Original Article, PET/ CT.

Value of Initial ^{18}F-FDG PET/CT in Change of Management of Patients with Differentiated Thyroid Cancer as Compared to Post Ablative Whole Body Iodine Scan.

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ABSTRACT

Differentiated thyroid cancers (DTC) are generally malignant endocrine tumors with good prognosis.
50-68% of patients with DTC's have local or regional recurrences depending on the patient's risk factors. **The aim of the work:** was to assess the rule of initial PET/CT in patients with DTC, evaluate the PET/CT as compared to post ablative WBS in DTC. The study included 124 patients with essentially pathologically proven differentiated cancer thyroid patients who had undergone or near total thyroidectomy and was eligible for RAI ablative dose. Pathological details, TG levels and post ablative I-131 WBS results were also reviewed and compared to PET/CT results. A short follow up period ranged from 4-6 months was used as a reference to validate the results of the current study.

Results: we found the majority were females (74.2%), The mean age was 42 years old, papillary thyroid cancer was the dominant type in (83.1 %). (55.6%) was of low risk according to ATA Risk stratification and of stage I, Serum TG levels varied widely from 0.04-13564 with a median value of 8.28 ng/ml. 38 patients out of 124 (30.6%) showed positive FDG uptake in following sites thyroid operative bed, cervical and mediastinal LNs, pulmonary and bone metastases with the majority of pathological FDG uptake being at the loco-regional area in 38 patients. It was observed that PET/CT had positive results in older age groups especially those above 50 years old, patients with elevated serum TG levels with a median value of 40 ng/ml, Hurthle cell type and Intermediate /High risk groups.

Therefore, patients with such criteria are more likely to benefit from initial PET/CT prior to their RAI dose. No significant correlation between the metabolic parameters and the avidity of RAI-131 positive findings was found. In 38 patients positive PET/CT results led to re-staging of 12 patients (9.6 %) and changed the management in 30 patients (24.2%).

Conclusions: PET/CT changed the management in around 25 % of Differentiated thyroid cancers (DTC) that helped in validating the "Theranostics" concept which aimed at individualized patient management to achieve the best outcome.

Key words: *Thyroid carcinoma, F-18 FDG PET/CT, Change in Management.*

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INTRODUCTION:

Cancer institute of Egypt-Cairo University, the primary malignant thyroid neoplasm constituted 1.97% of malignant neoplasms at NCI and 74.7% of malignant endocrine tumors with evident female predominance (ratio 2.6:1) and a mean age at diagnosis of 51 years [(2)].

Differentiated thyroid cancer refers to those derived from follicular cells, including papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), and Hurthle cell cancer. PTC is the most common histologic subtype of thyroid cancer, accounting for 90% of new cases, and has the best prognosis. Thyroid cancer has an estimated 5-year survival of 98.1% [(1)].

The application of PET/CT is considered for patients with differentiated thyroid carcinoma and suspicion of recurrence because of rising thyroglobulin levels and negative whole-body scintigraphy. Other indications for PET/CT in patients with thyroid carcinoma remains unclear whether the application of initial post-operative PET/CT in patients with thyroid cancer may affects the staging, therapeutic strategies and will have an impact on patient-relevant outcome [(3)].

Li et al., they demonstrated that 18F-FDG PET/CT performed concurrently with 131-I treatment can detect additional recurrent or metastatic lesions, which were negative on post therapy 131-I scan and the treatment strategy was changed in 89.2% cases of positive PET/CT scans [(4)].

The aim of the following work to investigate clinical utility of Fluorine 18-FDG PET\CT in patients with DTC as compared to post therapy I-131 WBS in change of management of such patients.

PATIENTS AND METHODS:

A) Study Population:

This prospective study was conducted in nuclear medicine unit in national cancer institute (NCI) on hundred twenty-four patients (92 females and 32 males) with pathologically proved differentiated cancer thyroid. Following near total thyroidectomy and /or lymphadenectomy when indicated. These patients underwent initial post-operative whole-body PET/CT prior to their ablative dose of RAI during the period from June 2019 to October 2019.

Inclusion criteria: Patients of all age groups and both sexes, pathologically proven DTC and didn't receive their RAI ablation dose yet.

Exclusion criteria: Undifferentiated or medullary cancer thyroid patients, patients with prior treatment with RAI, patients with double primary and pregnant women.

B) Study design:

All patients in the current study underwent clinical examination with gathering their data including age , gender, Serum TG level, histopathological characteristics (size, type, thyroid capsule and vascular invasion, lymph node involvement), details of treatment (surgery, lymphadenectomy, RAI dose), surgical operative notes, regional nodal involvement, other imaging investigations like ultrasonography/CT were recorded and postsurgical staging for each patient was determine.

F18-FDG PET/CT Imaging:

Patient preparation:

The patients were asked to fast for 4 - 6 hours prior to PET/CT study, Patients were instructed to avoid any kind of strenuous activity 24 hours prior to the examination to avoid physiologic muscle uptake of FDG, blood sugar levels were checked to ensure that there was no hyperglycemia; a level of less than 160 mg/dl is desirable. Six of the patients were diabetic they are rescheduled for PET\CT after diabetes control.

A dose of 0.14 mCi/kg body weight of FDG was injected IV one hour before imaging, patients sat quietly in a dimly lit room during the uptake phase and were asked to void just prior to imaging. Patients were allowed to drink water during the uptake period and patients were positioned with the arms down at both sides.

Imaging Protocol:

Forty-five to sixty minutes after FDG injection, the patients were placed supine on the imaging table acquiring at first the CT portion of the study. This was applied as whole-body scan (PET/CT).

Dual time F18-FDG PET/CT study was done using a dedicated PET/CT scanner (PET/CT 710, Discovery; GE). This machine integrates a PET scanner with a dual- section helical CT scanner (40 slice Emotion; GE) and allows the acquisition of co- registered CT and PET images in one session.

CT imaging Protocol:

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. Typical scanning parameters would be a collimator width of 3.0 mm, pitch of 1.5, gantry rotation time of 0.8 second, and field of view of 50 cm.

The resulting images from CT reconstructed with a 512 x 512 matrix and a 50 cm field of view, were converted using equivalent attenuation factors of 511 keV for attenuation correction.

PET imaging:

PET performed on a dedicated PET scanner with approximately six to eight bed positions that planned in the three-dimensional acquisition mode for scanning from the head to the mid thight with 1-2-minute acquisition at each bed position in a caudo-cranial direction. Each bed position is 15.5 cm long, and the table moves 11.5 cm following acquisition of data at each bed position, there is approximately a 4 cm (25%) overlap between table stations. The maximum length of the patient that can scan with the current PET/CT scanner is 180 cm**.**

Then PET and CT images were reviewed using a dedicated workstation and software (GE Medical Solutions), which allowed three-dimensional displays (trans-axial, coronal and sagittal) to be constructed using CT, PET and PET/CT images and maximum intensity projection displays of the PET data. The CT data were used for attenuation correction for the PET data and for lung lesion screening as far as possible.

For Image construction and the images were reconstructed using the standard ordered subset expectation maximization (OSEM; two iterations, eight subsets) algorithms. The reconstructed PET image voxel size was 1.7x1.7x2.4 mm.

1. Qualitative Imaging:

Two experienced nuclear physicians interpreted the FDG PET/CT studies, making a consensual diagnosis in the standard clinical fashion. All patients in the current study 18 FDG PET/CT images were assessed for presence or absence of thyroid bed, regional lymph nodes or metastatic sites lesion uptake compared to liver uptake.

2. Quantitative measurement with PET:

PET provides images of quantitative uptake of the radionuclide injected that can give the concentration of radiotracer activity by normal and pathologic tissues, such as the standardized uptake value (SUV max).

Image interpretation:

Sensitivity and specificity of the FDG PET results were determined by clinical follow-up and diagnostic procedures such as CT, neck U/S and TG measurement or by histological confirmation.

Post ablative body Iodine scans:

Patient preparation:

High level of TSH greater than 30 uU/ml is required to ensure detection of all thyroid cancers that are capable of function. The patient begins a low iodine diet as well as the medications that contain iodine content, and continuing until at least 24 hours after ablation or treatment with radioiodine. Low iodine diets can be effective in increasing uptake. Avoiding iodine based contrast given intravenously for C.T. for 1 month; Iodine based contrast given for myelo-graphy, cistern-graphy or broncho-graphy for at least 6 months.

The fasting patients received from (80-200 mCi) 131-I, and WBS was performed 5–7 days later. Planar I‑131 WHole‑body imaging was performed in both anterior and posterior projections on a dual head gamma camera using a using a large field of view of double-headed gamma camera on a photo peak of 364 kev with a high energy collimator with a scan speed of 15 cm/min and a matrix of 256×1,024 (Symbia S; Siemens).

Image interpretation:

Two experienced nuclear medicine physicians interpreted the scans. The scans were read as positive, negative or equivocal for abnormal I-131 uptake in the thyroid bed, regional cervical lymph nodes and sites outside the neck (distant sites). The uptake of tracer in the planar scans was considered positive when abnormal tracer uptake was clearly seen in thyroid bed. The uptake of tracer was considered suspicious for involvement of a particular site when it was difficult to ascertain the anatomic location or to characterize the uptake. Any uptake was characterized as negative when it was seen at the known physiological sites like salivary glands or the gastrointestinal or urinary tract.

Statistical Methods:

Data management and analysis was performed using Statically package for social sciences (SPSS) vs 25. Numerical data were checked for normality and were statically described in terms of mean (standard deviation) or median (range) as appropriate. Categorical data were described as numbers and percentages.

Comparison between numerical variables was done using student t-test when normally distributed and Mann Whitney U test if non-normally distributed. When comparing categorical data, Chi square test or Fishers exact test were performed as appropriate.

Logistic regression analysis was used for determining independent variables associated with PET/CT outcome. Forward LR variable selection method was used including any significant variables on the univariate analyses. Odds ratios with 95% confidence interval were calculated for the significant independent variables in the final step of the logistic regression**.** A P-value less than or equal to 0.05 level was considered statistically significant. All tests were two tailed.

RESULTS:

This prospective study included 124 thyroid cancer patients with their pathology essentially of the differentiated type. 92 were females (74%) and 32 WERE males (26%). Their age ranging from 13 to 83 years old with a mean age of 42 years (±15 years). Concerning the histopathological analysis, papillary type was the dominant type in 103 patients representing 83.1 % followed by much lower frequency of follicular type constituting 8% and Hurtle cell carcinoma occurring in 8.9% (n=11) of studied patients.

Regarding the extra-tumoral invasion status, it occurred in 47.6% and lymphatic invasion was the major type occurred in (26.6%) and regional cervical nodal involvement was seen in 40 patients (32.3%).

In respect to the TNM staging (8th edition) and ATA risk stratification, 48.8% of patients were of T1-2 N0M0 and the majority of patients (96.8%) were of low and intermediate risk (55.6% and 40.3% respectively).

Regarding the serum TG level, almost all patients had their TG level done at least one-month post operatively and 2-3 days before their dose of RAI where it ranged from 0.04 to 13,564 ng/ml with a median value of 8.28 ng/ml.

Post Therapy Iodine Whole body scan findings:

In the post therapy I-131 WBS, the radioiodine uptake sites included the thyroid bed (n=113) accounting for 91.3 % of patients, cervical LNs in 4 patients, lungs in also 4 patients and bone in only 1 patient and 3 patients showed no iodine uptake ***(Table 1).***

Table (1): Post therapy I-131 WBS findings in 124 patients with thyroid cancer.

Post-Therapy I-131 WBS	NUMBER / %	
Thyroid Bed	**113**	**(91.3%)**
Nodal Uptake	**4**	**(3.2%)**
Lung Uptake	**4**	**(3.2%)**
Bone Uptake	**1**	**(0.8%)**
No Uptake	**3**	**(2.4%)**

PET/CT uptake sites in the 38 positive thyroid cancer patients:

FDG-PET imaging done before I-131 ablation was positive in 65 sites in 38 out of 124 patients (30.6%). FDG positive sites included the thyroid bed (n = 22), cervical lymph nodes (n = 15), While 28 patients (22.6%) showed FDG accumulation at metastatic sites lung in 14 patients, mediastinal LNs in 8 patients and bone in 6 patients) ***(Table 2).***

Table (2): Loco-regional, nodal and distant PET/CT in 65 % positive sites in 38 patients.

PET/CT positive patients per site	Number of patients	% from the positive patients
Operative bed residual tumor	**22**	**17.7%**
Cervical LN metastatic deposits	**15**	**12. %**
Pulmonary metastatic deposits	**14**	**22.6 %**
Mediastinal LN Metastatic deposits	**8**	
Osseous metastatic deposits	**6**	

Concordance of PET/CT and post therapy I-131 WBS findings:

PET/CT versus radioiodine WBS in detecting operative bed lesions:-

Concordant positive lesions in thyroid bed by I-131 scan and PET/CT were seen in 16 patients indicating malignant thyroid residue. 97 patients had only I-131 uptake keeping with normal residual thyroid tissue. While additional PET/CT positive lesions were seen in only 3 patients in the thyroid operative bed with negative I- 131 scan suggesting de-differentiated residual thyroid tumor tissue ***(Table 3)***.

Table (3): PET/CT versus radioiodine WBS in detecting operative bed lesions

Item		PET/CT		P-value
		Negative operative bed (n=97)	**Positive operative bed (n=19)**	
WBS result**	No operative bed uptake (n=3)	Nil	3	<.001* [a]
	Positive operative bed uptake (n=113)	97	16	

** WBS not done in 8 patients (who had 18 PET/CT positive lesions)

PET/CT versus radioiodine WBS in detecting cervical nodal lesions:

In the cervical nodal lesions, thirteen patients had pathological cervical nodal FDG uptake with only three patients having similar uptake in the iodine WBS, whereas PET/CT detected cervical nodal lesions in 10 additional patients not evident in I-WBS (false negative by I-131 scan).

PET/CT versus WBS in detecting pulmonary lesions:

PET/CT detected positive pulmonary lesions in 14 patients with only 3 of them being detected by I-WBS. In contrast, only one patient had Iodine avid lung lesions and were non FDG avid confirming the well differentiation of these lung metastases.

Therapeutic impact on management according to PET/CT findings:

Based on PET/CT findings, patient management was changed from the standard RAI to more individual procedure in 38 patients out of the 124 patients (30.6 %). While, 86 patients out of the 124 included (69.3%) patients showed no uptake by the PET/CT, and had their standard RAI ablative dose (80-100 mCi).

Fifteen out of the 38 positive patients underwent surgery in order to remove the abnormal metabolic lesions in the thyroid bed and/or cervical LNs , where all of them were histopathologically confirmed to be true positive (tumor residual and/or lymph nodes metastases) and followed by higher RAI-131 therapy dose (125- 150 mCi).

Also, in 6 patients, the 18F-FDG PET/CT showed positive uptake in the thyroid operative bed and regional cervical LNs in four of them and subsequently confirmed to be negative using US or CT and serum TG remained undetectable (considered a false positive) and eventually received the same ablative dose of RAI. The other 2 patients were unfit for surgery and were eventually shifted to higher RAI therapy dose ***(Table 4)***.

Nine patients had FDG avid pulmonary nodules had their RAI dose increased to 150 mCi ***(Table 4) & (Figure 1).***

Only three Patients were considered to have advanced disease or de-differentiation evident by FDG-positive and iodine negative metastases, those patients were advised for systemic targeted therapy. ***(Figure 2).***

External beam irradiation was applied in three patients with positive bone deposits followed by RAI therapy dose (150-200 mCi).

PET/CT showed positive FDG uptake in mediastinal LNs in eight patients with only 2 of them had positive FDG uptake in the mediastinal LNs region only; those patients received their ablative RAI dose with no change in management.

Only one patient, showed diffuse pulmonary uptake compatible with lung metastases, which were negative on the 18F-FDG PET/CT scan (**false negative**), this patient was missed and received higher RAI ablative dose.

Table (4): Different management decisions for the 124 patients.

RAI dose (80-100 mCi	Surgery +RAI	RAI dose 150 mCi	TKI	RAI dose 150 mCi + Radio therapy
(74.2%)	(12.1%)	(8.9 %)	(2.4%)	(2.4%)
86 negative patients	**15 Patients**	**9 Patients with pulmonary metastases**	**3 Patients**	**3 Patients**
4 false positive PET/CT patients				
2 FDG positive mediastinal LNS		**2 patients unfit for surgery**		

For the study group of 124 patients, the PET/CT examination had a sensitivity and specificity of 91.6% and 94.4 % respectively. The positive and negative predictive values were 86.8% and 96.5% respectively (**Table 5**).

Table (5): Sensitivity, Specificity, PPV and NPV of 18F-FDG PET/CT in 124 patients of cancer thyroid patients.

18F-FDG PET/CT	Disease	No disease	Total
Positive	**33 (TP)**	**5 (FP)**	38
Negative	**3 (FN)**	**83 (TN)**	86
Total	34	90	124
Sensitivity: 91.6 %	Specificity:94.4%	PPV: 86.8%	NPV:96.5%

Se: sensitivity, Sp: specificity, PPV: positive predictive value, NPV: negative predictive value, TP: true positive, FP: false positive, FN: false negative, TN: true negative.

While regarding to the RAI-131 WBS, it was done for 116 patients and no scans were done for eight patients, the sensitivity was 99.1%, the specificity was 100%, the PPV was 99.1% and the NPV was 66.6%.

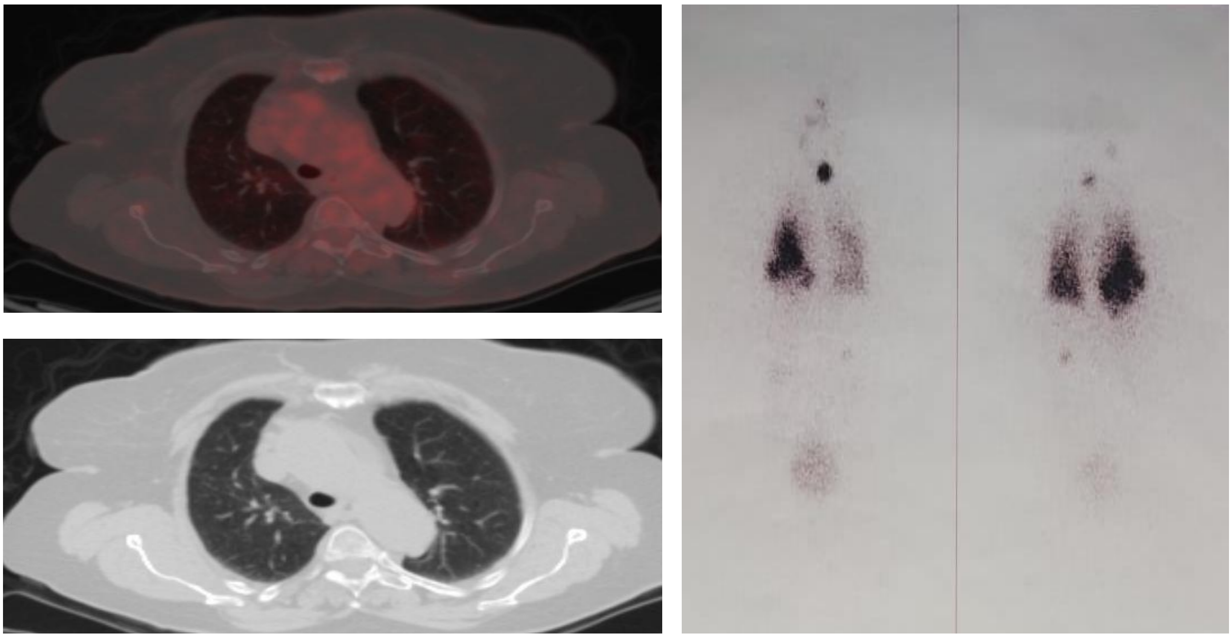

Figure (1): Anterior and posterior I-131 WBS and spot chest views post (100mci) with imaging after 7 days showing iodine avid residual functioning thyroid tissue and bilateral diffuse lung metastases while the PET/CT fused image and the CT image showed no metabolically active FDG avid lung lesions due to being diffuse micro metastases which predicts good prognosis and well differentiation.

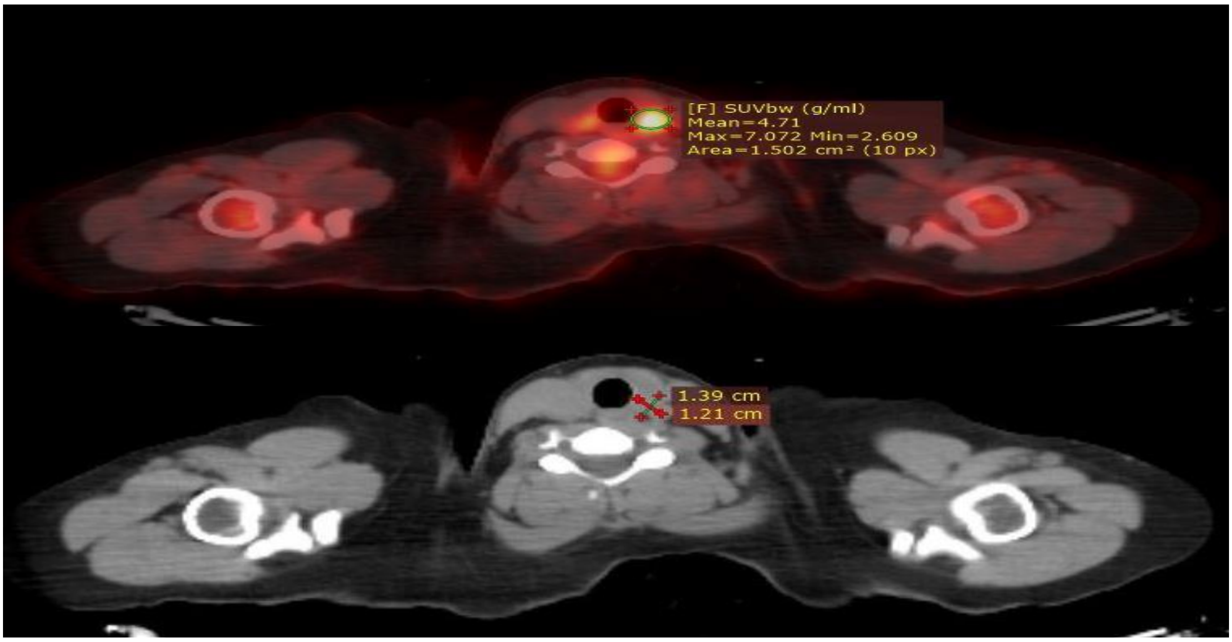

Figure (2): Initial pre-ablative PET/CT fused axial images and CT revealed FDG avid left thyroid operative bed nodule while the iodine scan did not show this nodule suggesting its malignant nature with dedifferentiation, then the patient underwent surgical consultation but refused and received RAI-131.

DISCUSSION:

Malignant thyroid tumors have a comparatively good prognosis; despite these some patients may suffer from persistent, metastatic and/or recurrent disease, which need a precise diagnostic evaluation to determine further treatment options which eventually improve outcomes and survival [5, 6].

According to the current guidelines, the application of PET/CT is not a standard diagnostic imaging in initial evaluation of DTC patients and it should only be considered for patients having suspicion of recurrence evident by rising thyroglobulin levels and negative whole-body scintigraphy [7]. However, several studies advocated the use of PET/CT in high-risk thyroid cancer patients for initial staging, prognostic evaluation, and assessment of treatment response [8].

Still little is known about the possible contribution of FDG PET/CT in the detection of persistent/recurrent disease or metastases before radioactive iodine (RAI) ablation. However, there's no actual evaluation of its clinical benefit nor its role in the new ongoing risk stratification of DTC recently published in different guidelines [9].

The aim of our work was to investigate the role of initial 18F-FDG PET/CT whether only or as compared to post radio iodine ablation WBS and hence influencing further therapy changes.

Our results established that 18F-FDG PET/CT scan performed early in the surveillance of certain DTC patients provided important additional information in 38/124 of patients (30.6%) with abnormal uptake in 18F-FDG PET/CT, which led to a change in treatment strategy.

^{18}F-FDG PET/CT is more avid in aggressive variants with less RAI avidity. Concerning hurthle cell tumors, 80% of patients have no iodine-avid tumor and therefore, ^{18}F-FDG PET/CT is a valuable tool providing additional findings not presented by I-131 WBS or other conventional imaging modalities [10]. Regarding the other aggressive subtypes, few studies consider ^{18}F-FDG PET/CT as a useful guide in the management of insular, sclerosing diffuse and tall cell variants [11, 12].

In our study, the results are more consistent with the findings in the literature as 7 patients (63.6%) of hurthle cell type patients had positive PET/CT findings as compared to 4 patients (36.4%) in the negative group with significant difference (**P<0.004**).

Our results were consistent with the retrospective study reported by **Nascimento et al,** they studied 38 patients, and eventually recommended routine ^{18}F-FDG PET/CT concomitantly with post therapy I-131 WBS in all patients with aggressive histological DTC **(13)**.

However, in the current study, each of the tumor size, multi-focality, invasion status and LN involvement showed no statistical difference between the 2 groups (PET/CT positive and PET/CT negative).

The present study established that 18F-FDG PET/CT scan performed early in the surveillance of patients with high/intermediate-risk thyroid carcinoma provides important additional information that is not accessible with conventional methods, as 25 out of the 38 positive patients (65.7 %) were of the intermediate/high risk group with subsequent change in the initial TNM staging in 12 patients.

A multicenter study conducted by **Lee et al (2013).,** retrospectively analyzed 286 patients with high/intermediate-risk thyroid carcinoma, they found that 18F-FDG PET/CT detected additional lesions in 39/286 patients (14 %) compared to the post-therapy 131-I scan and changed the therapy in 30 patients (10 %) **(14)**.

In the present work, among the 38 patients with 18F-FDG PET(/CT)- positive lesions, Loco-regional residual disease (residual tumor tissue and/or regional cervical LNs) is the most common.

This agrees with the results of ***Li et al*.,** who concluded that PET/CT is useful in localizing LN metastases that do not accumulate iodine in patients with elevated TG levels **(4)**.

Additionally, if there was evidence of distant metastases to the lungs or bones the patient should be upstaged to M1 and the therapeutic dose of RAI may increase between 150-200 mCi, and we expected that PET/CT could detect/confirm more lesions than the conventional imaging with a less critical change in the management eventually.

In this present work, PET/CT was positive in 14 patients with 3 of them was not detected by diagnostic CT. Whereas, 7 patients have been reported to have lung lesions in diagnostic CT were not avid in PET/CT with 6 patients of them had stationary tiny lesions in follow up CT and considered false positive.

Makeieff et al., stated that the relationship between cell differentiation of DTC patients and 131-I as well as 18F-FDG uptake has been explained according to the so-called flip-flop phenomenon; DTC cells with remaining functional differentiation for iodine uptake are known to exhibit low 18F-FDG uptake, whereas de-differentiated thyroid carcinoma cells with aggressive features show high 18F-FDG uptake with a loss of avidity for iodine uptake [15].

Also, ***Bertagna et al*.,** suggested that iodine and 18F-FDG metabolism in DTC could be, at least partly, unrelated [16].

In our study, beside the disability of detecting residual tumor tissue at the operative bed, only 5 of 23 sites (21.7%) of lymph node metastasis (including cervical and mediastinal LNs) that showed positive FDG-PET uptake were also positive on post therapy I-131 WBS. Only 3/14 had metastatic lung deposits by PET/CT showed simultaneous iodine uptake. This disagreement between PET results and radioiodine imaging is commonly observed. Lesions that are PET-positive and Iodine negative are believed to be metastases of high-grade. Poorly differentiated thyroid cancers may lose some of their differentiated functions, such as the uptake of iodine, and therefore are likely to be missed on post-therapy I-131 WBS. Therefore, for these metastases, additional I-131 treatment may not be valid.

***Mazzaferri et al*.,** showed that initial ablation decreased long-term recurrence and mortality rates, although some patients had recurrence after ablation. The results of this study suggest that these recurrent cases may include poorly differentiated thyroid cancer cells, which cannot have radioiodine uptake. FDG-PET concurrent with ablation can detect these patients in advance and may affect the choice and intensity of management options [5].

In our study, 18-FDG PET/CT results led to a change in management in 38 patients with re-surgery in 15 patients, increase the radioiodine doses in 11 patients, RTH referral in 3 patients, and trial for tyrosine kinase-inhibiting drugs in three patients**.**

In Agreement to our results, ***Salvatori et al*).,** emphasized the fact that the management changes could include the avoidance of surgical procedures or biopsies, further workup with imaging studies or initiation of unnecessary treatment such as external beam therapy or TKI therapy in the cases of advanced disease. In the same study, it was mentioned that positive 18F-FDG PET/CT findings changed the patient management in 20-40% of cases [17].

CONCLUSIONS:

18F-FDG PET/CT performed prior to 131-I ablation can detect residual viable tumor tissue at the thyroidectomy bed, iodine-negative local or distant metastatic foci in DTC patients, resulting in a change in further management of such patients. FDG avidity can help in identifying the loco-regional residual neoplastic disease especially in patient with inadequate surgery or suspicious operative bed and/or regional cervical LNs and need higher radioiodine therapy dose, also in high risk patients and in aggressive variants such as Hurthle type it may change the management.

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