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

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: $^{18}$F-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.\(^8\) $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) is being taken up by malignant cells, and positron emission tomography/computed tomography (PET/CT) using
18F-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.”[99] 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 18F-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.[17,18] 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 18F-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 18F-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.

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

18F-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 18F-FDG was done (dose ~ 3.7 MBq/kg body weight) followed by a saline flush. PET/CT imaging was performed by an integrated scanner (BiographTM 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 radiiodine 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 18F-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

18F-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 cytology or histology 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. 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.

18F-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.
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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. 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]. 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 1: Patient characteristic

| Lesions                        | 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 thyroidection | 7                   | 0                               |
| CCLND                          | 84                  | 12                              |
| Metastases in CCLND on HPE (HPECLND) | 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            |                     |                                 |
| **Thyroglobulin group**        |                     |                                 |
| Postsurgery positive WBS       | 115                 |                                 |
| Lymph node metastases on WBS   | 42                  |                                 |
| Distance metastases            | 26                  |                                 |
| Lung metastases                | 25                  |                                 |
| Bone metastases                | 10                  |                                 |
| Mediastinal lymph nodes        | 11                  |                                 |
| Tumor marker levels            |                     |                                 |
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| Distance metastases            | 26                  |                                 |
| Lung metastases                | 25                  |                                 |
| Bone metastases                | 10                  |                                 |
| Mediastinal lymph nodes        | 11                  |                                 |
| **Antithyroglobulin antibody group** |                     |                                 |
| Postsurgery positive WBS       | 115                 |                                 |
| Lymph node metastases on WBS   | 42                  |                                 |
| Distance metastases            | 26                  |                                 |
| Lung metastases                | 25                  |                                 |
| Bone metastases                | 10                  |                                 |
| Mediastinal lymph nodes        | 11                  |                                 |
| **WBS**                        |                     |                                 |
| The time between surgery and first RIA (months) | 3.3 (1-8)          |                                 |
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| Distance metastases            | 26                  |                                 |
| Lung metastases                | 25                  |                                 |
| Bone metastases                | 10                  |                                 |
| Mediastinal lymph nodes        | 11                  |                                 |
| **Tumor marker levels**        |                     |                                 |

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 | Antithyroglobulin antibody group |
|--------------------------------|---------------------|---------------------------------|
| Positive PET/CT                | 81                  | 7                               |
| Thyroid bed                    | 23                  | 3                               |
| Cervical lymph nodes           | 64                  | 7                               |
| Lung nodules (FDG positive)    | 18                  | -                               |
| Lung nodules (including nonavid nodules seen on CT) | 36                  | 2                               |
| Mediastinal lymph nodes        | 23                  | 3                               |
| Bone                            | 10                  | 0                               |

*SUVmax: Maximal Standardized uptake value, FDG: Fluorodeoxyglucose, CT: Computed tomography, Mean and interquartile range of the SUVmax are shown*
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. 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.

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.

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**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 odds ratio | Multivariate adjusted odds ratio |
|---------------------------|---------------|-----------------------|---------------------------------|
| Thyroglobulin level (ng/ml) | 157.9±105.1  | 1.001 (1.001-1.005)   | 1.006 (1.001-1.010)              |
| Sex (female) (%)          | 58 (71.6)     | 2.40 (1.09-5.29)      | 2.46 (1.07-5.67)                |
| HPECCLND (%)              | 46 (56.8)     | 0.58 (0.26-1.31)      | -                               |
| HPERLND (%)               | 17 (21)       | 0.43 (0.18-0.98)      | 0.40 (0.17-0.98)                |
| Lung metastases           | 18 (22.2)     | 1.31 (0.50-3.45)      | -                               |
| Distant metastases        | 18 (22.2)     | 1.11 (0.43-2.83)      | -                               |
| Bone metastases           | 7 (8.6)       | 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                  | Ribstein        | 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          |
| Zuijdewijk 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
Conflicts of interest

There are no conflicts of interest.

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