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Role of Thyroglobulin Doubling Time in Differentiated Thyroid Cancer and Its Relationship with Demographic-Histopathologic Risk Factors and 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Parameters

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Abstract

Background: Aim of this study was to investigate the relationship between thyroglobulin doubling time (TgDT) and basal risk factors and metabolic parameters derived from 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) in differentiated thyroid cancer (DTC).
Materials and Methods: An analysis of 95 DTC patients who had rising serum thyroglobulin (Tg) levels under levothyroxine (LT4) suppression after radioiodine therapy was made. TgDT was calculated for 28/95 patients. The relationship between TgDT and basal demographic and histopathologic risk factors, preablative Tg, and antithyroglobulin antibody (ATg) levels and metabolic parameters was analyzed.
Results: In 28 patients (15M, 13F, mean age: 52.6 ± 17.6) that TgDT could be calculated, 18F-FDG PET/CT was positive in 12 patients. Median TgDT was lower in 18F-FDG PET/CT positive patients compared to the negative cases ($p < 0.05$). Patients with skeletal metastasis or local recurrence had a shorter DT compared to the patients with lung metastasis. TgDT was correlated with peak standardized uptake value (SUVpeak) ($p < 0.05$). Maximum standardized uptake value (SUVmax) was correlated with tumor size ($p < 0.05$) and mean standardized uptake value (SUVmean) with tumor size and vascular invasion ($p < 0.05$). Median SUVmax and SUVmean were higher in follicular cancer or poor histological variants of papillary DTC compared to papillary cancer classical variant patients
Conclusion: TgDT may be predictive of a positive 18F-FDG PET/CT in DTC. Skeletal metastasis and local recurrence are related to shorter TgDT. Greater tumor size, vascular invasion, and follicular cancer or poor variants of papillary carcinoma are related with higher SUVmax and SUVmean. Larger scale studies are needed to confirm results and to calculate a possible cutoff of TgDT for a positive 18F-FDG PET/CT study.

Keywords: 18F-FDG PET/CT, thyroglobulin, doubling time, thyroid cancer

Introduction

Differentiated thyroid carcinoma (DTC) is the most frequently seen endocrine malignancy. Although DTC usually has relatively good prognosis, recurrence rates up to 20% and disease-related death rate of 8% were reported.[1] Serum thyroglobulin (Tg) is an important marker in the follow-up of these patients. A progressive elevation of serum Tg in DTC after total thyroidectomy, either followed by radioiodine (RAI) ablation or not, is highly predictive of recurrence or metastasis. In long-term follow-up, sequential Tg measurements are more accurate in the evaluation of therapy response.[2] Patients are recommended to be followed up by sequential Tg measurements according to revised version of American Thyroid Association (ATA) thyroid cancer management guidelines.[3]

Progressive increase in suppressed serum Tg levels has also been reported as an independent prognostic factor in DTC. Thyroglobulin doubling time (TgDT) is another parameter

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under focus, which has been proposed to be used in predicting survival, distant metastasis, and recurrence.[4]

In DTC patients with elevated serum Tg levels, neck ultrasonography (USG), computerised tomography (CT) of the neck and thorax, and I-131 whole body scintigraphy (WBS) are the conventional imaging methods for detection of recurrent or metastatic foci. However, all these modalities have several limitations.[5] In this patient group, 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) has been reported as an important functional imaging method.[6–8] The threshold of serum Tg over which 18F-FDG PET/CT is effective is variable.[9–11]

18F-FDG is the most widely used nonspecific tumor imaging agent. Its uptake in malignant cells depends on the glucose consumption, which is a measure of metabolic rate, aggressiveness, and thus differentiation of the tumor. Therefore, existence, localization, dimension, and extent of disease can be evaluated by 18F-FDG PET/CT, as well as the metabolic behavior of the tumor. Several methods to quantify this metabolic activity have been proposed to make accurate, objective, and comparable measurements of pathological uptake sites on 18F-FDG PET/CT studies.[12] Some of these parameters derived from the functional data of 18F-FDG PET/CT have also been correlated with survival and recurrence.[13]

In this study, the authors aimed to investigate if TgDT has a relationship between initial clinical-pathological risk factors and metabolic parameters derived from 18F-FDG PET/CT data in DTC patients with elevated serum Tg levels.

Materials and Methods

Patients

Clinical data of 3050 DTC patients who received RAI ablation in the department between January 1998 and January 2015 were retrospectively evaluated. Patients who had (1) histologically proven DTC by total thyroidectomy, (2) RAI ablation following surgery, (3) high serum Tg levels under levothyroxine (LT4) suppression therapy in the follow-up (serum Tg >2 ng/dL), (4) at least three consecutive Tg measurements obtained in the follow-up to be able to calculate TgDT, (5) inconclusive or negative neck ultrasonography and thorax CT results, and thus no true evidence of a structural disease causing Tg elevation, (6) 18F-FDG PET/CT performed for Tg elevation, and (7) at least 6 months of surveillance time after 18F-FDG PET/CT were included.

Exclusion criteria were as follows: (1) history of subtotal thyroidectomy, (2) history of low-risk DTC for whom RAI ablation is not necessary, (3) histology of anaplastic, undifferentiated, or medullary thyroid cancer, (4) antithyroglobulin antibody (ATg) positivity following total thyroidectomy and RAI ablation, (5) unavailability of three consecutive Tg measurements due to early surgeries or RAI therapies performed instead of waiting further to observe the rising trend of serum Tg levels, (6) unavailability of clinical follow-up data, and (7) existence of a secondary primary malignancy.

Among the whole DTC group, 95 patients had rising serum Tg levels under LT4 suppression in the follow-up after RAI ablation. Twenty-eight/95 patients who fulfilled the above-mentioned criteria were included in the study (Figure 1). RAI ablation was performed 4–6 weeks after total thyroidectomy, off LT4, after making sure that serum thyroid-stimulating hormone (TSH) levels are above 30 IU/mL. Preablative serum Tg and ATg values were noted under TSH stimulation. Fixed-dose protocol was used for ablation. One thousand one hundred and ten to 3700 MBq was administered for low-intermediate risk group (intrathyroidal tumors with no lymph node metastasis or <5 micrometastasis and no other risk factors were determined as low risk, minimal extrathyroidal invasion, aggressive

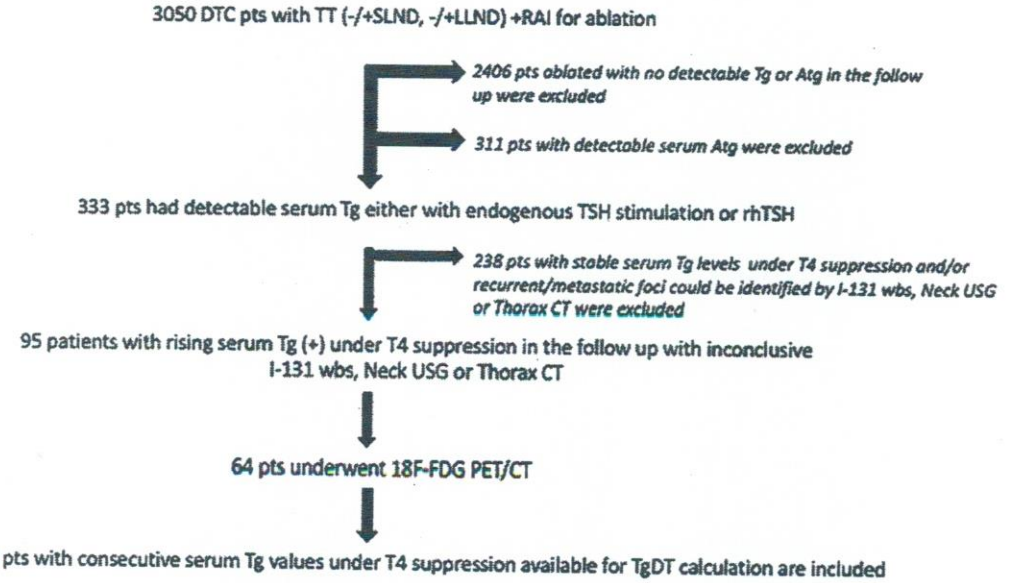


FIG. 1. The flow scheme demonstrating how enrolled patients were selected according to the inclusion and exclusion criteria. CT, computed tomography; FDG, fluorodeoxyglucose; LLND, lateral lymph node dissection; PET, positron emission tomography; RAI, radioiodine; SLND, central lymph node dissection; Tg, thyroglobulin; TgDT, thyroglobulin doubling time; TSH, thyroid-stimulating hormone; TT, total thyroidectomy; USG, ultrasonography.

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histology, existence of >5 lymph node metastasis with tumor diameter <3 cm, papillary cancer with vascular invasion, or multifocal microcarcinomas were categorized as intermediate risk) and 4625–5550 Mq for high-risk group (gross extrathyroidal extension, lymph node or distant metastasis, follicular cancer with vascular invasion, or incomplete resection of tumor was accepted as high risk). Prescribed ablation doses were not higher than 5550 MBq.

LT4 suppression therapy was started on the second day of RAI. A postablative I-131 WBS was obtained at 5–7 days of ablation. All patients also underwent diagnostic I-131 WBS performed by 185 MBq I-131 6–12 months later and stimulated Tg and ATg levels were again measured as well. First serum Tg measurement under LT4 suppression is obtained within 1 year after RAI. Neck USG was performed every year and suppressed serum Tg and ATg levels were measured every 6 months under LT4 suppression in the follow-up. In case serum Tg measurements showed a rising pattern, then measurements were performed more frequently and TgDT was derived from three consecutive Tg values measured within 6 months. 18F-FDG PET/CT was performed in patients with elevated serum Tg in less than 2 weeks after the last serum Tg measurement was used for TgDT calculation.

18F-FDG PET/CT protocol

Following 6 h of fasting, about 370 MBq 18F-FDG was injected intravenously, provided blood glucose level was <150 mg/dL. Whole-body PET/CT images were obtained by hybrid PET/CT scanner (Discovery ST; General Electric Company) from vertex to upper thigh, 60 min after radiopharmaceutical injection. PET scan was performed 3 min/-bed position. Attenuation correction was done by low-dose CT (140 kV, 70 mA, 0.5 s/tube rotation, and slice thickness 5 mm). Patients were allowed to breathe normally. Maximum intensity projection (MIP) and attenuation-corrected PET/CT fusion images were evaluated in three planes (transaxial, coronal, and sagittal) (Advance Workstation Volumeshare 5 GE Medical Systems).

Image analysis

Volumetric and semiquantitative data were calculated on workstation by using PET VCAR software (GE Healthcare). All 18F-FDG PET/CT images were retrospectively rereviewed by 2 experienced nuclear medicine specialists. The criteria of a positive PET/CT study was defined as existence of at least one focus of increased 18F-FDG uptake in comparison to background/blood pool activity, and intense foci of hypermetabolism distinguishable from the neighboring tissue with physiological uptake are accepted as pathological. Whole-body MIP images were used to decide the pathological hypermetabolic regions to be used in calculation. Volume of interest (VOI) was automatically drawn around the target lesions with isocontour method. Metabolic tumor volume (MTV), maximum standardized uptake value (SUVmax), mean standardized uptake value (SUVmean), and peak standardized uptake value (SUVpeak) were calculated for every separate hypermetabolic region distinguishable on MIP images. Total lesion glycolysis (TLG) was then obtained by multiplying SUVmean and MTV for the target lesions.

Data analysis

18F-FDG PET/CT images of 28 patients for whom TgDT calculation (with at least three consecutive serum Tg measurements) was possible were reevaluated under the scope of this study. Metabolic parameters were calculated in 12 patients with a positive 18F-FDG PET/CT study. As clinical prognostic factors, age, gender, extent of the thyroid surgery for the primary tumor, details of the histopathological results (thyroid cancer type, subvariants of the tumor, size of the tumor, existence of capsular or vascular invasion, and lymph node metastasis), and preablative stimulated Tg levels were noted for each patient for statistical analysis. Clinical follow-up data, including I-131 WBS, neck USG, thorax CT, and 18F-FDG PET/CT results, together with Tg levels under and/or LT4 suppression, were also used.

Statistical analysis

The descriptive statistics of the variables were performed (median and 25%–75% range). Normality was checked using the Kolmogorov–Smirnov test. For non-normally distributed variables, nonparametric tests were used. For comparison of two groups, Kruskal-Wallis and Mann-Whitney *U* tests were used. For correlation analysis, Spearman analysis was made.Values of $p < 0.05$ were significant. Statistical analysis was performed using the Statistical Package for Social Sciences—SPSS 17.0 (Chicago, IL).

Results

A total of 28 DTC patients (13F, 15M, mean age: 52.6 ± 17.6 years) with elevated serum suppressed Tg levels and TgDT that could be calculated were involved in the study. Among the study group, 22/28 patients (78.6%) had papillary, 4/28 (14.3%) follicular, and 2/28 (7.1%) papillary and follicular mixed-type DTC. Histological subgroups of papillary cancer patients were as follows: classical variant in 19/22 patients (86%), follicular variant in 1/22 patient (4%), tall cell variant in 1/22 patient (4%), and Hurthle cell variant in 1/22 patient (4%). Only total thyroidectomy was performed in 15/28 patients (53.6%), while total thyroidectomy and central lymph node dissection were performed in 6 patients (21.4%), and both central and lateral lymph node dissection, in addition to total thyroidectomy, were performed in 7 patients (25%). Following thyroid operation, 1100–5550 MBq RAI doses (mean: 5097.86 ± 930.18 MBq) were administered in the authors' department. Clinical follow-up after surgery ranged between 2 and 14 years (mean 7.08 ± 3.63 years)

18F-FDG PET/CT study was normal in 16/28 patients. In 12/28 patients with a distinguishable pathological uptake on 18F-FDG PET/CT scan, median MTV, SUVmax, SUVmean, SUVpeak, and TLG were calculated. Along with demographics, PET/CT findings are summarized in Table 1. All patients with local recurrence or metastasis in the neck had 18F-FDG avid lesions. However, some skeletal and lung metastasis were not positive on 18F-FDG PET/CT. These lesions were confirmed to be metastatic in the follow-up either because they were RAI avid or showed progression on CT. In the whole study group, local recurrence was detected in 9/28 patients, skeletal metastasis in 6/28 patients, lung metastasis in 15/28 patients, and brain metastasis

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TABLE 2. DIFFERENCE OF MEDIANS OF PARAMETERS ACCORDING TO 18F-FLUORODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY POSITIVITY

	Median	*Min*	*Max*	p
18F-FDG PET/CT findings				
TgDT				
Negative	10.75	3.23	37.50	0.023
Positive	3.80	1.84	19.41	
Vascular invasion				
SUVmean				
Negative	4.11	1.17	8.24	0.025
Positive	11.37	5.39	17.35	
Poor histologic variants				
SUVmean				
Negative	4.11	1.17	8.24	0.025
Positive	11.37	5.39	17.35	
SUVmax				
Negative	10.43	2.62	15.8	0.047
Positive	17	10.64	23.37	

CT, computed tomography; FDG, fluorodeoxyglucose.

in 1/15 patients, detected either by 18F-FDG PET/CT or other imaging tools.

Median TgDT calculated in the whole study group was 8.97 months (min:1.84–max:37.5 months). Statistically significant correlation was found between SUVpeak and TgDT ($p<0.05$). Median TgDT was significantly shorter in patients with a positive 18F-FDG PET/CT scan compared to the patients with a normal 18F-FDG PET/CT study (3.8 months, min:1.84–max:19.41 vs. 10.75 months min:3.24–max:37.5) ($p<0.05$). Although the ROC curve conducted was not discriminative enough, for a cutoff value of TgDT = 11.03 months, sensitivity and specificity for predicting a positive 18F-FDG PET/CT were 83% and 50%, respectively. In the whole study group, patients who had skeletal metastasis or local recurrence had a significantly shorter DT compared to the patients with lung metastasis only ($p<0.01$, median (min-max): for skeletal metastasis: 3.71 (3.49–4.07) months, for local recurrence or metastasis in the neck: 3.52 (2.26–10.77) months, and for lung metastasis: 15.12 (9.8–37.5) months.

Tumor size was correlated with SUVmax ($p<0.05$) and SUVmean with vascular invasion and tumor size ($p<0.05$). Median SUVmean was also found higher in patients with vascular invasion (11.37, min:5.39–max:17.35 in patients with vascular invasion vs. 4.11, min:1.17–max: 8.24 in patients without vascular invasion). No significant correlation was found between MTV, TLG, and any other clinical prognostic parameter. Median SUVmax and SUVmean were found higher in follicular type DTC or poor histological variants of papillary DTC compared to papillary cancer classical variant patients (for SUVmean: 11.37, min:5.39–max:17.35 vs. 4.11, min:1.17–max:8.24; and for SUVmax: 17.0, min:10.64–max:23.37 vs. 10.43, min:2.62–max:15.8) ($p<0.05$) (Table 2).

Discussion

In studies focusing on TgDT, shorter TgDT was found to be associated with poor clinical prognostic factors like 18F-FDG positivity and metastatic disease.[14] Similarly, in this study, median TgDT was significantly shorter in patients with a positive 18F-FDG PET/CT compared to the patients who had a normal PET/CT scan ($p<0.05$). This finding was also compatible with the previous findings, suggesting that TgDT was predictive of recurrence and metastasis. 18F-FDG PET/CT seems to be guiding in patients with shorter TgDT and thus with more aggressive tumors of a higher metabolic rate, which is reasonable, considering the general rule of higher 18F-FDG avidity in tumors with higher proliferation rate.

Giovanella et al. also showed that serum Tg levels were higher in 18F-FDG PET-positive patients. TgDT was calculated <1 year in these patients and TgDT was an independent prognostic factor for 18F-FDG positivity.[15] In this study, the authors also calculated the best cutoff value for TgDT to estimate a positive 18F-FDG PET/CT study as 11.03, although the ROC curve was not very convenient. In the opposite situation, when TgDT is calculated longer, it was also proven that "watchful waiting" would be sufficient in these patients, especially if 18F-FDG PET/CT was normal.[16] However, they observed that all patients with skeletal metastasis had a TgDT <5 months and some were not 18F-FDG avid. Thus, the authors propose that, short TgDT can be an effective indicative sign for local recurrence or metastatic disease. Even if 18F-FDG PET/CT is negative, skeletal metastasis should be suspected, especially because TgDT for lung metastasis and local recurrence are much longer and they are usually with positive PET/CT results. Conversely, because all recurrences or metastasis in the neck were 18F-FDG avid, PET/CT seems to have a reliable negative predictive role for screening the neck, although neck ultrasound is still inevitably the method of choice for neck imaging.

When it comes to the lungs, some lung metastases were 18F-FDG avid and some were not. In a study investigating lung metastasis in DTC patients, it was shown that lung metastasis had a relatively favorable outcome, except for macrometastasis.[17] In this series, the authors also observed that metastasis in the lungs usually remained stable in the follow-up, no matter how its 18F-FDG avidity is.

Skeletal metastases of DTC is known to have worse prognosis compared to lung metastases, which is probably due to less curative effect of RAI in large bone lesions, whereas millimetric lung metastases may benefit more.[17,18] Rössing et al. have showed that mortality risk was increased by two in patients with TgDT <5 months compared to TgDT >12 months. Survival analysis was out of the scope of this study, but, in the whole study group, patients who had skeletal metastasis appeared to have a significantly shorter TgDT compared to the patients with lung metastasis only, supporting these data.[19]

In a recent study, MTV and TLG were also calculated higher in patients with skeletal metastases and, although not statistically significant, in patients with TgDT <12 months.[20] In this study, among metabolic parameters derived from 18F-FDG PET/CT studies, only SUVpeak was found correlated with TgDT ($p<0.05$). Standardized uptake value (most commonly SUVmax) is the most widely used quantitative index for the measurement of cellular density of tumoral tissue.[21] SUVmax is a relative measurement of activity concentration in a given voxel in proportion to the total

injected activity. However, SUV is a calculation method standing on the assumption that the injected activity is uniformly distributed throughout the body and can be affected by many different factors like size of the tumor (due to partial volume effect), patient motion (including respiration), post-injection acquisition time, and image reconstruction method.[21–23] Although it is practical to use SUV, especially SUVmax, some other parameters have been proposed to be appropriate for quantification.[24–26]

MTV and TLG are very successful for an accurate quantification, and among SUV measurements, SUVpeak was reported to be the most reliable method. SUVpeak represents the mean SUV within a constant $1cm^3$ voxel drawn in the region with the hottest 18F-FDG uptake throughout the whole 18F-FDG avid tissue, which is apparently different from SUVmax, defined as the value of the pixel with the highest 18F-FDG uptake. Because SUVpeak does not reflect the value of a single pixel, but represents the mean value of more than one pixel, noise is less effective on SUVpeak than on SUVmax.[27] In many other oncology studies, SUVpeak was found as an important prognostic factor, while SUVmax was not correlated with survival at all. The authors also found a significant correlation between TgDT, a well-known prognostic factor, and SUVpeak, supporting these previous findings.

SUVmean is defined as mean value of radiopharmaceutical uptake of the pixels found in the chosen region of interest. Because determination of the borders of the lesion is closely related with noise, PET resolution, reconstruction method, and partial volume effect, SUVmean measurements are not always repeatable and accurate. This handicap is mostly valid for tumors with heterogenous uptake and practical use of SUVmean is thus limited.[28] In this study, the authors found a significant correlation between SUVmax and tumor size and between SUVmean and vascular invasion, as well as tumor size ($p<0.05$). In a study investigating the characteristics of patients with a false negative 18F-FDG PET study, tumor size >1 cm and lymphovascular invasion were the two independent determinants of a positive 18F-FDG PET.[29] The relationship between tumor size and 18F-FDG PET positivity has also been reported in some other series.[30] Thus, relatively higher levels of SUVmax and/or SUVmean calculated in patients with a higher tumor size and vascular invasion in this study is coinciding with the previous data.

Median SUVmax and SUVmean were higher in patients with follicular type or poor histologic variants of papillary cancer compared to classical variant papillary cancer patients ($p<0.05$). That finding was not surprising as 18F-FDG uptake was reported to be correlated with tumor dedifferentiation and aggressive clinical behavior.[31,32] Fast progression, metastasis, and poor clinical outcome can be seen in poor histologic variants of DTC and it has been proven that existence of these pathologic subgroups in initial surgery was indicative of a tumor with high metabolic activity and higher 18F-FDG uptake.[30,33]

The most widely used quantification method, SUVmax, does not represent the 18F-FDG uptake of the whole tumoral tissue, but reflects only the highest amount of 18F-FDG uptake in a given VOI.[34] This is why volumetric parameters like MTV and TLG, which are the measures of the total tumor load in the body, have been proposed as more accurate markers for quantification of disease severity and extension in many other cancers.

In a recent study by Nakajo et al., it has also been shown that on 18F-FDG PET/CT performed for preoperative staging and risk stratification of DTC, MTV calculated $>10.0\,cm^3$ was indicative of high-risk disease.[35] However, in this study, all 18F-FDG PET/CT examinations were performed after the primary tumor is removed and the authors found no correlation between volumetric parameters and TgDT or other clinical variables. Volumetric calculations may not be effective enough in DTC because they do not usually present with very extensive disease, including many metastatic-recurrent sites or bulky tumors, compared to the other relatively aggressive cancer types reported in the literature (like head and neck or lung cancer), which frequently show high tumoral volumes and metabolic activity on 18F-FDG PET/CT scans.[34,36–38] Although volumetric parameters have been suggested effective in predicting lateral lymph node metastasis in incidental DTC, there are no such data about the authors' study group, DTC patients who underwent 18F-FDG PET/CT for increased Tg levels after total thyroidectomy and RAI ablation.[39]

The main limitation of this study was that the study population was relatively small. Although the authors could still demonstrate statistically significant correlations between TgDT and 18F-FDG positivity, between TgDT and SUVpeak, and between SUV and some of the histopathologic poor prognostic factors, these results certainly would be more valuable if supported with further studies conducted in larger series. A cutoff value for TgDT indicative of a positive 18F-FDG PET study could be calculated, survival analysis would also be possible, and probable prognostic importance of TgDT could be interpreted.

Conclusion

18F-FDG PET/CT is an important functional imaging modality in detection and localization of recurrent or metastatic disease in DTC patients with elevated serum Tg. TgDT is shorter in DTC patients with a positive 18F-FDG PET/CT scan. Skeletal metastasis and local recurrence are also related to shorter TgDT. 18F-FDG PET/CT may be more helpful in the clinical follow-up of patients with a higher tumor size, vacular invasion, and follicular type or poor variants of papillary carcinoma, as calculated SUVmax and SUVmean are higher in these patients. Larger patient populations are needed to determine if TgDT is an independent prognostic factor for survival in DTC, to calculate a cutoff for TgDT and tumor size indicative of a positive 18F-FDG PET/CT study, and to support the novel finding that volumetric parameters are not correlated with TgDT or any previously proven histopathologic prognostic factors in DTC.

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Disclosure Statement

No competing financial interests exist.

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