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# PET/CT Variants and Pitfalls in Breast Cancers

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**There are a number of normal variants and pitfalls which are important to consider when evaluating F-18 Fluorodeoxyglucose (FDG) with Positron Emission Tomography (PET) in breast cancer patients. Although FDG-PET is not indicated for the initial diagnosis of breast cancer, focally increased glucose metabolism within breast tissue represents a high likelihood for a neoplastic process and requires further evaluation. Focally increased glucose metabolism is not unique to breast cancer. Other malignancies such as lymphoma, metastases from solid tumors as well as inflammatory changes also may demonstrate increased glucose metabolism either within the breast or at other sites throughout the body. Importantly, benign breast disease may also exhibit increased glucose metabolism, limiting the specificity of FDG-PET. Breast cancer has a wide range of metabolic activity attributed to tumor heterogeneity and breast cancer subtype. Intracellular signaling pathways regulating tumor glucose utilization contribute to these pitfalls of PET/CT in breast cancer. The evaluation of axillary lymph nodes by FDG-PET is less accurate than sentinel lymph node procedure, however is very accurate in identifying level II and III axillary lymph node metastases or retropectoral metastases. It is important to note that non-malignant inflammation in lymph nodes are often detected by modern PET/CT technology. Therefore, particular consideration should be given to recent vaccinations, particularly to COVID-19, which can commonly result in increased metabolic activity of axillary nodes. Whole body FDG-PET for staging of breast cancer requires specific attention to physiologic variants of FDG distribution and a careful comparison with co-registered anatomical imaging. The most important pitfalls are related to inflammatory changes including sarcoidosis, sarcoid like reactions, and other granulomatous diseases as well as secondary neoplastic processes.**
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## Introduction

Imaging increased tumor glucose utilization using the radiolabeled glucose analogue F-18 Fluorodeoxyglucose (FDG) with Positron Emission Tomography (PET) plays an important role in the management of patients with breast cancer. This includes initial staging and re-staging, assessment of treatment response, and evaluation of suspected disease recurrence.[1,2] The heterogeneity of breast cancer and different histologic and molecular subtypes result in a number of variations in FDG-PET/CT and potential pitfalls with interpretation.

Breast cancer includes a heterogeneous group of malignancies originating from terminal-duct lobular units within the breast parenchyma. Breast cancer recently has surpassed lung cancer as the most frequently diagnosed cancer worldwide with an estimated 2.3 million new cases diagnosed annually.[3,4] It is the second leading cause of cancer related death in women, and accounts for 15.5% of all cancer related deaths among women.[5,6] Due to its frequent aggressive behavior and often early spread of disease, screening mammography is commonly used for earlier stage detection.[7]

Histologically, approximately 70% of breast cancers are classified as invasive ductal carcinoma. The second most common histologic type, and most common special type of breast cancer is invasive lobular carcinoma, comprising 10-15% of all breast cancers. The remaining 15-20% of breast cancers consist of a number of rare special types of breast cancer, including tubular, mucinous, neuroendocrine,

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**Table 1** 4-year survival data for pathologic molecular subtypes of breast cancer. Data adapted from Howlader et al.[14] based on 196,094 women diagnosed with breast cancer from 2010 to 2013. HR, hormone receptor. HER2, human epidermal growth factor 2.

| Pathologic molecular subtype | Surrogate for intrinsic (gene expression-based) subtype | 4-year survival (%) | | |
|---|---|---|---|---|
| | | All stages | Stage I | Stage IV |
| $HR^+$ / $HER2^-$ | Luminal-A | 92.5 | 98.9 | 35.9 |
| $HR^+$ / $HER2^+$ | Luminal-B | 90.3 | 98.6 | 45.5 |
| $HR^-$ / $HER2^+$ | HER2-enriched | 82.7 | 96.9 | 33.9 |
| $HR^-$ / $HER2^-$ | Triple-negative (including basal-like) | 77.0 | 95.1 | 11.2 |

Data adapted from Howlader et al. (14) based on 196,094 women diagnosed with breast cancer from 2010 to 2013.
HR, hormone receptor.

apocrine, micropapillary, adenoid cystic, metaplastic, and medullary carcinoma.[8]

Ductal carcinoma in situ (DCIS) is a non-invasive form of breast cancer characterized by the presence of neoplastic cells confined to ducts and lobules and without invasion through the basement membrane into the surrounding stroma. The majority of DCIS are non-palpable, often associated with microcalcifications and most commonly diagnosed by mammography. DCIS is a non-obligate precursor of invasive breast cancer and associated with up to 10-fold increased risk of developing ipsilateral invasive breast cancer if untreated.[9] Of note, DCIS is generally associated with relatively low metabolic activity which limits its detection with FDG-PET.[10]

Breast cancer is further categorized into three major biologic subtypes based on the expression of estrogen (ER) or progesterone (PR) receptors and overexpression or amplification of human epidermal growth factor 2 (HER2, encoded by the *ERBB2* gene).[11] These three major subtypes include:

- hormone receptor positive/HER2-negative (70% of patients)
- HER2-positive (15%-20% of patients)
- triple-negative (tumors lacking ER, PR, and HER2) (15% of patients)

Comprehensive gene expression profiling has revealed five intrinsic molecular subtypes of breast cancer, including luminal A, luminal B, HER2-enriched, basal-like, and normal–like breast cancer.[8,12] Subsequently, integration of gene expression with copy number alterations has expanded the number of molecular subtypes to ten.[13]

The largest population based study reporting breast cancer-specific survival by molecular subtype by Howlader et al [14] analyzed outcome data of more than 196,000 women from the United States Surveillance, Epidemiology and End Results (SEER) cancer registry. This analysis included women diagnosed with breast cancer between 2010-2013, where data on hormone receptor and HER2-status was available for 91% of all cases to allow pathologic classification of molecular subtype, and multiple imputation technique was used to assign molecular subtypes for the remaining 9% of cases with missing hormone receptor or HER2 status. The distribution of molecular breast cancer subtypes included 67% hormone receptor-positive/HER2-negative (HR+/HER-) subtypes (corresponding to luminal-A), 10% HR+/HER2+ subtypes (corresponding to luminal B), 4% HR-/HER2+ (corresponding to HER2-enriched), and 11% HR-/HER2- (corresponding to triple-negative and basal-like) subtypes.

Breast cancer-specific survival differed by molecular subtype with the best 4-year survival (92.5%) observed for HR+/HER- subtypes, intermediate survival for HER2-positive (HR+/HER2+ and HR-/HER2+), and poorest 4-year survival (77.0%) for triple-negative cancers, across all disease stages (Table 1). Of note, although molecular subtype significantly impacted breast cancer-specific survival, disease stage at diagnosis remained the most important prognostic factor. Women with HR-/HER2+ and triple-negative subtypes had a 1.2-fold and 2.5-fold increased risk of death from breast cancer, respectively, while higher stage at diagnoses conferred a 4- to 33-fold increased risk of death from breast cancer for stages II – IV in multivariate analysis. Interestingly, and contrary to conventional thought, among women with de novo stage IV metastatic breast cancer, those with HR+/HER2+ subtypes had a better 4-year survival compared to those with HR+/HER- subtypes (45% vs 36%), likely attributable to advances in HER2-targeted treatment.[14]

Nevertheless, the simplified molecular classification by pathological surrogates to distinguish hormone-receptor and HER2 status currently remains the only clinically established tool to guide treatment decisions based on guidelines by the American Society of Clinical Oncology (ASCO) and the St. Gallen consensus conference .[11,15] HER2-positive and triple-negative tumors are generally more aggressive, without systemic therapy, compared to luminal-type breast cancers.

The variable appearance of breast cancer on FDG-PET imaging with different levels of altered tumor glucose metabolism is also reflected by its molecular heterogeneity. The major molecular breast cancer subtype exhibit different levels of tumor glucose metabolism. Although distinct histologic and molecular breast cancer subtypes show different levels of metabolic activity, there is great variability of FDG uptake even within each subtype, which contributes to pitfalls in FDG-PET imaging in breast cancer patients.

Rare presentations of breast cancers include inflammatory breast cancer, a locally advanced or metastatic breast carcinoma infiltrating the skin with resulting dermal

inflammation and edema, ranging from 1% to 5% of all breast cancers. Paget's disease (1-3%) of the breast is characterized by neoplastic cells involving the epidermis of the nipple and areola, most commonly originating from an underlying DCIS or invasive breast carcinoma. Other rare malignant breast tumors include sarcomas involving the breast parenchyma (< 1%) or the skin of the breast, such as breast angiosarcoma. Phyllodes tumors are a fibroepithelial neoplasm accounting for less than 1% of breast tumors. Most of these tumors are benign, although borderline and malignant phyllodes tumors also occur. These rare breast neoplasms show variable metabolic activity and FDG-PET has no specific role in diagnostic evaluation.

Staging of breast cancer commonly follows the American Joint Committee on Cancer (AJCC) TNM staging system, where stage 0 refers to carcinoma in-situ. At stages I, II, and III, including early to locally advanced disease, the cancer may be defined by the size of the primary tumor and the area that the cancer cells have spread, such as the chest wall, skin, or the regional lymph nodes surrounding the breast. At the advanced or metastatic stage (stage IV), the cancer cells have metastasized to other organs or distant lymph nodes.

## Breast Cancer Detection and Screening

It is important to note that studies have demonstrated that FDG-PET used as hybrid imaging together with computed tomography (CT) or magnetic resonance imaging (MRI) currently plays no role in breast cancer screening. There are different reasons. Firstly, PET technology and infrastructure is relatively expensive and not universally available. Second, PET involves radiation exposure beyond the breast to the whole body. Most importantly, the goal of breast cancer screening is to detect cancer at an early stage, and studies have shown that FDG-PET is not particularly effective in detecting small breast carcinomas.[16]

Screening mammography remains the gold standard for early detection of breast cancer in average risk women. Current recommendations for frequency of mammography screening vary greatly. In the United States, the American College of Radiology, National Comprehensive Cancer Network, and American College of Obstetricians and Gynecologists recommend starting screening mammography at age 40 and continuing annually.[17–19] The American Cancer Society, American Society of Breast Surgeons, and American Society of Clinical Oncology recommend women begin annual screening at age 45.[20,21] Women aged 55 years and older should transition to biennial screening or have the opportunity to continue screening annually. Finally, the US Preventative Services Task Force currently recommends women begin biennial screening mammography starting at age 50 and stopping at age 74.[7] For women with a greater than 20% lifetime risk of developing breast cancer, the American Cancer Society recommends breast MRI and mammography annually starting at age 30.[21] Some high-risk features include known germline mutations in the BRCA1 or BRCA2 gene, a first-degree relative with BRCA1 or BRCA2 gene mutations, history of chest radiation therapy of 20 Gy or more, or having a genetic syndrome with germline mutations including tumor suppressor or oncogenes such as Li-Fraumeni syndrome, Cowden syndrome, or Bannayan-Riley-Ruvalcaba syndrome. The diagnosis of breast cancer is based on clinical examination in combination with imaging and is confirmed by histopathological assessment, most commonly through core needle biopsies. Basic diagnostic imaging workup includes bilateral mammography and ultrasound of the breast and regional lymph nodes.

Although FDG-PET is not useful or recommended for breast cancer screening, it is important to note that focally increased glucose metabolism within the breast detected on FDG-PET cancer staging examinations for other malignancies or inflammatory processes are highly concerning for a neoplastic process within the breast. These findings require further diagnostic evaluation.

The reason for the variability in FDG uptake and the low metabolic activity of some breast cancer subtypes is not well understood. Although some studies have observed a positive correlation between proliferative rate and tumor FDG uptake, overall histologic parameters including tumor differentiation and grade, and hormone receptor and HER2 status showed no statistically significant correlation with glucose metabolism.[10,22,23] Histologic and molecular breast cancer subtypes show differences in the average level of tumor glucose metabolism. Invasive lobular breast cancer in particular is often characterized by low metabolic activity, even in larger tumors, and small tumors are often not well visualized with FDG-PET.[10] In contrast, triple negative breast cancer can present with very high tumor glucose metabolism with standardized uptake values (SUV) above 50.0 for FDG [22] as shown in Figure 1.

Mutations of oncogenes and tumor suppressor genes involved in breast carcinogenesis also alter intracellular signaling pathways involved in regulation of tumor glucose metabolism thereby contributing to individual variability and pitfalls in FDG-PET imaging of breast cancer.[24] Regulation of tumor glucose metabolism is governed by both oncogenes and transcription factors that include c-Myc, p53, and hypoxia-inducible factor (HIF) 1$\alpha$. There is a complex interaction of various signaling pathways, such as Notch, AKT, phosphoinositide-3-kinase (PI3K), PTEN, mammalian target of rapamycin (mTOR), and AMP-activated protein kinase (AMPK) [24], which affect tumor glucose metabolism and ultimately the visualization via FDG-PET. The PI3K/AKT/mTOR signaling pathway plays a key role in regulating cell proliferation and glucose metabolism. This has been shown to be deregulated in up to 70% of breast cancers. Overexpression of phospho-AKT proteins was found in 33% of ductal carcinoma in situ and in 38% of invasive breast cancers.[25,26] Deviations and modifications of the intracellular signaling pathways correspond to changes of tumor glucose metabolism and further studies are necessary to link the level of glucose metabolism detected by FDG-PET with aberrant cell signaling pathways in breast cancer.

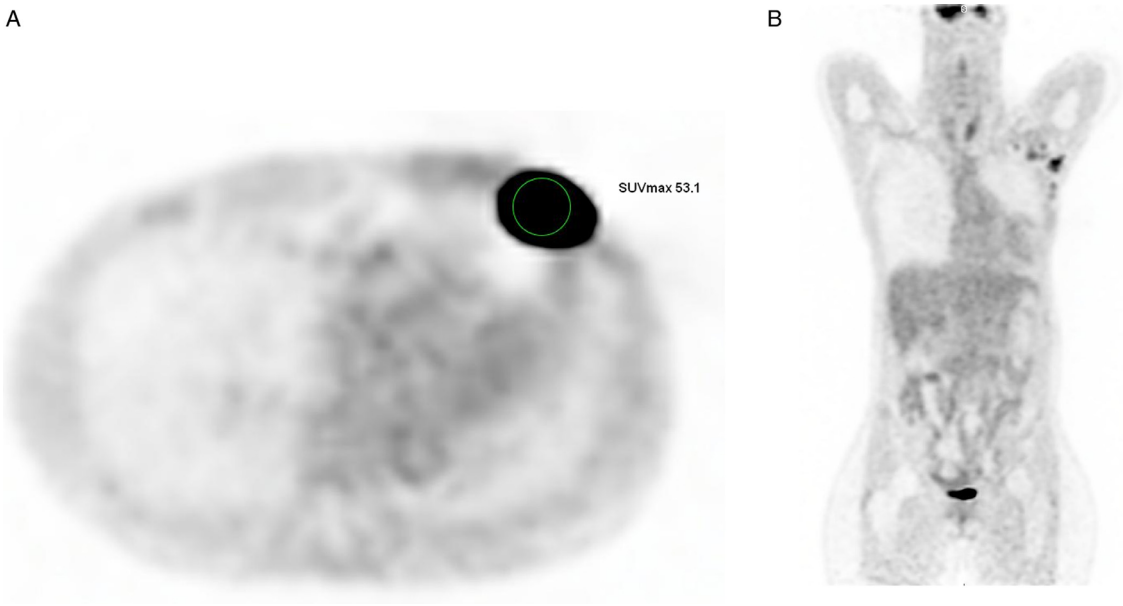


**Figure 1** 59-year-old female with a newly diagnosed breast mass with lymph nodes positive on histopathology. FDG-PET (Fig 1A) showed intensely increased metabolic activity within the left breast mass with SUVmax of 53.1. Coronal whole body images showed hypermetabolic left lymphadenopathy (Fig 1B). Histopathology revealed invasive ductal carcinoma negative for estrogen and progesterone receptors as well as HER2 (triple negative invasive ductal breast cancer).

## Diagnostic Performance of FDG-PET in Primary Breast Cancer

In patients with newly diagnosed abnormal breast masses, based on anatomical imaging or clinical examination, and prior to surgery, FDG-PET revealed a sensitivity and specificity ranging from 64-80%. Avril et al. reported one of the first studies in a larger patient population comprising 144 patients with 185 breast masses including 132 breast carcinomas and 53 benign masses.[16] The study showed an overall sensitivity of 64.4%, which increased to 80.3% when sensitive image reading was applied. However, the increase in sensitivity resulted in a noticeable decrease in specificity, from 94.3% to 75.5% using sensitive image reading. At stage pT1, only 30 (68.2%) of 44 breast carcinomas were detected, compared with 57 (91.9%) of 62 at stage pT2.[16] A higher percentage of invasive lobular carcinomas were false-negatives (65.2%) compared with invasive ductal carcinomas (23.7%). Nevertheless, focally increased glucose metabolism provided a high positive-predictive value (96.6%). An important advantage of this study is that all patients were imaged in the prone position, reducing breathing and motion artifacts. The study was performed with an earlier generation of PET scanners that utilized 2D mode, which could be seen as a potential limitation. However, the PET acquisition was focusing on breast and axilla and the acquisition time was approximately 10 minutes per bed position, which likely compensated for the higher sensitivity of the latest generation of PET scanners. Nevertheless, the findings regarding the limited diagnostic accuracy of FDG-PET for initial diagnosis of breast cancer were confirmed in several subsequent studies by other groups.[27,28,29] The limited sensitivity of FDG-PET in fully characterizing breast lesions represents an important limitation and pitfall of this modality in breast cancer screening.

Benign primary breast lesions are common and nearly 75% of initially suspicious breast biopsies yield a benign histologic diagnosis.[30] These include benign lesions such as fibroadenomas and intraductal papillomas, as well as reactive, hyperplastic and metaplastic processes, such as fibrocystic changes and apocrine metaplasia. Typically, these benign etiologies demonstrate no or mildly increased metabolic activity; however focally increased glucose metabolism may be seen in individual lesions mimicking a primary breast malignancy.[31,32] Figure 2 shows mild metabolic activity in the left breast corresponding to sclerosing adenosis with ductal hyperplasia and apocrine metaplasia with associated microcalcifications on histopathology.

A breast incidentaloma is defined as an unexpected imaging finding within the breast on a study in an asymptomatic

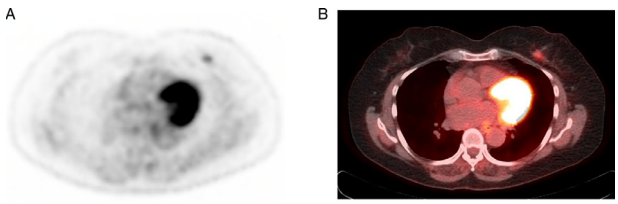


**Figure 2** 64-year old female who underwent FDG-PET/CT for evaluation of a solitary pulmonary nodule. A small lesion was found in the left breast (Fig 2A, 2B) with mild increased metabolic activity (SUVmax of 2.6). Subsequent biopsy showed a benign finding (sclerosing adenosis with ductal hyperplasia and apocrine metaplasia with associated microcalcifications.

patient or in a symptomatic patient where the breast abnormality was not related to the patient's presentation.[33] Bertagna et al. retrospectively reviewed nearly 43,000 FDG-PET studies performed for oncologic indications not related to breast disease to identify breast incidental uptake/breast incidentalomas. Out of 35 breast incidentalomas, 25 (72%) were malignant comprising predominantly invasive ductal carcinoma, while 10 (28%) were considered benign. Of the benign etiologies, 90% were fibroadenomas.[34]

Separately, Shin et al. retrospectively found that in 21,224 average risk women with no history of breast cancer who underwent FDG-PET, 91 hypermetabolic breast incidentalomas were identified.[35] Approximately 30% of those lesions were malignant while the remaining 70% were considered benign based on histology or imaging follow-up greater than 2 years. The majority of those benign lesions represented fibroadenomas, intraductal papillomas, and fibrocystic disease.

Notably, inflammatory changes, such as postsurgical inflammation, granulomatous processes, and infections may show markedly increased glucose metabolism, which is important for the interpretation of FDG-PET. Even physiologic metabolic activity of breast tissue, such as in a lactating woman, can present with diffusely increased metabolic activity.

Fat necrosis is a common benign inflammatory process within the breast which results from the disruption of adipocytes. The most common etiologies include trauma, surgery, and biopsy. With mammography and ultrasound evaluation, fat necrosis may present with malignant appearing imaging features and represents a diagnostic challenge. Unfortunately, FDG-PET does not aid in the differentiation of fat necrosis from other etiologies. The presence of metabolically active inflammatory cells may result in increased metabolic activity which is difficult to differentiate from a neoplastic process.[36,37] Knowing the patient's history and comparison with prior breast imaging significantly contributes to the appropriate image interpretation and management.

There are a wide range of infectious etiologies that may affect the breast. The frequency and severity of these pathologies vary based on the patient's age, level of acuity, and past medical history.[38] Mastitis is the most common form of breast infection and may be a simple local process or develop into a complicated form. Simple mastitis is most commonly found in lactating and pre-menopausal women with an underlying *Staphylococcus* culture source. Complex mastitis may occur as a worsening form of simple mastitis with development of a super-infected cyst, galactocele, or hematoma. Breast abscesses may be formed and lead to more serious complications requiring drainage and antibiotic treatment depending on their size and extent.[39] Of note, a breast seroma following surgical intervention may also present with increased glucose metabolism mimicking residual neoplastic disease as shown in Figure 3.

All of these etiologies may present with various ranges of increased metabolic activity corresponding to the extent of disease.[40] This may be focal metabolic activity within the breast parenchyma, peripheral increased activity surrounding an abscess, or diffuse increased FDG accumulation with skin thickening and breast enlargement.[41] Again, clinical history and presentation may assist with appropriate evaluation on an FDG-PET/CT and discriminate from other etiologies.

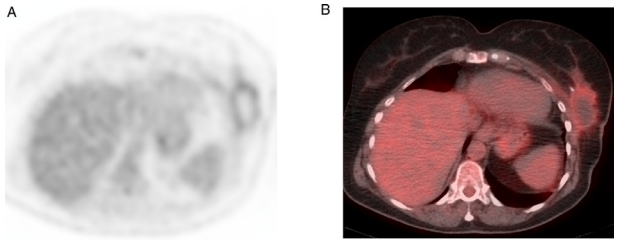


**Figure 3** 75-year-old female with invasive lobular carcinoma of the left breast. The patient underwent a left partial mastectomy and sentinel lymph node dissection. Postoperative axial PET and fused PET-CT images (A and B) showed a peripherally hypermetabolic mass in the left breast with central photopenia. Findings were consistent with a postoperative seroma.

As the use of silicone breast implants continues to increase for both post-surgical reconstruction as well for purely cosmetic reasons, there has been increasing incidence of related complications and imaging findings.[42] Free extracapsular silicone is one of the most common complications and involves microscopic or macroscopic leakage of silicone solution from an implant into the surrounding breast tissues. Additionally, while banned in the United States since the 1990s, free silicone breast injections continue to be performed in developing countries across the world.[43] Due to the reactive nature of free silicone and the resulting inflammation and host immune response within surrounding breast tissues, FDG-PET may demonstrate increased FDG uptake at sites of free silicone.[44–46] This may cause confusion and raise suspicion for a primary breast malignancy. While it is well established that breast augmentation with silicone implants does not carry increased risk for developing primary breast malignancy and screening recommendations are the same as those for patients without breast implants.[47], recognition of related imaging pitfalls is critical. Correlation with alternative imaging modalities including ultrasound and MRI can help confirm the diagnosis.

On mammography, free silicone may be identified as extremely dense mass with or without surrounding calcification.[43] Ultrasound features include a characteristic "snowstorm appearance" of echogenic foci within a contained mass. MRI remains the best method for evaluation of silicone breast implants and identifying the high T2 and low T1 imaging characteristics of silicone outside the capsule is diagnostic.[48] This should be considered when reporting positive findings on FDG-PET.

Patients younger than 40 years of age usually are diagnosed with more aggressive breast cancer phenotypes, which are more easily detected by FDG-PET and can be useful if younger age is associated with higher risk disease.

Investigation is ongoing regarding the clinical utility of specialized PET techniques including positron-emission mammography (PEM) with dedicated small-field devices in the evaluation of primary breast cancer.[49] Based on the molecular and metabolic characteristic of different breast cancer types, there is evidence to suggest that while PEM with FDG has lower sensitivity for small breast lesions than

MRI, specificity is higher. Nevertheless, when further breast imaging after mammography or ultrasound is required, breast MRI is the method of choice for detailed breast imaging. Dedicated breast nuclear imaging, such as PEM, could be considered when MRI is contraindicated.

As detailed above, focally increased glucose metabolism within the breast detected on FDG-PET/CT is highly concerning for a neoplastic process. However, there are several non-malignant etiologies that may occur with overlapping imaging findings.[50] Interpreting physicians must be familiar with these differential diagnoses and consider the patient's clinical and treatment history, comparative studies, and additional imaging modalities to guide interpretation of FDG-PET.

# Secondary Neoplastic Process

## Lymphoma

An important factor to note of FDG-PET imaging is that hypermetabolic malignancies other than breast cancer can be found within the breast. Although infrequent, involvement of the breast by primary or secondary lymphoma accounts for approximately 0.5% of malignant breast tumors. The most common breast lymphomas include diffuse large B-cell lymphoma, Burkitt and Burkitt-type lymphoma, or mucosa-associated lymphoid tissue (MALT)-type lymphoma. Primary breast lymphoma is defined as the breast being the site of the first or major manifestation of lymphoma with no presentation of lymphoma elsewhere, although involvement of ipsilateral axillary lymph nodes with enlargement and hypermetabolic activity may be present. Secondary lymphomas of the breast also are rare but represent the largest group of tumors metastatic to the breast.

Primary or secondary breast lymphoma usually presents as a painless unilateral breast mass; however bilateral disease is seen in approximately 10% of patients at the time of diagnosis. Breast lymphoma has no specific mammographic appearance - an important differential diagnosis includes poorly differentiated carcinoma. Calcifications are generally absent in breast lymphoma. FDG-PET/CT typically shows a mass within the breast with focally increased glucose metabolism and may be an incidental finding on whole body FDG-PET staging. Breast lymphoma is seen most frequently in women, and rarely in men. Figure 4 shows a 66-year-old female with a hypermetabolic new right breast mass consistent with marginal zone lymphoma.

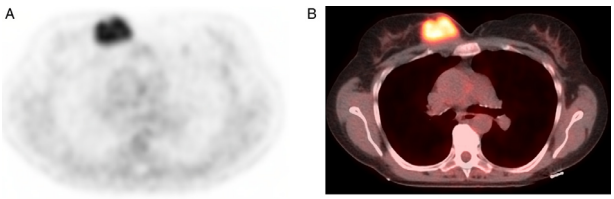


**Figure 4** 66-year-old female with a history of marginal zone lymphoma involving the left orbit treated with radiation who presented presenting with a new right breast mass. Mammographic and ultrasound workup was consistent with marginal zone lymphoma of the right breast. Axial PET and fused PET-CT images (Figure 4A, 4B) from initial staging demonstrated hypermetabolic activity associated with the large medial right breast mass. No other hypermetabolic areas of lymphomatous involvement were identified throughout the remainder of the body.

A less common clinical presentation of primary breast lymphoma is rapidly enlarging bilateral breast masses occurring in young women during pregnancy or postpartum, in which the histological appearance of the disease is typically consistent with Burkitt-type lymphoma. The presence of B-symptoms (fever, night sweats, and weight loss) is uncommon in extranodal lymphomas.

## Breast metastasis from extra-mammary solid malignancies

Metastases to the breast from solid malignancies are uncommon, accounting for less than 1% of all breast malignancies. When present, this typically is associated with widely metastatic disease.[51,52] Breast metastases tend to occur in the subcutaneous fat, whereas primary breast cancers originate in glandular tissue. Metastases to the breast tend to have a rounded and well circumscribed appearance. Subsequently, they present with focally increased FDG uptake within breast parenchyma. Often there is extensive hypermetabolic disease throughout the body. The most common extra-mammary cancers that metastasize to the breast include melanoma, sarcomas, lung cancer, gastric cancer, ovarian cancer, renal cell cancer, malignant mesothelioma, carcinoid tumor, carcinoma of the cervix, rectal cancer, and papillary thyroid carcinoma. Prostate cancer metastasis to the breast is considered one of the most frequent primary sites in men.

A study from Memorial Sloan-Kettering Cancer Center in New York analyzed 85 patients; 72 women and 13 men with breast metastasis from non-mammary malignancies and found that most were metastatic carcinoma (58%), followed by melanoma (22%), and sarcoma (20%).[53] Ovarian cancer was the most common primary site of origin of metastatic carcinoma, with metastatic high-grade serous ovarian carcinoma was most frequently misdiagnosed as a primary breast carcinoma. Melanoma was the single most common non-carcinomatous tumor type to involve the breast and/or axilla, and uterine leiomyosarcoma was the most common type of sarcoma. Most patients (77%) had other metastases at the same time of diagnosis of breast metastasis, but in 11%, the breast or axillary lesion was the first presentation. Rare cases of breast metastasis include medullary thyroid cancer and only approximately 20 cases have been reported so far.[54]

# Axillary and loco-regional Staging

Accurate staging is essential for proper management decisions and accurate prognosis assessment in patients with newly diagnosed or recurrent breast cancer. The initial diagnostic workup typically includes regional staging including axillary and internal mammary lymph node evaluation. Patients with a high risk of distant metastases also undergo

systemic staging including computed tomography and bone scintigraphy.

In the preoperative work-up of early-stage breast cancer with clinically negative axilla, FDG-PET rarely affects the initial staging and treatment planning. Evaluation of the axilla with sentinel lymph node biopsy is the preferred procedure. A number of studies have shown that FDG-PET is less sensitive in assessing axillary lymph node involvement compared to sentinel lymph node procedures.[55] A recent systematic review of the diagnostic performance of FDG-PET including 9 studies with 1,486 patients showed a sensitivity and specificity of 52.2% and 91.6%, respectively.[56] Using modern PET technology, there is not infrequently mild increased metabolic activity in axillary lymph nodes observed on whole body staging, which is related to inflammatory and reactive lymph node activation. Recent findings indicated increased metabolic activity within axillary lymph nodes following COVID-19 vaccination.[57,58] as shown in Figure 5. This included reactive axillary and supraclavicular hypermetabolic lymphadenopathy as well as ipsilateral increased metabolic activity at the deltoid muscle injection site. Metabolic activation of lymph nodes frequently has been observed following other vaccinations such as for influenza as well as possible response to viral infections.[59] Paravasation of tracer activity from intravenous injection can also result in increased FDG trapping in draining lymph nodes and result in false-positive findings in the axilla.

By contrast, in breast cancer patients with clinical axillary involvement, FDG-PET can be useful prior to surgery or neoadjuvant chemotherapy with a high rate of detection of distant metastases ranging from 6% to 26%. The percentage of patients with extra-axillary lymph node involvement detected by FDG-PET in locally advanced breast cancer varies from 10% to 29%.[60] Moreover, given the high prevalence of lymph node involvement (up to 80%) in this setting, the generally high negative predictive value of FDG-PET in lymph nodes adds to its clinical utility.

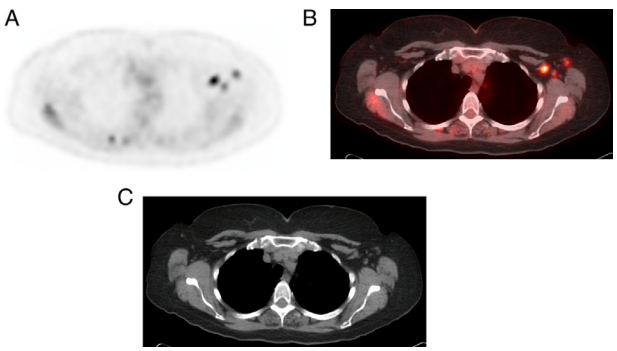


**Figure 5** 62-year-old female presenting for restaging PET-CT. Axial PET and fused PET-CT images (A and B) demonstrated hypermetabolic left axillary lymph nodes. Axial CT image (C) demonstrated multiple axillary lymph nodes not enlarged by CT criteria. No hypermetabolic sites of metastasis were identified elsewhere throughout the body. Note that the patient's FDG injection was right-sided. After additional history was asked of the patient, it was noted that the patient had received their first COVID-19 vaccine dose 1 week before the PET-CT with that injection occurring in the left deltoid. The finding was reported as reactive lymphadenopathy from recent vaccination.

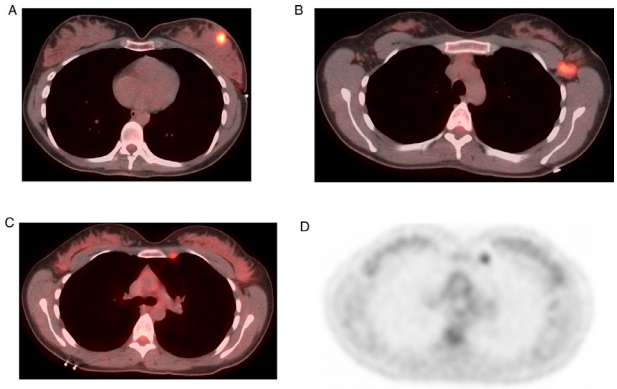


**Figure 6** 28-year-old female who initially presented with a palpable left breast mass and axillary lymphadenopathy. Ultrasound and mammographic workup was diagnostic for invasive ductal carcinoma with axillary metastasis. Axial fused PET-CT images (A and B) demonstrated hypermetabolic activity associated with the primary left breast mass and left axially lymph nodes. Fused PET-CT and axial PET images (C and D) also identified a hypermetabolic left internal mammary lymph node.

There are less frequent false-positive findings seen in locoregional extra-axillary lymph nodes which include internal mammary, infraclavicular, and supraclavicular lymph node levels.[61] Treatment strategies may also be influenced by detection of extra-axillary lymph nodes such as through radiotherapy or surgical approach.[62] Despite the heterogeneity of glucose metabolism in primary breast cancers, metastatic lesions are more frequently positive on FDG-PET and the sensitivity increases further in the recurrent disease setting. FDG-PET has been shown to be particularly useful in the non-invasive evaluation of internal mammary nodes which are not routinely assessed during surgery guided by sentinel lymphoscintigraphy. The generally favorable target-to background for locoregional extra-axillary lymph nodes also enables an accurate assessment of non-enlarged lymph nodes as shown in Figure 6.

Tran et al. examined breast cancer patients staged by FDG-PET and compared the rate of extra-axillary metastases between inner-quadrant breast cancer versus outer-quadrant breast cancer.[63] Their group found that inner-quadrant primary tumors had a 6-fold greater frequency of extra-axillary lymph node metastasis identifiable on FDG-PET compared to those with outer-quadrant breast cancer.[63] This suggested that FDG-PET could improve initial staging particularly for inner-quadrant breast cancer patients.

Groheux et al. completed a prospective analysis of FDG-PET/CT for 131 patients with breast cancers measuring >2cm and clinical stage IIA, IIB, or IIIA disease.[64] New clinically relevant information was detected in 13% of patients and extra-axillary regional lymph node metastases were detected in 5 patients (4%). Consequently, patients were upstaged, and this information altered their treatment course.

## Staging for Distant Metastases

Breast cancer can potentially metastasize to nearly any organ; most commonly to bone, liver, lung, and brain.[65] FDG-PET is a powerful tool for the staging of newly diagnosed or recurrent breast cancer and multiple studies have shown its utility compared to other modalities including nuclear bone scintigraphy, contrast-enhanced CT, and whole-body MRI.[1,66–69] In a recent prospective study, Hildebrandt et al. compared FDG-PET/CT, contrast-enhanced CT, and bone scintigraphy in 100 patients with suspected recurrence of breast cancer. The group found that FDG-PET resulted in no false negative findings and fewer false positive findings than the other imaging techniques concluding that FDG-PET/CT was accurate in diagnosing recurrence in breast cancer patients.[70] Changes in metabolic activity following treatment are important to note and active viable metastatic disease can be present together with treated metastases, particularly in the bone as shown in Figure 7.

Axial PET and fused PET-CT images during treatment (A and B) showed areas of focal hypermetabolic activity within the right sacrum and left ileum. Axial CT image (C) demonstrated mixed lytic and sclerotic areas throughout the sacrum and pelvis. Findings were suggestive of mixed areas of both active and treated osseous metastatic disease.

The pitfalls in whole body staging of breast cancer patients for distant metastases are shared with other tumor entities. Inflammatory changes are the most frequent findings presenting with increased metabolic activity, which are important in the differential diagnosis of breast cancer metastases. Inflammatory changes within the lungs are not infrequent, particularly in patients imaged following treatment. While pneumonia is often identified by a characteristic pattern and typical changes on the corresponding CT, reactive or inflammatory lung nodules pose a more difficult challenge in accurate characterization.[71] Comparison with clinical history and prior imaging are often helpful to avoid tissue biopsies for final diagnosis. Some medications prescribed in breast cancer can cause inflammatory changes in the lung. One example is the mTOR inhibitor everolimus. An analysis of 29 breast cancer patients with a total of 57 FDG-PET/CT studies found 62% pleuro-parenchymal abnormalities on FDG-PET/CT.[72]

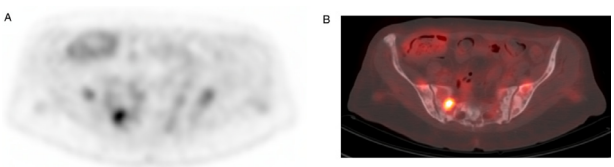


**Figure 7** A 79-year-old female with infiltrating ductal carcinoma of the bilateral breasts treated with partial mastectomy and adjuvant chemotherapy. She developed osseous metastatic disease and was treated with denosumab. Axial PET and fused PET-CT images during treatment (A and B) showed areas of focal hypermetabolic activity within the right sacrum and left ileum. Axial CT image (C) demonstrated mixed lytic and sclerotic areas throughout the sacrum and pelvis. Findings were suggestive of mixed areas of both active and treated osseous metastatic disease.

Inflammatory lung changes related to everolimus show a typical imaging pattern on FDG-PET with alveolar-interstitial opacities being associated with moderate metabolic activity, more or less extensive, mainly affecting the lower lobes.

Another group of inflammatory changes that can result in increased metabolic activity is related to immunotherapy. Current cancer immunotherapy focuses on the blockade of two important immune checkpoints - cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death receptor-1 (PD-1) and its ligand PD-L1. Both checkpoints are expressed on immune cells, with the ligand PD-L1 also being expressed by tumor cells, and result in an inhibition of immune response.[73,74] Although checkpoint inhibitors have been a major focus of drug development, only approximately 1-25% of patients with solid tumors – depending on the tumor type – respond to checkpoint blockade.

Among all breast cancer subtypes, triple-negative breast cancers demonstrate the highest levels of genomic instability, production of neo-antigens/immunogenicity, increased PD-L1 expression, and tumor infiltrating lymphocytes.[75] Checkpoint inhibitors targeting PD-L1 are currently FDA-approved in combination with chemotherapy for unresectable locally advanced or metastatic triple-negative breast cancer with positive PD-L1 expression. Treatment combinations including immune checkpoint inhibitors are currently under investigation in clinical trials for other breast cancer subtypes including hormone-receptor positive or HER2-positive and earlier stage disease.[76] Inflammatory changes are important side effects of immune checkpoint inhibitors including mucositis, colitis, pneumonitis, thyroiditis, pancreatitis and other sites of inflammation, which require specific attention regarding the interpretation of FDG-PET.[77]

Important pitfalls in FDG-PET imaging for evaluation of metastatic disease in breast cancer patients are related to systemic inflammatory diseases, in particular the presence or development of sarcoidosis and sarcoid-like reactions. Sarcoidosis is an autoimmune disorder and chronic inflammatory disease characterized by the formation of non-necrotizing granulomas that can affect multiple organs throughout the body. Histopathology shows the concentric accumulation of $CD8^+$ and $CD4^+$ T lymphocytes, B lymphocytes, monocytes, mast cells, and fibroblasts, which in turn are surrounded by lamellar rings of hyaline collagen. $CD4^+$ lymphocytes and activated macrophages express glucose transporters in the cell membrane, particularly GLUT-1 and GLUT-3, similar to neoplastic cells, resulting in increased FDG accumulation on FDG-PET.[78] Sarcoidosis can essentially affect any organ but the lungs are most frequently involved. Noteworthy, patients with sarcoidosis can develop breast cancer and breast cancer patients can develop sarcoidosis, which represents an important aspect in the differential diagnosis of hypermetabolic findings on FDG-PET in the evaluation of metastatic disease.

Sarcoid-like reactions are characterized by non-necrotizing granulomas with otherwise no signs or symptoms of sarcoidosis. Kendy et al. have shown several cases with sarcoid-like reactions.[79] in a variety of solid organ malignancies, including breast cancer. Sarcoid-like reactions may result in hypermetabolic

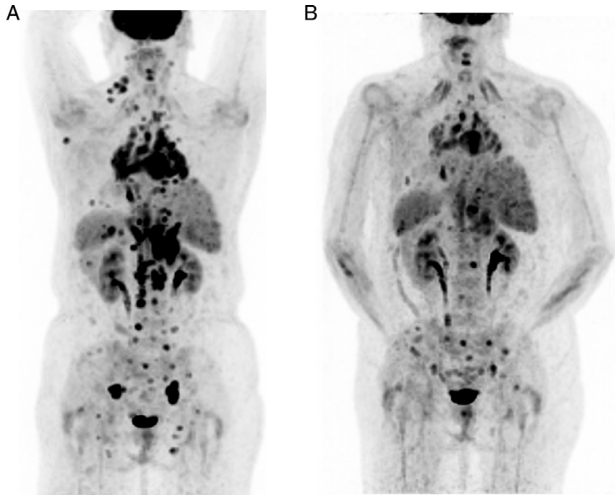


**Figure 8** 59-year-old female with left invasive breast cancer with lobular and ductal features also involving left axillary lymph nodes. She received chemoradiation but developed relapsed disease and ultimately underwent bilateral mastectomy. Additional past medical history included sarcoidosis. Maximum intensity projection PET image (A) showed extensive bulky hypermetabolic mediastinal and abdominopelvic lymph nodes. Given the concern for development of relapsed metastatic disease versus lymphoma, biopsies of the hilar, abdominal, and omental lymph nodes were taken. Pathology from all biopsied sites was consistent with non-necrotizing granulomas. Final diagnosis was drug-induced sarcoid reaction likely to trastuzumab. After discontinuation of trastuzumab, follow up PET 6 months later (B) showed interval improvement in the lymphadenopathy at all sites.

activity on FDG-PET resulting in false positive findings as shown in Figure 8. The radiographical pattern of disease is not distinctive between sarcoidosis and sarcoid-like reactions. The most frequent appearance is characterized by nearly symmetrical increase in metabolic activity within bilateral hilar and mediastinal lymph nodes. Additional sites of hypermetabolic lymphadenopathy include abdominal, pelvic, and inguinal nodes, as well as the spleen and lung parenchyma.[80] Importantly, sarcoid-like reactions can occur in lymph nodes draining a malignant tumor. Sarcoid-like reactions after antineoplastic therapy can occur up to several years after treatment.[78]

There are exciting new developments in the clinical availability of PET tracers for breast cancer in the United States. The FDA has approved F-18 fluoroestradiol (FES) for detection of estrogen receptor positive lesions via PET imaging as an adjunct to biopsy in patients with recurrent or metastatic breast cancer.[81] Estrogen receptor expression in breast cancer is an important treatment target and used in endocrine therapies. The recommended activity for intravenous injection is 222 MBq (6 mCi), with a range of 111 MBq to 222 MBq (3 mCi to 6 mCi) with a start time for image acquisition of approximately 80 minutes. F-18 Fluoroestradiol distributes primarily to hepatobiliary system, and also to small and large intestines, heart wall, blood, kidney, uterus and bladder.[82] Importantly, drugs such as tamoxifen and fulvestrant block the estrogen receptor and may reduce the uptake of fluoroestradiol in metastases. In metastatic disease it is often not possible to assess the estrogen receptor expression of individual metastases. In conjunction with FDG PET or other standard imaging, FES PET can be used to assess heterogeneity in estrogen receptor expression and identify sites that have lost estrogen receptor expression or functionality. The high tracer accumulation within the liver is a certain limitation in the evaluation of estrogen receptor expression in liver metastases.

## Conclusions

In summary, the FDG-PET variants and pitfalls in breast cancer imaging are described. This includes the underlying molecular tumor characteristics and altered cell signaling pathways regulating the level of tumor glucose metabolism. Benign findings, inflammatory changes and secondary neoplastic processes need to be considered in the interpretation of FDG-PET.

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## Conflict of Interest

The authors declare no conflict of interest.

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