MOLECULAR IMAGING AND BIOLOGY

Mol Imaging Biol (2019) 21:1–10
DOI: 10.1007/s11307-018-1181-3

Published Online: 7 March 2018

REVIEW ARTICLE

The Evolving Role of FDG-PET/CT in the Diagnosis, Staging, and Treatment of Breast Cancer

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Abstract

The applications of 2-deoxy-2-[^{18}F]fluoro-D-glucose positron emission tomography/X-ray computed tomography (PET/CT) in the management of patients with breast cancer have been extensively studied. According to these studies, PET/CT is not routinely performed for the diagnosis of primary breast cancer, although PET/CT in specific subtypes of breast cancer correlates with histopathologic features of the primary tumor. PET/CT can detect metastases to mediastinal, axial, and internal mammary nodes, but it cannot replace the sentinel node biopsy. In detection of distant metastases, this imaging tool may have a better accuracy in detecting lytic bone metastases compared to bone scintigraphy. Thus, PET/CT is recommended when advanced-stage disease is suspected, and conventional modalities are inconclusive. Also, PET/CT has a high sensitivity and specificity to detect loco-regional recurrence and is recommended in asymptomatic patients with rising tumor markers. Numerous studies support the future role of PET/CT in prediction of response to neoadjuvant chemotherapy (NAC). PET/CT has a higher diagnostic value for prognostic risk stratification in comparison with conventional modalities. With the continuing research on the treatment planning and evaluation of patients with breast cancer, the role of PET/CT can be further extended.

Key words: Breast neoplasms, Positron emission tomography/computed tomography, [^{18}F]FDG

Introduction

Breast cancer (BC) is the most common cancer among women in the Western world. Despite increasing incidence, early diagnosis and novel treatment strategies have led to a decline in mortality [1]. After the initial diagnosis is established, the extent of disease is determined through X-ray studies, ultrasonography (US), X-ray computed tomography (CT) scan, and magnetic resonance imaging (MRI). Treatment of primary BC includes curative surgery, adjuvant radiotherapy with or without chemotherapy, and hormone therapy [2, 3].

Imaging plays a pivotal role in the screening, diagnosis, staging, restaging, and treatment planning of BC. Although mammography is used as the imaging modality of choice for screening in the general population, limitations (its low specificity) warrant the application of further imaging

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modalities in certain cases [4–6]. Conventional imaging modalities such as US, CT scan, and MRI are performed for staging, assessment of response to therapy as well as monitoring recurrence in suspected cases. Nevertheless, CT scan and MRI may be inconclusive in a considerable fraction of patients; these modalities only reflect the morphological and anatomic changes at the site of primary tumor and distant metastases. Accordingly, molecular imaging modalities are superior in detecting response to therapy and recurrence, especially in the presence of treatment/surgery induced anatomic changes. 2-Deoxy-[^{18}F]fluoro-D-glucose ([^{18}F]FDG)-positron emission tomography/X-ray computed tomography (PET/CT) has proven to be of great benefit, especially when predicting response to neoadjuvant chemotherapy (NAC) and prognostic risk stratification are of concern [7].

Tumor cells are known to have enhanced glycolytic activity and increased uptake of FDG which allow for the visualization of pathologic foci by [^{18}F]FDG-PET/CT. The uptake of FDG might also be influenced by the phenotype, mitotic index and grade of the primary tumor [8]. In this review, we will discuss the applications of [^{18}F]FDG-PET/CT in the diagnosis, staging, prognosis assessment, recurrence, and restaging as well as treatment response of patients with BC.

Methods

To enroll eligible studies, http://ncbi.nlm.nih.gov/pubmed was searched with the use of following keywords in MeSH database: *positron emission tomography*, *FDG*, and *breast neoplasms*. The title and abstracts of related publications in English language on human subjects were screened by reviewers. Studies that met the following criteria were included: the role of [^{18}F]FDG-PET/CT in the (1) initial diagnosis, (2) staging, (3) evaluation of response to therapy, and (4) assessment of recurrence and restaging of patients with BC. For simplicity purposes, PET/CT encompasses [^{18}F]FDG-PET/CT in this review unless otherwise stated.

Diagnosis

According to the current literature and the National Comprehensive Cancer Network (NCCN) guidelines, PET/CT is not routine for early diagnosis of BC [7, 9, 10]. In addition to the high cost, use of PET/CT for establishing the diagnosis of early-stage breast cancer is hampered by its low spatial resolution, which reduces its sensitivity by missing small lesions (< 5 mm). However, PET/CT has a high specificity in diagnosing BC [10–13]. According to a recent review, use of PET/CT should be considered a supplement to conventional imaging procedures such as CT [13]. In a retrospective study on 164 patients with operable invasive cancer and negative lymph nodes, the sensitivity of PET/CT was 86 % [14]. Also, the PET findings were significantly correlated with tumor grade and size [14]. In studies that have been conducted to date, the sensitivity and specificity of PET/CT for the diagnosis of BC varies from 48 to 96 and 73 to 100 %, respectively [13].

Although PET/CT is not routinely recommended for establishing the diagnosis of BC, it may disclose important information about some histopathological features of the primary tumor [15–17]. Several reports have shown that the extent of FDG uptake by tumor cells is related to tumor grade and subtypes [17–19]. In a study performed by Yoon *et al*. on 43 patients with large or locally advanced invasive ductal carcinoma (IDC), FDG uptake was negatively correlated with hormonal receptor status [20]. In another study on 89 patients with invasive BC who underwent PET/CT and MRI pretherapy, maximum standardized uptake value (SUVmax) was positively associated with Ki-67 index ($p < 0.0001$), ER-negative status ($p = 0.0001$), and PR-negative status ($p = 0.047$) [21]. With regard to tumor subtypes, a retrospective study on 548 patients showed that triple-negative and HER2-positive breast cancers have higher SUVmax compared to luminal A tumors [22]. Moreover, the functional nature of PET imaging may provide the possibility of texture analysis in assessing tumor heterogeneity as a new tool for assessment of tumor aggressiveness [23]. Such findings may have future implications in the management of BC, since several efficient therapeutic options are only applicable to tumors with certain histopathological features. Nonetheless, the histopathologic features of breast tumor are of utmost importance in survival determination and patient prognosis and will be discussed further.

Staging

Primary Staging

Preoperative staging is critical for a proper treatment plan for any BC patient. Findings from numerous reports indicate that PET/CT may be useful only in the primary staging of patients who are at a considerable risk of metastasis [24]. However, prospective studies that have evaluated PET/CT for staging of primary invasive breast cancer are rather scarce, or have been done with a limited number of patients. In a prospective study of 70 BC patients, PET/CT identified the primary tumor in 64 of 70 patients [25]. Additionally, PET/CT identified axillary lymph node involvement in 19 of 70 patients, compared with 24 of 70 that were confirmed during surgery [25]. These reports indicate that PET/CT has limited application for primary staging of early-stage BC. Current guidelines suggest that PET/CT can be performed for systemic staging of the newly diagnosed stage III and, in some studies, stage IIB breast cancer. Moreover, there is concern about how the tumor type and histology can modify the applicability of primary staging with PET/CT at any stage [26, 27], an area of further investigation.

Lymph Node Metastasis

Lymph node metastasis is the single most important prognostic factor for the treatment plan in breast cancer [28]. Sentinel node biopsy (SNB) remains the gold standard of lymph node assessment; a positive finding on SNB warrants further investigations with axillary lymph node (ALN) dissection [29]. Studies have evaluated the accuracy of PET/CT compared to SNB in diagnosing lymph node metastasis. The results of 25 studies were assessed in a meta-analysis and systematic review to investigate the accuracy of PET/CT in comparison with SNB [28]. In this report, the performance of PET/CT was inferior to SNB; however, a high specificity of 94 % of PET/CT in ALN assessment (95 % CI = 91–96 %) may have a role under certain circumstances [28]. For example, a positive lymph node on a PET/CT in a woman with a high suspicion of advanced disease may spare SNB and lead to a direct ALN dissection [12]. In general, however, it seems that the sensitivity of PET/CT is limited in comparison with SNB and thus guidelines still consider SNB as the method of choice to diagnose ALN involvement.

The diagnostic accuracy of PET/CT for ALN involvement has been compared to other non-invasive methods such as US and MRI. Riegger *et al*. [30] compared the results of US and PET/CT on 90 patients to determine the accuracy of both methods in diagnosing ALN metastasis. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of PET/CT for the detection of ALN metastases were 54, 89, 77, 74, and 75 %, respectively; while for US, it was 38, 78, 54, 65, and 62 %, respectively. PET/CT was significantly more accurate than US for the detection of ALN metastases ($p = 0.019$). In another study, PET/CT, US, and MRI were performed in 215 women with breast cancer. The sensitivity, specificity, PPV, NPV, and accuracy for diagnosing ALN metastasis were 72.3, 77.3, 66.7, 81.6, and 75.3 % for US; 67.5, 78.0, 65.9, 79.2, and 74.0 % for MRI; and 62.7, 88.6, 77.6, 79.1, and 78.6 % for PET/CT, respectively [31]. The report concluded that there was no significant difference in diagnostic ability among the imaging modalities (*i.e.*, US, MRI, and PET/CT); however, the diagnostic ability of PET/CT in detecting ALN metastasis was significantly improved by combination with MRI ($p = 0.0002$) or US ($p < 0.0001$) [31]. In another study that compared the diagnostic performance of PET/CT and US with sonographically guided fine-needle aspiration biopsy (FNAB) in determining the ALN status, FNAB had a significantly higher specificity, PPV, accuracy, and area under curve (AUC) compared to both US and PET/CT [32]. The authors suggested that the combined use of both modalities, which significantly increases sensitivity, is more complementary for assessment of ALN status than using each modality alone [31, 32]. In conclusion, PET/CT has a good specificity for diagnosing ALN metastasis, although its sensitivity is limited, especially in early-stage cases [29, 33]. Delayed PET/CT scan 90 min after FDG administration was also unable to enhance the diagnostic accuracy for diagnosing ALN metastasis [18, 34]. Additionally, in certain BC subtypes such as ER-positive/HER2-negative and HER2-positive tumors, SUVmax may be considered as an imaging biomarker for predicting ALN metastasis [35].

Internal mammary node metastasis has also been subject to thorough assessments with PET/CT. In a retrospective assessment of 249 patients, PET/CT had a high PPV (87.1 %) in diagnosing internal mammary metastasis among stage III breast cancer patients [36]. One recent study suggested that PET/CT has a higher AUC (0.87) in comparison with US (0.83) for detecting internal mammary node metastasis [37]. Fig. 1 shows a case of internal mammary nodal metastasis that was detected by PET/CT and confirmed with follow-up imaging [38].

Distant Metastasis

The most common sites of distant metastasis in breast cancer are bones, lungs, liver, and brain, and the conventional imaging studies for detecting distant metastasis include contrast-enhanced CT, bone scintigraphy, and MRI [39]. The diagnostic accuracy of PET/CT for distant metastasis has been evaluated in multiple studies. The results of a meta-analysis suggested that PET/CT is a valuable alternative when conventional MRI shows indeterminate or benign lesions or is not applicable [40]. Pooled data from 42 studies showed no statistically significant difference between MRI and PET/CT with regard to diagnostic AUC [40]. On the other hand, a more recent meta-analysis has reported a sensitivity of 0.96 (95 % CI = 0.90–0.98) and a sensitivity of 0.95 (95 % CI = 0.92–0.97) for detection of distant metastasis by PET/CT [41], which was higher than conventional methods. Moreover, according to another recent meta-analysis, sensitivity, specificity, positive likelihood ratios, and negative likelihood ratios of whole-body PET or PET/CT were 0.99 (95 % CI = 0.88–1.00), 0.95 (95 % CI = 0.89–0.98), 21.1 (95 % CI = 8.2–55.5), and 0.02 (95 % CI = 0.001–0.13), respectively; while the same measures for conventional imaging studies were 0.57 (95 % CI = 0.37–0.74), 0.88 (95 % CI = 0.78–0.94), 4.8 (95 % CI = 2.8–8.2), and 0.49 (95 % CI = 0.33–0.74), respectively [42]. Such evidence suggests an emerging role for PET/CT as a novel tool for the detection of distant metastasis in patients with breast cancer [41, 43, 44]. However, the current guidelines recommend PET/CT as a valuable alternative when the results of conventional modalities are inconclusive [45].

Although PET/CT is currently considered as a good alternative for detection of distant metastasis, the functional nature of this modality gives it advantage for detecting early metastasis to the bone, the most common site of metastasis [46, 47]. For example, vertebral bones are among the most common sites of metastasis and may be visualized early as focal areas of increased FDG uptake using PET/CT, while these foci may remain undetected with bone scintigraphy

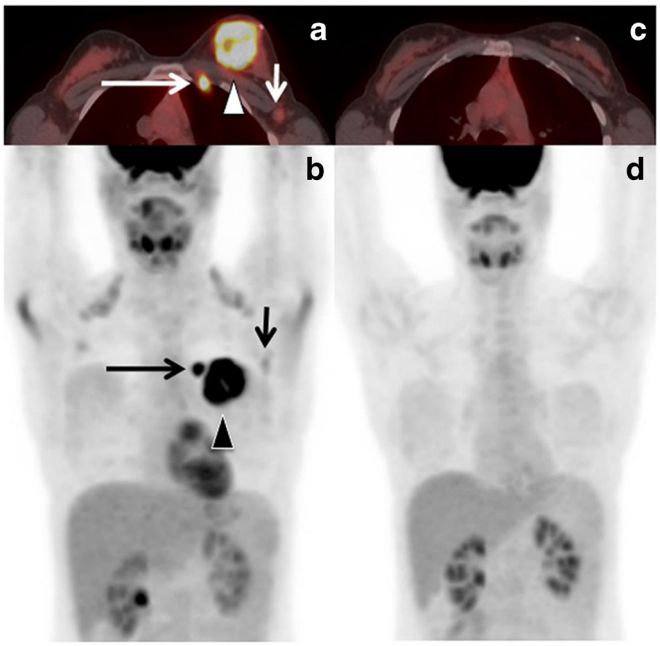

Fig. 1 A 38-year-old breast cancer patient with internal mammary nodal metastasis detected by PET/CT that was verified by imaging follow-up. **a** PET/CT and **b** PET images showed the primary breast cancer (arrowheads), axillary node (short arrows), and previously unknown left internal mammary node (long arrows). **c** PET/CT and **d** PET images following 5 months of neoadjuvant chemotherapy showed resolution of all FDG avid lesions. (This research was originally published in JNM. Riedl CC, Slobod E, Jochelson M, et al. Retrospective analysis of 18F-FDG PET/CT for staging asymptomatic breast cancer patients younger than 40 years. *J Nucl Med*. 2014;55:1578–1583. © by the Society of Nuclear Medicine and Molecular Imaging, Inc. [38]).

[46]. In a retrospective assessment of 198 patients with cancer (66 with breast cancer), PET/CT had a higher accuracy than CT for detection of bone metastasis [48], given that metabolic activity is increased prior to any anatomic changes. Another meta-analysis comparing PET/CT and bone scintigraphy for the detection of bone metastasis reported an AUC of 0.98 (95 % CI = 0.98–1.00) for PET/CT and 0.94 (95 % CI = 0.92–0.96) for bone scintigraphy, respectively [19]. Nonetheless, some authors have suggested that PET/CT and bone scintigraphy may have a complementary role in case of bone metastasis, since osteoblastic lesions are more accurately detected using bone scintigraphy and osteolytic lesions by PET/CT [46, 49].

PET/CT imaging is able to alter the treatment plan from neoadjuvant or surgical to palliative therapy in stage IIB and III BC especially in younger patients by detecting distant metastasis [50–53]. In a study of 134 patients with stage I to IIIC, PET/CT revealed distant metastasis in 17 % of asymptomatic stage II BC patients who were under 40 years old [38]. Figs. 2 and 3 represent two cases of BC that were upstaged following PET/CT [38].

Prognosis

An important component of initial evaluation for any BC patient is determination of prognosis, since it plays an important role in designing an individualized treatment plan. To date, a growing body of evidence supports the role of pretreatment PET/CT in risk stratification of advanced-stage breast cancer [17, 31, 54, 55]. Tumor cells with higher metabolic rate avidly take up FDG; thus, PET/CT allows for a more accurate prognostic stratification compared with conventional modalities that only assess the structural features of the primary tumor. In general, FDG uptake correlates with tumor aggressiveness and poorer prognosis [17, 31, 56, 57]. In fact, high pretreatment SUVmax predicts poorer outcomes in certain types of BC including the luminal type and IDC [17, 58–62], or in patients with bone metastasis [63]. In a study on 65 patients with IDC and without distant metastasis, T stage, N stage, estrogen receptor status, and nodal SUVmax significantly correlated with disease free survival (DFS) on univariate analysis [64]. However, only nodal SUVmax was found to be a single determinant of DFS by multivariate analysis (hazard ratio = 31.54; 95 % CI = 2.66–373.39; $p = 0.0065$) [64]. Higher SUVmax may also indicate a higher chance of disease recurrence especially in patients with hormone receptor-positive BC [65]. Moreover, SUVmax was recently reported to be positively correlated with the tumor size, clinical stage, certain histopathological subtypes (*i.e.*, triple-negative subtype), and Ki-67 index [66]. A retrospective review of PET/CT scans from 1906 postoperative patients suggested that a cutoff point SUVmax equal to 2.7 is a valuable measure for predicting outcomes such as progression free survival [67]. Nevertheless, pre-treatment SUVmax may have limited application for tumors that are inherently less FDG avid such as the ILC [68].

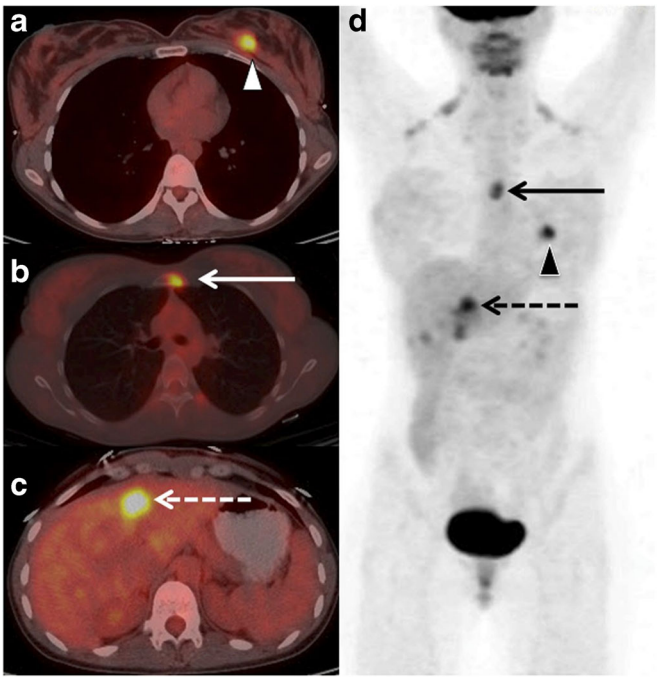

Fig. 2 A 29-year-old woman with stage IIA breast cancer was upstaged to stage IV by after doing PET/CT. Axial PET/CT images demonstrated known primary left breast cancer. The arrowhead shows **a** the primary breast cancer, while the solid arrow is **b** the previously unknown osseous metastasis and **c** the dashed arrow is the previously unknown liver metastasis. **d** The PET gives overview of all lesions. (This research was originally published in JNM. Riedl CC, Slobod E, Jochelson M, et al. Retrospective analysis of 18F-FDG PET/CT for staging asymptomatic breast cancer patients younger than 40 years. *J Nucl Med*. 2014;55:1578–1583. © by the Society of Nuclear Medicine and Molecular Imaging, Inc. [38]).

Based on the literature, it seems that PET/CT has advantage over conventional modalities in providing prognostic stratification [31]. In a prospective assessment of 142 patients with newly diagnosed BC and at least grade T2 tumor, patients were evaluated with conventional modalities (mammogram, US, bone scan, abdominal US, and/or CT, X-

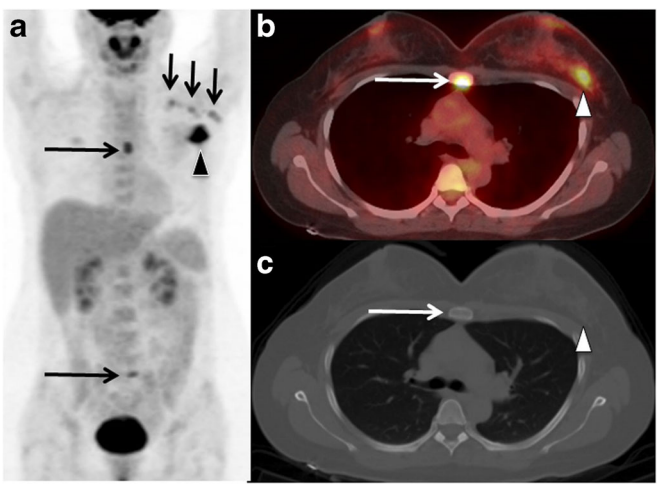

Fig. 3 A 32-year-old woman with clinical stage IIB breast cancer was upstaged to stage IV after performing PET/CT. The arrowhead shows **a** known primary breast cancer, short arrows show known axillary nodal metastases, and long arrows are two foci of FDG uptake in the midline of body. **b** Axial PET/CT and **c** axial CT through the chest showed primary breast cancer (arrowhead) and localized one of the midline foci to sternum without osteolytic or osteoslcerotic correlate on CT (long arrows). Biopsy of sternum demonstrated osseous metastasis unknown before PET/CT. The second midline focus was subsequently proven to be sacral metastasis (not shown). (This research was originally published in JNM. Riedl CC, Slobod E, Jochelson M, et al. Retrospective analysis of 18F-FDG PET/CT for staging asymptomatic breast cancer patients younger than 40 years. *J Nucl Med*. 2014;55:1578–1583. © by the Society of Nuclear Medicine and Molecular Imaging, Inc. [38]).

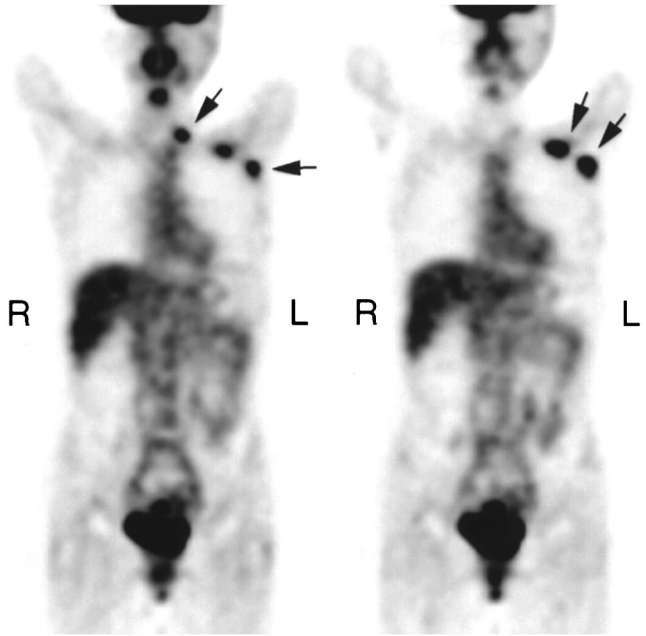

Fig. 4 PET images of patient with recurrent breast cancer involving left axillary and supraclavicular lymph nodes (arrows). MRI has been interpreted as consistent with fibrosis after radiation. PET findings were verified by biopsy. Left and right panels depict more anterior and more posterior coronal views, respectively. (This research was originally published in JNM. Vranjesevic D, Filmont JE, Meta J, et al. Whole-body (18)F-FDG PET and conventional imaging for predicting outcome in previously treated breast cancer patients. *J Nucl Med*. 2002;43:325–329. © by the Society of Nuclear Medicine and Molecular Imaging [95]).

rays, and/or CT of the chest), followed by pretreatment PET/CT [31]. After staging, patients were followed prospectively with a median follow-up of 30 months. The Cox proportional hazards model indicated that staging with conventional methods was significantly associated with progression free survival ($p = 0.01$); however, PET/CT staging provided stronger prognostic stratification ($p < 0.0001$) [31]. In a recent retrospective study on 240 patients, the tumor lesion glycolysis 30 % (TLG30%) from pretreatment PET/CT independently correlated with survival outcomes. Also, TLG30% was able to effectively stratify both patients with stage III and IV breast cancer [54]. In another study, whole-body total lesion glycolysis (WTLG) was identified as an independent prognostic factor of survival among patients who had metastasis as the initial presentation [69]. In fact, PET/CT can provide volume-based parameters such as metabolic tumor volume (MTV) and whole-body metabolic tumor volume (WB-MTV) that will enhance its predictive value for disease recurrence and prognosis determination [70].

Evaluation of Response to Neoadjuvant Chemotherapy

In patients that present with locally advanced breast cancer (LABC), primary surgery may not be applicable and NAC is used to provoke tumor shrinkage and allow for a lesser surgery. NAC is also applied in cases of large operable tumors when breast preservation is considered. It would be important to avoid unnecessary NAC in order to reduce cost or some significant adverse effects [71]. Accordingly, prediction of response to NAC as well as identification of NAC responders *versus* non-responders will provide for an early change of treatment strategy. Although response to NAC is commonly evaluated by US, mammography, and MRI, studies on the accuracy of PET/CT for evaluation of response to NAC have been encouraging [72–74]. It appears that higher baseline glycolytic activity and a bigger decrease in SUVmax following the early cycles of NAC are indicative of better histopathological status after the final course of NAC [72].

Most studies recommend adhering to a combination of imaging modalities in order to precisely predict complete pathological response (pCR) [75, 76]. This stems from the primary findings that reported a relatively low specificity for monitoring response to NAC [77, 78]. In a recent meta-analysis by Tian *et al*., 22 studies covering 1119 patients with known BC showed that pooled sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR−), and diagnostic odds ratio (DOR) of [^{18}F]FDG-PET/CT for treatment response prediction were 81.9 %, 79.3 %, 3.96, 0.23, and 17.35, respectively. Additionally, the included studies found that the sensitivity and specificity of [^{18}F]FDG-PET/CT ranged from 63 to 100 and 38 to 97 %, respectively. These wide ranges in

sensitivity and specificity may be due to heterogeneity between the studies [79].

An important determinant for prediction of pCR is the changes that occur in SUVmax from baseline following the early cycles of NAC [80–82]. In a prospective assessment of 40 patients with ductal carcinoma, the relative change in SUV (ΔSUV) after the second course of NAC was significantly higher for patients with pCR (−81.58 %) when compared to the non-pCR patients (−40.18 %) ($p = 0.001$) [83]. In a study conducted by Luo *et al.*, ΔSUVmax% after 2 and 4 cycles (ΔSUV1max, ΔSUV2max) of PET/CT had the ability to predict the pCR adequately. Combination of ΔSUVmax% and Ki-67 was even more predictive of response to NAC with the AUC of 0.824 compared to ΔSUV1max% and ΔSUV2max with AUC of 0.744 and 0.791, respectively [84]. In another study on 23 newly diagnosed patients with inflammatory BC, a 72 % cutoff for ΔSUV1-3 proved best to predict residual disease, with sensitivity, specificity, and accuracy of 61, 80, and 65 %, respectively [85]. Additionally, the 72 % cutoff for ΔSUV1-3 was the best predictor of distant metastasis-free survival ($p = 0.05$) [85].

Recurrence

Monitoring of loco-regional recurrence as well as distant metastasis after the initial treatment is of great importance [86]. Although recurrent disease carries a generally grave prognosis, early detection of the recurrence can improve survival. CT scan, MRI, and bone scintigraphy are the most commonly used modalities. Considering the high sensitivity and specificity of PET/CT in diagnosing distant metastatic foci, the accuracy of this modality for detecting loco-regional recurrence has also been studied. Results showed that PET/CT has at least equal accuracy to detect recurrent disease in comparison with MRI [87]. In a recent study, PET/CT was able to detect 97 % of the total 134 lesions (116 malignant, 18 benign) suspected of BC recurrence, while 4 bone metastases were missed. [^{18}F]FDG-PET/MRI, CT, and MRI detected 100, 96.2, and 74.6 % of lesions, respectively, which indicated that [^{18}F]FDG-PET/MRI was best suited for whole-body assessment of patients with recurrent BC, followed by [^{18}F]FDG-PET/CT [88]. Moreover, in a meta-analysis by Xiao *et al.* that included 26 studies with 1752 subjects, the results showed that the pooled sensitivity and specificity for PET/CT to detect recurrent BC was 90 and 81 %, respectively [89]. Of note, PET/CT screens the whole body in a single session, and also it can confirm disease in normal-sized nodes, which are advantages of PET/CT over CT and MRI in detecting recurrence [49].

Rising tumor marker levels (*i.e.*, CA 15-3 and CEA) in asymptomatic patients suggests recurrence, and PET/CT would be of high diagnostic yield in such cases [90, 91]. In a retrospective assessment of 228 asymptomatic patients that presented with rising CA 15-3 and/or CEA levels, sensitivity, specificity, PPV, NPV, and accuracy of PET/CT for diagnosing recurrence were 93.6, 85.4, 96.7, 74.5, and 92.1 %, respectively [91]. Other recent reports have recommended PET/CT as a priority imaging procedure in asymptomatic patients with rising CA 15-3 levels or for patients with suspected clinical or radiological recurrence [86, 90]. Additionally, restaging with PET/CT may be superior to restaging by conventional imaging procedures in recurrent cases [92]. In a retrospective assessment of 190 patients with breast cancer at all stages who underwent surgery and primary treatments, PET/CT was more accurate than CT in identification of disease recurrence [93]. However, assessment of lung nodules, liver disease, small recurrent tumors, and small metastasis may be limited due to decreased sensitivity of PET/CT [49]. Although PET/CT is not currently recommended for the routine follow-up, suspected cases of recurrence that have equivocal conventional studies would be the best candidates for PET/CT. In fact, PET/CT has been regarded as an imaging modality that can define the extent of disease burden in cases of loco-regional recurrence and distant metastasis [94]. Fig. 4 shows a case of recurrent BC that presented with left axillary and supraclavicular lymph nodes [95].

Conclusion

In many of the studies that evaluated the potential applications of PET/CT in patients with BC, the reported accuracy was comparable to that of conventional imaging modalities, though most were retrospective assessments and the level of evidence is not strong enough to suggest a definite role in most cases. However, PET/CT has a role in the staging, restaging, and management of advanced-stage BC [12].

PET/CT is not recommended for the initial diagnosis and it cannot replace SNB for axillary staging. PET/CT, however, can provide important information about some histopathological features of the primary tumor, while its practical importance and possible implications remain unknown. With regard to the primary staging, PET/CT is useful for systemic staging of newly diagnosed stage III and, in some studies, stage IIB BC. PET/CT has a good specificity for diagnosing ALN metastasis, although its sensitivity is limited, especially in early-stage cases. Also, reports suggest an emerging role for PET/CT as a novel tool for the detection of distant metastasis. In particular, the diagnostic accuracy of PET/CT for early bone metastasis may be greater than bone scintigraphy. PET/CT may have a predictive role in the evaluation of invasive BC and designation of treatment management. In fact, PET/CT may have a role in altering the treatment plan especially in patients with LABC. Considering determination of prognosis, PET/CT has an advantage over conventional modalities in providing prognostic stratification. Risk stratification by

pretreatment PET/CT is helpful in making clinical decisions about usefulness of NAC and directing treatment strategies. Additionally, encouraging results have been described in reports of studies that used PET/CT as a tool for evaluation of response to early cycles of NAC. PET/CT is not recommended for the routine follow-up of BC patients, but is highly recommended in an asymptomatic subject with rising tumor markers, especially if the results of conventional studies are equivocal. Certain issues need to be further addressed before PET/CT can be used in the routine care of patients with BC. Most importantly, the role that PET/CT may play in the management of early-stage BC needs to be further assessed through prospective randomized studies. With the continuing research on the treatment planning and evaluation of patients with BC, the exact role of PET/CT can be further identified.

Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflict of interest.

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