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Role of PET/CT in Differentiated Thyroid Carcinoma.

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INTRODUCTION:

Thyroid cancer is the most common endocrine malignancy worldwide being more common in women, with a 3:1 female-to-male ratio in and it is the fifth most common cancer in women [(1)].

Although malignant thyroid tumors have a comparatively good prognosis. Some patients suffer from persistent, metastatic and/or recurrent disease, which makes a precise diagnostic evaluation necessary to determine further treatment options.

As morphological imaging using neck U/S or CT often gives inconclusive information, especially post-operatively, the application of functional imaging may be useful.

F-18 FDG (PET/CT) is a functional imaging method used a prognostic tool used in the staging of various malignancies and the identification of metastatic lesions 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.

It especially remains unclear whether the application of initial post-operative PET/CT in patients with thyroid cancer affects the staging, therapeutic strategies and will have an impact on patient-relevant outcome [(2)].

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Theranostics in Differentiated Thyroid Cancer: The term Theranostics is the combination of a diagnostic tool that helps to define the right therapeutic tool for specific disease. It's based on the concept of knowing which sites require treatment (diagnostic scan) and confirming that those sites have been treated (post therapy scan)" demonstrating the achievable tumor dose concept. Theranostics is easy to apply and understand owing to the easy switch from diagnosis to therapy with the same vector. It helps in maximizing tumor dose & sparing normal tissue with high specific and rapid uptake in metastasis [(3)].

The oldest and the first treatment based on the Theranostics concept were performed on thyroid cancer patients with RAI in 1946. From then on management of differentiated thyroid cancer (DTC) has evolved on the multimodality concept. However, the initial surgical management followed by RAI as per the Theranostics has remained the mainstay in achieving a cure in most of DTC patients with levothyroxine (LT4)-induced suppression of thyroid-stimulating hormone (TSH). Treatment outcomes for DTC are generally excellent, with 98% disease specific survival at 10 years and variable rates of recurrence depending on disease characteristics. Patients with progressive or metastatic disease may benefit from additional surgery, RAI, local therapies (e.g., radiation or systemic therapies [(4)].

FDG PET/CT in Cancer Thyroid:

FDG PET-CT is currently being used in the diagnosis and management of DTC mainly to detect sites of disease which may not be RAI avid or as a result of tumor heterogeneity, which is more common in high risk patients and where FDG avid and non-avid disease may co-exist. The localization of FDG in DTC depends on a number of factors. It is known that GLUT receptors are abundantly expressed on thyroid cells particularly in aggressive variety of thyroid cancer cells.

In high risk disease FDG PET can identify clinically relevant sites of disease, assess the progress or response to treatment, identify the need for additional local intervention, surgical excision or RFA and response to targeted therapies.

FDG PET may be used during initial staging in patients with high TG at diagnosis associated with aggressive histological subtypes; such cases do not show RAI avidity and may not benefit from the Theranostics approach of treatment [(5)].

The most common indication of FDG PET-CT in DTC has been in patients with elevated TG levels and a negative RAI scan or the RAI scan is not corroborating with the expected disease burden in the patient. The disease in the latter group of patients undergoes gradual de-differentiation with activation of cellular glucose metabolism. This has been termed as a ‘flip flop 'phenomenon. Over the time we have realized that this phenomenon is not absolute and both RAI avid and RAI-refractory (FDG avid) can co-exist in the same patient. FDG has good sensitivity of detection in this setting and it varies between 70-90 % [(5)].

Clinical Applications of 18FDG-PET/CT in Cancer Thyroid patients:

A) Pre-operative 18F-FDG PET\CT in DTC:

In the 2015 American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer, 18F FDG PET/CT is not recommended for the preoperative evaluation of patients with "newly detected" thyroid nodules. However, the use of 18F-FDG PET/ CT to rule out malignancy in thyroid nodules with suspicious ultrasound features is supported by low-quality evidence, and further studies are warranted.

B) Prediction of biological behavior of primary DTC:

In thyroid nodules it is difficult to predict the aggressiveness of thyroid cancer pre-surgically.

The principal risk factors related to the biological activity of the tumor are revealed by neck ultrasonography.

Indeed, the size and position of the nodule, together with the presence of lymph-node enlargement, may identify which patients are likely to develop disease persistence/ recurrence after initial treatment.

Several studies showed that an intense 18F-FDG uptake by the primary DTC may help to identify a subgroup of patients with a high risk of disease progression. Nevertheless, when all other prognostic factors are taken into account, 18F-FDG uptake itself does not add further prognostic information [(6)].

C) Surveillance for DTC recurrence:

Recurrence of differentiated (epithelial) thyroid cancer is common, occurring in 3% to 13% of low-risk, 21% to 36% of intermediate-risk, and 68% of high-risk patients based on the American Thyroid Association's (ATA) risk classification. In almost all cases, these thyroid cancer recurrences arise from residual disease that escaped detection and treatment by primary surgical treatment with or without postoperative radioiodine. Consequently, anatomic and functional imaging techniques for surveillance are essential in patients whose thyroid cancer has recurred.

The thyroglobulin, as a tumor marker, frequently identifies clinically irrelevant residual normal thyroid or tumor tissue. In almost two-thirds of patients with no detectable serum thyroglobulin after surgery, there will be no structural disease localized, no treatment required and a generally excellent prognosis [(7)].

Currently, however, most loco-regional recurrences are detected by regular follow-up neck ultra-sonography in conjugation with the measurement of serum TG levels. Neck ultrasonography and CT, were effective for localizing recurrent lesions; However, predicting patients with recurrent disease using 18F-FDG PET/CT could help predict the de-differentiation of thyroid cancer via elevated SUV max therefore it should be considered for the prognostication rather than for the diagnosis of patients with recurrent disease [(8)].

D) Evaluation of Loco-regional LNs Metastases:

Loco-regional lymph node (LN) metastasis is typically one of the first steps in the progression of PTC to distant metastasis from the thyroid.

Ultrasonography limitations for the diagnosis of central compartment lymph nodal metastases is due to certain LNs are located in deep regions around trachea and surrounding structures with false positive results of inflammatory lymphadenopathy [(9)].

PET/CT has been applied for the evaluation and monitoring of PTC and nodal metastasis, particularly for patients with elevated serum TG levels but negative iodine-131 whole-body scan (WBS).

Pathology is the standard for diagnosing LN metastasis of thyroid carcinoma However; certain LNs are located deep in the neck, which presents difficulties for biopsy [(8)].

E) Prognostic role in DTC:

FDG uptake in metastatic DTC is usually seen in de-differentiated, aggressive variety with poor prognosis and reduced survival. In such cases and high risk DTC, total volume of FDG positive disease is the strongest prognostic indicator of survival. Low or no FDG uptake in RAI negative disease has better prognosis and in fact thyroxin suppression is adequate in the absence of any active management.

Nagamachi et al., showed that among several potentially prognostic factors, only a positive PET/CT and age older than 45 years have a significant negative impact on overall survival in patients with differentiated thyroid carcinoma in restaging.

Thus, 18-FDG PET/CT has been described as a promising technique in identifying DTC patients at higher risk of developing distant metastases or patients with distant metastases at higher risk of disease progression [(10)].

F) PET/CT in assessing the clinical utility of pre-ablative in cancer thyroid:

Thyroid cancer in a clinical setting of staging, restaging, or diagnosing tumor recurrence was studies. Out of 3,506 potentially relevant articles, 29 studies were included. Positive result of PET/CT in restaging patients with differentiated thyroid cancer yielded a significant decrease in overall survival. In patients with suspected recurrence of differentiated thyroid cancer, higher sensitivity of PET/CT (94.3%) compared with conventional imaging (65.4%), However there was comparable specificity for diagnosis of recurrence [(11)].

In 2012 ***Iwano et al*** evaluated 54 patients with histologically proven DTC underwent both FDG-PET and subsequent I-131 ablation to assess. FDG-PET ability to detect lymph node metastasis and for its role in the management of DTC patients. The study showed that FDG-PET imaging concurrent with I-131 ablation was positive in 18 patients (33%) and negative in 36 patients (67%). Five of 9 patients with an FDG accumulation in the thyroid bed showed local residual tumors in their surgical findings. It concluded that FDG-PET concurrent with I-131 ablation after total thyroidectomy could detect unexpected abnormal FDG accumulations in 33% of patients and therefore may influence the choice of management options [(12)].

Kim et al, studied 197 patients with PTC underwent FDG-PET it's assess its role in a preoperative diagnostic tool in papillary thyroid carcinoma (PTC). Among the 197 patients, 155/246 of PTC foci (63%) showed FDG uptake in neck node metastasis with high specificity and negative predictive value (NPV).

In four cases of nonspecific findings on ultrasonography, CT, FDG avidity was helpful to diagnose the presence of lymph nodes metastasis.

The maximum standardized uptake value (SUV max) of PET/CT was correlated with the maximum diameter of the involved nodes. FDG avidity did not show any significance in the recurrence-free survival of both the thyroid tumor and lymph nodes metastasis. However, FDG avidity showed high sensitivity and NPV, and could provide better information in cases of nonspecific findings on US and CT [(13)].

Nascimento et al. in a study of 38 consecutive patients with aggressive histology DTC, without known persistent disease at the time of postoperative radioactive iodine (RAI) ablation showed that FDG-PET/CT and the post-ablation whole body scan (RAI WBS) showed persistent disease in 15 and 12 patients, respectively. FDG-PET/CT was more sensitive than the WBS for the detection of individual lesions (69% vs. 59%).

Both imaging techniques where complementary with 41% of the lesions detected only by FDG-PET/CT and 31% only by RAI WBS.

The only risk factor of abnormal FDG-PET/CT was a stimulated TG level (TG/TSH) measured at ablation >10 ng/mL with persistent disease showing FDG uptake in 72% of the patients with a TG >10 ng/mL and in 10% of the patients with TG less than 10 ng/mL [(14)].

Ruhlmann et al. evaluated the prognostic impact of the initial FDG-PET/CT in 109 DTC patients who underwent radioiodine treatment (RIT) with FDG-PET/CT and a follow-up over three years. 24/109 patients (22%) presented FDG-positive lesions, 22/109 patients (20%) only iodine-positive lesions, and 63/109 patients (58%) neither FDG-positive nor iodine positive lesions. After three years, 83/109 patients (76%) revealed full remission, 15/109 patients (14%) tumor persistence and 11/109 patients (10%) a progressive disease. The negative predictive value was calculated for patients without FDG-positive lesions (85%) and patients without any lesions (91%) regarding full remission in the follow-up. So, FDG-PET/ CT should be performed in all high-risk DTC patients to improve patient management and risk stratification [(15)].

Manohar et al. Stated that [18F]-FDG PET/CT may predict progression versus stability of disease based on quantitative analysis of metabolic tumor volume (MTV)and total lesion glycolysis (TLG) by studying 62 patients with metastatic DTC to determine clinical outcomes with median follow-up from initial diagnosis of 11.1 years (8.38, 14.1). The results showed, the 5-year overall survival (OS) probability was 34%, and median OS was 3.56 years. Median values of MTV and TLG were associated with worse OS (P = 0.06) and PFS (P = 0.007).

They conclude that metabolic tumor volume and TLG may be used for dynamic risk stratification of patients with metastatic RAI-R DTC regarding PFS and complement TG-DT for prognosis of clinical disease course [(6)].

Also, Li et al. aiming to predict the prognostic value of FDG PET/CT in the metastatic lymph nodes (mLNs) of patients with papillary thyroid carcinoma (PTC) with a negative iodine-131 whole-body scan (WBS).

The study included 32 patients with PTC undergoing standard surgery and radioiodine treatment. 18F-FDG PET/CT imaging was done prior to and following therapy. All the patients were followed up for ≥ 9 months.

High uptake of 18F-FDG in cervical metastatic nodes was predictor for the clinical outcome of patients with PTC treated with radioiodine therapy, whereas high SUL peak and extra thyroidal extension were poor predictors for patients with mLNs receiving 131I therapy [(16)].

Kang et al. studied 54 metastatic DTC patients who underwent both RAI therapy scan and FDG PET/CT at the same period where therapeutic response of RAI was assessed as two categories: response rate (RR) and disease control rate (DCR). 22/54 patients (41%) had therapeutic response to RAI therapy, whereas 32/54 patients (59%) did not with no significant differences in age, sex, stage, histology, metastasis site, stimulated TG or TG-Ab, therapeutic doses, and even RAI uptake pattern among two groups. There was a significant negative correlation between FDG avidity of metastatic lesions and RR (OR = 0.233; p = 0.016). Whereas patient group with only RAI uptake showed a significant correlation with RR (OR = 5.833; p = 0.01), the patient group with both RAI and FDG uptake did not show any significant correlation with RR [(17)].

CONCLUSIONS:

FDG PET/CT as molecular imaging in differentiated thyroid cancer may detect unexpected abnormal FDG accumulations in thyroid bed or regional lymph nodes which may influence the choice of treatment options. Function metabolic parameters are predictor for the clinical outcome of patients with DTC treated with radioiodine therapy.

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