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Molecular Imaging of Breast Cancer

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Abstract: Breast cancer is one of the most common types of malignancy, with an increasing incidence worldwide. Breast cancers are subtyped based on their histopathological features and hormonal receptor expression status. Conventional radiological modalities such as mammography, ultrasonography, computed tomography, and magnetic resonance imaging play a major role in the diagnosis and initial staging of breast cancer. Positron emission tomography with F-18-fluorodeoxyglucose (FDG) has an established role in the staging of locally advanced breast cancers, along with its use in response assessment after systemic therapy. Non-FDG radiopharmaceuticals also have a potential role in breast cancer imaging. These include agents that target hormonal and tyrosine kinase receptors, tumor microenvironment, and fibroblast activation protein inhibitors. Gamma camera-based modalities such as breast-specific gamma imaging, sentinel lymph node imaging, and skeletal scintigraphy also play a significant role in the management of subsets of patients with breast malignancy.

Keywords: 18F-FDG; breast cancer; nuclear medicine imaging; PET-CT; staging

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INTRODUCTION

Female breast cancer is the most common type of malignancy detected worldwide, according to the recent GLOBOCAN 2020 estimates (1). Increasing incidence rates can be attributed to increased use of screening modalities (2). The risk of occurrence of breast cancer in females is 100-fold as compared to males, with an increasing incidence from the third to fourth decade of life onwards. Hereditary mutations (*BRCA 1/ 2*, *TP53*, *PTEN* gene, etc.), childhood exposure to chest wall radiation, lobular carcinoma in situ (LCIS), or the presence of benign breast lesions such as atypical ductal hyperplasia are associated with a higher risk of developing breast malignancy. First-degree relative with breast cancer, dense breast on mammogram, and age >35 years at first pregnancy are associated with moderate risk. In addition, increased estrogen levels as in early menarche, late menopause, nulliparity, estrogen-containing hormone replacement therapy, and obesity are associated with a mild risk (3).

HISTOPATHOLOGICAL SUBTYPES

The most common pathological type of breast cancer is carcinoma (which constitutes over 99% of all diagnosed breast malignancies), followed by sarcomas and other tumors specific to the breast, such as malignant phyllodes tumor. Most of the carcinomas that arise in the breast are adenocarcinomas (constituting about ~97–98%), of which the most common subtype is invasive ductal adenocarcinoma (~72.5%), followed by mixed invasive ductal-lobular type (9.8%), and pure lobular carcinoma (9.7%). Some of the rarer variants are the mucinous and papillary subtypes (2). Tumors in which there is no invasion of the basement membrane are labeled as carcinoma *in situ*. Ductal Carcinoma *in situ* (DCIS) is more common compared to lobular carcinoma *in situ* (LCIS).

Based on the expression levels of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor type 2 (HER2), and Ki-67, the tumors are classified into the following molecular subtypes:

i. Luminal A: ER/PR positive and HER2 negative with low Ki-67 levels.
ii. Luminal B: ER/PR positive and HER2 variable with higher Ki-67 levels.
iii. HER2 enriched: ER and PR negative with HER2 positive.
iv. Triple negative: ER/PR/HER2 – all negative.

Luminal A tumors are considered to have the best prognosis with a lower incidence of metastases and a longer survival duration, while HER2 positive and triple negative tumors have a higher incidence of metastatic disease. Patients with triple negative subtype have the lowest survival prospects (4).

STAGING OF BREAST CARCINOMA

The staging of breast carcinoma is done based on the latest TNM staging system given by the American Joint Committee on Cancer (AJCC, 8th edition, 2017). The T-stage

depends on the size of the tumor and the involvement of surrounding structures such as skin and chest wall, while the N-stage is based on the level of nodal involvement that includes the axillary, subpectoral, supraclavicular, infraclavicular, and internal mammary stations. The M-stage is based on the presence or absence of distant nodal, visceral, or skeletal metastatic disease. The sites of distant metastases that are commonly involved include the bones, followed by the lungs, liver, and brain (5).

MANAGEMENT OPTIONS

The established modalities for the treatment of breast carcinoma include surgery, hormonal therapy, chemotherapy, and radiation therapy. The order of preference and modality to be used depends mainly on the stage of the disease, the sites of involvement, and the hormone receptor expression. Breast cancer can be broadly divided into operable and inoperable breast cancer. Operable breast cancer includes T1–3, N0–1, and M0 tumors, while inoperable breast cancer includes locally advanced breast cancer (LABC). LABC includes tumors with chest wall or skin extension and inflammatory breast carcinoma (T4 disease) or involvement of ipsilateral matted or fixed axillary lymph nodes or internal mammary/infraclavicular/supraclavicular lymph nodes (N2/3 disease), or patients with distant metastases (M1).

Preoperative systemic therapy is planned for all patients with inoperable breast cancer and operable disease with unfavorable features such as HER-2 positive or a triple negative disease or relatively large size of tumor compared to the breast which is precluding breast conservation surgery (BCS).

Surgical options for resectable disease include lumpectomy, partial, or total mastectomy with surgical axillary staging. If more than four positive lymph nodes are noted in axillary staging, postoperative radiotherapy (RT) is administered to all the axillary lymph nodal stations along with RT to the breast (in case of lumpectomy) or chest wall (in case of mastectomy). In case of lumpectomy, if less than four axillary nodes are positive, RT is limited mainly to the breast. However, if mastectomy is the initial surgical procedure and if less than four axillary nodes are positive, RT is not required. If surgical margins are positive after mastectomy, re-excision is the preferred option until negative margins are obtained. Adjuvant systemic therapy after surgery is based on tumor hormonal receptor status of the tumor, size of the tumor and nodal staging (6).

CONVENTIONAL IMAGING MODALITIES IN BREAST CARCINOMA

The conventional radiological modalities such as mammogram, CT, and MRI find various applications at different stages of management of breast carcinoma including the initial diagnosis, staging and also in the post-treatment setting with their respective advantages and disadvantages inherent to each modality.

Ductal carcinoma in situ

In cases of suspected DCIS, the imaging workup consists of a diagnostic bilateral mammogram to look for multifocal or multicentric lesions within the same breast or in the contralateral breast. MRI using a dedicated breast coil is also helpful in the diagnosis of DCIS, with studies showing higher rates of diagnosis with MRI over mammography (92% vs. 56%) (7). However, overestimation of the extent of the disease on MRI remains a concern.

Diagnosis of breast carcinoma

The main imaging modalities in the diagnostic workup of breast cancer include bilateral mammography for evaluation of multifocality, multicentricity, and contralateral breast involvement. MRI is used in dense breasts where mammography is less sensitive; therefore, it can help detect more lesions than seen on mammography. However, MRI has comparatively low specificity and a biopsy of suspicious MRI findings must be performed for confirmation.

Staging of operable breast cancer

In the case of operable breast cancer (T0–3, N0–1, M0), according to NCCN guidelines, metastatic workup is indicated only if there are specific symptoms. If symptoms pertaining to the respiratory tract such as cough are present, a diagnostic chest CT should be performed. CT or MRI of the abdomen should be planned if the patient has abdominal symptoms, elevated liver function tests (LFT) or alkaline phosphatase (ALP) levels. A rise in ALP levels and symptomatic bone pain should raise suspicion of bone metastases and a bone scan should be planned.

Staging of inoperable breast cancer

In the case of inoperable breast cancers, such as LABC and metastatic breast cancer, the imaging workup prior to starting systemic therapy includes chest and abdominal CT or an abdominal MRI along with a bone scan or sodium fluoride PET/CT to look for bone metastases.

Recurrence evaluation

In case of a recurrence, other than the biochemical workup for elevated ALP and LFT values for suspected bone and liver metastases, imaging modalities to be used include a diagnostic CT of chest with a CECT or MRI of the abdomen. If bone metastases are suspected, a bone scan or sodium fluoride PET/CT is indicated. In the case of suspected brain metastases, a contrast-enhanced brain MRI is indicated. For surveillance, diagnostic mammography is the most recommended investigation to image the local site and the contralateral breast.

18F-FDG PET/CT IN BREAST CARCINOMA

FDG is an analogue of glucose, which is labeled Flourine-18, a positron emitting radionuclide. It acts as a molecular imaging marker of increased glucose

metabolism, which in turn is a marker of increased cellular activity and proliferation seen in malignant tumors. FDG is concentrated not only in tumor cells but also in benign diseases such as infectious and inflammatory processes.

18F-FDG PET/CT has no role in the management of a patient with DCIS. In the setting of a suspected breast malignancy, 18F-FDG PET/CT is not generally recommended as a suitable modality for the primary diagnosis of breast cancer in view of the poor sensitivity in *in-situ* malignancies and small tumors (<1cm). However, it may be useful in certain scenarios including evaluation of cases with dense breasts, breast implants and in cases where MRI is contraindicated. Dual time point imaging after 60 and 100 minutes of FDG injection may help in differentiating benign from malignant breast lesions. The malignant lesions are seen to show progressive increase in FDG avidity on delayed imaging with a 90.1% sensitivity for detecting malignant lesions larger than 1cm (8). Positron Emission Mammography (PEM) provides better diagnostic capabilities in view of improved spatial resolution and lesser attenuation induced effects. PEM machines can also have integrated targeted biopsy capabilities, which further facilitate accurate targeting and diagnosis. PEM is seen to have better specificity compared to MRI in the diagnosis of malignancy but with a slightly inferior sensitivity (9).

In early breast cancer, 18F-FDG PET/CT is not routinely recommended. This is in view of the low probability of metastases in these patients, the problem of increased false positive scans, the lower sensitivity of 18F-FDG PET/CT for axillary lymph-nodal disease and for identifying small tumors (<1cm) in the breast. Sentinel lymph node biopsy is helpful in evaluation of axillary disease in clinically N0 patients before planning definitive surgery.

In inoperable breast cancer, 18F-FDG PET/CT is considered as optional in these patients for metastatic workup according to NCCN guidelines (6). 18F-FDG PET and PET/CT had a pooled sensitivity of 63% in diagnosing axillary nodal metastases in a meta-analysis of 26 studies using PET and PET/CT. However, the specificity of 18F-FDG PET/CT for nodal metastasis is quite high (pooled specificity 94%). Analysis of only the combined PET/CT studies (n = 7), showed a slightly higher specificity of 96% but the sensitivity was still low (56%) while sentinel lymph node biopsy had a better sensitivity of about 93% (10). 18F-FDG PET/CT helps in identifying extra axillary sites of nodal disease which may render the patient inoperable. It has been seen to upstage the disease and change in management in about 27.3% of the patients in one study (11).

The common sites of distant metastases in breast carcinoma include bone, lung, liver, and brain. Among bone metastases, 18F-FDG PET/CT is more sensitive for lytic metastases, while sclerotic metastases are better diagnosed on a sodium fluoride PET/CT or bone scan. Liver metastases can be identified on a 18F-FDG PET/CT before the appearance of changes on CT, especially in a patient with a hypoattenuating fatty liver. Some lung metastases that are small (<1cm) may not be identified with 18F-FDG PET/CT due to the partial volume effect and respiratory motion. Although brain metastases can be seen on 18F-FDG PET/CT, it is not a very sensitive modality in view of the physiologically high background FDG uptake in the brain parenchyma. MRI of brain is the ideal modality for the evaluation of suspected brain metastases. In one meta-analysis, where 18F-FDG PET/CT was compared with conventional imaging modalities, PET/CT performed better with a sensitivity of 97% (vs. 56% for conventional modalities) and a specificity of 95% (vs. 91%) (12).

For response assessment, 18F-FDG PET/CT is useful in assessing response to chemotherapy, thereby preventing exposure of non-responders to toxic effects of systemic chemotherapy. 18F-FDG PET/CT has been found to have an accuracy of 87% in identifying responders after 2 cycles of chemotherapy. In another meta-analysis, PET/CT was superior to MRI in early assessment of response in interim setting while MRI performed better at the end of treatment (13, 14).

18F-FDG PET/CT is useful in cases of equivocal findings in routine imaging modalities. For recurrence evaluation, 18F-FDG PET/CT is more sensitive (95% vs 80%) and specific (89% vs. 77%) compared to CT. However, 18F-FDG PET/CT and MRI were comparable with each other (15). PET/CT was found to be more sensitive than conventional imaging modalities such as breast mammography and ultrasonography, chest X-ray, and whole-body bone scan for the evaluation of both local and distant recurrence. However, the specificities were comparable (16). However, PET/CT is not routinely recommended in surveillance.

Current guidelines

Current NCCN and ESMO guidelines do not recommend 18F-FDG PET/CT for initial diagnosis or surveillance of breast cancer. They recommend 18F-FDG PET/CT if other conventional modalities are equivocal in the case of early breast cancer. In locally advanced breast carcinoma, PET/CT is optional according to NCCN, while ESMO suggests that it is indicated for staging. 18F-FDG PET/CT is also optional for response assessment and recurrence evaluation according to NCCN while ESMO does not have definite recommendations in these settings (6, 17). The various types of breast lesions commonly encountered in 18F-FDG PET/CT and their imaging characteristics are summarized in Table 1 (18). The incremental benefit of performing an 18F-FDG PET/CT for staging breast cancer can be appreciated in Figure 1.

TABLE 1 **Various breast lesions with their corresponding FDG-PET and CT features**

Differential diagnosis of breast lesions	FDG-PET avidity	CT features
Physiological variants and non-neoplastic diseases		
Pregnancy and lactation	Diffuse increased avidity	Enlarged with bilateral cord-like tissue showing hyper attenuation
Breast abscess	Peripheral avidity	Cystic lesion with thick enhancing walls
Fat necrosis	Moderate avidity	Hyperdense, spiculated lesion
Seroma	Non to mild peripheral avidity	Cystic lesion with thin walls and mild peripheral enhancement

(Continued)

TABLE 1 Various breast lesions with their corresponding FDG-PET and CT features(*Continued*)

Differential diagnosis of breast lesions	FDG-PET avidity	CT features
Benign neoplasms		
Fibroadenoma	Usually non- to mildly avid. Rarely highly avid.	Well circumscribed, round to oval lesion. May show popcorn calcification.
Intraductal papilloma	Mild to high avidity in the nodule	Complex cystic lesion with a mural nodule
Malignant lesions		
Ductal Carcinoma in Situ	Mild avidity	Micro calcifications on mammography. May or may not be visualized on CT.
Invasive ductal carcinoma	Usually highly avid. Higher avidity in high grade and triple negative tumors.	Enhancing mass with rounded or spiculated borders. May contain necrotic areas or satellite nodules.
Invasive lobular carcinoma	Lower avidity than ductal carcinomas.	Asymmetric soft tissue density or mass.
Medullary carcinoma	High avidity	Oval or lobular shape with circumscribed margin.
Mucinous carcinoma	Low avidity due to lower cellularity	May show solid cystic areas because of mucin content
Lymphoma	Avidity based on grade of lymphoma.	May be unifocal or multifocal or diffuse lesions. May have involvement of other lymph nodal groups.
Malignant phyllodes tumor	Rare tumor. Case reports showing high avidity.	Enhancing lobulated lesion with smooth margin, cystic areas, septations and thick enhancing walls.
Metastases to breast	Avidity based on the primary site.	Mostly rounded borders without spiculations and calcifications.

Adapted from ref (18). FDG, 2-fluoro-2-deoxy-glucose; PET, Positron emission tomography; CT, Computed tomography

NON-18F-FDG PET/CT IMAGING IN BREAST CARCINOMA

Although FDG still remains the most established and widely used PET imaging agent for breast carcinoma, there is an advent of multiple new molecular imaging agents which have varied mechanisms of action including receptor targeted agents, proliferation agents, agents targeting the tumor micro-environment such as integrin, and fibroblast activation protein.

Hormone receptor targeted imaging

16α-18F-Fluoro-17β-estradiol (18F-FES), a novel radiopharmaceutical that specifically targets the estrogen receptors, is gathering increasing evidence for its role in

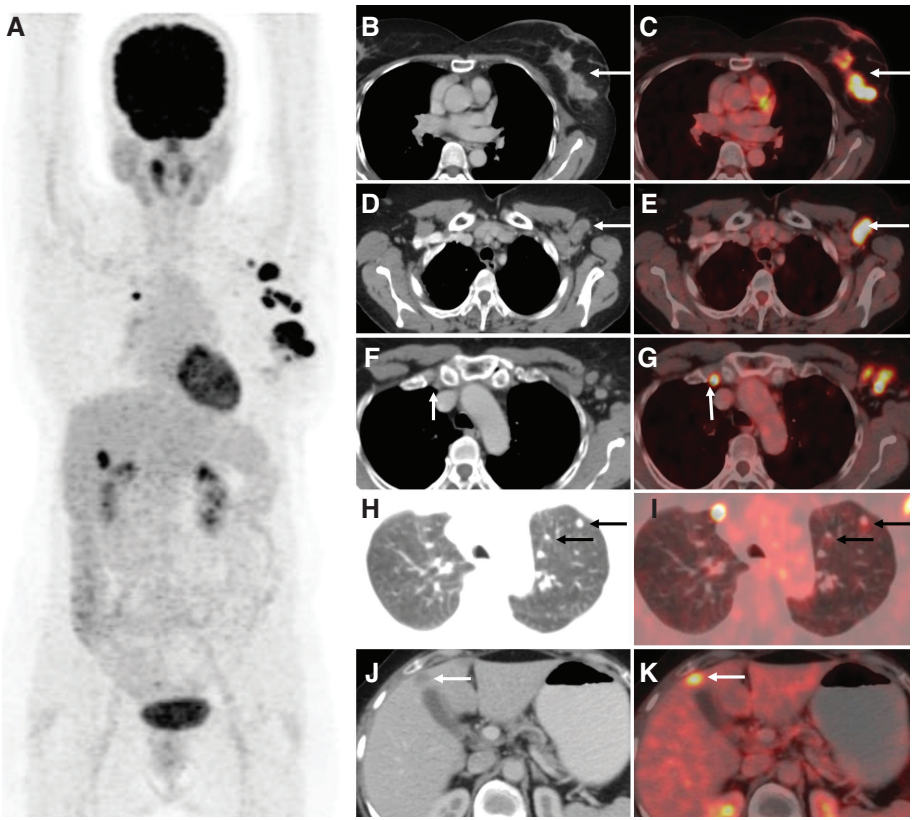

Figure 1. 18F-FDG PET/CT in carcinoma breast. A female with lump in the left breast, which was proven to be infiltrating ductal carcinoma on histopathology. Clinical stage was $T_2N_1M_x$ with palpable axillary lymph nodes. 18F-FDG PET/CT was performed for staging the disease as part of pre-operative workup, which showed multiple foci of increased FDG uptake in the chest and upper abdominal region on the MIP image **(A)**. The trans-axial CECT and fused PET/CT images showed a FDG avid heterogeneously enhancing lesion in the upper outer quadrant of left breast with multiple satellite nodules **(B, C)**, FDG avid enlarged left level I axillary lymph nodes **(D, E)**, a FDG avid sub centimeter right internal mammary lymph node **(F, G)**, lung nodules **(H, I)** and a FDG avid hypodense lesion in the liver **(J, K)**. The final stage post PET/CT was $T_3N_1M_1$, which led to a change in management from surgery to systemic chemotherapy as patient's classification was changed from having an operable breast cancer to an inoperable breast cancer with metastatic disease.

various stages of management of breast carcinoma. This property of specific receptor targeting helps in better staging of patients with variants such as invasive lobular carcinoma, which are known to have lower FDG avidity. In one study, 18F-FES was found to detect more metastatic lesions than FDG in patients with invasive lobular carcinoma (19). 18F-FES also acts as a predictive biomarker for patients with a higher SUV value having better response rates with hormonal agents such as tamoxifen (20). Routinely, immunohistochemistry is used to assess estrogen receptor expression in tumor cells for selecting patients for hormonal therapy. But this does not account for the phenotypical tumor heterogeneity (among the different lesions at any point of

time) or the temporal heterogeneity (change in receptor expression over a period of time due to the natural progression of the disease or due to the administered treatment) in various lesions, as they might not express the same level of estrogen receptors. 18F-FES PET/CT acts as a tool to assess receptor expression *in-vivo* in various metastatic lesions within the body and it has been seen that the intensity of tracer uptake correlates with the density of estrogen receptor expression (21). Another area of great potential use is in the setting of recurrent breast carcinoma, where recurrent lesions are usually sampled for assessing the receptor expression status. In this setting, 18F-FES PET/CT can act as a non-invasive tool for assessing receptor expression, especially when sampling the lesion is not possible as in cases of inaccessible lesions (22). Recent NCCN guidelines also suggest the use of 18F-FES PET/CT for assessing recurrent or metastatic disease in cases with known estrogen receptor positive tumors. A representative image of a PET/CT performed with 18F-FES is shown in Figure 2.

Progesterone receptor targeted F-18-fluorofuranyl norprogesterone and androgen receptor targeted 16β-[18F]fluoro-5α-dihydrotestosterone have shown their use for predicting response to hormonal therapy in PR+ carcinoma breast patients.

Tyrosine kinase receptor targeted imaging

Human epidermal growth factor receptor 2 (HER2) is a tyrosine kinase-based receptor that is overexpressed in certain subtypes of breast cancer, which is associated with poorer survival outcomes and more aggressive tumor biology. This is usually assessed using immunohistochemistry and fluorescent *in situ* hybridization techniques. A specific FDA approved monoclonal antibody targeting the HER2 receptor is Trastuzumab, which has been used routinely in the treatment of HER2 positive breast carcinoma. This potential of Trastuzumab to selectively bind to the HER2/neu receptors can be exploited by radiolabelling it with positron-emitting agents such as Gallium-68, Copper-64, or Zirconium-89. *In vivo* imaging with these agents helps in addressing the problem of tumor heterogeneity between the primary and metastatic sites, thereby acting as a better predictive biomarker for assessing response to targeted therapy and also acting as a potential theranostic agent by labeling with beta-emitting radionuclides (23).

Proliferation based imaging

18F-fluorothymidine (18F-FLT) is a radiolabeled thymidine analogue, which is involved in DNA synthesis and acts as a marker of the cellular proliferative activity. It is seen to concentrate on a wide variety of tumor types. In patients with breast carcinoma, the amount of 18F-FLT activity within the tumor cell is an indirect marker of the level of proliferation in the tumor microenvironment, which is shown to correlate with the Ki-67 proliferation index. It can also help predict response to therapy in patients after chemotherapy (24, 25).

Tumor microenvironment targeted imaging

Fibroblast activation protein (FAP) is a substance that is expressed in cancer-associated fibroblasts. It is seen to have dipeptidyl peptidase-4 activity and is expressed in the tumor microenvironment. It is not specific to breast carcinoma

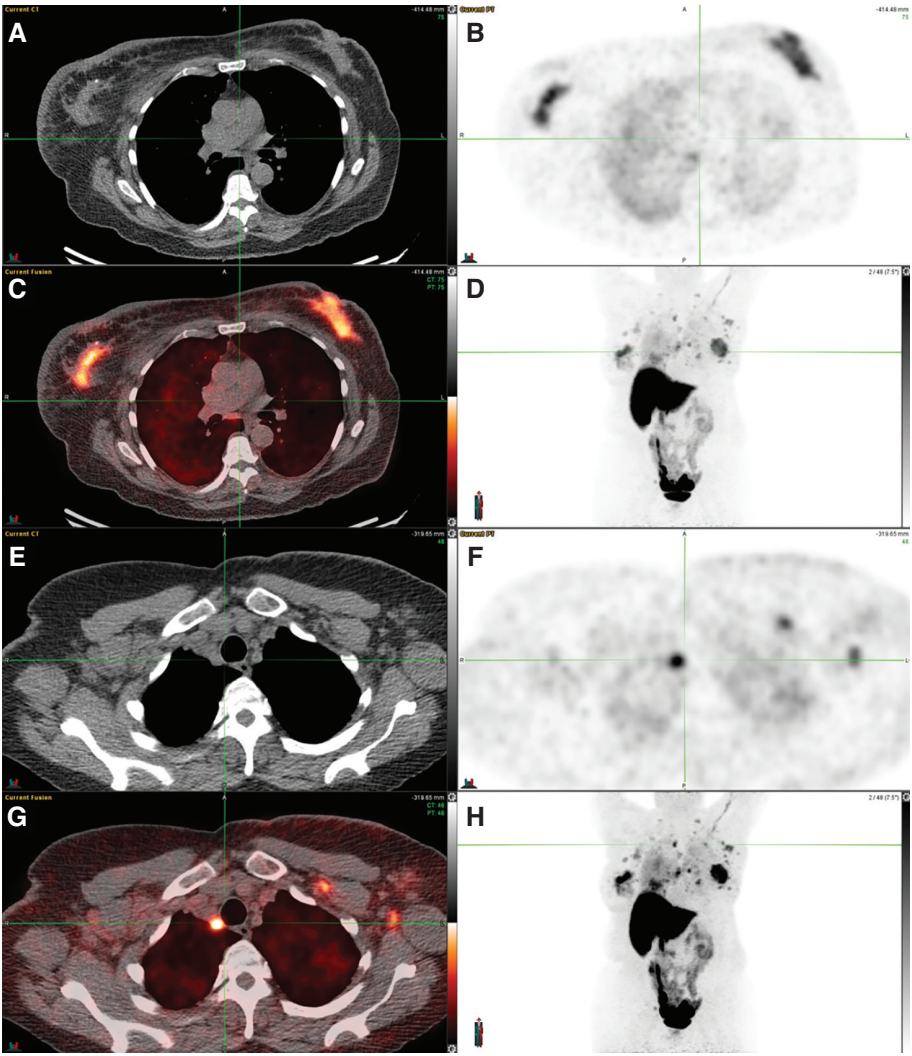

Figure 2. 18F-FES PET/CT in carcinoma breast. 18F-FES PET/CT in a patient with initially diagnosed left breast invasive ductal carcinoma (IDC), cT1cN0, ER+/PR+/HER-2 negative, Ki67 11%. Initially declined treatment and now with bilateral breast masses with Ki67 20%, bilateral lymphadenopathy, and pulmonary nodules. Images include: **(A)** axial CT, **(B)** axial FES PET, **(C)** fused axial PET/CT, **(D)** maximum intensity projection (MIP) image, **(E)** axial CT, **(F)** axial FES PET, **(G)** fused axial PET/CT, and **(H)** MIP image. 18F-FES PET/CT demonstrates increased FES uptake in the bilateral breast masses (images A-D), lymph nodes in the bilateral axillae, subpectoral regions, and mediastinum (images E-H), and bilateral pulmonary nodules (lung windows not included).

and is seen in a wide range of malignancies. Ga-68-labelled FAP-inhibitors (FAPI) have been used for imaging tumors. In a comparison study with 18F-FDG PET/CT, 68Ga-FAPI was found to have better lesion detectability due to the higher target-to-background ratio both in primary sites and metastatic foci. It was also helpful in detecting cerebral metastases due to the absence of normal physiological activity in the brain, which is seen with FDG (26).

Prostate specific membrane antigen (PSMA) is a transmembrane glycoprotein that is overexpressed in prostatic adenocarcinoma. It has recently been seen that it is also expressed in tumors showing neo-angiogenesis. To this effect, one of the studies by Sathekge et al. has shown that 68Ga-PSMA PET/CT identified up to 84% of tumor lesions that were detected with 18F-FDG PET/CT. They proposed that 68Ga-PSMA PET/CT may serve as a basis for selecting patients who could benefit from anti-angiogenesis therapy and may also pave the way for exploring PSMA-targeted theranostics (27). Another similar study using Arginine-Glycine-Aspartic Acid (RGD) peptides to target the $\alpha_v\beta_3$ integrin in neoangiogenesis vessels has shown no significant benefit in using 68Ga-RGD PET/CT, with 18F-FDG PET/CT performing better in cases of primary staging and response assessment (28).

Other novel targets

Gastrin releasing peptide receptor is seen to be over-expressed in a wide range of solid tumors. 68Ga-RM2 is an antagonist targeting these receptors. In one study, PET/CT with 68Ga-RM2 was performed in 18 diagnosed breast primaries, of which 13 showed PET positivity. The authors suggested a role for 68Ga-RM2 PET/CT in detecting distant and internal mammary nodal metastases, which may not be apparent with conventional imaging (29). However, most of these studies with these newer agents targeting angiogenesis and gastrin receptors are preliminary single-center proof-of-concept studies and larger clinical trials are still required to validate these findings.

GAMMA CAMERA IMAGING IN BREAST CANCER

Gamma camera imaging still plays a major role in the setting of breast cancer. Commonly used modalities include skeletal scintigraphy for assessing skeletal metastases, breast specific gamma imaging (BSGI) for characterizing primary breast lesions, and sentinel lymph node biopsy (SLNB) for assessing presence of axillary nodal disease in clinically axillary node-negative early breast cancer.

Skeletal scintigraphy

Skeletal scintigraphy is routinely performed with 99mTc-labelled phosphonates such as methylene-di-phosphonate (MDP). MDP undergoes chemisorption in the hydroxyapatite bone matrix and is concentrated more in areas with high bone turnover, such as osteoblastic lesions. Skeletal scintigraphy is more sensitive for detecting sclerotic metastases than 18F-FDG PET/CT, which is useful for detecting lytic and marrow-based metastases. F-18 Sodium Fluoride PET/CT is the PET

counterpart of 99mTc-MDP bone scan. Expert consensus advocates the use of skeletal scintigraphy in the setting of initial staging of early breast cancer with elevated alkaline phosphatase levels and in locally advanced breast carcinoma irrespective of alkaline phosphatase levels. Hybrid imaging with F-18 Sodium fluoride PET and CECT may provide a wholesome staging workup, acting as a one-stop-shop for metastatic evaluation in breast carcinoma. It is also recommended in patients with new-onset osseous symptoms such as bone pain or fracture or with raising alkaline phosphatase levels. However, this study is not recommended if FDG PET/CT is being done. It is also useful for assessing skeletal recurrence when evaluating for suspicious non-osseous recurrence (30).

Breast-specific gamma imaging

BSGI involves imaging of the breast with gamma-emitting agents such as 99mTc-Sestamibi and using a specialized gamma camera with a small field of view for high resolution images of the breast parenchyma. BSGI is useful to evaluate the primary site for multifocal or multicentric involvement, to look for recurrence of disease, and to evaluate indeterminate findings on mammography or ultrasound in patients in whom a breast MRI is indicated but is not technically feasible, or in patients in whom mammography is precluded due to dense breast or implants (31). BSGI has also been used as a tool for assessing residual tumor after neo-adjuvant chemotherapy where it has been found to have comparable sensitivity to MRI (70% vs. 83%) but with a higher specificity (90% vs. 60%) (32).

Sentinel lymph node biopsy

In patients with early breast cancer, sentinel lymph node imaging of the axillary region with biopsy helps in identification of the involved lymph nodes and thereby prevents unnecessary axillary dissection and its associated morbidities in patients who are negative on SLNB. The SLNB procedure can be performed by instillation of either a blue dye or a radiopharmaceutical such as 99mTc-sulphur colloid or 99mTc-tilmanocept in the peritumoral or subareolar region. The injection can be administered pre-operatively, where it can be combined with imaging, or intra-operatively, and the sentinel lymph node identified using intraoperative gamma-probe. This SLNB technique has a detection rate of more than 95% for identifying the sentinel lymph node (33, 34).

ROLE OF PET/MRI IN BREAST CANCER

The advent of PET/MRI has helped in combining the benefit of the functional information obtained from PET with the detailed and extensive anatomical information obtained from MRI scans. In the setting of breast cancer, MRI has a very high sensitivity with moderate specificity for detecting primary malignant tumors. The relatively lower specificity is greatly improved by performing a combined PET/MRI. PET/MRI is superior in tumor phenotyping and in detecting metastatic involvement in nodal and distant sites such as liver and bone, which might otherwise be undetected on a PET/CT. The use of MRI also significantly reduces the

radiation exposure to the patient. However, widespread use is still hampered by the associated costs and availability of hybrid PET/MRI scanners (35).

CONCLUSION

A wide range of molecular imaging-based modalities find a role in the management of patients with breast cancer. Some of them are well established techniques such as 18F-FDG PET/CT, skeletal scintigraphy and SLNB, which are already a part of the standard recommendations and guidelines of various renowned organizations and associations, while other newer molecular imaging agents using receptor, FAP and angiogenesis-targeted tracers for PET/CT are in the early stages of generating evidence. As and when further large trials are available for these newer agents, molecular imaging in breast carcinoma will become full-fledged with a wide array of not only diagnostic but also theranostic radiopharmaceuticals.

Conflict of Interest: The authors declare that they have no potential conflict of interest with respect to the research, authorship, and/or publication of this chapter.

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