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ORIGINAL ARTICLE

^{18}F-FDG uptake as a prognostic variable in primary differentiated thyroid cancer incidentally detected by PET/CT: a multicentre study

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Abstract
Purpose Our aim was to investigate the association between ^{18}F-fluorodeoxyglucose (FDG) uptake and event-free survival in patients in whom a differentiated thyroid cancer (DTC) was detected by ^{18}F-FDG positron emission tomography (PET)/CT.
Methods Among 884 focal ^{18}F-FDG PET thyroid incidentalomas referred to our 4 Nuclear Medicine Departments, we investigated 54 patients in whom a DTC was confirmed and a clinical follow-up was available. The ratio between maximum standardized uptake value (SUV_{max}) of DTC and SUV_{mean} of the liver (SUV ratio) was recorded for each scan. All patients underwent total thyroidectomy and ^{131}I remnant ablation. After a median follow-up of 39 months we assessed the outcome. The association between disease persistence/progression, ^{18}F-FDG uptake and other risk factors (T, N, M and histological subtype) was evaluated through univariate and multivariate analyses.
Results Of the 54 patients, 39 achieved complete remission. The remaining 15 showed persistence/progression of disease. High ^{18}F-FDG uptake, i.e. SUV ratio ≥3, showed a low positive predictive value (48 %). Low ^{18}F-FDG uptake (SUV ratio<3) displayed a high negative predictive value (93 %). The median of SUV ratios in T1–T2 (2.2), in M0 (2.7) and in non-virulent subtypes (2.7) were significantly lower (p<0.03) than in T3–T4 (5.0), M1 (7.3) and virulent subtypes (6.0). Kaplan-Maier analysis showed a significant association between high ^{18}F-FDG uptake and disease persistence/progression (p=0.001). When we adjusted risk estimates by using a multivariate Cox model, only T (p=0.05) remained independently associated with disease persistence/progression.
Conclusion An intense ^{18}F-FDG uptake of the primary DTC is associated with persistence/progression of disease. However, when all other prognostic factors have been taken into account, ^{18}F-FDG uptake does not add further prognostic information.

Keywords Differentiated thyroid cancer · ^{18}F-FDG · PET/CT · Thyroid incidentaloma · Prognostic value

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Introduction

Thyroid incidentalomas displaying focal ^{18}F-fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET)/CT are relatively frequent, with a reported incidence of about 2.5 % [1]. The majority of these findings are benign and about one third are malignant [1, 2]. No proper standardized uptake value (SUV) cut-off able to distinguish benign from malignant lesions has been identified [1, 2]. Thus, all ^{18}F-FDG PET thyroid incidentalomas need further clinical investigation, and, if hyperfunctioning nodules are excluded, fine-needle aspiration cytology (FNAC) is suggested [3]. Many authors have investigated the incidence of malignancy in PET incidentalomas [4–12], and more recently the role of ^{18}F-FDG uptake has been evaluated in thyroid nodules with indeterminate cytology [2, 13, 14]. However, to date little can be said about the prognostic significance of ^{18}F-FDG uptake in primary differentiated thyroid cancer (DTC) incidentally detected at the time of PET/CT for non-thyroid purposes. Indeed, no data are available in this field. Several articles support the hypothesis that ^{18}F-FDG uptake may have prognostic value in DTC. On the one hand, ^{18}F-FDG uptake in primary thyroid cancer is related to glucose transporter (GLUT) expression and differentiation [15–17]; on the other hand, an association between ^{18}F-FDG uptake and aggressive histological features [18], tumour size and lymph node metastases has been found [2]. Thus, the ^{18}F-FDG avidity of primary thyroid cancer might theoretically have prognostic implications, as reported for other tumours [19–21] and for DTC metastases [22].

The aim of this study was to assess the association between ^{18}F-FDG uptake and event-free survival (EFS) in primary DTC. We also tested the positive predictive value (PPV) of ^{18}F-FDG uptake with regard to persistence/recurrence of disease after total thyroidectomy followed by ^{131}I remnant ablation (initial treatment). We compared the PPV of ^{18}F-FDG uptake with that of the other initial prognostic parameters that influence the outcome of DTC patients. Finally, we also evaluated the association between ^{18}F-FDG uptake and all prognostic variables included in this study.

Materials and methods

From a total of 884 patients with focal ^{18}F-FDG PET thyroid incidentalomas referred to our 4 Nuclear Medicine Departments from 1 January 2006 to 31 December 2012, 219 patients underwent FNAC. We retrospectively investigated 54 patients in whom a DTC was histopathologically confirmed and clinical thyroid follow-up was available. None of the 54 patients had undergone chemotherapy during the last year. The principal indications for PET/CT study were colon/rectum cancer (n=11), non-Hodgkin's lymphoma (n=9), lung cancer (n=8), urogynaecological cancer (n=7), breast cancer (n=7), head and neck cancer (n=3), melanoma (n=1), other cancers (n=3) and characterization of lung nodules (n=5).

Imaging modality

In centres 1 and 2, ^{18}F-FDG PET/CT was performed in the fasting state (at least 6 h), when the glucose level was lower than 150 mg/dl. An ^{18}F-FDG activity of 5.5 MBq/kg was administered intravenously; 50 min after the injection, data were acquired in two-dimensional mode by means of a dedicated PET/CT system (Discovery ST, General Electric Healthcare Technologies, Milwaukee, WI, USA). The CT parameters used for acquisition were: 140 kV, 80 mA, 0.5 s per rotation and pitch 6:1, with a slice thickness of 3.25 mm equal to that of PET. PET was acquired from the upper neck to the upper thighs, by means of sequential fields of view, each covering 15 cm, over an acquisition time of 4 min.

In centre 3, patients fasted for at least 6 h before ^{18}F-FDG injection; serum glucose levels immediately before tracer injection were below 150 mg/dl in all patients. Sixty minutes after the i.v. injection of ^{18}F-FDG (2 MBq/kg) images were acquired in three-dimensional mode, corrected for attenuation by means of X-ray CT attenuation mapping and reconstructed by means of an iterative algorithm (ordered subset maximum likelihood expectation) on a Biograph 6 combined PET/CT scanner (Siemens Medical Solutions, Erlangen, Germany). The patients' arms were positioned alongside the body. Five or six sequential acquisition steps were performed to scan from the upper neck to the upper thighs.

In centre 4, ^{18}F-FDG PET/CT was performed in the fasting state (at least 6 h), when the glucose level was lower than 150 mg/dl. An ^{18}F-FDG activity of 3 MBq/kg was administered intravenously; 50 min after the injection, data were acquired in three-dimensional mode by using a dedicated PET/CT system (Discovery ST, General Electric Healthcare Technologies, Milwaukee, WI, USA). The CT parameters used for acquisition were: 140 kV, 80 mA, 0.5 s per rotation and pitch 6:1, with a slice thickness of 3.25 mm equal to that of PET. PET was acquired from the upper neck to the upper thighs, by means of sequential fields of view, each covering 12 cm, over an acquisition time of 3 min.

Imaging analysis

In each Nuclear Medicine Department the PET images were analysed visually and semi-quantitatively by measuring the SUV_{max}. However, no specific SUV_{max} cut-off value was considered in order to discriminate focal incidental uptake or physiological activity; for this purpose, only the deviation from the activity of the normal tissue or blood pool was used.

Nevertheless, the SUV_{max} of the thyroid nodules and the SUV_{mean} of the liver were recorded for each scan in each

department using a circular region of interest (ROI) of 8-mm diameter. The ratio between thyroid cancer SUV_{max} and normal liver SUV_{mean} (SUV ratio) was recorded for each scan. Considering that PET/CT scans were acquired in four different centres, we used the SUV ratio in order to properly semi-quantify the ^{18}F-FDG uptake since we had previously found a high correlation (r^2=0.75) between SUV_{max} and SUV ratio. SUV ratio should be less affected by the intrinsic characteristics of each tomograph and by each PET acquisition protocol [23]. The final diagnosis of DTC was confirmed by histological examination after surgery.

Treatment and follow-up

In accordance with our protocol, all patients underwent: (1) total thyroidectomy, (2) ^{131}I remnant ablation (radioactive iodine, RAI) with an activity ranging from 1,850 to 3,700 MBq 4–6 weeks after surgery [thyroid stimulating hormone (TSH) >30 μIU/ml] and (3) laevothyroxine (LT_4) suppressive therapy (serum TSH levels <0.2 μIU/ml). All patients underwent currently accepted follow-up protocols after RAI, in accordance with Pacini et al. [24]. Patients with locoregional recurrence/metastases underwent surgery whenever possible; patients requiring further ^{131}I treatment for distant metastases received fixed ^{131}I doses, as recommended by the "European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium" [24].

Each patient was risk-stratified by means of the American Joint Cancer Committee/Union Internationale Contre le Cancer (AJCC/UICC) staging system [25] and histological subtype (virulent, non-virulent) [26, 27]. All clinical data obtained over a median of 39 months' follow-up were used to assess the response to initial therapy and the outcome of each patient. We broke down our population into three different groups according to outcome: (A) complete remission after initial therapy (surgery+RAI), (B) persistence of disease after initial therapy and complete remission after further adequate treatment (surgery and/or ^{131}I administration) and (C) persistence of disease after initial therapy and persistence/progression of disease after further adequate treatment (surgery and/or ^{131}I administration).

Patients were deemed to be in complete remission at the final follow-up examination if they had an undetectable suppressive thyroglobulin(Tg) level (Tg<0.1 μg/l), negative neck ultrasonography (US) and TSH-stimulated Tg levels <2 μg/l [27]. Patients were considered to have persistence of disease if they displayed detectable suppressive Tg levels and evidence of disease confirmed by morphological or functional imaging. Patients were considered to have stable disease at the last follow-up examination if their suppressive Tg levels (≥10 μg/l) had remained stable over the last year (<20 % increase vs previous value) and evidence of disease was seen on morphological (RECIST for CT or MRI) or functional imaging [European Organization for Research and Treatment of Cancer (EORTC) criteria for PET] [28], whether or not confirmed by cytology or histopathology. Finally, patients were considered to have progressive disease at the final follow-up examination if they displayed a higher increase (>20 % increase vs previous value) in Tg levels (≥10 μg/l on suppressive LT_4 therapy) and/or evidence of disease on morphological (RECIST for CT or MRI) or functional imaging (EORTC criteria for PET), whether or not confirmed by cytology or histopathology.

Statistical analysis

Descriptive statistics included mean, standard deviation, median, percentiles, minimum and maximum of continuous factors and scores; in the case of categorical factors, number and percentage distributions were used. The Pearson chi-square and Kruskal-Wallis rank tests were used to compare categorical and continuous factors among the groups of response to initial therapy (A, B and C, as previously described). The Wilcoxon rank sum test was used to compare median SUV ratio levels between binary categories of European Thyroid Association (ETA) risk [24], tumour size, M, N and histological subtype.

PPV and negative predictive value (NPV) were used for descriptive purposes. Kaplan-Meier estimates of the cumulative probability of EFS, defined as the time from initial therapy to the onset of persistent/progressive disease, were obtained for all factors considered, including age, sex, tumour size (T), nodal status (N), distant metastases (M), histopathology, histological subtypes, divided into virulent (VS) and non-virulent subtypes (NVS), ETA initial risk classification (high/low risk) [24] and SUV ratio.

Univariate odds ratios (OR) and 95 % confidence intervals (CI) were the main measures of effect that we adopted to quantify the association between main characteristics of subjects and the persistence/progression of disease. Multivariate Cox regression analysis was adopted to assess the independent association between disease persistence/progression (EFS) and all factors under investigation.

SUV ratio was primarily tested as a continuous variable in the model (data not shown), then as a binary variable considering the median (3.0) value of the SUV ratio as a cut-off. To make the results more readable, we mainly expressed the results on the basis of this cut-off. Since SUV_{max} and SUV ratio were highly correlated, in order to avoid collinearity, we assessed SUV ratio and SUV_{max} separately in two multivariate Cox models, and showed the results of the model in terms of SUV ratio. However, due to the high correlation between SUV_{max} and SUV ratio, the two multivariate Cox models showed similar results.

All analyses were conducted by means of Stata (version 13, StataCorp, College Station, TX, USA) software. Two-tailed probabilities were reported and the p value of 0.05 was used to define nominal statistical significance.

Results

We retrospectively analyzed 54 DTC patients. The main characteristics of the patients are summarized in Table 1. Of 54 patients (group A), 39 achieved complete remission after initial treatment. Over a median follow-up of 39 months (range 3–78 months), we identified 15 patients with persistence of disease after initial treatment. Of these 15 patients (group B), 6 achieved complete remission after further adequate treatment, while the other 9 (group C) showed persistence of disease or disease progression despite further proper treatment. Of these nine patients, three, who were affected by poorly differentiated thyroid cancer, died of disease within 6 months after RAI. No difference in terms of follow-up length was found between these three groups (Table 1).

SUV ratio levels were significantly higher in groups B and C than in group A (Table 1). Specifically, 13 of 27 patients (48 %) with SUV ratio ≥3.0 (the overall median of the SUV ratio) belonged to groups B and C (Fig. 1). By contrast, only two patients (7 %) affected by DTC primary tumour with SUV ratio <3.0 developed persistence/progression of disease.

In patients who achieved complete remission after initial treatment (group A), the median of the SUV ratio (2.4) was significantly lower ($p<0.001$) than in patients with persistence or progression of disease (6.2). An SUV ratio ≥3.0 was observed in 69 % of high-risk patients (Fig. 2). Moreover, as shown in Fig. 2, high ^{18}F-FDG uptake was found in the majority of DTC patients with T3–T4 primary tumour (70 %), locoregional involvement (67 %), distant metastases (75 %) and virulent histological subtypes (64 %).

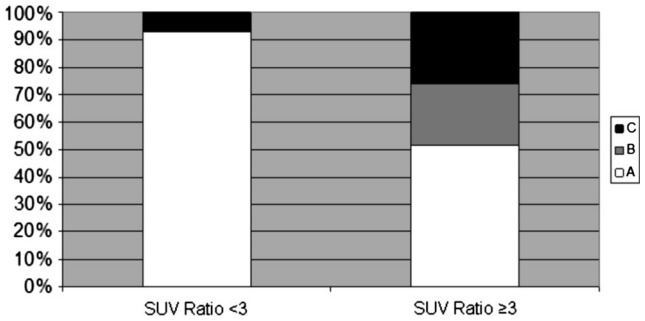

Fig. 1 Large part of patients (48 %) affected by DTC primary tumour with SUV ratio ≥3.0 developed persistence/progression of disease after initial treatment (belonging to groups B and C). By contrast, only two patients (7 %) affected by DTC primary tumour with SUV ratio <3.0 developed persistence/progression of disease

The median values of the SUV ratio in ETA low-risk patients (2.2), in T1–T2 (2.2), in M0 (2.7) and in non-virulent subtypes (2.7) were significantly lower ($p<0.03$) than in ETA high-risk patients (5.1), T3–T4 (5.0), M1 (7.3) and virulent subtypes (6.0).

Among the variables assessed, the presence of distant metastases (M1) displayed the highest PPV (100 %) for persistence of disease (Table 2). The ^{18}F-FDG uptake, as expressed by SUV ratio ≥3.0, showed a relatively low PPV (48 %). On the other hand, a low ^{18}F-FDG uptake (SUV ratio <3.0) displayed a high NPV (93 %).

Table 1 Main patient characteristics by groups of response to initial therapy ($n=54$)

		A $n=39$ n (%)	B $n=6$ n (%)	C $n=9$ n (%)	p^a
Sex	Male	15 (38)	2 (33)	6 (67)	0.3
	Female	24 (62)	4 (67)	3 (33)	
Histology	Follicular	6 (15)	1 (17)	3 (33)	0.5
	Papillary	33 (85)	5 (83)	6 (67)	
Histological subtypes	NVS	33 (85)	3 (50)	4 (44)	0.02
	VS	6 (15)	3 (50)	5 (56)	
Tumour size	T1–T2	25 (64)	0	0	<0.001
	T3–T4	14 (36)	6 (100)	9 (100)	
Nodal status	N0	37 (95)	5 (83)	6 (67)	0.05
	N1	2 (5)	1 (17)	3 (33)	
Distant metastases	M0	39 (100)	6 (100)	1 (11)	<0.001
	M1	0	0	8 (89)	
ETA risk	Low risk	26 (67)	0	0	<0.001
	High risk	13 (33)	6 (100)	9 (100)	
SUV ratio	Median (min.–max.)	2.4 (1.15–18)	6.9 (3.4–9)	5.5 (2.3–23)	0.001
Age at diagnosis (years)	Median (min.–max.)	62 (39–85)	59.5 (39–78)	72 (50–82)	0.09
Follow-up (months)	Median (min.–max.)	40 (15–76)	58 (7–78)	30 (3–78)	0.2

[a] Pearson chi-square or Kruskal-Wallis rank test

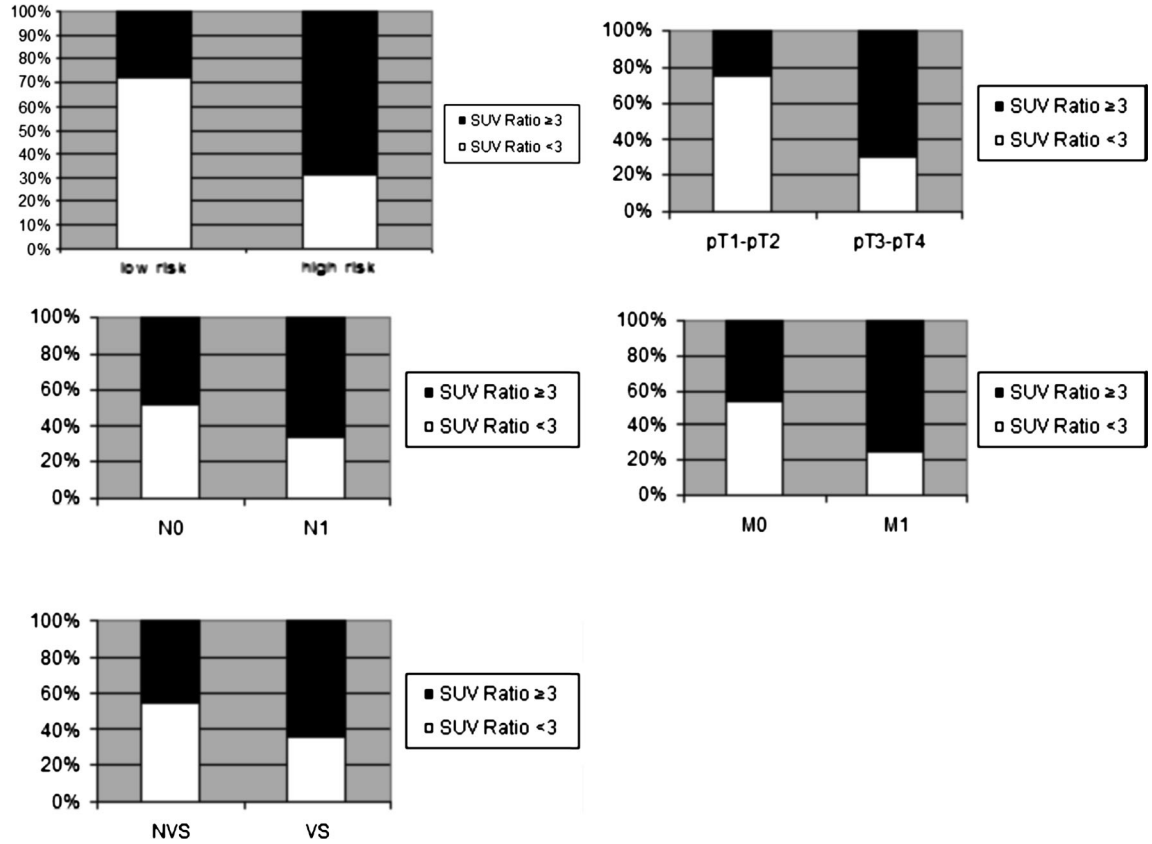

Fig. 2 SUV ratio ≥3.0 was observed in 69 % of ETA high risk patients. High ^{18}F-FDG uptake was found in the majority of DTC patients with T3–T4 primary tumour (70 %), locoregional involvement (67 %), distant metastases (75 %) and virulent histological subtypes (64 %)

In order to estimate the association between disease persistence (B and C type of response during follow-up) and all the main variables considered, we divided patients into two groups according to their response to initial treatment (surgery+RAI): patients with complete response (group A, "responders") and patients with persistence of disease (groups B+C, "non-responders"). On univariate analysis (Table 3), SUV ratio, tumour size, nodal status, distant metastases and histological subtype were all significantly associated with disease persistence. In particular, ^{18}F-FDG uptake was high in non-responders; indeed, we found that patients with an SUV ratio ≥3.0 had a risk of disease persistence/progression about 12-fold higher than patients with an SUV ratio <3.0 (OR=11.6, 95 % CI 1.8–73).

Figures 3 and 4 show Kaplan-Meier EFS curves for all of the main factors analysed in our study. However, when we adjusted risk estimates by using a multivariate Cox model, only T remained independently associated (p=0.05) with persistence/progression of disease (Table 4). Nonetheless, a trend towards a higher risk of disease persistence/progression emerged for patients with an SUV ratio ≥3, or with a virulent histological subtype or with positive lymph nodes (N1) or with metastases (M1), even though statistical significance was not reached, probably because of the low number of events.

Similar results (data not shown) were found using a different multivariate Cox model including SUV_{max} instead of SUV ratio.

Discussion

DTC localizations are often characterized by low ^{18}F-FDG uptake, especially in young patients affected by

Table 2 PPV and NPV of the variables studied with regard to persistence/recurrence of disease after initial treatment

	T		N		M		SUV ratio		Histological subtypes	
	T1–T2	T3–T4	N0	N1	M0	M1	<3	≥3	NVS	VS
PPV (%)	0	50	23	66	15	100	7	48	18	57
NPV (%)	100	50	77	33	85	0	93	52	82	43

Table 3 Univariate associations between main subject characteristics and persistence/progression of disease

		Complete response (A) *n*=39 *n* (%)	Persistence/progression of disease (B + C) *n*=15 *n* (%)	OR (95 % CI)	*p*
Age, years	≤65	21 (54)	6 (40)	1.0	0.4
	>65	18 (46)	9 (60)	1.75 (0.51–5.99)	
Sex	Male	15 (38)	8 (53)	1.0	0.3
	Female	24 (62)	7 (47)	0.55 (0.16–1.86)	
Histology	Follicular	6 (15)	4 (36)	1.0	0.3
	Papillary	33 (85)	11 (64)	0.50 (0.12–2.16)	
Histological subtype	NVS	33 (85)	7 (47)	1.0	0.005
	VS	6 (15)	8 (53)	6.29 (1.45–27.2)	
Tumour size	T1	17 (44)	0 (–)	3.91[a] (2.26–6.76)	<0.001
	T2	8 (21)	0 (–)		
	T3	14 (36)	7 (47)		
	T4	0 (–)	8 (53)		
Nodal status	N0	37 (95)	11 (64)	1.0	0.03
	N1	2 (5)	4 (36)	6.73 (0.97–46.7)	
Distant metastases	M0	39 (100)	7 (43)	[b]	[b]
	M1	0 (–)	8 (53)		
SUV ratio	<3 (median)	25 (64)	2 (13)	1.0	<0.001
	3+	14 (36)	13 (87)	11.6 (1.84–73.3)	

OR odds ratio, *CI* confidence interval

[a] This is an approximation to the OR for a one unit increase in tumour size class

[b] OR and *p* value were not calculable because all of M1 patients had persistence/progression of disease

well-differentiated thyroid cancer subtypes [29, 30]. Neck US and diagnostic ^{131}I whole-body scan (DxWBS) are the diagnostic techniques of choice when persistence/recurrence of disease is suspected in the presence of increased levels of suppressive/stimulated Tg after initial treatment [31]. ^{18}F-FDG PET and PET/CT are mainly used in the event of suspected DTC dedifferentiation associated with the inability of iodine uptake and increased gene expression of the GLUT type 1 (GLUT1) [1, 15]. In these cases, ^{18}F-FDG PET/CT may be helpful in detecting disease recurrence despite negative DxWBS and negative neck US findings. Moreover, as demonstrated by Robbins and colleagues [22], the detection of ^{18}F-FDG-avid metastases has important diagnostic and prognostic implications for DTC management [32–34] and is associated with an increased risk of mortality [22]. In this scenario, it is not clear why some primary DTC incidentally detected by PET/CT are characterized by high ^{18}F-FDG uptake. Several reports have shown that ^{18}F-FDG uptake by primary DTC is associated with the more aggressive histological subtypes [18]. Thus, it has been hypothesized that ^{18}F-FDG uptake may be considered a prognostic factor in primary DTC. However, to date, no data have shown a direct association between ^{18}F-FDG uptake and DTC outcome. Firstly, we evaluated the influence of histological parameters on the SUV ratio and confirmed that T and histological subtype are related to intense ^{18}F-FDG uptake. In addition, we reported that the primary DTC of the patients with distant metastases may more often show intense ^{18}F-FDG uptake.

Moreover, we assessed the prognostic implication of ^{18}F-FDG uptake in primary DTC. We studied 54 consecutive DTC patients among 884 patients with focal ^{18}F-FDG PET/CT thyroid incidentalomas and we found 29 patients at high risk (53 %) according to the ETA risk classification [24]. Specifically, 8 of 54 patients (15 %) presented distant metastases and 6 (11 %) showed lymph node involvement at the time of first diagnosis. Moreover, 15 of the 54 (28 %) showed persistence/progression of disease after initial treatment and 3 patients, affected by poorly differentiated cancer, died of disease. Thus, we probably identified a subgroup of DTC patients who are more likely destined to relapse than the general DTC population. When we identified the SUV ratio 3.0 as a cut-off point (3.0 is the median SUV ratio), we found that patients with higher ^{18}F-FDG uptake had a higher risk of persistence/progression of disease than patients with lower uptake. Similarly, all other risk factors included in our study (histological subtype, T, N and M) were correlated with persistence/progression of disease.

Although we were aware that the low number of events would have yielded a low statistical power on multivariate analysis, we nevertheless decided to run a Cox proportional hazard model to check for the independence of the associations found between EFS and the main factors considered in the univariate analysis. We found that, after adjusting for all other factors considered, tumour size was the only independent factor which remained associated with persistence/progression of disease (p=0.05). Although the significant association we found on univariate analysis between high

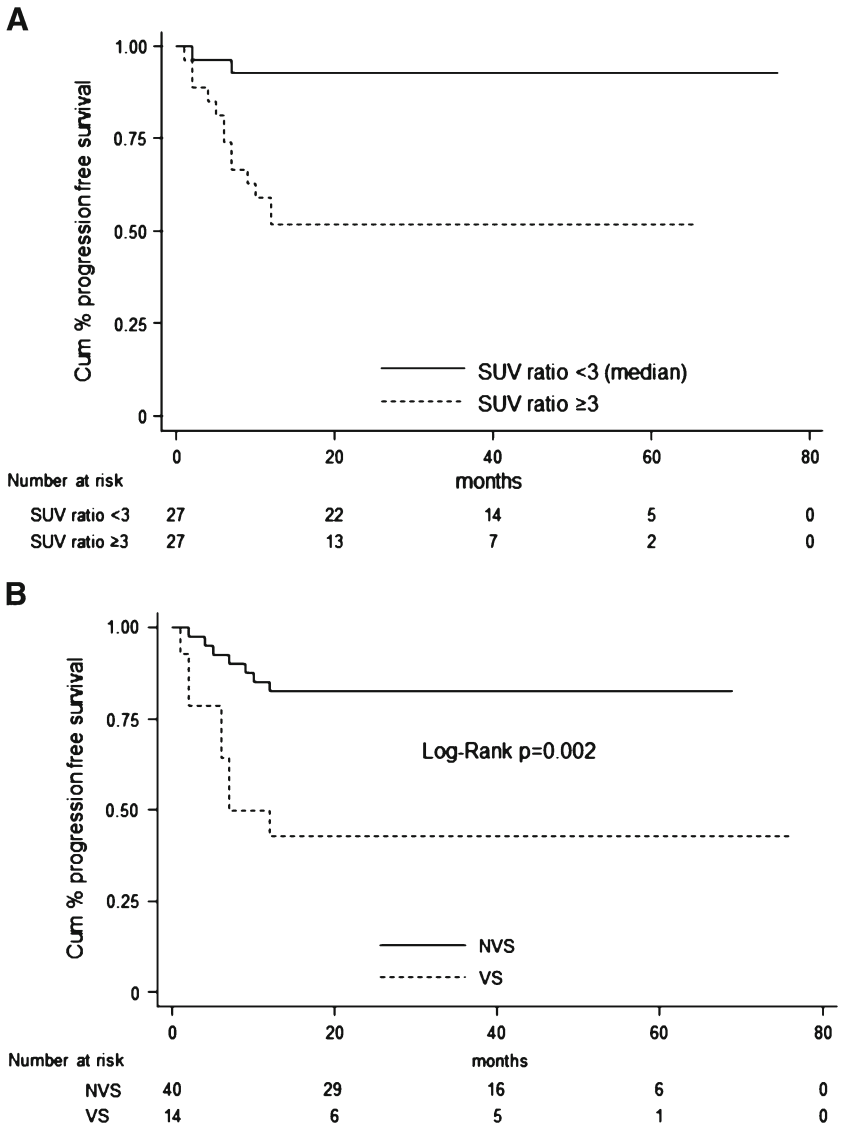

Fig. 3 Kaplan-Meier EFS curves relative to ^{18}F-FDG uptake, expressed by SUV ratio, and histological subtype [non-virulent subtype (*NVS*) and virulent subtype (*VS*)]

^{18}F-FDG uptake (SUV ratio≥3) and persistence/progression of disease was not confirmed in the multivariate model, the risk estimate (HR=1.75) revealed a trend towards a direct association between SUV ratio ≥3 and disease persistence/progression even after adjusting for all other factors. We must also consider the close relationship/correlation between variables such as tumour size/histological subtype and ^{18}F-FDG uptake [18], which, from a statistical point of view, leads to a risk of multicollinearity. Thus, the prognostic value of ^{18}F-FDG uptake might have been underestimated. Further prospective studies including a larger number of DTC patients may better clarify this important issue.

Our findings may open a door to some considerations regarding the real prognostic value of ^{18}F-FDG uptake in primary DTC. In other words, we can affirm that intense ^{18}F-FDG uptake by the primary DTC may be helpful in identifying a subgroup of patients characterized by high ETA risk. Moreover, high ^{18}F-FDG uptake is associated with persistence/progression of disease after initial treatment. Nevertheless, when all other prognostic factors are taken into account, ^{18}F-FDG uptake does not add further prognostic information.

When we considered the prognostic implication of other risk factors, such as distant metastases, we did not find a significant association between M1 and persistence/progression of disease on multivariate analysis. This finding is probably related to the low number of patients with distant metastases and to the fact that all M1 patients presented T3 and T4 primary tumours. In other words, in the multivariate Cox model, the close relationship between these two parameters underestimated the real prognostic value of M. However, when we analysed the PPV of all risk variables included in our study, we found that the highest PPV was displayed by M1 (100 %). By contrast, the PPV of SUV ratio≥3 was low (48 %), as was that displayed by N1 (66 %), T3–T4 (50 %) and VS (57 %).

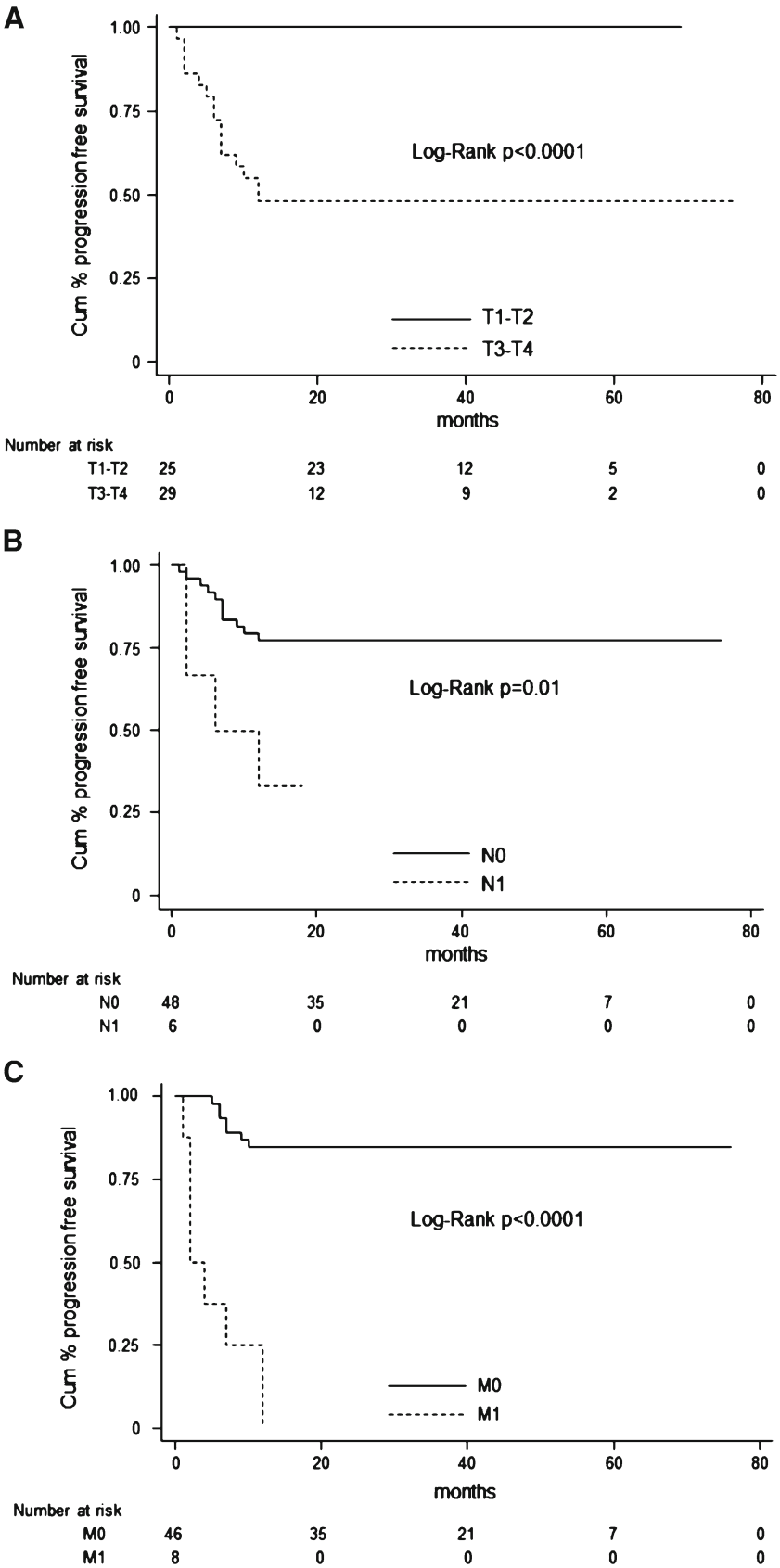

Fig. 4 Kaplan-Meier EFS curves relative to tumour size (*T*), lymph node involvement (*N*) and distant metastases (*M*)

Table 4 Multivariate Cox proportional hazard model of EFS (n=54)

	n	HR	95 % CI	p^a
SUV ratio				
<3	27	1.0		
≥3	27	1.75	0.29–10.64	0.5
Histological subtype				
NVS	40	1.0		
VS	14	2.45	0.62–9.65	0.2
Tumour size	54	4.14	0.99–17.2	0.05
Nodal status				
N0	48	1.0		
N1	6	1.16	0.22–6.02	0.9
Distant metastases				
M0	46	1.0		
M1	8	2.50	0.35–17.7	0.36

Risk estimates were adjusted for sex, age and histology and at diagnosis

HR hazard ratio, *CI* confidence interval, *NVS* non-virulent subtype, *VS* virulent subtype

[a] Two-sided Wald test. HR for tumour size is for a one unit increase in tumour size class

The present study has some limitations, in particular: (1) the retrospective evaluation of data and (2) the period of follow-up considered. Studies with a longer follow-up are probably needed in order to properly assess the risk of recurrence. However, our median 39-month follow-up seems to be a reasonable period in which to assess clinical outcome, particularly the risk of disease persistence. Another limitation lies in the relatively low number of patients and events considered in the study and in the fact that only DTC patients in whom clinical follow-up was available were included in the study. However, to our knowledge, no other papers have investigated the outcome of more than 50 cases of DTC discovered among patients with ^{18}F-FDG-PET focal thyroid incidentalomas.

We investigated only 54 patients from a total 219 patients who underwent FNAC. For all of these 54 patients, a DTC histopathological confirmation and a clinical follow-up were available. The other 165 patients showed negative cytological findings and for them neither histopathological confirmation nor clinical follow-up were available. This limitation reduces the possibility to find other unexpected DTC in these patients and to assess the association between ^{18}F-FDG uptake and persistence/recurrence of disease after initial treatment.

Because this was a multicentre study, different PET/CT scanners acquiring in two- or three-dimensional mode had been used. This limitation might have influenced the correct SUV assessment. To overcome this drawback, we introduced SUV ratio, which is less affected by the intrinsic characteristics of each tomograph and by each PET acquisition protocol [23].

Finally, we included patients affected by primary DTC, all of whom were characterized by high ^{18}F-FDG uptake on PET/CT. From a theoretical point of view, it would be more appropriate to also include patients affected by primary DTC without ^{18}F-FDG avidity. However, the selection of this type of patient is very difficult considering the relatively low value of ^{18}F-FDG PET/CT at the time of DTC diagnosis and staging. Moreover, we broke down our patients into low ^{18}F-FDG-avid primary DTC (SUV ratio<3) and high ^{18}F-FDG-avid primary DTC according to the intensity of tracer uptake. This approach might be sufficient to assess ^{18}F-FDG uptake as a prognostic variable.

Conclusion

The intense uptake of ^{18}F-FDG by primary DTC is influenced by tumour size and histopathology subtype. While a high SUV ratio was associated with persistence/progression of disease after initial treatment, it displayed low PPV. When all other prognostic factors were taken into account, ^{18}F-FDG uptake did not add further prognostic information.

Conflicts of interest None.

References

1. Bertagna F, Treglia G, Piccardo A, Giubbini R. Diagnostic and clinical significance of F-18-FDG-PET/CT thyroid incidentalomas. J Clin Endocrinol Metab 2012;97:3866–75.
2. Pak K, Kim SJ, Kim IJ, Kim BH, Kim SS, Jeon YK. The role of 18F-fluorodeoxyglucose positron emission tomography in differentiated thyroid cancer before surgery. Endocr Relat Cancer 2013;20:R203–13.
3. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167–214.
4. Nishimori H, Tabah R, Hickeson M, How J. Incidental thyroid "PETomas": clinical significance and novel description of the self-resolving variant of focal FDG-PET thyroid uptake. Can J Surg 2011;54:83–8.
5. Pagano L, Samà MT, Morani F, Prodam F, Rudoni M, Boldorini R, et al. Thyroid incidentaloma identified by 18F-fluorodeoxyglucose positron emission tomography with CT (FDG-PET/CT): clinical and pathological relevance. Clin Endocrinol (Oxf) 2011;75:528–34.
6. Zhai G, Zhang M, Xu H, Zhu C, Li B. The role of 18F-fluorodeoxyglucose positron emission tomography/computed tomography whole body imaging in the evaluation of focal thyroid incidentaloma. J Endocrinol Invest 2010;33:151–5.
7. Even-Sapir E, Lerman H, Gutman M, Lievshitz G, Zuriel L, Polliack A, et al. The presentation of malignant tumours and pre-malignant lesions incidentally found on PET-CT. Eur J Nucl Med Mol Imaging 2006;33:541–52.
8. Eloy JA, Brett EM, Fatterpekar GM, Kostakoglu L, Som PM, Desai SC, et al. The significance and management of incidental [18F]fluorodeoxyglucose-positron-emission tomography uptake in

the thyroid gland in patients with cancer. AJNR Am J Neuroradiol 2009;30:1431–4.
9. Kang BJ, O JH, Baik JH, Jung SL, Park YH, Chung SK. Incidental thyroid uptake on F-18 FDG PET/CT: correlation with ultrasonography and pathology. Ann Nucl Med 2009;23:729–37.
10. Bonabi S, Schmidt F, Broglie MA, Haile SR, Stoeckli SJ. Thyroid incidentalomas in FDG-PET/CT: prevalence and clinical impact. Eur Arch Otorhinolaryngol 2012;269:2555–60.
11. Pampaloni MH, Win AZ. Prevalence and characteristics of incidentalomas discovered by whole body FDG PET/CT. Int J Mol Imaging 2012. 10.1155/2012/476763.
12. Bertagna F, Treglia G, Piccardo A, Giovannini E, Bosio G, Biasiotto G, et al. F18-FDG-PET/CT thyroid incidentalomas: a wide retrospective analysis in three Italian centres on the significance of focal uptake and SUV value. Endocrine 2013;43:678–85.
13. Giovanella L, Suriano S, Maffioli M, Ceriani L. 18FDG-positron emission tomography/computed tomography(PET/CT) scanning in thyroid nodules with nondiagnostic cytology. Clin Endocrinol (Oxf) 2011;74:644–8.
14. Deandreis D, Al Ghuzlan A, Auperin A, Vielh P, Caillou B, Chami L, et al. Is 18F-fluorodeoxyglucose-PET/CT useful for presurgical characterization of thyroid nodules with indeterminate fine needle aspiration cytology? Thyroid 2012;22:165–72.
15. Feine U, Lietzenmayer R, Hanke JP, Held J, Wöhrle H, Müller-Schauenburg W. Fluorine-18-FDG and iodine-131-iodide uptake in thyroid cancer. J Nucl Med 1996;37:1468–72.
16. Ciampi R, Vivaldi A, Romei C, Del Guerra A, Salvadori P, Cosci B, et al. Expression analysis of facilitative glucose transporters (GLUTs) in human thyroid carcinoma cell lines and primary tumors. Mol Cell Endocrinol 2008;291:57–62.
17. Kaida H, Hiromatsu Y, Kurata S, Kawahara A, Hattori S, Taira T, et al. Relationship between clinicopathological factors and fluorine-18-fluorodeoxyglucose uptake in patient with papillary thyroid cancer. Nucl Med Commun 2011;32:690–8.
18. Are C, Hsu JF, Ghossein RA, Schoder H, Shah JP, Shaha AR. Histological aggressiveness of fluorodeoxyglucose positron-emission tomogram (FDG-PET)-detected incidental thyroid carcinomas. Ann Surg Oncol 2007;14:3210–5.
19. Al-Sarraf N, Gately K, Lucey J, Aziz R, Doddakula K, Wilson L, et al. Clinical implication and prognostic significance of standardised uptake value of primary non-small cell lung cancer on positron emission tomography: analysis of 176 cases. Eur J Cardiothorac Surg 2008;34:892–7.
20. Hyun SH, Choi JY, Shim YM, Kim K, Lee SJ, Cho YS, et al. Prognostic value of metabolic tumor volume measured by 18F-fluorodeoxyglucose positron emission tomography in patients with esophageal carcinoma. Ann Surg Oncol 2010;17:115–22.
21. Park JC, Lee JH, Cheoi K, Chung H, Yun MJ, Lee H, et al. Predictive value of pretreatment metabolic activity measured by fluorodeoxyglucose positron emission tomography in patients with metastatic advanced gastric cancer: the maximal SUV of the stomach is a prognostic factor. Eur J Nucl Med Mol Imaging 2012;39:1107–16.
22. Robbins RJ, Wan Q, Grewal RK, Reibke R, Gonen M, Strauss HW, et al. Real-time prognosis for metastatic thyroid carcinoma based on 2-[18F]fluoro-2-deoxy-D-glucose-positron emission tomography scanning. J Clin Endocrinol Metab 2006;91:498–505.
23. Watanabe H, Kanematsu M, Goshima S, Kondo H, Kawada H, Noda Y, et al. Adrenal-to-liver SUV ratio is the best parameter for differentiation of adrenal metastases from adenomas using (18)F-FDG PET/CT. Ann Nucl Med 2013;27:648–53.
24. Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W, et al. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006;154:787–803.
25. Lo CY, Chan WF, Lam KY, Wan KY. Follicular thyroid carcinoma: the role of histology and staging systems in predicting survival. Ann Surg 2005;242:708–15.
26. Baloch Z, LiVolsi VA, Tondon R. Aggressive variants of follicular cell derived thyroid carcinoma; the so called 'real thyroid carcinomas'. J Clin Pathol 2013;66:733–43.
27. Mazzaferri EL, Robbins RJ, Spencer A, Braverman LE, Pacini F, Wartofsky L, et al. A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. J Clin Endocrinol Metab 2003;88:1433–41.
28. Young H, Baum R, Cremerius U, Herholz K, Hoekstra O, Lammertsma AA, et al. Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. Eur J Cancer 1999;35:1773–82.
29. Treglia G, Bertagna F, Piccardo A, Giovanella L. 131I whole-body scan or 18FDG PET/CT for patients with elevated thyroglobulin and negative ultrasound? Clin Transl Imaging. 2013. doi:10.1007/s40336-013-0024-0.
30. Mazzaferri EL, Kloos RT. Current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab 2001;86:1447–63.
31. Schlumberger M, Berg G, Cohen O, Duntas L, Jamar F, Jarzab B, et al. Follow-up of low-risk patients with differentiated thyroid carcinoma: a European perspective. Eur J Endocrinol 2004;150:105–12.
32. Piccardo A, Foppiani L, Morbelli S, Bianchi P, Barbera F, Biscaldi E, et al. Could [18]F-fluorodeoxyglucose PET/CT change the therapeutic management of stage IV thyroid cancer with positive (131)I whole body scan? Q J Nucl Med Mol Imaging 2011;55:57–65.
33. Rosenbaum-Krumme SJ, Görges R, Bockisch A, Binse I. 18F-FDG PET/CT changes therapy management in high-risk DTC after first radioiodine therapy. Eur J Nucl Med Mol Imaging 2012;39:1373–80.
34. Lee JW, Lee SM, Lee DH, Kim YJ. Clinical utility of 18F-FDG PET/CT concurrent with 131I therapy in intermediate-to-high-risk patients with differentiated thyroid cancer: dual-center experience with 286 patients. J Nucl Med 2013;54:1230–6.