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Review

PET/CT in thyroid cancer — the importance of BRAF mutations

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Abstract

Thyroid cancer (TC) represents less than 1% of all newly diagnosed malignancies. In some selected cases, with a high clinical suspicion for disease but negative I-131 scan, positron emission tomography/computed tomography (PET) with F-18-Fluorodeoxyglucose (FDG) could be helpful in the detection of disease and the definition of its extent. FDG PET/CT, better if performed after TSH stimulation analogously to patient preparation done for radioiodine scintigraphy, could be useful mainly in the detection of metastatic and recurrent disease since the uptake and diagnostic sensitivity of FDG are increased by TSH stimulation. Recently, the role of oncogenic mutations in the tumorigenesis of TCs has become clearer. Among such mutations, $BRAF^{V600E}$ represents the most common genetic alteration. Mutated BRAF may define a more aggressive papillary carcinoma with poorer prognosis and therefore its analysis has been extensively studied as a rule-in test for thyroid carcinoma.

In this paper, we try to outline the possible role of FDG PET/CT in the management of patients with TC and positive BRAF mutations and the impact that it could have on their therapeutic algorithm, in terms of thyroidectomy and radioactive iodine (RAI) therapy.

KEY words: BRAF mutation; fluorodeoxyglucose F18; positron emission tomography; thyroid neoplasms

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Introduction

Thyroid nodules (TN) are extremely common in general population and also thanks to their subclinical detection via ultrasound imaging (US), the incidence of thyroid cancer is increasing [1]; in Europe for example, it has increased in the last decade by 69% in men and 65% in women. In fact, it has been estimated that one person out of five, despite gender, age and other epidemiological characteristics has a palpable thyroid nodule, which can be detected by US in most of cases [2]. The prevalence of TN is greater in women than in men, with multiple nodules that are more common than solitary ones [3]. In the diagnostic algorithm of TN, the differential diagnosis includes numerous clinical entities, both benign and malignant; therefore, the pathological examination has an important role in their evaluation. Thanks to fine needle aspiration cytology (FNAC) biopsy the identification of high-risk situations has significantly improved so that their management has now become more effective [4]. However, there are still cases in which patients require surgery for further confirmation of the disease, thus relying upon the pathologist to correctly characterize their nodule [4].

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Thyroid cancer (TC) instead, despite being the most common endocrine tumor, represents less than 1% of all newly diagnosed malignancies [2]. From a histological point of view, follicular cells within the thyroid gland are responsible for tumorigenesis and generate three main types of differentiated thyroid cancer (DTC): papillary (PTC), follicular (FTC) and mixed cell variants, which account for approximately 95% of all thyroid carcinoma, all of which are commonly well differentiated therefore these tumors are iodine avid and diagnosed/treated with I-123 or I-131, although they also include many subtypes that have different outcomes in terms of response to therapy and prognosis [5]. Undifferentiated and anaplastic tumors are not always iodine avid due to tumor dedifferentiation, which can occur even in case of tumor recurrence [5]. When thyroid neoplastic lesions lose the ability to synthesize hormones from iodine, they show increased glucose metabolism; therefore, patients will have high human thyroglobulin levels and negative I-131 scans. In such selected cases, with a high clinical suspicion for disease but negative I-131 scan, positron emission tomography/computed tomography (PET) with F-18-Fluorodeoxyglucose (FDG) could be helpful in the detection of disease and the definition of its extent [6]. The most recent American Thyroid Association (ATA 2015) guidelines for the management of adult patients with Thyroid Nodules and Differentiated Thyroid Cancer recommend total thyroidectomy for tumors greater than 1 cm and possible lobectomy for tumors ≤ 1 cm. In general, PTC and FTC prognoses are very good, with low risk of recurrence and distant

metastases; however, there are marked differences between the two groups [7]. In fact, PTC patients are usually younger than 50 years old, with smaller tumors and higher incidence of lymph node metastases, whereas FTC patients show more frequently distant metastatic disease and receive radioiodine [8]. In addition to these prognostic factors, more recently, the role of oncogenic mutations in the tumorigenesis of TCs has become clearer [9]. Among such mutations, $BRAF^{V600E}$ represents the most common genetic alteration in PTC, with approximately 45% prevalence. In fact, compared to PTC patients without *BRAF* mutation, positive ones tend to present at higher stage and with more frequent distant metastases [10]. Thus, mutated *BRAF* may define a more aggressive papillary carcinoma with poorer prognosis and therefore its analysis has been extensively studied as a rule-in test for thyroid carcinoma [11].

In this paper, we try to outline the possible role of FDG PET/CT in the management of patients with DTC and positive BRAF mutations and the impact that it could have on their therapeutic algorithm, in terms of thyroidectomy and radioactive iodine (RAI) therapy.

Molecular pathophysiology

Thyroid epithelial cells have a transport mechanism, the sodium/iodide symporter (NIS), which enables thyroid concentration of iodide to subsequently undergoe organification and incorporation into thyroid hormones [12]. This mechanism is influenced primarily by a pituitary hormone, the thyroid-stimulating hormone (TSH), which increases the transport of iodide [13]. B-type RAF kinase (BRAF) is a serine-threonine kinase that belongs to the rapidly accelerated fibrosarcoma (RAF) family, and represents the most potent mitogen activated protein kinase (MAPK) pathway activator [14]. The MAPK pathway is a signal transduction cascade driven by phosphorylation that leads to intracellular responses such as cell proliferation [15]. Thus, BRAF acts as a protooncogene and has an important function in cell growth, differentiation and apoptosis, with its point mutations that have been noted in various human cancers [16]. In PTC, a common mutation in the BRAF gene comprises a missense mutation that consists of a thymine-to-adenine transversion at nucleotide 1799 (T1799A) within exon 15, which leads to the substitution of a valine residue for a glutamate one at position 600 of the protein (V600E), with consequent gain of function, constitutive activation of MAPK pathway, *i.e.* $BRAF^{V600E}$ activating mutation is associated with tumorigenesis [17].

FDG PET/CT is routinely used to evaluate disease burden in a variety of neoplasms, with FDG uptake that is based on enhanced aerobic glycolysis in cancer cells, known as Warburg effect. In TC there is an inverse relationship between FDG avidity and radioiodine uptake mainly in case of metastatic lesions, a phenomenon which was originally described as 'flip-flop' [18–20].

Thyroid nuclear medicine imaging

Thyroid gland imaging is routinely done with different radiopharmaceuticals that are used in specific clinical contexts. Among them, Tc-99m-pertechnetate is widely used and owes its popularity to easy availability, low absorbed radiation dose compared to I-123 or I-131 and lower costs. The tracer is trapped by the thyroid, but it does not undergo organification, remaining in the gland for a relatively short period which allows imaging for diagnostic purposes mainly related to thyroid morphology and function, i.e hypo- or hyper-thyroidism [21].

^{99m}Tc-MIBI scintigraphy instead is more suitable than ^{99m}Tc-pertechnetate scintigraphy for TN differentiation between benign and malignant lesions, since nodules with increased uptake and late retention of ^{99m}Tc-MIBI are more suspicious for malignancy (sensitivity 82%, specificity 63%) [22].

Iodide radioisotopes (I-123, I-131) are trapped and organified inside the thyroid providing higher thyroid-to-background uptake ratios; however, in order to achieve sufficient iodine uptake into tumor cells, high levels of TSH are required (serum TSH levels > 30 mUI/L), thus implying either thyroid hormone withdrawal or intramuscular injection of rh-TSH (Thyrogen©). I-123 and I-131 could be used to interrogate the NIS symporter to assess thyroid nodule functioning in order to distinguish "hot" (autonomous) from "cold" (hypofunctioning) nodules but their main application is the detection of thyroid cancer metastases, which as the primary tumor are usually iodine avid [23].

FDG PET/CT in the management of patients with DTCs

As stated above, due to either $BRAF^{V600E}$ mutation or tumor dedifferentiation, when the ability to synthesize hormones from iodine is lost, tumors show increased glucose metabolism [24]. In such cases, patients will present with elevated human thyroglobulin levels (*i.e.* serum specific marker of TC) and with negative post-therapeutic I-131 whole body scans. Here, FDG PET/CT, better if performed after TSH stimulation analogously to patient preparation done for radioiodine scintigraphy, could be useful mainly in the detection of metastatic and recurrent disease since the uptake and diagnostic sensitivity of FDG are increased by TSH stimulation [25]. In fact, although the current ATA guidelines do not routinely recommended FDG-PET/CT for the diagnostic workup of indeterminate thyroid nodules due to limited clinical validation, several studies and meta-analysis already demonstrated the opposite [7].

More in particular in a recent paper by Piccardo et al., the Authors compared the accuracy of FDG PET/CT with Tc-99m-MIBI scintigraphy and multiparametric neck ultrasonography (US) demonstrating that the former has significantly higher performances in terms of sensitivity and NPV than the latters [26]. They also evaluated the possible role of FDG PET/CT in different diagnostic contexts in terms of impact on clinical management. It emerged that FDG PET/CT could be of use already at a preoperative stage to define the nature of indeterminate TNs thanks to its high sensitivity and NPV, especially in patients with lesions > 15mm with sensitivity ranging from 77 to 100% and NPV from 81 to 100% [26]. More specifically, we know that focal uptake of FDG within the thyroid gland, as incidental finding during evaluation of non-thyroid cancers, may be related to both benign and malignant pathology [27]. In this sense, De Koster et al. suggested that the number of futile hemithyroidectomies for benign nodules could be reduced thanks to the implementation of FDG-PET/CT by 66%, implying the cost-effectiveness of this technique in the pre-operative setting [28]. However, overall reported sensitivity and specificity of FDG-PET/CT in this specific scenario ranged from 77% to 100% and from 33% to 64%, respectively, with small nodule size being the main reason for false-negativity, since FDG-avidity in very small nodules may

be missed due to both low volume of malignant cells and partial volume effect, which underestimate the real FDG-concentration [28]. Moreover, the radiation exposure of FDG-PET/CT that patients should undergo before surgery represents another limitation to this possible application since it is largely accounted for by the FDG dosage (approximately 3 to 4 mSv for a typical activity of 185 MBq administered to an average adult) whereas the CT radiation dose greatly varies, being less than 0.5 mSv for a low-dose CT of the neck region only [29].

Pre-operative FDG PET/CT could also be used in the assessment of biological behavior of DTCs in order to predict the aggressiveness of the tumor pre-surgically [30]. In this sense, BRAF molecular test already represents the most reliable tool to identify the most aggressive subgroup of papillary thyroid carcinomas, but due to the relatively high costs and low availability, its use in clinical practice remains not applicable [31, 32]. Therefore, as some studies report, FDG PET/CT could be used to reduce costs and provide analogous information, with a more intense FDG uptake at pre-operative PET/CT that might be associated with a poorer prognosis and more aggressive histological subtype [33]. In this sense, Trimboli and colleagues used a SUV ratio of 3.0 as a cut-off to distinguish patients with higher rather than lower risk of disease progression. However, after a multivariate analysis, they concluded that only tumor size remained associated with disease persistence/progression; therefore, the evidence of this possible application of FDG PET/CT remains to be further evaluated [34].

Recent 2015 ATA Guidelines recommend neck US as first-line imaging technique to stage DTCs before thyroidectomy, whereas the use of CT or multiparametric magnetic resonance imaging (MRI) is reserved for high risk patients in which the probability to have distant metastases or mediastinal/neck nodal involvement at time of diagnosis is elevated [7]. In this context PET/CT does not have a role yet, even if some studies have been already published in this sense [35]. Specifically, Agate et al. compared the performance of FDG PET/CT, CT alone and US in the diagnosis of cervical lymph node metastasis in patients with PTC and concluded that US had the best diagnostic accuracy among the three (64.9%, 61.9% and 82% respectively) thus confirming ATA guidelines preference of neck US as best methodology for preoperative assessment of nodal status. However, FDG PET/CT might still be useful in aggressive DTC subtypes such as tall-cell, solid/trabecular, insular and diffuse sclerosing or in patients with suspected distant metastases for staging purposes and to predict the preoperatively the risk of recurrence [37]. A Japanese group retrospectively analyzed in a recent paper the benefit of FDG PET/CT at initial diagnosis in 114 patients with DTC for predicting the high-risk for recurrence by assessing seven parameters including among the others SUVmax, SUVmean and MTV (metabolic tumor volume expressed in cm^3). They identified 88 patients with FDG-avid tumor and 26 patients with FDG-non-avid tumor and demonstrated that the former group resulted to have significantly larger lesions (21 vs 13 mm), more advanced ATA-risk classification, but at the same time, only 10 out of 88 patients were classified as high-risk and the parameters themselves revealed a wide range of sensitivity, specificity and accuracy. So, they divided patients according MTV, if greater than 10.0 cm^3 or not, and introduced a scoring system that takes in consideration each of the seven diagnostic parameters assigning a score of 0 if negative for high-risk or 1 if positive using each threshold criterion. Summing these scores to differentiate between high-risk and non-high-risk patients they demonstrated that a summed score ≥ 5 in 44 patients with an MTV > 10.0 cm^3 was associated with 100% sensitivity, 91.7% specificity and 93.2% accuracy (AUC: 0.98) in predicting the high-risk for recurrence. Therefore, they concluded that FDG-non-avid primary DTCs are less inclined to post-operative recurrence whereas in FDG-avid primary DTCs with MTV > 10.0 cm^3, the combination of SUV-related, volumetric and texture parameters could significantly increase the ability to identify high-risk patients, thus confirming the prognostic value of FDG PET in advanced thyroid cancer [38].

Apart from the aforementioned scenarios in which FDG PET/CT might have or not a role in clinical practice, what remains clear as main indication for this technique is the post-operative stage, during follow-up, mainly in case of patients with aggressive histologies so to have a starting reference point or in chase of high or increasing Tg levels (Tg $>$ 10 ng/mL or doubling time of less than 1 year) with negative post-therapeutic I-131 whole-body scan [39]. A meta-analysis performed by Wan et al. [40] evaluated 17 studies with 571 patients who had recurrent or metastatic DTC and I-131 negative whole-body scan and determined that FDG-PET/CT a pooled sensitivity and specificity of 93.5% and 83.9%, respectively, with an overall diagnostic accuracy of 90.9%. Moreover, studies have shown that the positivity rate of FDG-PET/CT increases as Tg level rises, though there is lack of consensus on what the precise threshold level of Tg should be since positive findings have also been reported in 10–20% of DTC patients with Tg levels $<$ 10 ng/mL [41]. In this sense, becomes crucial the comparison of post-therapeutic I-131 whole-body scan with FDG-PET/CT because the latter could be helpful in the reduction of unnecessary second administration of high I-131 activities, which means direct implication on patients' clinical management [42]. In fact, the current guideline to define a radioactive iodine-refractory (RAIR) DTC is based on the clinical negative response to a cumulative I-131 dose of 600 mCi or more, which means at least 3 RAI therapies over a two-year period, taking in consideration a 6-month treatment interval [43]. This may lead to a therapeutic delay, i.e. to not receive an appropriate treatment at the earliest possibility [44]. FDG-PET/CT could be useful in this sense as an early response predictor, thus allowing the early implementation of alternate therapies such as Tyrosine Kinase Inhibitors (TKIs). Kang et al. recently studied this problem by evaluating 54 patients with metastatic DTC who underwent both RAI therapy scan and FDG PET/CT during the same period in order to predict the response rate of RAI itself. Of 54 patients, only 22 had a therapeutic response to RAI with a 43% rate of concordance between the two techniques and with significant negative correlation between FDG avidity of metastatic lesions and response rate. Therefore, they concluded that the patient group with FDG-avid metastasis showed poor response to RAI therapy regardless of the degree of RAI uptake at I-131 whole-body scan [45].

$BRAF^{V600E}$ and FDG PET/CT

Recent clinical studies demonstrated the relationship between $BRAF^{V600E}$ mutation and FDG uptake, showing that $BRAF^{V600E}$ mutation is associated with downregulation of the NIS symporter, loss of RAI avidity and increased glucose transporter (GLUT-1) expression in both primary and metastatic PTCs, thus determining poorer

prognosis, including events such as increased incidence of recurrence, extrathyroidal invasion and distant metastases [46]. More in particular, in $BRAF^{V600E}$-positive PTCs, several studies demonstrated that at mitochondrial level there is a reduction of O_2 consumption and increased glucose uptake, thus favoring an anaerobic glycolytic shift in cancer cells by targeting at transcriptional level both hypoxia inducible factor (HIF)-1 that acts on GLUT1, GLUT3 and hexokinase II, which play an important role in trapping FDG inside cancer cells and the M2 isoform of pyruvate kinase (the rate-limiting step of glycolysis) which showed significantly higher levels compared to BRAF wild-type PTCs [47]. Therefore, the association between $BRAF^{V600E}$ mutation and FDG uptake could be explained with the induction of MAPK transduction pathway and the subsequent activation of HIF-1 resulting in increased glycolysis and loss of RAI avidity [48]. In this sense, as a recent study reported, $BRAF^{V600E}$ mutations were present in 62% of RAIR recurrent/metastatic TCs; analogously, all patients with RAIR PTCs and FDG-PET/CT positive scan were $BRAF^{V600E}$-positive, compared to 45% of positive PET/CT scans in PTCs in general [49]. In a recent meta-analysis, Santhanam and colleagues not only show the significant correlation in DTC patients between $BRAF^{V600E}$-positiveness and the higher odds of having FDG-PET/CT avid lesions (OR = 2.12) but they also demonstrated that these patients tend to have relatively higher mean SUV values (although SUV values may vary greatly across institutions and the measurement itself depends on multiple factors), thus concluding that $BRAF^{V600E}$ mutation, when present, should prompt the treating clinician to consider FDG-PET/CT as a useful diagnostic test to localize residual disease [46]. Nagarajah et al. [50] specifically evaluated the differences in terms of glucose metabolism of the $BRAF^{V600E}$ versus $BRAF^{WT}$ in patients with DTC and poorly differentiated TCs. While in the first cohort median SUVmax was significantly higher in the mutated group versus wild-type (median SUVmax 6.3 versus 4.7), in the latter FDG uptake was not significantly different between the two groups.

A very interesting study design instead, was carried out by Choi et al. that retrospectively reviewed 106 patients with PTC who underwent FDG PET/CT scan before undergoing total thyroidectomy, scans that were subsequently compared with clinicopathological data collected from surgical specimens, such as primary tumor size, capsular invasion, metastases and $BRAF^{V600E}$ mutation among the others.

Reported SUVmax was significantly higher in primary tumors of size greater than 1 cm (SUVmax 6.6 vs 3.4), in PTCs with extra-thyroid extension of the tumor (SUVmax 5.8 vs 3.7) and in PTCs with $BRAF^{V600E}$ mutation (SUVmax 5.7 vs 3.0), whereas at a multivariate analysis only tumor size and $BRAF^{V600E}$ were significantly associated with the SUVmax of the primary tumor, as extra-thyroid extension and thyroid capsular invasion had no statistically significant association. Therefore, they concluded that FDG PET/CT may play an important role and yield additional information on tumor aggressiveness when associated to molecular biomarkers such as $BRAF^{V600E}$ mutation [51].

Conclusions

Differentiated thyroid cancers are the most common histological types of thyroid cancer which are characterized by a favorable prognosis thanks to surgical removal of the tumor and radioiodine ablation therapy, with an overall 5-year survival rate higher than 90%. However, in some patients we can have a more aggressive behavior that often becomes the cause of mortality due to tumor recurrence and RAI refractoriness. Neck US still represents the first-line imaging technique to stage DTCs before thyroidectomy and is the best methodology for preoperative assessment of nodal status; however, new possible scenarios of application seem to be possible when this PET/CT is associated with the presence of molecular biomarkers, such as $BRAF^{V600E}$ mutation. FDG PET/CT has already been used in clinical practice in cases of elevated serum thyroglobulin and negative I-131 whole-body scintigraphy, mainly to locate recurrent disease and for its prognostic role. Unfortunately, despite these promising reports, the relationship between F-18 FDG uptake and the $BRAF^{V600E}$ mutation for a possible pre-operative application is still poorly recognized as it will need further validation in consideration also of the genetic heterogeneity that has been reported (between different primary tumors and regional lymph node metastases), which requires that all lesions within the patient harbor the same genetic defect.

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