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EDITORIAL

# Role of $^{18}$FDG PET/CT in Breast Cancer

Nosheen Fatima and Maseeh uz Zaman

Breast cancer (BC) is the most common female cancer worldwide. Despite a well-documented decline in mortality from BC over the past two decades, the incidence rate continues to rise more rapidly. Asia has a greater disease burden as compared with South America and Africa.[1] Unfortunately, Pakistan has the highest incidence of BC and associated mortalities in Asia.[2] Situation gets more perplexed due to diverse behaviours of BC in Pakistan like onset at younger age, and higher odds in multiparous and well-lactating mothers, which contribute to documented high disease burden.[2] Despite continuous efforts by governmental and non-governmental organisations for enhancing awareness among females, diagnosis at an earlier stage has been disappointing.[3] Fifty-eight percent of Pakistani women do have stage III disease at the time of presentation.[4] Like other malignancies, early diagnosis and precise staging of BC can help in minimising disease-related mortality.

Diagnostic strategy includes breast self-examination, periodical mammogram, ultrasound or breast MRI in problematic cases, guided biopsy in cases if a lump is identified, contrast enhanced CT and bone scan for staging beyond T3N1 disease. Although 18-Flourodeoxyglucose ($^{18}$FDG) positron emission tomogram with CT (PET/CT) is a proven powerful imaging tool with established role in various malignancies, its role in BC is still evolving. This editorial will highlight the utility and limitations of $^{18}$FDG PET/CT in BC.

Uptake of $^{18}$FDG on PET/CT indicates utilisation of glucose by the tumor cells as energy source. However, the magnitude of $^{18}$FDG uptake depends upon certain biological factors, which need to be known before addressing the indications. Like all cancers, over-expression of glucose transporter GULT receptors, hexokinase enzymes and increased mitotic index are the primary determinants of labelled glucose uptake. In addition, other biological factors having direct association with glucose metabolism include histological grading, proliferative index (ki67), p53 mutation, tumor cell burden, micro-vascularity, necrotic volume. Simliarly, estrogen/progesterone/human epidermal growth receptors (ER/PR/HER-2, respectively) status also determines the radiotracer uptake (higher FDG uptake in triple negative BC).[5]

Standardised uptake value (SUV) is the semi-quantitative measure indicating the intensity of uptake and metabolism of $^{18}$FDG by tumor cells. In BC, the SUV has an established role in therapy response evaluation and prognostication. SUV has the direct correlation with complete pathological response (pCR) after neo-adjuvant chemotherapy (NAC) in BC and indirect correlation with progression-free survival (PFS) and overall survival (OS).

At present, various guidelines regarding management of BC have been published by professional societies, but no unanimity is found about the role of $^{18}$FDG PET/CT. National Comprehensive Cancer Network (NCCN) in its narrative summary, published in February 2016, discourages the use of $^{18}$FDG in staging of patients with primary operable and metastatic (stage IV) BC.[6] However, it favours the use of $^{18}$FDG in staging of locally advanced BC (LABC) and inflammatory BC (IBC). American Society of Clinical Oncology (ASCO) recommends $^{18}$FDG PET/CT for staging in patients with high clinical suspicion of metastasis and recurrence. Recently published appropriate use criteria (AUC) by Society of Nuclear Medicine and Molecular Imaging (SNMMI),[6] favour the role of $^{18}$FDG PET/CT in restaging and predicting response to therapy in BC. It is imperative for reporting physicians and referring oncologists to be cognizant of the justified indications of $^{18}$FDG PET/CT and also its limitations in different clinical scenarios. This strategy would ensure the optimal utilisation of this sensitive tool for patients with BC.

So far there is no consensus about utility of $^{18}$FDG PET/CT in the diagnosis of BC due to the finite resolution of PET scanners resulting in inability to identify a tumor less than 2 cm (<pT1) and higher false negative rate in lobular carcinoma (about 65%) due to low $^{18}$FDG avidity. Since early stage, BC (stage I and II) has a very low likelihood of distant metastasis; adding $^{18}$FDG PET/CT to the diagnostic paradigm, could be misleading due to false positive findings resulting in incorrectly upstaging or unjustified further investigations.[7] However, in challenging clinical scenarios like breast with prosthesis or dense breast, $^{18}$FDG-based positron emission mammography (PEM) is considered to have better sensitivity, specificity, and diagnostic accuracy due to higher resolution than existing PET/CT scanner.[8]

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$^{18}$FDG PET/CT can detect a malignant breast lesion in patients undergoing $^{18}$FDG PET/CT for other reasons or vice versa.[9]

Precise staging is the mainstay for selecting correct therapeutic strategy and ultimate prognosis in BC. In TNM (tumor, node, metastasis) staging, $^{18}$FDG PET/CT is complementary to conventional imaging (CI) in T staging due to its limited resolution, but superior to CI for detecting extra-axillary nodal and distant metastasis. American Joint Committee on Cancer (AJCC) and NCCN guidelines recommend use of $^{18}$FDG PET/CT in staging for IBC and LABC (Stage IIIA excluding T3N1b, IIIB and IIIC), and do not favour its use in staging of BC earlier than stage III or known stage IV disease.[10] Interestingly, there is reported evidence of about 30% additional extra-axillary node and distant metastasis detected by $^{18}$FDG PET/CT as compared with CI.[11] Ongoing studies are expected to change the existing recommendations in near future.

Due to the limited sensitivity (around 37%) of $^{18}$FDG PET/CT for axillary lymph node (ALN) metastasis, the sentinel lymph node (SLN) mapping is still considered standard of care for ALN staging.[12] However, a positive 18FDG PET/CT for ALN uptake, obviates the need of SLN mapping due to its higher positive predictive value and specificity, which is about 96%.[12] Similarly, $^{18}$FDG PET/CT compared with CI has better detection efficiency for internal mammary, supraclavicular and mediastinal groups of lymph nodes and has a definite impact on therapy decision. $^{18}$FDG PET/CT has higher sensitivity for marrow, osteolytic and mixed bony metastases, but has limited role for pure sclerotic bone and hyper-metabolic brain metastasis.[13] Subcentimeter pulmonary nodules pose diagnostic challenge to $^{18}$FDG PET/CT due to breathing artifacts and partial volume effect.[13]

Most of the guidelines strongly favour the use of $^{18}$FDG PET/CT in restaging the BC patients with high clinical suspicion of recurrence.[6,10] $^{18}$FDG PET/CT has been reported for modification in therapy decision in 48-57% patients with recurrent BC by viable tumor from post-therapy fibrosis and detecting the loco-regional and distant recurrence with high diagnostic accuracy.[13]

There is a general consensus that earlier and mid therapy $^{18}$FDG PET/CT is more efficient than end of therapy (EoT) in predicting the NAC response in BC patients. However, normalisation of $^{18}$FDG uptake and SUV in follow-up $^{18}$FDG PET/CT does not have a proven sensitivity for pCR, as it cannot rule out microscopic disease.[14] But residual $^{18}$FDG uptake or measureable SUV is a good predictor of treatment failure. To include $^{18}$FDG PET/CT in the management paradigm would enable oncologists to identify non-responder for timely therapy modification, and would save cost and unwanted exposure to cytotoxic agents.[15]

Currently, evidence is not sufficient to support the role of $^{18}$FDG PET/CT in predicting response to hormonal therapy. Transient increase in $^{18}$FDG uptake within 2 weeks after starting tamoxifen (metabolic flare) is consideres as a predictor of response; PET response correlated with PFS but not OS in ER positive and HER-2 negative BC patients. A 20% fall in SUVmax from baseline is considered as a strong predictor of pCR and cCR.[15] However, larger prospective multicentric trials can explore the validity of such important findings.

There is a growing evidence that the magnitude of SUV has direct correlation with poor outcome in BC.[13] So far, no validated cut-off value of SUV has been agreed upon for predicting response, and evidence from several on-going clinical trials is awaited.

Use of $^{18}$FDG PET/CT is strongly discouraged by major guidelines for surveillance of asymptomatic BC patients who have already achieved complete response (pCR and cCR) to therapy. The primary reason is the non-specificity of $^{18}$FDG uptake; and possible false positive results could result in unjustified and futile investigations.

Role of $^{18}$FDG PET/CT in diagnostic and management paradigm of BC has been evolving. Currently, it is not recommended for diagnosis, staging of operable (stage I, II, and T3N1b) and stage IV disease, and axillary nodal involvement or surveillance in asymptomatic patients. It is recommended in staging of IBC, LABC (IIIA-C excluding T3N1bM0), and in restaging of recurrent BC. $^{18}$FDG PET/CT is also considered an emerging tool in prognostic stratification and assessing early response to therapy. Although most of the BC patients in Pakistan present as LABC, yet $^{18}$FDG PET/CT is significantly underutilised due to limited PET/CT facilities, high cost, and lack of multidisciplinary approach in the existing clinical environment.

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