We review how radiolabeled glucose and estrogen analogs can be used in breast cancer patients. We focus this review on the application of positron emission tomography imaging to ER-positive metastatic breast cancer as an example of how imaging can guide breast cancer treatment.

Introduction

Breast cancer is the most common malignancy among women, with more than 200,000 women predicted to be diagnosed in 2014.[1] While most breast cancer is curable, 5% of newly diagnosed women have metastatic disease, and in this group the 5-year survival rate is 24%.[1] As the prevalence of metastatic breast cancer increases, the demand is also increasing for more efficacious, less toxic therapy and new methods of identifying which tumors will respond to therapy. For example, due to discordance of receptor status between a primary and metastatic lesion in approximately 25% of patients,[2,3] biopsy of metastatic lesions is recommended, if feasible.[4] At present, estrogen receptor (ER) expression and/or human epidermal growth factor receptor 2 (HER2/neu) positivity are used to guide clinical recommendations for systemic therapy. These test results are not perfect, however: 50% to 75% of patients with ER-positive breast cancer will respond to first-line endocrine therapy, whereas 25% of those beyond the first line will respond.[3] Response rates with HER2-directed therapy in patients with HER2-positive breast cancer are better, although these rates are generally inversely related to the line of therapy (ie, higher with first-line, lower with second-line, and lowest with third-line therapy).[5] Identification of patients who will not respond to endocrine or HER2-directed therapy would be clinically useful, as it would help to guide therapeutic decision making. Additionally, metastatic breast cancer is a heterogeneous disease; not all metastatic lesions from a particular breast cancer will have the same receptor expression.[6] Since biopsy of every metastatic lesion is not realistic, practitioners are often forced to use the receptor status from one metastatic lesion as the basis for treating all metastatic lesions. At present, there are no standard tools that examine tumor heterogeneity or determine who will respond to targeted therapy, although genomic profiling may be useful with the latter. Positron emission tomography (PET) imaging using various tracers may be useful for both purposes.

Body imaging (CT scan, x-rays, and magnetic resonance imaging [MRI scans]), more so than PET, has traditionally been used to detect the location of tumors and can assess the size and shape of malignant primary and metastatic disease. However, molecular imaging can also provide additional information on tumor biochemistry and molecular biology. PET is an imaging modality that uses radioactive nuclides. These nuclides can be coupled with radiopharmaceuticals that target specific molecular characteristics of tumors. When used for imaging, the amount of radiopharmaceutical administered is small (10^{-6} Ci to 10^{-9} Ci) and without pharmacologic effect. Thus, PET can assess molecular changes associated with disease, without modifying the underlying processes.[7] Based upon the observation that cancers have elevated rates of glucose consumption compared with normal tissues, PET was first introduced into clinical practice using a glucose analog with fluorine-18 substituted for the normal hydroxyl group at the 2' position ({^{18}}F-fluoro-deoxyglucose ({^{18}}F-FDG)). Fluorine-18 is a radioactive isotope and emits positrons, allowing three-dimensional imaging and quantification of regional {^{18}}F concentration. PET imaging is often used in conjunction with CT, where the CT is used for the purposes of anatomic localization and attenuation correction. {^{18}}F-FDG measures regional FDG uptake, largely in the form of trapped FDG-6-phosphate in images taken an hour after injection, and is thus a quantitative indicator of the cellular glycolytic rate. Here we will discuss the reliability of radiotracer imaging to detect breast cancer (focusing on metastatic...
disease), predict response to therapy in the neoadjuvant and metastatic settings, and assess response to breast cancer-directed therapy.

Detection of Metastatic Disease

In 2008, a panel of experts reported that $^{18}$F-FDG–PET is an important diagnostic tool for detecting metastatic or recurrent breast cancer.[7] Supporting this, a subsequent meta-analysis across studies involving 668 patients found that FDG-PET was more sensitive and specific than bone scintigraphy for the detection of breast cancer metastases to bone, with a sensitivity of 0.93 (95% confidence interval [CI], 0.82–0.98) and specificity of 0.99 (95% CI, 0.95–1.00) vs a sensitivity of 0.81 (95% CI, 0.58–0.93) and specificity of 0.96 (95% CI, 0.76–1.00), respectively.[8] A similar meta-analysis across studies with a total of 748 patients found that $^{18}$F-FDG–PET is more sensitive and specific than conventional imaging for detection of distant metastasis.[9] Currently, FDG-PET is an important modality for assessing regional nodal sites outside of assessment of the axilla (internal mammary chain) and distant metastatic staging.[10] It is recommended for consideration in the workup of stage III and higher breast cancer, according to the National Comprehensive Cancer Network (NCCN) practice guidelines.[4]

Determination of the hormone receptor status of primary breast tumors to stratify patients to appropriate therapy is standard clinical practice, but metastatic disease from breast cancer may be difficult to biopsy (eg, disease in the bones or brain), and the accuracy of biopsy may be confounded by tumor heterogeneity. Thus, an assay to determine the functional ER status of residual disease and monitor treatment response would be a valuable tool that could aid in therapeutic decision making. Measurement of tumor ER status could also be useful in determining effectiveness of novel ER-blocking therapies. PET imaging of ERs is described later.

Imaging to Assess or Predict Response to Targeted Therapy

While FDG-PET is a valuable tool for detecting distant breast cancer, it can also be used to predict and assess response to therapy. A recent meta-analysis of FDG-PET for early identification of response to therapy included 15 studies with a total of 745 patients; it reported a sensitivity of 80.5% (95% CI, 75.9%–84.5%) and a specificity of 78.8% (95% CI, 74.1%–83.0%).[11] FDG-PET has also shown promise in response assessment in metastatic disease,[12,13] and in predicting response to endocrine therapy.[14]

Besides FDG, there are also several radionuclides under investigation for use as diagnostic tools to aid in treatment selection and assessment of chemotherapy response. The most studied are $^{18}$F-fluoro-17β-estradiol (FES; to quantify ER activity), $^{18}$F-fluorothymidine (FLT; to measure cellular proliferation), and $^{18}$F-fluoromisonidazole to assess hypoxia. Among these, FES is emerging as a promising predictive biomarker that can help select candidates for endocrine therapy and monitor treatment response. FES uptake correlates strongly with ER expression as measured by radioligand binding in fresh tissue[15] and immunohistochemistry in fixed tissue.[16] Larger, multi-institutional studies are needed to determine the standardized uptake value (SUV) threshold for response as well as the sensitivity and specificity of FES for response prediction and breast cancer detection.[17] Moreover, FES may be especially helpful in bone-dominant metastatic disease from ER-positive tumors. Preliminary evidence suggests that FES PET is 100% specific and more sensitive than conventional imaging (CT and bone scan) for patients with metastatic disease who initially had an ER-positive breast cancer.[18] Clinical trials to better understand the role of FES imaging in metastatic breast cancer are currently under development.

Use of FDG PET and FLT PET in the Neoadjuvant Setting

FDG PET has been widely studied as a marker of breast cancer response to chemotherapy in the neoadjuvant setting, and has proved to be predictive of response and survival.[16] Recently, intriguing imaging of response to HER2-targeted therapy was published from the Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (Neo-ALTTO) study, which was a multicenter international prospective neoadjuvant clinical trial that compared lapatinib vs trastuzumab vs the combination in patients with locally advanced HER2-positive breast cancer; half of patients also had ER-positive disease. FDG-PET was used to assess metabolic response in a subset of the 455 patients enrolled, and studies were obtained at baseline, at 2 and 6 weeks post initiation of the targeted agent, and prior to the addition of weekly paclitaxel. Investigators found a strong correlation ($R^2 = 0.81$) between metabolic response at 2 weeks and the response at 6 weeks; those who responded at
2 weeks were likely to also respond at 6 weeks.[19] Metabolic response rates were observed in 71.6% and 60% of patients at weeks 2 and 6, respectively. Positive predictive value (PPV) of response at 2 weeks vs 6 weeks was 78.5%, and negative predictive value (NPV) was 90%. In total, 35.1% of subjects in this imaging cohort achieved a pathologic complete response (pCR). Subjects who achieved a pCR had greater SUV$_{\text{max}}$ reduction at both time points than those who did not have a pCR.[19] This study was the first prospective multicenter trial to examine the utility of FDG-PET as a pharmacodynamic biomarker in conjunction with HER2-directed therapy (and biological therapy) administered alone in patients with locally advanced breast cancer. FDG-PET is also being incorporated as an integral biomarker in future studies of chemotherapy and targeted therapy in the neoadjuvant setting.

The ability of FLT-PET to measure early response in the course of chemotherapy or hormonal therapy was demonstrated in two small studies of breast cancer patients.[20,21] Mean change in FLT-PET at 2 weeks after initiation of chemotherapy or hormonal therapy in 14 patients with breast cancer (primary or metastatic) correlated with changes in levels of tumor marker cancer antigen (CA) 27.29 at 5.8 months ($r = 0.79, P = .001$) and change in tumor size as measured by CT scan ($r = .74, P = .01$).[21] Moreover, comparison of FLT at baseline and 1 week post chemotherapy in 13 patients with stage II–IV breast cancer showed that reduction of FLT correlated with response assessed at day 60 on treatment.[20] At the 2013 San Antonio Breast Cancer Symposium, a 14-patient study underway at the University of Washington was presented that examines the association between response as measured by changes in Ki-67 levels and changes seen in serial FLT-PET scans during a short run-in of neoadjuvant endocrine therapy for early-stage ER-positive breast cancer. The goal of the study is to evaluate the ability of FLT-PET to noninvasively measure tumor proliferation. Eleven patients had undergone both imaging studies and definitive surgery at the time of the presentation. All patients had a decline in both FLT SUV and flux as well as Ki-67 levels; however, FLT flux was noted to correlate with Ki-67 changes both pre and post surgery (Pearson correlation coefficients 0.41 and 0.82, respectively).[22] These preliminary findings support the notion that quantitative FLT flux may provide information about tumor proliferation in ER-positive early-stage breast cancer that may be valuable in assessing response to endocrine therapy.

## Metastatic Disease

PET may be used to predict the likelihood of response to targeted therapy, specifically when it is performed using agents that measure target expression. Figure 1 shows FDG and FES images in one patient and highlights the different information that each of these scans provides. The value of baseline FES SUV to predict response to endocrine therapy has been examined in several small studies. Dehdashti and colleagues at Washington University in St. Louis performed two of these studies. Among 11 patients with metastatic ER-positive breast cancer about to receive tamoxifen therapy in the first study, the baseline FES of responders was higher than that of nonresponders ($\geq 2.2$ vs $\leq 1.7$).[23] In the second study of FES in patients receiving an aromatase inhibitor (AI) or fulvestrant, responders had higher tumor FES SUV than nonresponders ($3.5 \pm 2.5$ vs $2.1 \pm 1.8$, respectively). In logistic regression analysis, the odds of response increased by 40% for every unit increase in FES. On receiver operating characteristic (ROC) analysis, an FES SUV of 2.0 was determined to be the cutoff necessary to predict response to AI or fulvestrant therapy. Using the 2.0 cutpoint, investigators calculated the PPV of FES PET to be 50%, with an NPV of 81%.[24] Mortimer et al calculated slightly better PPV and NPV of FES-PET in their study of 40 ER-positive patients with metastatic breast cancer. When examining FES PET, responders had a higher mean baseline FES SUV than nonresponders ($4.3 \pm 2.4$ and $1.8 \pm 1.4$, respectively, $P = .0007$). PPV and NPV were calculated to be 79% and 88%, respectively, when 2.0 was used as the cutpoint.[25] In a study of patients with metastatic disease, most of whom were considered for salvage endocrine therapy, Linden et al examined baseline FES SUV and response to endocrine therapy at 6 months in 47 patients with metastatic ER-positive breast cancer previously treated with tamoxifen. Quantitative FES uptake was associated with response when using 1.5 as the cutpoint. Of 15 subjects with SUV $< 1.5$, none responded to hormonal therapy, whereas 11 of 32 with SUV $> 1.5$ responded ($P < .01$). Of note, none of the responders had HER2-positive disease.[26]

Combining results from these four studies, van Kruchten et al found that FES SUV below 1.5 predicted for lack of response to endocrine therapy in previously treated patients with ER-positive metastatic breast cancer.[27] Notably, when using 2.0 as the cutoff to analyze the data in these patients, 31% of patients who responded to endocrine therapy would have been considered FES-negative (and thus potentially would not have received the therapy to which they responded). A
fifth small study confirmed this finding in a group of 15 patients with newly metastatic ER-positive breast cancer who were scheduled to start endocrine therapy. Two of two patients with low baseline FES uptake had progressive disease at 6 months.[28] This is a potentially important and clinically useful finding. While it certainly needs prospective validation in larger trials, a single FES study prior to initiation of a new therapy could help clinicians determine the utility of treating a patient with further lines of endocrine therapy rather than moving on to other systemic therapies (chemotherapy). In particular, low baseline FES may help identify patients who will ultimately be refractory to endocrine therapy. Large prospective studies are needed to evaluate and validate this use for FES imaging, and multicenter studies are under development for follow-up on these promising early single-center results. Results from these studies may provide more evidence supporting the NPV of FES to anticipate lack of response to endocrine therapy in ER-positive metastatic breast cancer.

Serial PET imaging may also provide an effective and robust means of assessing treatment response at an early time point. Studies using FDG-PET or PET/CT in the metastatic setting have shown promising results; however, much of the data were generated in small studies. Timing between FDG-PET scans was not uniform across studies, and only one of these studies was prospective. The treatments used in patients in these studies were also heterogeneous. Many studies focused on patients with ER-positive metastatic disease, and two focused on those with bone-dominant disease. The first, published in 2002, was a feasibility study that identified 24 patients treated at the University of Washington. Clinical response (clinical factors and serum tumor markers) was compared to change in FDG SUV. When response assessment was categorized as response, stable disease, or progressive disease, investigators found a correlation between the change in SUV uptake and the response category. There was a moderate correlation between percent change in SUV and change in CA 27.29 (r = .56, P < .001).[29] Specht and colleagues further examined the change in FDG-PET SUV in 28 patients. Investigators examined whether absolute change in FDG SUV or percent change in FDG SUV were associated with time to progression or first skeletal-related event (SRE). The hazard of progressing was higher in patients with smaller percent decreases in FDG SUV in Cox modeling (hazard ratio [HR] = 1.02; 95% CI, 1.01–1.03). In survival analysis, percent change in FDG SUV (rather than absolute change in SUV or baseline SUV) was found to predict time to progression when dichotomized at the median, 41% (P = .0054). Six SREs were reported in the 28 patients studied; when dichotomized at the median of SUV 5, baseline SUV was associated with time to SRE (P = .028).[30]

Two additional studies underscore the importance of the complementary value of the CT component of PET/CT in following response in bony metastatic disease. These studies demonstrated that while PET can detect osteolytic lesions, CT detects osteosclerotic and osteoblastic lesions. Thus, when monitoring response, the integrated PET/CT scan has the ability to show that increased sclerosis on CT complements decrease in FDG uptake of a given lesion, indicating response to therapy.[31,32] Moreover, these studies showed that when a new blastic lesion is noted on serial CT with a decline in FDG SUV on PET images, it was likely a previously lytic lesion not well seen on baseline CT that became blastic with therapy. This is a clinically useful differentiation, as it tells the physician that the patient is not progressing and is responding well to the current treatment.

Finally, one prospective study examined FDG-PET at baseline and 10 weeks ± 4 weeks in 22 patients with ER-positive metastatic breast cancer whose treatment plan was initiation of a new endocrine therapy. Response, as assessed by FDG SUV using European Organisation for Research and Treatment of Cancer (EORTC) guidelines, was associated with progression-free survival (PFS). Median PFS was 20 months in patients with partial metabolic response (PMR), 27 months in those with stable metabolic response (SMR), and 6 months in those with progressive metabolic disease (PMD) (P < .0001; PMD vs SMR and PMR). No difference was observed in overall survival.[33] Although small numbers, these results provide preliminary evidence that reduction in FDG-PET SUV following initiation of a new therapy is associated with improved PFS.

Another study examining 47 patients with bone-dominant metastatic breast cancer was presented at the San Antonio Breast Cancer Symposium in 2013.[34] This study prospectively evaluated subjects with FDG- and FLT-PET scans at baseline and at approximately 12 weeks (mean, 4.6 months) after initiation of a new systemic therapy. Among the 24 subjects who had both scans at the two time points, change in FLT SUV was not found to be predictive of time to progression (TTP) (HR = 1.05; P = .914), whereas change in FDG SUV was statistically significantly predictive of TTP (HR = 0.317; P = .038).[34] Both absolute FDG and FLT SUV were predictive of time to SRE (FDG SUV > 6 vs < 6, HR = 4.61, P = .002; and FLT SUV > 25 vs < 25, HR = 4.57, P = .008).[34] This study provides further evidence that FDG-PET may be a useful tool in assessing TTP in patients with bone-dominant...
metastatic breast cancer. Larger prospective trials examining change in FDG SUV and timing of the “first look” PET following initiation of new therapy are needed to further characterize the utility of FDG in this setting. One such study is currently open at the University of Pennsylvania; it is prospectively examining FDG-PET before, and at 4 weeks and 12 weeks following initiation of a new endocrine therapy in women with bone-dominant ER-positive metastatic breast cancer. Figure 2 shows an example of baseline and 12-week PET/CT from one of the patients enrolled on this study. Serial imaging can also be used to predict response to endocrine therapy by demonstrating a metabolic “flare” in response to ER agonists. Clinical “flare” phenomenon is well described; it is short-term disease progression immediately following initiation of a new endocrine therapy; it typically occurs with therapies that have transient agonist action; and it is described as an increase in pain over disease-involved sites, enlargement of soft tissue tumors, and elevation in serum tumor markers. However, clinical flare is observed less than 5% of the time and is challenging to differentiate from actual disease progression.[35] Metabolic flare, increase in tumor FDG uptake after the start of a new endocrine therapy, can be detected more frequently and may be a good predictor of response to endocrine therapy.

Mortimer et al studied the use of FDG- and FES-PET in assessing metabolic flare after starting tamoxifen in 40 patients with metastatic ER-positive breast cancer, none of whom had received hormonal therapy in the metastatic setting.[25] Scans were obtained at baseline and 7 to 10 days after initiation of tamoxifen. The investigators determined that 52% (21 patients) responded to this therapy; 6 patients were thought to have a clinical flare (5 were responders and 1 had progressive disease). FDG-PET noted metabolic flare in 20 of the 21 responders; absolute change in SUV was 1.3 ± 1.4 for responders and −3.2 ± 11.6 in nonresponders, and mean percentage change was reported to be 28.4% ± 23.3% and −10.1% ± 16.2% for responders and nonresponders, respectively. PPV and NPV were calculated to be 91% and 94%, respectively, when an increase of FDG SUV of 10% or greater was used as the cutoff to define flare. However, unlike FDG PET, for which an increase in SUV was observed in responders, responders had a decrease in FES metabolic activity after 7–10 days of tamoxifen. The percent decrease was significantly higher in responders (54.8% ± 14.2%) than in nonresponders (19.4 ± 17.3%; P = .0003), as was the mean change in FES SUV (−2.5 ± 1.8 in responders and −0.5 ± 0.6 in nonresponders).[25] Given that FES measures available ER activity, decrease in FES after initiation of tamoxifen makes sense. Percent change in FDG SUV and baseline FES were the two strongest predictors of response in this study. These observations were also noted in another study.

Dehdashti and investigators prospectively examined flare in a heterogeneous group of 51 postmenopausal women with metastatic ER-positive breast cancer, as a method of predicting response to endocrine therapy with AI or fulvestrant; patients had received various previous therapies, including tamoxifen and chemotherapy. All subjects received baseline FDG- and FES-PET scans, and FDG-PET was repeated after injection of 30-mg estradiol. Seventeen subjects were deemed responders and 34 did not respond, based on the clinical judgment of the treating physician and standard Response Evaluation Criteria in Solid Tumors (RECIST). Using ROC analysis, ≥ 12% increase in FDG SUV was determined to be the cutoff differentiating patients with flare from those without. Only 5 patients were determined to have a clinical flare, whereas 17 were found to have a metabolic flare by FDG PET. Only responders experienced a metabolic flare following estradiol challenge, and responders had an average higher percent change in FDG SUV compared with nonresponders (20.9 ± 24.2 vs −4.3 ± 11, P < .0001).[24] Furthermore, metabolic flare predicted for improved overall survival (P = .0065 in those with flare vs those without). While small, this study demonstrates the ability of flare, as measured by increase in FDG SUV, in ER-positive metastatic breast cancer to predict for response to endocrine therapy and overall survival.

Ellis et al investigated whether metabolic flare as measured by FDG-PET could predict response to estradiol therapy in 66 patients in whom AI therapy had failed. Patients in this study were randomized to receive 6 mg or 30 mg of estradiol daily, with the hypothesis that AI therapy sensitized ER-positive breast cancer to estradiol. Forty-six patients had adequate FDG-PET imaging before and 24 hours after initiation of therapy. Metabolic flare was defined as an increase in 12% SUV; 15 patients were noted to have a flare, and 31 did not.[36] Combining the two treatment groups, flare was noted in 3 of 3 subjects with partial response, 9 of 13 patients with stable disease, and 3 of 30 with progression of disease. Presence of metabolic flare predicted for response to estradiol, with a PPV of 80% and NPV of 97%. Patients with metabolic flare had longer PFS than did those without a flare (log rank P = .02).[36] Thus, metabolic flare as measured by FDG-PET in predicting response to endocrine therapy has been confirmed in three prospective studies. While it is not used in routine clinical practice, examination of metabolic flare could be incorporated into clinical
Conclusions

FDG and other PET imaging agents may be used to detect the physical locations of breast cancers and provide information on the biology and heterogeneity of the disease. FES SUV prior to initiation of new therapy can give information about the presence of ER expression, inform about tumor receptor heterogeneity, and predict for response to endocrine therapy; importantly, low FES SUV predicts for lack of response to endocrine therapy. This is particularly useful in the setting of bone-dominant ER-positive metastatic breast cancer, as assessing response clinically can be challenging in this population. FLT-PET may be useful in assessing response to therapy in ER-positive breast cancer, although current studies are conflicting and larger trials are needed to fully understand the utility of FLT-PET in the breast cancer patient. Serial FDG-PET imaging can be used to follow disease response at traditional time points (2 to 3 months after initiation of treatment) in the neoadjuvant and metastatic settings. Early FDG-PET after initiation of therapy, including endocrine therapy, can also specifically assess for early increases in response to agonists (flare) and early declines in response to antagonists, which can help identify patients who are likely to respond to this treatment. Importantly, serial FDG-PET can also predict PFS. Similar to the development and use of novel radionuclides, such as radiolabeled HER2 and others, we believe PET imaging will be incorporated more frequently into clinical trials, and ultimately, clinical practice.

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