

The role of early 18F-FDG PET/CT in therapeutic management and ongoing risk stratification of high/intermediate-risk thyroid carcinoma

E. M. Triviño Ibáñez¹ · M. A. Muros¹ · E. Torres Vela² · J. M. Llamas Elvira¹

Received: 21 April 2015 / Accepted: 24 July 2015 / Published online: 30 July 2015
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Abstract Little is known about the role in ongoing risk stratification of fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) performed early after radioactive iodine (RAI) ablation in differentiated thyroid carcinoma (DTC). The aim of the study is to investigate whether 18F-FDG PET/CT performed early after RAI ablation is useful to detect disease and to influence therapy and ongoing risk stratification. Patients with high/intermediate risk of recurrent DTC were included. 18F-FDG PET/CT scan was performed within 6 months after RAI ablation. We confirmed results with other imaging techniques, pathology reports, or follow-up. We classified the patient response as excellent, acceptable, or incomplete. Modified Hicks criteria were used to evaluate clinical impact. We included 81 patients with high/intermediate risk of recurrent DTC. Forty-one (50.6 %) had positive uptake in 18F-FDG PET/CT, with negative ¹³¹I whole-body scan (¹³¹I WBS). Sensitivity, specificity, and diagnostic accuracy of 18F-FDG PET/CT were 92.5, 90.2, and 91.4 %, respectively. 18F-FDG PET/CT results had an impact on therapy in 38.3 % of patients. One year after initial therapy, 45.7 % showed excellent response, 8.6 % acceptable response, and 45.7 % incomplete response. A statistically significant relationship was found between negative 18F-FDG PET/CT and excellent response (80 vs. 12.2 %, $p < 0.001$; OR 52.8). 18F-FDG PET/CT scan performed early in surveillance of patients

with high/intermediate-risk thyroid carcinoma provides important additional information not available with conventional follow-up methods and had a high impact on therapy. A negative 18F-FDG PET/CT predicts an excellent response to therapy in the new ongoing risk stratification.

Keywords High/intermediate-risk thyroid carcinoma · Differentiated thyroid carcinoma · 18F-FDG PET/CT · Therapeutic management

Introduction

The incidence of thyroid cancer has increased over recent decades, and it has become the most prevalent endocrine neoplasm. Despite the high overall survival rate, the recurrence rate for thyroid cancer is not insignificant, ranging from 14 to 23 % [1].

Patient risk factors for recurrence and death include age at diagnosis, gender, and personal or family history. Tumor characteristics have also been related to prognosis, including size (>4 cm) [2–5], multifocality [6], extrathyroid invasion [2, 5], and presence of lymph node [5] or distant [7] metastases. In this context, high/intermediate-risk [8, 9] patients are defined as those who have any of the following features: large tumors (i.e., >4 cm); tumor extension beyond the thyroid capsule; lymph node metastases, and distant metastases. Complete surgical resection proved to be an independent prognostic indicator of survival in multivariate analyses [5].

Early detection of recurrence improves outcomes and survival [6, 10]. In differentiated thyroid carcinoma (DTC) patients with negative ¹³¹I whole-body scan (¹³¹I WBS) and detectable thyroglobulin (Tg) levels during follow-up,

✉ E. M. Triviño Ibáñez
eva_gor@hotmail.com

¹ Department of Nuclear Medicine, Virgen de las Nieves University Hospital, Granada, Spain

² Department of Endocrinology and Metabolism, San Cecilio University Hospital, Granada, Spain

a fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) scan plays an important role in localizing disease [11, 12]. In patients with high-risk thyroid cancer, the role of the 18 F-FDG PET/CT scan has expanded to initial staging, prognostic evaluation, and assessment of treatment response [8].

Little is known about the contribution of 18F-FDG PET/CT to the detection of persistent/recurrent disease or metastases early after radioactive iodine (RAI) ablation. There has been no evaluation of its clinical benefit [1, 13, 14] or role in the new ongoing risk stratification of DTC recently published in different guidelines [15].

The aim of this study was to investigate whether 18F-FDG PET/CT performed 3–6 months after RAI ablation could be useful in early detection of disease in high/intermediate-risk DTC patients and therefore influence therapy and ongoing risk stratification.

Materials and methods

Patients

A prospective study was carried out (June 2007–December 2013) in 890 patients from our reference area treated for DTC with total thyroidectomy and lymphadenectomy, when indicated, and referred to the Nuclear Medicine Department for RAI ablation therapy and ^{131}I WBS. 18F-FDG PET/CT study was performed in 81 selected patients with high/intermediate-risk according to the guidelines of the American Thyroid Association [8] in the first 6 months after RAI ablation. Intermediate-risk patients have any of the following: microscopic invasion of tumor into the perithyroidal soft tissues at initial surgery; cervical lymph node metastases or ^{131}I uptake outside the thyroid bed on the ^{131}I WBS done after thyroid remnant ablation; or tumor with aggressive histology or vascular invasion. High-risk patients have macroscopic tumor invasion, incomplete tumor resection, distant metastases, or thyroglobulinemia out of proportion to observations in the post-treatment scan. We grouped the histological variants considered in the literature to have the worst prognosis (Hürthle cell, papillary follicular variant, tall cell, diffuse sclerosing and solid variants) and compared them with classic papillary carcinoma.

Patients with a history of another malignancy, those with inflammatory or infectious disease, and those aged less than 18 years were excluded. All patients signed written informed consent.

The study protocol was approved by our local Ethics Committee.

Methods

DTC initial therapy: surgery and RAI ablation

Patients were treated with total or near-total thyroidectomy. Central neck compartment lymphadenectomy was performed in papillary thyroid carcinoma (PTC) and in follicular thyroid carcinoma (FTC) with adenopathies clinically palpable or detected by ultrasound (US). Patients were then referred to the Endocrinology Department for hormone replacement therapy and follow-up.

The RAI ablation dose ranged from 3.7 to 7.4 GBq and the time between surgery and RAI ablation ranged from 1 to 6 months (median 3 months). In all patients, replacement of L-thyroxine (T4) was discontinued for 4 weeks before ^{131}I treatment, and patients received L-triiodothyronine (T3) for the first 2 weeks and a low-iodine diet. At the time of RAI ablation, all patients had serum TSH levels >30 IU/mL.

^{131}I WBS was obtained 3–4 days after therapy, and additional spot images or single-photon emission computerized tomography (SPECT/CT) scans were acquired when results were positive. SPECT/CT images were recorded using a SYMBIA T2 gamma camera (Siemens, Inc., Knoxville, TN) equipped with high-energy general-purpose collimators and an integrated 16-slice helical CT scanner (120 kV, 3 mm slice). CT data were used for attenuation correction and anatomic information. SPECT/CT data were obtained on a dual-head camera in step-and-shoot mode using a noncircular orbit, 30–60 s per stop.

Serum TSH, Tg, and Tg-antibody determinations were performed at the time of the ^{131}I WBS. TSH levels were determined by an immunoradiometric procedure (CIS Bio, Cedex, France) that detects values from 0.03 to >55 IU/mL. Tg levels were measured by high-sensitivity immunoassay (Biocode, Liege, Belgium) with a minimum detection level of 1 ng/mL. The assay for autoantibodies was based on a solid-phase technique using coated tubes (Biocode, Belgium) with a sensitivity of 3 UI/L.

18F-FDG PET/CT

All patients underwent 18F-FDG PET/CT scan in the first 6 months after RAI ablation under euthyroidism conditions using an integrated PET/CT system (Siemens Biograph Sensation 16, Erlangen, Germany). The procedure protocol followed guidelines for patient preparation (at least 6 h fasting, resting, adequate hydration), administration of the 18F-FDG dose (previous blood glucose level test, radiopharmaceutical injection through peripheral vein, 60 min rest lying–sitting in a darkened room for 60 min after FDG injection) and imaging acquisition in supine position.

Patients were intravenously injected with 18F-FDG (3.7 MBq/kg) and administered an oral dose of 5 mg diazepam. Blood glucose levels were always <150 mg/dl. The acquisition protocol considered full-length examination of each patient from the base of the skull to the groin in 3D mode. The PET/CT study protocol began with the acquisition of a topogram (50 mA, 120 kV) and a helical CT examination of the specified area (170 mA, 120 kV), followed by positron emission imaging (3 min/bed). The information from the CT scan was used both for the anatomical localization of the lesions identified in the PET study and for the attenuation correction of PET imaging.

Two experienced nuclear medicine physicians reviewed the studies. The 18F-FDG PET/CT scans were considered positive if lesions with focally asymmetric increased tracer uptake were detected. Results were confirmed by pathology reports in surgically treated patients and other diagnostic imaging techniques (CT, US, or MRI) and/or outcome at 12 months after RAI ablation. 18F-FDG PET/CT findings were classified as true positive if disease was confirmed by histology or subsequent follow-up. 18F-FDG PET/CT findings were classified as false positive if lesions were found to be benign or not confirmed. Findings were classified as true negative if the patient showed no evidence of disease in subsequent follow-up or imaging techniques. Findings were classified as false negative if they were inappropriately reported as benign or equivocal and found to be malignant.

Therapeutic impact and ongoing risk stratification

The therapeutic impact of 18F-FDG PET/CT findings was determined according to the modified criteria of Hicks et al. [16] as follows: a change from one treatment modality to another (e.g., surgery to RAI dose therapy) or a change in treatment intent (curative to palliative) because of the 18F-FDG PET/CT was considered high impact. A change in delivery of the same modality (e.g., 18F-FDG PET/CT avoided the need for other diagnostic methods to locate the disease) represented medium impact. A low impact indicated no change in proposed management. If the 18F-FDG PET/CT result was ignored by physician, the impact was recorded as none.

The impact of 18F-FDG PET/CT findings on ongoing risk stratification was determined according to the criteria of Tuttle et al. [15] at 12 month assessment (Table 1).

Study variables

Data were gathered on patient age and gender, tumor characteristics (size, histological type, thyroid capsule and vascular invasion, lymph node involvement), and treatments (surgery, lymphadenectomy, RAI dose). ¹³¹I WBS

results, analytical determinations (Tg, anti-Tg antibodies, and TSH), and TNM stage (7th edition of AJCC) were also analyzed [17].

All statistical analyses were performed with SPSS 15.0 software (IBM, Chicago IL). Means with standard deviation were calculated for quantitative variables and relative frequencies for qualitative variables. Pearson's χ^2 test and Fisher's exact test were used for bivariate analyses. The Student's *t* test or Mann–Whitney *U* test was used for non-parametric quantitative variables, considering $p < 0.05$ to be statistically significant. The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were calculated to evaluate the diagnostic efficacy of PET/CT scanning.

Results

18F-FDG PET/CT scan and ¹³¹I WBS results

The study included 81 patients with DTC with high/intermediate risk of recurrence according to ATA criteria [8], in whom an 18F-FDG PET/CT scan was performed 3–6 months after RAI ablation therapy. Fifty-six patients (69.1 %) were female and the mean age at diagnosis was 50.1 ± 17.5 years. Characteristics of the enrolled 81 patients are summarized in Table 2.

The 18F-FDG PET/CT detected neoplastic involvement (cervical and/or distant) in 41 of the 81 patients (50.6 %), who were considered positive. In the 40 remaining patients (49.4 %), no neoplastic involvement was detected and they were considered negative. No statistically significant differences were found in gender or age between positive and negative patients (Table 3).

Among the 41 positive patients, 16 (39 %) had cervical lymph node involvement, 10 (24.4 %) had distant metastases, and 15 (36.6 %) had cervical lymph node involvement plus distant metastases. Overall, 25 of the 81 patients (30.9 %) had distant metastases detected by the 18F-FDG PET/CT scan.

The ¹³¹I post-ablation scan was positive in 9/81 patients (three in cervical lymph node and six had cervical lymph node plus distant metastases) and negative in 72/81 patients. The additional SPECT/CT images were always concordant with planar images.

Statistically significant differences were found between the patients with positive and negative 18F-FDG PET/CT in the presence of vascular invasion (14/30 vs. 5/25; $p = 0.038$), lymph node involvement (28/41 vs. 15/40; $p = 0.005$), and distant metastases (13/41 vs. 1/40; $p < 0.001$). We grouped the histological variants considered in the literature to have the worst prognosis (Hürthle cell, papillary follicular variant, tall cell, diffuse sclerosing

Table 1 Ongoing risk stratification of DTC

	Excellent response	Acceptable response	Incomplete response
Suppressed Tg	Undetectable	Detectable but <1 ng/mL	≥1 ng/mL
Stimulated Tg	Undetectable	<10 ng/mL	≥10 ng/mL
Anti-Tg antibodies	Absent	Absent or declining	Stable or rising
Neck ultrasonography	No evidence of disease	Non-specific changes in thyroid bed	Evidence of structurally significant recurrent or persistent disease in thyroid bed or cervical lymph nodes (>1 cm)
Diagnostic ¹³¹ I-WBS	No evidence for RAI-avid disease	No evidence for RAI-avid disease	Persistent or recurrent RAI-avid disease present
Cross sectional imagin (CT, MRI)	No evidence of disease	Non-specific changes	Structural disease present

Response to therapy

Table adapted from [15]

Tg thyroglobulin, WBS whole-body scan, CT computed tomography, MRI magnetic resonance imaging

Table 2 Characteristics of the study population

Characteristics	<i>n</i> or median ± SD	%, range
Age (years)	50.1 ± 17.5	20–85
Gender (male/female)	25/56	30.9 %/ 69.1 %
Histology		
Papillary	39	48.1
Follicular	8	7.4
Hürthle cell	9	11.1
Papillary, follicular variant	10	12.3
Tall cells	8	9.9
Diffuse-sclerosing variant	2	2.5
Solid variant	5	6.2
Tumor size (cm)	3.4 ± 1.8	0.8–9.5
TSH ablation (IU/mL)	80.8 ± 51.9	32.6–358
Tg ablation (ng/mL)	5.32 ± 4935.44	0.01–37635
RAI ablation dose (Mbq)	4247.6 ± 825.1	1110–6660
TNM (7th Ed. AJCC)		
T1-2 N0 M0	17	21.0
T1-2 N1 M0	13	16.0
T3-4 N0 M0	22	27.2
T3-4 N1 M0	15	18.5
TX NX M1	14	17.3
Surgery		
Near total or total thyroidectomy	37	45.7
TT + CCL	28	34.6
TT + CCL + LCL	16	19.7
Risk group		
Intermediate	33	40.7
High	48	59.3

AJCC American Joint Committee on Cancer, TT total thyroidectomy, CCL central neck compartment lymphadenectomy, LCL lateral neck compartment lymphadenectomy

and solid variants) and compared them with classic papillary carcinoma, finding that 18F-FDG PET/CT was positive in 16 of the 39 (41 %) patients with classic papillary carcinoma compared with 25 of the 42 (59.5 %) patients in the poor-prognosis variant group; but this difference was not statistically significant, ($p = 0.096$). All patients with follicular carcinoma and diffuse sclerosing-variant papillary carcinoma had a positive 18F-FDG PET/CT scan. No statistically significant differences were found as a function of the type of surgery, but patients with near-total thyroidectomy (2/2) had positive 18F-FDG PET/CT study and developed recurrence.

The ¹³¹I post-ablation scan was positive in 8 of the 41 patients with positive 18F-FDG PET/CT and in 1 of the 40 with negative 18F-FDG PET/CT, a statistically significant difference ($p = 0.015$, OR 9.45). No statistically significant differences were found in the RAI ablation dose between patients with positive and negative 18F-FDG PET/CT (4391.9 ± 506.9 vs. 4055.2 ± 1132.2 MBq, $p = 0.089$). The median Tg level at the time of the ablation therapy was 37.91 ng/mL in the positive 18F-FDG PET/CT group and 12.3 ng/mL in the negative 18F-FDG PET/CT group, a statistically significant difference ($p < 0.001$). Tg at the time of RAI ablation was negative (<1 ng/mL) in 17/81 patients and positive (≥1 ng/mL) in 64/81. 18F-FDG PET/CT was positive in 5/17 (29.4 %) patients with negative Tg compared to 36/64 (56.3 %) patients with positive Tg ($p = 0.049$, OR 3.87).

Parameters for diagnostic validity

The sensitivity and specificity of 18F-FDG PET/CT were 92.5 % (95 % CI, 80.1–97.4 %) and 90.2 % (95 % CI 77.5–96.1 %), respectively, calculated for the total of 81 patients with a diagnostic accuracy of 91.4 % (95 % CI of

Table 3 Factors analyzed related to PET/CT results and statistical significance (SS)

Variable	PET/CT positive <i>n</i>	PET/CT negative <i>n</i>	<i>p</i>
Age (years)	51.54 ± 18.21	48.78 ± 16.76	0.449
Gender (male/female)	11/30	14/26	0.426
Histology			
Presence of lymph node involvement	28/41	15/40	0.005
Vascular invasion	14/30	5/25	0.038
Distant metastases	13/41	1/40	<0.001
Tg stimulated (ng/mL)	37.91	12,3	<0.001
¹³¹ I WBS positive	8/41	1/40	0.015

¹³¹I WBS positive whole-body scan with ¹³¹I uptake outside thyroid bed

Table 4 Se, Sp, PPV, NPV and DA for the PET/CT study

18F-FDG PET/CT	Disease	No disease	Total
Positive	37 (TP)	4 (FP)	41
Negative	3 (FN)	37 (TN)	40
Total	40	41	81

Se: 92.5 %, Sp: 90.2 %, PPV: 90.2 %, NPV: 92.5 % and DA: 91.4 %.

Se sensitivity, Sp specificity, PPV positive predictive value, NPV negative predictive value, DA diagnostic accuracy. TP true positive, FP false positive, FN false negative, TN true negative

83.2–95.8 %). The positive and negative predictive values were 90.2 % (95 % CI, 77.5–96.1 %) and 92.5 % (95 % CI 80.1–97.4 %), respectively (Table 4).

The 18F-FDG PET/CT incorrectly classified seven patients. In four of these patients, it showed positive uptake that was not subsequently confirmed (false positives) and in the other three, the 18F-FDG PET/CT was negative but the patients had neoplastic involvement (false negatives).

In three of the four false positives, the presence of a cervical hypermetabolic focus was reported in the central compartment, suggestive of neoplasm. Two of these underwent surgery with negative results, while the other case was not confirmed with radiological imaging techniques (US, CT or MRI) and serum Tg remained undetectable (considered a false positive). In the fourth case, the 18F-FDG PET/CT study identified a spiculated pulmonary nodule with slight uptake, but was considered a false positive because it did not change in follow-up and Tg remained undetectable.

In two of the three false-negative cases, patients had cervical lymphadenopathy detected by US (size 1 and 1.5 cm, respectively) with ¹³¹I uptake in one of them. Neoplastic involvement was confirmed after surgery. In the remaining case, the ¹³¹I post-ablation scan showed diffuse pulmonary uptake compatible with lung metastases, which were negative on the 18F-FDG PET/CT scan but visible in the CT image.

Patient-based analysis comparing results of 18F-FDG PET/CT with ¹³¹I WBS (planar and SPECT) and

Table 5 Comparison of three imaging modalities: PET/CT, ¹³¹I-WBS-SPECT, and CT

Parameter	PET/CT (%)	¹³¹ I-WBS (%)	US, TC or MRI (%)
Sensitivity	92.5	22.5	77.1
Specificity	90.2	100	97.6
Accuracy	91.4	61.7	88.2

radiological techniques (CT, US, or MRI) highlights the improved diagnostic efficacy of 18F-FDG PET/CT (*p* < 0.001) (Table 5).

Modification of TNM and therapeutic impact

The results of the 18F-FDG PET/CT study led to a change in the initial staging based on the TNM classification in 21 of the 81 patients (25.9 %). Out of these 21 patients, 8 considered N0 were reclassified as N1a, 4 N1a patients were upgraded to N1b, and 9 patients without previous evidence of distant metastatic disease (M0) were classified as M1 because the 18F-FDG PET/CT study detected metastases. Out of these nine patients, two had bone metastases, six had lung metastases, and one had bone and lung metastases.

According to modified Hicks criteria [16], the 18F-FDG PET/CT findings had a high impact in 31 of the 81 patients (38.3 %), establishing the need for surgery in 20, RAI empiric therapy (3700–7400 MBq) in 6, thermal ablation

in 1, radiofrequency ablation in 1, and treatment with tyrosine kinase-inhibiting drugs in three cases.

In 5 of the 81 patients, the impact was moderate, with 18F-FDG PET/CT results leading to changes in the follow-up, such as the performing of other imaging techniques. In 44 of the 81 patients, the 18F-FDG PET/CT findings had a low impact, while these had no impact at all in only 1 of the 81 cases.

Dynamic risk stratification

Using Tuttle criteria [15], we classified our patient's responses to ablation therapy as excellent, acceptable, or incomplete at 12 months from the RAI ablation. We found statistically significant differences in response between the patients with positive and negative 18F-FDG PET/CT, such that the patients with negative 18F-FDG PET/CT had a higher excellent response rate (32/40) than those with positive 18F-FDG PET/CT (5/41) ($p < 0.001$) (Table 6). Of the 8/40 non-excellent responders patients with negative 18F-FDG PET/CT, four had an acceptable response (detectable suppressed Tg < 1 ng/ml but stimulated Tg < 10 ng/ml) and the remaining four patients had incomplete response (three patients with structural disease in radiological imaging techniques and stimulated Tg of 25 ng/ml in the other).

Discussion

Our results established that 18F-FDG PET/CT scan performed early in the surveillance of patients with high/intermediate-risk thyroid carcinoma provides important additional information that is not accessible with conventional follow-up methods. In our study, 41/81 patients (50.6 %) showed positive uptake in 18F-FDG PET/CT, which led to a change in the initial TNM staging in 21 of the 81 patients (25.9 %) and had a high impact in 31 of the 81 patients (38.3 %). Several recent studies analyzed whether an early 18F-FDG PET/CT in the follow-up of patients with high/intermediate-risk thyroid carcinoma could provide additional information over conventional imaging methods, with controversial results. Some studies concluded that 18F-FDG PET/CT could be useful, although it has a reduced role in this setting. A multicenter study [13] retrospectively analyzed 286 patients with high/

intermediate-risk thyroid carcinoma, and 18F-FDG PET/CT detected additional lesions in 39/286 patients (14 %) compared to the post-therapy ^{131}I scan and changed the therapy in 30 patients (10 %). Another study concluded that 18F-FDG PET/CT does not have a complementary role alongside conventional follow-up methods [1]. On the other hand, some studies found that 18F-FDG PET can play an important role in high/intermediate-risk thyroid carcinoma. Rosenbaum-Krumme et al. [18] performed 18F-FDG PET/CT close to the first ^{131}I treatment in 90 high-risk DTC patients, finding that 29 % had positive 18F-FDG PET/CT and changed the treatment strategy in 21 % of them. Iwano et al. [19] studied 54 DTC patients and performed 18F-FDG PET/CT with TSH stimulation 3–4 days before RAI ablation, reporting a positive 18F-FDG PET/CT in 33 % of the patients.

We studied 81 patients with high/intermediate risk of recurrence. The sensitivity, specificity, and diagnostic accuracy were 92.5, 90.2, and 91.4 %, respectively. In our study, 41/81 patients (50.6 %) showed positive uptake in 18F-FDG PET/CT, with negative ^{131}I WBS in 33 of them. This elevated proportion of positive 18F-FDG PET/CT, significantly higher than in the above studies, may be related to the widest possible high/intermediate-risk criteria used. Our study according to the guidelines of the American Thyroid Association [8], included a high proportion of T3–T4 patients (37/81, 45.7 %) and metastatic patients (14/81, 17.3 %) but also included aggressive histological subtypes (34/81, 41.9 %) and also other ATA criteria (macroscopic tumor invasion, incomplete tumor resection, thyroglobulinemia out of proportion to observations in the ^{131}I post-treatment scan). We recommend that 18F-FDG PET/CT should be used early in the initial diagnostic assessment of high/intermediate-risk thyroid carcinoma and suggest amplifying the indications according to ATA criteria. Several studies [20–23] gathered available experience with 18F-FDG PET/CT in aggressive histological subtypes of DTC (e.g., tall cell, diffuse sclerosing, solid/trabecular and insular variants) and proposed that 18F-FDG PET or 18F-FDG PET/CT appear to be very useful for the staging and restaging of these tumors. In our study, all patients with follicular carcinoma and diffuse sclerosing-variant papillary carcinoma had a positive 18F-FDG PET/CT scan. According to the present results, vascular invasion and metastatic and lymphatic spread are all correlated with positive results on 18F-FDG PET/CT.

Table 6 Treatment response according to Tuttle criteria (1 year after RAI ablation)

Treatment response	PET/CT negative <i>n</i> (%)	PET/CT positive <i>n</i> (%)	<i>p</i>
Excellent	32 (80 %)	5 (12.2 %)	<0.001
Acceptable	4 (10 %)	3 (7.3 %)	<0.001
Incomplete	4 (10 %)	33 (80.5 %)	<0.001

Capsule invasion [24] or vascular invasion [25] are negative prognostic factors in DTC and positively correlate with positive 18F-FDG-PET results. Other authors [26] concluded that PET positivity correlates with extrathyroidal spread and elevated Tg in recurrent/metastatic DTC.

We evaluated whether 18F-FDG PET/CT performed early in surveillance impacts on therapeutic management in DTC and found that the findings had a high impact in 31 of the 81 patients (38.3 %). Rosenbaum-Krumme et al. [18] found that 29 % of high-risk DTC patients had positive PET/CT findings and prompted changes in the treatment strategy of 21 %. Lee et al. [13] detected additional recurrent or metastatic lesions in 39/258 (14 %) patients and changed the therapy for 10–17 % of patients. In our study, the 18-FDG PET/CT results led to a change in the initial staging based on the TNM classification in 21 of the 81 patients (25.9 %). According to the modified Hicks criteria [16], the 18-FDG PET/CT findings had a high impact in 31 of the 81 patients (38.3 %), establishing the need for surgery in 20, additional radioiodine doses in 6, thermal ablation in 1, radiofrequency ablation in 1, and treatment with tyrosine kinase-inhibiting drugs in three cases. This high percentage compared with other studies may be a result of the different inclusion criteria used in the patient selection, which were based on TNM and ATA 2009 guideline recommendations [8].

Tuttle et al. published an ongoing risk stratification of DTC patients at 1 year after initial therapy [15]. They proposed a risk-adapted framework of DTC patients to guide the practicing clinician in the selection and timing of appropriate follow-up tests for individual patients. In our study, despite their poor initial prognosis, 45.7 % of the patients showed an excellent response 1 year after initial therapy, 8.6 % an acceptable response, and 45.7 % an incomplete response in ongoing risk stratification according to Tuttle criteria [15]. There were statistically significant relationships between an early negative 18F-FDG PET/CT scan and an excellent response (80 vs. 12.2 %, $p < 0.001$; OR: 52.8) in ongoing risk stratification. Robbins et al. established that the primary follow-up test predicting disease-specific death from thyroid cancer is 18F-FDG PET [27]. 18F-FDG-PET identifies undifferentiated, metabolically active, and non-RAI-avid thyroid cancers which seldom respond to RAI therapy [28]. Consequently, positive 18F-FDG PET scanning could be used as predictor of non-response to therapy [26, 29]. We provide the first report of a statistically significant relationship between a negative 18F-FDG PET/CT and an excellent response to therapy in the new ongoing risk stratification. In the same research area, a study protocol was recently published on 18F-FDG PET/CT plus iodine-124 (^{124}I) PET/CT and their potential to stratify DTC [30].

Numerous studies have described the importance of Tg and TSH values for optimal accuracy of 18F-FDG-PET/CT [31–36]. Our results agree with previous studies. In the present study, the median plasma Tg level was 37.9 ng/mL in the PET-positive group versus 12.3 ng/mL in the PET-negative group, a statistically significant difference ($p < 0.001$). Unfortunately, all patients underwent 18F-FDG-PET/CT scan in the first 6 months after RAI ablation under euthyroidism conditions. The performance of 18F-FDG-PET/CT scan in patients with high/intermediate-risk thyroid carcinoma during TSH stimulation may offer an improved capability to detect metastatic DTC and to change treatment strategy [36].

Conclusions

Our study confirmed that an 18F-FDG-PET/CT scan performed early in the follow-up of patients with high/intermediate-risk thyroid carcinoma provides important additional information not available with conventional follow-up methods and has a high impact on therapy. A negative 18F-FDG PET/CT predicts an excellent response to therapy in the new ongoing risk stratification. More studies are needed to confirm the usefulness of 18F-FDG PET/CT and the need for an 18F-PET/CT scan early in the follow-up.

Compliance with ethical standards

Disclosure The authors have nothing to disclose.

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