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Original

The role of ^{18}F-Fluorodeoxyglucose Positron Emission Tomography in patients with suspected recurrence or metastatic differentiated thyroid carcinoma with elevated serum thyroglobulin and negative I-131 whole body scan

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Abstract

BACKGROUND: The aim of this study is to evaluate the role of ^{18}F-FDG PET/CT in the detection of recurrence or distant metastasis in patients with differentiated thyroid carcinoma (DTC) with elevated serum thyroglobulin (Tg) and negative ^{131}I whole-body scan.
MATERIAL AND METHODS: The study included 19 patients (13 female, 6 male, average age 64 years) with DTC after total thyroidectomy and ^{131}I ablation therapy that had elevated stimulated Tg and negative whole-body radioiodine scan. In all patients, standard imaging methods showed no suspicious changes. ^{18}F-FDG PET/CT was performed after TSH stimulation with rhTSH or withdrawal of thyroid hormone. An evaluation of the dependence of the result of ^{18}F-FDG PET/CT on the stimulated Tg levels was made accordingly. The statistical analysis was performed using Kruskal-Wallis test and ROC curves.
RESULTS: Based on the results of the study ^{18}F-FDG PET/CT in 6 patients, the suspicion of metastasis involved: the cervical lymph nodes (3 patients, ~16%) and lungs (3 patients, ~16%). The patients underwent surgery. The histopathology confirmed metastatic thyroid cancer in all cases. High levels of TSH-stimulated Tg (Tg from 32 to >300 ng/ml, median of 59.7 ng/ml) in patients were reported. The group of remaining 13 patients (~68%) with negative ^{18}F-FDG PET/CT had low levels of TSH-stimulated Tg (Tg of from 1.76 to 10.2 ng/ml, median of 4.0 ng/ml). A particular correlation was observed between ^{18}F-FDG PET positivity and stimulated Tg levels. The receiver operating characteristic curve (ROC) analysis demonstrated a stimulated Tg cut-off of 28.5 ng/ml with 100% sensitivity and specificity. Stimulated Tg has a large and statistically significant ($p<0.0001$) accuracy in the detection of recurrence/metastasis.
CONCLUSION:
1. ^{18}F-FDG PET/CT is useful in the diagnosis of radioiodine-negative DTC in patients with high levels of stimulated Tg.
2. The sensitivity of ^{18}F-FDG PET/CT increases with stimulated Tg levels. At stimulated Tg > 28.5 ng/ml, the sensitivity of the study reaches 100%.

KEY words: ^{18}F-FDG PET/CT, differentiated thyroid cancer, radioactive-negative, elevated human serum thyroglobulin

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Background

Thyroglobulin (Tg) is a sensitive and specific tumor marker in patients with differentiated thyroid carcinoma (DTC) after total thyroidectomy and radioiodine treatment. Elevated serum Tg indicates residual or recurrent disease (recurrence/metastasis) [1]

and usually has positive radioactive iodine scan (WBS, whole-body scan) [2, 3]. In some cases, thyroid cancer tissue does not concentrate I-131 [4]. Non-radioiodine avid changes are often associated with an aggressive clinical course [5]. In this situation it is necessary to perform other tests to assist in the imaging. It has been shown that PET/CT using ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG PET/CT) in the DTC may be useful for the detection of recurrence or metastases with a high degree of sensitivity, which is particularly useful with negative I-131 whole-body scan.

The aim of this study is to evaluate the role of ^{18}F-FDG PET/CT in the detection of recurrence or distant metastasis in patients with differentiated thyroid carcinoma with elevated serum thyroglobulin and negative I-131 whole-body scan (Table 1).

Material and methods

The study included 19 patients (13 female, 6 male, average age 64 years) with DTC after total thyroidectomy and I-131 ablation therapy that had elevated stimulated Tg and negative whole-body radioiodine scan. In all patients, standard imaging methods (ultrasound neck, chest X-ray) showed no suspicious changes. PET/CT were performed on Siemens Biograph camera 64, 60 minutes after the administration of ^{18}F-FDG activity 4 MBq/kg and after TSH stimulation with rhTSH or withdrawal of thyroid hormone. An evaluation of the dependence of the result of ^{18}F-FDG PET/CT on the stimulated Tg levels was made accordingly. The statistical analysis was performed using Kruskal-Wallis test and ROC curves (Table 1).

Results

Based on the results of the study ^{18}F-FDG PET/CT in 6 patients, the suspicion of metastasis involved: the cervical lymph nodes (3 patients, ~ 16%) and lungs (3 patients, ~ 16%) (Figure 1–6) and recommended further treatment. The patients underwent surgery. The histopathology confirmed metastatic thyroid cancer in all cases. High levels of TSH-stimulated Tg (Tg from 32 to > 300 ng/ml, median of 59.7 ng/ml) in patients with a positive ^{18}F-FDG PET/CT scans were reported. The group of remaining 13 patients (~ 68%) with negative ^{18}F-FDG PET/CT (absence of hypermetabolic foci) remains under further observation. This group of patients had low levels of TSH-stimulated Tg (Tg of from 1.76 to 10.2 ng/ml, median of 4.0 ng/ml) as compared to the patients with a positive ^{18}F-FDG PET/CT. Tg concentration in patients with PET (+) was statistically significantly higher ($p = 0.0006$) compared with those of PET (−). The influence on the outcome of thyroglobulin antibody was excluded by determining the level of thyroglobulin antibody and Tg recovery test in all the patients.

A particular correlation was observed between ^{18}F-FDG PET positivity and stimulated Tg levels. The receiver operating characteristic (ROC) curve analysis demonstrated a stimulated Tg cut-off of 28.5 ng/ml with 100% sensitivity and specificity (Figure 7 and 8). Stimulated Tg has a large and statistically significant ($p < 0.0001$) accuracy in the detection of recurrence/metastasis.

Table 1. The data and results of the patients included in the study

Patient	Age, sex F —female M — male	Histological type: P — papillary carcinoma F — follicular carcinoma	pTNM	Tg [ng/ml] after stimulation TSH	Location glucose foci in PET	SUVmax	Confirmation of cancer in histopathology
1	75, F	F	pT2N1Mx	32.0	Cervical lymph nodes Figure 1	3.73	Confirmation
2	74, F	P	pT3N1Mx	39.6	Cervical lymph nodes Figure 2	3.75	Confirmation
3	66, M	P	pT3N1Mx	66.5	Cervical lymph nodes Figure 3	7.07	Confirmation
4	54, F	P	pT3NxM1	> 300	Lung Figure 4	4.27	Confirmation
5	79, F	F	pT3NxM1	124	Lung Figure 5	3.25	Confirmation
6	69, F	F	pT2N1M1	52.9	Lung Figure 6	8.05	Confirmation
7	59, F	P	pT3NoMx	7.2	Absence	-	No surgery
8	59, F	P	pT3N1Mx	3.2	Absence	-	No surgery
9	63, M	P	pT1N1Mx	5.11	Absence	-	No surgery
10	55, F	P	pT2NxMx	1.79	Absence	-	No surgery
11	62, F	P	pT3NoMx	3.05	Absence	-	No surgery
12	55, F	P	pT3N1Mx	10.2	Absence	-	No surgery
13	56, M	P	pT2N1Mx	9.2	Absence	-	No surgery
14	61, F	P	pT1NoMx	3.97	Absence	-	No surgery
15	77, M	F	pT1N1M1	10.1	Absence	-	No surgery
16	39, F	P	pT4N1M1	3.35	Absence	-	No surgery
17	57, F	F	pT1NxMx	1.76	Absence	-	No surgery
18	69, M	P	pT3NxMx	10.0	Absence	-	No surgery
19	65, M	F	pT3NxM1	3.4	Absence	-	No surgery

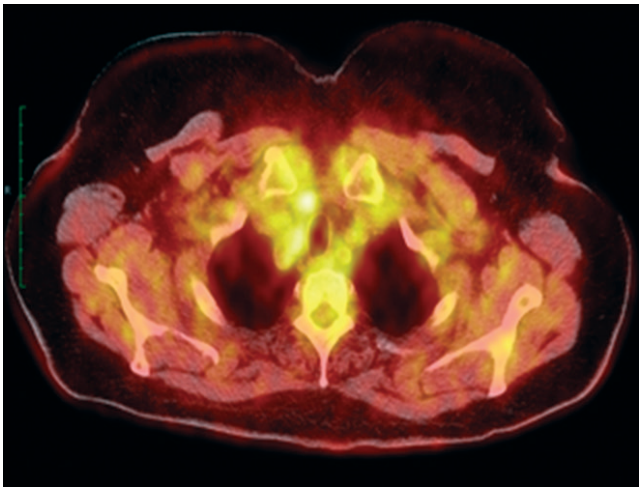

Figure 1. ^{18}F-FDG PET/CT revealed hypermetabolic uptakes in cervical lymph nodes and lungs in 6 patients

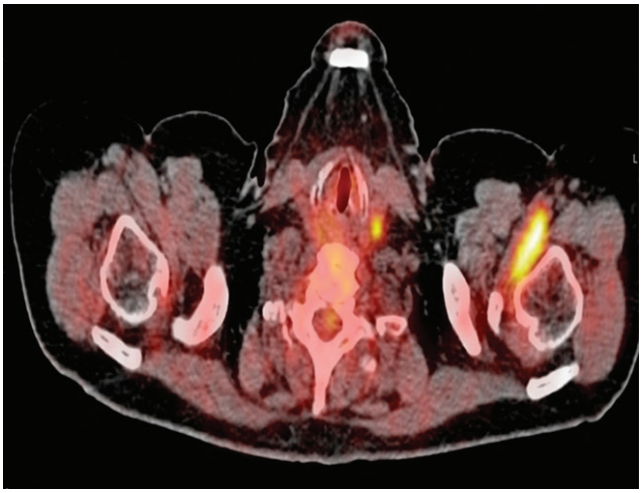

Figure 2. ^{18}F-FDG PET/CT revealed hypermetabolic uptakes in cervical lymph nodes and lungs in 6 patients

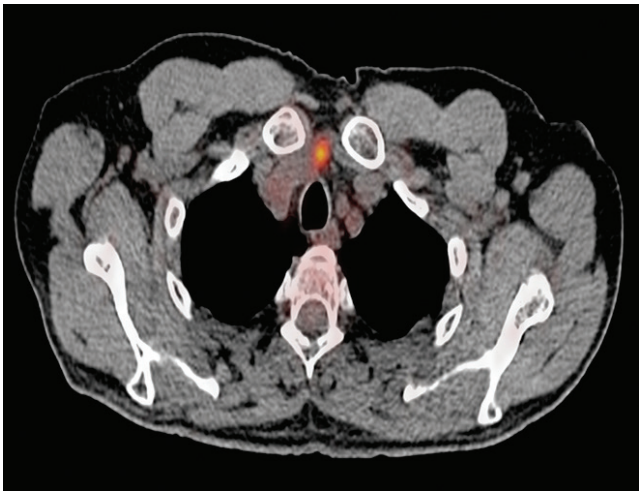

Figure 3. ^{18}F-FDG PET/CT revealed hypermetabolic uptakes in cervical lymph nodes and lungs in 6 patients

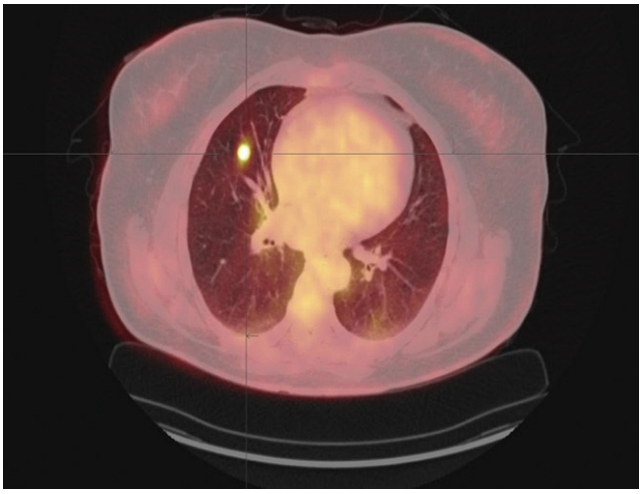

Figure 4. ^{18}F-FDG PET/CT revealed hypermetabolic uptakes in cervical lymph nodes and lungs in 6 patients

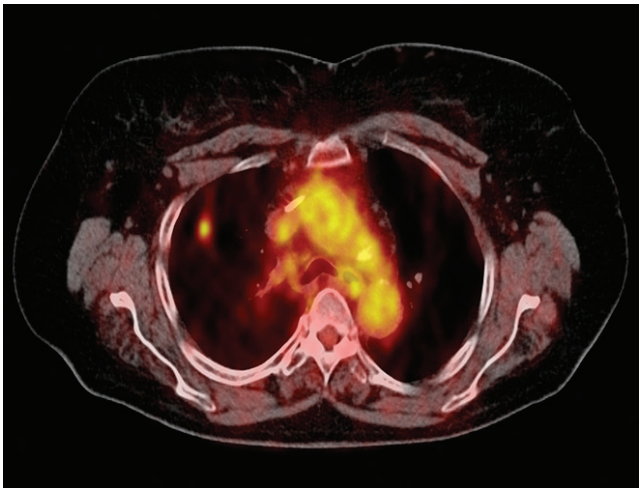

Figure 5. ^{18}F-FDG PET/CT revealed hypermetabolic uptakes in cervical lymph nodes and lungs in 6 patients

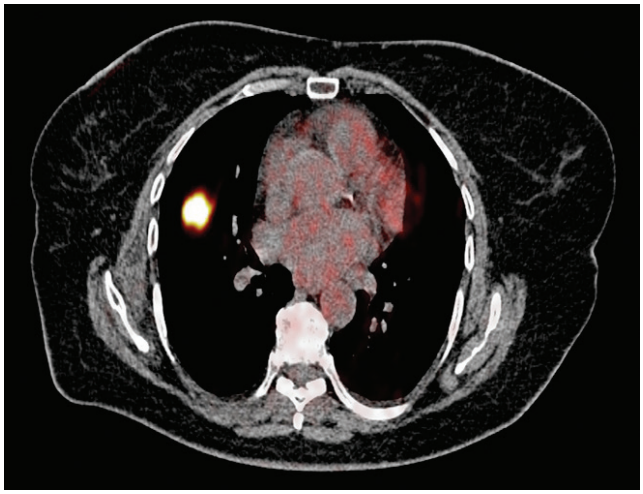

Figure 6. ^{18}F-FDG PET/CT revealed hypermetabolic uptakes in cervical lymph nodes and lungs in 6 patients

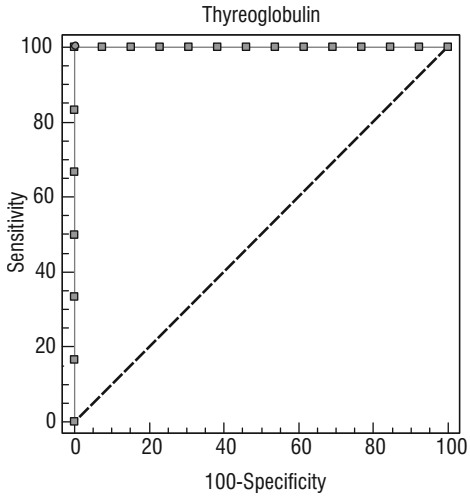

Figure 7. The ROC curve for stimulated Tg in the detection of recurrence/metastasis in PET

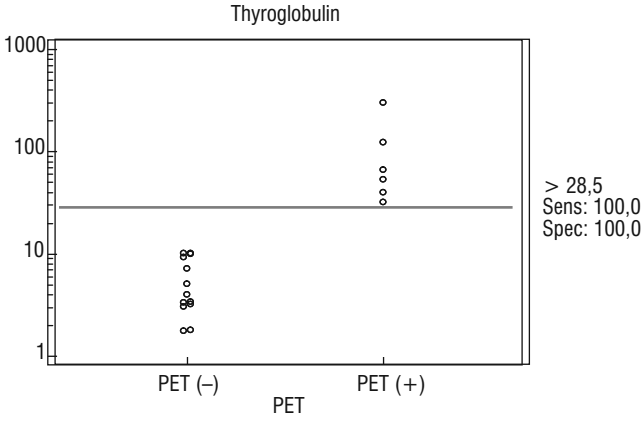

Figure 8. Stimulated Tg levels in PET (–) and PET (+). Logarithmic scale

Discussion

The first observations of fluorodeoxyglucose uptake in metastatic DTC were published more than 20 years ago [6]. Currently, PET/CT using ^{18}F-FDG is an increasingly useful tool in the detection of radioiodine-negative DTC [7–10].

The BRAF mutation, frequent in papillary thyroid carcinoma, leads to a reduced expression of sodium-iodine symporter (NIS) and increased expression of glucose transporter type 1 (GLUT1). Therefore, ^{18}F-FDG uptake indicates a low degree of differentiation and more aggressive tumor biology [11]. A lower probability of finding an increased metabolism of ^{18}F-FDG in radioiodine-positive DTC [12] was confirmed, in contrast to the radioiodine-negative lesions, which positively correlated with result of ^{18}F-FDG PET [7, 13, 14]. This correlation, known as the "flip-flop" phenomenon, has been also observed in our study [15].

Esterva et al. examined patients with DTC, elevated serum Tg and negative WBS after total thyroidectomy and I-131 ablation who underwent ^{18}F-FDG PET. The authors found a positive result in 32 of the 39 patients with confirmed metastatic or recurrent thyroid cancer. The latter group of patients (as compared to the group with the negative ^{18}F-FDG PET) showed significantly greater tumor size (2.82 cm v. 1.72 cm) [16]. This is consistent with our observations. In all of our patients with positive FDG PET, the tumor size was greater than 2 cm — T2 feature by the TNM classification (UICC 2010).

Rivera et al. studied the histology of the metastases from 70 patients with radioactive iodine refractory but characterized by a high metabolic activity demonstrated in a study of ^{18}F-FDG PET. Most of the changes were of more aggressive histological subtype than primary tumors. While comparing the histology of the primary tumor and its metastases, a gradual transformation of the less well-tumor differentiation was observed in most cases (primary tumor might not be FDG avid initially, whereas its metastases can be "positive FDG" over time) [17]. This phenomenon has been confirmed by molecular studies that have shown that mutations in the BRAF gene occur early in carcinogenesis of thyroid cancer, but mutations of PIK3CA and AKT1 are not to be found in primary cancers but in the metastases or recurrent cancers [18].

^{18}F-FDG PET/CT scans can be applied not only to detect radioiodine-negative recurrences or metastases [19, 20], or to obtain information on the biology of metastases, but also to obtain prognostic information. Many studies have shown that the results of ^{18}F-FDG PET correlate with overall survival [9, 10, 21]. Both positive ^{18}F-FDG PET in persistent/recurrent disease and a number of "FDG-positive metastases" are prognostic factors for survival [22, 10]. Patients with positive FDG-avid disease isolated to the regional lymph nodes had a low likelihood of death due to thyroid cancer (5-year survival of 91%) compared to 32% ($p = 0.0033$) for those with disease outside the regional lymph nodes [22]. Patients with SUV max greater than 10 respond less favorably to the radioiodine therapy and have a higher mortality rate in the observation of 3 years, as compared to patients without the FDG uptake [22, 23]. This information can be useful to justify the decision on the systemic treatment of patients with radioiodine-negative metastases and prognosis that patients can reach the maximum benefit from this treatment. In our study, all patients with positive foci of FDG PET underwent surgical treatment, which was followed by the observation of satisfactory levels of Tg.

FDG-PET is not sensitive enough to detect small (subcentimeter) metastases, as it is common in metastatic papillary thyroid carcinoma, and should therefore be used in conjunction with computed tomography (CT) imaging. In 2007, Shammas et al. evaluated the sensitivity and specificity of ^{18}F-FDG PET fused with CT, respectively 68.4% and 82.4% in 59 patients with radioiodine-negative, thyroglobulin-positive recurrent DTC [24]. Other studies have shown the sensitivity of 70–95% and a specificity of 77–100% [7, 8]. In our study, the sensitivity of FDG-PET in the detection of metastases is slightly lower than in previous reports. The differences may be due to patient selection. We qualified for the FDG-PET patients with relatively low levels of stimulated Tg (from 1.76 ng/ml), as compared to other works, where qualified patients had a significantly higher concentrations of stimulated Tg (even > 10 ng/ml).

Dietlein et al. also indicated that the degree of FDG uptake can vary in different organs and is the highest in the case of metastasis to the lymph nodes in the neck, and the lowest in the case of small (less than 1 cm) lung metastases [25]. In our work we have not identified any dependence between the average SUV max.

and the location of metastases (lung vs. nodes), but no material from our patients with small lung metastases was available to us.

TSH stimulates ^{18}F-FDG uptake by DTC cells [26]. TSH stimulation with rhTSH or withdrawal of exogenous thyroxin improves the sensitivity of PET [26–28]. It should be noted, however, that in a large multicenter study only 6% of the treatment planning was changed after identified FDG-avid lesions with rhTSH stimulation, as compared to studies with no stimulated FDG [28].

False positive results are an important issue. They can be caused by infections, granulomatous diseases (sarcoidosis) or postoperative inflammation in the changes that can coexist with thyroid cancer. False-positive results are reported in 11–25% of cases ^{18}F-FDG PET [29, 30]. Therefore, the nature of the suspected malicious "FDG positive changes," should be confirmed prior to further treatment of the disease. No false-positive results were observed in our study (all cases positive FDG PET changes were surgically removed and histologically confirmed as metastatic cancer). No false-positive results can thus occur in a relatively small group of patients studied.

The whole-body scintigraphy is not routinely performed to monitor disease remission in patients with DTC, and is displaced by the same concentration of Tg and neck ultrasound, because the chance of detecting radioiodine avidity recurrence without Tg increase is small. The criterion for the maintenance of remission after primary treatment is a negative ultrasound neck and the concentration of rhTSH-stimulated Tg below 1 ng/ml, in the absence of other feature of persistent or recurrent cancer, and in the absence of interfering factors, notably anti Tg. Scintigraphy using I-131 is performed with an increase of concentrations of Tg to search for recurrent or metastatic foci DTC.

In the clinical situation, where the increase of Tg levels is not accompanied by the detection of lesions in conventional imaging studies, or the whole body iodine scintigraphy, the application of ^{18}F-FDG PET/CT for the location of recurrence and metastasis of DTC is increasingly used.

Due to the high cost of PET/CT, it should be determined first at what concentrations of Tg we can expect positive results of PET.

In 2001, Schlüter et al. found that the test ^{18}F-FDG PET was the most promising at the concentrations of stimulated Tg > 10 ng/ml (TSH ≥ 30 μIU/ml). The authors reported that the true positive scans ^{18}F-FDG PET were positively correlated with increasing concentrations of Tg and were respectively 11%, 50% and 93% in patients with Tg < 10, 10–20 and >100 ng/ml [31].

In 2005, an assessment of imaging with ^{18}F-FDG PET in 54 patients with radioiodine-negative DTC, suspected of thyroid cancer recurrence because of elevated serum-stimulated Tg > 2 ng/ml (TSH ≥ 30 μIU/ml). During the PET patients received a full substitution of thyroid hormones. The presence of foci of increased glucose metabolism were found in 25/54 patients (46.29%) at concentrations of unstimulated Tg higher than 10 ng/ml [33].

The cut-off point of stimulated Tg > 10 ng/ml was then included in the American guidelines ATA (American Thyroid Association) in 2009 as a recommendation for the implementation of ^{18}F-FDG PET in patients with DTC and negative I-131 WBS [34].

In 2012, Polish authors reported the results of their study of 44 patients with DTC, Tg (+), WBS (−), indicating that the positive results of PET/CT using ^{18}F-FDG activity 5 MBq/kg was achieved in 18/44 patients (40.9%), with the concentrations of endogenous or exogenous stimulated Tg in excess of 30 ng/ml [35].

Additionally, Turkish authors in their study of 105 patients with DTC, negative WBS and elevated concentrations of Tg, published in Clinical Nuclear Medicine in 2012, reported 69 true-positive, 20 true-negative, 6 false-positive and 10 false-negative results of FDG PET/CT. A significant correlation was found between the positivity of PET and the high Tg levels (p = 0.0001). The ROC curve analysis demonstrated a Tg cut-off of 1.9 ng/ml under thyroid-stimulating hormone suppression, 38.2 ng/ml with thyroid-stimulating hormone stimulation [36].

In 2013, Van Dijk et al. [37] presented a study on 52 patients with DTC, Tg (+) during thyroxine withdrawal, who underwent FDG PET within three months after the negative posttherapeutic WBS. Additional tumor localization has been showed in 17% of patients, leading to a change in the clinical management in 13%. A clinically useful Tg cut-off value was not found, however 90% of positive FDG-PET scans occurred in patients with endogenously stimulated Tg > 2.00 ng/ml. At Tg-off cut-off value 38 ng/ml, the sensitivity and specificity were 67% and 95 %, and the area under the ROC curve was 0.82 (p < 0.01).

Assessing scans in 60 patients, the Korean authors [38] found that FDG PET/CT was useful in the detection and localization of recurrent thyroid cancer in patients with negative diagnostic WBS and stimulated Tg greater than 20 ng/ml or with a high anti-TgAb titer (> 70 IU/ml). In contrast, FDG PET/CT provides little additional information when stimulated Tg concentration was less than 5 ng/ml. In our study, we obtained the stimulated Tg cut-off of 28.5 ng/ml, while the sensitivity of ^{18}F-FDG PET/CT was 100%.

Also in 2013 Giovanella et al. [39] published a report, which evaluated the relationship between Tg levels, Tg doubling time (Tg-DT) under TSH suppression by levothyroxine treatment and the diagnostic usefulness of ^{18}F-FDG PET/CT in the detection of recurrence in 102 patients with DTC and WBS (−). Higher concentrations of Tg were reported in patients with positive FDG PET/CT scan (median 6.7 ng/ml, range 0.7–73.6 ng/ml) than in patients with negative scan (median 1.8 ng/ml, range 0.5––4.9 ng/ml, p < 0.001). In 43 (88%) of 49 patients with true-positive FDG PET/CT scan, was observed Tg> 5.5 ng/ml, in contrast to the 31 (74%) of 42 patients with true-negative results FDG PET/CT, where Tg levels were ≤ 5.5 ng/ml. A Tg doubling time (Tg-DT) < 1 year was found in 46 of 49 patients (94%) with true-positive FDG PET/CT scan. In contrast, in 40 of 42 patients (95%) of the true-negative scans Tg-DT had a stable or increased > 1 year. The accuracy of FDG PET/CT was significantly increased when the serum Tg level was greater than 5.5 ng/ml during levothyroxine treatment or when Tg-DT occurred in less than 12 months, independently of the absolute value. In our study, we assessed the relationship between stimulated Tg levels and FDG PET, but also retrospectively found Tg-DT < 1 year in 5 (83%) of 6 patients with PET FDG (+) and Tg-DT a stable or > 1 year of 12 (86%) of 14 patients with FDG PET (−).

In 2012, Leboulleux et al. [40] proposed FDG PET/CT as the preferred over empiric WBS in DTC patients who had suspected recurrence based on elevated serum Tg or Tg-Ab after a normal postablation WBS. The sensitivity of PET/CT in the detection of metastatic lesions was 88–97%, compared to 16–22% for the WBS.

The sensitivity of ^{18}F-FDG PET depends on the number of cancer cells correlated with serum Tg and the rate of glucose metabolism dependent on the malignancy of the tumor. The second parameter is the most likely factor in the differences in the sensitivity

of PET in patients with DTC with elevated concentrations of Tg. Undoubtedly, the existing achievements and new methods to be developed in the future will help explain the above differences and make the optimal use of imaging technique ^{18}F-FDG PET in patients with recurrent or metastasis DTC possible.

Conclusions

1. 18F-FDG PET/CT is useful in the diagnosis of radioiodine-negative DTC in patients with high levels of stimulated Tg.
2. The sensitivity of 18F-FDG PET/CT increases with stimulated Tg levels. At stimulated Tg > 28.5 ng/ml, the sensitivity of the study reaches 100%.

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