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^{18}F-Labeled Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography in Staging and Restaging Patients With Breast Cancer

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To plan optimal management in a patient with breast cancer (BC), accurate baseline staging and early detection and staging of recurrence are necessary.[1-3] Representatives from the European Association of Nuclear Medicine (EANM) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) recently published the joint European-American guidelines on the role of 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography ([^{18}F]FDG-PET/CT) in no special type (NST) BC, endorsed by several other imaging and clinical societies: the American College of Radiology (ACR), European Society of Surgical Oncology, European Society for Radiotherapy and Oncology (ESTRO), European Society of Breast Imaging, European Society of Radiology, and European Society of Breast Cancer Specialists (EUSOMA).[1] Considering the low [^{18}F]FDG-avidity in invasive lobular carcinoma (ILC), the EANM-SNMMI guidelines focused on NST BC. Guidelines from clinical societies such as the American National Comprehensive Cancer Network (NCCN),[4] European Society for Medical Oncology (ESMO),[5-7] and Advanced Breast Cancer (ABC) international consensus guidelines[8] also evaluate imaging techniques, but they include all histological subtypes of BC. There is a lack of consistency in the optimal utilization of [^{18}F]FDG-PET/CT among published guidelines. This manuscript summarizes available evidence, emphasizes the value of [^{18}F]FDG-PET/CT for staging and restaging of patients with BC, and highlights agreements and discrepancies among international guidelines.

I—Baseline Evaluation in Patients With Early-Stage Breast Cancer and Locally Advanced Breast Cancer (ABC)

[^{18}F]FDG-PET/CT is not aimed at evaluation of primary breast malignancy and axillary nodal metastases, which are better evaluated by mammography, ultrasound, magnetic resonance imaging (MRI), and sentinel lymph node biopsy as needed.[9-11] However, [^{18}F]FDG-PET/CT has high accuracy in detecting extra-axillary lymph nodes and distant metastases, especially in case of locally advanced breast cancer (LABC) or inflammatory BC,[12-18] allowing simultaneous evaluation of locoregional and distant metastases in a single whole-body scan. More recently, several studies have also shown that [^{18}F]FDG-PET/CT may be useful not only in patients with LABC but also in intermediate-risk patients,[19-35] and some studies offered information on costs, radiation dose, or change in management in comparison with conventional staging. A prospective, randomized, multi-institutional trial of [^{18}F]FDG-PET/CT versus CT and bone scan analyzed 369 patients with stage IIB or III NST BC[35] and demonstrated that [^{18}F]FDG-PET/CT identified more distant metastases, upstaging 12% more patients (23% *v* 11%) to stage IV.[35] Ko et al[33] observed that the overall upstaging rate with [^{18}F]FDG-PET/CT compared with conventional imaging modalities was 0% for stage IIA, 13% for stage IIB (10/79), 22% for stage IIIA (9/41), 17% for stage IIIB (5/30), 37% for stage IIIC (3/8), and 14% (27/196) for stage IV. [^{18}F]FDG-PET/CT had comparable costs to conventional imaging modalities and resulted in lower radiation dose exposure.[33] US Medicare reimbursement rates were $1,604.37 for [^{18}F]FDG-PET/CT and $1,679.94 for the combination of conventional imaging modalities.[33] A multicenter study by Hyland et al[34] compared [^{18}F]FDG-PET/CT with standard of care (SoC; chest, abdominal and pelvic CT and bone scan) and found that [^{18}F]FDG-PET/CT reduced false-positives by half, minimized the work-up for incidental findings, and allowed earlier treatment initiation.

Furthermore, [18F]FDG-PET/CT was cost effective, and at one institution, cost saving.[34] The mean cost per patient was $1,132 (SoC) versus $1,477 (PET/CT) using the US Medicare Physician Fee Schedule, with an incremental cost-effectiveness ratio (ICER) of $31. Using representative reimbursements to the University of California San Francisco, the mean cost per patient was $1,236 (SoC) versus $1,073 (PET/CT) for Medicare and $3,083 (SoC) versus $1,656 (PET/CT) for a private payer, with ICERs of −$15 and −$130, respectively.[34] However, differences in reimbursement vary widely.

Per ESMO guidelines, asymptomatic distant metastases are rare in early BC, and most patients do not benefit from systemic staging.[5] Staging, including chest CT, abdominal imaging (ultrasound, CT or MRI), and bone scan, can be considered for patients with clinically positive axillary nodes; large tumors (≥T3); aggressive biology; clinical signs/symptoms suspicious for metastases; or laboratory values suggesting metastases.[5] [18F]FDG-PET/CT may be used instead of CT and bone scan, particularly for high-risk patients and when conventional methods are inconclusive.[5] ABC 6 and 7 guidelines recommend [18F]FDG-PET/CT for staging of all subtypes except ILC.[8] In NCCN guidelines, routine systemic staging is not indicated for localized invasive, non-inflammatory M0 BC. However, before preoperative systemic therapy, in the case of T ≥T2 or cN+ disease (whatever the BC subtype) or T1c N0 (ie, stage I with a primary tumor >1 cm) for human epidermal growth factor receptor 2–positive (HER2+) BC or triple negative breast cancer (TNBC), an additional work-up can be considered if clinically indicated[4] (Table 1). In the case of inflammatory BC, systemic staging is recommended, with the combination of conventional imaging modalities (Table 1). For NCCN, "[18F]FDG-PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious. [18F]FDG-PET/CT may be helpful in identifying unsuspected regional nodal disease and/or distant metastases when used in addition to standard staging studies."[4] For patients undergoing primary surgery, NCCN recommends consideration of imaging for systemic staging in the case of four of more positive axillary nodes, including the combination of conventional imaging modalities with [18F]FDG-PET/CT as optional.[4]

The recent EANM-SNMMI guidelines now recommend [18F]FDG-PET/CT (instead of, and not in combination with, conventional imaging modalities) for patients with stage IIB (T2N1 and T3N0) BC or higher stages. This recommendation is based on studies showing [18F]FDG-PET/CT changes stage in almost 21% of patients with stage IIB BC.[1] In stage IIA, [18F]FDG-PET/CT is reserved for specific cases, and in stage I BC, [18F]FDG-PET/CT is not recommended, regardless of subtype. Although [18F]FDG-PET/CT has some limitations for low-proliferation, low-grade, and/or well-differentiated luminal tumors, [18F]FDG-PET/CT imaging might be useful for initial NST BC staging, regardless of tumor subtype and tumor grade. In a prospective study of 254 patients,[25] the rate of distant metastases was not related to tumor grade or receptor phenotype, as also found in other studies.[28,30,31] Importantly, however, the location of metastases differed according to primary tumor subtype: extraskeletal metastases were more prevalent in HER2+ BC and TNBC.[25] In contrast to the NCCN guidelines, the EANM-SNMMI guidelines do not require that [18F]FDG-PET/CT show consistent bone findings on both PET and CT components to avoid a bone scan or [18F]NaF PET/CT (Table 1). Morphological changes occur after metabolic changes, and an [18F]FDG-avid hypermetabolic focus with normal bone on CT images is highly suspicious for early bone/bone marrow metastasis.[9,36]

Takeaway Point 1

The recent EANM-SNMMI guidelines recommend [18F]FDG-PET/CT for patients with stage IIB or higher NST BC. Most clinical guidelines suggest systemic imaging for baseline staging of nonmetastatic BC if clinically indicated. Once a decision to perform systemic imaging is made, [18F]FDG-PET/CT may be better than conventional CT/bone scan for NST BC whatever the subtype (TNBC, HER2+ and estrogen receptor [ER]+/HER2−). The cost of staging with [18F]FDG-PET/CT was not significantly different than the combination of conventional imaging modalities.[33,34] Because of inconstant [18F]FDG uptake in ILC, the usefulness of [18F]FDG-PET/CT is limited for this histology.

II—Work-Up for Metastatic Disease, Suspected Recurrence, and Response Evaluation

[18F]FDG-PET/CT has better performance than conventional imaging for detecting distant metastases.[37,38] In 154 consecutive patients, the sensitivity and specificity for detecting distant metastases by [18F]FDG-PET/CT versus conventional imaging were 100% versus 61.5% and 96.4% versus 99.2%, respectively.[37] [18F]FDG-PET/CT has high sensitivity for identifying BC recurrence[39–54] and offers a whole-body approach to determine the extent of disease, improving prognostic stratification by distinguishing patients with isolated locoregional recurrence from those with distant metastases.[51,53] Five meta-analyses showed the high performance of [18F]FDG-PET(/CT) to detect recurrent BC.[55–59] In one meta-analysis, MRI and [18F]FDG-PET(/CT) were more effective than ultrasound and CT,[56] and in another, [18F]FDG-PET/CT had significantly higher sensitivity than CT, whereas the difference in specificity was not significant.[57]

In clinical stage IV BC, EANM-SNMMI recommend [18F]FDG-PET/CT for determining the precise extent of metastatic disease and to improve treatment planning.[1] Similar to earlier stages, [18F]FDG-PET/CT should be done instead of, and not in addition to, conventional imaging.[1] In the detection of recurrence, EANM-SNMMI recommend [18F]FDG-PET/CT when conventional imaging methods are equivocal, in patients with signs or symptoms suggestive of metastatic

TABLE 1. Summary of the Recommendation of the EANM-SNMMI, NCCN, ESMO, and ABC Considering Imaging Modalities to be Used in the Staging and Restaging of Patients With Breast Cancer Based on AJCC Stage According to the Clinical TNM Classification

Clinical Scenario	EANM-SNMMI[a]	NCCN[b]	ESMO[c]	ABC 6 and 7[d]
Baseline systemic staging in M0 patients	Stage I: [^{18}F]FDG-PET/CT is not recommended[1] Stage IIA: [^{18}F]FDG-PET/CT is optional[1] Stage IIB-III: [^{18}F]FDG-PET/CT is recommended[1]	Imaging recommendations for localized invasive noninflammatory M0 breast cancer[4] Diagnostic bilateral mammogram Ultrasound as necessary Breast MRI (optional) Consider additional imaging studies only in the presence of signs and symptoms of metastatic disease and for patients who are clinically high risk For patients undergoing preoperative systemic therapy, additional imaging tests to consider as clinically indicated, for T >cT2 or cN+, or cT1c cN0 HER2+ BC or cT1c cN0 TNBC[4] Chest diagnostic CT ± contrast Abdomen ± pelvis diagnostic CT with contrast or MRI with contrast Bone scan or sodium fluoride PET/CT [^{18}F]FDG-PET/CT[e] For patients undergoing primary surgery, consider imaging for systemic staging of patients with four or more positive axillary LNs, including chest/abdomen ± pelvis diagnostic CT with contrast, bone scan, and optional [^{18}F]FDG-PET/CT[4] For inflammatory BC [4] Chest diagnostic CT ± contrast Abdomen ± pelvis diagnostic CT with contrast or MRI with contrast Bone scan or [^{18}F]FDG-PET/CT[f]	Assessment of distant metastases is recommended only in patients with stage IIB and higher disease (especially with extended LN involvement), patients with a high risk of recurrence at first diagnosis, and/or symptomatic patients[5] Staging, including chest CT, abdominal imaging (US, CT or MRI), and bone scan, can be considered for patients with: clinically positive axillary nodes; large tumors (≥T3); aggressive biology; clinical signs/symptoms suspicious for metastases; or laboratory values suggesting metastases[5] [^{18}F]FDG-PET/CT may be may be used instead of CT and bone scan particularly for high-risk patients and when conventional methods are inconclusive[5]	Minimal staging work-up for ABC includes a history and physical examination, hematology and biochemistry tests, and imaging of the chest, abdomen, and bone with CT + bone scan or [^{18}F]FDG-PET/CT (instead of and not in addition to CT and bone scan)[8] [^{18}F]FDG-PET/CT is the preferred imaging for the staging of all subtypes except invasive lobular cancers, as it is more sensitive and may up-stage inflammatory and locally advanced cancers in up to 52% of cases, detecting one third more metastases[8] In ILC, CT and bone scan or whole-body MRI are preferred
Stage IV BC: Assessing recurrence and Restaging	Stage IV: [18F]FDG-PET/CT is recommended[1] Restaging and Assessing recurrence: [^{18}F]FDG-PET/CT is recommended when CM are equivocal and when there is clinical or laboratorial suspicion of recurrence[1]	For systemic staging of stage IV or recurrent BC Chest diagnostic CT ± contrast Abdomen ± pelvis diagnostic CT with contrast or MRI with contrast Brain MRI with contrast if suspicious CNS symptoms Spine MRI with contrast if back pain or symptoms of cord compression Bone scan or sodium fluoride PET/CT Useful in certain circumstances: [^{18}F]FDG-PET/CT (consider FES-PET/CT for ER+ disease) X-rays of symptomatic bones and abnormalities on bone scan	The minimum imaging work-up for staging includes CT of the chest and abdomen and bone scan[6,7] [^{18}F]FDG-PET/CT may be used instead of CT and bone scan[6,7]	[^{18}F]FDG-PET/CT is the preferred imaging modality for the restaging of ABC of all subtypes except ILC. If recurrence is highly suspected (ie, symptoms or elevated tumor markers) and CT scan and bone scan fail to detect it, [^{18}F]FDG-PET/CT should be performed [^{18}F]FDG PET/CT should be performed to confirm oligometastatic disease Brain imaging should be done only in symptomatic patients and staging of patients with LMD should include full spine imaging with MRI with gadolinium

Abbreviations: [^{18}F]FDG-PET/CT, ^{18}F-labeled fluorodeoxyglucose-positron emission tomography/computed tomography; ABC, advanced breast cancer; BC, breast cancer; BM, bone metastases; BSS, baseline systemic staging; CM, conventional imaging modalities; EANM, European Association of Nuclear Medicine; ER, estrogen receptor; ESMO, European Society for Medical Oncology; FES, fluoroestradiol; HER2, human epidermal growth factor receptor 2; ILC, Invasive lobular carcinoma; LMD, leptomeningeal disease; LN, lymph nodes; M+, metastatic; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; NST, No Special Type; pCR, pathological complete response; PST, primary systemic treatment; SNMMI, Society of Nuclear Medicine and Molecular Imaging; TNBC, triple negative breast cancer; US, ultrasound.

[a]EANM-SNMMI guidelines are focused on no special type BC and were published in 2024.[1]

[b]NCCN "*Clinical Practice Guidelines in Oncology- Breast Cancer- Version 6.2024.*"[4]

[c]ESMO guidelines were updated in 2024 for *Early breast cancer*[5] *and ESMO guidelines for metastatic breast cancer* have been published in 2021[6] and are regularly updated on the ESMO Web site (ESMO metastatic breast cancer living guidelines[7]).

[d]ABC 6 and 7 Consensus Guidelines were published in 2024.[8]

[e]The NCCN guidelines state, "[^{18}F]FDG-PET/CT is most beneficial and accurate for advanced disease (stage III) and invasive ductal (compared to ILC) histology, but may be useful in selected circumstances of earlier stage disease (stage IIA disease: T1N1, T2N0) such as: equivocal CT + bone scan results; suspicion of undetected nodal and/or distant disease; and treatment assessment. An [^{18}F]FDG-PET/CT may be utilized as an adjunct to, or in lieu of, initial standard staging and may be performed simultaneously with diagnostic CT. Conversely, a bone scan or [^{18}F]sodium fluoride PET/CT may not be needed if an upfront [^{18}F]FDG-PET/CT clearly indicates consistent findings on both PET and CT components."[4]

[f]The NCCN guidelines state: "[^{18}F]FDG-PET/CT can be performed at the same time as diagnostic CT. [^{18}F]FDG-PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious. [^{18}F]FDG-PET/CT may be helpful in identifying unsuspected regional nodal disease and/or distant metastases when used in addition to standard staging studies."

disease, with rising serum tumor markers, to guide biopsy site, and to improve radiation therapy planning. [18F]FDG-PET/CT can substitute for CT and/or bone scan for detecting bone metastases.[1] However, [18F]FDG-PET/CT has low performance for brain metastasis detection. In general, MRI is the preferred imaging modality when suspecting CNS metastases.

For ABC 6 and 7 guidelines, [18F]FDG-PET/CT is also the preferred imaging modality for staging metastatic and recurrent BC of all subtypes, except ILC.[8] ESMO recommends CT chest-abdomen and bone scan for work-up of stage IV disease, and [18F]FDG-PET/CT may be used instead of conventional imaging.[6,7] In stage IV disease, NCCN recommends a panel of conventional imaging tools. Importantly, for all guidelines, the imaging modality chosen at baseline should be applied for disease monitoring to ensure comparability. NCCN recommends using widely accepted criteria for assessing treatment response, such as the RECIST[60] criteria and WHO criteria.[61] Unlike PET imaging, CT is recognized as an effective tool for evaluating patients included in therapeutic trials with precise, validated, and objective evaluation criteria. For NCCN, PET imaging is challenging because, unlike CT, it does not have a comparable reproducible, validated, and widely accepted set of standards for disease activity assessment.[4] For EANM/SNMMI, [18F]FDG-PET/CT may play a role in monitoring treatment response in metastatic BC and is particularly useful to assess bone metastases and enable early response to treatment evaluation. For precise and objective assessment of metastatic BC using [18F]FDG-PET/CT, EANM/SNMMI recommends using certified scanners (according to the EANM Research GmbH [EARL] or ACR/Intersocietal Accreditation Commission accreditation[62–64] and EORTC/PERCIST reporting criteria).[65,66] Prospective trials showed that disease progression was detected earlier by 18F-FDG PET/CT than by contrast-enhanced computed tomography.[67,68]

Takeaway Point 2

EANM-SNMMI recommend [18F]FDG-PET/CT for staging patients with stage IV BC and for assessing recurrent BC. However, [18F]FDG-PET/CT has low diagnostic accuracy for detecting CNS metastases. For ABC 6 and 7 guidelines, [18F]FDG-PET/CT is also the preferred imaging modality for metastatic and recurrent BC of all subtypes, except ILC. ESMO recommends conventional imaging for the work-up of stage IV disease, although [18F]FDG PET/CT may replace them. NCCN recommends a panel of conventional imaging modalities. Importantly, for all guidelines, the imaging modality chosen at baseline should be applied for disease monitoring to ensure comparability.

In conclusion, there are substantial differences among international guidelines for the optimal use of [18F]FDG-PET/CT in patients with BC.

The Joint EANM/SNMMI guidelines recommend the use of [18F]FDG-PET/CT, substituting conventional staging techniques, more often than other international guidelines. ESMO still has specific indications for [18F]FDG-PET/CT for BC and, similarly to ABC 6 and 7, specifies when it can replace conventional imaging modalities. NCCN provides less specific recommendations regarding the use of [18F]FDG-PET/CT and usually states that it is indicated/useful only in certain circumstances. The Joint EANM/SNMMI guidelines are specific to NST BC and acknowledge that accurate imaging of ILC, particularly for systemic disease, is still challenging and controversial. Because ILC is often ER-positive, [18F]fluoroestradiol (FES)-PET/CT may offer higher sensitivity compared with [18F]FDG-PET/CT for ILC.[69] In a study by Ryu et al,[70] [18F]FES-PET/CT modified the management of recurrent or metastatic BC in 139 (40%) of 344 patients. Recent studies have demonstrated that [68Ga] fibroblast activation protein inhibitor (FAPI) PET/CT outperformed [18F]FDG PET/CT in ILC.[71,72] Further studies are needed to compare and validate the diagnostic accuracy of [18F]FDG-PET/CT with [18F]FES and [18F/68Ga]FAPI-PET/CT in ILC.

The existing literature on [18F]FDG-PET/CT for BC, including prospective trials, has demonstrated the clinical value of [18F]FDG-PET/CT for staging and restaging patients with BC, particularly when compared with CT and bone scan, which are often emphasized in clinical guidelines. Harmonization of imaging and clinical guidelines is needed to improve health care delivery for patients with BC. Moreover, the position of [18F]FDG-PET/CT as complementary to conventional imaging modalities needs to be questioned. Also, inclusion of [18F]FDG-PET/CT in clinical trials should be supported.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

^{18}F-Labeled Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography in Staging and Restaging Patients With Breast Cancer

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