose.

Although FDG tumor uptake and accumulation is likely to be determined by a combination of several factors (e.g., cellular density, macroscopic and microscopic blood supply, fraction of hypoxic tissue, and different enzyme systems), blood flow, the up-regulation of transmembrane glucose transporter proteins (GLUTs), high glycolytic rate, and relative hypoxia are considered to be the most important mechanisms (1, 13) (Fig. 1).

After reaching its target, FDG enters cells through the same pathways of facilitated diffusion as glucose (i.e., via GLUTs) and is subsequently phosphorylated by hexokinase (HK) to FDG-6-phosphate. Because FDG-6-phosphate

Figure 1

Molecular basis of glucose uptake in normal thyroid cells and in thyroid tumor cells. Modified from Bongiovanni M, Paone G, Ceriani L & Pusztaszeri M. Cellular and molecular basis for thyroid cancer imaging in nuclear medicine. *Clinical and Translational Imaging* 2013 1 149–161.

is not a suitable substrate for glucose-6-phosphate isomerase, and because the enzyme level of glucose-6-phosphatase is generally low in tumors, FDG-6-phosphate is not further metabolized significantly, and because it is negatively charged, it remains trapped within cells (14). Because of its hydrophilic character, glucose requires GLUTs in order to cross the cell membrane, and the overexpression of GLUT1 on the cell membrane of thyroid neoplasms is closely related to tumors that have more aggressive biological behavior (15). Thyrotropin (TSH) influences virtually all aspects of thyroid cell metabolism, including the stimulation of glucose transport and glycolytic activity in thyrocytes (Figs 1 and 2) through the translocation of GLUT1 from an intracellular pool to the plasma membrane as well as the neosynthesis of GLUT1 by the activation of its gene expression (15, 16, 17).

Tumor cells are highly glycolytic because they express enhanced levels of glycolytic enzymes, especially highly active HK bound to tumor mitochondria. However, the target enzyme (HK) is not specific for cancer, and the clinical utility of FDG-PET resides in the enhanced functional activity of HK that is displayed in malignancy rather than in a high degree of selectivity in terms of the molecular target (13).

Several authors have evaluated whether biomarkers of primary DTC can help guide the decision of whether or not to perform FDG-PET/CT in cases of suspected DTC

recurrence (18, 19). Hooft *et al.* (18) found that HK1 negativity of primary tumor specimens as measured by immunohistological analysis indicated a low likelihood of PET positivity, which suggests that testing HK1 expression in primary tumor could identify candidates for FDG-PET/CT. These results were not confirmed by Lansoy-Kuhn *et al.* (19), who evaluated the immunochemical profile of the primary tumor using nine antibodies and concluded that 'at present, immunochemistry does not appear to be a definitive tool for predicting the results of FDG-PET/CT in cases of recurrence.' Because glucose metabolism traced by FDG is not tumor-specific, FDG uptake is not unique to cancer cells and can also occur in such benign cells as macrophages and granulocytes, which are present in the foci of infection and inflammation (2).

Clinical indications

Although FDG-PET/CT is used in the pre-surgical management of DTC, its routine preoperative use is usually considered inappropriate (20). On the contrary, FDG-PET/CT is widely used in the postoperative follow-up of DTC, mainly after RAI ablation in patients with elevated serum thyroglobulin (Tg) levels but negative WBS (5). Recently, FDG-PET/CT has been applied in such clinical situations as the initial staging and follow-up of high-risk patients with poorly DTC, the identification of patients at the highest risk for disease-specific mortality, and the evaluation of response to local and systemic therapy of metastatic or locally advanced RAI-negative disease (5). In general, the indications for FDG-PET/CT scanning depend on the clinical setting and the thyroid cancer histology (5). Table 1 shows the indications for FDG-PET/CT divided into strong defined indications and weaker or not completely defined indications (21, 22).

Defined indications

In patients with elevated Tg levels but negative neck ultrasound and radioiodine WBS

Most patients with DTC are cured after total thyroidectomy and RAI ablation. However, after initial treatment, <20% of patients have Tg elevation but negative WBS, and these cases represent a major diagnostic challenge (23). In this context, Padovani *et al.* (24) reported that 25% of patients who had submitted to total thyroidectomy and RAI ablation required 18 months or longer to reach the lowest Tg serum levels. Consequently, in many cases, the Tg level decreases spontaneously over months to years

Figure 2

Molecular basis of the accumulation of ^{18}F -FDG, radioiodine, and $^{99\text{m}}\text{TcO}_4^-$ in normal thyroid cells. Modified from Bongiovanni M, Paone G, Ceriani L & Pusztaszeri M. Cellular and molecular basis for thyroid cancer imaging in nuclear medicine. *Clinical and Translational Imaging* 2013 1 149–161.

Table 1 Defined and not completely defined indications for FDG-PET/CT in patients with thyroid carcinoma (modified from Hall NC & Kloos RT. PET imaging in differentiated thyroid cancer: where does it fit and how do we use it? *Arquivos Brasileiros de Endocrinologia e Metabologia* 2007 51 793–805).

Defined indications

In patients with elevated thyroglobulin levels but negative cervical ultrasound study and radioiodine whole-body scan
As a tool of prognostic significance

Not completely defined indications

In patients with radioiodine refractory disease
To evaluate the response to molecular-targeted therapies
In the initial staging and follow-up of patients with aggressive histological subtypes
In thyroid nodules with indeterminate fine-needle aspiration cytology
(^{18}F FDG) For radio-guided surgery

after the initial treatment without additional therapy, which underlines the importance of re-stratification and dynamic risk assessment (25). On the contrary, a rising unstimulated or stimulated serum Tg over time will typically identify patients that have a residual disease that is likely to become clinically apparent. In these patients, neck ultrasound (US) is highly sensitive in the detection of cervical metastases, and it can also guide fine-needle aspiration for cytology (FNAC) and identify Tg in needle washout fluid (5).

Cases of detectable Tg levels and negative neck US are common in daily practice. These patients are usually evaluated by means of magnetic resonance imaging (MRI), CT, and WBS with diagnostic activity of RAI (DxWBS, 74–185 MBq, 2–5 mCi). However, the role of DxWBS has been questioned because this technique is rarely able to localize disease (5). If no disease sites are identified by chest CT or DxWBS, FDG-PET/CT or empiric RAI therapy followed by WBS (TxWBS) should be performed to identify recurrent or metastatic disease (26, 27, 28) (Fig. 3).

A meta-analysis of the diagnostic accuracy of FDG-PET and FDG-PET/CT in DTC patients who presented with elevated serum Tg post-thyroidectomy and negative DxWBS or TxWBS reported that these methods had a good diagnostic accuracy, with pooled sensitivity and specificity values of 88.5 and 84.7% respectively (27). The pooled values of sensitivity increased when only FDG-PET/CT studies were considered in the analysis (93.5%); consequently, PET/CT had a higher diagnostic accuracy than that of PET alone (27).

The sensitivity of FDG-PET/CT may be significantly affected by the detection system (i.e., PET or PET/CT), by the selection of patients (i.e., the Tg cutoff value, clinical

characteristics, histological subtype, etc.), and by TSH stimulation (see the subsequent section on controversies and areas of uncertainty). False-negative scans can also result from the negligible accumulation of FDG, especially near regions of physiological FDG uptake (e.g., palatine tonsils, soft palate, lingual tonsils, and tongue) and from small tumors that are below the spatial resolution of PET. Finally, well-differentiated thyroid tumors often exhibit inherently low rates of glycolysis and result in a low FDG uptake (1, 3, 4).

Inflammatory lymph nodes, suture granulomas, and increased nonspecific muscle uptake of FDG can cause false-positive results and a consequent lower specificity. Therefore, cytologic or histologic confirmation may be required before one can be certain that an FDG-positive lesion represents metastatic disease (3, 4). Although earlier literature suggested that FDG-PET/CT and TxWBS provide complementary information for detecting metastases in the work-up of DTC patients with increased serum Tg levels (12, 21), recent studies have seemed to indicate the superiority of FDG-PET/CT and have suggested that empirical RAI therapy be used only in patients with negative or not significant FDG uptake (26, 27).

Leboulleux *et al.* (28) evaluated the sensitivity of TxWBS vs FDG-PET/CT in 23 DTC patients with elevated serum Tg levels. The sensitivities for the detection of individual lesions and for the diagnosis of metastatic organs were 88 and 97% for FDG-PET/CT and 16 and 22% for TxWBS respectively. FDG-PET/CT was abnormal in 22 patients, five of whom also had an abnormal TxWBS. Only one patient had an abnormal TxWBS and a normal FDG-PET/CT. The authors concluded that in patients with suspected recurrence based on the Tg level after a first

Figure 3

(A) Negative radioiodine anterior whole-body scan in a 37-year-old male patient with elevated serum Tg levels, (23 ng/ml). (B,C) FDG-PET/CT scan showing a focus of increased tracer uptake in the left lung that corresponds to a lung metastasis.

normal TxWBS, FDG-PET/CT, rather than a second TxWBS, should be used to localize the disease.

Iwano *et al.* (29) evaluated the diagnostic accuracy of FDG-PET/CT scans performed concurrently with initial TxWBS in 54 patients who underwent RAI ablation. FDG-PET/CT was positive in 25 sites of 18 patients (33%), and only five of the 16 lymph nodes (31%) that were PET-positive were also positive on TxWBS. The success rate of Tg-negative after ablation was significantly lower for patients with PET-positive scans than it was for those with PET-negative scans.

Kim *et al.* (30) reported that empiric RAI therapy and TxWBS were neither diagnostically nor therapeutically useful in 39 patients with elevated stimulated Tg, negative DxWBS, and negative FDG-PET after initial treatment. Should these preliminary data be confirmed, the increased use of FDG-PET/CT scanning 'is expected to reduce the number of blinded administrations of high activities of ^{131}I for diagnostic rather than therapeutic (*sensu strictu*) purposes' (31).

In addition to diagnostic data, positive PET/CT findings in patients with elevated Tg levels but negative WBS may also change patient management in 20–40% of cases (31). These management changes could include the initiation or avoidance of surgical procedures, further work-up with imaging studies or biopsies, the initiation and guidance of external beam radiotherapy, and conversion from treatment with a curative intent to palliative management in the setting of advanced disease (5).

Khiewvan *et al.* (32) reviewed 55 studies published between 1978 and 2010 to evaluate the cost-effectiveness of FDG-PET/CT in detecting tumor recurrence or metastasis in well-DTC patients with elevated Tg levels but negative WBS. The strategy of using FDG-PET/CT for the detection of recurrence or metastases and for possible curative surgery in operable cases and high-dose ^{131}I therapy in inoperable cases resulted in the highest life years gained (27.08), with a cost of US \$2926.24 and an acceptable incremental cost-effectiveness ratio, namely, US \$224.98 per life year gained, as compared to seven other strategies analyzed by the decision tree model (32).

Clinical evidence is emerging to suggest that the performance of FDG-PET/CT in detecting Tg-positive and RAI-negative DTC metastases is better after TSH stimulation (by either hormone withdrawal or rhTSH administration), but no clear cutoff Tg value can be established to identify candidates for FDG-PET/CT testing. Both of these issues are discussed in the subsequent controversies and areas of uncertainty section.

As a tool of prognostic significance

Most patients with metastatic DTC have high FDG uptake, which suggests more dedifferentiated, aggressive, and metabolically active tumor cells and thereby indicates poorer prognosis and reduced survival. Conversely, a negative FDG-PET/CT predicts a more favorable prognosis in patients that have a positive RAI scan (33) (Fig. 4).

The volume of FDG-avid lesions, maximum standardized uptake value (SUVmax), and number and location of metastases can correlate with outcome and survival in univariate and multivariate analyses (34, 35). Similarly, Wang *et al.* (36) found that the total volume of FDG-avid disease correlated with prognosis and was the strongest single factor for predicting survival in 125 patients with elevated Tg and negative WBS who were monitored for up to 41 months. Multivariate analyses showed that a high volume (>125 ml) of FDG-avid disease provided stronger prognostic information than did age, sex, initial histological type or grade, RAI uptake, or modified American Joint Committee on Cancer (AJCC) stage. In addition, SUVmax was significantly correlated with a high volume of FDG-avid disease, which suggests that tumors with the highest metabolic activity might be those that have the most rapid growth potential.

Figure 4

Radioiodine anterior whole-body scan (A) and FDG-PET scan (B) in a 48-year-old female patient submitted to total thyroidectomy and radioiodine therapy for lymph node and lung metastases. Note the intense radioiodine uptake, which corresponds to lung and lymph node metastases, and the absence of FDG uptake.

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These results were retrospectively confirmed in 400 thyroid cancer patients with high-risk features by comparing FDG-PET positivity with overall survival. In a univariate analysis, age, initial stage, histology, Tg level, ^{131}I uptake, and PET findings all correlated with survival. However, only age and PET results continued to be strong survival predictors in multivariate analyses. Initial AJCC stage was not a significant survival predictor in multivariate analyses. There were significant inverse relationships between survival and both the glycolytic rate of the most active lesion and the number of FDG-avid lesions.

Deandreis *et al.* (35) demonstrated that FDG uptake is highly prognostic for survival and that FDG-avid cancers should be considered highly aggressive. They reported that FDG uptake was the only significant prognostic factor for survival ($P=0.02$) and that SUVmax and number of FDG avid lesions were also related to prognosis ($P=0.03$ and $P=0.009$ respectively) in 80 patients with metastatic thyroid cancer. These data highlight the clinical importance of FDG-PET/CT in the management of patients with metastatic thyroid cancer.

Vural *et al.* (37) evaluated the prognostic significance of negative FDG-PET/CT scans in DTC patients with negative WBS and elevated stimulated Tg levels that could be suppressed by hormone therapy. No recurrence was detected in PET-negative patients with undetectable/suppressible Tg levels on levothyroxine therapy. These patients had a more favorable prognosis in terms of mortality and risk of recurrence, and that prognosis seemed to be unrelated to Tg levels in 'off-therapy.' The authors hypothesized that these patients were affected by metastatic cancer that was suppressible by keeping TSH levels very low, although the source of the serum Tg might also have been related to nonfunctioning or very poorly functioning thyroglossal tract tissue that was not visualized by WBS but was able to synthesize Tg, as was suggested by Marcus in a letter to the editor (38).

Not yet completely defined indications

In patients with radioiodine refractory disease

After initial treatment, thyroid cancer recurrences occur in 10–15% of cases, mostly in patients with extensive disease and in those with an aggressive histologic type. In 75% of cases, recurrent disease is located in the neck only, but distant metastases are observed in the remaining patients (39).

Only two-thirds of metastatic patients show substantial RAI uptake; complete remission is achieved in more

than two-thirds of patients with recurrent lymph node disease and in only one-third of patients with distant metastases. The remaining subjects are not responsive to RAI therapy and are defined as patients with 'RAI-refractory disease,' for which an expert panel recently proposed a working definition and treatment algorithm (40). According to that panel, most patients with RAI-refractory DTC fall into one of four categories: i) patients with metastatic disease that does not take up RAI at the time of initial treatment; ii) patients whose tumors lose the ability to take up RAI after previous evidence of uptake; iii) patients with RAI uptake retained in some lesions but not in others; or iv) patients with metastatic disease that progresses despite substantial uptake of RAI (40).

In these RAI-refractory patients, in addition to neck US, CT scan of the neck, chest, and abdomen, and MRI of the brain, spine, and pelvis, FDG-PET/CT should be used both to complete the staging and to assess the disease progression rate (5, 41). FDG-PET/CT can help identify clinically relevant sites of disease, including those that are large enough to be serially assessed in order to determine the progression and the response to therapy as well as those that might require additional localized intervention, such as surgery, external radiation therapy, radio-frequency ablation, cryotherapy, cement injection, or embolization. These treatment modalities could permit a physician to postpone the onset of a systemic treatment.

To evaluate the response to molecular-targeted therapies

The survival of patients with metastatic RAI-refractory DTC is variable, with indolent disease in some patients and rapid disease progression in others. Patients with extensive metastatic involvement, RAI-refractory disease, and positive FDG-PET/CT scans are more likely to have progressive disease and to have a median survival of <5 years (34).

The recent explosion of data regarding the molecular and cellular pathogenesis of cancer in these patients has led to the development of a range of novel therapies that are now undergoing clinical evaluation, including inhibitors of oncogenic signaling pathways, modulators of growth or apoptosis, angiogenesis inhibitors, immunomodulators, and gene therapy (5).

In recent years, several multi-targeted tyrosine kinase inhibitors (TKIs) that have the ability to inhibit both Ret and VEGFR have been used in clinical trials with the aim of inhibiting the MAPK pathway and angiogenesis (42). The use of TKIs should be limited to a highly selected group of

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metastatic patients, because their toxicities are numerous, frequently serious, and occasionally fatal (42). In this context, FDG-PET/CT can provide a basis for more uniform patient selection than traditional selection criteria, such as evidence of disease progression by changes in tumor size (i.e. RECIST criteria), can (41). In addition, by detecting metabolic changes within the tumor, FDG-PET/CT may enable early assessment of the effect of treatment. However, FDG-PET/CT should be applied using specific standard protocols, and the European Association of Nuclear Medicine (EANM) has recently provided recommendations for the standardization of the acquisition and interpretation of FDG-PET/CT images (43).

Carr *et al.* (44) conducted a single-institution phase II trial to assess the efficacy of the continuous administration of sunitinib (37.5 mg daily) in patients with metastatic RAI-refractory DTC. They considered at least one FDG-PET/CT-avid lesion with uptake clearly above the blood-pool background to be the objective criterion for trial entry, and they assessed the response via FDG-PET/CT after 7 days of treatment as an early indicator of response. The rate of disease control was high (78% of patients had some degree of tumor reduction) and had a significant association with average SUV percent change and RECIST response. Patients with a partial/complete response and stable disease had a significant decline in average SUV as compared to patients who were affected by progressive disease. The early repeat FDG-PET/CT proved to be an early indicator of response that could serve to identify patients unlikely to respond to sunitinib and thus could spare them the expense and toxicity of treatment.

Marotta *et al.* (45) reported their experience of the off-label use of the TKI sorafenib in the treatment of 17 cases of advanced RAI-refractory DTC. To assess the early metabolic response, 11 patients underwent FDG-PET/CT assessment at baseline within 7 days of the first dose of the study drug and then again 15 days after treatment onset. Baseline average SUVmax was significantly higher in patients with disease progression but was not correlated with progression-free survival. This means that FDG-PET/CT assessment at baseline could predict radiological response but not clinical outcome.

Kloos *et al.* (46) conducted a phase II clinical trial of sorafenib, which targets RAF and VEGF kinases in papillary thyroid cancer, and the secondary end point of the study was to evaluate the functional response as measured by FDG-PET/CT in 14 patients. No clear correlation was noted between FDG-PET/CT response (percent changes in SUVmax and metabolic volume as compared with pre-therapy values) and RECIST response. There was no

consistent pattern of change in SUVmax and metabolic volume among several index lesions in a given patient.

Larger randomized studies are needed to verify whether FDG-PET/CT evaluation in multicenter clinical trials can help identify patients who are more likely to achieve a morphological response or who are unlikely to respond to new molecular-targeted therapies.

In the initial staging and follow-up of high-risk patients with aggressive histological subtypes

Patients with DTC and advanced tumor stage or distant metastases at initial diagnosis and those with aggressive histological subtypes are considered to be at high risk. In these patients, lesions frequently do not show RAI uptake and consequently do not benefit from RAI therapy.

In addition to the first TxWBS, Rosenbaum-Krumme *et al.* (47) performed FDG-PET/CT at initial diagnosis after thyroidectomy in 90 DTC patients with advanced tumor stage to assess the extent of the disease and the possible role of FDG-PET/CT in changing clinical management. About one-third of patients (29%) had FDG-positive tumor lesions, one-third (36%) had RAI-positive lesions, and 8% had matching RAI-positive and FDG-positive lesions. FDG-PET/CT improved initial staging in 9% of patients and changed patient management in 21% of cases, mainly those with T3bN1 staging and those with distant metastases.

Aggressive histologic subtypes of thyroid carcinoma, namely Hürthle cell carcinoma (HCTC), poorly differentiated thyroid carcinoma, and anaplastic thyroid carcinoma (ATC), are uncommon; these tumors usually do not concentrate significant amounts of RAI and have a worse prognosis than that of well-differentiated thyroid carcinomas. The few studies that have evaluated the role of FDG-PET or FDG-PET/CT in these histologic subtypes of thyroid carcinoma have shown that these techniques can provide information at the initial diagnosis about the extent of the disease and prognostic information (48).

HCTC account for ~3.6% of all thyroid cancers. This tumor type has a higher incidence of metastases than other DTCs do as well as a worse prognosis, and recurrences have a low iodine uptake (49) (Fig. 5). Little is known about the use of FDG-PET/CT in the diagnostic assessment of HCTC. The largest study to date was the one conducted by Pryma *et al.* (50). They enrolled 44 patients with HTC who underwent FDG-PET at the initial post-operative staging, and they found that this technique had a diagnostic sensitivity and specificity of 95.8 and 95%

Figure 5

(A) FDG-PET/CT scan in a 45-year-old male patient with history of total thyroidectomy for Hürthle cell thyroid carcinoma demonstrating high metabolic activity in two latero-cervical lymph nodes. The patient presented with serum-stimulated Tg levels of 47.5 ng/ml and a negative radioiodine whole body

scan. (B) Histological examination of the cervical nodes from the neck dissection showed the presence of a metastatic focus of Hürthle cells with a trabecular arrangement. Upper:lower magnification; bottom:higher magnification.

respectively, which thereby provided more information than conventional imaging would have provided. In addition, the intensity of FDG uptake in metastatic lesions provided important prognostic information; in fact, SUVmax values of >10 correlated strongly with an increased risk of mortality (50). Lowe *et al.* (51) reported an FDG-PET sensitivity of 92% in 14 patients with HCTC; PET findings were positive in all but one patient with known disease, and in seven patients PET scans alone diagnosed disease that was not identified by other techniques. Plotkin *et al.* (52) evaluated 17 HCTC patients with FDG-PET and demonstrated a sensitivity of 92%, a specificity of 80%, a positive predictive value (PPV) of 92%, a negative predictive value (NPV) of 80%, and an accuracy of 89%.

ATC represents $<5\%$ of all thyroid carcinomas and is one of the most aggressive cancers, with a median survival of 3 months in the absence of effective treatment (53). Death is more often related to distant metastases than to local disease progression. Poisson *et al.* (54) observed that FDG-PET/CT was the reference imaging modality for ATC at initial staging because it was more effective than CT was in detecting cervical and mediastinal lymph nodes. FDG-PET/CT was more sensitive than bone scintigraphy; the volume of FDG uptake (>300 ml) and the intensity of

FDG uptake ($\text{SUV}_{\text{max}} \geq 18$) were significant prognostic factors for survival; FDG-PET/CT was also more efficient in the early assessment of tumor volume and in the response to treatment than CT was. Bogsrud *et al.* (55) investigated the role of FDG-PET/CT in the management of 16 patients with ATC by comparing PET data with other diagnostic tools and with clinical follow-up. In all of the patients, PET records were true positive for primary tumors, and in 50% of patients, PET data influenced the clinical management. These authors concluded that FDG-PET/CT could improve disease staging and thereby potentially change the clinical management of patients with ATC.

In thyroid nodules with indeterminate fine-needle aspiration cytology

Thyroid nodules with indeterminate or suspicious FNAC account for 15–30% of specimens, and in these patients diagnostic hemithyroidectomy is indicated to exclude malignancy, which is pathologically confirmed in only 20–30% of cases (56, 57).

In addition to genetic (*BRAF*, *RAS*, *RET/PTC*) and protein markers (galectin-3), the efficiency of FDG-PET/CT in predicting the malignant potential of indeterminate thyroid nodules has been extensively evaluated.

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Unfortunately, the studies conducted thus far have yielded variable and sometimes conflicting results. This is reflected in the American Thyroid Association (ATA) guidelines, which, in fact, recommend neither for nor against the use of FDG-PET (5). de Geus-Oei *et al.* (58) evaluated the diagnostic efficacy of FDG-PET imaging in 44 patients (six with DTC and 38 with benign lesions) who had inconclusive FNAC results before surgery. All six patients with DTC had a positive FDG-PET finding, with a NPV of 100%. FDG accumulated in 13 of the 38 patients with benign lesions. According to these authors, FDG-PET reduces the number of futile hemithyroidectomies by 66%. Similarly, Sebastianes *et al.* (59) and Traugott *et al.* (60) reported that FDG-PET/CT had an NPV of 100 and 93% respectively. However, less satisfactory NPVs have also been reported (61, 62, 63), which thus limits the value of FDG-PET/CT in excluding malignancy in thyroid nodules with indeterminate FNAC.

In a recent meta-analysis by Wang *et al.* (64), which updates a smaller study by Vriens *et al.* (65), seven studies with a total of 267 patients were reviewed. The pooled sensitivity and specificity of FDG-PET or FDG-PET/CT for the detection of cancer was 89.0% (95% CI 79.0, 95.0%) and 55.0% (95% CI 48.0, 62.0%) respectively. A large number of false-positive results were recorded. Other studies found that SUV values tended to be higher in Hürthle adenomas than in carcinomas (58, 63, 66). The best cutoff value of SUVmax for differentiating malignant from benign lesions was 2.05 and had a sensitivity as high as 89.8% but a low specificity (42.0%). In five of the eight false-negative cases, the lesion was ≥ 2 cm, which suggests that factors other than size could cause false-negative results. According to the meta-analysis by Wang *et al.* (64), PET correctly diagnosed 63.7% (170/267) of patients with indeterminate FNAC results. Although there were some false-positive cases, more than half of the patients (108/197) were spared unnecessary surgery after PET. Similar cumulative results were recently reported in a review by Pak *et al.* (67). When an FDG-PET scan with a nodule uptake that was higher than the normal thyroid background was considered positive, the cumulative sensitivity, specificity, PPV and NPV of FDG-PET in detecting malignancy were 84, 52, 43, and 88% respectively. Although the high NPV can help exclude malignancy in nodules that show no FDG uptake and can therefore help rule out surgery, some cancers would be missed because of a certain number of false-negative results.

Recently, Vriens *et al.* (68) evaluated the cost-effectiveness of FDG-PET/CT in patients with indeterminate FNAC who were scheduled for surgery. Their study

demonstrated that full implementation of FDG-PET/CT could lead to a decrease in costs as compared to diagnostic surgery and a molecular test standard of care in the United States (167 gene-expression classifier). These results were primarily based on a decrease in the costs and complications of surgery in patients with benign thyroid nodules that are not resected for being symptomatic (68).

FDG-PET/CT and ^{18}F -FDG for radioguided surgery

In addition to its diagnostic applications, ^{18}F -FDG can be used during radioguided surgery (RGS) to identify cervical recurrence of RAI-negative DTC using a handheld γ probe; this is similar to RGS with ^{131}I , which is used to locate RAI-positive loco-regional metastases (69, 70, 71, 72, 73). This technique is also useful in locating lymph node metastases that have been identified by FDG-PET/CT scan, particularly those that are in unusual sites or are embedded in a scarred and fibrotic surgical bed. Moreover, a handheld ^{18}F -FDG probe can detect additional metastatic lymph nodes that are invisible on an FDG-PET/CT scan and may help confirm the complete excision of pathologic tissues (69, 70, 71, 72, 73, 74, 75).

Occupational radiation exposure to intraoperative and perioperative personnel involved in FDG RGS is very low; in fact, the highest radiation dose received by the surgeon was found to be between 10 and 580 μSv per case (74).

RGS with FDG has been reported for a wide range of malignancies (colorectal carcinoma, malignant melanoma, breast carcinoma, and metastatic head and neck squamous cell carcinoma) (70). Fewer studies have evaluated the feasibility of this procedure for DTC patients with iodine-negative cervical recurrences (69, 70, 71, 72, 73).

Kraeber-Bodere *et al.* (69) used the procedure in ten patients with one to five RAI-negative lesions detected by FDG-PET scans. RGS proved to be complementary to FDG-PET/CT imaging and detected all of the tumor foci that had been identified preoperatively. A γ probe used during surgery did not reveal any lesions that had not been visualized preoperatively; however, it enabled the surgeon to verify whether all of the detected foci had been completely resected.

Kim *et al.* (72) evaluated 12 patients who underwent modified radical, selective, and central neck dissection by FDG RGS. All of the lesions that had been identified by preoperative PET were identified by intraoperative PET probe, and lesions that were not found on the preoperative

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PET were detected by PET probe in seven patients. After surgery, all postoperative stimulated Tg levels were decreased to <2.0 ng/ml, except in one patient. In a small retrospective study, Francis *et al.* (73) described their experience with an intraoperative ^{18}F -FDG handheld γ probe in five of 13 DTC patients who had submitted to RGS. The procedure confirmed the sites of recurrent disease that had been suggested by preoperative FDG-PET/CT but did not identify new foci. The use of FDG RGS reduced Tg to undetectable levels in two of the five patients.

In case of a low *in situ* target-to-background ratio, ^{18}F -FDG-avid tissue sites can be identified using the K- α probe design in conjunction with the three-sigma statistical threshold criteria method (75). Although the intraoperative PET probe appears to be of value for detecting small occult neoplasms or metastatic lymph nodes, the method may have some limitations (72). First, it may not be cost-effective, and it is important to carefully select the patients who might benefit from this technique. Second, false-positive results can occur as a result of inflammation or during the evaluation of level II lymph nodes that are located close to the submandibular gland and pharynx, which have a physiologically high FDG uptake. Finally, preoperative probes designed for the detection of high-energy photons emitted by ^{18}F are not readily available.

Controversies and areas of uncertainty

Cutoff value of Tg for the selection of patients for FDG-PET/CT

The primary clinical application of FDG-PET/CT in the management of patients with DTC is to identify sites of cancer recurrence in patients with elevated serum Tg but negative RAI WBS and neck US (4). According to the ATA guidelines (5), FDG-PET/CT should be performed only when unstimulated Tg levels exceed 10 ng/ml, and in the United States, most insurance providers only cover FDG-PET/CT in patients with a Tg level above 10 ng/ml. However, the ATA recommendation is principally based on the results obtained by comparing serum Tg levels with PET alone (i.e., without concurrent CT scanning). PET/CT hybrid scanning has significantly increased both the specificity and sensitivity of FDG-PET scans because of its greatly improved morphological correction vs PET alone. The specificity of PET alone was found to be 50% vs 89% for PET/CT (76).

Although serum Tg levels correlate with tumor load and true-positive FDG-PET/CT scans increase as Tg levels increase, several authors have suggested that a cutoff value

of 10 ng/ml for unstimulated Tg is at best a suboptimal criteria for the selection of patients for FDG-PET/CT (77, 78, 79). Giovanella *et al.* (77) reported true-positive FDG-PET/CT examinations in 14 of 30 patients (46%) with Tg levels of <10 ng/ml, and Vera *et al.* (78) reported FDG-PET/CT positive findings in 20 of 44 DTC patients (45%) with Tg levels of <10 ng/ml during LT4 therapy and with negative DxWBS. Although they did not find a significant relationship between FDG-PET/CT results and Tg concentrations, there was a trend toward significance for unstimulated Tg ($P=0.07$).

Shammas *et al.* (76) reported that eight of 32 patients (25%) with Tg levels below 10 ng/ml had true-positive scans, which suggests that FDG-PET/CT could also be helpful in selected cases of Tg levels below 10 ng/ml. However, the FDG-PET/CT results were evaluated in relation to Tg levels irrespective of TSH suppression or stimulation. Moreover, Tg autoantibodies, which could interfere with Tg measurements, were not available for all patients. Na *et al.* (79) reported positive FDG-PET/CT scans in ten of 26 patients (38%) with stimulated Tg levels between 5 and 10 ng/ml, which suggests that FDG-PET/CT might also be useful in patients that have a relatively low stimulated Tg.

Recently, nonstimulated serum Tg velocity and Tg doubling time (Tg-DT) have been shown to be predictors of survival, distant metastases, and loco-regional recurrences in patients with DTC (80, 81). Because a shortened Tg-DT indicates rapid tumor growth, patients with a shortened Tg-DT are likely to have a more aggressive disease, which is usually detectable by FDG-PET/CT imaging even when absolute Tg levels are only slightly elevated during TSH suppression. Consequently, some authors have proposed that an FDG-PET/CT scan should be performed in any patient that has sequentially increasing Tg levels, even if those levels remain below any defined cutoff (82, 83). Giovanella *et al.* (82) found a Tg-DT of <1 year in 94% of patients that had a true-positive FDG-PET/CT scan, including three patients with a Tg level below the cutoff level of 5.5 ng/ml, and a stable or increased Tg-DT in nearly all patients that had a true-negative FDG-PET/CT scan. Kelders *et al.* (83) observed that eight of nine patients with a median Tg-DT of 148 days had FDG-positive scans, and only one patient (Tg-DT: 252 days) was FDG-negative.

Given these findings, it appears that no clear cutoff Tg value can be established, and the decision of whether or not to perform FDG-PET/CT should be made for each patient depending on the clinical setting and individual risk.

FDG-PET/CT scanning with TSH stimulation

Increased uptake of FDG by DTC metastases can be expected under TSH stimulation because of the higher metabolic demand of the stimulated thyroid tissue. Physiologic studies have shown that TSH stimulates the glucose transport system by enhancing the number of functional GLUT transporters in the plasma membrane and by stimulating the glycolytic pathway (17). However, whether FDG-PET/CT for the detection of cancer recurrence in DTC patients that have elevated serum Tg but negative WBS and neck US should be performed under TSH stimulation or suppression remains controversial. According to the ATA guidelines, the sensitivity of FDG-PET/CT scanning may be marginally improved with TSH stimulation (especially in patients with low Tg values), but the clinical benefit of identifying these additional small foci has yet to be proven (5).

In a meta-analysis by Ma *et al.* (84), seven prospective controlled clinical trials involving 168 patients who submitted to FDG-PET/CT for elevated serum Tg but negative RAI WBS were examined to establish the effects of TSH stimulation on the uptake of FDG. TSH-stimulated FDG-PET/CT scans were compared to FDG-PET/CT scans under TSH suppression (23, 85, 86, 87, 88, 89, 90). That meta-analysis revealed statistically significant differences between the number of patients with PET true-positive lesions, those with PET-detected lesions, and those with and tumor-to-background ratios. PET scans taken under TSH stimulation altered clinical management in 12/130 (9%) patients in five paired studies. The mean SUVmax of the PET-detected lesions did not differ among the patients, probably because of the well-known limited reproducibility of the SUVindex (84).

Taken together, these results suggest that TSH stimulation after T4 withdrawal or rhTSH administration significantly improves the sensitivity of FDG-PET/CT and that TSH stimulation should be recommended for DTC patients who are undergoing PET scanning for elevated Tg levels and iodine-negative scanning. Using rhTSH stimulation, which avoids the deleterious impact of hypothyroidism on quality of life, FDG-PET/CT scans can be performed either 24 or 48 h after rhTSH administration without any significant difference in the results (23). However, the clinical significance of identifying additional small foci of recurrent thyroid carcinoma has yet to be proven, and further well-designed studies are required to ascertain the clinical benefit of altered management by FDG-PET/CT under TSH stimulation.

Clinical significance of thyroid PET incidentaloma

Thyroid incidentaloma diagnosed by FDG-PET/CT is defined as thyroid FDG uptake incidentally and newly detected in a patient who is being studied for a nonthyroid purpose. With the increasing clinical use of FDG-PET/CT for the staging and restaging of various malignancies, thyroid incidentalomas are being reported with increasing frequency (91) (Fig. 6). Most thyroid incidentalomas are benign, some are malignant, and some are secondary lesions from other primary tumors. Diffuse FDG uptake usually indicates chronic or acute thyroiditis, whereas focal FDG uptake in the thyroid gland indicates a significant risk of malignancy.

A proportion meta-analysis performed by Bertagna *et al.* (92) with a total of 147 505 subjects from 27 studies revealed a pooled incidence and a malignancy ratio of 2.46% (95% CI 1.68, 3.39%) and 34.6% (95% CI 29.3, 40.2%) respectively. Soelberg *et al.* (91) calculated the prevalence and the risk of malignancy of thyroid incidentalomas reported in 22 selected studies involving 125 754 subjects. They found unexpected focal thyroid hypermetabolic activity in 1994 (1.6%) subjects and thyroid malignancy in 366 (34.8%) of 1051 patients with focal uptake and assigned diagnosis. A pooled prevalence of 1.92% (95% CI 1.87, 1.99%) and a pooled risk of malignancy of 36.2% (95% CI 33.8, 38.6%), without significant differences among various geographic areas, was found in 34 selected studies with a total of 215 057 patients (93).

In order to determine an SUVmax cutoff value over which a malignant lesion should be suspected, Bertagna *et al.* (94) retrospectively examined 729 (1.5%) thyroid

Figure 6

FDG-PET/CT (A) performed in a 66-year-old female patient for the restaging of multiple myeloma. The scan revealed an intense focal FDG uptake in the right thyroid lobe (SUVmax = 12.6). The neck US confirmed the presence of a hypoechoic nodule in the right lobe (not shown), and the fine-needle aspiration showed multiple clusters of Hürthle cells, which suggested a Hürthle cell neoplasm (B).

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incidentalomas diagnosed among 49 519 patients who underwent FDG-PET/CT for oncologic purposes in three Italian nuclear medicine centers. Despite a significant difference between SUVmax of benign and malignant incidentalomas in two of the three centers, the authors concluded that SUV value is usually high in malignant lesions, but no safe definite cutoff could be established to discriminate benign from malignant lesions. Stangierski *et al.* (95) recently reported that, in addition to a higher risk of malignancy in nodules with higher SUVmax, there was a positive correlation between SUVmax and nodule diameter. The authors commented that especially smaller lesions with low uptake should be interpreted with caution.

These studies show that the incidence of thyroid incidentalomas, although low as a percentage, is not negligible, and that about one-third of clinically asymptomatic patients would have had a late diagnosis of thyroid cancer had they not undergone a PET scan. In these cases, the most frequent malignant histological type that was responsible for FDG-PET/CT thyroid incidentaloma was papillary thyroid cancer, and there is no safe SUV cutoff for which it is certain or reasonably safe to either suspect or rule out malignancies (92).

Although the management of thyroid incidentalomas is not yet well established, the ATA recommends further testing, including a cytologic and/or histologic diagnosis (5). However, there are no data on the cost-effectiveness of such a strategy. Moreover, it is not clear whether there are differences in the management of patients diagnosed by FDG-PET/CT and patients

diagnosed when the nodular thyroid disease is clinically evident (91).

Further studies and prospective protocols are needed to ascertain the real meaning of PET incidentaloma, its prognostic value, and its relationship to iodine metabolism and thus to establish the correct position of PET on the diagnostic flowchart.

Main recommendations of international thyroid societies for the use of FDG-PET/CT in patients with thyroid cancer

Table 2 lists the main recommendations for the use of FDG-PET/CT in patients with thyroid cancer made by the British Thyroid Association (BTA) (96), the ATA (5), the National Comprehensive Cancer Network (NCCN) (97), the Latin American Thyroid Society (LATS) (98), the European Society for Medical Oncology (ESMO) (99), and the European Thyroid Association (ETA) (100). The recommendations are described in the setting of the preoperative use of FDG-PET/CT, in the management of patients with elevated serum Tg levels and negative neck US and DxWBS, and in patients with high-risk DTC or aggressive histology.

Conclusion

The use of FDG-PET/CT has gradually increased to become an essential imaging modality in the postoperative management of patients with DTC. Although its most common use remains the assessment of patients with elevated Tg but

Table 2 Main recommendations of international thyroid societies for the use of FDG-PET in thyroid cancer.

	BTA	ATA	NCCN	LATS	ESMO	ETA
Preoperative use		No		Aggressive cancers	Undifferentiated thyroid cancers	No
Elevated Tg and negative WBS	Tg on LT4 ≥ 10 ng/ml; rising Tg on LT4	Tg on LT4 ≥ 10 ng/ml	Tg on LT4 ≥ 10 ng/ml; TSH-Tg $> 2-5$ ng/ml	Tg on LT4 ≥ 10 ng/ml	Tg on LT4 ≥ 10 ng/ml; rising Tg on LT4	Tg on LT4 ≥ 10 ng/ml; TSH-Tg $> 2-5$ ng/ml
High-risk patients and aggressive histology		High-risk DTC; poor DTC; invasive Hürthle cell carcinoma; after systemic or local therapy of metastases	Poor DTC; invasive Hürthle cell carcinoma			pT4 tumors; poor DTC; invasive HCC; before aggressive therapy

BTA, British Thyroid Association; ATA, American Thyroid Association; NCCN, National Comprehensive Cancer Network; LATS, Latin American Thyroid Society; ESMO, European Society for Medical Oncology; ETA, European Thyroid Association; DTC, differentiated thyroid cancer; Tg, thyroglobulin; WBS, whole-body scan.

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negative WBS, FDG-PET/CT may also play a role in the identification of those patients who are at the highest risk of disease-specific mortality, in the management of patients with RAI-refractory disease, in clinical trials of novel targeted therapies in patients with advanced metastatic disease, in the initial staging and follow-up of high-risk patients with aggressive histological subtypes, and in the evaluation of thyroid nodules with indeterminate FNAC.

Notably, although the detection rate of metastatic lesions increases with Tg serum levels, no absolute minimum cutoff can be established in cases in which FDG-PET/CT performed in patients with elevated Tg levels but negative ¹³¹I WBS. In such cases, the decision to perform FDG scans should be made for each patient based on the clinical and laboratory findings and that patient's risk profile.

It remains to be established whether or not all patients submitted to FDG-PET/CT should undergo TSH stimulation (either hypothyroid or rhTSH), despite data that suggest that there is a better detection rate when FDG-PET/CT is performed after TSH stimulation than when it is performed after TSH suppression.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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