

The Role of the FDG-PET in the Staging of Patients with Differentiated Thyroid Cancer

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Introduction: The objective of this study is to determine the role of the FDG-PET in the staging of patients with Differentiated Thyroid Cancer (DTC) who have high Tg levels after thyroidectomy.

Material and Methods: Thirty three DTC patients who performed FDG-PET scan after thyroidectomy were selected for this retrospective study. All patients had Tg levels over 10 ng/ml. FDG-PET was performed to patients 6 weeks after surgery. And 2 weeks later FDG-PET imaging, patients received 131-I radioiodine treatment (RIT) except who had lymph node involvement. After RIT, post-ablation whole body scan (TWBS) was performed to the patients.

Results: Twelve patients (36.4%) who had not involvement outside the thyroid bed both on the FDG-PET and TWBS, were remitted completely. In 21 patients (63.4%), there was involvement outside the thyroid bed on the FDG-PET and/or TWBS. Eleven of these patients with (33.3%) had distant organ involvement on the FDG-PET and/or TWBS. Patients with involvement outside the thyroid bed had higher Tg than others. The disease was complete or partial regressed in the patients with distant organ involvement who had negative FDG-PET scan and positive TWBS results. In the patients with distant organ involvement who had higher SUVmax on FDG-PET, the disease tended to progress.

Conclusion: Our data suggest that FDG-PET scan which performed to the DTC patients with high Tg levels at the time of staging, would be the right approach. This approach will be very useful especially in demonstrating lymph node involvement and predicting prognosis. Results of FDG-PET may also change the treatment management.

Keywords: FDG-PET, DTC, Tg, Thyroidectomy

Introduction

Differentiated thyroid cancer (DTC) is the most common endocrine cancer with good prognosis (1, 2). The main treatment method for DTC is total/nearly total thyroidectomy followed by 131-I radioiodine treatment (RIT) (3). After the thyroidectomy and before the RIT; patients are evaluated with some laboratory and imaging technics for detecting residual thyroid tissue

and remnant tumor tissue. The main laboratory tool and most sensitive biochemical method for evaluating of DTCs are the measurement of serum thyroglobulin (Tg) with anti-Tg antibody (Tg-Ab) and thyroid-stimulating hormone (TSH) (4). Tg is important tumor marker for follow-up of DTC patients. Despite the residual thyroid tissue, Tg level which measured before the RIT

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can be useful and high Tg levels are correlated with local and distant metastases (5-8). Detailed neck ultrasound and thyroid scintigraphy are imaging modalities which routinely used at the staging of DTC. F-18-fluorodeoxyglucose position emission tomography (FDG-PET) is not routine imaging tool for staging of DTC. However, FDG PET is strongly recommended in the follow-up of patients with high/elevated serum Tg and negative whole body radioiodine scanning (WBS). On the other hand, there are some studies that provide the benefit of FDG-PET in the staging of selected DTC patients who have intermediate-high risk (9-13).

The aim of this study is to determine the role of the FDG-PET in the staging of DTC patients who have high Tg levels after thyroidectomy.

Material and Methods

Ethical Statement

Approval was obtained from the institutional review board of Gaziantep University. All patients signed an informed consent form that allows the participating institution to use their clinical data (Ethics approval No: 2023/172 and date: 24/05/2023).

Study Design

Thirty three DTC patients (19 women, 14 men with mean age 39.9 ± 12 years) who performed FDG-PET after total/nearly total thyroidectomy between January 2019 and January 2023 were selected for this retrospective study. Histopathological examination revealed papillary thyroid carcinoma (PTC) in 32 patients and follicular thyroid carcinoma (FTC) in 1 patient. All patients had Tg over 10 ng/ml with negative Tg-Ab (Tg-Ab < 0.2 IU/mL) when TSH > 30 IU/mL. Tg levels were measured using immune-radiometric analyser that uses paramagnetic microparticles and chemiluminescent detection technology with a lower detection limit of 0.2 ng/ml. FDG-PET was performed to patients 6 weeks after surgery. And 2 weeks after the FDG-PET imaging, patients received RIT except who had head-neck lymph node involvement.

The patients with head-neck lymph node involvement went to neck dissection or fine needle aspiration biopsy and histopathological data were evaluated. After the RIT, post-ablation therapy whole body scan (TWBS) was performed to patients. FDG-PET and TWBS findings were correlated. Mean follow up time of the patients was 16.2 ± 4.2 months (min 6-max 36). On the follow up, TWBS and DWBS were performed some patients, and stimulated/non-stimulated Tg levels were measured.

FDG-PET Imaging

After 12-h fasting, patients whose glucose levels under 150 mg/ dL were injected with intravenous (iv) 5 Mbq/kg ^{18}F FDG. The PET/CT imaging was acquired with Siemens Biograph 2 LSO combined PET/CT device (Biograph LSO/ Somatom Emotion; Siemens Medical Solutions) 60 minutes after the injection. Sequential transmission and emission images of patient's body between the base of the skull and the proximal femur with the patient in a supine position were obtained. The PET/CT images were evaluated by two experienced nuclear medicine specialists. Uptake areas higher than ground activity which calculated as maximum standard uptake (SUVmax) were detected. The patients were classified according to whether they had pathological FDG uptake outside the thyroid bed or not.

Whole Body Radioiodine Scan

Patients except who had head-neck lymph node involvement, were given RIT after total or near-total thyroidectomy. Before RIT patients did not take levothyroxine, and they had a low-iodine diet for 2 weeks (12 days before and 2 days after I-131 administration). Patients were treated according to fixed dosage protocol: 50-100 mCi ^{131}I in cases without known lymph node or distant metastasis, 150 mCi ^{131}I in cases with lymph node involvement detected pre-or perioperatively and 200 mCi ^{131}I in cases of known distant metastasis. TWBS was performed a week after RIT. The patients were classified according to whether they had

pathological radioiodine uptake outside the thyroid bed or not. For the DWBS, patients discontinued taking thyroxine and followed a low-iodine diet during 3 weeks. Just before DWBS, stimulated Tg and Tg-Ab levels were measured when TSH>30 IU/ml. After a TSH stimulation, 5 mCi (185 MBq) ¹³¹I was given orally to the patients and 2-3 days later, DWBS was performed.

Statistical Analysis

Data of the patients were obtained from the computer system of the hospital (electronic record system of health data) and PET/CT images in our clinic. Data obtained were analysed with SPSS 18.0 statistical software programme. The descriptive values such as mean, standard deviation and percentage were used for age, gender and sensitivity. Quantitative variables were expressed as mean±standard deviation in the case of normal distribution, and median [IQR, interquartile range] in the case of non-normal distribution.

The means between 2 groups were compared using Student's t-test for normal distributions and Mann-Whitney U-test for abnormal distributions. Spearman's correlation analysis was used to reveal the relationship between biochemical tumour markers and imaging findings. P<0.05 was considered significant.

Results

Mean Tg level of all of patients was 166.6±324 ng/ml (min 10.5-max 515). 12 patients (36.4%) had no pathological FDG uptake on the FDG-PET. Mean Tg of these patients was 31.5±18.8 ng/ml (min 10.5-max 88). RIT was given to the patients. On TWBS performed after RIT, patients had radiotracer involvement only in the thyroid bed. There was not extrathyroidal involvement. For all these 12 patients, DWBS which performed 6 months after RIT were normal. Also stimulated Tg level measured before DWBS was under 2 ng/ml for all patients. Tg-Abs were negative. For this reason, these patients were considered in remission.

Table 1. The features of patients who had distant metastasis

Patient	H. P.	Tg (ng/ml)	PET-CT	SUVmax	TWBS	Follow-up
45-M	FTC	515	Lungs and bones	Lungs: 4.7 Bones: 15.6	RTT Lungs and bones	Progression
38-F	PTC	36	No pathological FDG uptake	-	RTT Single bone	Complete remission
76-M	PTC	430	Lungs	2.8	RTT	Progression
22-F	PTC	430	Lungs	2.8	RTT Lungs (intense)	Regression
39-F	PTC	515	Lungs	3.9	RTT Lungs (intense)	Regression
58-F	PTC	217.5	No pathological FDG uptake	-	RTT Lungs (diffuse)	Regression
41-F	PTC	480	Lungs	2.3	RTT Lungs (diffuse)	Regression
62-M	PTC	477	Lungs	Lungs: 8.9	RTT	Progression
52-M	PTC	450	Lungs and bones	Lungs: 11.1 Bones: 10.2	RTT Lung and bones	Progression
62-M	PTC	18	Left lung	9.1	RTT	Progression
29-M	PTC	200	No pathological FDG uptake	-	RTT Single bone	Regression

** PTC: Papillary thyroid carcinoma, FTC: Follicular thyroid carcinoma, H.P: Histopathology, RTT: residual thyroid tissue

In twenty-one patients (63.4%), there were pathological involvements outside the thyroid bed on FDG-PET and/or TWBS. The mean Tg level of these patients was 243.8 ± 222 ng/ml (min 18-max 515).

Table 2. Correlation of FDG PET and TWBS findings for the patients who had distant organ involvement

Variables	Remission	Regression	Progression
FDG Positive-DWBS Positive	-	3 patients	2 patients
FDG Positive-DWBS Negative	-	-	3 patients
FDG Negative-DWBS Positive	1 patient	2 patients	-

Table 3. The relationship between Tg levels and disease involvement patterns

Variables	Tg level
Only Thyroid Bed Involvement	31.5 ± 18.8 ng/ml (Min: 10.5- max: 88)
Only Lymph Node Involvement	135.1 ± 331 ng/ml (Min: 46-max: 515)
Distant Organ Involvement	342.6 ± 222 ng/ml (Min: 18-max: 515)

The difference between serum Tg of the two groups was significant ($p < 0.01$). Ten of these patients (30.3%) with a mean Tg level of 135.1 ± 331 ng/ml (min 46-max 515), had head-neck lymph node involvements. The patients with head-neck lymph node involvements were referred to surgery. The mean SUVmax for these patients was 9.1 ± 3.2 (min 2-max 21.2). After neck dissection, histopathological data were compatible with lymph node metastases for patients. Eleven of patients with pathological involvements outside the thyroid bed (33.3%) had distant organ or lymph node involvements on the FDG-PET and/or TWBS. The mean Tg of these patients was 342.6 ± 222 ng/ml (min: 18-max: 515). The difference between serum Tg of the patients with distant organ involvements and only head-neck lymph node involvements was not significant. The features of patients who had distant organ involvement are given on the table 1. Seven patients (63.6%) had only lung

involvement, 2 patients (18.2%) had only single bone involvement and 2 patients (18.2%) had lung and bone involvements.

In the patients with negative FDG-PET scan and positive TWBS findings for distant organ involvement (3 patients), the disease was complete or partial regressed (Fig 1). In the patients with positive FDG-PET and negative TWBS findings for distant organ involvement (3 patients), the disease was progressed. In the patients with positive FDG-PET scan and positive TWBS findings for distant organ involvement (5 patients), the disease was progressed in 2 patients and partial regressed in 3 patients. Correlation of FDG PET and TWBS findings for the patients who had organ involvement, were given on table 2. Also, for the patients with distant organ involvement who had higher SUVmax levels on FDG PET, the disease tended to progress (Table 2).

Discussion

Tg measurement is one of the main tools in the management and follow-up of patients with DTC after the RIT (7,14,15). Stimulated Tg measurement is more sensitive than the basal Tg (16). Although Tg measurement is used in the follow-up DTC patients for detection of residual and recurrence disease, there are some studies that showing the benefit of Tg levels which measured after total/nearly total thyroidectomy and before RIT. Higher Tg level which measured at the staging, is correlated with local/distant metastasis and it can be useful for predicting of prognosis (5-8). Especially Tg levels higher than 300 ng/ml, are suggestive of distant metastasis (8).

In our study, patients with involvement outside the thyroid bed had higher Tg levels than others. Additionally, the patients with distant organ involvement had higher Tg levels than patients with only lymph node involvements. The benefit of FDG-PET has been proven in the DTC patients with positive Tg level and negative whole body radioiodine scan (WBS). A negative

WBS result with elevated serum Tg level (>10 ng/ml) is the main indication for FDG-PET (17,18). But the role of FDG-PET in initial staging of DTC patients after surgery is controversial and information on this subject is limited. There are some studies that provide the benefit of FDG-PET in the staging of selected DTC who have suspicious findings such as high Tg, aggressive histopathological subtype (9-13).

There is no specific cut-off value of Tg for performing FDG-PET at the time of staging. But our clinical experience has shown that Tg level is usually under 10 ng/ml after a successful thyroidectomy if the patient does not have locally or distant metastases. For this reason, we chose the cut-off value as 10 ng/ml. Liu et al were chose the cut-off value of Tg as 10 ng/ml

too for performing FDG-PET to DTC patients at the staging time (9). Iwano et al. concluded that FDG-PET performed concurrently with RIT can detect lymph node metastases in which radioiodine does not accumulate and this situation may influence the management and treatment options for DTC patients (10). In our study 10 patients who had lymph node metastases were referred to resurgery before RIT. Thus, the treatment management has changed in these patients.

In a retrospective study by Nascimento et al, FDG-PET was performed 38 DTC patients with aggressive histology without known persistent disease at the time of postoperative RIT (11). They concluded that postoperative FDG-PET should be performed routinely in DTC with

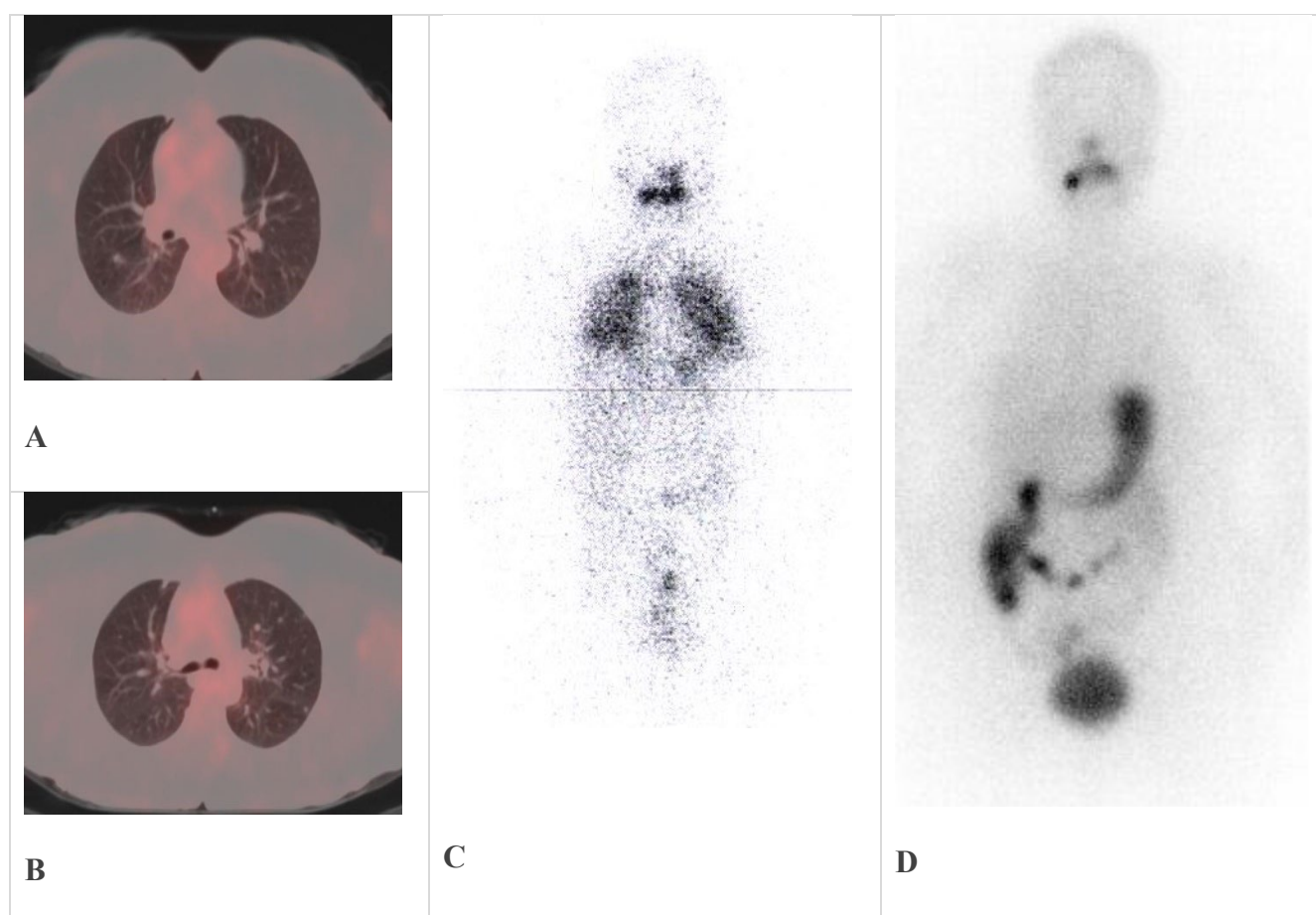


Figure 1. Fifty-eight years old female patient who had no pathological uptake on FDG-PET (Picture A and B) but diffuse lungs uptake on TWBS (Picture C). Tg level of patient after thyroidectomy was 217.5 ng/ml. On the follow up, there was biochemical and anatomic response to RIT (Picture D). Final Tg level of patients was 68 ng/ml.

aggressive histology. The FDG-PET scan also provides prognostic information. 18F-FDG-avid metastatic DTC lesions are usually resistant to 131-I treatment. Gartner et al concluded that FDG PET performed at the time of thyroid remnant ablation in high-risk patients with DTC is highly predictive for survival (12). The patients with positive FDG-PET findings showed worse biochemical response and lower survival as compared with patients who had negative FDG-PET scan. And complete remission was more common in patients with negative FDG-PET scan findings. Our study confirmed this status. We found that the disease was complete or partial regressed in the patients with distant organ involvement who had negative FDG-PET scan and positive TWBS results. On the contrary in the patients with distant organ involvement who had positive FDG-PET scan and negative TWBS, our findings showed that the disease was progressed. Liu et al. suggested that FDG-PET can play vital role in identifying metastases in postoperative DTC patients with elevated Tg levels (>10 ng/mL) before RIT (9). Also, FDG-PET positive metastatic foci with SUVmax of greater than 4.0 possesses higher probability of non-avidity to radioiodine. In our study, most of the patients with distant metastasis who progressed on the follow-up had higher SUV max than 4.0.

Conclusion

In conclusion our data suggest that FDG-PET scan which performed to the DTC patients with high Tg levels at the time of staging, would be the right approach. This approach will be very useful especially in demonstrating lymph node involvement and predicting prognosis. Results of FDG-PET may also change the treatment management. Especially in the DTC patients with distant organ metastasis, FDG-PET scan which correlated with WBS, should be used in both staging and follow-up. Thus, radioiodine avid disease and radioiodine-refractory patients can be selected.

Author contributions

The study conception, designed, wrote, and edited the manuscript by Ebuzer Kalender

Conflict of Interest

The authors declare no conflict of interest for the present study.

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