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18F-FDG PET/CT in breast cancer: Evidence-based recommendations in initial staging

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Abstract

Current guidelines do not systematically recommend 18F-FDG PET/CT for breast cancer staging; and the recommendations and level of evidence supporting its use in different groups of patients vary among guidelines. This review summarizes the evidence about the role of 18F-FDG PET/CT in breast cancer staging and the therapeutic and prognostic impact accumulated in the last decade. Other related aspects, such as the association of metabolic information with biology and prognosis are considered and evidence-based recommendations for the use of 18F-FDG PET/CT in breast cancer staging are offered. We systematically searched MEDLINE for articles reporting studies with at least 30 patients related to clinical questions following the Problem/Population, Intervention, Comparison, and Outcome framework. We critically reviewed the selected articles and elaborated evidence tables structuring the summarized information into methodology, results, and limitations. The level of evidence and the grades of recommendation for the use of 18F-FDG PET/CT in different contexts are summarized. Level III evidence supports the use of 18F-FDG PET/CT for initial staging in patients with recently diagnosed breast cancer; the diagnostic and therapeutic impact of the 18F-FDG PET/CT findings is sufficient for a weak recommendation in this population. In patients with locally advanced breast cancer, level II evidence supports the use of 18F-FDG PET/CT for initial staging; the diagnostic and therapeutic impact of the 18F-FDG PET/CT findings is sufficient for a strong recommendation in this population. In patients with recently diagnosed breast cancer, the metabolic information from baseline 18F-FDG PET/CT is associated with tumor biology and has prognostic implications, supported by level II evidence. In conclusion, 18F-FDG PET/CT is not recommended for staging all patients with early breast cancer, although evidence of improved regional and systemic staging supports its use in locally advanced breast cancer. Baseline tumor glycolytic activity is associated with tumor biology and prognosis.

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Introduction

Among females worldwide, breast cancer (BC) is the most frequently diagnosed cancer, with a 5-year prevalence of 31.4% and is the leading cause of cancer death, accounting for 15.5% of all cancer deaths.[1,2] The diagnosis of BC is based on clinical examination in combination with imaging and is confirmed by histopathological assessment. Imaging includes bilateral mammography and ultrasound of the breast and regional lymph nodes.

Accurate staging is important for management decisions and prognosis in patients with newly diagnosed BC. All patients with newly diagnosed BC undergo regional staging including axillary and internal mammary lymph node evaluation and those with a high risk of early distant metastases also undergo systemic staging including sites beyond the regional lymph nodes. Magnetic resonance imaging (MRI) of the breast and fluorine-18 fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) are not routinely recommended for initial staging.[3–8]

Apart from imaging, in patients with clinically positive axilla, pre-treatment disease staging includes histopathological examination of the primary tumor and cytology/histology of the axillary lymph node (ALN) specimens obtained using ultrasound-guided fine-needle aspiration biopsy or core biopsy to determine whether ALN dissection is needed. In patients with clinically negative axilla, the current standard of ALN staging in early-stage BC is sentinel lymph node biopsy.[5,6]

According to BC guidelines such as National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO), Spanish Society of Medical Oncology (SEOM), and the National Institute for Care Excellence (NICE), 18F-FDG PET/CT is not indicated in women with apparently early-stage (I or II) BC or even in those with operable stage III BC;[3–8] it is considered optional for women with suspicious or equivocal findings on CT or MRI and for women with locally advanced BC, especially those with advanced axillary nodal disease, because the risk of early distant metastases is high enough to justify systemic staging as part of the initial evaluation. In this setting, 18F-FDG PET/CT can detect metastases that are not visible on other modalities, and these findings can change treatment options. However, the levels of evidence and the recommendations for the use of 18F-FDG PET/CT vary among guidelines, basically because different guidelines use different quality evaluation scales and most are designed for the assessment of treatment-related studies rather than for diagnosis. Table 1 summarizes the current guidelines recommendations and level of evidence for using 18F-FDG PET/CT in BC staging.

Given the evolving role of 18F-FDG PET/CT in the management of BC patients and the low level of evidence for its use in initial staging reported in the guidelines, we reviewed and summarized the current evidence to offer evidence-based recommendations for the use of PET/CT in this setting.

Materials and methods

The search strategy was structured following the PICO framework, in which

- *P* stands for patient or problem: patients diagnosed with BC and initial staging prior to treatment.
- *I* stands for intervention: 18F-FDG PET or 18F-FDG PET/CT for the assessment of N (lymph nodes) and M (metastases).
- *C* stands for comparison or control: histopathology was the reference standard. Alternatively, conventional imaging (CT, ultrasonography (US), and/or bone scintigraphy (BS)) was used.
- *O* stands for outcome: sensitivity, specificity, change in stage compared to staging done by conventional imaging, prognosis, and costs.

We searched MEDLINE to identify studies published in English between January 2006 and March 2016 that contained the above-mentioned PICO terms or synonymous terms in titles and/or abstracts. To select studies, one investigator reviewed the titles of all the studies identified in the search and excluded those not related with the main objective: initial PET (staging). Next, we reviewed the abstracts of the included titles and obtained the complete articles of those that reported systematic reviews or original studies using 18F-FDG PET, 18F-FDG PET/CT, or both techniques in a sample at least of 30 patients.

Two investigators examined all the papers that fulfilled these criteria and excluded duplicated studies and reviewed articles or meta-analyses that were superseded by more recent ones. Moreover, studies included in systematic reviews or meta-analyses were excluded when a systematic review or meta-analysis answered the question they explored.

We critically reviewed the selected articles and elaborated evidence tables, structuring the summarized

Table 1. Evidence level and grade of recommendations for 18F-FDG PET/CT in staging breast cancer as reported in current clinical guidelines.

Guideline	Evidence level /grade of recommendation	Recommendation description
SEOM 2015	I/A[a]	Suspicion of distant metastases: When anomalies are detected in laboratory tests, or when disease is detected at advanced stage (stage III), a more extensive study is performed using PET/CT or thoracic–abdominal CT and bone scan (if bone symptoms, elevation of alkaline phosphatase, lactose dehydrogenase, or calcium are present).
	III/C[a]	Determination of metastatic spread in standard staging.
ESMO 2015	V/A[b]	Locally advanced breast cancer with inconclusive conventional diagnostic methods.
	V/B[b]	PET/CT scanning can replace traditional imaging for staging in high-risk patients who are candidates for neoadjuvant chemotherapy, as well as those with locally advanced and/or inflammatory disease due to their high risk of having metastatic disease.
NCCN 2016	II/B[c]	Bone scan or sodium fluoride PET/CT: only in patients presenting with localized bone pain or elevated alkaline phosphatase. FDG PET/CT is most helpful in situations where standard imaging results are equivocal or suspicious. However, limited studies support a potential role of FDG PET/CT to detect regional node involvement as well as distant metastases in locally advanced breast cancer, including T3, N1, and M0 disease. The NCCC panel suggests that bone scan may be omitted if FDG PET/CT results are positive for bone metastases.
NICE 2015	Not referred	PET/CT should only be used to make a new diagnosis of metastases for patients with locally advanced breast cancer whose imaging is suspicious but not diagnostic of metastatic disease.

18F-FDG PET/CT: fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography; NCCC: Norris Cotton Cancer Center.
[a]Strength of recommendation (five categories, A–E)/quality of evidence (three categories, I–III).
[b]Grade of recommendation (six categories, 1A–2C).
[c]Categories of evidence and consensus (four categories, 1, 2a, 2b and 3).

information into methodology, results, and limitations. We assessed the level of evidence for the use of 18F-FDG PET in each situation and established the recommendation grades following the NICE adaptation[9] of the levels of evidence for diagnostic studies of the Oxford Centre for Evidence-Based Medicine and the Centre for Reviews and Dissemination (Table 2). Recommendations were simplified to consider grade A or B as a strong recommendation and grade C or D as weak recommendation.

Cost-effectiveness studies were evaluated using the Scottish Intercollegiate Guidelines Network (SIGN)[10] scale, which ranges from (++), when the study fulfilled all or most of the quality criteria, to (−), when it fulfilled few or none of the quality criteria.

In the assessment of each study, the gold standard considered valid was histological confirmation of lymph node or distant metastases.

We reviewed all the information from the literature searches to answer the following main question:

Question (a): Is it necessary to introduce 18F-FDG PET/CT imaging in conventional staging in all cases or only in cases with certain clinical stages or molecular characteristics (risk stratification)?

Moreover, we considered other, secondary questions to answer the main question:

Question (b): What is the diagnostic accuracy of 18F-FDG PET/CT compared with other diagnostic techniques in regional lymph node staging and in the detection of distant metastases?
Question (c): What is the percentage of cases in which the staging changed due to the18F-FDG PET/CT findings?
Question (d): Do 18F-FDG PET/CT findings result in a significant change in therapeutic management?

Finally, we considered other questions about 18F-FDG PET/CT that were not strictly related with initial staging:

Question (e): Is glycolytic activity associated with tumor biology?
Question (f): Does the metabolic information from a baseline 18F-FDG PET/CT have implications for the patient's prognosis?
Question (g): Is staging with 18F-FDG PET/CT cost-effective?

Results

The levels of evidence and grades of recommendations for the answers to the questions were as follows:

Table 2. Levels of evidence and grades of recommendation established in the National Institute for Clinical Excellence guidelines.

Levels of scientific evidence	Type of scientific evidence
Ia	Systematic review (SR) with homogeneity of level 1+ studies.
Ib	Level 1 studies.
II	Level 2 studies. SR of level 2 studies.
III	Level 3. SR of level 3 studies.
IV	Consensus, expert opinions with no explicit critical evaluation.
Level 1 studies	Meet the following criteria: • Blinded comparison with a valid ("gold standard") comparator test. • Suitable range of patients.
Level 2 studies	Show only one of these biases: • Non-representative population (the sample does not reflect the population in which the test will be used). • Comparison with unsuitable comparator ("gold standard"). The test to be assessed is part of the gold standard or the result of the test affects the performance of the gold standard. • Non-blinded comparison. • Case and control studies.
Level 3 studies	Meet two or more of the criteria stated for level 2 studies.
Recommendation grade	Interpretation of evidence
A	Evidence level Ia or Ib studies.
B	Evidence level II studies.
C	Evidence level III studies
D	Evidence level IV studies

Question (a): Is it necessary to introduce 18F-FDG PET/CT imaging in conventional staging in all cases or only in cases with certain clinical stages or molecular characteristics (risk stratification)?

1a 18F-FDG PET/CT imaging is not recommended in early-stage BC. Level of evidence II, strong recommendation.[11–28] For more information see Tables 3–5.

2a. 18F-FDG PET/CT should be used in locally advanced BC for initial staging. Evidence level II, strong recommendation.[11–28] For more information, see Tables 3–5.

3a. 18F-FDG PET/CT should be used in high-risk patients, such as those with inflammatory BC. Evidence Level II, strong recommendation. In triple-negative BC, there is limited evidence to recommend the systematic use of the technique.[29–35] For more detailed information, see Table 6.

4a. Patients' age at diagnosis is not in itself, independent of clinical stage or molecular biology, a sufficient criterion to indicate 18F-FDG PET/CT.[35] Evidence level IV, weak recommendation.

Question (b): What is the diagnostic accuracy of 18F-FDG PET/CT compared with other diagnostic techniques in regional lymph node staging and in the detection of distant metastases?

In patients with recently diagnosed BC, the diagnostic effectiveness of 18F-FDG PET/CT is superior to that of other diagnostic techniques. *Evidence level III, weak recommendation*.[14,17–28,36–46] For more information, see Tables 4, 5, and 7.

Question (c): What is the percentage of cases in which the staging changed due to the18F-FDG PET/CT findings?

In patients with recently diagnosed BC, the percentage of cases in which 18F-FDG PET/CT changed the staging with respect to conventional imaging is high enough to recommend it. *Evidence level III, low recommendation*.[14,20,36–46] For more detailed information, see Table 7.

Question (d): Do 18F-FDG PET/CT findings result in a significant change in therapeutic management?

In patients with recently diagnosed BC, 18F-FDG PET/CT results in a significant enough change in the therapeutic management to recommend it. *Evidence level III, low recommendation*.[14,20,36–46] For more detailed information, see Table 7.

Question (e): Is glycolytic activity associated with tumor biology?

In patients with recently diagnosed BC, the baseline glycolytic activity on 18F-FDG PET/CT is associated with tumor biology. *Evidence level II*[47–56] (Table 8).

Question (f): Does the metabolic information from a baseline 18F-FDG PET/CT have implications for the patient's prognosis?

In patients with recently diagnosed BC, the metabolic information from a baseline 18F-FDG PET/CT has implications for the patient's prognosis. *Evidence level II*[28,32,33,39,47,57–61] (Table 9).

Question (g): Is staging with 18F-FDG PET/CT cost-effective?

There is not enough evidence to address the cost-effectiveness of 18F-FDG PET/CT[62,63] (Table 10).

Discussion

18F-FDG PET/CT in regional and distant staging

In the preoperative work-up of early-stage BC with clinically negative axilla, 18F-FDG PET/CT can be omitted because it hardly affects the initial staging and treatment planning in most patients. In regional staging, 18F-FDG PET/CT is less sensitive than sentinel lymph node biopsy in assessing ALN involvement. The low prevalence of distant metastases and the risk of false-positive findings retract from the usefulness of 18F-FDG PET/CT for distant staging in these patients.[11–13]

By contrast, in patients with positive axilla, especially those with locally advanced BC, 18F-FDG PET/CT can be

Table 3. Locoregional breast cancer staging: FDG PET/CT lymph node assessment in early and locally advanced disease.

References	Methodology	Results	Limitations	Level of evidence
Early BC				
Koolen et al.[11]	• Prospective. 62 patients. • Inclusion criteria: T1 (early BC). • Objective: detection of lymph node involvement. • Evaluation criteria: moderately intense FDG uptake (higher than background) and for lesions near 1 cm, any uptake slightly higher than background. Blinded assessment. • Reference standard: histopathology.	• Positive axillary nodes by PET/CT in 19 patients and positive node in periclavicular region in 2 patients (3%). • Se, Sp, PPV, and NPV of PET/CT were 73%, 100%, 100%, and 72%, respectively.	• ALN involvement could not be assessed in 29% of patients because of an SLNB procedure prior to PET/CT.	II
Bellevre et al.[12]	• Prospective. 50 patients. • Inclusion criteria: Operable BC. • Objective: OSEM reconstruction and PSF reconstruction in detection of lymph node involvement. • Evaluation criteria: FDG uptake higher than background. Blinded assessment. • Reference standard: histopathology.	• 34 (68%) had nodal involvement. • PSF reconstruction detected more involved nodes than OSEM reconstruction ($p = 0.003$). • The Se of PSF reconstruction was superior to OSEM reconstruction independent of lymph node size.	• Non-representative, heterogeneous population (Tx–T4).	II
Jeong et al.[13]	• Retrospective. 178 patients • Inclusion criteria: T1–T3 and clinically negative axillae (early BC). • Objective: detection of lymph node involvement • Evaluation criteria: FDG activity higher than the mediastinum • Reference standard: histopathology.	• 178 patients: 93 (52%) underwent SLNB and 14 (8%) ALND; 71 (40%) underwent both SLNB and ALND. Abnormal 18F-FDG-avid axillary nodes were detected in 27 of the 178 patients on 18F-FDG PET/CT, and histology confirmed metastases in 48 (27%). • The Se, Sp, PPV, NPV, and Acc of PET/CT in the detection of axillary nodes were 21%, 87%, 37%, 75%, and 69%, respectively. • Extra-axillary node metastasis was identified in 2 patients (1%) who had internal mammary nodes. There was no distant metastasis, but coexisting primary tumors were detected in 5 (3%) patients.	• Retrospective. Non-representative population.	I
LABC				
Fuster et al.[14]	• Prospective. 60 patients. • Inclusion criteria: LABC (BC >3 cm). • Objective: detection of lymph node involvement. • Evaluation criteria: SUVmax > 2.5. Blinded assessment. • Reference standard: histopathology.	• ALN metastases were found in 20/52 patients with ALND. • The Se and Sp of PET/CT in the detection of ALN involvement were 70% and 100%, respectively.	• Small sample.	II

(continued)

Table 3 (continued)

References	Methodology	Results	Limitations	Level of evidence
Koolen et al.[15]	• Retrospective. 311 patients. • Inclusion criteria: LABC (BC > 3 or N1 scheduled for NAC) • Objective: detection of lymph node involvement. • Evaluation criteria: 4-degree scoring system. Blinded assessment. • Reference standard: histopathology of ALNs and some extra-axillary locations.	Assessment of axillary nodes with PET/CT was impossible in 21 patients; thus, 290 patients were evaluated. (196 TP, 4 FP, 48 TN, and 42 FN). • Intense FDG uptake (score 2–3) was seen in 200 (69%) patients. • PET/CT obtained Se, Sp, PPV, NPV, and Acc of 82%, 92%, 98%, 53%, and 84%, respectively. • Occult lymph node metastases in the internal mammary chain and periclavicular area were detected in 26 (8%) and 32 (10%) patients, respectively, resulting in changed regional radiotherapy planning in 50 (16%).	• Retrospective but representative population. • No histological confirmation in all the extra-axillary locations. FDG-avid extra-axillary nodes were considered metastatic, based on the previously reported high PPV of the technique.	II
Seo et al.[16]	• Retrospective. 249 patients. • Inclusion criteria: stage III BC. • Objective: internal mammary lymph node assessment. • Evaluation criteria: 4-degree scoring system. Blinded assessment • Reference standard: histopathology, but not in all the cases.	• FDG PET/CT detected internal mammary lymph node metastasis in 62/216 (29%) patients and histological confirmation was obtained in 31.	• Retrospective. • The order in which FNAB and FDG PET/CT were performed was variable: PET/CT was performed after FNAB in 45% (14/31) of patients. • No histological confirmation in all the cases.	III

BC: breast cancer; NAC: neoadjuvant chemotherapy; ALN: axillary lymph node; SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection; Se: sensitivity; Sp: specificity; NPV: negative predictive value, PPV: positive predictive value; Acc: accuracy; TP: true positive; FP: false positive; TN: true negative; FN: false negative; OSEM: ordered subset expectation maximization (iterative reconstruction); PSF: point spread function; LABC: locally advanced breast cancer; FNAB: fine-needle aspiration biopsy; PET/CT: positron emission tomography/computed tomography; FDG: fluorodeoxyglucose; SUV: standardized uptake value.

Table 4. Locoregional breast cancer staging: comparison of FDG PET/CT lymph node assessment in early and locally advanced disease with other diagnostic techniques.

References	Methodology	Results	Limitations	Level of evidence
Cooper et al.[17]	• Systematic review: 26 studies evaluating PET or PET/CT. • Objective: clinical effectiveness of ALN involvement diagnosis in early BC. Comparison of PET versus PET/CT versus MRI. • Reference standard: 8 studies used ALND for all patients, 12 used a combination of ALND and SLNB, 3 did not specify (only stating "histology"), and 3 used other methods for some patients.	• PET or PET/CT (26 studies, 2591 patients): Mean Se 63% (95% CI: 52%–74%; range 20%–100%) and mean Sp 94% (95% CI: 91%–96%; range 75%–100%). • PET/CT (7 studies, 862 patients). Mean Se 56% (95% CI: 44%–67%) and mean Sp 96% (95% CI: 90%–99%). • PET only (19 studies, 1729 patients). Mean Se 66% (95% CI: 50%–79%) and mean Sp 93% (95% CI: 89%–96%). • Micrometastasis: Mean Se 11% (95% CI: 5%–22%) for micrometastases (≤2 mm; 5 studies; 63 patients), and 57% (95% CI: 47%–66%) for macrometastases (>2 mm; 4 studies; 111 patients). • Ultrasmall super-paramagnetic iron oxide (USPIO)-enhanced MRI (5 studies, 93 patients). Mean Se 98% (95% CI: 61%–100%) and mean Sp 96% (95% CI: 72%–100%). • Gadolinium-enhanced MRI (3 studies, 187 patients). Mean Se 88% (95% CI: 78%–94%) and mean Sp 73% (95% CI: 63%–81%). • In vivo proton magnetic resonance spectroscopy (1 study, 27 patients). Se 65% (95% CI: 38%–86%) and Sp 100% (95% CI: 69%–100%).	• None of the studies included directly compared PET with MRI. • Patients were not recruited prospectively and consecutively (3 studies); unclear inclusion in 12. • Blind interpretation of reference standard results was under-reported with 20 studies scoring "unclear." • The reference standard was adequate (ALND or SLNB) in nearly all studies.	III
Hwang et al.[18]	• Retrospective. 349 patients. • Inclusion criteria: T1 BC. • Objective: Comparison of PET/CT with US and cMRI for lymph node detection. • Evaluation criteria: higher level of FDG uptake than the background • Reference standard: histopathology.	• In total, 26% of patients had ALNMs. • The Se, Sp, PPV, NPV, and Acc of US for determining ALNMs were 45%, 89%, 59%, 82%, and 77%, respectively. • The Se, Sp, PPV, NPV, and Acc of PET/CT were 45%, 94%, 73%, 83%, and 81%, respectively. • The combination including cMRI and PET/CT was the most accurate with Se, Sp, PPV, NPV, and Acc of 39%, 99%, 92%, 82%, and 83%, respectively.	• Retrospective. • Non-blinded with CI. Interpreters of the cMRI and PET/CT had knowledge of the US results in most cases.	II
Ergul et al.[19]	• Prospective. 24 patients. • Inclusion criteria: Early-stage BC. • Objective: Comparison of PET/CT versus cMRI and DWI-MRI for lymph node involvement. • Evaluation criteria: both apparent and suspected FDG accumulations were considered to be positive. • Reference standard: histopathology.	• In 15/24 (63%) patients, axillary nodal involvement was evident by pathological examination after ALND. Micrometastases were detected in two patients. • SLNB afforded the highest Se (93%) in terms of detection of axillary metastasis. • PET/CT detected ALNM in 11 patients (1 FP). PET/CT did not detect metastases in 5 patients with axillary involvement (2 had micrometastases and 3 had subcentrimetric metastases). • The sensitivity, NPV, and Acc of PET/CT were 67%, 62%, and 75%, respectively, thus higher than the equivalent values of either DCE-MRI or DWI.	• Small population. • Non-blinded evaluation between the diagnostic tests.	III

(continued)

Table 4 (continued)

References	Methodology	Results	Limitations	Level of evidence
Segaert et al.[20]	• Retrospective. 70 patients. • Inclusion criteria: IIB-III LABC. • Objective: comparison of PET/CT versus conventional staging for lymph node involvement. • Blinded assessment. • Evaluation criteria: a focally increased FDG activity above physiological mediastinal tracer uptake. • Reference standard: histopathology or clinical and imaging follow-up.	• 14/70 patients had primary surgery with ALND (8 with involved lymph nodes). In 56 others, neoadjuvant or systemic therapy was administered prior to local therapy. • PET/CT: Se, Sp, and NPV for nodal status were 63%, 100%, and 67%, respectively. • Conventional staging : Se, Sp, and NPV for nodal involvement were 88%, 100%, and 86%, respectively.	• Retrospective. Non-representative population. • Histopathological confirmation not available in all cases.	III
Choi et al.[21]	• Retrospective. 154 patients. • Inclusion criteria: Early and LABC. • Objective: PET/CT versus US and MRI for lymph node involvement. • Evaluation criteria: foci with pathologic uptake higher than the liver activity. • Reference standard: Histopathology or additional images and follow-up.	• PET/CT detected extra-axillary lymph node metastases in 8 patients and distant metastasis in 13. • Histological confirmation of ALNMs in 51 patients. PET/CT detected metastatic axillae with 37% Se and 96% Sp; US had 41% Se and 94% Sp and MRI had 40% Se and 88% Sp.	• Retrospective. Non-representative and heterogeneous population. • Non-blinded evaluation with CI. • Histopathological confirmation not available in all cases.	III
Riegger et al.[22]	• Retrospective. 90 patients. • Inclusion criteria: stages: pTx–pT4 and pN0–pN3. • Objective: PET/CT versus US for lymph node involvement. Blinded assessment. • Evaluation criteria: focally increased PET signal. • Reference standard: histopathology.	• Histopathology classified 54 axillary lymph nodes as negative and 37 as positive for ALNM. • PET/CT: Se, Sp, PPV, NPV, and Acc for the detection of ALNMs were 54%, 89%, 77%, 74%, and 75%, respectively. • US: Se, Sp, PPV, NPV, and Acc were of 38%, 78%, 54%, 65%, and 62%, respectively. • FDG PET/CT was significantly more accurate than ultrasound and detected extra-axillary locoregional lymph node metastases that had not been detected by another imaging modality in 7 (8%) patients.	• Retrospective. Non-representative population.	II
García-Vicente et al.[23]	• Prospective. 75 patients. • Inclusion criteria: LABC. • Objective: PET/CT versus conventional staging for lymph node detection. • Reference standard: Histopathology or conventional staging.	• Prevalence of lymph node involvement was (63/75) 84% patients. • Extra-axillary lymph node involvement was detected by • PET/CT in 20/75 (26.7%) patients. • PET/CT: Se 97% and Sp 75%. • PET/CT changed the previous clinical N stage in 29/75 patients and was correct in 37%.	• Non-blinded evaluation with CI or no gold standard in some cases. • Histopathological confirmation not available in all cases (in cases with evident clinical lymph node involvement, confirmatory biopsy was avoided).	III

Se: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; Acc: accuracy; SLNB: sentinel lymph node biopsy; ALNM: axillary lymph node metastases; ALND: axillary lymph node dissection; LABC: locally advanced breast cancer; US: ultrasonography; cMRI: contrast-enhanced magnetic resonance imaging; DWI-MRI: diffusion-weighted magnetic resonance imaging; CI: conventional imaging; PET/CT: positron emission tomography/computed tomography; BC: breast cancer; 95% CI: 95% confidence interval.

Table 5. Distant metastases detection: FDG PET/CT compared with other diagnostic techniques.

References	Methodology	Results	Limitations	Evidence level
Hong et al.[24]	• *Meta-analysis*. 8 studies (748 patients). • Inclusion criteria: all cases regardless of treatment status. • Objective: PET versus CS in the detection of distant metastases. • Reference standard: histopathological analysis and/or clinical and imaging follow-up.	• PET: Se 0.97, Sp 0.95 (95% CI: 0.93–0.97), DOR 598 (95% CI: 108–3309), PLR 20.8 (95% CI: 13.1–32.9), and NLR 0.03 (956% CI: 0.01–0.18). • CS: Se 0.56 (95% CI: 0.38–0.74), Sp 0.91 (95% CI: 0.78–0.97), DOR 13.7 (95% CI: 4.3–43.8), PLR 6.5 (95% CI: 2.5–17.2), and NRL 0.48 (95% CI: 0.31–0.72).	• Few studies included. • 5/8 were retrospective. • Wide variation (e.g. in-patient population, imaging techniques, study design, and quality) among the selected studies. • Comparison with unsuitable gold standard.	III
Rong et al.[25]	• *Meta-analysis*. 7 studies (668 patients). • Inclusion criteria: all patients regardless of treatment status (clinical stages I–IV). • Objective: PET or PET/CT versus BS for the detection of bone metastases. • Reference standard: histopathological analysis and/or clinical and imaging follow-up.	• PET: Se 0.93 (95% CI: 0.82–0.98) and Sp 0.99 (95% CI: 0.95–1.00). • BS: Se 0.81 (95% CI: 0.58–0.93) and Sp 0.96 (95% CI: 0.76–1.00). • PET/CT plus BS, Se 0.98 (95% CI: 0.98–1.00) and Sp 0.94 (95% CI: 0.92–0.96).	• Few studies included. • One study included had only 20 patients • 5/7 were retrospective. • There was no single follow-up strategy and time. • No phenotype analysis.	III
Sun et al.[26]	• *Meta-analysis*. 6 studies (609 patients). • Inclusion criteria: all patients regardless of treatment status. • Objective: PET and PET/CT versus CS for the detection of distant metastases. • Reference standard: histopathological analysis and/or clinical and imaging follow-up.	• PET: Se 0.99 (95% CI: 0.88–1.00), Sp 0.95 (95% CI: 0.89–0.98), PLR 21.1 (95% CI: 8.2–55.5), and NLR 0.02 (95% CI: 0.001–0.13). • CS: Se 0.57 (95% CI: 0.37–0.74), Sp 0.88 (95% CI: 0.78–0.94), PLR 4.8 (95% CI: 2.8–8.2), and NLR 0.49 (95% CI: 0.33–0.74), respectively.	• Few studies included. • 2/6 studies were retrospective. • There was no single clinical and imaging follow-up strategy, which may have affected the evaluation of whole-body PET/PET-CT. • Wide variation in patient population, imaging techniques, study design, and quality in the selected studies.	III
Segaert et al.[20]	• Retrospective. 70 patients. • Inclusion criteria: LABC (IIB–III). • Objective: PET/CT versus CS (chest X-ray, abdominal US, and BS) for M1 detection. • Blinded assessment. • Reference standard: clinical and imaging follow-up.	• Global Se and Sp in the M1 diagnosis of CS: 70% and 98%, respectively. • Se was 86% for CS, 75% for PET, and 96% for PET/CT. • PET/CT did change stage IV and treatment in 10%.	• Retrospective. Selection bias. • Patient-based analysis. • Comparison with unsuitable gold standard.	III
Manohar et al.[27]	• Prospective. 43 patients. • Inclusion criteria: histopathologically proven LABC with negative CS results for distant metastases (chest radiography, BS, abdominal US). • Objective: M1 detection. • Reference standard: biopsy or follow-up ≥6 months.	• PET/CT findings suggestive of M1 were noted in 11/43 patients (10 confirmed by biopsy or follow-up). • PET/CT had 100% Se, 96.8% Sp, 91% PPV, and 100% NPV for identifying M1 missed by CS. • Change in stage was noted in 40% of patients, 10 M1.	• Small sample. • The findings could not be confirmed with histopathology. Short follow-up.	III
García-Vicente et al.[28]	• Prospective. 198 patients. • Inclusion criteria: LABC. • Objective: M1 detection. • Blinded evaluation. • Reference standard: clinical and imaging follow-up.	• PET/CT detected M1 in 38/198 (19%) patients.	• No histological confirmation of distant metastases detected by PET/CT.	II

CS: conventional staging; BS: bone scintigraphy; Se: sensitivity; Sp: specificity; DOR: diagnostic odds ratio; PLR: positive likelihood ratio; NRL: negative likelihood ratio; CI: confidence interval; AUC: area under curve; M1: distant metastases; US: ultrasound; PET/CT: positron emission tomography/computed tomography; LABC: locally advanced breast cancer.

Table 6. Staging in function of groups of risk: inflammatory breast cancer, triple-negative breast cancer, and young patients.

References	Methodology	Results	Limitations	Level of evidence
Inflammatory breast cancer				
Carkaci et al.[29]	• Retrospective. 41 patients. • Patients included: unilateral IBC. • Objective: staging. • Blinded assessment with reference standard. • Reference standard: histopathological confirmation or additional imaging techniques.	• Distant metastases were found in 20 (49%) patients at staging, 7 (17%) of whom were not known to have metastases before undergoing PET/CT.	• Retrospective. • Small population. • Histological confirmation in only 7 (17%) patients with distant metastases. • Comparison with unsuitable reference standard.	III
Alberini et al.[30]	• Prospective. 62 patients. • Patients included: unilateral IBC. • Objective: comparison of PET/CT versus CS. • Reference standard: histopathological confirmation or additional imaging techniques.	• PET/CT increased the stage in 35 patients and decreased the stage in 5. • In 7 of 9 cN0 patients, the axillary lymph node positivity on PET/CT was correct. • PET/CT diagnosed extra-axillary involvement in 33 patients and distant lesions in 18/59 (31%).	• Small population. • Comparison of whole-body PET and CT scans was not feasible. • Comparison with unsuitable reference standard. Blinded assessment is not stated.	III
Groheux et al.[31]	• Prospective. 117 patients. • Patients included LABC (stage III): 35 with IBC and 82 with non-IBC. • Objective: Comparison of PET/CT vs CS. • Blinded assessment. • Reference standard: Histopathological confirmation, additional imaging techniques, or follow-up.	• PET/CT changed the clinical stage in 61 patients (52%). • PET/CT diagnosed M1 in 46% of IBC and 33% non-IBC. The difference did not reach statistical significance. • Unguided CS detected metastases in only 28/43 (65%) patients classified M1 with PET/CT.	• PET/CT findings were compared with biopsy results, further work-up, or patient follow-up. • Comparison with unsuitable reference standard.	II
Champion et al.[32]	• Retrospective. 50 patients. • Patients included: unilateral IBC. • Objective: comparison of PET/CT versus DCE-CT. • Reference standard: histopathological confirmation, additional imaging techniques or follow-up.	• Concordance between PET/CT and DCE-CT was good for breast tumor localization, poor for skin infiltration, and fair for axillary node involvement. • 19 (38%) patients had metastases on PET/CT.	• Retrospective. • Comparison with unsuitable reference standard. • No blinded assessment.	III
Triple-negative breast cancer				
Groheux et al.[33]	• Prospective. 85 patients. • Patients included: Consecutive TNBC. Stage II/III. • Objective: comparison of PET/CT versus CS. • Blinded evaluation. • Reference standard: histopathological confirmation or additional imaging techniques.	• PET/CT revealed distant metastases in 11/85 (12.8%).	• Single-center design. • No histological confirmation of all distant metastases.	II

(continued)

Table 6 (continued)

References	Methodology	Results	Limitations	Level of evidence
Ulaner et al.[34]	• Retrospective. 232 patients. • Patients included: TNBC. Stages I–III. • Objective: staging and prognosis. • Blinded assessment. • Reference standard: histopathological confirmation or additional imaging techniques.	• PET/CT revealed distant metastases in 13% (15% in clinical stage IIB and 33% in clinical stage III). • Shorter survival for stage IIB patients who PET/CT changed to stage IV.	• Retrospective. • Single-center design. • Selection biases. Unsuitable range of patients. • No histological confirmation in 4/30 cases with distant metastases and most patients classified with unsuspected regional nodal metastases.	III
Young patients				
Riedl et al.[35]	• Retrospective. 134 patients. • Patients included: patients younger than 40 years with stage I to III cancer. • Objective: comparison of PET/CT versus CS. • Blinded evaluation. • Reference standard: histological confirmation of distant metastases or follow-up imaging.	• PET/CT changed the stage up to stage III or IV in 28 (21%) patients. • Unsuspected extra-axillary regional nodes were found in 15/134 (11%) patients and distant metastases in 20/134 (15%), and both were found in 7/134 (5%).	• Retrospective. • Selection bias: clinical stage and histological subtypes. • No histopathological confirmation of extra-axillary lymph node metastases. • Comparison with unsuitable reference standard. The test assessed is part of the gold standard for internal mammary nodes.	III

IBC: inflammatory breast cancer; CS: conventional staging (breast magnetic resonance imaging, chest CT, liver ultrasonography, bone scintigraphy); DCE-CT: dynamic contrast-enhanced CT; LABC: locally advanced breast cancer; TNBC: triple-negative breast cancer; PET/CT: positron emission tomography/computed tomography.

Table 7. Changes in stage and treatment resulting from 18-F-FGD PET findings.

References	Methodology	Results	Limitations	Level of evidence
Fuster et al.[14]	• Prospective. 60 patients. • Inclusion criteria: LABC. • Objective: comparison of PET/CT versus CS for staging and therapeutic impact. • Blinded assessment. • Reference standard: histopathology or ≥1 year follow-up.	• Change in stage in 42% of patients (18/60): stage correctly lowered in 7; 10 patients had ALNM; stage correctly increased (M1) in 5 and metastatic extra-axillary lymph nodes in 3. • Treatment change: 7%.	• Small sample, but representative population. • No histological confirmation of all the locations.	II
Segaert et al.[20]	• Retrospective. 70 patients. • Inclusion criteria: IIB–III LABC. • Objective: comparison of PET/CT versus CS and change in therapy. • Blinded assessment. • Reference standard in stage IV: clinical and imaging follow-up.	• Change in stage and therapy: 10% (stage IV).	• Retrospective. • Changes in nodal status are not reported. • No histological confirmation of all suspected internal mammary nodes nor M1 by PET/CT.	III
Nikura et al.[36]	• Retrospective. 225 patients. • Inclusion criteria: stage I–IV BC patients with available report of PET/CT for staging purposes. • Objective: comparison of PET/CT versus CS. • Reference standard: biopsy, subsequent imaging, or clinical follow-up.	• Change in stage: 15 patients with distant metastases (11 confirmed by subsequent biopsy or conventional imaging studies)	• Retrospective. • No histological confirmation of all suspected M1 by PET/CT. • No blinded assessment.	III
Groheux et al.[37]	• Prospective. 131 patients. • Inclusion criteria: IIA–IIIA. • Objective: comparison of PET/CT versus CS for staging and therapeutic impact. • Blinded assessment. • Reference standard: histopathology or follow-up.	• PET/CT changed staging, with impact on therapeutic management in 2/36 (6%) of stage IIA patients, in 10/77 (13%) of stage IIB plus primary operable stage IIIA patients, and in 10/18 (56%) of patients with stage IIIA due to N2 disease	• Not all FDG foci were biopsied.	II
Riegger et al.[38]	• Retrospective. 106 patients. • Inclusion criteria: T1–T4 BC with equivocal findings on CS or the presence of lesions suspected of being metastatic. • Objective: comparison of PET/CT versus CS. • Blinded assessment. • Reference standard: Histopathology, imaging, or clinical follow-up.	• Synchronous tumors or locoregional extra-axillary lymph node or distant metastases were detected in 14 patients (13%) by FDG PET/CT. • Management of 15 patients (14%) was altered based on the FDG PET/CT findings. FDG PET/CT was significantly more accurate for detecting axillary lymph node and distant metastases ($p = 0.012$ and $p < 0.005$, respectively)	• Retrospective. • Selection bias. • Histopathology was not available for all lesions. Comparison with unsuitable reference standard (PET/CT is part of the gold standard).	III
Groheux et al.[39]	• Prospective. 254 patients. • Inclusion criteria: stage II or III. • Objective: comparison of PET/CT versus CS. • Blinded assessment. • Reference standard: histological confirmation or additional imaging or follow-up.	• Change of clinical stage in 30% of patients (increased to stage IV in 2% of stage IIA, 11% of stage IIB, 17% of stage IIIA, 36% of stage IIIB, and 47% of clinical stage IIIC BC).	• Histopathology was not available for all distant metastases.	II
Koolen et al.[15]	• Retrospective. 311 patients. • Inclusion criteria: LABC (BC > 3 or N1 scheduled for NAC) • Objective: detection of distant metastases. Change in previous clinical stage. • Reference standard: additional imaging.	• The TNM stage was changed by PET/CT in 38 (12%) patients because of newly discovered N3-disease; 10 patients were classified as stage IV because of distant metastatic disease.	• Retrospective although representative population. • No histological confirmation.	II

(continued)

Table 7 (continued)

References	Methodology	Results	Limitations	Level of evidence
Koolen et al.[40]	• Prospective. 154 patients. • Inclusion criteria: stage II–III. • Objective: comparison of PET/CT versus CS for staging and therapeutic impact. • Reference standard: histological confirmation or additional imaging or follow-up.	• PET/CT detected 42 additional distant lesions in 25 patients and confirmed in 20 (13%) patients. PET/CT misclassified the presence of metastatic disease in 5 (3%). • In 16/20 (80%) patients, additional lesions were exclusively seen with PET/CT, leading to a change in treatment in 13/154 (8%) patients.	• No blinded association with other techniques. • Different reference standard.	III
Bernsdorf et al.[41]	• Prospective. 103 patients. • Inclusion criteria: operable early BC. • Objective: comparison of PET/CT versus CS. • Blinded assessment • Reference standard: histological confirmation or additional imaging or follow-up.	• PET/CT identified a primary tumor in all but 3 patients (97%). • PET/CT solely detected M1 in 6 patients and new primary cancers in another 2, as well as 12 cases of extra-axillary lymph node involvement. • In 15 (15%) p, extra-axillary malignancy was detected by PET/CT only, which led to increase in initial staging in 14/103 (14%). • Treatment change: 8/103 (8%) patients.	• No histological confirmation of IMN. • Comparison of M1 with unsuitable reference standard. • Specificity of MRI for IMN adenopathy was not well studied.	III
Groheux et al.[31]	• Prospective. 117 patients. • Inclusion criteria: LABC: IBC (35 patients) and non-IBC (82 patients). • Objective: comparison of PET/CT versus CS in staging and therapeutic impact. • Blinded assessment. • Reference standard: histopathology, imaging, or clinical follow-up.	• PET/CT changed the clinical stage in 52% of patients, revealing unsuspected M1 stage in 46% IBC and in 33% non-IBC. • PET/CT revealed unsuspected N3 stage in 28%. • Potential impact on management in 52%.	• Heterogeneity of BC disease. • Comparison with unsuitable reference standard	II
Sen et al.[42]	• Retrospective. 77 patients. • Inclusion criteria: Stages I–III. • Objective: comparison of PET/CT versus CS. • Reference standard: histology or clinical follow-up.	• PET/CT revealed unsuspected distant metastases in 12/77 (16%). • Changes in disease stage occurred in (20%). The stage was increased in 18% and decreased in 1%. • No information about treatment changes.	• Retrospective. • Comparison with unsuitable reference standard. • No blinded assessment	III
Manohar et al.[27]	• Prospective. 43 patients. • Inclusion criteria. LABC (IIB–IIIC). • Objective: comparison of PET/CT versus CS. • Reference standard: histology or follow-up ≥ 6 months.	• PET/CT changed the previous stage in 40%: 10 M1 and 7 N3.	• Small sample. • Different reference standard tests. • Blinded assessment is not stated.	III
Seo et al.[16]	• Retrospective. 249 patients. • Inclusion criteria. Stage III. • Objective: detection of IMN. • Blinded assessment. • Reference standard: histological data of IMN.	• In 33 patients, PET/CT discovered distant metastases. • 62/216 patients had visible IMNs on FDG PET/CT, and histological confirmation was obtained in 31 patients: 27 metastatic and 4 non-metastatic nodes (PPV 87%).	• Retrospective. • PET/CT was performed after FNAB in 45% of patients. • No histological confirmation in all cases.	III
Cochet et al.[43]	• Prospective. 142 patients. • Inclusion criteria: Stages II–IV. • Objective: comparison of PET/CT versus CI for staging and therapeutic impact. • Reference standard: histological confirmation or additional imaging or follow-up.	• PET/CT increased stage in 30 (21%) patients, including 12 (8%) from stage II or III to stage IV. • PET/CT decreased stage in 23 (16%) patients, including 4 (3%) from stage IV to stage II or III. • PET/CT had a high or medium impact on management planning for 18 (13%) patients.	• Heterogeneity of BC stages. • Histological confirmation in only 25% of cases. • No blinded assessment	III

(continued)

Table 7 (continued)

References	Methodology	Results	Limitations	Level of evidence
Jeong et al.[13]	• Retrospective. 178 patients. • Inclusion criteria: BC with clinically negative axillary node. • Objective: diagnostic and therapeutic impact evaluation. • Reference standard: histopathology, additional images or follow-up.	• Extra-axillary node metastasis was identified in 1% who had IMN. • There was no distant metastasis, but coexisting primary tumor was detected in 3%. • PET/CT changed treatment in 4%. • PET/CT hardly affected the initial staging or treatment plan of BC with clinically negative axillary node	• Retrospective. • No blinded assessment.	II
Koolen et al.[11]	• Prospective. 62 patients. • Inclusion criteria. T1 early BC. • Objective: staging impact. • Blinded assessment. • Reference standard: histopathology or imaging.	• 10 patients were diagnosed with M1 and 2 with N3. • PET/CT changed the previous clinical stage in 19%.	• Reduced sample. • Probable selection bias: cases selected from a previous prospective study. • No histological confirmation in all cases.	III
Hogan et al.[44]	• Retrospective. 146 p. • Inclusion criteria: Stage III ILC. Control group: 89 IDC. • Objective: Staging impact. • Blinded assessment. • Reference standard for distant metastases: pathologic verification or follow-up imaging.	• ILC: PET/CT increased the stage to stage IV in 8/146 (12%): in 3, stage increased only by the CT component (FDG negative metastases). • IDC: PET/CT increased stage in 20/89 (22%). All distant metastases were FDG-avid.	• Retrospective. Potential selection bias. • Lack of histological verification of nodal disease. • No information about lymph node status changes.	III
Kramer et al.[45]	• Prospective. 101 patients. • Inclusion criteria: All stages BC. • Objective: comparison of PET/CT versus CS for staging and treatment impact. • Blinded assessment. • Reference standard: histological confirmation or additional imaging or follow-up.	• PET/CT changed the TNM stage in 20%. • Treatment changed in 11 (11%): 2 to surgery and extended field of RT, 5 to extended field of RT, and 4 to palliative approach.	• No histological confirmation of all suspicious findings on PET/CT.	II
Nursal et al.[46]	• Retrospective. 419 patients. • Inclusion criteria: early BC. Clinical stages I–II. • Objective: comparison of PET/CT versus CS for staging • Reference standard: histopathology or additional imaging.	• Distant metastases were detected in 42 patients (10%). • PET/CT increased the stage in 31 (30%) clinical stage I patients. • In clinical stage II, PET/CT increased the stage in 41 (13%) and decreased the stage in 40 (13%).	• Retrospective. • No blinded assessment • Non-representative population. • No histological confirmation in all the cases.	III

CS: conventional staging (breast magnetic resonance imaging, chest computed tomography, liver ultrasonography, bone scintigraphy); IMN: internal mammary nodes; ALNM: axillary lymph node metastases; ILC: invasive lobular carcinoma; IDC: invasive ductal carcinoma; M1: distant metastases; IBC: inflammatory breast cancer; BC: breast cancer; FNAB: fine-needle aspiration biopsy; TNM: tumor, node, and metastases stage; LABC: locally advanced breast cancer; PET/CT: positron emission tomography/computed tomography; FDG: fluorodeoxyglucose; NAC: neoadjuvant chemotherapy.

Table 8. Relation of metabolic variables with tumor biology (histopathological prognostic factors and molecular phenotypes).

References	Methodology	Results	Limitations	Evidence level
Ueda et al.[47]	• Prospective. 152 patients. • Inclusion criteria: stages I–III operable BC • Objective: clinicopathological correlation with the level of SUVmax in primary tumor. • Reference standard: pathological assessment.	• Multivariate analysis showed significant correlation of invasive tumor size, nuclear grade, and ER negativity with SUV.	• Non-blinded evaluation.	II
Groheux et al.[48]	• Prospective. 132 patients. • Inclusion criteria: T2–T4 BC. • Objective: correlation of SUV with biological characteristics. • Reference standard: pathological assessment.	• FDG uptake was highest in patients with poor prognostic features (high grade, hormone receptor negativity, triple negativity, metaplastic tumors).	• Non-blinded evaluation.	II
Koolen et al.[49]	• Prospective. 214 patients. • Inclusion criteria: stages II–III BC with at least one tumor-positive ALN before chemotherapy. • Objective: correlation of SUVmax of the primary tumor with age, TNM stage, histology, hormone and HER2 status, grade, Ki-67, and molecular subtype. • Reference standard: pathological assessment.	• SUVmax was significantly higher in patients with distant metastases, non-lobular carcinomas, tumors with negative hormone receptors, triple-negative tumors, grade 3 tumors, and tumors with a high proliferation index (Ki-67 expression). • TN and grade 3 tumors were significantly associated with a higher SUVmax in multiple linear regression analysis.	• Non-blinded evaluation.	II
Sanli et al.[50]	• Retrospective. 79 patients. • Inclusion criteria: BC with indication for neoadjuvant chemotherapy. • Objective: comparison of SUVmax with ER and PR, expression of HER2, tumor grade, and tumor size. • Reference standard: pathological assessment.	• Tumors with negative ER were associated with higher SUVmax. Tumors with overexpression of HER2, tumor grade 3, axillary lymph node involvement, tumor histopathology, and increased tumor size were associated with higher SUVmax. However, PR status was not associated with SUVmax.	• Retrospective study. Non-representative population. • Non-blinded evaluation. • Lack of complete surgical removal of the tumor for estimating the total tumor volume.	III
García-Vicente et al.[51]	• Prospective multicenter study. 168 patients. • Inclusion criteria: LABC. • Dual time-point acquisition (whole-body + thoracic acquisition). • Objective: correlation of SUVmax (SUV-1 and SUV-2) and RI with molecular subtypes. • Reference standard: pathological assessment.	• There were significant differences between SUV-1 and SUV-2 and the different subtypes, with higher SUV values in pure HER2 (+) and TN. No significant differences were found with respect to RI.	• Non-blinded evaluation. • Multicenter nature meant that data accessibility was limited in some cases and the heterogeneity in the histopathological evaluations and reports of the primary tumors could have affected the statistical reliability of the results.	II
Ekmekciglu et al.[52]	• Retrospective. 136 women and 4 men. • Inclusion criteria: T1–T3 BC. • Objective: comparison of SUVmax of primary tumor with histopathological and immunochemical prognostic factors. • Reference standard: pathological assessment.	• Primary tumor 18F-FDG uptake and tumor-to-background SUVmax ratios were significantly associated with tumor size, histological type, histological grade, pleomorphism, mitosis count, lymphatic invasion, necrosis, estrogen negativity, high Ki-67 level, axillary lymph node involvement, and triple negativity.	• Retrospective. Non-blinded evaluation. • The region of interest to measure SUVmax was drawn manually. • Limited information was available regarding tumor pathology in some patients.	III

(continued)

Table 8 (continued)

References	Methodology	Results	Limitations	Evidence level
Koo et al.[53]	• Retrospective. 548 patients/552 tumors. • Inclusion criteria: operable BC. • Objective: correlation between SUVmax and the subtypes of BC. • Reference standard: pathological assessment.	• FDG uptake was independently associated with the subtype of invasive BC. TN and HER2-positive tumors had 1.67-fold ($p < 0.001$) and 1.27-fold ($p = 0.009$) higher SUVmax values, respectively, than luminal A tumors.	• Retrospective. Non-blinded evaluation. • PET/CT imaging was acquired on two different PET/CT systems, which could have affected the interpretation of SUVmax.	II
García García-Esquinas et al.[54]	• Prospective. 43 patients. • Inclusion criteria: stages II–III BC. • Objective: SUVmax of the locoregional disease versus histopathology. • Reference standard: pathological assessment.	• A statistically significant association between elevated SUVmax and the absence of ER expression was found. • Locoregional disease with HER2(+) had significantly greater SUVmax values than luminal A (ER and/or PR positive with Ki-67 < 15%) and B (ER and/or PR positive with Ki-67 ≥ 15%). • TN phenotype had higher SUVmax than luminal A and B. Positive correlation between the percentage of the Ki-67 proliferation index and SUVmax. High-grade disease had a higher SUVmax than low grade.	• Small sample. Single-center design. • Non-blinded evaluation.	II
Yoon et al.[55]	• Prospective. 43 patients. • Inclusion criteria: LABC and IDC. • 68Ga-RGD PET/CT and 18F-FDG PET/CT. • Objective: correlation of functional imaging parameters (SUVmax and SUVavg) with immunohistochemical parameters and molecular subtypes. • Blinded assessment. • Reference standard: pathological assessment.	• Quantitative FDG PET parameters (SUVmax and SUVavg) were significantly higher in the ER-negative and the PR-negative groups. • Only the ER/PR−, HER2− subgroup showed a significant positive correlation between FDG and RGD PET parameters ($r = 0.59$, $p = 0.03$ for SUVmax).	• Small sample. • Particularly, the ER/PR+ and HER2(+) subgroup tended to have a large standard error; thus, the related results might be affected by a certain degree of bias.	II
Kitajima et al.[56]	• Retrospective. 306 patients/308 mass-type invasive BC. • Inclusion criteria: Pre-therapy BC (stages I–IV) patients • Objective: correlation between SUVmax and molecular subtype. • Blinded assessment. • Reference standard: pathological assessment.	• Significant associations were found between SUVmax and phenotypes with higher values for non-luminal A tumors with respect to luminal A ($p < 0.0001$); for HER2(+) tumors with respect to non-HER2(+) tumors ($p < 0.0001$), and for TN tumors with respect to non-TN tumors ($p < 0.0001$).	• Retrospective. Single-center design (selection bias). • The entire tumor was not evaluated in 165/306 patients (NAC or endocrine therapy), resulting in degradation of the reliability of the histopathological results.	I

68Ga-RGD: 68Ga-labeled arginine–glycine–aspartic acid; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; RI: retention index; TN: triple negative; SUVmax: maximum standardized uptake value; SUVavg: average standardized uptake value; RI: retention index; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; LABC: locally advanced breast cancer; NAC: neoadjuvant chemotherapy; BC: breast cancer; TNM: tumor, node, and metastases; ALN: axillary lymph node.

Table 9. Relation of metabolic information derived from basal 18F-FDG PET/CT with prognosis.

References	Methodology	Results	Limitations	Level of evidence
Ueda et al.[47]	• Prospective. 152 patients. • Inclusion criteria: stages I–III (operable) BC. • Objective: SUVmax in primary tumor with prognosis. • Reference standard: simulated prognosis derived from computed program Adjuvant!	• Tumors with high SUV (cutoff value = 4.0) showed higher relapse and mortality rate compared to those with low SUV ($p < 0.0001$).	• Computer program for the prognostic assessment.	II
Song et al.[57]	• Retrospective. 65 patients. • Inclusion criteria: IDC with confirmed metastatic ALN without distant metastasis. • Objective: relation of metastatic ALN SUVmax and other clinicopathological parameters for DFS. • Reference standard: follow-up. Median follow-up of 36 months.	• ALN SUVmax was significantly higher in patients with recurrence than in those who were disease-free (recurrence group: 5.2 ± 2.3 vs disease-free group: 1.9 ± 1.9, $p = 0.0001$). • Univariate analysis revealed that T stage, N stage, ER status, and primary-tumor and nodal SUVmax correlated significantly with DFS. Multivariate analysis found only nodal SUVmax was a single determinant of DFS (HR: 31.54; 95% CI: 2.66–373.39; $p = 0.0065$).	• Retrospective. • Only node-positive patients were enrolled. • Axillary region of interest was manually drawn. • SUV of small metastatic ALN may be underestimated because of partial-volume effect and the limited resolution of PET. • Short follow-up (3 years).	III
Groheux et al.[39]	• Prospective. 254 patients. • Inclusion criteria: clinical stages II–III BC. • Objective: impact of PET stage on prognosis. • Reference standard: follow-up for 2 years (189 patients evaluated).	• Survival was significantly shorter in the 47 patients scored M1 on 18FDG-PET-CT than in those scored M0, with a 3-year disease-specific survival of 57% versus 88% ($p < 0.001$). In multivariable analysis, only distant disease on PET-CT and triple-negative phenotype were significant prognostic factors. The relative risk of death was 26.60 (95% CI: 6.60–102.62) for M1 vs M0 patients.	• Single-center design. • Short follow-up.	II
Joo Hyun et al.[58]	• Retrospective. 441 patients. • Inclusion criteria: operable BC. • Objective: SUVmax of primary tumor and ALN with clinicopathological parameters to predict recurrence within 2 years after the end of first-line therapy. • Reference standard: clinical follow-up (2 years)	• Logistic regression found FDG uptake in ALN, pT, and pN stage grouping and neoadjuvant chemotherapy history was prognostic for early recurrence, while primary-tumor SUVmax, age, and ER or PR status were not. • Primary-tumor FDG uptake measured by SUVmax, and visual assessment of FDG uptake in the ALN in the initial staging PET/CT of patients with BC may not have additional prognostic value compared with conventional staging.	• Retrospective. • SUVmax measurements acquired from two different PET/CT scanners. • There was no ALN quantification due to very low SUV in many ALNs. • Short follow-up (2 years).	II
Champion et al.[32]	• Retrospective. 50 patients. • Inclusion criteria: IBC. • Objective: PET/CT versus DCE-CT. Primary-tumor SUVmax and tumor enhancement with prognosis. • Reference standard: clinical follow-up (median follow-up of 37 months).	• PET/CT M0 compared with M1 patients showed significantly better PFS ($p = 0.001$), but OS was not significantly different between the metastatic and non-metastatic groups ($p = 0.1$). • No significant differences in OS or PFS were observed between patients with high and moderate tumor FDG uptake using a SUVmax cutoff of 5, or between those with high and moderate tumor enhancement on DCE-CT.	• Retrospective. • Small sample. • Short follow-up.	II

(continued)

Table 9 (continued)

References	Methodology	Results	Limitations	Level of evidence
Kadoya et al.[59]	• Retrospective. 344 patients. • Inclusion criteria: stages I–III operable BC. • Objective: Relation of SUVmax and prognosis (recurrence-free survival). • Reference standard: clinical follow-up (median follow-up of 52 months).	• Patients were divided according to SUVmax values (<3.0 vs >3.0) established from ROC analysis of recurrence (AUC = 0.713). • Multivariate analysis using Cox proportional hazard regression model revealed high SUVmax and negative ER status as significant prognostic factors.	• Retrospective. • Mixed SUV values from ER-positive, HER2-positive, and triple-negative breast cancers.	II
Chen et al.[60]	• Retrospective. 240 patients. • Inclusion criteria: stages III–IV BC. • Objective: relation of primary-tumor SUVmax, MTV, and TLG with prognosis (PFS and OS). • Reference standard: clinical follow-up (median follow-up of 67 months).	• High risk: triple-negative or a TLG30% > 158 g or both. The 5-year PFS rates for stage III disease among patients with low-risk BC was 85% versus 68% among those with high-risk BC. For patients at stage IV, the 5-year PFS rates were 45% for patients with low-risk BC and 9% for patients with high-risk BC. Patients with stage III and high-risk BC had OS rates similar to those for patients with stage IV and low-risk BC ($p = 0.552$). • The TLG30% from pre-treatment PET/CT was independently associated with survival outcomes and appears to be able to effectively stratify patients with both stage III and stage IV BC.	• Retrospective. • Non-representative population with variations in the number of treatment cycles and regimens, which might affect survival.	II
Aogi et al.[61]	• Retrospective. 262 patients. • Inclusion criteria: Stages I–III BC (most in stages I and II, only luminal A and B). • Objective: relation of SUVmax and prognosis (relapse-free survival and overall survival). • Reference standard: clinical follow-up.	• SUVmax cutoff (ROC analysis) was predictor of OS (≤6.0 group vs >6 group, AUC = 0.742). • RFS was significantly better for SUVmax ≤ 6.0 than for SUVmax > 6.0 (p = 0.004). Similarly, SUVmax was significant for OS (p = 0.007 and p = 0.008). OS was significantly different between the SUVmax <6.0 and >6.0 groups (p = 0.001).	• Retrospective. Selection bias. • No adjustment of SUV according to tumor diameters to diminish partial-volume effect. • The median follow-up time is not reported.	III
Groheux et al.[33]	• Prospective. 98 patients. • Inclusion criteria: Consecutive TNBC. Stage II/III. • Objective: Assessment of prognosis. • Reference standard: clinical follow-up (2 years)	• PET/CT revealed distant metastases in 14 %. • Two-year disease-specific survival was 18% among patients with distant metastases on baseline PET/CT. • In patients without distant metastases, a high SUVmax at baseline was associated with shorter EFS.	• Single-center design. • No histological confirmation in all the cases with distant metastases. • Short follow-up (2 years).	II
Garcia Vicente et al.,[28]	• Prospective. 198 p. • Inclusion criteria: LABC. • Objective: relation of SUVmax in breast tumor and ALN and prognosis (OS and DFS) • Reference standard: clinical follow-up (mean: 34.8 months).	• Using cutoff values, a primary-tumor SUVmax ≥ 6.05 or a nodal SUVmax ≥ 2.25 were significantly correlated with DFS and OS. • In multivariate analysis, only metabolic stage was a significant predictor of OS (p = 0.001).	• Short follow-up	I

PFS: progression-free survival; MTV: metabolic tumor volume; TLG: total lesion glycolysis; IDC: invasive ductal carcinoma; ALN: axillary lymph node; DFS: disease-free survival; EFS: event-free survival; OS: overall survival; ROC: receiver-operating-characteristic curve; AUC: area under the curve; IBC: inflammatory breast cancer; DCE-CT: dynamic contrast-enhanced computed tomography; TN: triple negative; ER: estrogen receptor; HR: hazard ratio; BC: breast cancer; 95% CI: 95% confidence interval; PR: progesterone receptor; PET/CT: positron emission tomography/computed tomography; FDG: fluorodeoxyglucose; RFS: recurrence-free survival; SUVmax: maximum standardized uptake value.

Table 10. Cost-effectiveness of basal 18-F FDG PET/CT.

References	Methodology	Results	Limitations	Levels of evidence
Sloka et al.[62]	• Early BC (stages I–II) in Canada. • Theoretical sample of 1000 patients in each strategy. • Cost-effectiveness of PET/CT versus ALND in staging of BC. • Outcome: cost and life expectancy calculated using a standard decision analysis software package.	• A cost savings of US$695 per person is expected for the PET strategy, with an increase in life expectancy (7.4 days), when compared with the non-PET strategy. • This cost savings remained in favor of the PET strategy when subjected to a sensitivity analysis and is largely a result of the avoidance of the costs of both the ALND procedure and the subsequent 4.9-day hospital stay.	• Incremental cost-effectiveness ratio (ICER) was not calculated. • Palliative care costs, emotional support, and costs associated with quality of life were not included.	(−)
Meng et al.[63]	• Early BC in United Kingdom. • Cost-effectiveness of MRI and PET compared with SLNB for assessment of axillary lymph node metastases. • Individual patient discrete-event simulation model.	• SLNB strategy was not as cost-effective as replacing SLNB with either MRI or PET. • The strategy of replacing SLNB with PET had a net monetary benefit of £1085 (measured in UK £30,000 per QALY). • The strategy of replacing SLNB with MRI had the highest total QALYs and lowest total costs, but was subject to greater uncertainty.	• The evidence for MRI is based on a limited number of small studies. • The quality of evidence is poor to evaluate costs of lymphedema.	(−)

BC: breast cancer, ALND: axillary lymph node dissection, QALY: quality-adjusted life years, SLNB: sentinel lymph node biopsy; PET/CT: positron emission tomography/computed tomography; MRI: magnetic resonance imaging.

useful prior to surgery or neoadjuvant chemotherapy, based on the high rate of detection of distant metastases, ranging from 6% to 26%.[16,20,23,27] The percentage of patients with extra-ALN involvement detected by PET/CT in locally advanced BC ranges from 10% to 29%.[14–16] Moreover, in this setting, given the high prevalence of lymph node involvement (up to 80%), 18F-FDG PET/CT's high negative predictive value in lymph nodes adds to its usefulness.[12,15]

Patients younger than 40 years usually have more aggressive phenotypes of BC, which are more easily detected by 18F-FDG PET/CT.[30,31] Thus, PET/CT can be useful if younger age is associated with higher risk disease.

Comparison of 18F-FDG PET/CT with other diagnostic techniques

Several studies have found that 18F-FDG PET/CT is more accurate than conventional imaging (e.g. US) in the detection of axillary and extra-axillary (internal mammary) lymph node metastases and bone metastases.[16–18,20,23,24,36,38] However, methodological shortcomings in some of these studies reduce their value in addressing the real diagnostic impact of 18F-FDG PET/CT. The superiority of 18F-FDG PET/CT with respect to conventional imaging for detecting extra-ALNs and metastatic disease acquires more relevance in locally advanced BC.[20,21,23] Unfortunately, the three meta-analyses that examined 18F-FDG PET/CT's value in detecting distant metastases were limited by the inclusion of patients regardless of their treatment status.[24–26]

Diagnostic and prognostic impact of 18F-FDG PET/CT

18F-FDG PET/CT imaging changes the initial staging by conventional imaging in 5% to 52% of cases; the percentage is lower in patients with early-stage or operable BC[13] and higher in those with locally advanced BC or inflammatory BC.[11,41,42,46] 18F-FDG PET detects distant metastases in more than 20% of patients with locally advanced BC[14,16,20,27,28,31,37,39,40] and changes the initial staging in up to 52% of patients with inflammatory BC.[29–32] Other authors have reported changes in N stage based on the diagnosis of unsuspected metastatic extra-ALNs (N3). These findings are significantly more likely in patients with at least stage IIB BC (considered locally advanced BC by some authors or at least BC in which neoadjuvant chemotherapy is indicated), in whom PET/CT detected extra-ALN in 5%–29%.[14,16,37,39,40,43,46] Although the evidence seems stronger for stages IIB and III BC, the heterogeneous populations and the predominantly retrospective design used in the studies may explain the differences obtained and the lack of reproducibility of the results.

Another limitation is that most of the studies evaluated did not histologically confirm all the suspicious or pathological lesions detected by 18F-FDG PET/CT; some

studies used other imaging techniques to confirm the lesions, although they are less accurate than 18F-18F-FDG PET/CT, especially for bone and morphologically normal structures such as small-size lymph nodes. However, despite our strict reference standard, we recognize that it would be unethical to obtain specimens for histological confirmation from all the lesions detected by PET. Given the greater accuracy of 18F-FDG PET/CT with respect to the most morphological imaging techniques, pathologic findings on PET/CT should be considered suspicious for metastases in the absence of other explanations.

Therapeutic impact consists of changes from curative to palliative treatment, changes to the extent of the radiotherapy field, or additional surgical treatment.[40] 18F-FDG PET/CT changes the initial treatment in 1%–8% of patients with early-stage BC, in 7%–13% of those with locally advanced BC,[13,14,20,37,40,41,43] and in up to 52% of those with more aggressive tumors such as inflammatory BC.[31] Nevertheless, the therapeutic impact of 18F-FDG PET/CT in early-stage BC is controversial. Jeong et al.[13] reported that the impact of 18F-FDG PET/CT on the initial staging and treatment in patients with early BC with clinically negative axillary nodes was practically null. By contrast, Bernsdorf et al.[41] found a substantial impact on initial staging and on clinical management in patients with early-stage BC and tumors ≥2 cm. Thus, there is insufficient evidence to establish the therapeutic impact of 18F-FDG PET/CT in early-stage BC. By contrast, 18F-FDG PET/CT has a greater therapeutic impact in locally advanced BC.[14,20,31,37] The retrospective nature and lack of histological confirmation were the main limitations of most of the studies included, reducing their evidence level, despite the large number of patients evaluated in some. However, the evidence seems stronger for stages IIB and III of BC.

Glycolytic activity with 18F-FDG PET/CT, tumor biology, and prognosis

Semiquantitative metabolic parameters obtained with 18F-FDG PET/CT provide information about tumor biology. Maximum standardized uptake value (SUVmax) increases with the biological aggressiveness of the tumors; high-grade, hormone receptor–negative, and triple-negative tumors have higher SUVmax than low-grade and hormone receptor–positive tumors.[47–56] However, a reproducible SUVmax cutoff that would predict tumor biology has yet to be established. A mean SUVmax close to 10 has been reported in triple-negative BC, although the wide dispersion makes it impossible to define an effective cutoff.[51–53] Differences in SUVmax values are mainly due to the enormous biological heterogeneity of BC, even among tumors of the same molecular phenotype, although differences in PET acquisition (supine vs. prone position) and in the way the region of interest was selected (automatically vs. manually) may also contribute to variation among studies.[49,52] Another factor making comparisons among studies difficult is that molecular subtype based on immunohistochemistry might not correspond with the molecular subtype determined by the gene expression profile; furthermore, especially in advanced stages where neoadjuvant treatment is indicated, immunohistochemistry is done on imaging-guided core-needle biopsy specimens, so the results are not as reliable as analyses of the entire tumor.[56] However, despite these limitations, 18F-FDG-PET has demonstrated a good correlation with the molecular phenotypes.[51,53,55,56]

18F-FDG-PET can have an impact on the patient's prognosis in two ways: by detecting distant metastases occult to other techniques and by detecting glycolytic activity in the primary tumor and ALN. Various authors have compared prognostic stratification at initial staging by 18F-FDG-PET versus conventional imaging.[31,43] The detection of occult distant metastases on 18F-FDG PET/CT is associated with shorter survival independent of the molecular phenotypes.[28,32,33,39] With respect to the semiquantitative information from 18F-FDG PET/CT, the prognostic impact of the SUVmax of the primary tumor is controversial. Whereas some authors found no association between tumor 18F-FDG uptake and prognosis,[32,58] others reported that patients with high tumor uptake had worse outcomes.[28,47,59,61] Furthermore, a single and reproducible SUVmax has yet to be established; cutoff values range from 3 to 6.[28,59,61] The variability among studies is probably due to the different immunohistochemical characteristics of the tumors rather than to differences in methodology. However, it is noteworthy to consider how this semiquantitative metric affects the prognosis of both operable and advanced BC, regardless of the biology of the tumor.[28,32,33,39,47,57–61] The lack of reproducibility of SUV has led to explorations of other metrics, such as total lesion glycolysis, although more studies are necessary to assess their impact.[60] The evidence for the prognostic value of SUVmax in ALN is limited, although higher values have been associated with higher recurrence rates.[28,57,58]

One important aspect is the applicability of the prognostic information derived from 18F-FDG PET. Whereas 18F-FDG PETs increasing the stage initially diagnosed with conventional imaging may modify the planned treatment, the use of information about tumor glycolysis is more controversial, although patients with tumors with high SUVmax should perhaps undergo stricter follow-up than those with tumors with low SUVmax. Thus, despite the high heterogeneity among the studies with respect to clinical stages, tumor biology (inflammatory BC, triple-negative BC), end-points (overall survival (OS), progression-free survival (PFS), disease-free survival (DFS)), methodology (breast, ALN), and design (retrospective or prospective), all the studies found that PET/CT has prognostic value in BC.[28,32,33,39,47,57–61]

Cost-effectiveness of 18F-FDG PET/CT

The evidence on the cost-effectiveness of 18F-FDG-PET or PET/CT in BC is limited. Meng et al.[63] concluded that MRI was the most cost-effective strategy to replace sentinel lymph node biopsy, but also pointed out that further studies using up-to-date techniques in larger samples are required to obtain more accurate data on the sensitivity and specificity of MRI. Sloka et al.[62] used PET/CT to calculate the cost savings for lymph node staging in early BC against ALN dissection, a context with reduced applicability. In summary, more studies are needed to evaluate cost-effectiveness of 18F-FDG-PET in patients with BC.

Conclusion

18F-FDG PET/CT is not recommended in early BC, although evidence supports its use in locally advanced BC based on improved regional and distant staging. The evidence for systematically recommending 18F-FDG PET/CT in triple-negative BC is more limited, and further studies are necessary to assess the real diagnostic and therapeutic impact. There is insufficient evidence to address the cost-effectiveness of 18F-FDG PET/CT. Baseline tumor glycolytic activity is associated with biology and prognosis. Well-designed prospective studies are necessary to determine the real impact of 18F-FDG PET/CT in the more controversial settings of BC staging.

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Compliance with ethical standards

Neither animals nor human subjects were used in this study.

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