Role of PET/CT Imaging Thyroid Cancers

Maseeh Uz Zaman and Nosheen Fatima

Department of Radiology, The Aga Khan University Hospital, Karachi, Pakistan

Thyroid malignancy is an often encountered malignancy. According to GLOBOCAN (an online database providing global cancer statistics), in 2020 an estimated 586,000 cases of thyroid cancer (TC) were reported worldwide and ranked as the 10th most common cancer. The incidence of TC in females is three times more common than in males (449,000 *vs*. 137,000).[1] The reported frequency in Pakistan is National Cancer Registry data.[2]

Thyroid malignancies are categorised based on the type of cells from which these cancers grow.

Papillary thyroid cancer (PTC) is the most common well-differentiated thyroid cancer (WDTC) and constitutes up to 80% of thyroid cancers. It is slow-growing, often spreads to cervical lymph nodes but responds very well to treatment with an excellent life expectancy.[3] However, the World Health Organisation (WHO) classification[4] has outlined ten more papillary cancer sub-types (such as tall cell, columnar cell, and hobnail, *etc*.) with variable risk stratifications and more unfavourable outcomes.[3] The reported 10-year overall survival (OS) rate for PTC is 97%.[5] Follicular thyroid cancer (FTC) is another WDTC which constitutes about 15% of the total and unlike PTC more likely to spread to bones and lungs (haematogenous route). The reported 10-year OS rate for FTC is 89%.[5] Medullary thyroid cancer (MTC) constitutes about 2% of all thyroid cancers, originating from parafollicular cells which secrete calcitonin. About 75% of MTCs are sporadic (no specific cause) but 25% of are inherited or familial (multiple endocrine neoplasia type 2; MEN-2).[6] Anaplastic thyroid cancer (ATC) constitutes about 2% of all thyroid cancers and is thought to originate from follicular or uncommitted epithelial cells. It predominantly involves older patients and is the most aggressive tumour with a high propensity to infiltrate into surrounding structures, distant metastasis and dismal prognosis.[7]

Ultrasound-guided fine needle aspiration (FNA) is the first modality of choice for diagnostic evaluation of palpable neck mass or thyroid nodule.

Correspondence to: Dr. Maseeh Uz Zaman, Department of Radiology, The Aga Khan University Hospital, Karachi, Pakistan
E-mail: maseeh.uzzaman@aku.edu

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Cross-sectional imaging such as contrast-enhanced computerised tomography (CT) and magnetic resonance imaging (MRI) due to their high special resolution are used for better staging in MTC, ATC, and high-risk PTC, and FTC. However, hybrid imaging modalities as PET/CT with various positron emitting substrates are often utilised as a troubleshooting diagnostic tool, particularly in metastatic disease with unknown primary and extension of disease in poorly-differentiated subtypes.[8]

In this editorial, we will describe various PET/CT imaging procedures used in the diagnosis, staging, and follow-up of the above-mentioned varieties of thyroid cancers.

Normal thyroid tissue usually shows little or no FGD uptake as it uses free fatty acid (FFA) as substrate. However, incidental FDG uptake over the thyroid seen in patients having FDG PET/CT for non-thyroidal indications is not uncommon. Diffuse FDG uptake over the thyroid is reported in 0.6-3.3% cases and is considered benign due to thyroiditis or toxic goitre.[9] Focal FDG uptake in one or both thyroid lobes has a reported incidence of 1-2% in FDG PET/CTs done for non-thyroidal cancers and must be considered for FNA as 27-50% of these incidental nodules have predominantly papillary cancer.[8] Similarly, well-differentiated thyroid cancers (PTC and FTC) are iodine avid and do not use glucose as substrate. Due to this well-established fact, radioiodine-131 (I-131; gamma and beta particle emitter) has been in use for treating thyroid cancer since 1942 when it was first used by Samuel Seidlin.[10] However, after repeated treatment with I-131, especially in older patients, PTC and FTC cells lose their iodine avidity and start taking up glucose. This shift of thyroid cancer cells from iodine avidity to glucose avidity is called the flip-flop phenomenon.[11] As a result, thyroid cancer foci which were previously visible on whole-body iodine scan (WBIS) are not appreciable on follow-up WBIS despite high serum thyroglobulin (thyroid tumour marker) due to loss of iodine avidity. The American Thyroid Association (ATA) in its 2015 guidelines recommends (Recommendation # 68) to use of FDG PET/CT in patients with WDTC having negative WBIS but serum thyroglobulin level >10 ng/ml (Thyroglobulin-elevated negative iodine scan; TENIS).[11] The presence of FDG avid thyroid foci on PET/CT indicates poor prognosis and helps the surgeons to decide about surgical decisions.[12]

Iodine-124 (I-124) PET/CT in WDTC is a positron emitter having a half-life of 4.2 days. I-124 PET/CT has significantly higher diagnostic accuracy in the detection of iodine avid disease and is used as a modality of choice for personalised dosimetry calculation of I-131 in patients with iodine avid localised or metastatic thyroid cancers.[13] However, the availability of I-124 is the major limitation.

PET/CT imaging in ATC are highly aggressive tumours with poor prognosis and always considered stage IV at diagnosis (IV-A: Localised to thyroid ± regional nodes; IV-B: Extrathyroidal extension but no distant metastasis; IV-C: With distant metastasis).[7]

FDG PET/CT is the most effective modality in initial staging, treatment decision, and response assessment after radiation, chemo or targeted therapy in patients with ATC.[14]

Sporadic MTCs are usually unilateral, but familial MTCs, are usually multicentric and bilateral. Five-year survival of stage I-III is 93%, however, 28% for stage IV disease.[6] Ultrasound, CT, and MRI are the primary modalities used in diagnosis, staging, and response assessment. However, PET/CT using various substrates are proved to be useful in detecting recurrence and metastases. FDG PET/CT is the most easily available sensitive technique, but it is not specific indeed. Gallium-68 labelled somatostatin receptor analogue (SSRA) such as Ga-68 DOTATE PET/CT has better diagnostic accuracy than FDG due to the expression of somatostatin receptors over MTC. However, fluorine-18 dihydroxyphenylalanine (FDOPA) is the most specific modality for the detection of recurrent MTC, *albeit* availability is limited.[15]

PET/CT is an established hybrid modality in the management of advanced or recurrent de-differentiated or poorly-differentiated, medullary and, ATCs. In FDG, PET/CT performed for non-thyroidal cancer, diffuse radiolabelled glucose uptake is considered benign but focal hypermetabolic uptake warrants US-guided FNA to rule out PC. FDG PET/CT is recommended for WDTC patients with TENIS (Thyroglobulin Elevated Negative Iodine Scan) to localise dedifferentiated malignant thyroid foci which have lost iodine avidity (flip-flop phenomenon). I-124 PET/CT has a significantly higher spatial resolution, diagnostic accuracy, and precise modality for personalised I-131 dosimetry in patients with WDTC. In ATC, FDG PET/CT is the modality of choice for diagnosis, staging, surgical decision making, and response assessment. In MTC, FDOPA PET/CT has better diagnostic accuracy than Ga-68 DOTATATE and FDG PET/CT although its availability is an important limitation. It is pertinent to mention that for precise post-treatment response evaluation using serial PET/CT, adopting a standardised imaging and reporting protocol is crucial.

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