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Prognostic Value of FDG PET/CT in Differentiated Thyroid Cancer Patients

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ABSTRACT

Background: The most prevalent endocrine cancer is differentiated thyroid carcinoma, which accounts for 80%–90% of all thyroid malignancies as the most prevalent histologic subtype.

Objective: To evaluate the role of F18-FDG PET/CT in the prognosis and diagnosis of cases with differentiated thyroid cancer who have high thyroglobulin levels and negative I131 WBS.

Materials and methods: This prospective study was conducted on 52 patients with pathologically proven differentiated thyroid carcinoma. Those patients were under follow-up at Al Kasr Alaieny Hospital, Cairo University, between May 2018 and December 2020. We reviewed those patients; all patients had persistently elevated Tg levels after total thyroidectomy and remnant ablation with RAI, with no thyroid residual tissue. The patients' follow-up was done by measuring stimulated thyroglobulin level and anti-TG level, neck U/S, and DXWBS. Patients presenting no radiological evidence of recurrence and elevated Tg values, are included for studying FDG-PET/CT was performed.

Results: The sensitivity and specificity of FDG PET/CT were 92% and 72% respectively compared to 43% and 71% for I131 WBS. SUVmax cutoff point was at 1.5. On the other hand, DX WBS using I131 had sensitivity and specificity of 43% and 71% respectively. Patients with lesions attaining avidity for both iodine and FDG have better OS than those with lesions avid for FDG and lost iodine avidity.

Conclusion: FDG PET/CT provides additional information in the prediction of RAI therapy response and further contributes to the establishment of a proper therapy strategy for metastatic DTC in the early period.

Keywords: Differentiated thyroid cancer, 18F-fluorodeoxyglucose (18F-FDG), PET/CT, SPECT/CT.

INTRODUCTION

The differentiated thyroid carcinoma is the most common endocrine cancer, and its incidence has increased in recent decades it constitutes 80%-90% of all thyroid cancers as the most common histologic subtype [(1-2)]. Although it usually has an excellent prognosis, it recurs in 20% of patients[(3)].

Generally, thyroglobulin (TG) level and radioactive iodine (RAI) diagnostic whole-body scan (dx-WBS) correlate well with each other in follow-up studies for differentiated thyroid cancer (DTC) after thyroid remnant ablation. Negative dx WBS despite an elevated serum TG level occurs in 10–15% of these patients[(4)]. On the other hand, the presence of anti-TG antibodies in the systemic circulation interferes with the measurement of serum TG[(5)].

Loss of ability to trap RAI by metastatic DTC is associated with worse survival, and such cases often present aggressive clinical behavior[(6)]. Several studies have shown that fluorine-18-fluorodeoxyglucose positron emission tomography (18F-FDG PET) and 18F-FDG PET/CT can detect recurrence or metastasis with a high degree of sensitivity (80%-90%) in DTC of especially the non-trapping RAI cases [(7)], differentiated thyroid cancer (DTC) sends metastasis in approximately 10% of all patients, and radioactive iodine (RAI) therapy is well-known to be the first line of therapy [(8)].

Around 33%-50% of metastatic patients eventually become refractory to RAI[(9)], and those patients generally have a poorer prognosis. The median survival for RAI-refractory DTC patients with distant metastases is estimated to be 2.5-3.5 years[(9,10)]. Nowadays, tyrosine kinase inhibitor (TKI) medications, such as sorafenib and lenvatinib, have been introduced in these RAI-refractory patients with an expectation of improved prognosis[(11)]. Therefore, it is crucial to identify RAI-refractory DTC patients early and establish appropriate treatment strategies from a long-term perspective. Generally, high uptake of RAI in metastatic carcinoma suggests an excellent therapeutic effect, and several studies have reported a dose-response relationship[(12)].

Aim of the study was to evaluate the value of F18 FDG PET/CT in the prognosis of differentiated thyroid cancer cases.

MATERIALS AND METHODS

We reviewed the medical records of 52 patients prospectively. Those patients were under follow-up at Al Kasr Alaieny Hospital, Cairo University, Clinical Oncology, and Nuclear Medicine Department (NEMROK) between May 2018 and December 2020. 33 women and 19 men; mean age 42.08 ± 15.7 years with histological diagnosis of differentiated cancer thyroid. All patients had persistently elevated TG levels after both total thyroidectomy and remnant ablation with RAI; no residual thyroid tissue was included. Follow-up of all patients was done by measuring stimulated serum thyroglobulin level and anti-TG level, neck US, and DXWBS. Patients presenting no radiological evidence of recurrence and elevated TG values after four weeks of L-thyroxine withdrawal and low iodine diet are included for studying.

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FDG-PET/CT was performed 1 to 6 months later after 4 weeks of L-thyroxin withdrawal thyroid-stimulating hormone Levels at 30 micro International Units (uIU).

Inclusion criteria: Patients with initial histologically proven differentiated thyroid cancer who have high thyroglobulin or high anti-Thyroglobulin levels with no structural evidence of disease.

Exclusion criteria: Patients less than 18 years old, double primary malignancy, pregnancy, diabetes mellitus, and undifferentiated thyroid cancer at initial diagnosis

1. DXWBS:

Patient preparation: hormone withdrawal (L-thyroxin) for at least four weeks getting TSH at 30 uIU. Low iodine diet three weeks before the study and avoid contrast materials containing iodine that is used in imaging studies. Fasting for 2-4 hours before iodine administration is recommended.

Imaging: patient received 2-5 mCi orally and imaged 48-72 hours later. Imaging was obtained using a SPECT-CT gamma camera using a high energy collimator. Anterior and posterior view by the dual-head gamma camera. Large field of view, window photo peak centered at 364 Kev and matrix size 1024x256, 8cm/min bed speed. SPECT and Low dose CT 16 slices are obtained. Whole-body CT study (neck, chest, abdomen, and pelvis), scanning began at the level of the skull base and extended caudally to include the involved tumor site. The resulting images from CT reconstructed with a 512x 512matrix and a 50 cm field of view were converted using equivalent attenuation factors for attenuation correction. The interpretation was done by two experienced nuclear medicine physicians. The scans were read either as positive, negative, or equivocal I131 uptake in the thyroid bed, regional cervical lymph nodes, and sites outside the neck.

2. 18F-FDG PET/CT protocol:

Patients were prepared according to the EANM procedure guidelines for 18F-FDG PET/CT tumor imaging: Version 2.0[13]. The scanner used in NEMROCK was Ingenuity TF 64 (Philips Healthcare, Cleveland, OH, USA) a PET/CT scanner combining a modular, LYSO-based PET component with a 64-channel CT component. The CT was based on the Ingenuity CT (Philips Healthcare). Acquisition and reconstruction protocols were previously described. Briefly, a low-dose non-contrast CT scan was performed first, followed by a whole-body PET acquisition later, and a whole-body contrast-enhanced CT scan. Low-dose CT was acquired in a helical mode, using 120kV, 60 mAs, and a 512 × 512 matrix size, acquiring a field of view (FOV) of 700mm. This CT scan was used for attenuation correction. PET scan was acquired in a three-dimensional mode over the same anatomical regions starting from the skull vertex to the level of the mid-thigh. The acquisition time was 2min per bed position, in nine-bed positions. The reconstructed slice thickness was 5mm. Immediately after completing PET acquisition, a diagnostic CT with contrast was acquired using 120kV, 300 mAs, and a 512 × 512 matrix size. The acquired FOV was 500mm using dose automatic modulation in the Z direction. Slice thickness was 1.0mm. The whole study took about 20–30min. Raw data were reconstructed using a standard manufacturer's iterative algorithm. Axial PET and CT images were obtained and then reformatted into sagittal and coronal images to allow easier image interpretation.

PET/CT interpretation: PET/CT analysis for each PET-CT exam has been done by two experienced nuclear medicine physicians. The scans were read either as positive, negative, or equivocal.

Qualitative Interpretation: All patients in the current study 18FDG PET/CT images were assessed for the presence or absence of thyroid bed, regional lymph nodes, or metastatic sites lesion uptake compared to mediastinal blood pool and liver uptake.

Quantitative measurement with PET: maximum SUV (SUVmax), lean body SUV max (SULmax), and mean Hounsfield units (HU) were measured using an automatic 3cm diameter volume of interest (VOI) set in the site of recurrent tumoral lesion, SUVmax, and SULmax in the mediastinum were measured in an automatically placed 1cm diameter and 2cm height cylinder in the descending thoracic aorta. In baseline examinations and a case of remaining lesions in interim and EOT/FU examinations, the most intense target lesion was located by upscaling the base of the look-up table on the 3D MIP view. SUVmax and SULmax were computed as follows:

SUVmax=Measured activity X body weight (kg)/injected dose (MBq)SULmax=measured activity X LBM (kg)/injected dose (MBq).

Ethical consent:

An approval of the study was obtained from Cairo University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

All data were expressed as mean ±standard deviation or as a percentage, as appropriate. Differences between groups were X^2 analyzed or by Student t-test or analysis, as appropriate. Data were verified, coded by the researcher, and analyzed using SPSS version 25*. Descriptive statistics: Means, standard deviations, medians, ranges, and percentages were calculated. ROC curve depicted the diagnostic performance of the highest SUV maximum (SUVmax) for the prediction of iodine and FDG uptake, analyzed as the area under the

curve (AUC), standard error (SE), and 95% CI. Validity statistics (sensitivity, specificity, positive and negative predictive value –PPV & NPV-) were calculated. A p-value less than 0.05 was considered significant.

RESULTS

I. PET/CT and DXWB imaging results:

As regards PET/CT results, (22.2%) eleven patients showed no pathological FDG uptake and 4 patients (7.7%) had faint pathological FDG uptake although the majority of 37 patients (71.1%) had positive pathological uptake (**Table 1**).

PET alone has 71.6% sensitivity and 53.5% specificity with SUV max ranging from >0 up to 38 with a cut-off at 1.5 (compared with a gold standard, in the form of diagnostic imaging CT, MRI, and/or pathology of a recurrent lesion) and median at 3, mean ± SD 7.06 ± 1.4.

Table (1): Imaging Characteristics of the FDG PET/CT studied Cohort

Parameter	Category	(n = 52)
FDG Uptake	Negative	11 (21.2%)
	Positive	37 (71.1%)
	Faint Uptake	4 (7.7%)
SUV Maximum	Mean ± SD	7.06 ± 1.4
	Median (Range)	3 (0 - 38)

FDG PET/CT in our study demonstrated 92% sensitivity of recurrence detection and 72% specificity with 90% and 77% negative and positive predictive values respectively (**Fig1**). On the other hand, DX WBS demonstrated 43% sensitivity and 71% specificity. The negative and positive predictive values are 77% and 35% respectively (**Fig2**).

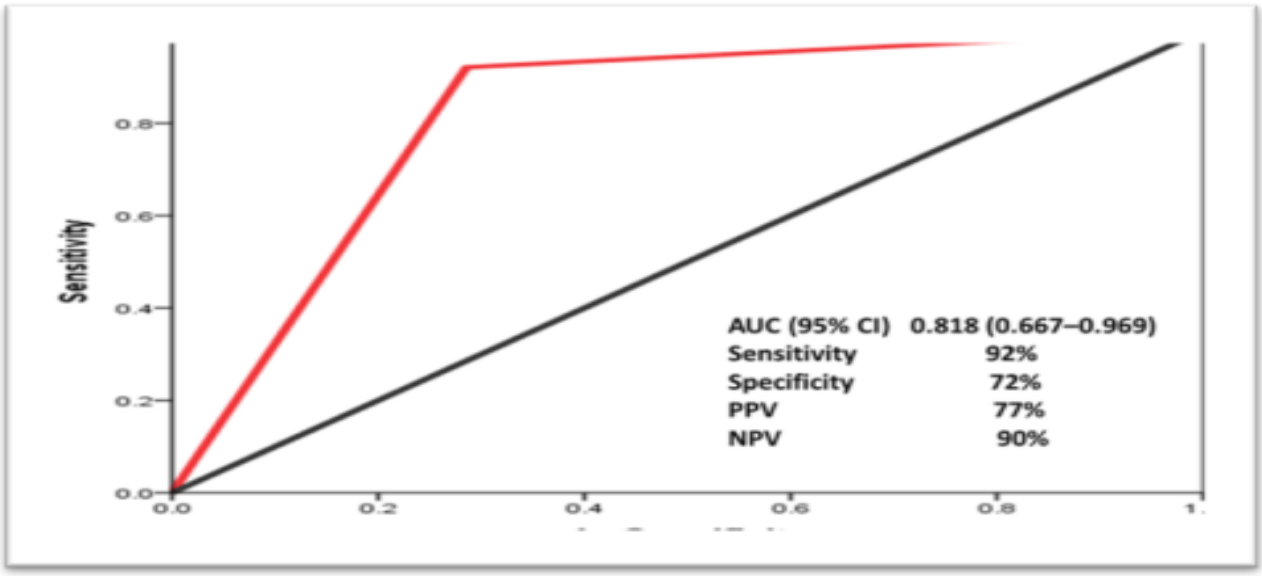


Fig. (1): ROC Curve of FDG Uptake for Prediction of Disease.

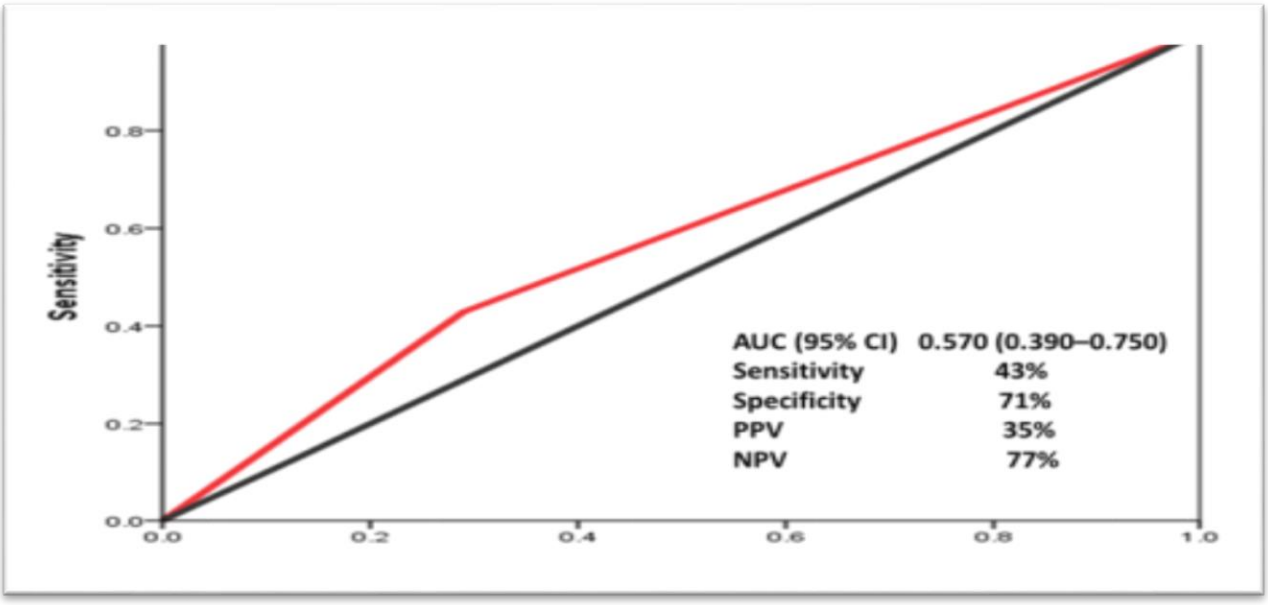


Fig. (2): ROC Curve of RAI-uptake for Prediction of Disease (Gold Standard).

We had 20 patients (38.5%) demonstrate local recurrence in thyroid bed in PET/CT study, 13 of them had also cervical LN metastasis. There were 29 patients with metastasis to cervical LNS with the majority in levels II & VI. Surprisingly, the highest SUVmax levels were related to loco-regional lesions rather than distant metastatic lesions and the lower SUVmax are seen related to lung metastasis.

Distant metastatic lesions were 15 lesions, 2 of them to the bone, another 2 in mediastinal lymph nodes, and 11 lesions to the lung.

Recurrence time since the first therapeutic RAI131 dose ranged from 12-36 months with a median of 20 months and mean ± SD = 20.95 ± 4.9. Level II neck lymph nodes and level VI are the most cervical lymph nodes affected by metastasis representing 21.2% and 25% respectively. Three cases demonstrated multiple levels of lymphadenopathy and one case demonstrated level V affection. On matching iodine and FDG uptake we found that patients are divided into four groups as follows: Group I (NN): patients with no iodine uptake and no FDG uptake. Group II (PP): patients with faint iodine uptake and positive FDG uptake. Group III (PN): patients with faint iodine uptake but no FDG uptake. Group IV (NP): patients with negative iodine uptake but positive FDG one.

Group I includes 8 patients, group II 12 patients, group III 5 patients, and 27 patients fall in group IV (representing the majority of patients). The group with no iodine uptake and positive FDG uptake (NP) is the largest group containing 27 patients representing 51.9% of cases (**Fig3 & Table2**).

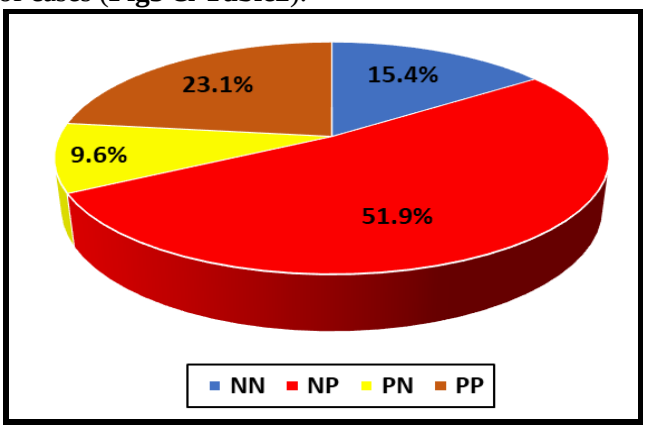


Fig. (3): Distribution of the sample according to Iodine/FDG Uptake.

Table (2): Relationship between Iodine and FDG Uptake

Parameter	FDG Uptake		P-value*
	Negative N=13	Positive N=39	
Iodine Uptake			
• **Negative**	8 (63.6%)	27 (68.3%)	= 0.517
• **Positive**	5 (36.4%)	12 (31.7%)	

***Chi-square test was used to test the difference in frequency between groups**

The group with positive iodine/negative FDG uptake (PN) is the smallest group containing only 5 patients and representing 9.6% while those with positive iodine and FDG uptake (PP) are 12 (23.1%) and negative iodine and FDG uptake are 8(15.4%). We noticed that about 46% of tumors of group II (PP) patients have SUV max >5, most of them are with> 10 SUV max and the highest SUV max=38 are in this group (iodine non-avid/FDG avid).

II. Follow up and impact on management according to PET/CT results:

Patients who fall in Group II (iodine avid and FDG avid tumors) and patients who fall in group IV (iodine non-avid but FDG avid tumors) are compared, Complications (dedifferentiation, death, and leukemia as a side effect of iodine therapy) occurred in 35.7% of group IV (NP) patients compared to 30.8 % in group II (PP) patients.

On follow-up, 14 patients manifested complications (e.g. recurrence and dedifferentiated tumor pathology). Patients who demonstrated recurrence and persistent increasing thyroglobulin levels were managed in a suitable way e.g re-surgery, chemo- and/or radiotherapy, or just follow-up.

On follow-up, 75% of patients in the NN group showed biochemical regression in the form of thyroglobulin level decrease, 83.4% in the PP group, and 62.9% in NP groups as well. No cases of group NN demonstrated progression (the best prognosis of all groups) followed by the PP group as regards prognosis **Table 3**.

Table (3): Relationship between TG level on follow up and Iodine/FDG Uptake

	PP n=12	PN n=5	NN n=8	NP n=27	P-value
25% decrease	**10 (83.4%**	**2 (40%)**	**6 (75%)**	**17 (62.9%)**	**0.58**
25% increase	**1 (8.3%)**	**2 (40%)**	**---**	**4 (14.8%)**	**0.50**
Stable	**1 (8.3%)**	**1 (20%)**	**2 (25%)**	**6 (22.3%)**	**0.52**

*Chi-square test was used to test the difference in frequency between groups
PP=positive iodine uptake and positive FDG uptake,
PN=positive iodine uptake but negative FDG uptake
NN=negative iodine uptake and negative FDG uptake,
NP=negative iodine uptake but positive FDG uptake

22/31 patients who demonstrated response by decreasing TG level were managed by surgery. Patients who demonstrated an increase in TG level total are 9 patients and there is no significant difference in management way in this group of patients. While 9/16 patients who demonstrated stability in TG level were on follow-up.

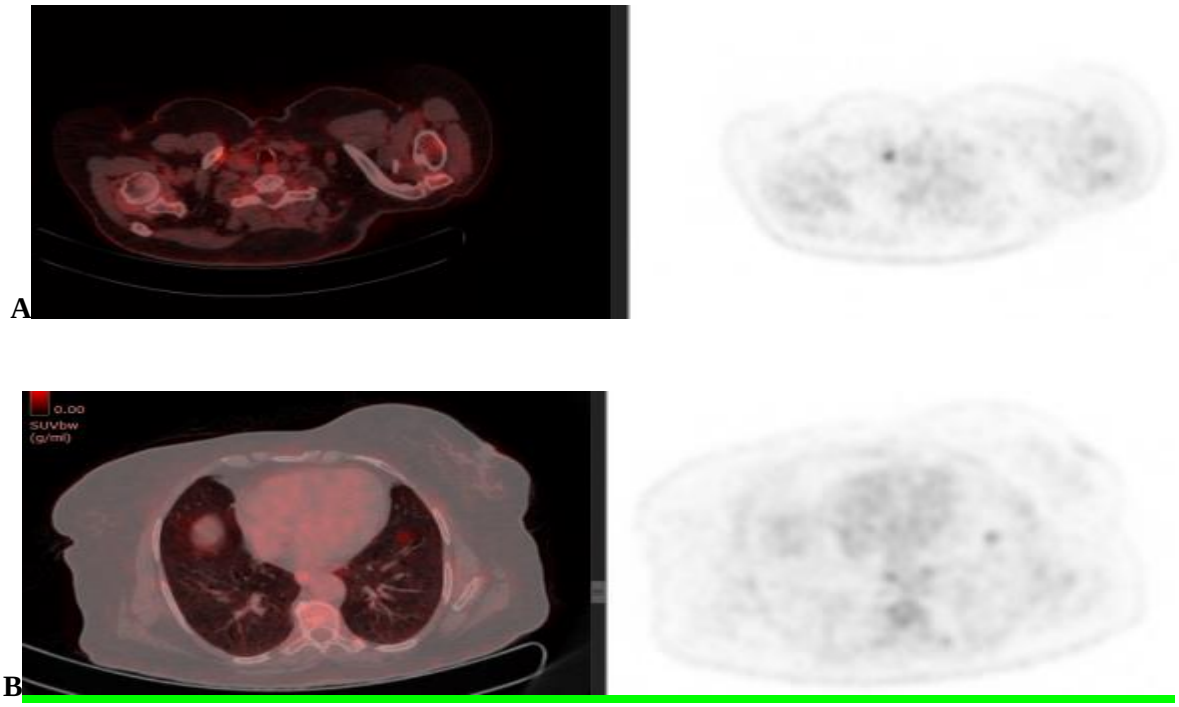


Figure (4): A: PET and PET/CT images showing FDG uptake by right supraclavicular lymph node. **B**: PET and PET/CT images demonstrate FDG uptake by multiple bilateral lung metastatic micro-nodules more on the left lung.

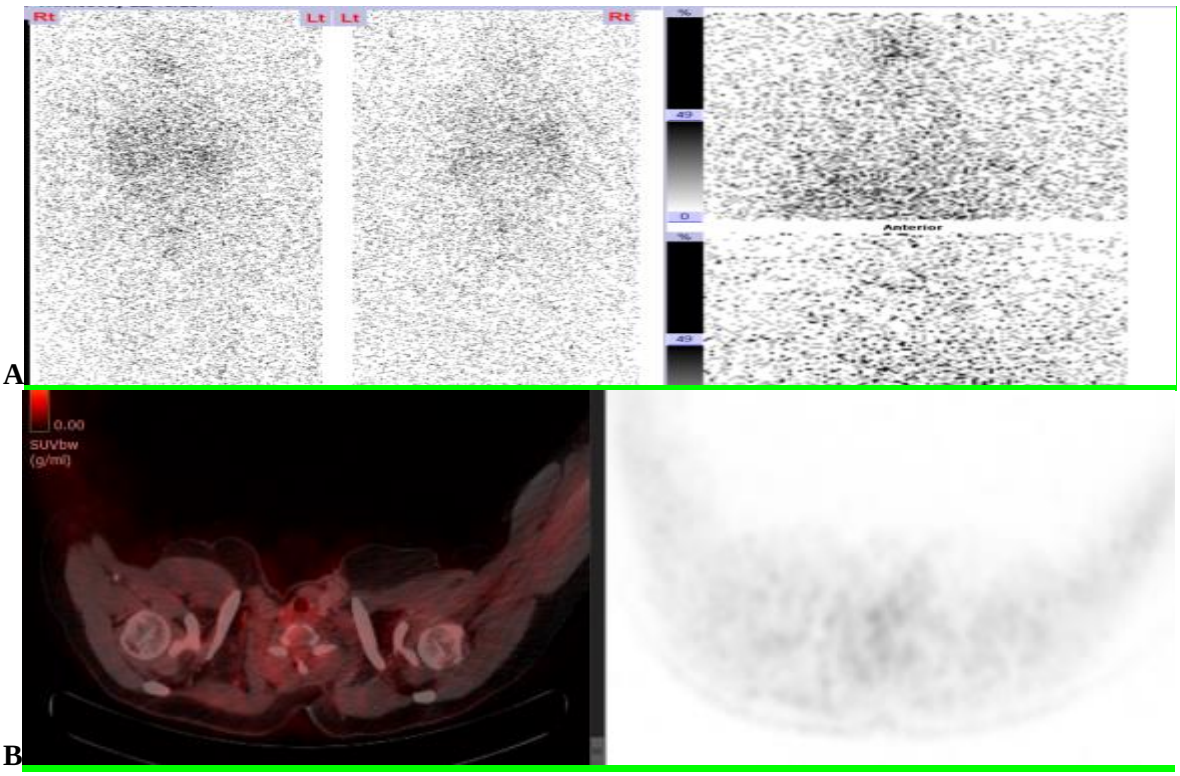
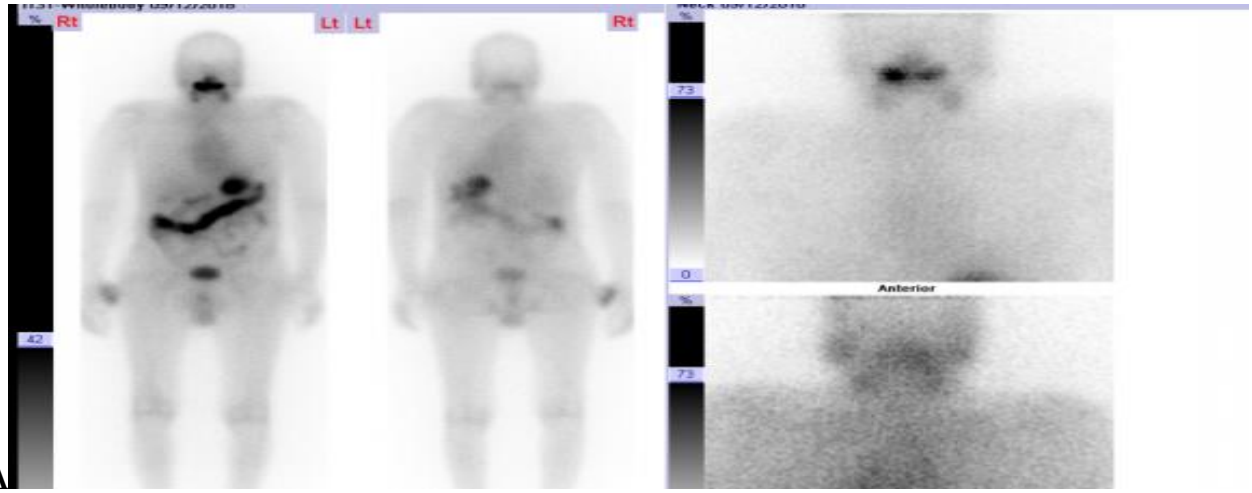


Fig. (5): A: DX WBS has been done before PET/CT by 3 mCi RAI show normal biodistribution with no uptake in thyroid bed neither iodine avid metastasis **B:** FDG PET/CT revealed low-grade FDG uptake by small right paratracheal LNs by pathology it has metastatic papillary thyroid carcinoma.



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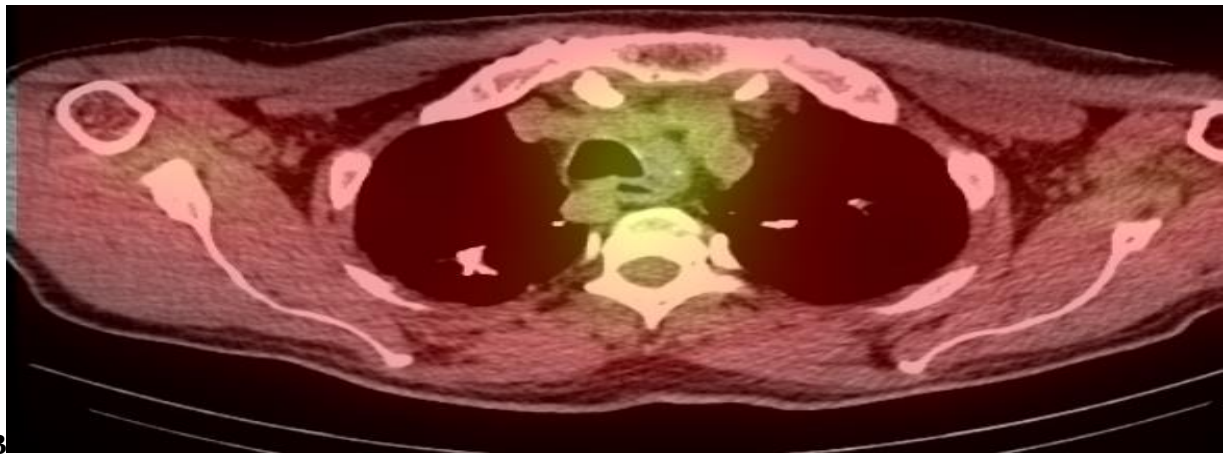

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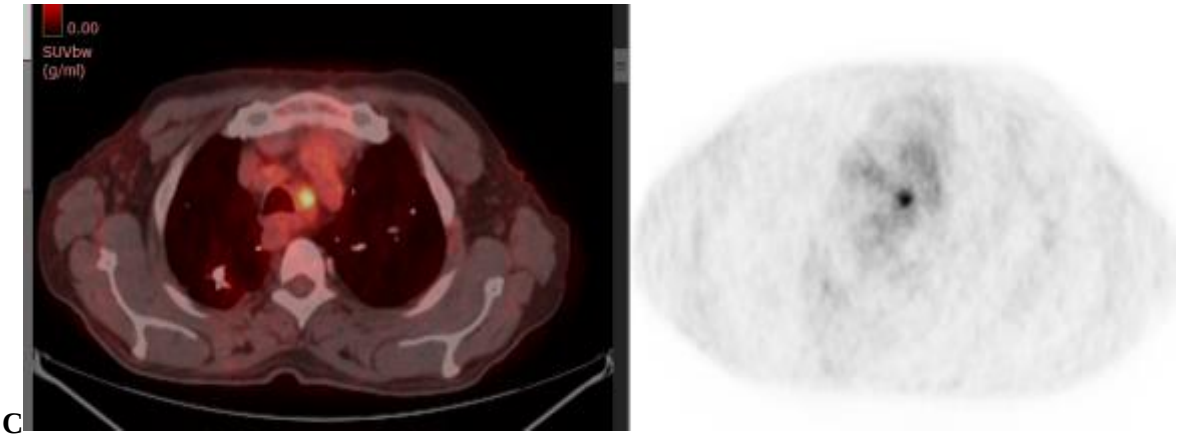
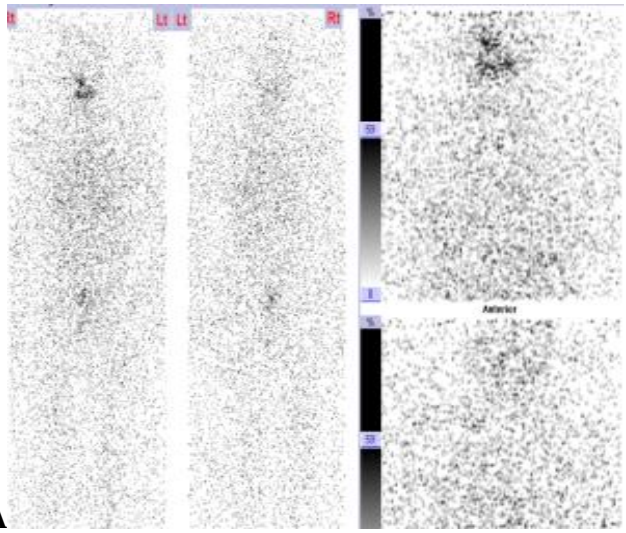


C

Figure (6): A: DX WBS demonstrates physiological iodine uptake with intense GIT uptake due to the effect of hypothyroidism (TSH 48 uIU/L). No iodine avid recurrent nor metastatic lesions **B:** fused SPECT-CT image demonstrate iodine non-avid calcified superior mediastinal LN **C:** F18-FDG PET/CT study demonstrated FDG avid superior mediastinal LN measuring 1.5 CM with SUVmax 8.



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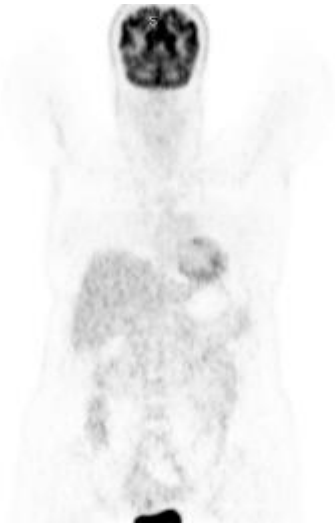

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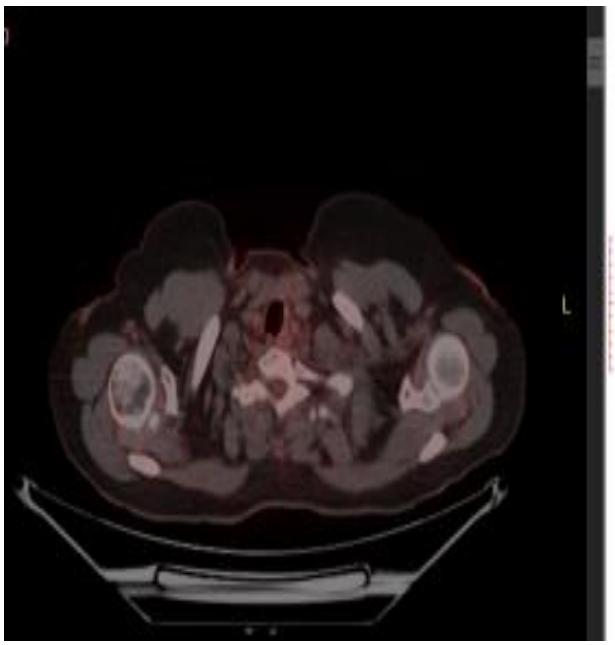

C

Figure (7): A: DX WBS shows normal biodistribution with no uptake in thyroid bed nor iodine avid metastasis. **B**: MIP image of FDG PET is normal FDG distribution. **C:** normal PET/CT study with no FDG avid cervical LNs no thyroid bed lesions.

DISCUSSION

Post-therapy RAI scan alone was not sufficient to predict RAI therapy response in patients with metastatic DTC. The patients with FDG avid-metastasis showed poor response to RAI therapy regardless of the degree of RAI uptake.

Recurrent metastatic differentiated cancer thyroid and 131I uptake:

The current study revealed that 35 cases were non-iodine avid. In addition, 24/41 (58.5%) cases with abnormally high TG levels showed negative 131I uptake with the note that all the studied patients received either ablation or adjuvant radioactive iodine-131 therapy. On the other hand, 32/41 (78%) with high TG levels showed positive FDG uptake.

Reasons for poor or no 131I uptake:

Min *et al.* [14], reported that all specimens from patients without 131I uptake were negative by NIS immuno-histochemical staining and all recurrent lesions in patients whose primary lesions were NIS-positive on immune-histochemical staining took up radio-iodine. Thus, the positive predictive value of NIS immune-histochemical staining concerning 131I uptake in recurrent cancer was 100%. This means one of the reasons for no radio-iodine uptake in the recurrent lesions, whether local or distant metastasis is loss of NIS.

Another important reason is the BRAF-V600E gene mutation, one of the most common mutations in PTC[15,16]. BRAF-V600E activates the production of genes responsible for the mitogen-activated proteins kinase (MAPK) pathway. Consequently, this pathway downregulates NIS causing inaccurate NIS localization and failing 131I uptake by tumor cells[17,18]. Previous meta-analyses have published a variability in the prevalence of BRAF-V600E mutation in papillary thyroid cancer to be ranged from 29 to 83%[19,20]. They attributed this wide range due to variations in papillary thyroid cancer subtype, geographical spots, and subjects. On the other hand, the incidence of BRAF-V600E gene mutation in Egyptian patients with PTC was 55.6% [21]. This means that the presence of BRAF-V600E is a high possibility in the current study and is a cause of absent iodine uptake. It had been reported that there was no statistical difference in BRAFV600E gene mutation incidence between different age groups [22]. This might explain the insignificant difference in age and non-avid radio-iodine uptake in the studied patients.

Recurrent tumor lesions and Flip/flop phenomenon:

Deandreis *et al.* [23] reported that most of their patients showed FDG uptake (72%), and only 45% presented radio-iodine uptake. The current study revealed that 75% of the studied patients were FDG avid, and 32.7% were radio-iodine avid. The present study was subdivided accordingly into four groups according to the presence or absence of both/ or either radio-iodine or FDG uptake. The first group comprised (NN) 8 cases (15.4%), more or less similar to that reported by **Kang *et al.*** [24]. The second group (NP) comprised 27 (51.9%) and represented the biggest group of the studied patients, contrary to **Kang *et al.*** [24] who reported a lower incidence (24%). The third group (PN) included only 5 cases (9.6%), which is again lower than that reported by **Kang *et al.*** [24] similarly, the current study reported a lower incidence of patients in the fourth group (PP) 12 cases (23.1%) compared to 43% reported by **Kang *et al.*** [24]. It should be noted that group I (NN) represented differentiated (i.e., no GLUT1 expression yet) recurrent lesions with lost NIS [25]. This was the case in the current study where 3 cases with regular Tg. These 3 cases were diagnosed only by CT. none of the rest (5 cases) could be interpreted by any other modalities. Bongiovanni *et al*. stated that these cases mostly had micro-metastases that could not be detected except for the high TG levels.

Also, the current study revealed that most of the detected recurrent lesions in the NN group were in lymph nodes which proved to be the most non-iodine avid [25]. According to Bongiovanni *et al.*, once the differentiated micro-metastases grow up, the avidity with consequent positivity of radio-iodine uptake would be seen, and yet no FDG uptake. This is what happened in the current study in the PN group (5 cases). The TG level in this group was abnormally high in all. Ultrasonography and CT were found to be unhelpful in these cases[25] [25].

Suh *et al.* [26] stated that the progression of cancer cells required a higher amount of energy in the form of augmented aerobic glycolysis in the advanced stages. This will cause overexpression of GLUT1 and/or GLUT3 to increase glucose influx. That is why in the current study, two groups had been designed, one with positive both 131I and FDG uptake was still there was some degree of differentiation for 131I uptake (PP group). In the other group, where the dedifferentiation becomes progressive and loss of NIS was inevitable, glycolysis becomes the primary energy source with consequent FDG uptake (NP). These findings were matched with several previous results stating that: 1) poorly differentiated thyroid cancers required higher demand of glucose uptake through GLUT expression, 2) Inverse correlation between tumor differentiation score (TDS) [calculated by expression values of a set of specific genes] and GLUT expression, 3)A proportional

correlation between TDS score and glycolysis. **Suh *et al.*** [26] described the relation between the papillary thyroid cancer differentiation and glycolysis as a 'U shape' pattern with two limbs of high glycolysis signatures. One seen in anaplastic thyroid cancer (which was represented in the current study as NP group) and the other limb in some types of well-differentiated papillary thyroid cancer (PP group in the current study).

As a consequence of the above findings, the combined 131I and FDG uptake scale could be sequenced in the following manner according to the disease progression: NN, then PN, then PP, and finally NP.

Combined imaging and management changes:

Alnafisi *et al.* [27] found that PET changed management in 7 of 11 patients. **Goshen *et al.*** [28] reported change in management in 6 of 20. For example, when the radio-iodine scan was negative, identifying a focal 18 F-FDG PET lesion can make surgery an option. Several authors reported that we should change the management of cancer thyroid according to the findings of combined radio-iodine-FDG imaging so that those with negative iodine cases should avoid radio-iodine therapy and shift to either surgery external radiation according to the site of the recurrence. This is what happened in the studied patients where surgical management had been done in 26 patients (50%) of patients (NP group). In the current study, in the 20 cases of the NP group where PET/CT had detected cervical lymphadenopathy, surgery was the first line for removing these lymph nodes. However, 16/20 (80%) neck US was used for FNA to confirm cancer pathology before surgical removal. This was similar to **Karwowski *et al.*** [29], who used neck US to confirm localization and to do FNA. Also, chemo-radiotherapy had proceeded in 10 cases of iodine negative.

Prognostic value of combined imaging:

The prognosis of the flip/flop phenomenon had been reported as follows: Multivariate analysis suggested that radioactive iodine uptake, even if it does not significantly affect overall survival, it is predictive of longer disease-free survival, even in patients with FDG uptake. This agrees with the most critical clinical paper in this field (Robbins and colleagues), who retrospectively analyzed the initial FDG PET/CT uptake behavior in 400 DTC patients. They examined the predictive value of clinical variables, namely gender, age, serum TG levels, stage, histology, radioactive iodine avidity, F18-FDG-PET positivity, number of FDG-avid lesions, and the glycolytic rate of the most active lesions. They found that only age and 18F-FDG PET/CT results were strongly associated with survival on multivariate analysis. Furthermore, they disclosed a significant inverse relationship between survival and both the glycolytic rate of the most active lesions and the number of FDG-avid lesions[30,31]. They also reported that 18F-FDG avidity in metastatic thyroid cancer is observed in undifferentiated, aggressive variety with poor prognosis and reduced survival. In such cases, together with high-risk thyroid cancer, the total volume of 18F-FDG avidity is the strongest independent predictor of survival. Low or no FDG uptake in RAI-negative disease has a better prognosis, and in fact, thyroxin suppression is adequate in the absence of any management[10,32]. **Nagamachi *et al.*** [33]**,** also showed that only a positive PET/CT and age older than 45 years have a significant negative impact on overall survival in patients with cancer thyroid in restaging among several potentially prognostic factors. Thus, 18-FDG PET/CT has been described as a promising technique in identifying DTC patients at higher risk of developing distant metastases or those with distant metastases at higher risk of disease progression. A finding matched the current study.

CONCLUSION AND RECOMMENDATIONS

FDG PET/CT provides additional information in the prediction of RAI therapy response and further contributes to the establishment of a proper therapy strategy for metastatic DTC in the early period. Genetic studies should be done in all cases of cancer thyroid for precision treatment.

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