



Baseline FDG PET-CT imaging is necessary for newly diagnosed inflammatory breast cancer patients: a narrative review

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Objective: To review and discuss the rationale behind performing baseline 18-fluorodeoxyglucose positron emission tomography-computed tomography imaging for staging of inflammatory breast cancer patients.

Background: In the past three decades, the epidemiology of inflammatory breast cancer has resulted in separation of this entity from other breast cancer in staging and treatment. Advances in cancer imaging from 18-fluorodeoxyglucose positron emission tomography to 18-fluorodeoxyglucose positron emission tomography-computed tomography have now allowed for anatomic and functional correlation in evaluating extent of disease in cancer patients. Furthermore, studies throughout the past two decades have highlighted how 18-fluorodeoxyglucose positron emission tomography-computed tomography may play a role in staging inflammatory breast cancer patients given the uniqueness of this entity when compared to other breast cancers.

Methods: Narrative overview of the literature summarizing findings in the literature from searches in computerized databases and authoritative texts. The use of 18-fluorodeoxyglucose positron emission tomography-computed tomography with respect to regional nodal staging and distant metastasis detection in inflammatory breast cancer patients is reviewed. In addition, an overview of studies conducted to date comparing the sensitivity and specificity of 18-fluorodeoxyglucose positron emission tomography-computed tomography for baseline staging in inflammatory breast cancer patients is also provided. Therapeutic influences and effect on overall survival is discussed.

Conclusions: Baseline 18-fluorodeoxyglucose positron emission tomography-computed tomography allows for more optimal nodal staging, which has implications in prognosis and treatment of inflammatory breast cancer patients. It also allows for improved detection of metastasis on baseline presentation allowing therapy to potentially target these additional sites of disease.

Keywords: Inflammatory breast cancer (IBC); fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT); staging

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Introduction

Inflammatory breast cancer (IBC) is a rare and very aggressive type of locally advanced breast cancer with poor prognosis (1). The frequency of IBC in the United States is approximately 1–5% of all diagnosed breast cancers (1)

with newly diagnosed IBC patients being over 20% more likely to have distant metastasis at the time of diagnosis compared to 5% of non-IBC patients (2). It is characterized clinically by its rapid onset of skin erythema (peau d'orange) and breast edema. IBC tends to affect younger age groups in women and is often hormone receptor negative, thereby

limiting treatment with hormonal therapies (1). IBC represents a distinct entity amongst all other breast cancers. The purpose of this paper is to review the current literature on the added benefit of FDG PET-CT evaluation in the initial staging of inflammatory breast cancer patients.

We present the following article in accordance with the Narrative Review reporting checklist (available at <https://dx.doi.org/10.21037/cco-21-82>).

Standard of practice

Current imaging modalities available for detection and staging of all breast cancer, including IBC, include mammography (with or without tomosynthesis), contrast-enhanced mammography, breast and nodal basin ultrasound, breast magnetic resonance imaging (MRI), molecular breast imaging (MBI), contrast enhanced computed tomography (CT) of the chest, abdomen and pelvis, 18-fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT), and bone scan.

The current guideline for staging of all invasive breast cancer patients with radiological tests, published by the National Comprehensive Cancer Network (NCCN), recommends bilateral diagnostic mammography, ultrasound as necessary, and optional breast MRI with special consideration in patients who have mammographically occult malignancy (3). For patients with IBC, the recommendations remain similar with the addition of bone imaging (bone scan or sodium fluoride PET-CT) and contrast enhanced CT chest, abdomen and pelvis both as category 2B recommendations. Category 2B recommendation is defined as “based upon lower level evidence, there is NCCN consensus the intervention is appropriate” (3). FDG PET-CT is noted to be optional with the added note that it “may be performed at the same time as a diagnostic CT, is most helpful when standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease and may also be helpful in identifying unsuspected regional nodal disease and/or distant metastasis in locally advanced breast cancer when used in addition to standard staging studies” (3).

Objectives

The purpose of this paper is to review the current literature on the added benefit of FDG PET-CT evaluation in the initial staging of inflammatory breast cancer patients. We present the following article in accordance with the

narrative review reporting checklist.

Narrative search question: What is the basis for including FDG PET-CT in the baseline staging of IBC patients? Specifically, how does baseline FDG PET-CT compare to conventional staging of regional lymph nodes and distant metastasis? How do baseline FDG PET-CT findings affect treatment decisions?

Methods

A literature search was conducted using the electronic databases PubMed, GOOGLESCHOLAR, and Medline to identify publications on the topic of imaging examinations in staging of inflammatory breast cancer. Retrospective and prospective English-language papers published through the years 2000–2021 were included.

PET/CT exam

The use of FDG uptake in imaging patients with cancer has been well established. The advantage of FDG imaging is characterized by its ability to provide functional imaging based upon the knowledge that tumor cells tend to express transport proteins with greater affinity for glucose compared to normal cells, with greater influx of glucose into tumor cells (4,5). Once in the tumor cells, FDG undergoes enzymatic changes resulting in trapping of FDG within the tumor cells causing greater uptake on imaging exams. FDG PET images can be evaluated semi-quantitatively for increased uptake with a standardized uptake value (SUV) (4,6). The SUV reflects the degree of FDG uptake within a volume of interest (7). Traditionally, FDG PET imaging was performed as a strictly functional imaging exam; however, in the late 1990s, FDG PET-CT was introduced allowing co-registration of FDG PET images and CT images allowing for more accurate anatomic correlation (4,8,9). Typical scanning protocols involve imaging beginning 60 minutes after intravenous FDG injection with CT and PET imaging performed independently and subsequently fused (7). Patients generally fast for at least 4 to 6 hours prior to the exam. Imaging extends from the vertex or base of the skull to the mid-thigh unless otherwise clinically indicated. In some cases, SUV cutoff values of 2–2.5 have been described for differentiating benign from malignant lesions (4,10,11).

Previous studies evaluating the use of imaging examinations characterized by FDG uptake in breast cancer patients have demonstrated that within the breast, FDG uptake of breast cancer depends on the histologic and

biologic characteristics of the tumor (7,12–17). For example, studies have demonstrated milder uptake in ductal carcinoma *in situ* and invasive lobular carcinoma compared to invasive ductal carcinoma, and higher uptake with grade 3 tumors compared to grade 1 and 2 tumors (7,12–18). Lack of FDG uptake in the breast does not exclude the presence of breast malignancy, especially noninvasive malignancy or well-differentiated primary breast cancers such as DCIS, tubular carcinoma and invasive lobular carcinoma (4,10,17,19,20). And while FDG PET-CT has demonstrated 96–100% sensitivity for the diagnosis of the primary breast tumor in IBC patients, it has also demonstrated false positive findings particularly in cases of mastitis where SUV values were elevated and unable to reliably differentiate between malignancy and inflammation (21,22). In addition, limited spatial resolution also limits detection of small lesions. In a retrospective review performed by Carkaci *et al.*, most false negative findings on FDG PET-CT involved small lesions <1.3 cm (19). Therefore, FDG PET-CT is not routinely used in staging work-up of stage 1 or early stage 2 breast cancer patients (19). As such, the existing dedicated breast imaging examinations are utilized to evaluate local disease in the breast, however studies have shown a role for FDG PET-CT in evaluating locoregional disease, specifically within the nodal basins and distant metastasis.

Regional nodal staging

Axillary nodal status is an important prognostic factor in IBC as it is a predictor of survival outcome (23). Axillary nodal metastasis is associated with shorter disease-free and overall survival compared to patients without nodal disease (24–26). Axillary nodal disease has been reported in 55–85% of IBC patients at initial staging (27). Preoperative radiologic staging is routinely performed using ultrasound. In 2009, Alberini *et al.* published the largest prospective study at the time evaluating FDG PET-CT in the staging and prognosis of patients with suspected IBC which highlighted advantages of FDG PET-CT in regional nodal staging (21). In the study's population of 59 IBC patients, 12% of the patients were found to have axillary nodal metastasis demonstrated by PET-CT which was not suspected by clinical examination and an additional 56% of patients were noted to have extra-axillary lymph node metastasis diagnosed by PET-CT (only 5/33 patients with extra-axillary lymph node metastasis were detected by clinical examination and confirmed with FNA upon detection) (21). Extra-axillary was defined as retropectoral,

infraclavicular, supraclavicular and internal mammary nodal basins/regions (21).

A retrospective study published in the same year by Carkaci *et al.* demonstrated high sensitivity of FDG PET-CT in diagnosing regional nodal metastasis with 37/41 (90%) of ipsilateral axillary metastasis and 18/41 (44%) of subpectoral metastasis detected on FDG PET-CT (19). In addition, 22% of the patients had internal mammary and 15% had supraclavicular nodal disease (19). Given the variability of the appearance of lymph nodes on sonography and CT examinations, FDG PET-CT proves invaluable in providing functional evaluation of the regional nodal basins in IBC patients. A subsequent 2012 retrospective study by Carkaci *et al.* found that evaluating the SUVmax of regional lymph nodes on FDG PET-CT may help quantitatively differentiate benign from malignant nodes in IBC patients with a SUV cutoff value of 2.0 demonstrating a sensitivity of 89% and specificity of 99% in diagnosing metastatic disease for this cohort (24).

Although regional nodal staging is most commonly done by ultrasound; there is great variation amongst institutions on the evaluated regions and management. While some practices may evaluate the ipsilateral axillary level I region, others may evaluate bilateral regional nodal basins on baseline ultrasound staging of IBC patients. Additionally, regardless of the nodal basins evaluated, inter-operator variability may exist with ultrasound examination. As such, FDG PET-CT provides advantages by standardizing staging in patients who may have extra-axillary or contralateral nodal metastasis which may otherwise be undetected. It is important to note that as yet, FDG PET-CT has not been able to completely replace sonographic staging as small axillary metastasis, including micrometastases may be missed on FDG PET-CT due to the limited spatial resolution (7,19). However, as uptake also relies on FDG avidity and other non-imaging related parameters (such as respiratory motion), in certain favorable conditions, smaller (<1 cm) lesions may still be detected (7).

Distant metastasis

IBC patients presenting with distant metastasis are treated with primary systemic therapy to achieve local response and subsequently evaluated for potential surgery and radiation therapy (28). Identifying metastatic disease may lead to local treatment of the metastatic lesion or changes in systemic therapy (29,30). Therefore, optimizing treatment for IBC patients requires identification of distant metastasis at

baseline staging.

In the 2009 prospective study by Alberini *et al.*, FDG PET-CT suggested distant metastasis in 31% of patients (18/59 patients) with only 6 of them demonstrated by routine workup (21). Sites of distant metastasis included the mediastinum, bone, liver, lung, contralateral axilla, peritoneum/ovary, cervical nodes and contralateral breast (21). This study was further corroborated by the 2009 retrospective review by Carkaci *et al.* of 41 IBC patients who underwent staging FDG PET-CT which found 20/41 patients (49%) to have distant metastasis on initial staging FDG PET-CT (19). The most common sites of metastasis were found to be mediastinal lymph nodes (24%), bone (22%), and liver (15%) (19). Contralateral nodal metastasis was also demonstrated in 17% of patients (19). Less common sites of metastasis included pulmonary metastasis (5%) and abdominal nodal metastasis (7%) (19). Additionally, in this study, 7/41 (17%) of the patients were not suspected of having metastasis clinically or on baseline imaging (19).

Similar findings were noted in a subsequent 2013 prospective study by Groheux *et al.* of 117 patients comparing FDG PET-CT performance with conventional work-up (bone scan, chest radiograph/chest CT, abdominal ultrasound/CT abdomen) in patients with locally advanced or inflammatory breast cancer (31). Overall, FDG PET-CT was noted to change the stage in 52% of patients with the stage modified more frequently (46%) in patients with IBC compared to noninflammatory locally advanced breast cancer (33%), though this was not found to be statistically significant (31). In this same study, all patients with osseous metastasis on bone scan were also positive on FDG PET-CT with FDG PET-CT also finding an additional 7 cases of osseous metastasis seen solely on FDG PET-CT (31). Additionally, while prior studies have demonstrated lower SUV values in osteoblastic metastasis thereby limiting evaluation on traditional FDG PET studies without anatomic correlation, as the blastic features are visible on traditional CT, the hybrid FDG PET-CT scan can outperform bone scan (31).

Comparative analysis

Osseous metastasis has been traditionally described as the most common site of distant disease in breast cancer (32). These metastatic lesions may be lytic, blastic, or a combination of both. Several studies have demonstrated PET/CT to be superior to bone scan in detecting lytic metastasis

(33–40) (*Figure 1*).

In a 2008 prospective study by Fuster *et al.*, preoperative staging of 60 patients with large primary breast cancer with FDG PET-CT compared to conventional imaging procedures (chest CT, liver ultrasound, and bone scan) demonstrated the sensitivity and specificity for FDG PET-CT in detecting axillary nodal metastasis to be 70% and 100%, respectively (41). In the same study, the sensitivity and specificity of FDG PET-CT in detecting distant metastasis was 100% and 98% respectively, compared to sensitivity of 60% and specificity of 83% with conventional imaging, with FDG PET-CT leading to a change in initial staging of 42% of patients (41). It is important to note that this study was not solely conducted on IBC patients and did not utilize CT abdomen in evaluating for abdominal metastases. However, given the relatively higher percentages of regional nodal metastasis and distant metastasis present in IBC patients, the sensitivity of FDG PET-CT in IBC patients is hypothesized to be higher (*Figure 2*).

In a subsequent retrospective study of 225 patients with primary breast cancer by Niikura *et al.* in 2011, even when eliminating patients with stage IV disease, the sensitivity and specificity of FDG PET-CT compared to conventional staging modalities (contrast enhanced CT, US, radiography and bone scan) was 96% and 91%, respectively compared to 84% and 67%, respectively (42). In addition, the sensitivity and specificity of FDG PET-CT compared to bone scan for detecting osseous metastasis was 98% and 96%, respectively compared to 76% and 86% (42). With respect to hepatic metastasis, FDG PET-CT and abdominal CT performed similarly with FDG PET-CT demonstrating a sensitivity and specificity of 100% and 99%, respectively, compared to 100% and 95%, respectively, for abdominal CT (42).

Therapeutic influences and survival

Radiation therapy plays a key role in treatment of IBC as patients diagnosed with IBC without evidence of distant metastasis generally receive systemic chemotherapy followed by mastectomy with axillary node dissection and adjuvant radiation therapy (23). It is important to adequately stage IBC patients on baseline imaging to identify involved regional nodal basins so post mastectomy radiation therapy can treat surgically resected and unresected nodal basins (23,43). In a retrospective study of 62 patients by Walker *et al.* in 2012, findings of FDG PET-CT led to changes in post mastectomy radiation therapy for IBC patients in 17.7% of patients (44). Potential changes to standard post

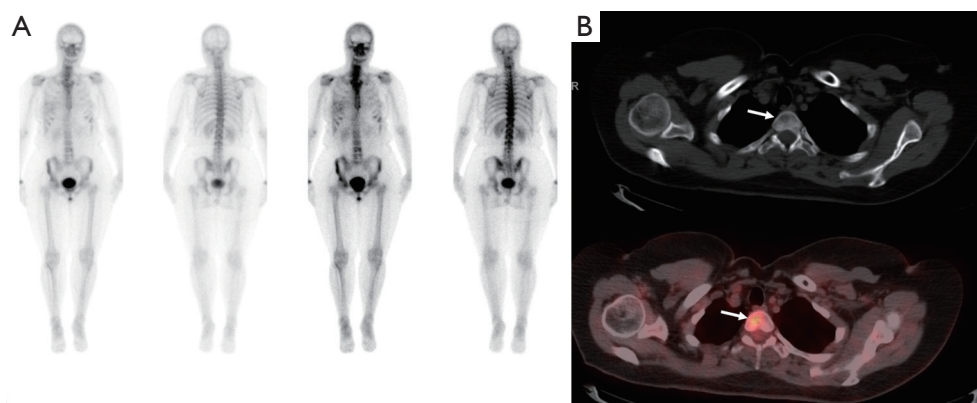


Figure 1 Supplemental case of a 54-year-old female with newly diagnosed right inflammatory breast cancer. (A) Bone scan performed at the time of diagnosis demonstrates focus of increased activity in the right 8th rib and increased uptake in the right sacroiliac joint/iliac crest with no uptake in the spine. The patient subsequently underwent CT chest and abdomen with contrast (not pictured) demonstrating no evidence of osseous metastasis. (B) FDG PET-CT demonstrates focal lytic T2 vertebral body abnormality with increased FDG uptake (arrows) suspicious for metastasis which was confirmed on subsequent MRI thoracic spine with contrast.

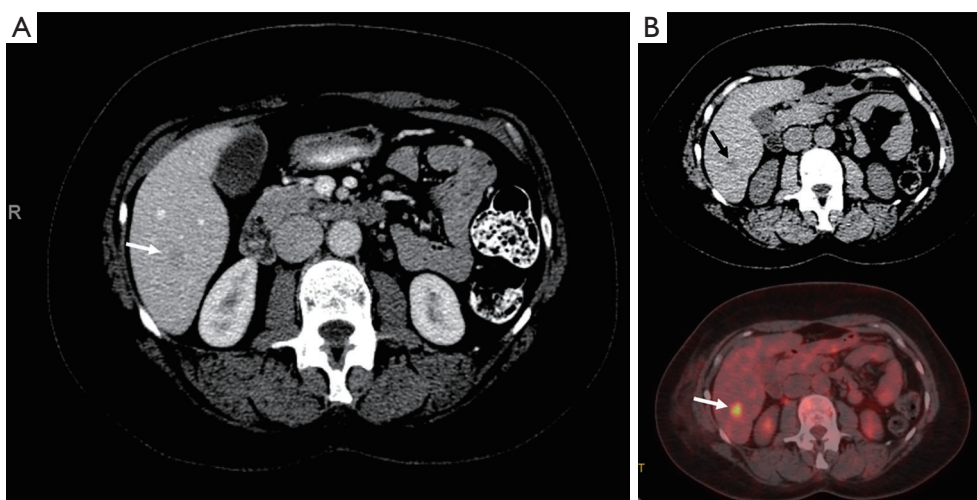


Figure 2 Supplemental case of a 54-year-old female with newly diagnosed right inflammatory breast cancer. (A) CT chest, abdomen and pelvis with contrast noted a subtle hypoattenuating lesion (arrow) in the posterior right hepatic lobe only seen on one slice, difficult to characterize. Additional correlation with MRI was recommended. (B) FDG PET-CT demonstrates the same focal hypoattenuating lesion in the posterior right hepatic lobe (black arrow) with associated FDG uptake (white arrow), maximum SUV 7.7, consistent with metastasis.

mastectomy radiation therapy may include modification to the radiation field design and radiation dose prescription (44). This retrospective study dedicated to IBC patients also found that, similar to the retrospective comparative analysis studies described above, FDG PET-CT found new areas of disease in 44% of patients which were not appreciated by routine imaging (44). In addition to nodal involvement, the extent of pretreatment skin involvement plays a role in determining

post mastectomy radiation treatment (23). As IBC is noted to infiltrate the dermal lymphatics, it can present with a high risk of local recurrence (23). Baseline pre-treatment imaging of skin involvement may also play an important role in differentiating from post-radiation therapy skin thickening.

Thus far, survival benefits of changes in radiation plans due to FDG PET-CT in IBC patients has not been demonstrated. However, previous studies have

demonstrated that the use of FDG PET-CT in IBC patients showed improved relapse-free survival (45).

Limitations

One limitation of all studies performed to date is that not every site of presumed metastasis detected on FDG PET-CT was biopsy proven. Corroboration with pathology and additional imaging modalities, for example MRI if indicated, was attempted. It is important to note that even in a prospective trial, it may simply not be feasible to biopsy every possible metastatic site detected on FDG PET-CT. An additional limitation is in performing comparative analysis between FDG PET-CT and baseline staging, there is institutional and provider variation on what baseline exams were performed. While some patients may have received CT chest and a hepatic ultrasound, others may have received CT chest, abdomen, and pelvis.

Limitations of FDG PET-CT in evaluation for metastasis must also be noted. One limitation of FDG PET-CT is brain metastasis due to the baseline high uptake in the brain (31). In such situations, dedicated brain imaging with CT or MRI is recommended. An additional limitation of FDG PET-CT is evaluation of pulmonary metastasis given lack of sensitivity for small nodules especially considering respiratory motion and partial volume effects (31).

Future research

Thus far, the literature has demonstrated value in adding baseline staging FDG PET-CT for IBC patients, particularly in the realm of nodal staging, distant metastasis, and affecting post mastectomy radiation therapy. Prospective comparative studies evaluating the performance of current baseline imaging examinations to include contrast enhanced CT chest, abdomen and pelvis compared to FDG PET-CT specifically in IBC patients have yet to be performed. Further cost analysis in such a study may ultimately lead to changes in staging recommendations. From this, it may even be of added benefit to consider starting with FDG PET-CT in patients already diagnosed with IBC prior to additional mammographic or sonographic evaluation to reduce imaging time and further reduce cost of imaging examinations and shorten the time from diagnosis to treatment. Further evolution to include contrast enhanced FDG PET-CT and PET/MR may have added value in the staging of IBC patients. Ultimately, prospective studies

assessing the use of baseline FDG PET-CT and the effect on overall survival would be highly beneficial.

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