Original Article

A Review of TENIS Syndrome in Hospital Pulau Pinang

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Abstract

Introduction: The treatment for differentiated thyroid cancers (DTCs) has always been radioactive iodine 131I therapy after definitive surgical management. Clinicians are faced with therapeutic challenges when dealing with patients having thyroglobulin-elevated negative iodine scintigraphy (TENIS) syndrome (elevated serum thyroglobulin [Tg] levels but negative whole-body scans [WBSs]). **Objective:** The aim of the study was to determine the prevalence of TENIS syndrome in our local setting and to evaluate the use of 18-fluoro-2-deoxyglucose (18F-FDG) positron emission tomography-computed tomography (PET-CT) in the management. **Methodology:** The data from DTC patients treated in the Department of Nuclear Medicine, Hospital Pulau Pinang from December 1, 2010, to November 30, 2016, with negative WBS and elevated Tg were reviewed. These patients should have undergone 18F-FDG PET-CT to be included in the study. **Results:** Only forty (10.4%) out of a total of 386 patients treated in Hospital Pulau Pinang during the study fulfilled the inclusion criteria. There were 28 women (70%) with median age of 59 years old. Thirty-four patients (85%) had papillary thyroid cancer (PTC) and six patients had follicular thyroid cancer. The use of 18F-FDG PET-CT revealed 23 patients (57.5%) with 18F-FDG avid metastases suggesting dedifferentiation of thyroid cancers. Based on this study, the probability of detecting FDG-avid disease is higher (P = 0.03) if 18F-FDG PET-CT was performed when Tg ≥15 ng/mL. **Conclusion:** TENIS syndrome constitutes a significant number of cases in our setting. Our data suggest a cutoff Tg ≥15 ng/mL for performing 18F-FDG PET-CT for these patients would be more beneficial than the currently American Thyroid Association recommended cutoff of 10 ng/mL.

Keywords: *Differentiated thyroid cancer, 18F-FDG positron emission tomography-computed tomography, iodine-131, thyroglobulin*

Introduction

Thyroid cancers account for approximately <1% of the total cancers cases in Malaysia. Differentiated thyroid cancers (DTCs) make up the majority of cases whereas only a small percentage is undifferentiated thyroid cancers. DTC is easier to treat and have better long-term survival. However, if the DTC becomes dedifferentiated, the cells are no longer 131I (radioactive iodine [RAI])-avid and become more difficult to treat. The prevalence of thyroglobulin-elevated negative iodine scintigraphy (TENIS) syndrome has never been documented in Malaysia. An indication that the cancer has dedifferentiated would be the presence of elevated serum thyroglobulin (Tg) levels, negative whole body scans (WBSs) and positive 18-fluoro-2-deoxyglucose (18F-FDG) positron emission tomography-computed tomography (PET-CT).

Objective

The aim of the study was to determine the prevalence of such cases in our local setting and to evaluate the use of 18F-FDG PET-CT in the management.

Methodology

All the available data from DTC patients treated in the Department of Nuclear Medicine, Hospital Pulau Pinang from December 1, 2010, to November 30, 2016, were collected and reviewed. Only data from patients with elevated Tg levels, negative WBS and had undergone 18F-FDG PET-CT after the diagnosis were collected. Tg levels were measured with immunometric assay (IMA) after 4 weeks of L-thyroxine withdrawal or after the use of recombinant human TSH (rhTSH). PET-CT images were acquired using discovery ST PET-CT scanner (General Electric Medical Systems, WI, USA) in the Department of Nuclear Medicine, Hospital Pulau Pinang. The PET scanner uses Bismuth Germanium

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Oxide crystals and scans in two-dimensional mode. The CT component is used for attenuation correction and anatomical localization. The followings are the CT parameters used in the study: voltage: 140 kV, current: 120 mA, scan speed of 0.8 s per revolution, and slice thickness of 3.75 mm. As for the PET component, the scans were carried out with the following parameters: Detector field of view of 50 cm and 5–7 bed positions with 3.270 mm overlap (3 min per bed position). The dose exposure from CT (CTDIvol) is 8.06 mGy (dose efficiency: 87.10%). The effective dose exposure from 10 mCi of F-18 FDG is approximately 7 mSv. The scans were acquired from the skull to the mid-thigh with total scan time of approximately 20 min.

The 18F-FDG PET-CT was performed using PET-CT camera as described earlier with 18F-FDG administered doses based on the body weight (0.17 mCi/kg). Patients were fasted at least 4 h before the IV administration of 18F-FDG, and the PET-CT imaging was acquired 60 min after the administration of 18F-FDG with patients in the supine position and arms elevated above the head. The 18F-FDG PET-CT studies were done without thyroxine withdrawal or using rhTSH.

Results

A total of 386 patients with well DTCs were treated in the Department of Nuclear Medicine, Hospital Pulau Pinang for 6 years between December 1, 2010, and November 30, 2016. Forty of them (10.4%) had TENIS syndrome and thus enrolled in the study.

Twenty-eight (70%) patients were women. The age of the patients recruited in the study ranged from 27 to 77 years old with a median of 59 years old. Twelve patients (30%) were ≤45 years old whereas the remaining 28 patients (70%) were >45 years. Of those aged >45 years old, 18 patients (66.7%) had positive 18F-FDG PET-CT. Five patients (41.7%) <45-year-old had positive 18F-FDG PET-CT. There was no correlation between the age groups and PET-CT findings ($P = 0.296$).

Only two patients had elevated Tg level with positive anti-Tg titers. However, both of these patients had Tg levels of <10 ng/mL and negative 18F-FDG PET-CT. The other 38 patients had negative anti-Tg levels with elevated Tg levels as shown in Table 1. 18F-FDG PET-CT showed FDG-avid disease in 23 patients (57.5%). The FDG uptake was seen in the brain, thyroid bed, cervical and mediastinal nodes, lungs, bone, muscles, and liver [Table 2]. There were no clinical correlation ($P = 1.00$) between the types of thyroid cancers and 18F-FDG PET-CT findings. Twenty out of 34 patients (58.8%) with papillary thyroid cancers and 3 of 6 patients (50.0%) with follicular thyroid cancer had positive 18F-FDG PET-CT findings.

Based on the American Thyroid Association (ATA) recommended cutoff Tg >10 ng/mL, there were 22 patients with Tg >10 ng/mL and positive 18F-FDG PET-CT. Only one patient had Tg <10 ng/mL (1.9 ng/mL) with positive 18F-FDG PET-CT findings (FDG-avid metastases to the cervical nodes, lungs, and liver). No correlation between Tg levels and 18F-FDG PET-CT findings if the cutoff Tg value was set at 10 ng/mL ($P = 0.30$). Based on receiver operating characteristic (ROC) curve analysis, we found that the cutoff Tg ≥15 ng/ml was the best compromise for sensitivity and accuracy (87% and 70%, respectively) in predicting positive 18F-FDG PET-CT finding [Figure 1]. With the cutoff Tg ≥15 ng/mL, there is a significant correlation ($P = 0.03$) between the scan findings and Tg levels [Table 3].

Five patients with elevated Tg levels but negative WBS and 18F-FDG PET-CT were given trials of high-dose RAI. None showed RAI uptake nor reduction in Tg levels. These five patients and the other patients who did not undergo empirical high-dose RAI therapy were referred to the oncologist for further management. However, only two patients had been started on tyrosine kinase inhibitor (TKI) to this date with limited success. The rest were only monitored as their disease remained fairly stable with no significant increment in Tg levels.

Table 1: Demographic data of the study patients

Demographic data	Frequency (%)
Race (*n*=40)	
Malay	12 (30.0)
Chinese	22 (55.0)
Indian	4 (10.0)
Others	2 (5.0)
Age (years) (*n*=40)	
≤45	12 (30.0)
>45	28 (70.0)
Histology (*n*=40)	
Papillary thyroid carcinoma	34 (85.0)
Classical variant	29 (72.5)
Follicular variant	2 (5.0)
Tall cell variant	1 (2.5)
Poorly differentiated	
Follicular thyroid carcinoma	6 (15.0)
Elevated Tg levels with negative anti-Tg (*n*=38) (ng/mL)	
>2-<10	4 (10.5)
≥10-<20	9 (23.7)
≥20	25 (65.8)
Metastases (*n*=40) detected on 18F-FDG PET-CT	
18F-FDG avid locoregional and metastases distant	23 (57.5)
No 18F-FDG avid disease	17 (42.5)

18F-FDG: Fluoro-18-deoxyglucose, PET: Positron emission tomography, CT: Computed tomography, Tg: Thyroglobulin

Discussion

According to the most recent Malaysia National Cancer Registry published in 2011, thyroid cancer accounts

Table 2: Description of study variables and fluoro-18-deoxyglucose positron emission tomography - computed tomography findings

Patient	Age (years)	Gender	Histology	Tg (ng/mL)[#]	Anti-Tg*	PET-CT findings	Site of FDG-avidity
1	47	Female	Follicular thyroid CA	243	Negative	Positive	Thyroid bed
2	63	Female	Follicular thyroid CA	>300	Negative	Positive	Lungs
3	61	Male	Papillary thyroid cancer	44	Negative	Positive	Mediastinal node
4	64	Male	Papillary thyroid cancer	109	Negative	Positive	cervical nodes, bone
5	76	Male	Papillary thyroid cancer	114	Negative	Positive	Bone
6	32	Female	Papillary thyroid cancer	180	Negative	Positive	Mediastinal node
7	45	Male	Papillary thyroid cancer	208	Negative	Positive	Cervical nodes, lungs
8	57	Male	Papillary thyroid cancer	239	Negative	Positive	Brain, cervical and mediastinal nodes, muscle
9	74	Female	Papillary thyroid cancer	>300	Negative	Positive	Mediastinal node and thyroid bed
10	64	Female	Papillary thyroid cancer	8.3	Positive	Positive	Cervical nodes
11	52	Female	Poorly differentiated thyroid cancer	17	Positive	Positive	Lungs and thyroid bed
12	42	Female	Papillary thyroid cancer	300	Negative	Positive	Cervical nodes and bone
13	56	Male	Papillary thyroid cancer	300	Negative	Positive	Bone
14	64	Male	Papillary thyroid cancer	300	Negative	Positive	Bone
15	70	Female	Papillary thyroid cancer	300	Negative	Positive	Cervical nodes
16	72	Female	Papillary thyroid cancer	300	Negative	Positive	Cervical and mediastinal nodes
17	61	Male	Papillary thyroid cancer	241	Negative	Positive	Cervical and lungs
18	35	Female	PTC, follicular variant	159	Negative	Positive	Thyroid bed
19	60	Female	Papillary thyroid cancer	108	Negative	Positive	cervical nodes
20	41	Female	Papillary thyroid cancer	87	Negative	Positive	mediastinal nodes
21	46	Male	Follicular thyroid CA	15	Negative	Positive	Thyroid bed
22	70	Female	Tall Cell thyroid cancer	10	Negative	Positive	cervical nodes, thyroid bed and lungs
23	77	Female	Papillary thyroid cancer	1.9	Negative	Positive	cervical, lungs, liver
24	74	Female	Follicular thyroid CA	31.6	Negative	Negative	None
25	55	Female	Follicular thyroid CA	4.7	Negative	Negative	None
26	42	Female	Papillary thyroid cancer	10.7	Negative	Negative	None
27	65	Female	Papillary thyroid cancer	12.5	Negative	Negative	None
28	37	Female	Papillary thyroid cancer	13.2	Negative	Negative	None
29	75	Female	Papillary thyroid cancer	14.9	Negative	Negative	None
30	27	Female	Papillary thyroid cancer	41	Negative	Negative	None
31	42	Female	Papillary thyroid cancer	166	Negative	Negative	None
32	30	Male	Papillary thyroid cancer	175	Negative	Negative	None
33	28	Female	PTC, follicular variant	6.9	Negative	Negative	None
34	59	Female	Papillary thyroid cancer	300	Negative	Negative	None
35.	74	Female	Papillary thyroid cancer	300	Negative	Negative	None
36	45	Male	Follicular thyroid CA	300	Negative	Negative	None
37	66	Female	Poorly differentiated papillary thyroid cancer	36	Negative	Negative	None
38	60	Female	Papillary thyroid cancer	17	Negative	Negative	None
39	63	Female	Papillary thyroid cancer	12	Negative	Negative	None
40	58	Male	Papillary thyroid cancer	1	Negative	Negative	None

[#]Due to laboratory limitations, Tg results could only be read up to 300 ng/mL, *Anti-Tg were processed in different centers and some centers do not provide their full titers results. 18F-FDG: 18-Fluoro-2-deoxyglucose, PET: Positron emission tomography, CT: Computed tomography, PTC: Papillary thyroid carcinoma, Tg: Thyroglobulin

for <1% of total cancer cases and 3% of the total cancer cases affecting women alone.[1] The Department of Nuclear Medicine in Hospital Pulau Pinang treats patients not only from within the state itself but also from the northern states of Malaysia. The total numbers of DTC patients referred to us since the RAI therapy services was started in 2010 stood at 386 patients as of November 30, 2016. This number does not truly reflect the actual prevalence of the disease in northern states of Malaysia as some patients were referred to other government hospital such as that Hospital Kuala Lumpur and National Cancer Institute as well as those treated in private medical centers.

Table 3: Outcome of fluoro-18-deoxyglucose positron emission tomography - computed tomography if performed when thyroglobulin >15 ng/mL[#]

Tg (ng/mL)	18F-FDG PET-CT (*n*=40)		
	Positive (%)	Negative (%)	*P**
<15	3 (7.5)	8 (20.0)	0.03
≥15	20 (50.0)	9 (22.5)	
Total	23	17	

[#]Taken arbitrarily as 15 ng/mL, *Chi-square test; significant if *P*<0.05. Tg: Thyroglobulin, 18F-FDG: Fluoro-18-deoxyglucose, PET: Positron emission tomography, CT: Computed tomography

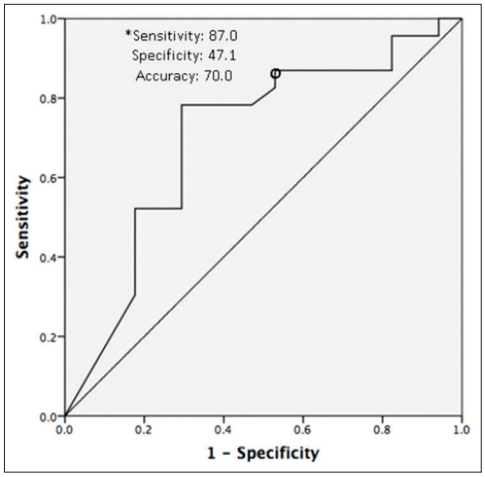

Figure 1: Receiver operating characteristic curve showing 18F-FDG positron emission tomography-computed tomography findings correlated with thyroglobulin levels

According to the most recent National Population Distribution and Basic Demographics Characteristics published in 2011, the Chinese and Malays account for 45.6% and 43.2% of the total Pulau Pinang population respectively. As for the other northern states in Peninsular Malaysia, Malays are the majority race.[2] According to the statistics compiled in the department till November 30, 2016, the racial distribution of the 386 thyroid cancer patients were as follow Chinese (55%), Malays (30.0%), Indians (21%), and other races (3.5%). Interestingly, our study cohort demonstrated a predominantly Chinese distribution (55%, *n* = 22)] having TENIS syndrome. However, there is no local data for thyroid cancers or TENIS syndrome in Pulau Pinang and other nearby Northern states. The study by Shamim *et al*. had an overwhelming Malay predominance (80%, *n* = 28) with TENIS syndrome compared to other races.[3] The conflicting data may be attributed to the racial distribution in the states of interest. Further studies and a national thyroid cancer database would be needed to truly evaluate the extent of TENIS syndrome in Malaysia.

Despite the wide age range (27–77 years old) of the patient with TENIS syndrome, there was no significant age-group predominance in the cohort. The median age (59 years old) of the patients with TENIS syndrome in this study is closely similar to the median age of TENIS syndrome in other centers.[4,5] There was no relationship between patients aged >45-year-old with positive 18F-FDG PET-CT findings in this study as compared to that by Shamim *et al*. in 2013.[3] In view of the small sample size in this study cohort, further studies with a larger sample would be needed to evaluate the relationship of age and TENIS syndrome.

Patients with TENIS syndrome accounts for 10.4% (*n* = 40) of cases seen in our center. This group of patients is of significant interest as their management is challenging. The underlying thyroid cancer in this syndrome has dedifferentiated and is no longer iodine-avid. Thus, treatment with 131-I will be rendered useless. Dedifferentiated DTC responds poorly to chemo- and radiation therapies.

Deandreis *et al*. demonstrated that 18F-FDG uptake in metastatic thyroid cancer is highly prognostic for survival. With correlations to the clinical factors, the 18F-FDG uptake in such cases predicts poor survival.[6]

The outcome of DTCs remains relatively poor even with the use of TKIs. There are limited data on the actual prolongation of survival currently and the impact of the drug toxicity on the quality of life as well as the development of escape phenomenon hinders the use of these drugs in the early stages of the disease.[7]

All 40 patients with TENIS syndrome in this study were further investigated with 18F-FDG PET-CT. Only 23 (57.5%) of these patients actually had FDG-avid disease demonstrated on 18F-FDG PET-CT whereas the remaining 17 patients had both negative radioiodine and 18F-FDG PET scans. Correlation with Tg level is important as the level increases with tumor size. However, there is still no conclusive cutoff value for Tg in patients with TENIS syndrome that would yield accurate results in 18F-FDG PET-CT.[8] Giovanella *et al*. (2012) reported that 18F-FDG PET-CT are more likely to be positive if Tg were >4.6 ng/ml.[9] The ATA guidelines published in 2015 recommended a higher Tg cutoff value (Tg >10 ng/ml) for the use of 18F-FDG PET-CT for high-risk TENIS syndrome patients.[10] Based on the ROC curve analysis, we found that Tg ≥15 ng/mL gave the best compromise in terms of sensitivity (87%) and accuracy (70.0%). As aforementioned, there was significant correlation with 18F-FDG PET-CT findings (*P* = 0.03) if the cutoff for performing 18F-FDG PET-CT was Tg ≥15 ng/mL. Thus, it would be more useful to perform 18F-FDG PET-CT only on patients with higher Tg levels (Tg ≥15 ng/mL) as compared to the ATA-recommended cutoff of 10 ng/mL. Bertagna *et al*. also described higher Tg cutoff (21 ng/mL) for performing 18F-FDG PET-CT in TENIS syndrome.[8] Essentially, both Bertagna *et al*. and our data had small sample size of 52 and 40 patients, respectively. Therefore, larger sample size would be needed to further evaluate this correlation.

Another important factor to consider is the presence of small-volume disease which may not be detected with the current imaging techniques. The apparently negative whole body 131I scan may actually be attributed to the limited resolution of the gamma cameras, of which in our center, is up to 10 mm. Similarly, the resolution of the current PET detectors may also affect the detection of small-volume disease. The PET cameras are not able to discriminate the emitted radioactive activity in from small-volume disease to that of the background activity. In our center, the PET resolution is only 3.3 mm, and thus, any disease smaller than this size may be missed. Colinearity and range of positrons may affect the image resolution. All of these factors have to be considered when interpreting negative scans in patients with TENIS syndrome.

An important aspect in all functional imaging techniques is patient preparation. Our center adheres to the policy of low-iodine diet regime for at least 2 weeks before treatment. Failure to observe this preparation has been shown to increased stable iodide pool. This would subsequently lead to decreased 131I uptake and thus reduced or nonvisualization of the tumor on WBS.[11] Therefore, it is essential for clinicians to evaluate negative WBS with caution if their patients are suspected not to be adherent to low-iodine diet. The best method of evaluating their compliance would be with the monitoring of urine iodine levels, but due to cost and technical issues, this monitoring was not carried out in our center and instead, we rely on patients' feedback.

Another crucial aspect to consider in patients with elevated Tg levels with negative WBS and also 18F-FDG PET-CT would be the measurement of Tg itself and the presence of anti-Tg. If the patients had positive anti-Tg, there might be a possibility of falsely elevated Tg levels secondary to heterophile antibodies. However, in this series, most of the patients had negative anti-Tg and thus rules out the possibility of falsely elevated levels. The use of similar machine for testing Tg levels has always been advocated to reduce technical discrepancies and to facilitate comparison.[12] The any spurious fluctuation of Tg levels due to the different processing techniques, chemicals, and machines are thus eliminated. In this study, all the blood samples for Tg and anti-Tg testing were sent to the same laboratory and using the same machines each time. Most centers are using IMA and it is recommended that Tg testing be calibrated against the CRM-457 international standards to reduce variability and ensure uniformity.[10]

The management of TENIS syndrome is difficult as the patients are unlikely to be responsive to RAI therapy. Empirical radioiodine 131I therapy (EIT) for patients with TENIS syndrome remains controversial.[13-17] In the literature review by Ma *et al*., EIT may have therapeutic effect when Tg level was considered an index of tumour burden.[16] However, the study by Kim *et al*. demonstrated that EIT and posttherapy WBSs were not useful diagnostically or therapeutically in patients with positive serum-stimulated Tg if they had negative ultrasound and 18F-FDG PET-CT.[17] As seen in our retrospective study, none of the patients responded to EIT. Due to financial constraints, the use of the expensive TKI in these patients are limited.

Conclusion

TENIS syndrome constitutes a significant number of cases in our setting. 18F-FDG PET-CT should be performed for these patients especially when their Tg ≥15 ng/mL, rather than the ATA-recommended 10 ng/mL. Although the outcome is poor, many of these patients remain relatively well for many years with only thyroxine suppression therapy. Managing TENIS syndrome is without a doubt challenging especially in centers with limited resources and financial constraints. Essentially, clinicians should be aware of the fallacies in diagnosing TENIS syndrome notably the technical limitations (Tg testing and scanner resolutions) and human factors (low-iodine diet and presence of anti-Tg).

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Conflicts of interest

There are no conflicts of interest.

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