Breast cancer is the most frequently diagnosed form of cancer and the leading cause of cancer death in women worldwide. The first commercial positron emission tomography/computed tomography (PET/CT) unit was introduced in 2000, as a noninvasive, one-stop evaluation, merging anatomic localization with a functional image that enables measurements of physiological function in the region scanned. So far, the most useful application of PET/CT has been in monitoring breast cancer recurrence and evaluating response to therapy by detecting changes in 18F-fluorodeoxyglucose (18F-FDG) uptake. In this paper, current applications of PET/CT in the management of breast cancer are summarized.

Monitoring Recurrence

Under standard protocols, following treatment for their initial breast cancer, patients are routinely followed up with clinical examinations and mammography for at least five years. Recurrence or metastases usually happen in the first two to three years. Recurrence may be localized (in the breast), regional (affecting lymph nodes in the ipsilateral axilla), or cancer may recur as distant metastases (in tissues such as bone, liver, lungs or brain). One study by Elder et al. showed that the median interval from primary surgery to recurrence was 2.3 years; 27% of 456 patients with recurrence had bone metastases, 27% had local recurrence, 16% had lung metastases and 13% had liver metastases [1]. Current strategies for the detection of breast cancer recurrence include computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US) and bone scintigraphy (BS). In addition to conventional technologies, PET/CT has recently been shown to have relevance in the detection and management of breast cancer recurrence.

In breast cancer patients, accurate restaging of recurrence after systematic therapy is crucial.
for the selection of the most appropriate therapeutic strategy. In comparison with conventional methods, such as US, CT, BS and mammography, PET/CT has been shown to have superior specificity and sensitivity in the detection of distant metastases [2]. False negative PET/CT results can occur because of low FDG uptake in some conditions, such as invasive lobular carcinoma, less well visualized lesions in the visceral cavity and poor imaging of the limbs and brain. False positive results, on the other hand, may occur in inflammations. In a meta-analysis by Pennant et al. [3], PET/CT had significantly higher accuracy as compared with CT or PET alone for the diagnosis of recurrent breast cancer. No significant differences were found in the sensitivity or specificity of PET (with or without CT) when compared with MRI [3–4]. Since PET/CT and MRI have shown considerable effective in the verification of breast cancer recurrence or metastases, PET/MRI may become a powerful and promising technique in clinical oncology in the near future.

Schmidt et al. found PET/CT to be more sensitive than whole body-MRI (WB-MRI) in detecting lymph node involvement [4]. In addition, PET-CT detected more osteolytic-type bone lesions than osteoblastic lesions as compared with BS [5]. One possible reason for this difference may be that osteoblast proliferation in osteosclerotic lesions increases the bone matrix, where FDG uptake is lower. Osteoblastic metastases usually do not show increased glucose intake and are better detected with BS.

Evangelista et al. carried out a systematic review involving 13 studies from 2001 to May 2011, which showed that fluorodeoxyglucose PET, and in particular PET/CT, allows 83% accuracy in the assessment of the site and extent of the recurring disease when the clinician is confronted with suspicious elevated serum tumor markers in asymptomatic breast cancer patients following primary treatment and negative conventional imaging findings [6].

In breast cancer patients suspected of disease recurrence, CA15-3 levels, as well as increases in CA15-3 levels over time, have proven systematically higher in PET-positive patients when compared with PET-negative patients. However, no single cut-off value yielding an acceptable sensitivity and specificity has been identified for either variable. Rather, it is the combination of increases in CA15-3 over time along with a clinical suspicion of disease progression that should prompt the clinician to perform PET/CT imaging. The limited data available further suggests that this approach will likely affect treatment management in up to 50% of patients [7]. Evangelista et al. retrospectively studied 60 breast cancer patients who had already undergone systemic therapy for primary disease. Three serial measures of Ca15-3 were collected individually within one year before PET/CT examination: at 12–9 months, at 9–3 months, and at 3–0 months. The study showed that an increase in CA15-3 at 9–3 months and 3–0 months correlates with accurate positive PET/CT results and disease relapse (p < 0.05). During a breast cancer patient’s follow-up, serial elevated Ca15-3 could be a hint to the clinician to perform a PET/CT examination to detect disease relapse when the disease is more treatable [8].

These findings indicate that PET/CT is an accurate, sensitive and reliable modality for the screening and detection of breast cancer recurrence. According to the 2014 National Comprehensive Cancer Network guidelines (NCCN 2014 v. 3) FDG PET/CT is highly recommended for the detection of suspicious or equivocal metastatic lesions and bone metastasis [9].

FDG-PET/CT appears to be an effective surveillance tool; the technique is able to assess the whole body in a single procedure and performs well. More prospective studies are needed to determine whether this technology could potentially replace conventional imaging tests used today to monitor breast cancer recurrence.

Assessment of Response to Therapy

Neoadjuvant chemotherapy (NAC) has long been a standard therapy for stage II and III breast cancer [10]. It is generally accepted that an absence of residual cancer cells in the primary tumor following NAC is strongly associated with improved disease-free survival and overall survival [11]. However, in most NAC studies less than 30% of patients achieve complete response [12]. Thus, find an effective way to predict response early during NAC is important so that physicians can change strategies in case of ineffectiveness, thereby avoiding unnecessary side effects to patients.

A correlation has been demonstrated between early changes in the maximum standardized uptake value (after one or two courses of chemotherapy) and the final treatment response at the completion of NAC [13–15]. Relative changes in both the maximum standardized uptake value (SUV-max) and standardized uptake value (SUV) have been proposed as a means to discriminate metabolic responders from nonresponders or to differentiate between pathological complete response (pCR) and non-pCR [13–15]. Recently, a study by
Andrade et al. demonstrated that the optimal percentage change in post-treatment SUV scores relative to baseline (ΔSUV) to discriminate between pCR and non-pCR was $-71.8\%$ (83.3\% sensitivity; 78.5\% specificity); the optimal ΔSUV threshold to discriminate between NAC responders and non-responders was $-59.1\%$ (68\% sensitivity; 75.0\% specificity) [16]. Unfortunately, the optimal threshold value varies dramatically across studies.

There are still studies suggesting that other imaging tests, such as MRI, when combined with tumor diameter detection, are better than the change in SUV for evaluating response to NAC [17]. However, in general more and more data support the role of FDG PET/CT in the early evaluation of response to NAC. Better defined criteria for PET/CT evaluation are needed. MRI is also useful in the early evaluation of response to NAC, and the place of PET/CT in comparison with MRI needs to be better determined [18].

It is possible that PET/CT can detect tumor response metabolically earlier than morphologic imaging methods in order to evaluate treatment response in metastatic breast cancer. First, for targeted therapies, tumors always change metabolically earlier than their size changes. Second, for endocrine therapy, several studies have shown that an increase in tumor FDG uptake 7–10 days after initiating endocrine therapy is predictive of a good response [19–20]. This phenomenon can be explained by the fact that endocrine therapy has initial agonist effects before antagonist effects dominate. Therefore, an increase in SUV in tumors soon after the initiation of hormone therapy is predictive of a good therapeutic response. One study by Mortazavi-Jehanno et al. found that “metabolic response assessed by FDG PET/CT imaging in metastatic breast cancer treated with endocrine therapy is predictive of the patients’ (progression-free survival)” [21]. However, data are lacking on the delayed effect of endocrine therapy on tumor metabolism. Third, PET/CT is also helpful in providing evidence of a heterogeneous response (that is, the co-existence of responding and non-responding lesions within the same patient) [22].

Newer evaluation criteria are needed that take into account not only the PET but also the CT of hybrid imaging. Although there are few studies evaluating PET/CT in metastatic breast cancer treatment, this modality does have some advantages over other imaging. More data are needed, and standardization in the criteria for evaluation is necessary.

Previous research has evaluated correlations between the difference in SUV in dual time-point imaging and biological prognostic factors [23–25]. Little is known, however, as to whether the metabolic characteristics of breast cancer differ in relation to molecular subtypes. Triple-negative breast tumors (negative for estrogen and progesterone receptors, and no HER2/neu overexpression) are currently the subject of major interest because of the aggressiveness of these tumors, their poor prognosis and the lack of targeted therapy. Some studies focusing on triple-negative breast cancer (TNBC) have shown that the SUV of the primary lesion in the TNBC group was significantly higher than in non-TNBC [23, 26]. One study by Keam et al. showed that the estrogen receptor-negative phenotype had a higher percentage change in SUV and pre-chemotherapy SUV than other phenotypes [26]. Non-TNBC has lower pre-chemotherapy SUV than TNBC patients ($9.8 \text{ vs. } 6.4$, $p = 0.008$) [25]. Early metabolic non-response was always associated with pathologic non-response and a poor prognosis in ER-positive/HER2-negative patients. In this subtype, PET/CT might be useful to select patients who will probably benefit from early therapeutic strategy modifications [27, 28].

Recently, Koolen et al. evaluated the effect of 18F-FDG PET/CT in monitoring responses to NAC in 98 breast cancer patients. They found that the accuracy of response monitoring with PET/CT was much higher in the ER-positive/HER2-negative and triple-negative subtypes than in the HER2-positive subtype. They speculated that this phenomenon could be explained by an initial inflammatory response induced by trastuzumab treatment in HER2-positive subtype patients [29].

There are other oncologic PET-tracers for the management of breast cancer. PET with 18F-FLT enables investigators to quantify the proliferation fraction of tumors [30] and has been proposed as a better biomarker than FDG-PET for measuring response to therapy [31]. In a study of 14 breast cancer patients, FDG-PET and FLT-PET were performed at baseline, two weeks after the first cycle of chemotherapy or endocrine therapy and after the completion of treatment [32]. Early changes in FLT uptake showed a stronger correlation with clinical outcome than did FDG. According to preliminary results from a pilot study, changes in the number of circulatory tumor cells (CTCs) seem to be correlated with changes in FLT-PET uptake in metastatic lesions during the course of therapy [33]. Larger prospective trials are needed to define the potential role of FLT-PET for treatment monitoring.

Another biomarker, 16a-18F-fluoro-17b-estradiol (FES), is a steroid-based positron emission tomography tracer that has been shown to be a reliable tracer for the management of ER-positive breast cancer patients. Low FES uptake in tumor lesions shows a strong predictive value for failure of antihormonal therapy [34]. Yet another bio-
marker, 21-[F-18]-fluoro-16a,17a-[(R)-(19-a-furyl methylidene)dioxy]-19-norpregn-4-ene-3,20-dione (FFNP), shows a high affinity and selectivity for progesterone receptors (PR) [35]. In the future, FFNP-PET may allow for the non-invasive detection and quantification of PR-positive lesions.

[Zr89]-trastuzumab, which shows an excellent uptake in HER2-positive lesions in liver, lung, bone and brain metastases, may allow for a whole-body assessment of the HER2 receptor status in metastatic/recurrent breast cancer. However, so far few reports have described the use of this biomarker in breast cancer patients [36].

Piccardo et al. found that (18) F-Fluoride-PET/multi-detector row spiral CT (MDCT) with 1.25 mm section thickness image reconstruction has a higher diagnostic accuracy for bone metastases than does PET/CT and MDCT [37].

It has also recently been argued that 18 F-sodium fluoride (18F-NaF) PET/CT might prove a useful alternative to detect bone reaction to metastatic involvement. Combined NaF/FDG-PET/CT has shown promising early results using the same amount of radiation as BS and FDG-PET/CT [38]. According to Gradishar et al., if a FDG PET/CT scan clearly indicates bone metastasis on both the PET and CT components, a bone scan or sodium fluoride PET/CT may not be needed [9]. In some conditions, considering the coexistence of both lytic and sclerotic lesions and the different mechanisms of radiotracer uptake, PET and BS are mutually complementary methods for the diagnosis of bone metastasis [38].

Conclusions

Studies to date support the following conclusions: 1) PET/CT can be used earlier than morphologic imaging methods to evaluate the response to chemotherapy, targeted therapy and endocrine treatment in breast cancer. 2) Serial elevated Ca15-3 could be a hint to the clinician to perform a PET/CT examination to detect disease relapse when the disease is at a more treatable stage. 3) TNBC was significantly associated with a higher SUV (max) and relatively good response to NAC. 4) New PET biomarkers, including those that detect the rate of cell proliferation and the expression of estrogen receptors, seek to improve patients’ restaging information and the evaluation of therapeutic effectiveness. Further studies are needed to evaluate these new imaging strategies and their clinical utility. It is likely that in the future those patients who are unlikely to benefit from chemotherapy could be identified by a pretreatment PET/CT test.

References

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