Risk factors and stratification for recurrence of patients with differentiated thyroid cancer, elevated thyroglobulin and negative I-131 whole-body scan, by restaging ^{18}F-FDG PET/CT

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Keywords: -Elevated thyroglobulin level -^{18}F-FDG PET/CT -Negative I-131 whole-body scan -Recurrent thyroid cancer

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Received:
21 July 2016
Accepted revised:
6 September 2016

Abstract

Objective: In nearly 20%-30% of patients with differentiated thyroid carcinoma (DTC) relapse and 7% of them die during the next 10 years after initial diagnosis. In 10%-30% of patients with DTC after ablation therapy during the follow-up show a negative iodine-131 (^{131}I) whole-body screening test (^{131}I WBS) and increased serum thyroglobulin (Tg) level. Loss of ability of DTC metastatic lesions to trap ^{131}I is associated with pure survival and often aggressive disease. Several studies have shown that in DTC cases non trapping ^{131}I, fluorine-18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) can detect recurrence or metastases with high sensitivity (80%-90%). The purpose of this study was to investigate the clinicopathologic features and other related risk factors of patients with DTC having elevated Tg levels and negative ^{131}I WBS in which recurrence was detected by ^{18}F-FDG PET/CT. We tried to study and stratify patients in this grey zone who could benefit from ^{18}F-FDG PET/CT for the detection of metastasis/ recurrence according to predefined risk factors not investigated by other researchers. **Subjects and Methods:** We studied retrospectively 165 DTC patients with elevated Tg levels and a negative ^{131}I WBS during their follow-up between 2004-2015. Metastases/recurrence was found in 49% of the patients on restaging with ^{18}F-FDG PET/CT and were compared with nonmetastatic group according to predefined risk factors. These factors were also evaluated in true positive and false negative cases. **Results:** The sensitivity and specificity of ^{18}F-FDG PET/CT for detecting recurrent/metastatic disease were 90% and 98.5%, respectively. No apparent predefined risk factor impacting a false negative ^{18}F-FDG PET/CT was found. Findings in follicular carcinoma, Hürtle cell carcinoma and papillary carcinoma were not different from positive PET findings. The variants of papillary carcinoma also had no statistically difference with regard to ^{18}F-FDG results. **Conclusion:** The most important factors affecting a true positive ^{18}F-FDG PET/CT study were: ETE, high total ^{131}I dose and the SUVmax values over 4.5.

Hell J Nucl Med 2016; 19(3): 208-217 *Epub ahead of print: 8 November 2016* *Published online: 10 December 2016*

Introduction

Differentiated thyroid carcinoma (DTC) constitutes 80%-90% of all thyroid cancers as the most common histologic subtype [1]. Nearly 20%-30% of them recur and 7% of these patients die within 10 years after initial diagnosis [2]. During the follow-up of patients with DTC treated by total thyroidectomy and radioactive iodine (RAI) ablation therapy, an elevated serum thyroglobulin (Tg) concentration indicates persistent or recurrent disease as a sensitive tumor marker [3]. Elevated serum Tg level is usually associated with a positive iodine-131 whole-body screening test (^{131}I WBS) [4]. However, some patients have metastases not taking up ^{131}I even after therapeutic doses [5]. Loss of ability to trap iodine by metastatic DTC is associated with a worse survival and such cases often present aggressive clinical behavior [6, 7]. About 10%-30% of the patients with recurrent DTC have a negative ^{131}I WBS and increased Tg level [8].

Morphologic imaging methods including ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI) or nuclear imaging procedures which are able to detect and spot the lesions, facilitate patient management proposing the appropriate therapeutic option. But they are often inconclusive in the evaluation of postsurgical neck [9]. Several studies have shown that fluorine-18-fluorodeoxyglucose positron emissiontomography (^{18}F-FDG PET) and ^{18}F-FDG PET/CT can detect recurrence or metastasis with a high degree of sensitivity (80%-90%) in DTC of especially the non-trapping RAI cases [10, 11]. The purpose of this study was to investigate the clinicopatho-

logic features and other related risk factors of patients with DTC having elevated Tg levels and negative ^{131}I WBS in which metastasis/recurrence was detected by ^{18}F-FDG PET/CT during the follow-up after ablation therapy. We tried to stratify patients who could benefit from ^{18}F-FDG PET/CT for the detection of metastasis/recurrence according to predefined risk factors. This is the first study which evaluates comprehensive risk factors impacting on a positive ^{18}F-FDG PET scan in the literature.

Patients and Methods

Nearly 3500 patients with DTC were treated with RAI and followed up by our Nuclear Medicine Department of the Training and Research Hospital of Medical School between 1991-2016. One hundred eighty patients from this population treated and followed up at our department with the diagnosis of pathologically proven DTC were included in this retrospective cohort study between 2004-2015. Mean age of the patients was 47±15 years (13-80). 68.5% of the patients were female (n:113) and 31.5% (n:52) male (female/male ratio: 2.17). 8/165 (5%) of the cases were follicular carcinomas, 13/165 (8%) Hürtle cell carcinomas and 144/165 (87%) papillary carcinomas. The variants of papillary carcinoma were tall cell in 22 patients, insular in 8, follicular in 21, columnar in 10, diffuse sclerosing in 4, classic in 48, microcarcinoma in 11, encapsulated follicular in 6 and oncocytic in 14. 78/165 (47%) of the patients were at stage I, 26/165 (16%) at stage II, 32/165 (19.5%) at stage III, 29/165 (17.5%) at stage IV. Mean TS was 25.6±15mm (range: 2-90mm, median: 24mm). Capsule invasion and ETE were positive in 36% (59/165) and 31% (51/165) of the cases, respectively. 111/165 of the patients (67%) underwent initial LN neck dissection. Mean administered total ^{131}I dose was 13.1±7.5 GBq (range: 2.75-38.85GBq, median: 13.3GBq). Iodine-131 was administered to 61/165 of the patients (37%) only once, while more than one (1-6 times) to 104/165 (63%). Fifty nine patients (36%) underwent local surgery of (successive) cervical LN dissections (1-3 times) later after the ablation therapy. Mean time interval from initial dignosis to restaging ^{18}F-FDG PET/CT was 53.7±47 months (range: 5-284, median: 37). Mean Tg level was 180ng/mL (range: 2-3340ng/mL, median: 16ng/mL).

The initial treatment of the the patients consisted of bilateral total thyroidectomy (BTT)±cervical lymph node (LN) dissection followed by ^{131}I therapy (determined by a thyroid advisor council and were calculated according to tumor size (TS), multifocality (MF), capsule invasion (CI), extrathyroidal extension (ETE), vascular invasion (VI), LN and/or distant metastasis) with doses of 1.85-7.4GBq ^{131}I for the ablation of thyroid remnants. One hundred eleven patients (67%) underwent initial LN dissection (together with BTT) from neck. During the follow-up, some patients received additional therapeutic doses of ^{131}I (1-6 times) to treat persistent or recurrent disease with an average cumulative dose of 13.1GBq (maximum cumulative dose of 38.85GBq). Fifty nine patients (36%) also required local surgery of successive cervical LN dissections (1-3 times) later on after first ^{131}I ablation. The patients were routinely followed up by neck US, serum Tg, anti-thyroglobulin antibody (anti-Tg) and thyroid-stimulating hormone (TSH) measurements every 6 months.

In the follow-up period, when Tg level was over 2ng/mL during TSH suppression or/and there was a suspicious lesion on a conventional imaging test, a whole-body screening test with 185MBq ^{131}I (DxWBS) was performed. A diagnostic dose of 185MBq ^{131}I was given orally to each patient 4-5 weeks after withdrawal of thyroid hormone replacement therapy (TSH levels were at least over 30mIU/L). Consequently, whole-body scanning was performed 24 and 48 hours later using a dual-head large-field gamma camera equipped with a high-energy collimator (Philips Forte Jet STREAM, Holland). If an evident focus of abnormal uptake was not observed by visual inspection provided that there was no ^{131}I contamination, DxWBS results were accepted as negative. If there was no evident focus ^{18}F-FDG PET/CT was performed to find a possible recurrent or metastatic focus. In case of an increase in Tg levels after TSH suppression, blood samples for measuring serum Tg, anti-Tg and TSH were tested just before ^{131}I administration. This value of Tg was used for each case and not the one during routine follow-up. Serum Tg levels were considered abnormal, if values >2ng/mL were found under TSH stimulation. Anti-Tg measurements were negative in all patients according to study design. Fifteen patients having high anti-Tg levels were excluded from the study. Eventually under these conditions, during the follow-up we performed restaging by ^{18}F-FDG PET/CT for the 165 patients with elevated Tg levels and/or any doubtful lesionS detected by any conventional imaging modalities (US, CT, MRI, bone scintigraphy) and also a negative DxWBS. The mean time interval between DxWBS and ^{18}F-FDG PET/CT was 20 days (14-40).

Files of the patients retrieved from the archives of the Nuclear Medicine Department of our hospital were examined retrospectively. The patients were divided in 2 groups. Those in which ^{18}F-FDG PET/CT found metastasis/recurrence (81/165 (49%) patients) which formed Group A and those with negative findings (84/165 (51%) patients) which formed Group B. The evaluated risk factors were sex, age, histopathology (variants), TS, CI, ETE, initial metastatic LN (neck) dissection, stage, cumulative ^{131}I dose, count of ^{131}I therapy, local cervical surgery for LN metastasis/recurrence during the follow-up period, the time from initial diagnosis to restaging ^{18}F-FDG PET/CT, Tg and SUVmax. These factors were evaluated in true positive (TP) and false negative (FN) patient population and compared between groups A and B. Fluorine-18-FDG uptake in histopathologically confirmed metastases was accepted as TP. Metastases which were not detected by ^{18}F-FDG PET and confirmed histopathologically or detected by MR, HRCT or bone scintigraphy were accepted as FN. The clinical and pathologic staging were performed according to TNM classification for thyroid cancer designated by the American Joint Committee on Cancer [12]. The study was approved by our hospital's ethics

committee. Thyroglobulin and anti-Tg levels were determined by radioimmunoassay (BioRad Tg, Pasteur, France; Dynotest antiTgn, Brahms, France).

Imaging protocol

Patients fasted for 6 hours and their blood glucose level had to be under 150mg/dL before the injection of 370-555MBq of ^{18}F-FDG according to patient's weight. Image acquisitions were performed 1 hour later with an integrated PET/CT scanner (Discovery 690-GE Healthcare). Unenhanced low dose CT and PET emission data were acquired from mid-thigh to the vertex of the skull in supine position with the arms raised over the head. Computed tomography data was obtained by automated dose modulation of 120kVp (maximal 100mA), collimation of 64×0.625mm, measured field of view (FOV) of 50cm, noise index of 20% and reconstructed to images of 0.625mm transverse pixel size and 3.75mm slice thickness. Positron emission tomography data were acquired in 3D mode with scan duration of 2min per bed position and an axial FOV of 153mm. The emission data were corrected in a standardized way (random, scatter and attenuation) and iteratively reconstructed (matrix size 256×256, Fourier rebinning, VUE Point FX [3D] with 3 iterations, 18 subsets). Maximum standardized uptake value (SUVmax) was the semi-quantitative PET/CT parameter used in the study. It was calculated according to a standard protocol on a dedicated workstation (Volumetrix for PET/CT and AW volume share 4.5, GE Healthcare, Waukesha, WI, USA). Maximum standardized uptake value corrected for body weight was computed by standard methods from the activity at the most intense voxel in three-dimensional tumor regions from the transaxial whole-body slices on attenuation-corrected PET/CT images. Transaxial, sagittal, and coronal images were shown on a computer display monitor. They were interpreted independently by two experienced physicians of Nuclear Medicine unaware of the clinical situation. Any disagreement was resolved by consensus. A visually abnormal focus of ^{18}F-FDG accumulation was defined as a focal uptake relatively higher than that of the surrounding tissue with no similar activity seen in the contralateral side of the body indicative of metastasis/recurrence reinforced by the related CT findings. these abnormal foci were removed surgically and confirmed by histopathology. Lung accumulations in more than 3 sites were determined as metastases.

Additional conventional imaging procedures performed for suspicious lesions with regard to metastasis or recurrence included HRCT (high resolution computed tomography) (n=20), thoracic CT (n=12), MRI (n=14), plain X-ray graphy of thorax (n=8) and bone scintigraphy (n=15).

Statistical analysis

Tumor detection rates were expressed as the percentage of patients with positive sites and compared using χ^2 test. Semi-quantitative data were expressed as mean with ranges and qualitative data were expressed in number and percentage. Risk factors in the metastases/recurrent group were analyzed by univariate logistic regression. Mann-Whitney U test was used for continuous predictor variables in patients with metastatic findings (positive contributory versus all others) and chi square test for categorical predictor variables. All reported P values were two-sided and the significance level was 0.05. The whole data were analysed using IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Number and percentage values were used for the description of categorical data; mean, median, standard deviation (SD). Minimum (min) and maximum (max) values were used for the description of continuous data. Univariate and multivariate logistic regression analyses were performed to detect predefined risk factors impacting on metastasis/recurrence shown by the contribution of ^{18}F-FDG PET/CT in TP and FN cases. Statistical significance level was considered as ($P \geqslant 0.05$).

Results

Mean SUVmax value was 5.5 (range: 0.9-36, median: 3.2). ROC curve for SUVmax was demonstrated in Figure 1. A cut-off value of 4.5 for SUVmax to detect metastasis/recurrence had a sensitivity and specificity of 74% and 100%.The Pearson correlation test between serum Tg levels and SUVmax correlated significantly (r=0.229, P=0.03) in the study group. Neverthless, it was not meaningful in groups A and B. All these patients characteristics, demography, clinicopathologic features, follow-up data and other pre-defined risk factors were summarized separately for groups A and B in Tables 1, 2. Eighty one of 165 patients (49%) had metastases/recurrence and 84/165 of the patients (51%) had not. Seventy of the 165 patients (42.5%) had local (cervical) LN metastasis and/or local recurrence, 34/165 (20.5%) had distant metastasis (lung, bone, brain, mediastinal or supraclavicular LN), 23/165 (14%) had both. There was isolated local LN metastasis/recurrence in 47/165 of the cases (28.5%), isolated distant metastasis in 11/165 of the cases (6.5%). Fluorine-18-FDG PET findings were positive in 74/165 (45%) of the patients. Seventy three of them were true positive. One pati-

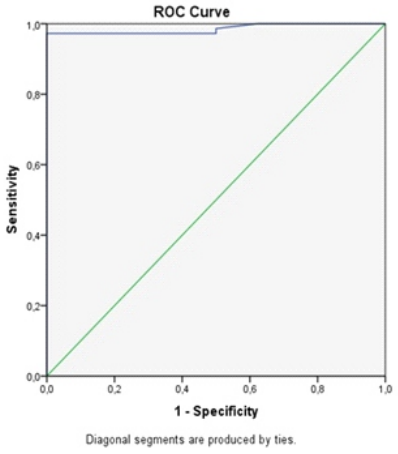

Figure 1. The ROC curve for SUVmax according to metastasis/recurrence.

Table 1. *Univariate analysis of continuous predictor variables in patients with metastatic findings (positive contributory versus all others).*

Variable	Metastasis (+) Median (Min-Max)	Metastasis (-) Median (Min-Max)	P-Value*
Age (years)	52 (13-80)	45 (13-77)	0.054
Tumor size (mm)	25 (3-90)	20 (2-50)	0.030
Total iodine dose (GBq)	14.8 (2.77-38.85)	7.4 (3.7-29.6)	<0.001
Time to ^{18}F-FDG PET (months)	50 (6-212)	28.5 (5-284)	0.011
Tg (ng/mL)	53.5 (2-3340)	6.5 (2-800)	<0.001
SUVmax	8.9 (0.9-36)	2.27 (1-15.7)	<0.001

** Mann-Whitney U test*

Table 2. *Univariate analysis of some categorical predictor variables (except variants) in patients with metastatic findings (positive contributory versus all others).*

Variable		Metastasis (+)		Metastasis (-)		P value*
		Number	%	Number	%	
Sex	Male	30	57.7	22	42.3	0.134
	Female	51	45.1	62	54.9	
CI	(+)	42	39.6	64	60.4	<0.001
	(-)	42	71.2	17	28.8	
ETE	(+)	38	74.5	13	25.5	<0.001
	(-)	71	62.3	43	37.7	
ILND	(+)	66	59.5	45	40.5	<0.001
	(-)	15	27.8	39	72.2	
Stage	I	28	35.9	50	64.1	<0.001
	II	10	38.5	16	61.5	
	III	21	65.6	11	34.4	
	IV	22	75.9	7	24.1	
Iodine number	1	18	29.5	43	70.5	<0.001
	>1	41	39.4	63	60.6	
Local surgery	(+)	41	69.5	18	30.5	<0.001
	(-)	40	37.7	66	62.3	
PET	(+)	73	100.0	0	0.0	<0.001
	(-)	8	8.7	84	91.3	

**Chi square test, CI:Capsule invasion, ETE:Extrathyroidal extension, ILND:Initial lymph node dissection*

ent thought to be metastatic (mediastinal LN metastases) because of her high SUVmax value (15.7) was diagnosed as tuberculosis with biopsy and this case was considered false positive. Fluorine-18-FDG PET findings were negative in 91/165 (55%) of the patients. Eighty three of them were true negative while 8 cases were false negative. Seven of false negatives had micronodular lung metastasis, one case a mediastinal lesion. The sensitivity and specificity of ^{18}F-FDG PET/CT for detecting recurrent/metas-tatic disease was 90% and 98.5%, respectively.

LN metastases were established by excisional biopsy. It was not possible to confirm lung metatases by biopsy. They were decided by HRCT. Diminishing of size and number of micronodular lesions on follow-up HRCT, uptake on RxWBS and a decrease in Tg values after ^{131}I treatment were accepted as metastasis criteria for these patients. Single bone metas-tasis was well confirmed by biopsy. Multiple bone metastases were imaged by bone scintigraphy and MR.

Positron emission tomography scanning detected cervical (including supraclavicular and upper paratracheal) and mediastinal LN in 61 patients (37 cervical, 11 mediastinal, 13 cervical and mediastinal). It depicted local recurrence within the thyroid bed in 23 patients and revealed distant organ metastases in 32 patients (25 lung, 12 bone, 1 brain, 2 liver). Fluorine-18-FDG imaging failed to detect a mediastinal LN metastasis with bilateral multiple micronodular pulmonary metastases and a mass lesion (conglomerated metastatic LNs) in 2 patients. Lymph nodes were removed surgically and confirmed by histopathology. There were 7 patients with bilateral multiple micronodular lung metastases shown by HRCT, but not seen on ^{18}F-FDG PET. Isolated lung metastasis was the only finding in 4/7 while liver metastasis accompanied another case. On the other hand, isolated lung metastasis was the only finding in 3 patients detected by both ^{18}F-FDG and HRCT (Figure 2). Bone metastasis was the only finding in 3 patients (2 cases with only one focus (pelvic bone, femur) and one case with 2 foci (L4, T7 vertebrae)). These foci were confirmed by biopsy or histopathology after surgical resection. One patient had local recurrence invading the sternum. Other bone metastases were concurrent with distant organ or LN metastases and mostly multiple.

Risk factors in metastatic/recurrent group according to positive findings on ^{18}F-FDG PET/CT analyzed by univariate logistic regression were CI, ETE, initial metastatic LN dissection from neck, stage, cumulative ^{131}I dose, count of ^{131}I therapy, existence of local cervical surgery for LN metastasis/recurrence during the follow-up, Tg and SUVmax ($P<0.001$ for all). After univariate and multivariate Cox regression analysis of factors impacting a true positive ^{18}F-FDG PET/CT; ETE, total iodine dose and SUVmax remained statistically significant ($P=0.048$, $P=0.002$ and $P<0.001$, respectively) (Tables 3, 4). No apparent predefined risk factor impacting a false negative ^{18}F-FDG PET/CT was found after univariate Cox regression (Table 5). There was no difference for follicular carcinoma, Hürtle cell carcinoma and papillary carcinoma according to positive PET findings. The variants of papillary carcinoma had also no statistically meaningful difference with regard to ^{18}F-FDG results.

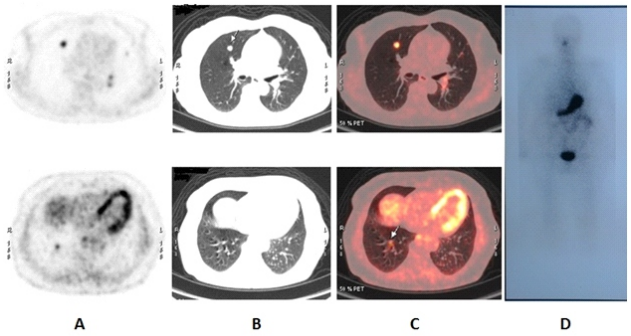

Figure 2. A 47 years old female with tall cell variant papillary thyroid cancer, a serum Tg level of 14ng/mL and negative DxWBS (D) 19 months after 5550MBq ^{131}I ablation therapy. Transaxial ^{18}F-FDG PET (A), CT (B) and fusion (C) images on restaging indicated two macronodular metastases in the right lung (arrows).

For all types of thyroid cancer and their variants, the detection rate was higher for stages III and IV (60.5%) than for stages I and II (53.5%) ($P=0.65$). The PET findings led to a change in the management of all the metastatic/recurrent patients. Fifty patients underwent surgery for removal of cervical LN and a residual tumor. Twenty four of these patients achieved disease-free status with a mean follow-up interval of 66 months (range, 13-124). The disease recurred and these patients were reoperated by local surgical procedures. Thirty two patients with distant organ metastases were given additional higher repetitive doses of ^{131}I.

Ninteen out of twenty five of the lung metastases (patients with mostly micronodular and milier metastases) and 4/12 of the bone metastases were considered to be healed because of a striking decrease in Tg levels and disappearance of ^{18}F-FDG uptake or because other imaging techniques after repetitive ^{131}I treatment were normal. In some of the remaining cases of this group, ^{131}I therapy was supported by chemotherapy. Two patients with macronodular lung metastases and 5 patients with bone metastases were treated surgically with pulmonary wedge resection and bone excision. Two patients (one with multiple mediastinal and lung metastases and one with brain metastasis) were treated by radiotherapy. Metastatic disease persisted with still elevated but decreased Tg values in 6 lung metastases and 3 bone metastases. These patients were followed up until the end of the study.

Discussion

Aggressive histologic variants such as poorly differentiated carcinoma, tall cell, columnar cell, oncocytic cell, insular, diffuse sclerosing variants of papillary or follicular and Hürthle cell carcinoma constitute a minor portion of DTC. Persistent or recurrent disease after initial treatment is seen in 22%-65% of these patients [13]. They are frequently resistant to radioactive iodine treatment (RAI) and their median OS after detection of distant metastasis is only 3-5 years [14]. According to the American Thyroid Association classification, there is an intermediate to high risk of persistent/recurrent

Table 3. *Univariate Cox regression analysis of factors impacting a true positive ^{18}F-FDG PET/CT.*

Factors	Sig. (P value)	Hazard ratio Exp (B)	95% CI for Exp.(B) Lower	Upper
Age	0,035	1	0,902	0,996
Pathology*	0,974			
Pathology (1)	0,998		0,000	
Pathology (2)	0,482		0,031	5,151
Pathology (3)	0,999		0,000	
Pathology (4)	0,999		0,000	
Pathology (5)	1,000	3230949729	0,000	
Pathology (6)	0,071		0,009	1,210
Pathology (7)	0,999		0,000	
Pathology (8)	1,000	3230949729	0,000	
Pathology (9)	0,600	1	0,037	6,683
Pathology(10)	0,999		0,000	
Tumor size	0,132	1	0,889	1,015
Capsule invasion	0,541	2	0,225	17,165
ETE	0,576	1	0,145	2,929
CLND (during TT)	0,621	1	0,118	3,590
Stage	0,648			
Stage (1)	0,463	2	0,294	14,766
Stage (2)	0,463		0,040	4,318
Stage (3)	0,850	1	0,127	5,479
Total iodine dose	0,390	1	0,994	1,002
Count of iodine therapy	0,495	2	0,244	18,508
Local surgery during FUP	0,146		0,055	1,536
Time to ^{18}F-FDG PET	0,926	1	0,985	1,016
Tg	0,926	1	0,999	1,001
SUVmax	0,020		0,007	0,659

ETE: Extrathyroidal extension, CLND: Cervical lymph node dissection,
TT:Total thyroidectomy, FUP:Follow-up period
**Reference pathologic variant was classic, Pathology (1) follicular variant, Pathology (2) tall cell, Pathology (3) insular, Pathology (4) Hürtle cell cancer, Pathology (5) columnar, Pathology (6) diffuse sclerosing, Pathology (7) microcarcinoma, Pathology (8) encapsulated follicular, Pathology (9) follicular cancer, Pathology (10) oncocytic*

Table 4. *Multivariate Cox regression analysis of factors impacting a true positive ^{18}F-FDG PET/CT*

Factors	Sig. (P value)	Hazard ratio Exp (B)	95% CI for Exp.(B) Lower	Upper
ETE	0,048	3,252	1,013	10,442
Total iodine dose	0,002	1,004	1,002	1,007
SUVmax	0,000	2,436	1,742	3,159

ETE: Extrathyroidal extension

disease depending on the stage and completeness of surgical resection reflected by ETE [15]. We also found ETE a serious risk factor in our study. According to the European Thyroid Association classification, these patients with ETE are at high risk of persistent disease [16].

Some subtypes of DTC and recurrent DTC are not iodine-avid. Fluorine-18-FDG PET/CT was the only imaging technique demonstrating lesions not detected by RxWBS in 70% of the patients [17, 18]. More iodine refractory cases were thus detected in persistent disease by preablation ^{18}F-FDG PET/CT and found in 13%-33% of the patients [19, 20]. Many investigators have recently shown that DTC can take-up ^{18}F-FDG in varying degrees with or without concurrent ^{131}I uptake [21].

In aggressive DTC, ^{18}F-FDG PET/CT is currently performed for diagnostic and prognostic purposes. A positive ^{18}F-FDG PET/CT correlates with reduced survival and predicts OS and the response of neoplastic foci to RAI treatment [22]. To the best of our knowledge, our study is the first one focusing on the risk

Table 5. *Univariate Cox regression analysis of factors impacting a false negative ^{18}F-FDG PET/CT.*

Factors	Sig. (P value)	Hazard ratio Exp (B)	95% CI for Exp.(B) Lower	Upper
Age	0,035	1	0,902	0,996
Pathology*	0,974			
Pathology (1)	0,998		0,000	
Pathology (2)	0,482		0,031	5,151
Pathology (3)	0,999		0,000	
Pathology (4)	0,999		0,000	
Pathology (5)	1,000	3230949729	0,000	
Pathology (6)	0,071		0,009	1,210
Pathology (7)	0,999		0,000	
Pathology (8)	1,000	3230949729	0,000	
Pathology (9)	0,600	1	0,037	6,683
Pathology (10)	0,999		0,000	
Tumor size	0,132	1	0,889	1,015
Capsule invasion	0,541	2	0,225	17,165
ETE	0,576	1	0,145	2,929
CLND (during TT)	0,621	1	0,118	3,590
Stage	0,648			
Stage (1)	0,463	2	0,294	14,766
Stage (2)	0,463		0,040	4,318
Stage (3)	0,850	1	0,127	5,479
Total iodine dose	0,390	1	0,994	1,002
Count of iodine therapy	0,495	2	0,244	18,508
Local surgery during FUP	0,146		0,055	1,536
Time to ^{18}F-FDG PET	0,926	1	0,985	1,016
Tg	0,926	1	0,999	1,001
SUVmax	0,020		0,007	0,659

ETE: Extrathyroidal extension, CLND: Cervical lymph node dissection,
TT:Total thyroidectomy, FUP:Follow-up period
**Reference pathologic variant was classic, Pathology (1) follicular variant, Pathology (2) tall cell, Pathology (3) insular, Pathology (4) Hürtle cell cancer, Pathology (5) columnar, Pathology (6) diffuse sclerosing, Pathology (7) microcarcinoma, Pathology (8) encapsulated follicular, Pathology (9) follicular cancer, Pathology (10) oncocytic*

factors impacting a positive ^{18}F-FDG PET/CT in recurrent/metastatic DTC with elevated Tg levels and a negative DxWBS. The great number of patients studied in our institution eliminates bias due to referrals. Metastatic disease was shown in 49% of our patient population in this study. Most of them were local LN (cervical) metastasis and ^{18}F-FDG uptake was seen in 44%. Nascimento et al. (2015) in 38 patients found persistent aggressive disease in more than half of their patients, most of them with distant metas-tasis [13]. But they examined risk factors for a positive ^{18}F-FDG PET/CT in ^{131}I scan after postoperative ^{131}I ablation therapy (RxWBS) and found ^{18}F-FDG uptake in 75%, RAI uptake in 60% in their selective subgroup. We tried to determine whether ^{18}F-FDG PET/CT could be beneficial for a particular histotype of DTC but there was statistically no difference for follicular carcinoma, Hürtle cell carcinoma and papillary carcinoma. The variants of papillary carcinoma had also no statistical difference with regard to ^{18}F-FDG results.

The absence of thyroid remnants after total thyroidectomy plus RAI therapy in most cases allows for a better evaluation of the origin of elevated Tg levels. An elevated serum Tg level in such cases is highly suspicious of persistent or metastatic disease and RAI uptake may be absent because of aggressive histology. Some studies have found a correlation between increased glucose transporter-1 (GLUT1) expression and dedifferentiation of thyroid cancer [23]. Our study of 165 DTC patients with elevated Tg levels showed that ^{18}F-FDG PET has a high metastasis detection rate in cases undetected by ^{131}I posttherapy whole-body scanning. Leboulleux et al. (2007) in a meta-analysis reported that the sensi-

tivity and specificity ^{18}F-FDG PET for localization of recurrent DTC range was between 45%-100% and 42%-90%, respectively [24]. In our study, ^{18}F-FDG findings were positive in 76% of patients and accurately localized the disease in 89% of them.

Fluorine-18-FDG PET appears to offer an accurate functional method highly sensitive for the detection of thyroid carcinoma metastases especially in the absence of ^{131}I uptake [25]. The PET scanner makes it possible to perform a whole-body examination with tomographic imaging providing a high spatial resolution and sensitivity. Furthermore, PET/CT has the diagnostic advantage of better identification between physiologic and pathologic foci [26]. The question is that ^{18}F-FDG PET/CT should be performed for which risk factors. We studied positive ^{18}F-FDG and negative ^{18}F-FDG groups of metastatic DTC patients with DxWBS, while most of others studied DTC patients with negative ^{131}I results obtained from scanning performed after therapeutic doses of ^{131}I [27]. Wang et al. (1999) suggested that ^{18}F-FDG uptake may correlate with the TNM stage of thyroid cancer [11]. We found a significant correlation between ^{18}F-FDG uptake and the stage of the thyroid cancer in both papillary thyroid cancer and follicular thyroid cancer and also showed lesions in low stage patients unlike Wang et al. (1999), because 28 of our 71 patients with positive ^{18}F-FDG findings were confirmed with stage I cancer and 10/71 with stage II.

Fluorine-18-FDG PET/CT alters the clinical management in 14%-78% of patients with DTC [21, 28, 29]. Our findings led to a change in the management of all the metastatic/recurrent patients. Fifty patients underwent surgery for removal of cervical LN and a residual tumor. Our results are concordant with literature in this regard. The time from initial dignosis to restaging with ^{18}F-FDG PET/CT and the functional tumor volume are prognostic factors [21]. The time from initial dignosis to restaging ^{18}F-FDG PET/CT was not statistically significant, but functional tumor volume reflected by SUVmax was an important prognostic factor impacting on metastatic disease.

We found that the ideal cutoff value for SUVmax to detect metastasis was 4.5, similar to that in the literature [17, 21]. Micronodular lung metastasis and isolated ^{18}F-FDG-avid bone metastasis are certain patterns of distant organ metastasis with indolent course and bad prognosis [30] similar to our findings. The first concise multicenter study over this subject was performed by Kist et al. (2014) [31]. They aimed to evaluate the potential value of combined 124I and ^{18}F-FDG PET/CT imaging for the prevention of futile ^{131}I therapies in patients with biochemically suspected recurrence of DTC in a prospective cohort study of 100 cases [31]. This study is a vanguard for the future projects about the issue.

The possible effect of thyroxine on the accumulation of ^{18}F-FDG in thyroid metastases has not yet been established. Although many authors have not observed any significant correlation between ^{18}F-FDG uptake and thyroid hormone levels [25], others have reported a significant increase in ^{18}F-FDG uptake in response to TSH stimulation [32]. Positron emission tomography scanning failed to show any tumor tissue in 91 patients (55%) with persistent disease and 8 of them were false negative in our study. Seven of false negatives had micronodular lung metastasis. This may have been attributable to some methodologic problem instead of stimulation of tumor foci by TSH, because all our patients were on withdrawal of thyroxine therapy. The threshold of a TSH-stimulated Tg at 10ng/mL was reported to have the best sensitivity, specificity to predict persistent disease [33] and the higher the stimulated Tg level, the greater the risk of persistent disease [34]. Although Tg is an important factor for having positive findings on ^{18}F-FDG PET/CT in the metastatic/recurrent group, it was not a main determinant for a TP ^{18}F-FDG PET in our study.

Robbins et al. (2006) declared in their retrospective study of 400 DTC cases that age older than 45 years, the number of ^{18}F-FDG-avid lesions and SUVmax correlated significantly with survival [35]. Age is not a risk factor in our study, but the number of ^{18}F-FDG-avid lesions are in line with increased metastasis probability. Two year survival was 52% in the quartile of highest SUVmax compared with 98% in the quartile of lowest SUVmax [35]. The median survival of patients with ^{18}F-FDG-avid lesions was 53 months and they had 7.3 times higher risk of dying than patients with a negative PET/CT scan [35]. We did not study the relationship between survival (OS) and predefined factors. Local LN metastasis in the neck had a more favorable prognosis than regional nodal metastasis (mediastinal, supraclavicular) and ^{18}F-FDG-positive distant metastasis displayed the worst survival [35]. Our findings were also similar. Schreinemakers et al. (2012) found that patients with ^{18}F-FDG-avid lesions had higher Tg levels, more advanced stage and larger tumor size [1]. Disease-free survival (DFS) was 15 months in the ^{18}F-FDG-positive group and 41 months in the ^{18}F-FDG-negative group [1]. Our results are in accordance with these findings. Creach et al. (2013) claimed that the time to PET after initial diagnosis is a predictor parameter for survival (median 3.5 years, range: 7 months-28 years) in their study (Tg level was higher than 3ng/mL) in 76 DTC patients [36]. We did not find this parameter a significant risk factor in metastatic/recurrent group according to ^{18}F-FDG PET/CT positivity.

Advantages and Limitations

The advantages of our study can be lined as large sampling with a more homogeneous patient population, clear indication for ^{18}F-FDG PET/CT, performation of PET scan under TSH stimulation for all cases, inclusion of all variants of DTC, long follow-up period, appropriate handling of conventional imaging methods concurrently and histopathologic confirmation of the results by excisional biopsy.

Our study is the first one evaluating comprehensive risk factors impacting on a positive ^{18}F-FDG PET scan to the best of our knowledge. Main limitation of our study was its retrospective design raising concern for referral bias. The study should be ideally conducted with a prospective cohort design. No prospective study has yet been performed on this issue. Another limitation is the choice of cut-off value for Tg. It has been proven that the likelihood of a positive ^{18}F-FDG PET/CT scan increases when serum Tg exceeds 10ng/mL [21]. However, the reported sensitivities and specificities fluctuate and vary widely by the merging of intrinsic and extrinsic factors. There was not a definite reference standard for Tg in several studies in literature. Some of them accepted

levels as low as 0.2ng/mL for their inclusion criteria. Inclusion of patients with low pretest probability may falsely diminish the proportion of positive results. So, we were very elaborate and attentive while establishing the reference standard cut-off value for Tg in the study. We chose 2ng/mL during the follow-up while the patient was on TSH supression with thyroid hormone replacement therapy. Wewould prefer 4ng/mL on TSH stimulation by withdrawal of thyroid hormone replacement therapy for 4-5 weeks.

In conclusion, it is the opinion of the authors that ^{18}F-FDG PET/CT should be performed routinely in DTC patients with elevated Tg levels and a negative DxWBS especially in the existence of risk factors to show metastasis/recurrence. The most important factors effecting a true positive ^{18}F-FDG PET/CT are ETE, total iodine dose and SUVmax. No apparent predefined risk factor exists for false negative ^{18}F-FDG PET/CT scan. Less important risk factors were CI, stage, Tg, count of ^{131}I therapy and local cervical surgery for LN.

The authors declare that they have no conflicts of interest

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Being ourselves. Our eternal identity

Being is the ontological and functional essence of the real identity of the human person. It is a continuous process starting from the very beginning of life and aims at knowing and understanding ourselves. According to the encephalocentric theory, introduced by Alcmaeon from Croton and supported by the Pythagoreans, Hippocrates, Erasistraus, Galen and others, the brain is the principal organ which rules and controls all mental functions and activities of the human being. The authentic expression of our Being is the Reason, the Word and the Mind. It is impossible to find the boundaries of soul… (Heraclitus, Fragm. B45). Being is a very positive and dynamic, searching, always for truth (Parmenides), an upward process to light, truth, virtue and eternity [Popper K et al (2013), Baloyannis S J (2004)]. According to Plato the Being is our eternal self-identity [Plato Republic II, 318b].

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