Original Article

The Utility of ^{18}F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in Differentiated Thyroid Cancer Patients with Biochemical Recurrence and Negative Whole-Body Radioiodine Scintigraphy and Evaluation of the Possible Role of a Limited Regional Scan

Manish Ora, Aftab Hasan Nazar, Prasanta Kumar Pradhan, Prabhakar Mishra[1], Sukanta Barai, Amitabh Arya, Manish Dixit, Ashutosh Parashar, Sanjay Gambhir

Departments of Nuclear Medicine and [1]Biostatistics and Health Informatics, SGPGIMS, Lucknow, Uttar Pradesh, India

Abstract

Purpose of the Study: ^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is used in the management of recurrent differentiated thyroid cancer (DTC) patients presented with rising thyroglobulin (Tg) or anti-Tg antibody (Atg) levels and negative whole-body I-131 scan (WBS). We aimed to evaluate the utility of regional or limited PET/CT in a large population preset with variable Tg/(ATg) levels. **Materials and Methods:** In a retrospective study, we analyzed 137 PET/CT done on DTC patients presented with raised Tg/Atg and negative WBS. Retrospective evaluation of other available clinical information was done. **Results:** One hundred and thirty-seven patients aged 8–72 years (41 ± 17.7 years) were included in the study. Eighty-nine (64.9%) patients had positive findings on ^{18}F-FDG PET-CT. It included thyroid bed recurrence, cervical, mediastinal lymphadenopathy, lung, and bone lesions. In addition, 36 patients had metabolically inactive lung nodules detected on CT. Serum Tg and female sex were the only predictors for a positive PET scan. In most (97.1%) of the patients, the disease was limited to the neck and thoracic region. **Conclusions:** PET/CT is an excellent imaging modality for evaluating DTC patients presented with biochemical recurrence. It not only finds the disease in more than 80% of the patients but also detects distant metastatic disease, which precludes regional therapies. Lesions were noted mostly in the neck and thoracic region with very few distant skeletal metastases (4/137 patients). In most of the patients, routine vertex to mid-thigh imaging could be avoided.

Keywords: *18F-fluorodeoxyglucose positron emission tomography/computed tomography, recurrent thyroid cancer, serum antithyroglobulin antibody, serum thyroglobulin, thyroglobulin elevation/negative iodine scintigraphy syndrome, thyroid cancer*

Introduction

Differentiated thyroid cancer (DTC) is the most common malignant endocrine tumor.[1] It has a favorable prognosis, with reported 5-year survival rates of 95% for women and 87% for men.[2] The incidence of DTC has increased over the past two decades, with an increase in small, low-risk tumors.[3] The standard treatment depends on the tumor stage and risk category. It includes total thyroidectomy, followed by radioiodine remnant ablation (radioactive iodine [RAI]) and further thyroid hormone replacement therapy.[4] A whole-body scan (WBS) with radioiodine (^{131}I) is the most effective method for tumor detection and staging posttotal thyroidectomy.[5] It determines the differentiation of the tumor based on its avidity to iodine, identifies remnant thyroid tissue, and evaluates distant metastases.[6]

Because of the risk of recurrence, these patients are kept on long-term follow-up with the periodic measurement of serum thyroglobulin (Tg) and anti-Tg antibody level (ATg) with or without WBS.[7] In a few patients, cancer cells undergo dedifferentiation, but continue to secret Tg or Atg. These cells lose the ability to concentrate iodine. Thus, a negative WBS is noted.[8] 18F-fluorodeoxyglucose (^{18}F-FDG) is being taken up by malignant cells, and positron emission tomography/computed tomography (PET/CT) using

How to cite this article: Ora M, Nazar AH, Pradhan PK, Mishra P, Barai S, Arya A, *et al*. The utility of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in differentiated thyroid cancer patients with biochemical recurrence and negative whole-body radioiodine scintigraphy and evaluation of the possible role of a limited regional scan. Indian J Nucl Med 2020;35:203-9.

Address for correspondence:
Prof. Sanjay Gambhir, Department of Nuclear Medicine, SGPGIMS, Lucknow - 226 014, Uttar Pradesh, India.
E-mail: gaambhir@yahoo.com

Received: 07-01-2020
Revised: 09-03-2020
Accepted: 12-03-2020
Published: 01-07-2020

Access this article online

Website: www.ijnm.in

DOI: 10.4103/ijnm.IJNM_5_20

Quick Response Code:

^{18}F-FDG is an established modality in oncology. Feine *et al*. demonstrated that PET/CT scan might detect tumor lesions that are missed by I-131-scintigraphy known as "flip-flop phenomenon."[9] DTC cells show iodine uptake due to the expression of sodium-iodide symporter (NIS) and low glucose uptake, representing the low metabolic activity. Less differentiated cells that cease to express NIS exhibit upregulated glucose transporter and FDG uptake.[10,11]

Initial evaluation with neck ultrasonography or CT could be done in these patients. Several meta-analyses have shown that ^{18}F-FDG PET is a useful method for detecting recurrent DTC.[12,13] PET scanning has also shown a promising role in patients presenting with raised Atg.[14,15] Surveillance, Epidemiology, and End Results-Medicare databases have shown a significant increase in the utilization of the PET scans in the postoperative surveillance of DTC patients.[16] The authors have demonstrated that FDG uptake has prognostic significance for survival, and avid cancers are considered more aggressive.[17-19] Few studies have demonstrated that PET/CT may change therapy management in a substantial number of patients.[20,21] DTC usually spreads to cervical and thoracic regions and distant bones with relative sparing of other visceral organs. The prevalence of metastasis to the other sites is low.[22]

We retrospectively evaluated the performance of ^{18}F-FDG PET in DTC patients presented with raised serum Tg or Atg levels and negative WBS. This study also evaluated the predictors of the positive FDG PET/CT scan. At last, this study explores the possibility of a regional "limited PET/CT" protocol in these patients rather than whole-body PET/CT protocol.

Materials and Methods

Subjects

We retrospectively analyzed DTC patients who underwent ^{18}F-FDG PET/CT at a tertiary care hospital between January 2015 and December 2018. We routinely performed serial Tg, ATg measurement, and WBS after high dose (RAI). These investigations were done 4 weeks after thyroid hormone withdrawal. The radioiodine scans were performed 48 h after administration of 111 MBq of I-131 using a dual-head gamma camera. Tg, Atg, and thyroid-stimulating hormone (TSH) levels were measured using the sandwich chemiluminescent immunoassay. All patients were kept in the serial follow-up of 6–9 months in low or intermediate risk and 4–5 months in the high-risk category till remission. We did yearly follow-up for 5 years after that.

The inclusion criteria for the study were patients with pathologically proven DTC, posttotal thyroidectomy followed by RAI, and a negative follow-up low-dose diagnostic WBS with serially rising serum Tg or Atg level. Retrospective evaluation of medical records was done and clinical data were extracted.

^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography imaging and image analysis

^{18}F-FDG PET/CT was performed after endogenous TSH stimulation (TSH >30 IU/mL) within 1 week of negative WBS in all patients. Blood glucose level was measured after 6-h of fasting. After written informed consent, intravenous injection of ^{18}F-FDG was done (dose ~ 3.7 MBq/kg body weight) followed by a saline flush. PET/CT imaging was performed by an integrated scanner (Biograph™ scanners, PET/CT scanner, Siemens Healthineers). A noncontrast CT was done from vertex to mid-thigh, followed by PET imaging of 2 min per bed position. PET images were reconstructed using the iterative method. Attenuation correction was done using a CT attenuation correction series generated by CT images. Sagittal, coronal, and transverse images of the PET were obtained. PET images, CT images, and fused PET/CT images were simultaneously analyzed.

Image interpretation

All PET/CT images were analyzed visually by two experienced nuclear medicine physicians. Any difference in opinion was resolved by consensus. The PET/CT diagnostic criterion was hypermetabolic foci with CT findings suggestive of malignancy, such as necrosis, cystic change, and calcification. Images were assessed semiquantitatively, and maximum standard uptake value of a region of interest was measured on the syngo.via (Siemens Healthineers).

Lesion assessment and reference standard

Any lesion suggestive of recurrence on PET images was confirmed on CT images, and fine-needle aspiration cytology or biopsy was done if feasible. Metabolically inactive lung nodules were noted. They were considered metastatic based on their numbers, margin, shape, attenuation, and distribution. All cases with positive cytology, histopathology, or imaging findings suggestive of recurrence and persistently raised Tg or ATg levels in follow-up were considered as recurrence. None of the patients was given empirical radioiodine therapy after the scan.

Statistical analysis

The normality of the continuous variables was assessed. Descriptive statistics of the continuous data were presented in median (interquartile range), whereas categorical data were presented in frequency (%) as appropriate. Binary logistic regression analysis (univariate/multivariate) was used to identify the predictors of the PET-positive groups, whereas receiver operating characteristic (ROC) curve was used to determine the diagnostic accuracy of serum Tg and Atg to predict the PET positivity. $P < 0.05$ was considered statistically significant. All data analyses were done on the IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

Results

Demographic features

One hundred and thirty-seven patients aged 8–72 years (41 ± 17.7 years) were included in the study. All patients had well-differentiated carcinoma. Papillary, follicular, and follicular variants of the papillary carcinoma were noted in the 110, 14, and 13 patients, respectively. Table 1 shows the initial clinical parameters and low-dose WBS findings. One hundred and thirty patients with first positive WBS were given 3.3 GBq (1.1–5.5 GBq) for the first RAI. Repeated RAI was given if the patient had positive WBS in follow-up. The cumulative RAI dose was 6.9 GBq (1.1–37.9 GBq). All patients were advised for ^{18}F-FDG PET/CT, who had raised Tg or Atg level with negative WBS. The mean time interval between the first RAI to PET/CT scanning was 62 months (10–120 months). The tumor marker levels of the patients are summarized in Table 1.

Findings on fluorodeoxyglucose positron emission tomography/computed tomography

^{18}F-FDG PET/CT was positive in 88 (64.2%) patients. Details of PET/CT findings in both Tg and Atg groups are shown in Table 2. PET/CT detected pathological lesions in the thyroid bed, cervical lymph nodes, mediastinal lymph nodes, lungs (18 patients on PET and 38 on CT only), and bones. Brain lesions and axillary lymph nodes are seen in one patient each. Fifty-eight patients had lung nodules, out of which only 18 showed FDG avidity. Local recurrences or metastases were confirmed by cytopathology or histopathology in 46 cases. In the rest of the patients, the metastatic nature of the disease was assumed based on clinical presentation (high Tg, negative WBS, and metabolic activity on PET with CT abnormalities).

Univariate and multivariate analysis was done to know the predictors of the positive PET/CT in the raised serum Tg group [Table 3]. ROC curves were plotted for both raised serum Tg and Atg groups to identify the positive PET/CT scan. The results showed that serum Tg was significant but moderate predictor (AUC = 66.5%, 95% CI = 55.7%–77.3%, P = 0.004) of positive PET/CT. Atg was found to be insignificant as well as random predictors (AUC = 49.3%, 95% CI = 20.5%–78.1%, P = 0.961) for PET/CT positivity.

Distribution of the lesions

We further noticed that most of the lesions were noted in the region of the neck and thorax apart from one brain and few distant skeletal lesions. Bone metastases were identified in the base of the skull, dorsal vertebra, scapula, ribs, acetabulum, and sacrum. We observed that a limited PET/CT from the base of the skull to the adrenal region was sufficient for most of the patients. In only four patients (2.9% of the total patients and 4.5% of PET/CT positive patients), lesions were noted outside the proposed regional "limited PET/CT." Out of these four patients, three had bone metastases which were already known by previous positive WBS. All these patients had concomitant lung metastases. The fourth patient with brain lesions had already undergone craniotomy and decompression. In most of the patients ~97% (133/137) lesions were found in the region of neck and thorax. Lesions in the brain of below diaphragm was a rare finding.

Discussion

Patients with DTC, who present with high serum Tg or Atg levels and a negative WBS, present an essential and challenging clinical scenario.[23] This Tg elevation and a negative iodine scintigraphy entity have described by the acronym TENIS (Tg elevation/negative iodine scintigraphy syndrome). Due to a no uptake on the WBS, RAI is less likely to show significant clinical benefit. Empirical RAI is this setting is reserved for few specific clinical settings.[24] Several imaging modalities are used to evaluate this entity with variable results. A sensitive and accurate imaging modality is required to disclose the locoregional disease status but also explore systemic metastases. Imaging should be able to guide surgical resection of the disease, thus avoiding unnecessary local radical treatments in the presence of systemic metastases.

^{18}F-FDG PET/CT has proved its efficacy and clinical utility in DTC patients. Dong *et al*. carried out a meta-analysis of DTC patients with a negative WBS scan and included 25 studies (789 patients). They found a sensitivity and specificity of 94% and 84%, respectively.[25] A similar performance of PET/CT has noted in a recent meta-analyses that included 34 (2639 patients) and 20 studies (958 patients).[12,13] In our single-center study, which includes a large number of patients, similar results are observed. We found FDG positive lesions in ~ 64% (88/137) of patients. In addition, one-fourth (38/137) of the patients had metabolically inactive lung lesions on the CT. Histopathological analysis of all lesions could not be done as many of them were noted in the mediastinum and lung. The biopsy was difficult, and many patients did not give consent for the invasive procedure.

The American Thyroid Association guidelines suggest obtaining PET/CT in high-risk DTC patients with elevated Tg levels (more than 10 ng/dl) and a negative WBS.[24] However, some studies have demonstrated the utility of PET/CT scans in patients with lower Tg levels, which may reflect the production of mutant Tg not detectable by conventional assays or loss of Tg synthesis.[26] In our study, we found that a rising serum Tg level predicts the positive PET/CT. However, other multiple factors, such as metastases to central or lateral compartment lymph node and distant metastases, could not predict it. Serum Atg levels were not a predictor of a positive PET/CT scan. Female sex was significantly associated with a more positive scan (71.6%) in comparison to male patients (51.3%). This finding needs further evaluation

Table 1: Patient characteristic

	Thyroglobulin group	Antithyroglobulin antibody group
Surgery		
Patients	120	17
Age (years)	39 (30.3-55.0)	43.0 (23.5-53.5)
Sex (female) (%)	78 (65)	11 (64.7)
Total thyroidectomy	113	17
Hemithyroidectomy followed by completion thyroidectomy	7	0
CCLND	84	12
Metastases in CCLND on HPE (HPECCLND)	73	10
LLND	37	7
Malignancy in LLND (HPELLND)	32	5
RLND	37	6
Malignancy in RLND (HPERLND)	32	3
WBS		
The time between surgery and first RIA (months)		3.3 (1-8)
Postsurgery positive WBS	115	15
Lymph node metastases on WBS	42	8
Distance metastases	26	1
Lung metastases	25	1
Bone metastases	10	0
Mediastinal lymph nodes	11	0
Tumor marker levels		
	98 (48.3-254) ng/ml	1204 (665-3546) IU/mL

CCLND: Central compartment lymph node dissection, HPE: Histopathological examination, LLND: Left cervical lymph node dissection, RLND: Right cervical lymph node dissection, WBS: Whole-body scan

Table 2: Findings of the 18F-fluorodeoxyglucose positron emission tomography/computed tomography

Lesions	Thyroglobulin group	SUVmax	Antithyroglobulin antibody group	SUVmax
Positive PET/CT	81	-	7	-
Thyroid bed	23	4 (2-6)	3	8 (4-CNC)
Cervical lymph nodes	64	4 (3-8)	7	6.5 (4-10.5)
Lung nodules (FDG positive)	18	4 (2.5-7.5)	-	-
Lung nodules (including nonavid nodules seen on CT)	36	-	2	-
Mediastinal lymph nodes	23	5 (4-8.75)	3	6 (3-CNC)
Bone	10	6 (3-9.5)	0	-

*CNC: Couldnt compute (due to small sample size), SUVmax: Maximal Standardized uptake value, FDG: Fluorodeoxyglucose, CT: Computedtomography, Mean and interquartile range of the SUVmax are shown

in future studies. This result also indicates that male sex is associated with a larger number of PET/CT-negative biochemical recurrence. Few studies have demonstrated a change in therapy management using PET/CT.[20,21] Although we did not intend to document it, we observed that many patients with thyroid bed or cervical lymph node recurrence had coexisting mediastinal lymphadenopathy or lung metastases that excluded radical local treatments.

Most of the patients in our study had a very high serum Tg or Atg level. Even at this high level of tumor markers, most of the patients had lesions limited to the neck and thoracic region. We did not note any evidence of the metachronous cancers in any of the 137 patients. Few previous studies have also shown that most of the recurrences are noted in the area of the neck and thorax, although most of them have not detailed the sites of distant metastases [Table 4].[18,27-33] In our study, only four patients showed distant metastases to the brain, skull, acetabulum, and sacrum outside the proposed limited PET CT field of view. However, all these lesions were known by previous WBS or clinical history.

In our study group, more than half of the patients (79 out of 137) were of <40 years of age. Out of these, fifty were female. It would be an ideal strategy to decrease the overall radiation exposure and minimizing pelvic radiation in patients of the reproductive age. Radiation exposure remains a significant concern for PET/CT imaging. We use CARE Dose4D (Siemens Healthineers) to keep the radiation exposure to the optimized level. A limited PET/CT will decrease the scan length to half, thus effectively reducing radiation

Table 3: Predictors of the positive positron emission tomography/computed tomography scan in patients presented with raised serum thyroglobulin (*n*=120)

Variable	PET/CT result		Univariate	Multivariate
	Positive	Negative	Odds ratio	Adjusted odds ratio
Thyroglobulin level (ng/ml)	157.9±105.1	105.6±95.6	1.001 (1.001-1.005)	1.006 (1.001-1.010)
Sex (female) (%)	58 (71.6)	20 (51.3)	2.40 (1.09-5.29)	2.46 (1.07-5.67)
HPECCLND (%)	46 (56.8)	27 (69.2)	0.58 (0.26-1.31)	-
HPERLND (%)	17 (21)	15 (38.5)	0.43 (0.18-0.98)	0.40 (0.17-0.98)
HPELLND (%)	17 (21)	15 (38.5)	0.43 (0.18-0.98)	-
Lung metastases	18 (22.2)	7 (17.9)	1.31 (0.50-3.45)	-
Distant metastases	18 (22.2)	8 (20.5)	1.11 (0.43-2.83)	-
Bone metastases	7 (8.6)	3 (7.7)	1.13 (0.28-4.65)	-

Outcome variable (PET/CT Scan [positive/negative]), binary logistic regression analysis used variable's showing significant (P<0.05). PET/CT: Positron emission tomography/computed tomography

Table 4: Studies utilizing fluorodeoxyglucose positron emission tomography/computed tomography in thyroid cancer patients

Author	Year	Number of patients	FDG PET/CT positive	Bone metastases	Cervical + thoracic findings
Giovanella *et al*.[27]	2013	102	52	6 (*NA)	Rest of the patients
Na *et al*.[28]	2011	68	45	Ribs	Rest of the patients
Özdemir *et al*.[29]	2014	71	38	2 distant metastases; NA	Rest of the patients
Triviño Ibáñez *et al*.[30]	2016	81	41	3 (NA)	Rest of the patients
van Dijk *et al*.[31]	2013	52	12	Not mentioned	Not mentioned
Vural *et al*.[18]	2012	105	75	8 (brain, bones and soft tissue)	Rest of the patients
Zuijdwijk *et al*.[32]	2008	31 patients (38 scans) rising Tg group	21	NA	Not mentioned
Parihar *et al*.[33]	2020	44	33	3	Not mentioned

*NA: Details are not available

exposure by CT component of PET/CT study to the half. It has recommended that all efforts should take to eliminate unnecessary imaging examinations and to lower the amount of radiation used in necessary imaging examinations to only that needed to acquire appropriate medical images.[34] Limited PET/CT will also lead to reducing scan time by 8–10 min. This decrease in acquisition time would be welcome by the patient and may reduce movement-related artifacts. By reducing the acquisition time, overall patient throughput may be increased. A similar observation is noted in head and neck cancer patients undergoing limited PET/CT.[35] However, in patients presenting symptoms outside the planned limited PET/CT or known distant skeletal metastases, the field may be extended.

Our study has a few significant limitations. It was a single-center retrospective study. As patients have very high Tg or Atg levels, a large proportion of the patients have metastatic disease. We did not compare the findings of PET/CT with other imaging modalities. Histopathological confirmation could not be done in half of the patients. A cost-effective analysis or radiation burden measurement was not done.

Clinicians should consider the availability, cost of PET/CT, and risk of radiation exposure. A neck USG followed by a chest CT may be done if PET-CT is not available. It offers advantages of wide availability, lesser radiation, and possibly lower cost. A regional limited PET/CT suffices the need of most of the patients with a minimal possibility of missing distant metastases below the diaphragm. In a resource-limited developing country, regional "limited PET/CT" may result in shorter imaging timing, better patient throughput, thus increasing performance in busy nuclear medicine facility.

Conclusions

^{18}F-FDG PET/CT is an excellent investigational modality in DTC patients presenting with biochemical recurrence either in the form of raised serum Tg or Atg level. It finds the disease spread and guides in restaging and management decision-making of more than 80% of the patients. Hence, we propose that regional "limited PET/CT" from the base of the skull to the adrenal region is sufficient for most of the patients. It may lead to shorter procedure time, more comfortable with possible lesser radiation exposure. Further prospective and cost-effectiveness studies are needed before this approach is incorporated into clinical practice.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9-29.
2. Cancer Registry of Norway. Cancer in Norway 2012. Cancer Incidence, Mortality, Survival and Prevalence in Norway. Oslo: Cancer Registry of Norway; 2014. Available from: https://www.kreftregisteret.no/en/The-Registries/Cancer-Statistics/. [Last accessed on 2020 Apr 01].
3. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA 2006;295:2164-7.
4. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, *et al*. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.
5. Grünwald F, Menzel C, Bender H, Palmedo H, Willkomm P, Ruhlmann J, *et al*. Comparison of 18FDG-PET with 131 iodine and 99mTc-sestamibi scintigraphy in differentiated thyroid cancer. Thyroid 1997;7:327-35.
6. Treglia G, Bertagna F, Piccardo A, Giovanella L. 131I whole-body scan or 18FDG PET/CT for patients with elevated thyroglobulin and negative ultrasound? Clin Transl Imaging 2013;1:175-83.
7. Tuttle RM, Tala H, Shah J, Leboeuf R, Ghossein R, Gonen M, *et al*. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: Using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. Thyroid 2010;20:1341-9.
8. Pacini F, Agate L, Elisei R, Capezzone M, Ceccarelli C, Lippi F, *et al*. Outcome of differentiated thyroid cancer with detectable serum Tg and negative diagnostic (131) I whole body scan: Comparison of patients treated with high (131) I activities versus untreated patients. J Clin Endocrinol Metab 2001;86:4092-7.
9. Feine U, Lietzenmayer R, Hanke JP, Wöhrle H, Müller-Schauenburg W. 18FDG whole-body PET in differentiated thyroid carcinoma. Flipflop in uptake patterns of 18FDG and 131I. Nuklearmedizin 1995;34:127-34.
10. Moon SH, Oh YL, Choi JY, Baek CH, Son YI, Jeong HS, *et al*. Comparison of 18F-fluorodeoxyglucose uptake with the expressions of glucose transporter Type 1 and Na+/I- symporter in patients with untreated papillary thyroid carcinoma. Endocr Res 2013;38:77-84.
11. Grabellus F, Nagarajah J, Bockisch A, Schmid KW, Sheu SY. Glucose transporter 1 expression, tumor proliferation, and iodine/glucose uptake in thyroid cancer with emphasis on poorly differentiated thyroid carcinoma. Clin Nucl Med 2012;37:121-7.
12. Haslerud T, Brauckhoff K, Reisæter L, Küfner Lein R, Heinecke A, Varhaug JE, *et al*. F18-FDG-PET for recurrent differentiated thyroid cancer: A systematic meta-analysis. Acta Radiol 2016;57:1193-200.
13. Caetano R, Bastos CR, de Oliveira IA, da Silva RM, Fortes CP, Pepe VL, *et al*. Accuracy of positron emission tomography and positron emission tomography-CT in the detection of differentiated thyroid cancer recurrence with negative (131) I whole-body scan results: A meta-analysis. Head Neck 2016;38:316-27.
14. Qiu ZL, Wei WJ, Shen CT, Song HJ, Zhang XY, Sun ZK, *et al*. Diagnostic performance of 18F-FDG PET/CT in papillary thyroid carcinoma with negative 131I-WBS at first postablation, negative Tg and progressively increased TgAb level. Sci Rep 2017;7:2849.
15. Choi SJ, Jung KP, Lee SS, Park YS, Lee SM, Bae SK. Clinical usefulness of F-18 FDG PET/CT in papillary thyroid cancer with negative radioiodine scan and elevated thyroglobulin level or positive anti-thyroglobulin antibody. Nucl Med Mol Imaging 2016;50:130-6.
16. Wiebel JL, Banerjee M, Muenz DG, Worden FP, Haymart MR. Trends in imaging after diagnosis of thyroid cancer. Cancer 2015;121:1387-94.
17. Deandreis D, Al Ghuzlan A, Leboulleux S, Lacroix L, Garsi JP, Talbot M, *et al*. Do histological, immunohistochemical, and metabolic (radioiodine and fluorodeoxyglucose uptakes) patterns of metastatic thyroid cancer correlate with patient outcome? Endocr Relat Cancer 2011;18:159-69.
18. Vural GU, Akkas BE, Ercakmak N, Basu S, Alavi A. Prognostic significance of FDG PET/CT on the follow-up of patients of differentiated thyroid carcinoma with negative 131I whole-body scan and elevated thyroglobulin levels: Correlation with clinical and histopathologic characteristics and long-term follow-up data. Clin Nucl Med 2012;37:953-9.
19. Wang W, Larson SM, Fazzari M, Tickoo SK, Kolbert K, Sgouros G, *et al*. Prognostic value of [18F] fluorodeoxyglucose positron emission tomographic scanning in patients with thyroid cancer. J Clin Endocrinol Metab 2000;85:1107-13.
20. Pomerri F, Cervino AR, Al Bunni F, Evangelista L, Muzzio PC. Therapeutic impact of (18) F-FDG PET/CT in recurrent differentiated thyroid carcinoma. Radiol Med 2014;119:97-102.
21. Rosenbaum-Krumme SJ, Görges R, Bockisch A, Binse I. 18F-FDG PET/CT changes therapy management in high-risk DTC after first radioiodine therapy. Eur J Nucl Med Mol Imaging 2012;39:1373-80.
22. Zunino A, Pitoia F, Faure E, Reyes A, Sala M, Sklate R, *et al*. Unusual metastases from differentiated thyroid carcinoma: Analysis of 36 cases. Endocrine 2019;65:630-6.
23. Silberstein EB. The problem of the patient with thyroglobulin elevation but negative iodine scintigraphy: The TENIS syndrome. Semin Nucl Med 2011;41:113-20.
24. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, *et al*. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid 2016;26:1-33.
25. Dong MJ, Liu ZF, Zhao K, Ruan LX, Wang GL, Yang SY, *et al*. Value of 18F-FDG-PET/PET-CT in differentiated thyroid carcinoma with radioiodine-negative whole-body scan: A meta-analysis. Nucl Med Commun 2009;30:639-50.
26. Salvatori M, Biondi B, Rufini V. Imaging in endocrinology: 2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography in differentiated thyroid carcinoma: Clinical indications and controversies in diagnosis and follow-up. Eur J Endocrinol 2015;173:R115-30.
27. Giovanella L, Trimboli P, Verburg FA, Treglia G, Piccardo A, Foppiani L, *et al*. Thyroglobulin levels and thyroglobulin doubling time independently predict a positive 18F-FDG PET/CT scan in patients with biochemical recurrence of differentiated thyroid carcinoma. Eur J Nucl Med Mol Imaging 2013;40:874-80.
28. Na SJ, Yoo IeR, O JH, Lin C, Lin Q, Kim SH, *et al*. Diagnostic accuracy of (18) F-fluorodeoxyglucose positron emission tomography/computed tomography in differentiated thyroid

cancer patients with elevated thyroglobulin and negative (131) I whole body scan: Evaluation by thyroglobulin level. Ann Nucl Med 2012;26:26-34.
29. Özdemir E, Yildirim Poyraz N, Polat SB, Turkolmez S, Ersoy R, Cakir B. Diagnostic value of 18F-FDG PET/CT in patients with TENIS syndrome: Correlation with thyroglobulin levels. Ann Nucl Med 2014;28:241-7.
30. Triviño Ibáñez EM, Muros MA, Torres Vela E, Llamas Elvira JM. The role of early 18F-FDG PET/CT in therapeutic management and ongoing risk stratification of high/intermediate-risk thyroid carcinoma. Endocrine 2016;51:490-8.
31. van Dijk D, Plukker JT, Phan HT, Muller Kobold AC, van der Horst-Schrivers AN, Jansen L, *et al*. 18-Fluorodeoxyglucose positron emission tomography in the early diagnostic workup of differentiated thyroid cancer patients with a negative post-therapeutic iodine scan and detectable thyroglobulin. Thyroid 2013;23:1003-9.
32. Zuijdwijk MD, Vogel WV, Corstens FH, Oyen WJ. Utility of fluorodeoxyglucose-PET in patients with differentiated thyroid carcinoma. Nucl Med Commun 2008;29:636-41.
33. Parihar AS, Mittal BR, Kumar R, Shukla J, Bhattacharya A. 68Ga-DOTA-RGD2 positron emission tomography/computed tomography in radioiodine refractory thyroid cancer: Prospective comparison of diagnostic accuracy with 18F-FDG positron emission tomography/computed tomography and evaluation toward potential theranostics. Thyroid. 2020. doi: 10.1089/thy.2019.0450. [Epub ahead of print].
34. Brink JA, Amis ES Jr. Image wisely: A campaign to increase awareness about adult radiation protection. Radiology 2010;257:601-2.
35. Ua J, Rj K, Dq W, Iw G. Limited PET/CT – A new concept in follow-up of head and neck cancer patients. Mol Med Clin Appl 2018;2:DOI: http://dx.doi.org/10.16966/2575-0305.111. Available from: https://www.sciforschenonline.org/journals/molecular-biology-medicine/JMMCA-2-111.php. [Last accessed on 2019 Sep 11].