

# Comparative diagnostic accuracy of $^{18}\text{F}$ -FDG PET/CT for breast cancer recurrence

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**Abstract:** In the last decades, in addition to conventional imaging techniques and magnetic resonance imaging (MRI),  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) has been shown to be relevant in the detection and management of breast cancer recurrence in doubtful cases in selected groups of patients. While there are no conclusive data indicating that imaging tests, including FDG PET/CT, produce a survival benefit in asymptomatic patients, FDG PET/CT can be useful for identifying the site of relapse when traditional imaging methods are equivocal or conflicting and for identifying or confirming isolated loco-regional relapse or isolated metastatic lesions. The present narrative review deals with the potential role of FDG PET in these clinical settings by comparing its accuracy and impact with conventional imaging modalities such as CT, ultrasound, bone scan,  $^{18}\text{F}$ -sodium fluoride PET/CT ( $^{18}\text{F}$ -NaF PET/CT) as well as MRI. Patient-focused perspectives in terms of patients' satisfaction and acceptability are also discussed.

**Keywords:** breast cancer, positron emission tomography, restaging

## Introduction to the types and rates of breast cancer recurrence

Breast cancer is the most common type of cancer and the second leading cause of cancer-related death among women. It affects more than 1 million women worldwide.<sup>1</sup> Available data show an estimated incidence at 1.67 million of new cases in the world by year;<sup>2</sup> moreover, approximately 30% of patients relapses within 15 years after initial treatment.<sup>1</sup>

Breast cancer is a highly heterogeneous disease, which is currently classified into several different subtypes; this information is useful for predicting response to treatment.<sup>3</sup> The most relevant prognostic factors in the prediction of treatment outcome, recurrence-free survival and disease-specific survival are: tumor nodes metastasis (TNM) stage, histological evaluation, gene expression profiling and age.<sup>4,5</sup>

From the staging point-of-view, survival for breast cancer is strongly related to the baseline TNM evaluation (Table 1 for details on TNM staging in breast cancer patients). In fact, 1-year survival for breast cancer is highest for patients diagnosed at stage I and lowest for those diagnosed at stage IV.<sup>1</sup>

Other than the TNM staging, the tumor is classified on morphological bases. The most common type of breast cancer is invasive ductal carcinoma not otherwise specified (ductal NOS; 70% of breast cancer cases). Ductal NOS corresponds to a heterogeneous group of tumors that fail to exhibit sufficient characteristics to achieve classification as a specific histological type, such as lobular or tubular carcinoma.<sup>6</sup> The second most

**Table I** TNM classification for breast cancer

pT	Tumor size		
Tis	In situ		
T1a (cm)	≤0.5		
T1b (cm)	0.5–1		
T1c (cm)	1–2		
T2 (cm)	2–5		
T3 (cm)	>5		
T4a	Extension to chest wall (does not include pectoralis muscle invasion)		
T4b	Ulceration, ipsilateral satellite skin nodules, skin edema		
T4c	a+b		
T4d	Inflammatory cancer		
pN	Lymph node		
N0	No lymph node metastasis		
N1a	1–3 axillary nodes		
N1b	Internal mammary nodes with metastasis by sentinel node biopsy but not clinically detected		
N1c	a+b		
N2a	4–9 axillary nodes		
N2b	Internal mammary nodes, clinically detected, without axillary nodes		
N3a	>10 axillary nodes or infraclavicular		
N3b	Internal mammary nodes, clinically detected, with axillary nodes or >3 axillary nodes and internal axillary mammary nodes with microscopic metastasis by sentinel node biopsy but not clinically detected		
N3c	Supraclavicular		
M	Metastasis		
M0	No distant metastasis		
M1	Distant metastasis		
Stage	T	N	M
<i>Breast cancer staging</i>			
0	Tis	N0	M0
IA	T1	N0	M0
IB	T0/T1	N1 micro	M0
IIA	T0/T1	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0/T1/T2	N2	M0
	T3	N1/N2	M0
IIIB	T4	N0/N1/N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

**Abbreviations:** pT, tumor size; TNM, tumor, node, metastasis.

frequent type of breast cancer is the invasive lobular carcinoma (ILC). It represents 5%–15% of invasive breast tumors and appears as an invasive carcinoma, usually associated with lobular carcinoma in situ. It is composed of non-cohesive cells, individually dispersed or arranged in single-file linear pattern in a fibrous stroma.<sup>6</sup> Finally, medullary carcinoma represents between 1% and 7% of breast cancer. It is a well-circumscribed carcinoma composed of poorly differentiated

cells arranged in large sheets, with no glandular structures, scant stroma and a prominent lymphoplasmacytic infiltrate.<sup>6</sup>

With respect to gene expression profiling, the St. Gallen International Expert Consensus proposed a new intrinsic biological classification system, based on the expression of the estrogen receptor (ER), progesterone receptor, human epidermal growth factor receptor 2 (HER2) and Ki-67. The classification system categorizes invasive breast carcinomas into the following 5 distinct molecular subtypes: luminal A, luminal B (HER2-), luminal B (HER2+), HER2 and triple negative/basal-like subtypes. These different subtypes are managed with different therapeutic approaches and are linked with different recurrence risk as well as with distinct prognostic stratification.<sup>7</sup> The luminal-like tumors express hormone receptors (HRs), with expression profiles reminiscent of the luminal epithelial component of the breast.<sup>8</sup> They are the most common subtype among breast cancers, with luminal A being the majority. The luminal-like tumors carry a good prognosis although luminal B tumors have a significantly worse prognosis and high recurrence scores compared to the luminal A subtype. Luminal tumors respond well to hormone therapy, but poorly to conventional chemotherapy. ER-positive tumors are associated with a higher recurrence rate but are less frequently fatal.<sup>9</sup> Conversely, over-expression of HER2 predicts a poor prognosis; these tumors are more sensitive to cytotoxic therapy. The triple-negative/basal subtypes are associated with young patient age and present an aggressive clinical course. These tumors are also associated with a lower disease-specific survival and higher risk of local and regional relapse.<sup>10</sup>

Recurrence can occur as: 1) local recurrence when the relapsing lesion is in the same area of the breast (ipsilateral) or in the mastectomy scar; 2) regional recurrence (lymph nodes in the ipsilateral axilla); 3) distant recurrence (more frequently mediastinal lymph nodes, bones, lungs, liver and brain.). Two-thirds of breast recurrences are local and occur more frequently within 5 years of the initial diagnosis.<sup>5</sup>

Finally, age is also a relevant prognostic factor as younger age is related to a greater chance of recurrence.<sup>5</sup>

## Summary of current diagnostic methods

### Local and regional recurrence

The most common site of local recurrence after breast conserving surgery and adjunct whole-breast irradiation, is the site of the primary breast cancer, representing 88% of local recurrences. Other manifestations of local recurrence are found in the same breast, in a different breast quadrant or as radiation-induced carcinoma within the treatment portal.<sup>11</sup>

Early detection and treatment of isolated locoregional recurrences before symptomatic onset may have a beneficial effect on the prognosis, by improving local treatment feasibility rate and by avoiding the situation of uncontrollable locoregional disease.<sup>12–14</sup> According to these data, National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology guidelines recommend routine follow-up visits, including clinical breast examination and mammography (Mx) for at least 5 years. In particular, clinical breast examination is recommended every 3 months and a mammogram every 6 months for the first 2 years, followed by a mammogram once a year with clinical breast examination twice a year for the next 3 years.<sup>12,15</sup> Current strategies for the local breast cancer recurrence detection mainly include Mx, ultrasonography (US) and magnetic resonance imaging (MRI).<sup>16</sup> Digital tomosynthesis is gaining an emerging role in the evaluation of radiographically dense breasts.<sup>17</sup>

Regular Mx is recommended in the follow-up program for all breast cancer patients as up to one-third of local recurrences are detected by Mx alone (more likely in the conserved breast). The recurrence usually presents similar mammographic features with respect to the original tumor.<sup>12,18</sup> Advantages of Mx comprise wide availability, reduced cost and a high diagnostic accuracy in reference centers. This satisfactory performance reflects an established approach and a consolidated standardization, making Mx a non-operator-dependent technique. However, the sensitivity of Mx in the detection of local recurrences ranges from 55% to 68%, being influenced by an insufficient morphological distinction between therapy-induced edema and lymphangiosarcoma or between radially striated scar tissue and tumor recurrence. In fact, the treated breast may be more difficult to position because of surgical deformities or may be relatively noncompressible because of pain or structural changes. Changes following breast-conserving surgery can include hematoma, seroma, fat tissue necrosis, scar tissue development and dystrophic calcifications. Radiotherapy-induced alterations can include vascular dilatation, capillary damage, microcirculatory changes and consequent edema. The summation of these changes complicates the interpretation of clinical examination and Mx due to focal thickening, decreased compressibility and increased density at the surgical site.<sup>19</sup> In this scenario, US has high sensitivity if performed at regular intervals, because of the detection of hypoechoic nodules within fibrous hyperechoic tissue.<sup>12,19</sup>

Early detection of regional breast cancer recurrence in asymptomatic patients has a positive effect on survival but may be difficult for several reasons. First, there is no reliable

screening or diagnostic tool to evaluate the axillary and supraclavicular lymph node areas, which are useful predictors of concurrent or subsequent distant metastasis. Moreover, the false-negative rate of the axilla at physical examination is high, reaching up to 39%. Physical examination of regional lymph nodes is hindered by factors such as anatomic location (beneath the clavicle or deep in subcutaneous fat tissue), scar tissue due to previous axillary lymph node dissection or radiation, obesity and small size of the recurrence. Since the false-negative rate of physical examination of the axilla is so high and the field of view of Mx does not include this entire area, US after breast cancer surgery is recommended, also in asymptomatic patients, in order to detect lymph node region recurrence.<sup>13,20</sup> However, US sensitivity is user-dependent and may be diminished in the presence of small or noninvasive lesions, especially in fatty breasts.<sup>12,19</sup>

MRI may be superior to traditional imaging in diagnosis of recurrence in the presence of scar tissue when performed at least 12–18 months after breast conserving surgery and at greater intervals from radiotherapy.

Sensitivity levels of MRI for diagnosis of suspected breast cancer recurrence ranged from 75% to 100% while specificity ranged from 66% to 100%. Sensitivity and specificity were consistently higher for MRI compared with Mx or ultrasound alone. MRI has shown an extremely high negative predictive value (98.8%) in the detection of breast cancer recurrence, including lesions not related to the surgical scar, thus allowing avoidance of the need for further biopsy in the presence of negative MRI. Moreover, in published studies, MRI has been demonstrated to detect cancers in contralateral breasts that were overlooked by clinical examinations, Mx and sonography at the time of initial diagnosis in 3.1%–18.6% of patients.<sup>13,21–23</sup> In summary, MRI has a sensitivity ranging from 75% to 100% for detecting suspected breast cancer recurrence in women previously treated for breast cancer with either breast conserving surgery and radiotherapy or mastectomy. Given its higher costs and lower availability, MRI cannot be recommended in the routine surveillance for breast cancer recurrence, but should be used in the case of suspected recurrence when clinical, mammographic and/or sonographic findings are inconclusive or other investigations have equivocal findings.<sup>19,23</sup> Finally, MRI is particularly useful for surveillance of young women due to its proven higher sensitivity compared with Mx, especially in dense breasts.<sup>24–28</sup>

## Distant metastasis

Most frequently, metastases from breast cancer occur within the mediastinal lymph nodes (frequently first

ipsilateral and then contralateral), bones, lungs, liver and brain. Different patients' and tumor characteristics are related to different patterns of distant relapse: bone metastases are more likely to be diagnosed in patients with HR-positive disease, while lung and liver metastases are more common in patients with a more advanced stage at the time of diagnosis; finally, brain metastases were mostly observed in patients with HR-negative disease.<sup>29,30</sup> Currently, restaging of breast cancer patients is predominantly based on physical examination, blood parameters, computed tomography (CT), MRI, US and X-rays (XR) as well as bone scintigraphy. Distant metastases are revealed in 16%–20% of patients.

CT is able to assess the most frequent sites of metastases and is widely available. CT is the primary modality used to detect intrathoracic lymph node enlargement (whenever the short-axis diameter of a lymph node exceeds 1 cm).<sup>31</sup> Skeletal tissue is the second most common (30%–85%) site of distant localization and the first site of metastasis in up to 50% of all stage IV breast cancer. Breast cancer metastasis in the bone alters osteoclast and osteoblast function, resulting in bone destruction, which can be detected by CT.<sup>16,32,33</sup> On CT, skeletal metastasis appears as lytic, sclerotic, or mixed lesions that may be complicated by pathologic fracture or spinal cord compression. Sagittal CT reformations are better than XR and bone scintigraphy (BS) for detecting vertebral body compression fractures and epidural extension of metastasis.

BS remains the most suitable technique for whole-body screening of bone metastasis due to its low cost and high availability. However, it often requires integration with other modalities (XR, CT or MRI).<sup>34,35</sup> BS sensitivity ranges from 62% to 100% and its specificity is between 78% and 100%.<sup>35</sup> BS is more sensitive than CT and XR for the early detection of skeletal metastasis, but it has lower specificity and higher false-positive rates than XR because the uptake of radionuclide in BS reflects the metabolic reaction of bone caused by benign alterations (e.g., fracture, arthritis, or infection).<sup>36</sup> Moreover, a significant proportion of breast cancer bone metastases are osteolytic. In the case of rapid osteolytic growth, when bone turnover is slow, or when the site is avascular (photon-deficient lesions; "cold spots"), bone scans are often falsely negative.<sup>16</sup> In summary, although planar bone scanning has recognized limitations, in particular poor specificity in staging and response assessment, it continues to be the mainstay of skeletal staging in patients at risk of bone localizations. Moreover, the accuracy of bone scanning can be improved

with the addition of single-photon emission (SPECT)/CT owing to the greater contrast resolution of SPECT, to the elimination of summation artifacts characteristic of planar images, as well as for the ability to reduce false-positive findings through correlation with CT.<sup>37</sup>

XR has been historically used in metastatic breast cancer to study a limited bone anatomical region as a complement to BS and for settling equivocal findings (e.g., "suspicious" lesions or a single "hot spot"). However, metastatic lesions on XR may not appear for several months, as 30% to 75% of normal bone mineral content must be lost before lesions become visible.

Finally, <sup>18</sup>F-sodium fluoride positron emission tomography/CT (NaF-PET/CT) provides very sensitive detection and visualization of breast cancer bone metastases. <sup>18</sup>F-sodium fluoride (<sup>18</sup>F-NaF) reflects the increased regional blood flow and osteoblastic bone reaction. In particular, greater activity of bone turnover determines greater blood flow and exchange surface for <sup>18</sup>F-fluoride ion absorption and subsequent irreversible incorporation into the bone matrix as fluorapatite. In a recent study, sensitivity and specificity for NaF-PET were 91% and 91%, respectively, compared with 77% and 93% for CT. The integrated assessment of NaF-PET/CT yielded a sensitivity of 98%, with a corresponding specificity of 93%.<sup>16</sup> <sup>18</sup>F-NaF is characterized by an extremely high sensitivity rather than low specificity for both sclerotic and lytic lesions; thanks to its better spatial resolution this tracer is even capable of capturing the increased mineral metabolism related to the thin reactive border that may surround a lytic lesion. In a recent study, Capitanio et al suggested that the extremely high sensitivity of <sup>18</sup>F-NaF uptake could be advantageous in specific clinical settings (such as small CT-evident sclerotic lesions), possibly changing patient staging or management, particularly when performed in patients who would be candidates for regional therapy (i.e., surgery or radiotherapy), with the aim of excluding further occult metastases. In conclusion, patients could benefit from <sup>18</sup>F-NaF PET when, in the presence of suspected biochemical or clinical disease relapse, other imaging tests give a negative result. Therefore, <sup>18</sup>F-NaF PET/CT is emerging as a "second-line" functional imaging tool, which may be of use in patients selected on the basis of their specific clinical history.<sup>38</sup>

MRI is more sensitive in detecting soft tissue metastases, particularly in the brain and the liver. Studies have also established the diagnostic advantage of whole-body MRI (sensitivity of 92% and specificity of 90%) over BS (sensitivity of 83% and specificity of 80%). Furthermore, MRI

can provide detailed images of the bone and bone marrow, which physiologically show a high-intensity signal on T1 imaging, whereas metastases appear as areas of reduced signal, reflecting the replacement of fat in the marrow by the tumor. Additionally, bone marrow signal can be canceled by techniques that saturate the intrinsic fat content thus highlighting small lesions with specific sequences like short-tau inversion recovery, T2 weighted fat-saturated turbo spin echo (TSE) and diffusion-weighted sequences.<sup>39,40</sup> Even if MRI is better than CT for detecting bone marrow lesions or spinal cord and nerve root compression, CT may be preferable for assessing destruction of bone structure in axial bone localizations. In fact, cortical bone does not produce a signal and appears black both on T1 and T2-weighted sequences.<sup>16,31,35</sup>

## Review of the diagnostic accuracy of <sup>18</sup>F-fluorodeoxyglucose (FDG) PET/CT for breast cancer recurrence compared with other diagnostic methods

In the last decades, in addition to conventional imaging techniques (CT, BS) and MRI, <sup>18</sup>F-FDG PET/CT has shown a relevant impact in the detection and management of breast cancer recurrence, especially in selected groups of patients presenting doubtful findings. According to European Society for Medical Oncology (ESMO) clinical guidelines on breast cancer, detection of early local recurrences and identification of contralateral relapses are the principal aims in the surveillance in these patients.<sup>41</sup> However, the same guidelines state that no conclusive demonstration exists that imaging tests, including FDG PET/CT, can produce a survival benefit in asymptomatic patients.<sup>41</sup> By contrast, ESMO guidelines on locally recurrent and metastatic breast cancer as well as NCCN guidelines suggest that FDG PET/CT can be useful for identifying the site of relapse when traditional imaging methods are equivocal or conflicting. Moreover, this imaging modality can improve the identification of isolated loco-regional relapse as well as isolated metastatic lesions, that is, a situation where patients may benefit from a more aggressive multidisciplinary approach.<sup>42,43</sup> Similarly, <sup>18</sup>F-FDG PET/CT has been proposed in the case of increasing tumor markers and inconclusive conventional imaging. In all these settings, FDG PET/CT allows meeting of this target owing to its high sensitivity (77%–90%) and specificity (69%–80%).<sup>44</sup> These rates are even higher in patients with increased serum CA15.3 levels (cut-off 31.3 U/mL) and a radiologic suspicion of recurrence. For those, a sensitivity of 92.7% is reported.<sup>44</sup>

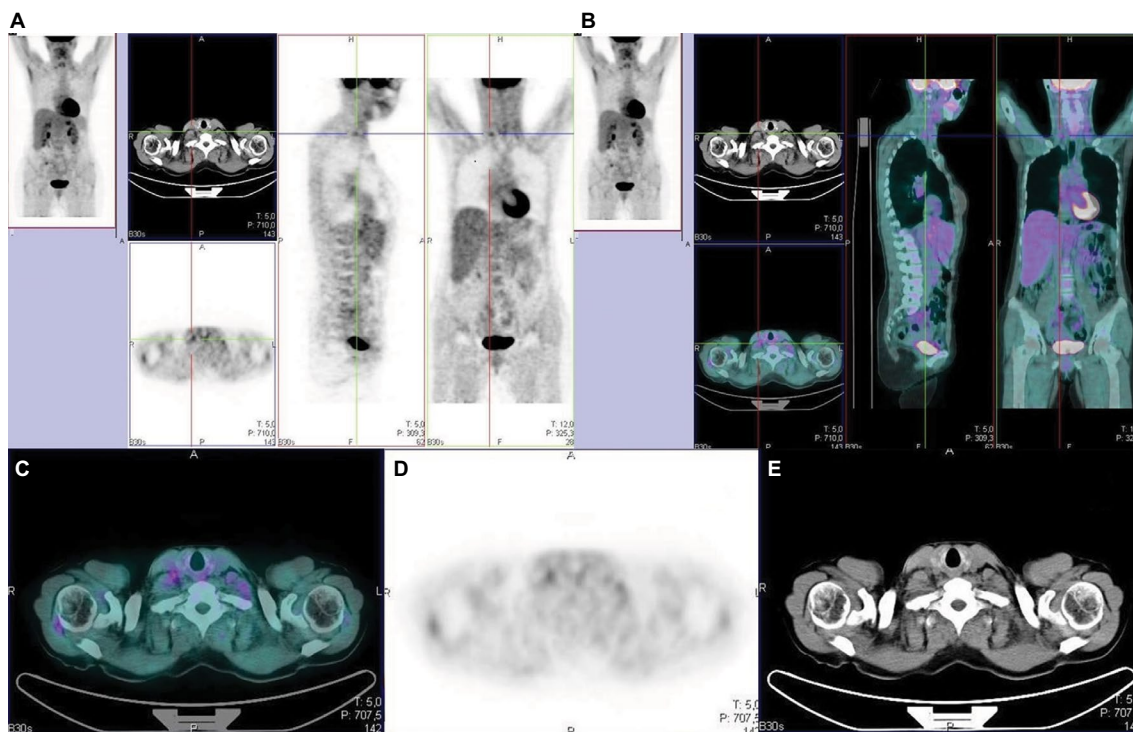
FDG PET uptake in breast cancer lesions is influenced by several factors. In fact, the aggressiveness of breast cancer, based on histological features, is directly related to glucose metabolism. Similarly, invasive ductal carcinoma type, triple negative receptorial pattern, elevated Ki-67 and undifferentiated histopathology (G3) all correlated with a higher <sup>18</sup>F-FDG uptake at PET/CT.<sup>45</sup> By contrast, false-negative PET/CT results can occur due to low FDG uptake in some conditions, such as ILC, ongoing endocrine therapy, and small highly sclerotic skeletal lesions with low rate of actively replicating cells. Finally, the relatively low specificity of PET/CT in patients with high levels of tumor markers might be related to bone degenerative disease, lung inflammation, reconstruction artifacts, in particular in patients with breast expanders, as well as to other inflammations that are the common cause of false-positive findings with FDG.<sup>46</sup>

## Increasing tumor markers

In patients with suspected recurrent disease because of increased CA15.3, carcinoembryonic antigen (CEA) or cancer antigen 125 (CA125), FDG PET/CT has demonstrated a high positive predictive value (PPV) (97%) and accuracy (83%–86%).<sup>46–48</sup> In fact, compared with other methods (CT or MRI), FDG PET/CT shows a higher accuracy in the differential diagnosis between loco-regional recurrence and post-treatment scar or inflammation phenomena.<sup>49–51</sup> On the other hand, the negative predictive value (NPV) is <60%.<sup>50</sup> One possible explanation is that lesions with a diameter <5 mm are below the spatial resolution of PET/CT. Nevertheless, FDG PET/CT shows an improved NPV in the early evaluation of HR+ patients during therapy, allowing identification of the non-responders, characterized by a poorer prognosis.<sup>52</sup>

Suárez et al reported that CA15.3 blood levels >60 U/mL were always associated with positive PET, while CA15.3 blood levels <50 U/mL were always associated with a negative one.<sup>53</sup> Similarly, Liu et al showed that the diagnostic sensitivity and accuracy of FDG PET in patients with suspected recurrent breast cancer and asymptotically elevated tumor markers, were 96% and 90%.<sup>54</sup> On the other side, a systematic review by Evangelista et al showed that PET/CT allows 83% accuracy in the assessment of the site and extent of the recurring disease, irrespective of the value of CA15.3 and CT findings. However, no single cut-off value yielding an acceptable sensitivity and specificity has been so far identified.<sup>46</sup> Figure 1 shows a representative example of a breast cancer patient submitted to FDG PET because of increasing tumor markers in the presence of a negative CT scan.





**Figure 1** Breast cancer patient with rising tumor marker (cancer antigen 15.3) and negative CT scan.

**Notes:** FDG-PET highlights an 11 mm lymph node with moderate FDG uptake. The presence of disease relapse within this lymph node was confirmed by means of ultrasound-guided biopsy. Three-section imaging (**A**: PET; **B**: three-slices fused imaging); transaxial section (**C**: fused imaging; **D**: PET; **E**: CT).

**Abbreviations:** CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography.

## Restaging in inconclusive cases and metastatic patients who are candidates for surgery

Accurate restaging is of pivotal importance in patients with suspicion of loco-regional cancer recurrence, as a limited relapse extent implies the possibility of a salvage surgery. The clinical management and prognosis of these patients are, in fact, mainly based on the extent of the loco-regional recurrence and on the absence of distant metastases.<sup>49</sup> In this setting, some authors demonstrated that FDG PET/CT had a substantial impact on clinical management in 51%–69% of patients.<sup>48,55,56</sup>

In a study by Cochet et al<sup>56</sup> conventional imaging (CI) findings were indicative of relapse in the majority of patients (54/66); however, <sup>18</sup>F-FDG PET/CT downstaged 12 patients, providing a better negative predictive value when compared with CI alone. These findings suggest that FDG PET/CT is not only effective for relapse detection in patients with negative conventional imaging findings, but also may provide a better lesions' characterization in patients with a strong suspicion of relapse. In this clinical scenario, several studies documented that PET is superior to chest radiography for the detection of pulmonary metastases.<sup>57,58</sup> Integration of PET with CT could further increase the sensitivity in the detection

of recurrent disease in the chest compared with radiography. PET efficiently detects supra-centimetric disease-related pulmonary nodules and liver lesions; however, because of the partial-volume effect and respiratory movements, PET lacks in sensitivity for smaller lesions. In this context, as CT might be more to detect smaller lesions, also ones within the liver, hybrid imaging with FDG PET and full diagnostic contrast-enhanced CT has been proposed and might be of use in selected cases.<sup>59</sup> However, it has to be underlined that MRI has been demonstrated to be superior to both CT and FDG PET for the detection of small liver lesions with the use of hepatic-specific MR contrast agents.<sup>60</sup>

Finally, restaging of breast cancer patients at high risk for liver metastasis might be a potential indication for PET/MRI. However, only preliminary experience is available and studies in larger number of patients are needed.<sup>16</sup>

Distant metastases from breast cancer most frequently occur in the skeleton<sup>61,62</sup> and, on the basis of radiographic appearance, they can be classified as osteoblastic, osteolytic or mixed pattern.<sup>63</sup> The pathological osteoblastic activity may be indistinguishable on imaging from reactive and reparative activity after a successful treatment of bone metastases. The uptake of <sup>18</sup>F-FDG in viable bone metastases is assumed to be mainly within breast cancer tumor cells rather than in

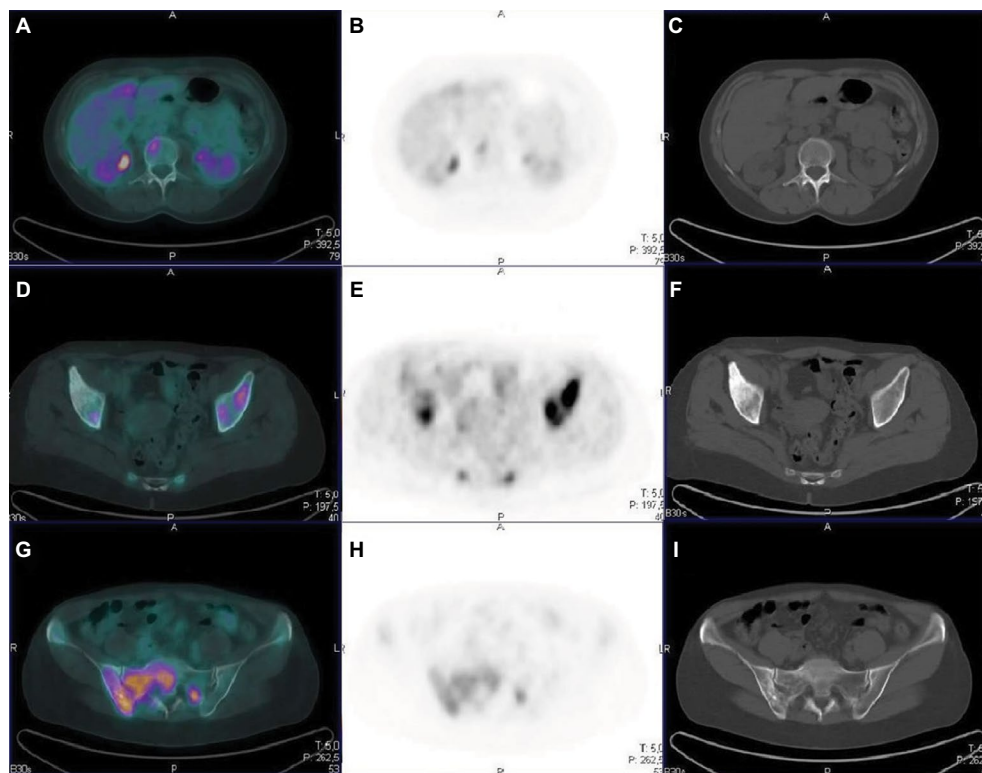
osteoblasts; therefore, it can be considered as a tumor-specific tracer rather than a direct index of alteration of bone micro-environment. Several authors have reported lower sensitivity for  $^{18}\text{F}$ -FDG PET in osteoblastic lesions than in osteolytic ones.<sup>64–73</sup> Different factors may contribute to the differences in  $^{18}\text{F}$ -FDG avidity between osteoblastic and osteolytic metastases. Histologic subtype could also be an important factor: ILC has been reported to show osteoblastic metastases with poor  $^{18}\text{F}$ -FDG uptake more frequently than invasive ductal carcinoma.<sup>66</sup> Previous treatments are also relevant, as many  $^{18}\text{F}$ -FDG-negative skeletal metastases may appear sclerotic as a consequence of previous systemic therapy, making tumor cells nonviable, even though ongoing reparative osteoblastic activity, as seen with BS or  $^{18}\text{F}$ -NaF PET, may persist.<sup>67</sup> Figure 2 shows some representative examples of bone metastasis from breast cancer patients positive to either CT or FDG PET scan or to both examinations.

In a retrospective study, Tateishi et al highlighted the importance of standardized uptake value (SUV) as a predictor of disease progression, although both a change in FDG uptake and increased bone sclerosis on CT images predicted the time to progression.<sup>68</sup> Therefore, FDG PET can improve the specificity of the bone metastases treatment response assessment. However, with respect to CI,  $^{18}\text{F}$ -FDG PET/CT may be able

to tell the response or non-response to systemic therapy with more accuracy and at an earlier time point, changing the clinical management of breast cancer patients.<sup>69</sup> For the detection of skeletal metastases and staging of cancer,  $^{18}\text{F}$ -FDG PET or PET/CT has shown higher sensitivity and specificity than BS in many studies<sup>70,71</sup> and meta-analyses.<sup>54,72,73</sup> Benefits in specificity can derive from the lower numbers of false-positive uptakes of  $^{18}\text{F}$ -FDG with respect to the bone-seeking tracers. The improvement in sensitivity over bone scan may be also due to the ability of PET/CT imaging to detect metastatic tumor cells within bone marrow before there is a sufficient osteoblastic reaction to permit the detection by bone-specific tracers. However, utility of  $^{18}\text{F}$ -FDG PET/CT can be limited in the case of small bone lesions, showing no visible morphologic changes in the co-registered CT images or absence of significant tracer uptake, in particular for lesions whose size is  $<2$  times the spatial resolution of the scanner (4–6 mm).

### Feasibility and patient outcomes

Compared with other imaging modalities,  $^{18}\text{F}$ -FDG PET/CT allows achieving the evaluation of the whole body with a single examination, avoiding delays in disease restaging. Although low-dose CT is principally used for attenuation correction, it also allows an anatomical localization of glucose



**Figure 2** Comparison between PET and CT in different types of bone lesions.

**Notes:** A–C: vertebral lesion with high FDG uptake in the absence of structural lesion on CT (metastasis in the bone marrow); D–F: CT sclerotic lesion in the right iliac bone with no concentration of FDG (likely a lesion with low cellularity); G–I: mixed bone lesion in the right sacroiliac bone on CT images markedly positive on the FDG PET scan. **Abbreviations:** CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography.

avid areas, adding the morphological data to the metabolic results. FDG PET/CT is a non-invasive examination of relatively short duration and not requiring special preparation, other than a 6-hour fasting. Furthermore, the impact of FDG PET/CT restaging on patients' management is noteworthy, as it has been reported to modify the treatment decisions in a not negligible number of cases.<sup>47,48,74</sup> In this framework, it has to be underlined that although guidelines do not recommend FDG PET for the surveillance of asymptomatic patients with non-metastatic breast cancer, FDG PET/CT is commonly required by clinicians in routine clinical practice. Accordingly, there is an urgent need for accurate economic evaluations of breast cancer management so as to ensure efficient use of healthcare resources as well as to avoid the use of third level examination such as FDG PET when impact on patients' outcome is not proven.<sup>75</sup>

FDG PET can add, to the restaging capabilities, a significant prognostic relevance, as the survival of patients who develop an isolated loco-regional recurrence differs significantly from patients who have distant relapse. Consequently, determination of both the locations and the extent of the recurrent disease is essential to guide therapeutic decisions and estimate prognosis. Some authors have suggested that FDG PET/CT can have a significant impact on the therapeutic management; however, information concerning its utility for a long-term prognostic stratification, when compared with CI, is limited.<sup>48</sup> In particular, there is no consensus about the best PET-derived parameters to predict patients' prognosis and/or survival.<sup>76</sup> First published studies were focused on the prognostic value of  $SUV_{max}$ , without testing other PET parameters.<sup>76</sup> More recently, other PET-derived parameters such as metabolic tumor volume (MTV) and total lesion glycolysis have demonstrated to potentially improve risk stratification, in this specific subtype of breast cancer patients.<sup>77-80</sup>

Finally, tumor heterogeneity as measured by means of textural analysis has also emerged as a potential prognostic factor in BC patients.<sup>81,82</sup> However, a multivariate analyses performed by Groheux et al<sup>79</sup> demonstrated that MTV, but not textural analysis of PET images, was an independent prognostic indicator in ER+/HER2- breast cancer patients, before neoadjuvant chemotherapy. As a matter of fact, there is an increasing need to characterize biological processes for early prediction and monitoring of response to therapy in breast cancer patients and <sup>18</sup>F-FDG PET has been tested and compared with other PET probes also in this setting.<sup>83</sup>

Although comparative studies using multiple FDG probes are relatively scarce and most frequently performed in animal

models, available data suggest that other molecular imaging tools, such as <sup>18</sup>F-fluoroestradiol PET/CT, can provide a more precise early prediction of tumor response, especially to endocrine therapy in ER<sup>+</sup> breast cancer.<sup>83</sup>

## Patient-focused perspectives such as quality of life, patient satisfaction/acceptability

Quality of life, evaluated in quality-adjusted life years (QALY)<sup>84</sup> represents one of the main hallmarks of patient care. This approach implies that the benefits of any medical procedure should always be considered in light of the patients' well-being.<sup>85</sup> This aspect is of particular importance in breast cancer survivors, given the high prevalence of this disease, the elevated 5-year survival rate and the importance of early detection of any disease recurrence.<sup>86</sup>

The advent of PET and PET/CT was able to bring about remarkable improvements, as the use of these techniques afforded higher QALY and decreased the error rate, with respect to conventional imaging.<sup>87</sup> It does, however, require higher costs and for this reason is not accessible to all patients in all countries.

Moreover, another important aspect to consider is whether the execution of additional tests can increase the anxiety levels in these patients. Fear of tumor relapse is a well-recognized cause of decreased quality of life;<sup>88</sup> patients affected by fear of relapse tend to associate the number of visits/imaging sessions with improved outcome. A study by Hong et al indicated that virtually all patients demand the execution of tumor markers and PET/CT, regardless of their initial staging and risk class.<sup>84</sup> Actually, execution of repeated medical imaging might be a double-edged sword: on one side, it could reassure the patient on the absence of disease; on the other hand, it can increase, or at least perpetuate, the patient's anxiety before the examinations and in the case of false-positive results.<sup>89</sup>

These considerations are also valid for PET/CT, which is an expensive image modality that should not be used for mere patient "reassurance".<sup>90</sup> However, this image modality is also characterized by an improved specificity with respect to conventional imaging.<sup>91</sup> In light of this, the accurate selection of patients who could actually benefit from the execution of this imaging approach appears to be of pivotal importance. On the other hand, patients in whom PET/CT surveillance is not indicated should be reassured about their condition and instructed on the rationale of the follow-up modality, so as to promote their psychological well-being.<sup>88</sup>



## Conclusions

In conclusion, while there are no conclusive data indicating that FDG PET/CT produces a survival benefit in asymptomatic patients, FDG PET/CT can be useful in identifying the site of relapse when CI is equivocal and confirming isolated loco-regional relapse or isolated metastatic lesions in patients who are candidates for surgery or loco-regional treatment. In all these settings, FDG PET/CT has demonstrated high sensitivity (77%–90%) and specificity (69%–80%) and has a substantial impact on clinical management in a relevant number of patients. By contrast, information concerning its utility for long-term prognostic stratification, when compared with CI, is limited and further studies will aid in better defining the role of PET during breast cancer follow-up. In the meantime, it appears of utmost importance to always discuss and evaluate on a patient-by-patient basis the benefits and risks of a PET-based follow-up, in terms of outcome as well as psychological well-being and quality of life.

## Disclosure

The authors report no conflicts of interest in this work.

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