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PET/CT in the management of differentiated thyroid cancer

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ABSTRACT

The standard treatment of differentiated thyroid cancer (DTC) consists of surgery followed by iodine-131 (^{131}I) administration. Although the majority of DTC has a very good prognosis, more aggressive histologic subtypes convey a worse prognosis. Follow-up consists of periodically measurements of serum thyroglobulin, thyroglobulin antibodies and neck ultrasound and ^{123}I/^{131}I whole-body scan. However, undifferentiated thyroid tumors have a lower avidity for radioiodine and the ability of DTC to concentrate ^{131}I may be lost in metastatic disease. Positron emission tomography (PET)/computed tomography (CT) has been introduced in the evaluation of patients with thyroid tumors and the 2-[18F]-fluoro-2-deoxyd-glucose (^{18}F-FDG) has been largely validated as marker of cell's metabolism. According to the 2015 American Thyroid Association guidelines, ^{18}F-FDG PET/CT is recommended in the follow-up of high-risk patients with elevated serum thyroglobulin and negative ^{131}I imaging, in the assessment of metastatic patients, for lesion detection and risk stratification and in predicting the response to therapy. It should be considered that well-differentiated iodine avid lesions could not concentrate ^{18}F-FDG, and a reciprocal pattern of iodine and ^{18}F-FDG uptake has been observed. Beyond ^{18}F-FDG, other tracers are available for PET imaging of thyroid tumors, such as Iodine-124 (^{124}I), ^{18}F-tetrafluoroborate and Gallium-68 prostate-specific membrane antigen. Moreover, the recent introduction of PET/MRI, offers now several opportunities in the field of patients with DTC. This review summarizes the evidences on the role of PET/CT in management of patients with DTC, focusing on potential applications and on elucidating some still debating points.

1. Introduction

Differentiated thyroid cancer (DTC) represents the majority of thyroid cancers and generally has a very good outcome, with an overall risk of relapse that never exceed 20% [1,2]. Among DTC, aggressive tumors with a worse prognosis are less frequent. The standard treatment consists of total or near-total thyroidectomy followed by iodine-131 (^{131}I) ablation therapy. Follow-up in patients with DTC consists of periodically measurements of thyroglobulin (Tg), Tg antibodies (Tg-Ab) and neck ultrasound. Other conventional imaging methods used in the workup of thyroid cancer include also computed tomography (CT) and magnetic resonance imaging (MRI), which can provide important anatomic information on the thyroid and surrounding structures. The ^{123}I/^{131}I whole-body scan (WBS) is largely used in patients with high- or intermediate-risk of persistent disease [3,4]. However, although the majority of tumor cells in DTC retain the ability to trap iodine, undifferentiated thyroid tumors have a lower avidity for radioiodine. Furthermore, the ability of DTC to concentrate ^{131}I may be lost in metastatic disease, most likely because of transformation to less-differentiated tumors. In these patients WBS scan shows poor sensitivity, resulting in negative findings in 10% to 15% of patients, thus making management of such patients still challenging [5].

The introduction of positron emission tomography/computed tomography (PET/CT) in the clinical use has substantially changed the management of patients with cancer [6]. 2-[18F]-fluoro-2-deoxy-d- glucose (FDG) has been largely validated as marker of cell's metabolism, due to over-expression of regulatory glycolytic enzymes and transporters in less-differentiated cells [7–9]. Since the first report in 1987, ^{18}F-FDG PET/CT has emerged as an important tool for the management of patients with DTC and an increased

Abbreviations: AJCC/UICC, American Joint Committee on Cancer/Union for International Cancer Control; ATA, American Thyroid Association; DTC, differentiated thyroid cancer; FDG, 2-[18F]-fluoro-2-deoxy-d-glucose; MRI, magnetic resonance imaging; NIS, sodium iodide symporter; PET/CT, positron emission tomography/computed tomography; PSMA, prostate-specific membrane antigen; SUV, standardized uptake value; TFB, tetrafluoroborate; Tg, thyroglobulin; Tg-Ab, thyroglobulin-antibodies; TNM, tumor node metastasis; WBS, whole-body scan.

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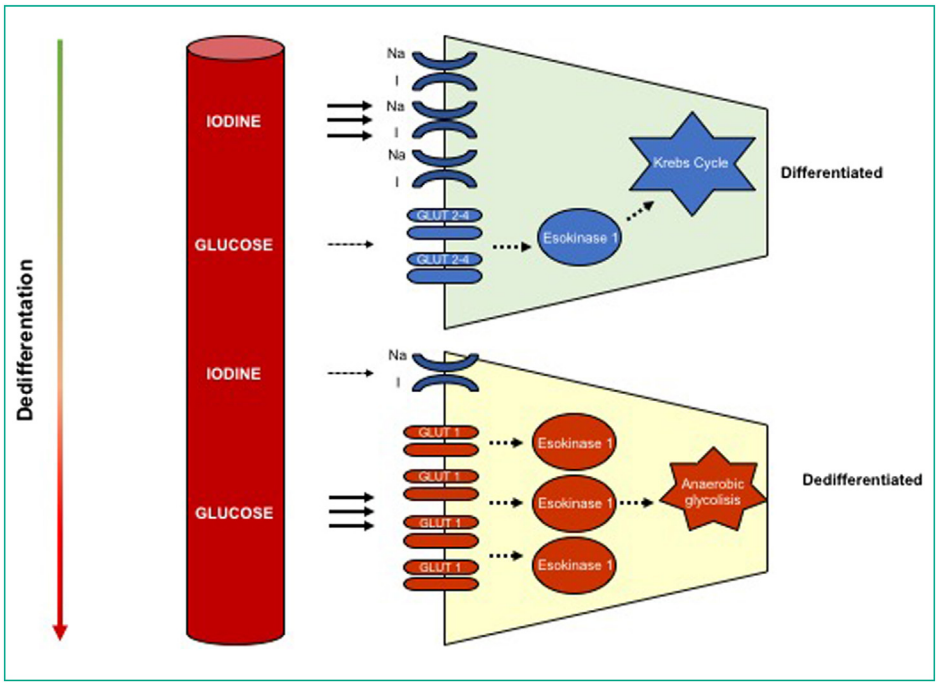

Fig. 1. Diagram illustrates the flip-flop phenomenon, which is the molecular basis of dedifferentiation.

uptake has been observed in more aggressive tumors [10]. According to the 2015 American Thyroid Association (ATA) guidelines, ^{18}F-FDG PET/CT is not recommended for the evaluation of thyroid nodules or as routine preoperative scanning [11]. However, ^{18}F-FDG PET/CT is strongly recommended in the follow-up of high-risk patients with elevated serum Tg and negative ^{131}I imaging. ^{18}F-FDG PET/CT can be also indicated for the evaluation of response to therapy, for lesion detection in metastatic patients and for prediction of outcome in high-risk patients. In addition, the results of ^{18}F-FDG PET/CT may modify the indications for ^{131}I treatment or surgery, when small areas of FDG uptake are detected. It should be considered that well-differentiated iodine avid lesions could not concentrate ^{18}F-FDG, and a reciprocal pattern of iodine and ^{18}F-FDG uptake, or "flip-flop relationship", has been confirmed in large series of patients [12]. Iodine-124 (^{124}I) has been introduced for the evaluation of patients with differentiated tumors by using PET/CT imaging.

The objective of this review was to summarize the evidences on the role of PET/CT in the management of patients with DTC, focusing on potential applications and on elucidating some still debated issues.

2. PET/CT technique

PET imaging is a tomographic method which allows non-invasive quantitative assessment of biochemical and functional processes. PET technology uses a ring detector system for detection of coincidences, by using positron-emitting radionuclides. The radionuclides decay by positron emission and the annihilation of positron and electron results in two 511 keV γ photons. A wide range of positron-emitting radionuclides are available in PET imaging, and many of them have a short half-life, which requires an expensive cyclotron production facility on the same site. On the other hand, ^{18}F (half-life 110 minutes) and ^{124}I (half-life 4.2 days) have a slightly longer half- life allowing them to be transported from the production facility to other imaging sites. This explains the popularity of these PET radiopharmaceuticals into the daily practice.

Integrated PET with CT in a single unit (PET/CT) provides several advantages, including a more accurate localization and characterization of detected lesions than either PET or CT alone [13]. Moreover, the addition of CT leads to perform accurate attenuation correction, which is necessary for the evaluation of some areas, such as brain, neck or chest. Beyond visual analysis, PET/CT provides semi-quantitative measurements of tracer's uptake, including standardized uptake values (SUV). With its high sensitivity and resolution, PET/CT has emerged as a robust diagnostic tool by comparison with other contemporary imaging modalities.

3. ^{18}F-FDG uptake in DTC

The glucose analogue^{18}F-FDG is the most commonly used radiotracer into oncological imaging, for staging, restaging and evaluation of response to therapy in several tumors [14,15]. It is taken up into cells via the glucose transporters (GLUT), but it cannot be metabolized to FDG-6-phosphate. Therefore, its uptake reflects normal and abnormal metabolic activities and it is used for cancer detection, staging and recurrence. In patients with DTC, it has been largely observed that lesions with high ^{18}F-FDG and low radioiodine uptake, are more clinical aggressive [16,17]. The "flip-flop phenomenon" consists of a mismatch between glucose and iodine uptake in patients with DTC, due changes in cell metabolism during dedifferentiation process (Fig. 1).

^{18}F-FDG-avid lesions provide potentially relevant information on tumor biology and help identify patients with high-grade tumors and poor prognosis [12]. Rivera et al. performed histological examination of metastatic tissue from 70 patients with negative radioiodine and positive ^{18}F-FDG PET/CT imaging [18]. They found that 33 patients (47%) had poorly differentiated thyroid tumors, 14 (20%) tall cell variant, 16 (23%) well DTC, 6 (9%) Hurtle cell carcinoma and 1 (1%) anaplastic disease. Moreover, in 63% of patients, metastatic sites showed a progression to a higher grade when compared to the primary tumor. These findings suggest that the lowest is the degree of differentiation of malignant cells, the highest is their ability to take up ^{18}F-FDG.

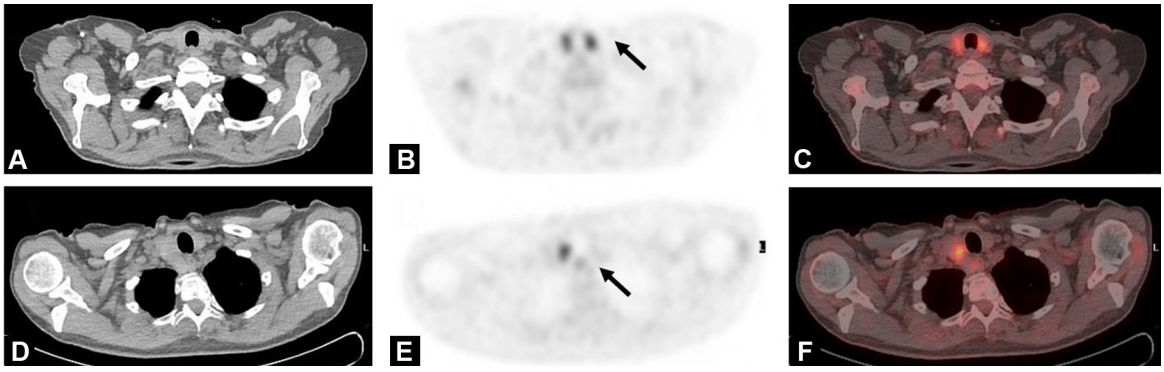

Fig. 2. Representative example of diffuse (A, B, C) and focal (D, E, F) uptake pattern at ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) imaging.

The expression of GLUT in thyroid carcinoma cells tissues has been also evaluated [19–21]. It has been observed an increased expression of GLUT-1 and GLUT-3 in malignant tissue with an overexpression in less-differentiated cells. Haber et al. found that at immunohistochemical evaluation GLUT-1 was strongly expressed in 52.9% of patients with papillary thyroid cancer (PTC) and in 100% of those with anaplastic cancer [19].

Reduced sodium iodide symporter (NIS) and increased GLUT-1 expression were also observed in PTC refractory to radioiodine and in DTC with BRAF mutation [20]. Moreover, Ricarte-Filho et al. reported that DTC non-avid for ^{131}I and positive for ^{18}F-FDG PET/CT, more frequently harbored RAS mutations than BRAF in primary tumors, while the opposite was found in metastases [21]. The same researchers observed that, if BRAF were mutated in the primary tumor, then the metastases would likely harbor the defect [21]. These findings suggest that metastases positive at ^{18}F-FDG and negative at radioiodine would have a mutational profile and several molecules may play a role leading to enhanced glucose uptake.

4. Thyroid incidentalomas

Thyroid incidentaloma is a thyroid gland lesion discovered during radiological examination in patients without history of thyroid disease. The widespread use of ^{18}F-FDG PET/CT leads to an increasing number of thyroid incidentalomas, identified as abnormal focal or diffuse FDG uptake into the thyroid bed. The prevalence of FDG-avid thyroid incidentaloma ranges between 0.2% and 8.9% [22–25]. Kang et al. found 1151 FDG-avid thyroid incidentalomas in a total of 12,840 patients, with a prevalence of 8.9% [23]. On the opposite, the lowest prevalence was reported by King et al., with 22 FDG-avid thyroid incidentalomas observed among 15,711 patients (0.2%) [24]. It should be considered that glucose uptake can be nonspecific and the incidence of malignancies amongst thyroid incidentalomas ranges between 8 and 64% [20]. Hagenimana et al. reviewed 40,914 patients who underwent ^{18}F-FDG PET/CT [26]. They found that thyroid incidentaloma was relatively infrequent, with a prevalence of 0.74%, but with a high potential risk of malignancy (8%) [26].

A systematic review and meta-analysis by Nayan et al. found a pooled proportion of malignancy of 19.8% among 31 reports analyzed [27]. A higher risk of cancer seems to be related to focal or unilateral uptake of ^{18}F-FDG, in particular in lesions with higher standardized uptake value (SUV) or suspicious CT, while diffuse uptake is mainly associated with benign lesions [23]. An example of focal and diffuse uptake pattern of ^{18}F-FDG uptake is depicted in Fig. 2. Among patients with focal uptake, ^{18}F-FDG PET/CT show a sensitivity of 100%, a specificity of 69%, a positive predictive value of 62% and a negative predictive value of 100% for detection of malignancies [28]. A wide range of values has been reported for sensitivity (60 to 80%) and specificity (66 to 91%) [29]. Iagaru et al., in patient with DTC, found that ^{18}F-FDG PET/CT had high sensitivity (88%) and specificity (89%) during for follow-up [30].

There are discordant approaches toward ^{18}F-FDG-avid thyroid incidentalomas. Some authors suggest no need to perform further evaluation, unless a strong clinical suspicious is present, considering that the majority of ^{18}F-FDG-avid thyroid incidentalomas are benign lesions. By contrast, other authors concluded that the relatively high prevalence of malignancy in these patients mandates additional evaluation to rule out possibility of malignancy. In this field, ultrasound has been identified as a reliable tool to stratify the risk of malignance in focal uptake at ^{18}F-FDG PET/CT imaging. This approach has been proposed as a gatekeeper in selecting patients for further investigations [31].

5. Initial staging and risk stratification

In patients with DTC, preoperative staging for evaluation of the primary tumor and nodal metastasis is important for determining the extent of surgery and proper management. The current ATA guidelines do not recommend ^{18}F-FDG PET/CT as routine preoperative scanning [11]. In particular, ^{18}F-FDG PET/CT imaging demonstrated low sensitivity (30%), despite a good specificity (94%) for the evaluation of nodal status [32]. Postoperative decision-making is guided by clinical and pathological information, based on the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) Tumor Node Metastasis (TNM) staging system and the ATA risk stratification system. The AJCC/UICC TNM system is a standard tool for the initial risk assessment of patients with DTC, able to predict mortality but not the risk of recurrence. Thus, the ATA risk stratification system has been proposed to assess the risk of recurrence or persistence disease in patients with DTC [11]. The administration of ^{131}I is indicated in ATA high-risk patients, but not in those at low-risk with tumor size > 1 cm. Differently, in low-risk patients with tumor size > 1 cm as well as in those at low-to-intermediate-risk, the indication to treatment is related to other factors, including age or risk of persistent or recurrent disease [11]. Post-therapy ^{131}I WBS is able to detect the presence distant metastasis earlier [33]. However, in patients with high-grade tumors, post-therapy ^{123}I/^{131}I WBS may be false negative and the overall extent of disease may not be demonstrated. In those patients, the results of ^{18}F-FDG PET/CT improve risk stratification during initial staging of patients with DTC and modify the indications to ^{131}I treatment.

It has been reported that ^{18}F-FDG PET/CT concurrent with ^{131}I therapy could detect abnormal uptake areas in 33% of the patients with locoregional disease and cervical lymph node metastasis [34]. Table 1 summarizes the results of ^{18}F-FDG PET/CT performed at the time of ^{131}I ablation therapy. Lee et al. evaluated 258 patients at intermediate- and high-risk DTC and they found that, among 50

Table 1
^{18}F-FDG PET/CT in the evaluation of patients at the time of 131I treatment.

Author	Patients (*n*)	PET+	Study population
Lee et al. [35]	258	17%	Intermediate-to-high ATA risk
Nascimento et al. [36]	38	53%	Aggressive tumor at histopathological analysis
Rosenbaum-Krumme et al. [37]	90	29%	High ATA risk
Liu et al. [38]	104	88%	DTC patients with high serum Tg
Al-Zahrani et al. [39]	26	69%	Newly diagnosed DTC patients
Gaertner et al. [40]	141	33%	Newly diagnosed DTC patients
Pace et al. [41]	60	17%	Low, intermediate and high ATA risk

^{18}F-FDG: 2-[18F]-fluoro-2-deoxy-d-glucose; PET/CT: positron emission tomography/computed tomography; ATA: American Thyroid Association; DTC: differentiated thyroid cancer; Tg: thyroglobulin.

patients with positive ^{18}F-FDG PET/CT imaging, 39 (78%) of them did not show pathological findings at post-therapy ^{123}I/^{131}I WBS [35]. These researchers observed that the presence of pathological uptake at ^{18}F-FDG PET/CT, as well as a change in treatment strategy, varied according to histopathologic stage of the patients [35]. In particular, the frequency of additional lesions and treatment change according to ^{18}F-FDG PET/CT findings were greater in patients at T3 or T4 and N1 stage with tumor size > 2.0 cm, suggesting that both stage and size can predict ^{18}F-FDG PET/CT results [35]. These findings were further confirmed in 38 patients with aggressive tumors at histopathologic analysis [36]. Abnormal uptake findings at ^{18}F-FDG PET/CT imaging were found in 15 (39%) of patients, with a higher prevalence in those with TSH-stimulated Tg levels > 10 ng/mL evaluated [36].

The role of ^{18}F-FDG PET/CT in changing management was evaluated by Rosenbaum-Krumme et al. in 90 high-risk patients [37]. They found that 26 patients (29%) of the overall population had positive ^{18}F-FDG PET/CT findings, leading to a change of TNM stage and treatment strategy in (19) 21% patients. A significant difference in Tg values was observed according to ^{18}F-FDG PET/CT results [37]. This is probably explained by the evidence that a rising in Tg levels may be due by a higher tumor burden rather than by less-differentiated tumor cells. ^{18}F-FDG PET/CT can identify these patients with high postoperative Tg levels, which may not benefit from iodine treatment leading to an improved management of disease [38]. A SUVmax value > 4 has been identified as a good cutoff in identifying non-avid ^{131}I lesions. These evidences suggest that patients with aggressive histology and elevated Tg levels may benefit from ^{18}F-FDG PET/CT.

When ^{18}F-FDG PET/CT is performed at the time of ^{131}I ablation, it seems able to predict response to therapy and stratify patients according to the risk of persistence or recurrence of disease. Alzahrani et al. compared ^{18}F-FDG PET/CT and post-therapy ^{123}I/^{131}I WBS findings in 26 DTC patients [39]. ^{123}I/^{131}I WBS was positive in all patients, while ^{18}F-FDG PET/CT in 18 (69%) of those. During a follow-up of 30 months, remission was observed in 7 (87.5%) patients with 8 negative ^{18}F-FDG PET/CT examinations, while 10 (56%) patients with abnormal ^{18}F-FDG PET/CT examination had persistent disease or progression [39].

A complete remission was more frequently observed among patients with negative ^{18}F-FDG PET/CT as compared to those with positive scans. Gaertner et al. observed that patients with positive ^{18}F-FDG PET/CT scan at the time of ablative ^{131}I therapy showed poorer biochemical response and lower survival as compared with those with negative scan [40]. As compared to post-therapy ^{123}I/^{131}I WBS findings, survival rates were 61% in patients with positive and 58% in those with negative scan. Earlier deaths were found in patients with positive ^{18}F-FDG PET/CT imaging and negative ^{123}I/^{131}I WBS, maybe due to the presence of dedifferentiated cancer cells. However, from these data neither age nor the presence of distant metastases at conventional imaging resulted as predictors of overall survival. ^{18}F-FDG PET/CT seems to be more predictive for long-term survival, whereas radioiodine uptake is more important for short-term response. In particular, overall survival was 48.5% in patients with positive ^{18}F-FDG PET/CT and 100% in those with a negative scan [40]. In another report, Pace et al. evaluated the impact of ^{18}F-FDG PET/CT performed after surgery but before radioiodine treatment [41]. Among 60 patients enrolled, 10 (17%) had abnormal ^{18}F-FDG PET/CT findings, and half of them were in stage I. During a median follow-up of 48.5 months, patients with positive ^{18}F-FDG PET/CT scan showed a higher rate of recurrence. Thyroglobulin, neck ultrasound, stage and ^{18}F-FDG PET/CT resulted as independent predictors of outcome and patients with a negative ^{18}F-FDG PET/CT scan showed better survival either in the overall population as well as in patients with elevated Tg level [41].

Although the majority of studies are retrospective, the population analyzed is heterogeneous in term of stage, risk class and histology, and differs in end-point selection, the results are quite consistent. The prevalence of positive ^{18}F-FDG PET/CT varies from 17 to 88%, in particular in high and intermediate-to-high-risk patients, leading to a change in management up to 38% of patients. Patients with a negative ^{18}F-FDG PET/CT show higher response to radioiodine ablation therapy than those with a positive one, with stronger evidence in high-risk DTC and in those with aggressive histology. In patients undergoing initial ^{131}I ablation, ^{18}F-FDG PET/CT can help the choice of the most appropriate treatment modality adding a more objective tool to the currently widely used staging systems.

6. ^{18}F-FDG PET/CT during follow-up

Despite a good prognosis, 15% of patients with DTC show progression of disease during follow-up, with local or regional recurrence in 5–20% of patients and distant metastases of lungs and bones in up to 10% [42,43]. According to ATA guidelines, follow-up is usually performed by Tg serum dosage, neck ultrasound and ^{123}I/^{131}I WBS in intermediate–high-risk DTC [11]. However, in patients with more aggressive disease ^{123}I/^{131}I WBS may result false negative and ^{18}F-FDG PET/CT may be superior in disclosing the presence of distant metastases.

The sensitivity, specificity and accuracy of ^{18}F-FDG PET/CT in detecting recurrence of DTC were 93%, 81% and 93% respectively [44]. Haslerud et al. found that pooled sensitivity and specificity of ^{18}F-FDG PET/CT in detecting recurrent DTC after thyroidectomy and radioiodine therapy were both 79.4% [45]. Similarly, Schütz et al. found that sensitivity was greater when ^{18}F-FDG PET/CT was compared to conventional imaging (94.3 *vs.* 65.4%, respectively) [46]. From these data ^{18}F-FDG PET/CT emerged as a useful tool for detecting recurrent DTC in patients undergone ^{131}I ablative therapy. Greater sensitivity has been reported in DTC patients with poorly differentiated tumors or follicular histology [47]. Moreover, in DTC BRAFV600E mutations are associated with greater ^{18}F-FDG avidity and SUV max values as compared to BRAFV600E mutation negative status. In particular, the pooled mean SUV difference between BRAF V600E positive and negative patients resulted to be 5.1 (CI: 4.3–5.8) [48].

Table 2
Prognostic role ^{18}F-FDG PET/CT during follow-up.

Author	Patients (*n*)	PET+	FU time (month)	OS (PET+/PET-)	PFS (PET +/PET-)
Deandreis et al. [55]	45	75%	24	60–80	N.A.
Marcus et al. [56]	202	49%	94	40–90	N.S.
Vural et al. [57]	105	71%	36	92–100	47–67
Masson-Deshayes et al. [58]	37	N.A.	42	NA	8–40
Terroir et al. [59]	55	N.A.	6	66–93	N.A.

^{18}F-FDG: 2-[18F]-fluoro-2-deoxy-d-glucose; PET/CT: positron emission tomography/computed tomography; FU: follow-up; N.S.: not significant at statistical analysis; N.A.: not available; PFS: progression-free survival; OS: overall survival.

According to ATA guidelines, the main indication for ^{18}F-FDG PET/CT is in patients with elevated thyroglobulin level but negative ^{123}I/^{131}I WBS [11]. A meta-analysis on the impact of ^{18}F-FDG PET/CT patients with elevated serum Tg and negative ^{131}I WBS reported sensitivity and specificity values of 93% and 85%, respectively [49]. ^{18}F-FDG PET/CT showed moderate sensitivity (84%) and specificity (78%) for the detection of recurrent diseases also in patients with elevated Tg-Ab levels and negative ^{131}I WBS [50]. The performance of^{18}F-FDG PET/CT in detecting Tg-positive and radioiodine-negative metastases of DTC is also improved after TSH stimulation [51]. Triviño Ibáñez et al. found that ^{18}F-FDG PET/CT performed 3–6 months after RAI was found able to change treatment management plans and initial staging in intermediate–high-risk patients [52]. An excellent response to therapy was observed in patients with a negative ^{18}F-FDG PET/CT [48]. Kim et al. confirmed that ^{18}F-FDG PET/CT has high negative predictive value (92%) in 70 patients up to 12 months after ablation [53].

The main role of ^{18}F-FDG PET/CT during follow-up is related to high negative predictive value. Moreover, a better outcome is observed when appropriate therapies are performed in subjects with a positive ^{18}F-FDG PET/CT. Dennis et al. found that a good biochemical response was obtained when patients with positive ^{18}F-FDG PET/CT were addressed to additional survival or radiation therapy as compared to a conservative approach [54]. During long-term follow-up, ^{18}F-FDG PET/CT findings show high prognostic impact (Table 2) [55–59]. In 80 patients with recurrent metastatic DTC, Deandreis et al. found that ^{18}F-FDG uptake was the only significant prognostic factor for overall survival while ^{131}I WBS was more predictive for stable disease [55]. Marcus et al. investigated the prognostic impact of ^{18}F-FDG PET/CT performed more than 6 months from ablative therapy in 202 patients and found that ^{18}F-FDG PET/CT, stage and time-to-scan were the only variables associated with outcome [56]. Similar results were observed by Vural et al. in 105 patients with elevated Tg but negative ^{131}I WBS [57]. Among patients with negative ^{18}F-FDG PET/CT, no recurrences occurred in patients with undetectable Tg values. On the contrary, ^{18}F-FDG positivity was related with extra thyroidal spread and elevated Tg values. The combined evaluation of Tg levels and ^{18}F-FDG PET/CT was crucial in management of patients negative ^{123}I/^{131}I WBS. A negative ^{18}F-FDG PET/CT is able to predict a favorable prognosis and lack of recurrence during follow-up in patients with undetectable Tg. The overall survival is also related to both the number of lesions detected by ^{18}F-FDG and the intensity of uptake. These data were confirmed by Masson-Deshayes et al. in 37 patients with metastatic DTC [58]. Both the number (≤ 10 vs. > 10) and activity (measured as SULpeak: ≤ 5 vs. > 5) of lesions at ^{18}F-FDG PET/CT imaging, were prognostic factors for progression-free survival. Differently, Terroir et al. found that metabolic activity of detected lesions was not related with the rate of tumor growth at 1 year [59]. However, overall survival correlated with the overall tumor burden, expressed as metabolic rate volume. Despite from these data intensity of ^{18}F-FDG uptake did not result as marker for tumor growth, a tumor burden index as metabolic rate volume obtained by ^{18}F-FDG PET/CT seems to be a powerful prognostic indicator.

From the literature data, it can be suggested to perform ^{18}F-FDG PET/CT in the follow-up of patients at intermediate–high-risk, particularly in those with high Tg level and negative WBS.

7. ^{18}F-FDG PET/CT in empiric RAI treatment

In patients with detectable Tg levels and negative ^{123}I/^{131}I WBS, also in absence of morphological findings during follow-up, empiric therapy with ^{131}I can be performed to better detect sites of disease and for the treatment not amenable to surgery [11,60]. To prevent the administration of inappropriate ^{131}I doses to patients likely to have a late response to initial treatment, an accurate selection of patients who need a further empirical ^{131}I therapy is necessary. In this context nuclear imaging modalities, including ^{123}I/^{131}I WBS and ^{18}F-FDG PET/CT, may play a major role. Although these methods provide complementary information, extra thyroidal uptake is more frequently detected at ^{18}F-FDG PET/CT [61].

Leboulleux et al. evaluated 34 patients with DTC before empiric ^{131}I therapy and found that ^{18}F-FDG PET/CT was more sensitive than ^{131}I post-therapy WBS (88% *vs.* 16%, respectively) in detecting disease [62]. This finding is not surprising since it has been reported that tumors with high ^{18}F-FDG PET/CT uptake generally fail to concentrate ^{131}I, and thus ^{131}I could be less appropriate in these patients [61–63]. Rosario et al. evaluated 24 subjects with rising Tg values and negative findings on ^{131}I WBS, ultrasound, CT and ^{18}F-FDG PET/CT [63]. The presence of elevated Tg values or metastases during follow-up were observed in a 6 of them ($n = 6/24$; 25%). Similarly, Salvatore et al. evaluated 45 patients undergoing ^{18}F-FDG PET/CT before a second ^{131}I therapy based upon rising of Tg levels [64]. The response to therapy was assessed by serum Tg dosages during a median follow-up of 15 months. ^{18}F-FDG PET/CT was positive in 34 (69%) and negative in 15 (31%) patients [64]. They found that normalization of Tg values was more frequent in patients with negative ^{18}F-FDG PET/CT ($n = 11$; 73%) as compared to those with positive scan ($n = 8$; 23%). Overall, longer survival has been reported in patients with negative ^{18}F-FDG PET/CT than in those with positive scans [55–59,64,65].

The use of empiric ^{131}I therapy could be suggested only in patients showing progression of Tg values and without ^{18}F-FDG PET/CT uptake. Both response rate to empiric ^{131}I therapy and overall survival are consistently higher in subjects with negative ^{18}F-FDG PET/CT than in those with positive findings [65]. Thus, empiric iodine-^{131}I therapy should be avoided in ^{18}F-FDG PET/CT positive patients, whereas it is appropriate for those who are ^{18}F-FDG PET/CT scanning negative. A significant decrease in serum Tg values without any treatment during follow-up is frequently observed and thus the decision to perform an empiric ^{131}I therapy should be tailored to the individual patient. A representative case of a patient candidate to empiric ^{131}I therapy, negative ^{131}I WBS and positive ^{18}F-FDG PET/CT is reported in Fig. 3.

According to the 2015 ATA guidelines, ^{18}F-FDG PET/CT can be useful prior to consider an empiric therapy when Tg levels are > 10 ng/mL [11]. However, no clear cutoff value of Tg has been established in clinical routine. There is a greater probability of pos-

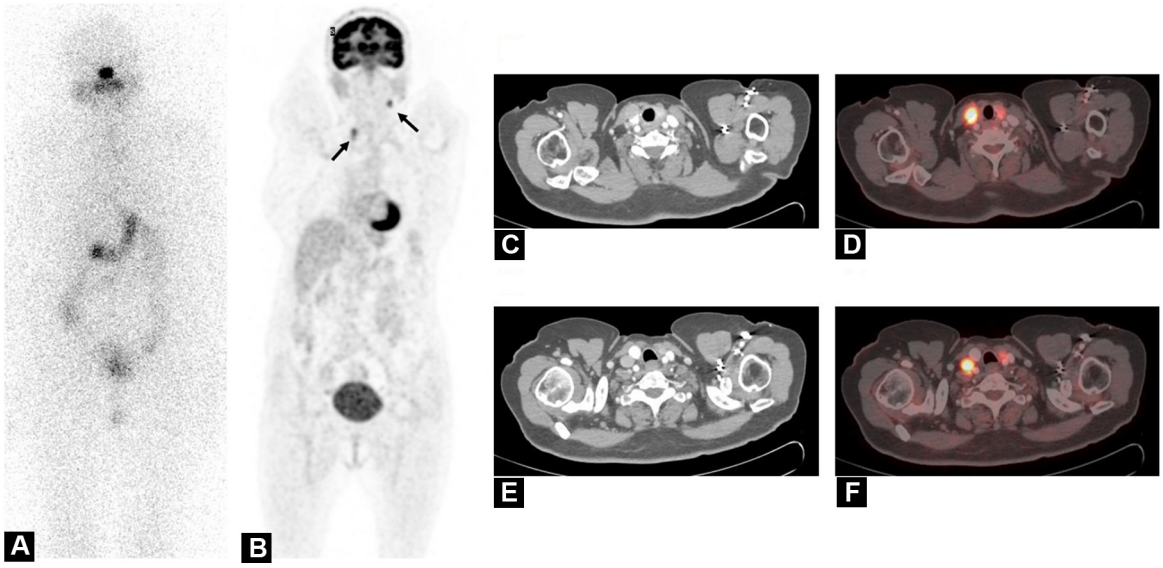

Fig. 3. A 54-year-old woman with papillary thyroid cancer, treated with surgery and ^{131}I ablative therapy 6 years ago. Because of rising thyroglobulin (Tg) values during follow-up, a diagnostic ^{131}I whole-body scan (WBS) (185 MBq of ^{131}I) (A) and 2-[18F]-fluoro-2-deoxy-d-glucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) (B, C, D, E, F) were performed. ^{18}F-FDG PET/CT evidenced two areas of focal uptake (arrows). Diagnostic ^{131}I WBS was negative.

itive ^{18}F-FDG PET/CT when Tg level is > 5 ng/mL and Tg doubling time is < 1 year [66,67]. Albano et al. observed a higher diagnostic performance of ^{18}F-FDG PET/CT when doubling time is less than or equal to 2.5 years, as compared with using the absolute Tg level [68]. Thus, a possible approach could be the execution of ^{18}F-FDG PET/CT only in patients with rapidly rising Tg, in which an empiric ^{131}I therapy could be administered in the presence of a negative scan. On the contrary, in patients with positive ^{18}F-FDG PET/CT scan, alternative therapy must be considered.

8. ^{124}I-PET/CT

Despite suboptimal physical features, ^{124}I-PET imaging is feasible, offering several technical advantages, including better spatial resolution and diagnostic sensitivity, than ^{131}I SPECT imaging [69]. Moreover, using particular scanner settings, simultaneous administration of a therapeutic dose of ^{131}I and a tracer dose of ^{124}I allows for accurate measurement of iodine uptake during therapy [68]. ^{124}I show longer half-life as compared to ^{18}F-FDG, and the first scan is usually taken at 24 h after tracer administration. Images can be obtained up 120 hours after the administration, allowing performing dosimetric studies [70].

In a meta-analysis, diagnostic capability of ^{124}I-PET/CT in identifying DTC lesions has been tested and an excellent sensitivity (94.2%) but a low specificity (49.0%) were found [71]. The authors concluded that ^{124}I-PET/CT is a sensitive tool to identify DTC lesions. Moreover, ^{124}I-PET/CT showed better performance than ^{123}I/^{131}I WBS [72–74]. In particular, it has been observed that diagnostic accuracy of ^{124}I-PET/CT is higher than diagnostic ^{123}I/^{131}I WBS, but equivalent to post-therapy ^{123}I/^{131}I WBS planar imaging. However, ^{124}I-PET/CT imaging is able to better detect abnormal uptake areas as compared to planar imaging [72]. Capoccetti et al. found that ^{124}I-PET/CT improved the detection of previously unknown both lymph node and distant metastases [73]. These data were confirmed by Rosenbaum-Krumme et al. who analyzed kinetic quantities by determining the maximum activity concentration and effective half-life of each lesion [74]. Therefore, in patients with suspected recurrence of disease, with elevated thyroglobulin values and negative ^{123}I/^{131}I WBS conventional imaging, the use of ^{124}I-PET/CT has been proposed in order to overcome the lack of sensitivity of conventional planar imaging [75]. Freudenberg et al. compared ^{124}I and ^{18}F-FDG PET/CT in the detection of recurrent DTC lesions in patients with increasing Tg but without cervical pathology on ultrasonography [76]. The sensitivities for detection of recurrences were 60% for ^{124}I and 65% for ^{18}F-FDG PET/CT, with one-third of lesions showing abnormal findings at both ^{124}I and ^{18}F-FDG PET/CT [76]. These data suggest that the combined evaluation of both imaging modalities could improve restaging in recurrent DTC. The widespread use of this technique is limited by some pitfalls, including the high prevalence of nonspecific uptake near the trachea and the low accuracy in detecting lung metastases [77,78].

In DTC, the main and more promising application for ^{124}I seems to be the estimation of the absorbed dose to thyroid cancer lesions. The amount of ^{131}I activity to be administered before radioiodine therapy is usually obtained by using a "standard" activity approach. The "dosimetric" approach consists on the administration of an optimum therapeutic activity individually estimated for every single patient. The dosimetric approach lead to obtain a therapeutic effect keeping the administered ^{131}I activity below the patient's toxicity limit of the organs at risk, primarily the bone marrow and the lungs. Dosimetry using ^{124}I-PET is a complex procedure that can be performed in order to improve staging and to optimize administred activity for remnant ablation. Moreover, in patients with multiple metastases, ^{124}I-PET dosimetry is used to establish the maximum dose that can be delivered to each lesion, avoiding side effects on organs at risk. For this purpose, serial ^{124}I-PET/CT scans are performed to determine the time uptake curves and to delineate the volumes of the lesions. The ^{124}I data obtained are then used to project the absorbed dose per unit administered ^{131}I activity. This model was first applied by Freudenberg et al. using a protocol of five PET acquisitions, in order to estimate the absorbed lesion dose per GBq of administered ^{131}I and thus to calculate the minimum effective activity. The efficacy is low for lesions receiving < 80 Gy, while when the estimated dose is < 40 Gy, other therapeutic option have to be considered [79]. The EANM dosimetry committee proposed a dosimetric operational model in order to standardize pre-therapeutic procedures [80,81]. Moreover, a simplified protocol with two PET acquisitions has been proposed for the convenience of patients and staff and to reduce healthcare costs [82].

9. New advances in PET tracers

In some challenging patients, traditional radiotracers may fail in detecting the presence and the extent of disease. For this purpose, new promising tracers have been developed for the evaluation of patients with thyroid tumors [83]. The ^{18}F-tetrafluoroborate (^{18}F-TFB) is an anion analog of iodine, recently proposed as novel PET tracer for imaging the human NIS [84]. The radiolabeling with fluorine provides several advantages as compared to ^{124}I, including lower effective dose due to optimal half-life and the lack of on-site cyclotron. The biodistribution of ^{18}F-TFB have been tested in patients with thyroid cancer and it was similar to 99mTc-pertechnetate [84]. Once injected, ^{18}F-TFB shows specific accumulation in thyroid and high thyroid-to-blood concentration ratio. Samnick et al. compared ^{18}F-TFB and ^{124}I in 9 patients with newly diagnosed DTC. The PET/CT showed abnormal uptake areas in all patients at both imaging modalities, with an overall agreement at per-lesion analysis of 91% [85]. Interestingly, ^{18}F-TFB demonstrated higher accumulation in secondary lesions, resulting able to identify additional cervical lymph node metastases in 2 patients [85]. This could be explained considering that, unlike to iodine, ^{18}F-TFB do not undergo organification, resulting in a relatively lower uptake in normal thyroid tissue. More recently Dittmann et al. compared ^{18}F-TFB and ^{131}I d-WBS in 25 patients with recurrent DTC [86]. ^{18}F-TFB PET/CT imaging detected structural recurrence from DTC in significantly more patients as compared to traditional ^{131}I imaging. Moreover, 6 patients showed abnormal ^{18}F-TFB and ^{18}F-FDG uptake by cervical lymph nodes that were not observed with ^{131}I d-WBS [86]. The detection of NIS on cell surface changed the patient's management: the patients with ^{18}F-TFB uptake were reclassified as only partly dedifferentiated [86]. It should be considered that 5–15% among patients with DTC become refractory to ^{131}I treatment due to tumor's dedifferentiation [86]. Those patients show poor prognosis and alternative therapies are needed. The prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein receptor, mainly expressed in prostate carcinoma but also in the neovasculature of several tumors, including dedifferentiated thyroid carcinoma [87]. The ^{68}Ga-PSMA has been proposed as potential target for theranostics in DTC, in order to select the patients eligible for 177-Lutethium (^{177}Lu)-PSMA therapy [87,88]. Lawhn-Heath et al. evaluated 11 patients with thyroid carcinoma; of those, 7 showed dedifferentiated disease. Among 43 lesions, a lower detection rate was found for ^{68}Ga-PSMA as compared to ^{18}F-FDG [88]. Differently, de Vries et al. evaluated 5 patients with thyroid tumors refractory to found that ^{68}Ga-PSMA PET/CT appears to have added value in patients with RAI-refractory to ^{131}I treatment [87]. They found that ^{68}Ga-PSMA was able to detect lesions more accurately than ^{18}F-FDG. The agent 2-(3-{1-carboxy-5-[(6-[(18)F]fuoropyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid (DCPyl) labeled with ^{18}F is a PSMA imaging agent, recently proposed as PET agent for the evaluation of DTC [87]. An exploratory study by Santhanam et al. tested ^{18}F-DCPyl in 5 patients with DTC refractory to ^{131}I treatment and it was found to be able in detecting neoangiogenesis within the tumor [89].

Further prospective studies are needed in order to validate those promising tracers in management of patients with DTC.

10. PET-MRI: a new technologic advance

Magnetic resonance imaging (MRI) is a sensitive imaging modality, able to localize the site of potential recurrence of DTC in the neck, mediastinum, bones and liver, despite a lower accuracy in detection of lung lesions [90]. Simultaneous PET/MRI is a promising tool with a great potential to provide complementary data acquired at the same time and conditions. Moreover, MRI leads to a substantial reduction of the total radiation dose to the patient compared to PET/CT [91].

A few studies including limited numbers of patients, evaluated the role of PET/MRI in the management of DTC patients [92–95]. A complementary role of ^{18}F-FDG PET/CT and MRI was first observed by Hempel et al. in 46 patients with elevated serum Tg levels, negative neck ultrasound, and negative ^{131}I WBS and found a complementary role for the two imaging modalities [92]. Vrachimis et al. evaluated 12 patients with DTC and they observed an excellent agreement between ^{18}F-FDG PET/CT and PET/MR despite, as expected, an inferior sensitivity of MRI in detection of lung metastases [93]. These findings were confirmed by Varoquaux et al. in 32 patients with head and neck tumors [94]. More recently, Klain et al. sequentially performed ^{18}F-FDG PET/CT and ^{18}F-FDG PET/MR in 40 consecutive patients with DTC previously treated with total thyroidectomy and radioiodine ablation [95]. ^{18}F-FDG PET/MRI showed positive findings in 11/40 (27.5%) patients and ^{18}F-FDG PET/CT in 10/40 (25%) [95]. In particular, ^{18}F-FDG PET/MRI and ^{18}F-FDG PET/CT were able to detect 33 and 30 tumor foci, respectively [95]. During a short-term follow-up, among 12 patients with a detectable serum Tg and without abnormal findings at baseline PET imaging, neck recurrence occurred in only 1 patient. Moreover, in the 17 patients with an initial serum Tg level < 2 ng/mL, no patients had neck recurrence [95]. Despite the limited number of available data, PET/MRI seems to be a promising tool in the evaluation of patients with DTC. When available, PET/MRI might be performed in selected patients to reduce radiation exposure and in those for whom a MRI is indicated.

11. Conclusion

Based on this review of literature, PET/CT emerged as a useful tool in the management of patients with DTC. ^{18}F-FDG PET/CT should be performed at initial evaluation in patients with intermediate-to-high-risk DTC. During follow-up ^{18}F-FDG PET/CT is recommended in those with rising Tg and shorter Tg doubling time. Moreover, patients scheduled for empiric radioiodine therapy should undergo ^{18}F-FDG–PET/CT since a positive scan could identify patients with a low response to radioiodine. Beyond ^{18}F-FDG, other tracers including ^{124}I showed encouraging results in dosimetric approach. Moreover, the availability of new tracers, including ^{18}F-TFB and ^{68}Ga-PSMA, and new cameras such as PET/MRI, opened new opportunities in selecting patients with DTC to specific treatment or when MRI is indicated.

Human rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patients.

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