Impact of TSH stimulation on 2-[^{18}F]FDG PET/CT results in patients with papillary thyroid carcinoma presented with elevated serum thyroglobulin level and negative diagnostic iodine-131 whole-body scan

Original Article

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ABSTRACT

Introduction: 2-[^{18}F]fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography (2-[^{18}F]FDG-PET/CT) is implemented in papillary thyroid cancer (PTC) patients with elevated Thyroglobulin (Tg) and negative Iodine-131 whole-body scan (^{131}I-WBS). Here, we evaluated the impact of TSH stimulation after levothyroxine withdrawal on the detection rate of 2-[^{18}F]FDG-PET/CT.

Methods: A prospective study was performed on 60 PTC patients, presented with negative ^{131}I-WBS and elevated or unjustifiably high Tg. 2-[^{18}F]FDG-PET/CT was performed in 30 patients while they were on levothyroxine therapy (unstimulated-TSH [uns-TSH]) and after Levothyroxine withdrawal in the other 30 patients (stimulated-TSH [s-TSH]). Results of the two groups were compared using nonparametric tests. Receiver operating characteristic curve was used to find Tg cutoff values for predicting positive scan results.

Results: Overall, 2-[^{18}F]FDG-PET/CT was positive in 63.3% of the patients, 80% (24/30) in s-TSH and 46.7% (14/30) in uns-TSH group. The detection rate was higher in s-TSH group (p=0.007). It was still significant in multiple regression analysis (p=0.041). In uns-TSH group, 2-[^{18}F]FDG-PET/CT was more often positive in patients with higher uns-Tg level (p=0.002). An uns-Tg level of ≥19.00 ng/mL predicted positive results with the sensitivity of 0.786 and specificity of 0.750 (area under curve=0.819). Although statistically insignificant (p=0.055), s-Tg was higher in patients with positive 2-[^{18}F]FDG-PET/CT studies in the s-TSH group. No relation was demonstrated between TSH and anti-Tg-antibody levels and 2-[^{18}F]FDG-PET/CT positivity.

Conclusion: TSH-stimulation after levothyroxine withdrawal might enhance the detection rate of 2-[^{18}F]FDG-PET/CT in PTC patients. Additionally, 2-[^{18}F]FDG-PET/CT is more often positive in patients with higher Tg levels.

Key words: Differentiated thyroid cancer; Levothyroxine withdrawal; 2-[^{18}F]FDG PET/CT; Elevated thyroglobulin; Negative radioiodine scan

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INTRODUCTION

Differentiated thyroid cancer (DTC) is a relatively prevalent but treatable disease. Given the considerable recurrence rate of 25% [1], especially in the first 10 years after diagnosis [2], follow-up evaluations over the years after the treatment is essential [3]. Routine follow-up in these patients is a tripartite approach, including anatomical (neck ultrasonography) and functional ([^{131}I]-iodine whole-body scan ^{131}I-WBS]) imaging concomitant with biochemical assay (Thyroglobulin [Tg] and anti-Thyroglobulin antibody [anti-Tg]) [3-5]. This approach is usually efficient and categorizes patients into four groups of excellent response, biochemical incomplete response, structural incomplete response, and indeterminate response [3, 4].

Generally, if possible, surgical resection is preferred in recurrent disease prior to the systemic treatment; however, in cases with increasing Tg or anti-Tg levels with negative ^{131}I-WBS and neck ultrasonography, there is no obvious structural tumoral disease to be removed [3]. Therefore, a sensitive tool is required to differentiate those with no structural involvement from patients with the structural disease, but with no radioactive iodine (RAI) avidity. 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (2-[^{18}F]FDG PET/CT) is usually performed when the contrast-enhanced CT of the neck and chest is inconclusive [3, 6, 7].

2-[^{18}F]FDG PET/CT is a valuable method to find non-RAI-avid lesions with the overall sensitivity, specificity, and accuracy of 68.4%, 82.4%, and 73.8%, respectively [8]. 2-[^{18}F]FDG uptake occurs secondary to the dedifferentiation or losing the ability of iodine uptake [9, 10]. Also, the better spatial resolution of the PET scanners might help to detect small discrete lesions which might be missed on ^{131}I-WBS due to inherent poor spatial resolution [10, 11].

Studies have shown that thyroid-stimulating hormone (TSH) stimulation can increase 2-[^{18}F]FDG uptake in tumoral thyroid cells [12, 13]. Hypothetically, there is a paradoxical effect of TSH stimulation after levothyroxine withdrawal, which may lead to generalized hypometabolism, but stimulated thyroid cell function. It has been reported that the level of TSH affects the sensitivity of 2-[^{18}F]FDG PET/CT [11, 13-15]. While some authors reported that the higher levels of TSH result in higher detection rates [11, 13, 14], a meta-analysis claimed that there is no significant advantage of performing 2-[^{18}F]FDG PET/CT after TSH stimulation [16].

Moreover, serum Tg levels may play a significant role in 2-[^{18}F]FDG PET/CT positivity. It has been suggested by guidelines to perform 2-[^{18}F]FDG PET/CT in patients with Tg levels higher than 10 ng/ml [3]. 2-[^{18}F]FDG PET/CT studies may more often find tumoral lesions in patients with higher levels of Tg [17]. However, it also detects metastatic or recurrent lesions in patients with lower Tg levels [8].

In this prospective study, 2-[^{18}F]FDG PET/CT was performed for papillary thyroid carcinoma (PTC) patients presented with elevated serum Tg level but negative ^{131}I-WBS. Theoretically, applying simultaneous TSH stimulation and high-resolution PET imaging can be useful in detecting small discrete metastases. The main objective was to evaluate the effect of TSH stimulation after levothyroxine withdrawal in increasing the detection rate of 2-[^{18}F]FDG PET/CT. The second aim was to find cut-off levels for TSH and Tg, which are the best predictors of positive results.

METHODS

Study population

Sixty PTC patients (male: 55%, female: 45%), with a mean age of 52.3 ± 17.0 years (range: 17-87), were enrolled in this prospective study. All had elevated Tg level and negative ^{131}I-WBS and were classified as biochemical recurrence. Patients were divided into two groups according to their willingness for levothyroxine withdrawal. However, they had comparable age, sex, RAI cumulative dose and disease stage. Half of the patients underwent 2-[^{18}F]FDG PET/CT in stimulated TSH status after levothyroxine withdrawal (s-TSH) and the other half under suppressed TSH condition taking the proper dose of levothyroxine (uns-TSH).

Patients who met the following criteria were included: (a) histologically proven PTC, (b) history of total thyroidectomy, (c) history of at least one episode of RAI therapy, (d) s-Tg level > 10 ng/ml, (e) negative cervical ultrasonography, (f) and negative ^{131}I-WBS. Additionally, patients with small suspicious cervical lymph nodes or thyroid bed nodules or minimal RAI uptake in the cervical region that could not justify the significantly elevated Tg levels were enrolled.

Serum TSH, Tg and anti-Tg levels were evaluated in all patients on the day of the study. Moreover, the most recent unstimulated-TSH, Tg and anti-Tg levels were retrieved from the system database for the s-TSH group. Likewise, the most recent stimulated-TSH, Tg and anti-Tg levels were collected for the uns-TSH group.

The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1396.4648).

2-[^{18}F]FDG PET/CT acquisition

Before 2-[^{18}F]FDG PET/CT imaging, patients fasted for 4-6 hours (allowed to drink water), adhered to a

low carbohydrate diet, and avoided heavy physical activity the day before the scan. Premedication with propranolol and alprazolam was performed to reduce possible cervical brown fat and muscle uptake. They received 2-[^{18}F]FDG, only when the level of blood sugar was < 150 mg/dl. The scan was performed 60 minutes after intravenous injection of approximately 370 MBq of 2-[^{18}F]FDG using Biograph 6 PET/CT scanner (Siemens Medical Solutions, Erlangen, Germany).

Image acquisition was performed from vertex to mid-thigh in a caudocranial manner, in 3D mode with 3 minutes per bed position. Also, non-diagnostic CT (80 mAs, 80-130 keV, pitch of 0.8 and slice thickness of 5 mm) was done prior to the PET acquisition for purpose of attenuation correction and localization. The PET images were reconstructed using CT for attenuation correction and ordered subset expectation maximization algorithm (four iterations and eight subsets).

Image interpretation

Two experienced nuclear medicine physicians, who were aware of the patients' clinical history, but blinded to the TSH status, reviewed the images. When the results were discordant, a third physician was consulted and the final result based on a consensus. The interpretation of PET findings was based on visual assessment and maximum standardized uptake value (SUV_{max}) calculated semi-automatically using Syngo softwareTrueD (Siemens Medical Systems). The findings were considered as positive when the uptake was not contributed to the physiologic 2-[^{18}F]FDG uptake and it was higher than background activity or any amount of tracer accumulation in the areas with discrete findings on CT.

Statistical analysis

Numerical data are provided as median or mean ± standard deviation (SD). To check the normal distribution, the Kolmogorov–Smirnov test was used. Data showed no normal distribution and were analyzed using the nonparametric tests. Chi-Square analysis was used to compare the overall scan results, as well as results based on anatomical regions between the two groups. The Mann Whitney U-test was applied to demonstrate the relation between TSH, Tg, and anti-Tg levels and scan positivity in each group, as well as maximum-SUV_{max} (M-SUV_{max}) with other parameters. Spearman correlation coefficient used for evaluation of the correlation between nonparametric values (metabolic activity and TSH level). Additionally, logistic regression analysis was performed to assess relationships between patients' age, sex, and TNM stage with the scan result. A p-value of less than 0.05 was considered significant. The receiver operating characteristic (ROC) curve was used to establish Tg cutoffs. Statistical analysis was conducted with dedicated software (SPSS 22.0; IBM Corp., Armonk, NY).

RESULTS

There was no statistically significant difference between two groups considering age, sex, TNM stage, and accumulated RAI therapy dose. Summary of patients' characteristics, lab data, and 2-[^{18}F]FDG PET/CT results are shown in Table 1 and 2.

Table 1: Patients' characteristics.

		s-TSH group	uns-TSH group	All patients	P-value
Age: mean±SD; rang (years)		51.83±17.09; 19-81	52.87±18.87; 17-87	52.35±17.85; 17-87	0.86
Sex (Male: Female)		16:14	17:13	33:27	0.79
Number of patients		30	30	60	-
TNM stage	I	50.0%	37.5%	43.5%	0.64
	II	0.0%	0.0%	0.0%	
	III	9.1%	25%	17.4%	
	IVa	40.9%	33.3%	37%	
	IVb	0.0%	0.0%	0.0%	
	IVc	0.0%	4.2%	2.2%	
RAI cumulative dose: (mean ± SD; range (GBq))		15.46±7.06; 5.55-750	15.84±10.45; 3.7-49.02	15.66±8.93; 3.7-49.02	0.77

RAI: radioactive iodine; s-: stimulated; TSH: thyroid-stimulating hormone; uns-: unstimulated.

Table 2: Laboratory data and 2-[^{18}F]FDG PET/CT results of PTC patients with elevated serum Tg level and negative ^{131}I-whole-body scan in stimulated- and unstimulated-TSH groups

	TSH mean±SD (range)	s-Tg mean±SD (range)	uns-Tg mean±SD (range)	Anti-Tg mean±SD (range)	2-[^{18}F]FDG PET/CT result	Lesion M-SUV$_{max}$ mean±SD (range)
s-TSH group	64.25±24.90 (25.50-100.00)	62.01±68.56 (10.20-250.00)	14.16±16.34 (0.80-75.00)	162.32±193.73† (3.00-900.00)	N: 6 (20%) P: 24 (80%)	17.26±14.72 (4.00-53.00)
uns-TSH group	0.74±0.48 (0.05-1.55)	92.92±80.35 (17.00-250.00)	25.95±21.66 (11.00-130)	80.70±219.26‡ (2.00-1200.00)	N: 16 (53.3%) P: 14 (46.7%)	17.21±17.67 (2.60-65.31)
Total	-	75.74±74.93 (10.20-250.00)	21.9±20.43 (0.80-130.00)	-	N: 22 (36.7%) P: 38 (63.3%)	17.24±15.66 (2.60-65.31)
P-value	-	0.02	<0.001	-	0.007	0.545

†stimulated level; ‡unstimulated level; 2-[^{18}F]FDG PET/CT: 2-[^{18}F]fluoro-2-deoxy-D-glucosepositron emission tomography/computed tomography; anti-Tg: anti- Thyroglobolin antibody; M-SUV$_{max}$: maximum-maximum standardized uptake value; N: negative; P: positive; PTC: papillary thyroid cancer; s-: stimulated; Tg: Thyroglobolin; TSH: Thyroid-stimulating hormone; uns-: unstimulated.

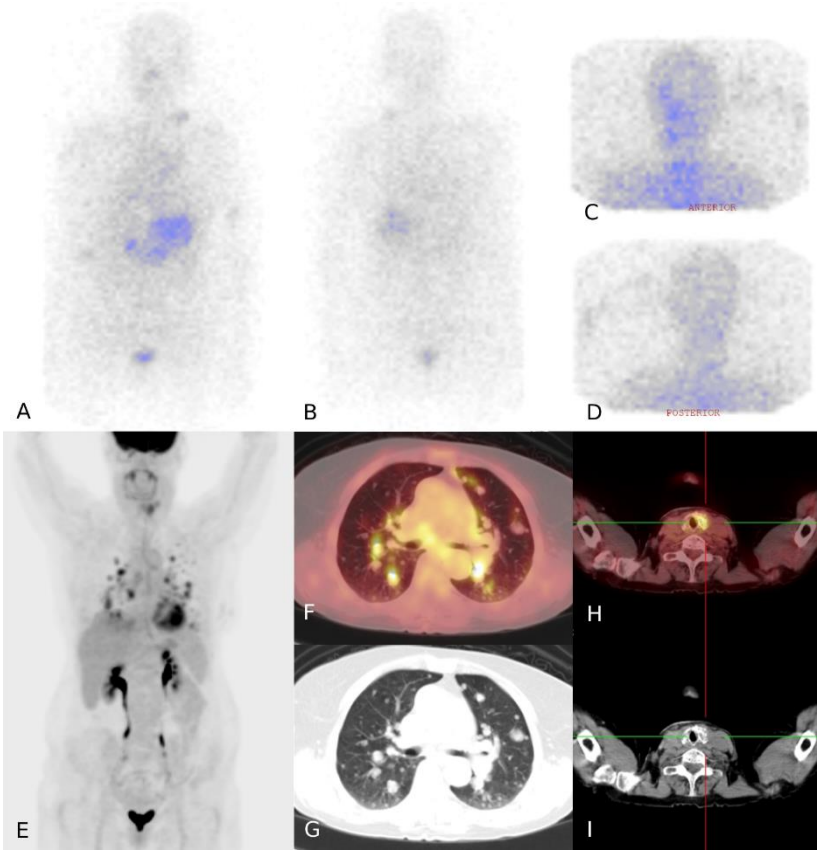

Fig 1. A case of papillary thyroid cancer with negative diagnostic ^{131}I-whole-body scan (WBS) and positive 2-[^{18}F]fluoro-2-deoxy-D-glucosepositron emission tomography/computed tomography (2-[^{18}F]FDG PET/CT), performed after levothyroxine withdrawal (stimulated thyroid-stimulating hormone (TSH) status). The anterior (A) and posterior (B) projections of ^{131}I-WBS show physiological radioiodine distribution. The focal uptake on the side of the neck is due to contamination, which is cleared after clothes removal (B and C). Maximum intensity projection (MIP; E) and trans-axial images of 2-[^{18}F]FDG PET/CT demonstrate multiple Hypermetabolic lesions in both lungs (F and G) and left thyroid bed (H and I).

Table 3: Pattern of metastases in s-TSH and uns-TSH groups.

	Number of patients with involvement (patient-based)							
	Total positive scan result	Local recurrence	Cervical lymph node metastases	Mediastinal lymph node metastases	Abdominal lymph node metastases	Lung metastases	Bone metastases	Brain metastases
s-TSH	24	7	21	8	0	14	7	2
uns-TSH	14	7	10	5	1	7	4	1
Total	38	14	31	13	1	21	11	3

s-: stimulated; TSH: thyroid-stimulating hormone; uns-: unstimulated.

Of all 60 cases with negative ^{131}I-WBS, 22 (36.7%) had negative and 38 (63.3%) had positive 2-[^{18}F]FDG PET/CT result. Laboratory data and results of 2-[^{18}F]FDG PET/CT are provided in Table 2. The images of a patient with negative ^{131}I-WBS and positive 2-[^{18}F]FDG PET/CT are illustrated in Figure 1.

Patient-based analysis

Unstimulated-TSH (uns-TSH) group

Among the uns-TSH group, 16/30 (53.3%) of 2-[^{18}F]FDG PET/CT scans interpreted as negative and 14/30 (46.7%) scans interpreted as positive. All positive cases had lymph node involvement (cervical: n = 10, mediastinal: n = 5, and abdominal: n = 1) and 5 patients showed local recurrence in the thyroid bed. The lung (n = 7), skeleton (n = 4), and brain (n = 1) were other sites of metastatic involvement.

In the uns-TSH group, 2-[^{18}F]FDG PET/CT result was more positive in patients with higher serum uns-Tg level (p = 0.003). On ROC curve analysis, AUC was 0.819 ± 0.076 (0.671-0.968) for uns-Tg level. The uns-Tg level of ≥ 19.00 ng/mL could predict the positive result with sensitivity of 0.786 and specificity of 0.750. Considering the previously recorded data, the latest s-Tg level was higher in patients with positive scans (p = 0.002) with AUC of 0.867 ± 0.073 (0.724-1.010). There was no relation between serum uns-TSH (p = 0.377) or uns-anti-Tg (p = 0.473) level with positive scan results.

Stimulated-TSH (s-TSH) group

In the s-TSH group, 6/30 (20%) scans were negative, and 24/30 (80%) were positive. All positive cases showed lymph node involvement (cervical: n = 21 and mediastinal: n = 8) and 5 patients had thyroid bed recurrence. In addition, there were lung (n = 14), skeleton (n = 7), and brain (n = 2) metastases.

Similar to the uns-TSH group, there was no relation between serum s-TSH (p = 0.350) or s-anti-Tg (p = 0.622) level and scan positivity, in the s-TSH group. Although the serum s-Tg level was higher in the cases with positive 2-[^{18}F]FDG PET/CT, no statistically significant relation was demonstrated between these two parameters (p = 0.055). Moreover, regarding the previously recorded data, uns-Tg was significantly higher in patients with positive scan result (p = 0.048).

Comparison between s-TSH and uns-TSH groups

The positive scan results were significantly higher in the s-TSH group (p = 0.007). After performing logistic regression analysis to detect possible confounding factors, there was still a significant trend for more positive results in s-TSH group (p = 0.041, odds ratio [OR]: 5.1, 95% confidence interval [CI], 1.1-24.3). P-values were insignificant for other factors, namely age, sex, and stage (p = 0.553, 0.343, and 0.898, respectively).

The average M-SUV$_{max}$ of lesions was not remarkably different (p = 0.545) between s-TSH and uns-TSH groups (Table 2). Taking M-SUV$_{max}$ as an indicator for metabolic activity, there was no correlation between TSH level and metabolic activity in positive 2-[^{18}F]FDG PET/CT scans in none of the groups (p = 0.589 for the s-TSH group and p = 0.471 for the uns-TSH group).

Anatomical region

The number of patients with metastases in different anatomical regions are shown in Table 3. No difference was found for local recurrence (p = 1.0) and extra-nodal involvement (including lung [p = 0.058], bone [p = 0.317], and brain [p = 0.554]) between the two groups. However, the s-TSH group showed higher numbers of patients with cervical lymph node metastases (p = 0.004).

DISCUSSION

DTC has an excellent prognosis, with an overall survival rate of 98.3% [18]. It is primarily related to the successful treatment of the disease with surgical

resection followed by RAI ablation of the residual disease and subsequent TSH suppression therapy [19]. The treatment is straightforward in patients with RAI-avid recurrent lesions while in cases with biochemical recurrence the therapeutic approach is less defined [20, 21]. In this context, 2-[^{18}F]FDG PET/CT is being used For the localizing the recurrent lesions [3, 22].

The diagnostic value of 2-[^{18}F]FDG PET/CT in oncology is related to its high sensitivity [23, 24]. However, the indolent nature of some types of cancer, including DTC, may diminish the detection performance of this invaluable modality [25, 26]. Iodine uptake is an indicator of thyroid cancer differentiation, and it is affected by the expression of sodium-iodide symporter and thyroid peroxidase [27]. Loss of some or all of these characteristics is usually concomitant with loss of ability to concentrate iodine, dedifferentiation and aggressiveness, as well as increased glucose uptake [27]. Therefore, 2-[^{18}F]FDG PET/CT can be performed for cases with evidence of dedifferentiation or invasiveness, including high-risk patients with elevated serum Tg and negative RAI imaging, poorly differentiated thyroid cancers and invasive Hurthle cell carcinomas, as well as patients at highest risk for rapid disease progression and disease-specific mortality [3, 25].

In the current study, we performed 2-[^{18}F]FDG PET/CT for DTC patients with biochemical recurrence. The overall detection rate was 63.3%. Similar to ours, Shammas et al. reported an overall sensitivity of 68.4% for rather a similar patient group [8]. The majority of their patients had undergone 2-[^{18}F]FDG PET/CT under TSH stimulation. The sensitivity for the subgroup with Tg > 10 ng/mL was 72% [8]. In another study, the overall sensitivity of 2-[^{18}F]FDG PET/CT for DTC (all patients) and DTC patients with RAI-refractory disease were up to 75% and 85%, respectively [22]. Overalls, the sensitivity of 45-100% has been reported in the literature, depending on the tumor burden and differentiation of the lesions, as well as to a lesser extent, TSH level [3, 28]. It is important to define an optimal 2-[^{18}F]FDG PET/CT imaging protocol to increased 2-[^{18}F]FDG avidity in the cancerous cells and increase the sensitivity. It has been shown that high TSH level stimulates the glucose transporter expression and increases glucose uptake, as well as glycolysis [29]. In previous studies, it was demonstrated that both endo- and exogenous TSH stimulation increases the detection rates, similarly [11, 14]. In this study, we evaluated the impact of endogenous TSH stimulation on 2-[^{18}F]FDG PET/CT results. We found that the detection rates were 80% for s-TSH and 46.7% for uns-TSH groups, which was significantly higher in the former (p = 0.007). After performing logistic regression analysis, there was still a significant trend for more positive results in the s-TSH group (p=0.041, OR: 5.1, 95% CI: 1.1-24.3). None of the other factors, namely age, sex, and the stage was significant (p = 0.553, 0.343, and 0.898, respectively). Other studies confirmed the beneficial effect of TSH stimulation using recombinant TSH on the 2-[^{18}F]FDG PET results [30, 31]. In one study by Kukulska on 110 patients (85 in TSH stimulated status and 25 in unstimulated status), the detection rate in the uns-TSH group was 28%, while it was 50% in the s-TSH group (p=0.069). They reported no difference between endogenous or exogenous TSH stimulation [11]. A prior meta-analysis by Ma et al. [14] including seven prospective controlled clinical trials with 168 patients, showed that TSH stimulation (either by thyroid hormone withdrawal or recombinant TSH) compared with TSH suppression improves the diagnostic performance of 2-[^{18}F]FDG PET/CT for detecting Tg-positive, radioiodine-negative metastatic DTC (OR 4.92, 95% CI 2.70–8.95), leading to 9% management change. On the other hand, in a recent meta-analysis, Qichang et al. [16] claimed that the TSH stimulation may have no impact on the study result. However, they included studies with different patient population, and they recommended for further studies evaluating the additional value of TSH stimulation on patients' management.

The other concern in patients with biochemical recurrence is when to perform 2-[^{18}F]FDG PET/CT. Finding an optimum Tg cutoff with the highest efficiency has been the subject of some surveys, and different Tg cutoff values have been reported [8, 20, 32]. However, there is no definite cutoff yet. It is recommended to perform 2-[^{18}F]FDG PET/CT with Tg level > 10 ng/mL [3, 11]. However, some studies have shown the efficacy of -[^{18}F]FDG PET/CT in lower levels of Tg [8, 20]. Hypothetically, higher Tg levels indicate more or larger tumoral lesions, increasing the chance of detectability.

In a review study based on European multicenter study, the sensitivity for Tg level > 5 ng/mL was 100%; however, it was 87% in patients with Tg level < 5 ng/mL [22]. Chai et al. showed that s-Tg level of > 49 ng/mL provides the best accuracy (sensitivity of 89.5% and a specificity of 90.9%) [29]. Giovanella et al. proposed uns-Tg level of ≥ 5.5 ng/mL with 88 % sensitivity and 74 % specificity [20]. Finally, Vural et al. demonstrated that uns-Tg ≥ 1.9 ng/mL, or s-Tg≥ 38.2 ng/mL has the best accuracy to detect recurrent disease [33].

In our study, in the s-TSH group, the s-Tg level was higher in patients with positive 2-[^{18}F]FDG PET/CT, although it demonstrated no statistical significance (p = 0.055). This is mainly attributed to the lower number of patients in our study. In a larger population, it might be statistically significant. However, in the same group, the last previously recorded uns-Tg was significantly higher in patients with positive scan result (p = 0.048).

On the other hand, in the uns-TSH group, the ROC curve analysis showed that uns-Tg cutoff of ≥ 19 ng/mL is combined with best accuracy with sensitivity of 0.786 and specificity of 0.750 (p = 0.003). These findings are interesting not only emphasizing on the role of uns-Tg level on predicting the scan result but also demonstrate that if 2-[^{18}F]FDG PET/CT is obtained in the stimulated-TSH status, lower Tg cutoff can be considered. In addition, considering the previously recorded data, the s-Tg level was higher in patients with positive scans (p = 0.002). Furthermore, our data showed that the difference between the s-TSH and uns-TSH groups was mostly related to the cervical lymph nodes, which were more detected in the s-TSH group (p = 0.004). Additionally, some studies have shown that the intensity of 2-[^{18}F]FDG uptake is related to TSH level [13, 16, 28]; however, in Ma et al. study [14], no significant difference was noted in SUV_{max} of the detected lesions according to the TSH status. [14]. In addition, in our study, M-SUV_{max} was not different between two groups (p = 0.588) and did not correlate with TSH level.

Limitations

One of the limitations of our study was the lack of histopathology for positive results. Since most of the patients were not candidates for surgery, multiple invasive biopsies for all detected lesions were clinically unnecessary and unethical to perform. The second limitation was the low number of patients. This is mainly due to the indolent nature of DTC and rare incidence of RAI-refractory cases referred for evaluation with 2-[^{18}F]FDG PET/CT. Furthermore, the patients were not randomized, although most of the characteristics were comparable between two groups. The Tg level was different; however, this would not negatively affect the final results. According to the Tg level, patients in the uns-TSH group presumably had a higher disease burden; therefore, we expected a higher detection rate. We believe that if the Tg level was comparable between two groups, the positive impact of levothyroxine withdrawal on the detection rate would be more pronounced. Moreover, we did not perform SPECT/CT for all patients, which may influence the results of ^{131}I-WBS scans (increasing false-negative results). However, we do not perform SPECT/CT on all patients; hence, the results of this study mirror the common practice in our center. Additionally, this would impact both groups equally. Therefore, we believe that the lack of SPECT/CT has minimal effect on results of the current survey.

CONCLUSION

2-[^{18}F]FDG PET/CT in PTC patients with elevated Tg and negative ^{131}I-WBS is a valuable diagnostic tool. According to our findings, TSH stimulation after levothyroxine withdrawal might increase the detectability of the lesions by 2-[^{18}F]FDG PET/CT scan; therefore, it might be preferred to conduct 2-[^{18}F]FDG PET/CT imaging following TSH stimulation in patients experiencing biochemical recurrence with no definite structural involvement in ^{131}I-WBS. Furthermore, the higher Tg level predicts the higher chance of positive 2-[^{18}F]FDG PET/CT results, particularly in unstimulated-TSH status.

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