Present and future role of FDG-PET/CT imaging in the management of breast cancer

Kazuhiro Kitajima¹ · Yasuo Miyoshi²

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Abstract Integrated positron emission tomography/computed tomography (PET/CT) with 2-[¹⁸F]fluoro-2-deoxy-D-glucose (FDG) is a useful tool for acquisition of both glucose metabolic and anatomic imaging data using a single device in a single diagnostic session, and has opened a new field in clinical oncologic imaging. FDG-PET/CT has been used successfully for the diagnosis, initial staging, restaging, early treatment response assessment, evaluation of metastatic disease response, and prognostication of breast cancer as well as various malignant tumors. We herein review the current place and role of FDG-PET/CT in the management of breast cancer, focusing on its usefulness and limitations in the imaging of these patients.

Keywords Fluorodeoxyglucose (FDG) · Positron emission tomography/computed tomography (PET/CT) · Breast cancer · Staging · Restaging

Introduction

In the late 1990s, positron emission tomography (PET) with 2-[¹⁸F]fluoro-2-deoxy-D-glucose (FDG), which exploits the increased utilization and high uptake of glucose

by malignant cells, opened a new field in clinical oncologic imaging. Recently, integrated positron emission tomography/computed tomography (PET/CT), in which a full-ring-detector clinical PET scanner and multidetector-row helical CT scanner are combined, has made it possible to acquire both metabolic and anatomic imaging data using a single device in a single diagnostic session, and provides precise anatomic localization of suspicious areas of increased FDG uptake. When used in a clinical setting, FDG-PET/CT leads to a significant improvement in diagnostic accuracy and has had a considerable impact on patient management, including diagnosis, initial staging, optimization of treatment, restaging, monitoring of the response to therapy, and prognostication of various malignant tumors. We herein review the current and future roles of FDG-PET/CT in the management of breast cancer, discussing its usefulness and limitations for imaging in these patients.

Diagnosis

FDG-PET imaging has poor sensitivity (<50 %) for sub-centimeter breast cancers [9, 10]. This is due to the limited spatial resolution of PET and, in some cases, by tumor characteristics (e.g., low FDG avidity in grade 1 cancer, ductal carcinoma in situ, or lobular carcinoma) [1, 2]. Specificity can also be altered by variations of FDG uptake in certain benign conditions, such as infection, fibroadenoma, ductal adenoma, inflammatory granulomatous mastitis, and fibrocystic changes [3].

In order to improve specificity, some authors would obtain a second series of PET images centered on the breast approximately 2 h after FDG injection (dual-time imaging) [4]. Indeed, FDG uptake seems to increase with time in the case of malignancy, while some inflammatory lesions show stable or decreasing uptake [4]. However, dual-time

✉ Kazuhiro Kitajima
kitajima@med.kobe-u.ac.jp; kazu10041976@yahoo.co.jp
Yasuo Miyoshi
ymiyoshi@hyo-med.ac.jp

¹ Department of Nuclear Medicine and PET Center, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan

² Department of Breast and Endocrine Surgery, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan

imaging is time-consuming, and its usefulness has not yet been demonstrated in large series.

FDG-PET/CT is not a substitute for diagnostic biopsy of breast cancer. However, when an unexpected focus of FDG uptake is detected in the breast during an FDG examination performed for other reasons, it is necessary to explore it with conventional imaging and possible biopsy because of the high risk of malignancy [5]. In a meta-analysis of 13 studies, Bertagna et al. [5] reviewed the breast incidental FDG uptake (BIU) detected by PET or PET/CT and demonstrated that the pooled prevalence of BIU on all scans was 0.4 % [95 % confidence interval (CI) 0.23–0.61 %], the pooled prevalence on scans on female patients only was 0.82 % (95 % CI 0.51–1.2 %), the pooled risk of malignancy of BIU when further analyzed was 48 % (95 % CI 38–58 %) and the pooled risk of malignancy of BIU with histological examination was 60 % (95 % CI 53–66 %).

In a FDG-PET cancer screening program held in Japan, conventional whole-body FDG-PET detected 161 breast cancers in 62,054 asymptomatic subjects (0.26 %) with a 83.9 % sensitivity and 41.7 % positive predictive value (PPV), and 83 % of them were detected at stage 0 or 1 [6]. Although radiation exposure and high cost are two major problems in breast cancer screening by FDG-PET, cost-effectiveness of FDG-PET in breast cancer has not been clarified [7]. In recent years, high-resolution positron emission mammography (PEM) systems have emerged as breast-specific PET devices producing 3D breast images with an in-plane spatial resolution of 2 mm. They show very high sensitivity and specificity for detecting breast cancer, and are more sensitive than conventional whole-body PET [8, 9]. In a study of 109 primary invasive breast cancers with a mean tumor size of 1.6 ± 0.8 cm, Kalinyak et al. [8] found that the detection rates obtained with PEM and conventional PET/CT were 95 and 87 %, respectively, the difference being significant ($p < 0.029$). A meta-analysis that evaluated 8 studies comprising 873 breast lesions showed a pooled sensitivity of 85 % (95 % CI, 83–88 %) and a specificity of 79 % (95 % CI, 74–83 %) on a lesion basis, using FDG PEM in women with suspected breast malignancy [9].

In summary, most breast cancer histological subtypes are FDG-avid, such as invasive ductal carcinoma (IDC); however, FDG-PET shows limited detection of breast cancer. Although FDG PEM appears to have potential for breast cancer screening, further analysis is needed.

Factors correlated with FDG uptake in primary breast tumors

Many groups have demonstrated good correlations between primary tumor FDG uptake on PET/CT, expressed as the maximum standardized uptake value (SUV_{max}), and

clinicopathological findings that are known to be important prognostic indicators in breast cancer patients [10–17]. A higher SUV_{max} is reported to be significantly associated with estrogen receptor (ER) negativity, progesterone receptor (PR) negativity, human epidermal growth factor receptor 2 (HER2) positivity, a high Ki-67 index, a bigger tumor size, a higher histological grade, presence of axillary lymph node (LN) metastasis, and a higher stage.

FDG uptake, on the other hand, is correlated with molecular subtype, i.e., luminal A, luminal B (HER2-negative), luminal B (HER2-positive), HER2 positivity and triple-negativity [16, 17]. Kitajima et al. [17] have demonstrated that the triple-negative subtype and HER2-positive subtype show a higher SUV_{max} , whereas the luminal A subtype often shows a lower SUV_{max} . They also reported that a cut-off value of 3.60 yielded a sensitivity of 70 % and a specificity of 66 % for predicting that a tumor was of the luminal A subtype, and that a cut-off value of 6.75 yielded a sensitivity of 65 % and a specificity of 75 % for predicting a HER2-positive subtype.

In summary, SUV_{max} , a semiquantitative metabolic parameter obtained by FDG-PET/CT, is significantly correlated with clinicopathological findings and molecular subtype.

Assessment of multifocality and T staging

PET/CT remains inadequate for accurately defining the extent of a tumor, which is an especially important consideration for planning of optimal breast conservation surgery. Over the last decade, dynamic contrast-enhanced breast magnetic resonance imaging (DCE-MRI) has emerged as an important tool for preoperative evaluation of breast cancer in patients contemplating breast conservation surgery, owing to its high sensitivity for detection of small multifocal/centric and synchronous contralateral disease unrecognized on conventional assessment, as well as in patients with locally advanced disease for assessment of the response to therapy. Among 40 women undergoing PET/CT and DCE-MRI [18], MRI aided correct classification of the T category in 77 % of cases, whereas PET/CT aided such classification in only 54 % of cases ($p = 0.001$).

In a recent study by Berg et al. [19], 388 women who were offered breast-conserving surgery underwent DCE-MRI and FDG-PEM. PEM and MRI had comparable breast-level sensitivity, although MRI had greater lesion-level sensitivity and more accurately defined the need for mastectomy. Eighty-nine (23 %) participants required more extensive surgery, and among those women, 61 (69 %) were identified by MRI and 41 (46 %) by PEM ($p = 0.003$). However, PEM has not yet entered routine clinical practice. Moreover, PEM allows only regional evaluation, and tumor deposits outside the breast remain non-visualized.

Other work in progress concerns the development of PET/MRI hybrid systems [20, 21]. In an analysis of 36 patients with 37 breast cancers, Taneja et al. [20] demonstrated that PET/MRI achieved a higher accuracy of staging with increased diagnostic confidence relative to PET or DCE-MRI, and led to a change in management in 12 (33.3 %) of the patients.

In summary, FDG-PET/CT remains inadequate for accurately defining the extent of tumors, relative to DCE-MRI.

Axillary lymph node staging

The management and prognosis of breast cancer depends on the size and grade of the tumor, endocrine (hormonal) receptor status, HER2 status, axillary LN involvement and metastatic spread. Of these, the most reliable predictor of survival is axillary LN metastasis [22]. Knowledge of axillary nodal status before treatment is important because it influences management decision-making. In recent years, sentinel LN biopsy (SLNB) has become widely accepted as a less invasive alternative to axillary LN dissection (ALND) and has become the standard procedure for patients with small primary tumors [23]. This procedure is still invasive and carries a risk of surgical complications such as lymphedema, axillary paresthesia, seroma, and wound infection. Therefore, a noninvasive technique that can accurately identify LN metastasis would be valuable.

Several groups have demonstrated that, in most cases, FDG-PET or PET/CT has a low sensitivity (range 24–82 %) but a high specificity (range 80–100 %) and high positive predictive value (PPV) of more than 80 % [24–33]. In a review of 472 patients examined using FDG-PET/CT, the pooled sensitivity was relatively low (60 %) but the pooled specificity was very high (97 %) [34]. This high specificity and PPV of PET/CT imaging suggests that patients who have a PET-positive axilla should undergo ALND rather than SNB for axillary staging, reducing the need for unnecessary SLNB [25, 34]. In contrast, PET/CT showed poor sensitivity for detection of axillary metastases, confirming the need for SLNB in cases where PET/CT findings are negative in the axilla. As PET/CT cannot detect tiny LN metastases because of its limited spatial resolution, it cannot replace invasive approaches for axillary staging. The diagnostic performance of PET/CT does not seem to be superior to that of ultrasonography (US) [26, 30]. Ahn et al. [30] demonstrated that for detection of lymph node metastasis, the diagnostic accuracy of US was 78.8 % and that of FDG-PET was 76.4 %, whereas accuracy was improved (91.6 %) when US and FDG-PET were combined. New techniques for improving the spatial resolution of PET/CT are needed in order to increase the detectability of small LN metastases.

In summary, the spatial resolution of PET (approximately 5–6 mm) is not sufficient to allow detection of early axillary node involvement and micrometastases, and PET/CT cannot replace staging by the sentinel node procedure. A representative case is shown in Fig. 1.

M staging

Bone is one of the most frequent sites for distant metastases of breast cancer, accounting for about 65 % of patients with distant metastases [35]. Bone scintigraphy has been the standard procedure for detection of bone metastases in breast cancer patients. Many groups have found that, while PET is more efficient than CT or bone scintigraphy for depicting lytic or mixed bone metastases and bone marrow lesions, PET can lack sensitivity for demonstrating purely sclerotic bone metastases [36, 37]. For this reason, some clinicians perform bone scintigraphy even in patients who have undergone FDG imaging. However, FDG-avid sclerotic bone metastases are often observed in breast cancer patients [38], and purely sclerotic bone metastases show osteocondensation on CT images, allowing them to be detected using the hybrid PET/CT procedure [39]. Several authors have demonstrated that PET/CT is more accurate than scintigraphy for depiction of bone metastases [18, 40, 41], and a recent systematic review and meta-analysis (668 patients in total) concluded that FDG-PET/CT (sensitivity, 93 %; specificity, 99 %) performed better than bone scintigraphy (sensitivity, 81 %; specificity, 96 %) [42].

Assessment of bone lesions that are responding to treatment is difficult in practice; bone scans may remain positive because of uptake related to the osteoblastic process, and CT scans may be interpreted as showing persistence or worsening of the disease on the basis of increased sclerosis evident in the lesions. On the other hand, FDG-PET reflecting glucose metabolism may be more specific for assessment of the treatment response in bone lesions.

In the pulmonary parenchyma, FDG-PET can efficiently depict supracentimetric pulmonary nodules. However, because of the partial volume effect and respiratory movements, PET lacks sensitivity for smaller nodules. Careful scrutiny of the CT data obtained during hybrid PET/CT examination can reveal small nodules without FDG uptake. It should be noted that free-breathing CT is less efficient than standard diagnostic thoracic CT.

Finally, the main limitation of PET/CT is its lack of sensitivity for brain metastases, because of physiologic FDG uptake in the brain.

In summary, FDG-PET/CT yielding both glucose-metabolic and anatomic imaging data is a useful modality for detection of bone metastases, showing high sensitivity and specificity (Table 1).

Fig. 1 A 68-year-old woman with ipsilateral axillary lymph node metastases arising from invasive ductal carcinoma of the right breast at initial staging. **a** Maximum intensity projection (MIP) of the FDG-PET image shows intense uptake points in the right breast and ipsilateral axillary fossa. **b** PET/CT and **c** the CT portion show abnormal FDG uptake corresponding to two metastatic ipsilateral axillary nodes 7 and 8 mm in shortest diameter, suggesting the absence of nodal cancer spread. Histopathological specimen of the dissected axillary lymph node revealed extensive cancer involvement

Table 1 Studies evaluating FDG-PET/CT or PET for axillary lymph node staging in patients with breast cancer

References	No. of patients	Modality	Gold standard	FDG-PET/CT or PET result				
				Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy
Wahl et al. [24]	360	PET	ALND	61	80	62	79	NA
Veronsei et al. [25]	236	PET	SLNB	37	96	88	66	70 %
Ueda et al. [26]	183	PET/CT	SLNB and/or ALND	58	95	85	83	83 %
Kim et al. [27]	137	PET/CT	ALND or SLNB	77	100	100	94	94 %
Heusner et al. [28]	61	PET/CT	SLNB	58	92	82	77	79 %
Taira et al. [29]	90	PET/CT	SLNB and/or ALND	48	92	72	81	89 %
Ahn et al. [30]	250	PET	SLNB	43	90	65	79	76 %
Koolen et al. [31]	290	PET/CT	SLNB or US-FNA	82	92	98	53	84 %
Pritchard et al. [32]	325	PET/CT	SLNB or ALND	24	100	96	75	78 %
Zhang et al. [33]	164	PET/CT	ALND	46	91	63	84	80 %

ALND Axillary lymph node dissection, SLNB sentinel lymph node biopsy, PPV positive predictive value, NPV negative predictive value, NA not available

Initial staging

In breast cancer, accurate initial evaluation of disease spread is important for treatment selection and prognostication. For the initial staging work-up, many conventional imaging modalities, such as X-ray mammography, MR mammography, chest plain radiography, bone scintigraphy, and breast, axillary and liver ultrasonography, have been widely utilized. In recent years, several groups have

evaluated the clinical role of FDG-PET/CT for pretreatment evaluation of breast cancer in comparison with conventional imaging tools [18, 39, 43–54] (Table 2). These studies revealed that FDG-PET/CT is generally helpful, but particularly valuable for detection of extra-axillary (infraclavicular, supraclavicular and internal mammary) nodal metastasis and occult distant metastasis relative to conventional modalities, especially in patients with inflammatory breast cancer [43, 46, 47] and stage II–III disease [18,

Table 2 Studies evaluating FDG-PET/CT for initial staging in patients with breast cancer

References	Setting	No. of patients	Effect of FDG-PET/CT results			
			Detection of unknown node metastasis	Detection of unsuspected distant metastasis	Modification in initial staging	Modification in treatment plan
Yang et al. [43]	Inflammatory breast cancer	24	25 % ^a	38 % ^a	NA	NA
Groheux et al. [39]	II–III	39	8 %	10 %	18 %	13 %
Heusner et al. [44]	T1–T3	40	8 %	8 %	NA	13 %
Fuster et al. [45]	Large (>3 cm)	60	5 %	9 %	42 %	7 %
Carkaci et al. [46]	Inflammatory breast cancer	41	15 %	17 %	NA	NA
Alberini et al. [47]	Inflammatory breast cancer	59	56 % ^a	31 % ^a	NA	NA
Aukema et al. [48]	II–III	60	17 %	NA	17 %	12 %
Segaert et al. [39]	IIB–III	70	13 %	10 %	NA	NA
Groheux et al. [49]	II–IIIA	131	IIA:3 %, IIB–IIIA:11 %	IIA:3 %, IIB–IIIA:15 %	IIA:6 %, IIB:15 %, IIIA:28 %	NA
Riegger et al. [50]	I–III	106	8 %	4 %	13 %	14 %
Gunalp et al. [51]	I–IIIB	151	10 %	29 %	I:26 %, IIA:29 %, IIB:46 %	I:15 %, IIA:25 %, IIB:48 %
Koolen et al. [52]	II–III	154	NA	13 %	NA	8 %
Cochet et al. [53]	Large (T2–T4)	142	33 %	11 %	37 %	13 %
Riedl et al. [54]	I–III	134	NA	I:5 %, IIA:5 %, IIB:17 %, IIIA:31 %, IIIB:50 %, IIIC:50 %	NA	NA

NA not available

^a Some metastases were also detected by using conventional imaging

39, 44, 45, 48–54]. Additional findings revealed by PET/CT may prompt a substantial change in the management of breast cancer patients. Cochet et al. [53] demonstrated that FDG-PET/CT provided staging information that more accurately stratified prognostic risk in 142 patients with newly diagnosed large breast cancers (T2–4) in comparison with conventional modalities (mammography and/or breast ultrasound, bone scan, abdominal ultrasound and/or CT, X-ray and/or CT of the chest) alone.

PET/CT is very useful for diagnosis of metastasis at extra-axillary sites, including the internal mammary chain, infraclavicular region, supraclavicular fossa, the breast itself, and the interpectoral space, thus impacting on staging and the subsequent treatment strategy. In a patient scheduled to undergo surgery, the results of PET/CT may indicate that this disease is not primarily treatable with surgery, and requires preoperative chemotherapy.

However, the exact clinical stage at which PET/CT can be performed with favorably balanced cost-effectiveness is uncertain. The 2013 guidelines of the National Comprehensive Cancer Network consider that PET/CT scanning

should be performed for patients with stage III disease, or when standard staging studies yield equivocal or suspicious results [55].

In summary, FDG-PET/CT is efficient for staging of inflammatory and locally advanced breast cancer (clinical stage IIB and primary operable stage IIIA), because it allows detection of extra-axillary LNs and distant metastases. A representative case is shown in Fig. 2.

Restaging

The accurate restaging of recurrent breast cancer is important for identifying patients with limited disease who could potentially benefit from curative treatment. Traditionally, routine evaluation of suspected recurrent breast cancer has involved physical examination, testing for biological markers (cancer antigen 15-3 and/or carcinoembryonic antigen) and a multi-modality conventional imaging approach including mammography, breast US and MRI for local recurrence, and chest radiography, whole-body CT and bone scanning for distant recurrence. However, this

Fig. 2 A 44-year-old woman with invasive ductal carcinoma of the left breast and multiple lymph node, bone, liver, lung and adrenal metastases at initial staging. **a** Axial fat-suppressed dynamic contrast-enhanced T1-weighted image shows a strong contrast-enhanced mass with necrotic change in the left breast, suggesting cancer. **b** Maximum intensity projection (MIP) of the FDG-PET image shows multiple intense uptake points in the left breast, lymph nodes, bone, liver, and left adrenal gland. **c** PET/CT shows abnormal FDG uptakes corresponding to left breast cancer, and metastasis to the vertebra and liver. **d** PET/CT shows abnormal FDG uptakes corresponding to ipsilateral axillary node metastasis, mediastinal node metastases, and spinal metastasis. **e** PET/CT shows abnormal FDG uptakes corresponding to bilateral infraclavicular node metastases. **f** PET/CT shows abnormal FDG uptakes corresponding to abdominal node metastasis, hepatic metastases, left adrenal metastasis, and metastases to the vertebra and rib. **g** PET/CT and **h** the CT portion show abnormal FDG uptakes corresponding to multiple bone metastases and mediastinal node metastases. However, **(h)** no abnormal change was observed in multiple bone metastases

Table 3 Studies evaluating FDG-PET/CT for restaging in patients with breast cancer

References	No. of patients	FDG-PET/CT result				
		Sensitivity	Specificity	PPV	NPV	Accuracy
Fueger et al. [56]	58	94 %	84 %	89 %	91 %	90 %
Radan et al. [57]	46	85 %	76 %	81 %	81 %	81 %
Haug et al. [58]	34	96 %	89 %	96 %	90 %	94 %
Veit-Haibach et al. [59]	44	NA	NA	NA	NA	91 %
Schmidt et al. [60]	33	91 %	90 %	96 %	81 %	91 %
Dirisamer et al. [61]	52	95 %	100 %	100 %	83 %	96 %
Aukema et al. [62]	56	97 %	92 %	94 %	96 %	95 %
Grassetto et al. [63]	89	NA	NA	NA	NA	NA
Evangelista [64]	111	81 %	52 %	41 %	87 %	60 %
Champion et al. [65]	228	94 %	85 %	97 %	74 %	92 %
Murakami et al. [66]	47	96 %	91 %	92 %	95 %	94 %
Manohar et al. [67]	111	99 %	85 %	93 %	97 %	95 %
Cochet et al. [68]	63	93 %	90 %	95 %	86 %	92 %
Junng et al. [69]	1161	98 %	99 %	96 %	99 %	99 %

PPV positive predictive value, NPV negative predictive value, NA not available

conventional approach is often time-consuming and potential false-negative findings may delay appropriate therapy.

FDG-PET/CT can evaluate the whole body (except the brain) in a single examination and is very useful for detecting recurrent or residual tumors because of its high sensitivity and specificity in comparison with conventional techniques. Table 3 shows the results of major studies that have evaluated the role of PET/CT [56–69]. We excluded studies in which staging and restaging populations were mixed. The sensitivity of FDG-PET/CT ranged between 85 and 99 %, the specificity between 52 and 100 %, and the accuracy between 60 and 99 %. Based on 1819 PET/CT examinations and conventional imaging including mammography, breast ultrasound, bone scintigraphy, and chest radiography for postoperative surveillance in 1161 breast cancer patients, Jung et al. [69] demonstrated that the sensitivity, specificity, and accuracy of these methods were 97.5 versus 75.4 %, 98.8 versus 98.7 %, and 98.5 versus 92.5 %, respectively.

FDG-PET/CT has an important role in providing incremental information that may lead to a change in management [60, 65, 67, 68] and refine the prognostic stratification [68].

In summary, FDG-PET/CT is useful for restaging of cancer in patients with documented breast cancer recurrence or in those in whom it is suspected, and is more efficient than PET alone and conventional imaging methods. A representative case is shown in Fig. 3.

Early treatment response assessment

Neoadjuvant chemotherapy (NAC) has been used widely for patients with locally advanced breast cancer to

downstage the primary tumor before surgery, thereby increasing the breast conservation rate. Previous studies have shown that histopathological examination after breast surgery is the standard for evaluating the response to NAC, and the histopathological response is thought to be prognostically informative; disease-free survival (DFS) and overall survival (OS) rates are higher among patients who show a complete response [70]. Early identification of poor responders is important because they require aggressive treatment, and the use of ineffective, toxic chemotherapy agents should be avoided in these patients.

In many studies [71–90] that have evaluated a possible role for metabolic evaluation with FDG-PET and PET/CT, investigators demonstrated a correlation between early changes in FDG uptake, mostly in terms of the SUV_{max} value, after one or two courses of chemotherapy and the final pathologic response upon completion of chemotherapy, or patient outcome (Table 4). A review article including 745 patients in 15 studies indicated that the pooled sensitivity and specificity of FDG-PET for early separation of responders from non-responders could reach 80.5 % (95 % CI, 75.9–84.5 %) and 78.8 % (95 % CI, 74.1–83.0 %), respectively [91]. The review concluded that FDG-PET has moderately high sensitivity and specificity for early delineation of responders from non-responders, and can be applied for evaluating the response of breast cancer to neoadjuvant chemotherapy.

On the other hand, breast cancer is heterogeneous (ER-positive tumors, HER2-positive tumors, triple-negative tumors) and shows differences in the rates of response to chemotherapy, the risks of relapse, treatment options, and prognoses. Several reports have described early treatment

Fig. 3 A 65-year-old woman treated 9 years previously with right mastectomy and axillary lymph node dissection plus adjuvant chemotherapy due to invasive ductal carcinoma of right breast cancer, showing multiple recurrent lesions consisting of local recurrence, supraclavicular nodal metastasis, pleural dissemination, and multiple bone metastases at restaging. **a** Maximum intensity projection (MIP) of the FDG-PET image shows multiple intense uptake points in the right chest wall, the right supraclavicular fossa, the right pleura, spiral vertebra, and right pelvic bone. **b** PET/CT and **c** the CT portion show abnormal FDG uptake corresponding to local recurrence at the right chest wall, pleural dissemination, and vertebral metastasis

response assessment using FDG-PET in specific subtypes of breast cancer, including ER-positive tumors [79, 83, 85, 86], HER2-positive tumors [82, 84, 85, 87], and triple-negative tumors [85, 88].

However, there are several problems in such studies. First, in many cases, an optimal threshold value for the decrease in SUV_{max} has been proposed for discriminating metabolic responders (where diminution of SUV is superior to the threshold value) from non-responders. The cut-off value chosen is considered to facilitate optimal prediction of the final pathologic response. Unfortunately, the specific threshold value proposed has varied markedly across studies. Moreover, there are other parameters such as the absolute SUV_{max} after one or two cycles [83, 86] and the percentage change in total lesion glycolysis [81, 83]. Second, the definition of what constitutes a good histopathologic response varies. For example, Rousseau et al. [73] defined a tumor regression superior to 50 % as a good response, whereas Schwarz-Dose et al. [78] considered no residual invasive tumor or only a few scattered foci of microscopic residual tumor to indicate a satisfactory pathologic response. Third, the optimal timing of interim

PET remains unclear. For several teams, performing PET after the second course of NAC has been considered a good compromise for clarifying the effects of chemotherapy while still allowing an early change of treatment in the event of ineffectiveness [71, 73, 76, 77, 79–81, 83, 84, 88]. However, performing a response assessment as early as the first cycle might also be valuable [74, 86, 87, 89].

In summary, FDG-PET/CT is emerging as a promising tool for early monitoring of the effectiveness of neoadjuvant chemotherapy; however, there are substantial disparities in the way assessment of the response is performed, and there is a need for standardization. Two representative cases are shown in Figs. 4 and 5.

Evaluation of the response of metastatic disease

Anatomic imaging, predominantly CT, is currently used to obtain measurements of tumor lesions before and after treatment for response assessment and follow-up. However, several cycles of treatment are needed before a change in tumor size can be assessed using anatomic imaging. Changes in metabolic activity generally occur

Table 4 Studies evaluating FDG-PET/(CT) for early treatment response assessment of NAC in patients with breast cancer

References	Modality	Setting	No. of patients	No. of NAC cycles	Timing of PET evaluation	Optimal PET	Optimal SUV threshold (percent change)
Schelling et al. [71]	PET	Large (>3 cm) and LABC	22	2–4	After 1 and 2 cycles	After 2 cycle	–55 %
Smith et al. [72]	PET	Large (>3 cm) and LABC (T3–4Nx or TxN2)	30	8	After 1 and 4 cycles and before surgery	NA	NA
Rousseau et al. [73]	PET/CT	Stage IIB–IIIC	64	4–6	After 1, 2 and 3 cycles and before surgery	After 2 cycles	–40 %
Berriolo-Riedinger et al. [74]	PET	Large and LABC	47	4–6	After 1 cycle	–	–60 %
McDermott et al. [75]	PET	Large and LABC (T3–4Nx or TxN2)	96	6 or 8	After 1 cycle, at midpoint and at end point	Between the end of the 1st cycle and the midpoint	–24 % after 1 cycle, –58 % at midpoint, and –64 % at end point
Duch et al. [76]	PET/CT	Stage IIB–IIIC	50	4	After 2 cycles	–	–40 %
Kumar et al. [77]	PET/CT	Stages IIB–IIIB	23	6	After 2 cycles	–	–50 %
Schwarz-Dose et al. [78]	PET	Large and LABC (T2–4, N0–2)	104	4–6	After 1 and 2 cycles	After 1 and 2 cycles per-form equally	–45 % after 1 cycle
Martoni et al. [79]	PET/CT	Large and LABC, ER-positive (T2–4, N0–3)	34	6–8	After 2 and 4 cycles and before surgery	After 2 cycles	–50 %
Tateishi et al. [80]	PET/CT	Stages I–IIIC	142	16	After 2 cycles	–	–83 to 88 %
Hatt et al. [81]	PET/CT	Stages IIB–IIIB	51	8	After 2 cycles	–	TLG (–56 %)
Gebhart et al. [82]	PET/CT	HER2-positive	86	9	After 1 and 3 cycles	After 3 cycles	–25 %
Groheux et al. [83]	PET/CT	ER-positive and HER2-negative	64	8	After 2 cycles	–	TLG (–71 %)
Groheux et al. [84]	PET/CT	HER2-positive	30	8	After 2 cycles	–	3.0 at 2 cycles
Koolen et al. [85]	PET/CT	ER-positive, HER2-positive, 107 (50, 26, 31) and Triple negative	NA	NA	After 1–2 and 3–4 cycles	Different to molecular subtypes	SUV at 3 cycles (ER positive and triple negative), decreasing change (HER2-positive)
Humbert et al. [86]	PET/CT	hormone-sensitive, HER2-negative	40	6	After 1 cycle	–	–16 %
Humbert et al. [87]	PET/CT	HER2-positive	57	6	After 1 cycles	–	2.1 at 1 cycle
Lim et al. [88]	PET/CT	Stages IIB–IIIB	54	3	After 1 cycle	–	–41 %
Groheux et al. [89]	PET/CT	Triple negative	50	4	After 2 cycles	–	–42 %
Lee et al. [90]	PET/CT	Stage IIA–IIIC	36	4–6	After 2 cycles	–	NA

NAC neoadjuvant chemotherapy, LABC locally advanced breast cancer, NA not available, ER estrogen receptor, HER2 human epidermal growth factor receptor 2, TLG total lesion glycolysis

Fig. 4 A 32-year-old woman with invasive ductal carcinoma of the right breast, showing a pathological complete response (pCR) at early evaluation of response to neoadjuvant chemotherapy (NAC) using FDG-PET/CT. **a** FDG-PET/CT shows that, at the baseline, SUV_{max} in the tumor was 6.2. **b** FDG-PET/CT shows that after one course of primary tumor chemotherapy, the SUV_{max} was 1.9, corresponding to a 69 % decrease. Mastectomy performed upon completion of NAC (eight courses) showed a pCR

earlier than changes in tumor size. This is particularly the case for targeted therapies, because such treatments can render tumors metabolically inactive without any substantial modification of their size. Functional imaging techniques such as FDG-PET can be used earlier than morphologic imaging methods to evaluate treatment response [92].

There is some evidence that FDG-PET/CT can provide additional and useful information for evaluating the response to systemic chemotherapy. Tateishi et al. [93] demonstrated that an increase in attenuation in bone metastases (measured in Hounsfield units) and a decrease in SUV are overall potential predictors of response duration. Another important finding is that PET/CT allows evaluation of response in many different metastases. Huyge et al. [94] have demonstrated that PET/CT is helpful for indicating a heterogeneous response (coexistence of responding and non-responding lesions within the same patient). In

Fig. 5 A 58-year-old woman with invasive ductal carcinoma of the right breast, showing no pathological complete response (pCR) at early evaluation of response to neoadjuvant chemotherapy (NAC) using FDG-PET/CT. **a** FDG-PET/CT shows that, at the baseline, SUV_{max} in the tumor was 7.1. **b** FDG-PET/CT shows that after one course of primary tumor chemotherapy, the SUV_{max} was 6.7, corresponding to a 6 % decrease. Mastectomy performed upon completion of NAC (eight courses) showed no pCR

the future, it will be necessary to evaluate the association between treatment response and patient survival outcome.

A paradoxical increase of FDG uptake during the initial days after initiation of hormone therapy has been observed in patients showing a good therapeutic response. This phenomenon has been referred to as metabolic flare [95]. This effect typically occurs during the 10 days after initiation of hormone therapy [95].

In summary, PET/CT is a promising method for evaluating the response of metastatic disease, although more data are needed.

Prognostic value

The prognostic value of FDG-PET for predicting clinical outcomes has not been fully assessed and is still

controversial. Several authors have suggested that SUV in primary breast cancer [10, 96–99] or in axillary LN metastasis [34, 100] could be predictive of outcome. Jo et al. [99] evaluated whether preoperative SUV_{max} of the primary tumor was associated with DFS in 508 patients with invasive ductal breast cancer, along with histological and biological factors such as tumor size, histological grade, or hormonal receptor expression status, and concluded that a high primary tumor SUV_{max} is an independent factor associated with recurrence.

The FDG response of metastatic disease also has prognostic value. In a group of 47 patients, Cachin et al. [101] showed that OS was significantly better for patients with negative findings on a PET scan after chemotherapy, in comparison with those showing persistent FDG uptake (24 vs 10 months, $p < 0.001$).

In summary, FDG-PET/CT may have prognostic value, but more studies are needed to clarify this.

Conclusion

FDG-PET/CT can allow combined metabolic and morphological assessment of breast tumors, offering significant improvements in diagnostic accuracy, and having a considerable impact on patient management, initial staging (especially extra-axillary node staging and detection of metastatic lesions), restaging, early treatment response assessment, evaluation of the response of metastatic disease to therapy, and prognostication.

Compliance with ethical standards

Conflict of interest We declare no financial support or relationship that may pose a conflict of interest.

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