Dedicated Breast Positron Emission Tomography for the Evaluation of Early Response to Neoadjuvant Chemotherapy in Breast Cancer

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Clinical Practice Points

- Neoadjuvant chemotherapy provides an opportunity to assess tumor response to targeted therapies in vivo, and imaging plays a critical role in assessing the effectiveness of such therapies.
- Currently no clinical standard exists for evaluating response to neoadjuvant chemotherapy, although positron emission tomography (PET) and contrast-enhanced magnetic resonance imaging (MRI) are promising candidate technologies.
- Positron emission tomography with fluorodeoxyglucose provides information about tumor metabolism that can powerfully predict treatment response early in the course of therapy, before anatomic changes become evident on MRI scans.
- The recent development of a high-resolution, breast-specific PET imaging system allows more detailed characterization of the primary breast tumor than conventional whole body PET systems.
- We report on the usage of dedicated breast PET to provide early assessment of treatment response in a patient with bilateral synchronous breast cancers.

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Introduction

Breast cancer is increasingly recognized to represent a heterogeneous group of diseases that vary in their treatment response, recurrence risk, and overall prognosis.[1] Since Perou et al[2] first described 4 distinct subtypes of breast cancer on the basis of gene expression profiles, there has been growing emphasis on the molecular characteristics of breast cancer and personalized medicine. In the neoadjuvant chemotherapy setting, imaging plays a critical role in noninvasively assessing the response of the intact primary tumor to targeted systemic therapies. The response of the primary tumor serves as a surrogate marker for the effect of chemotherapy on systemic micrometastases. Thus imaging evaluation of the primary tumor during treatment can provide important prognostic and predictive information.[3,4]

Although contrast-enhanced magnetic resonance imaging (MRI) depicts changes in tumor morphology and vascularity in response to neoadjuvant chemotherapy,[5] positron emission tomography (PET) provides complementary information about tumor metabolism that can powerfully predict treatment response early in the course of therapy.[6,7] The recent development of a high-resolution, breast-specific PET imaging system allows detailed characterization of the primary breast tumor. We report on the usage of dedicated breast PET (dbPET) in conjunction with MRI to provide early assessment of treatment response.

Case

A 32-year-old female *breast cancer 1 (BRCA1)* gene mutation carrier presented with a self-palpated right breast mass and was discovered on subsequent imaging workup to have bilateral synchronous breast cancer. The patient had 2 biopsy proven Grade 3 invasive ductal carcinomas in the right breast, one of which was estrogen receptor (ER)-positive (ER$^+$), progesterone receptor (PR)

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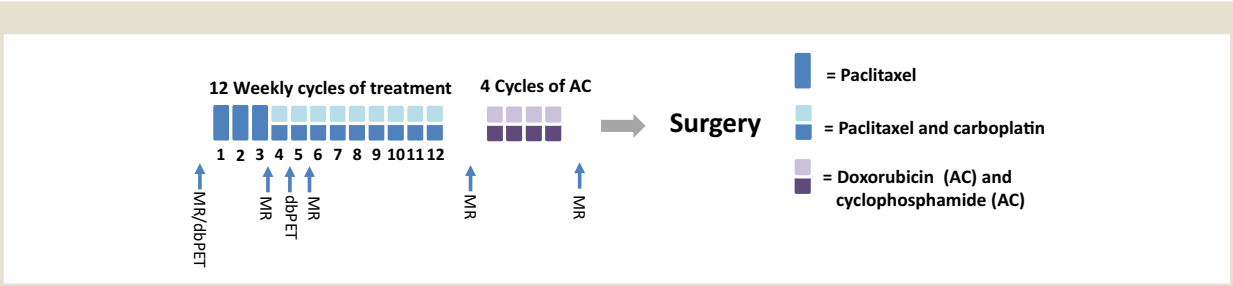
Figure 1 This Schema Shows the Timeline of the Patient's Treatment and Imaging Schedule. Magnetic Resonance Imaging (MRI) and MAMMI (OncoVision) Dedicated Breast Positron Emission Tomography (dbPET) Examinations Were Performed Before Treatment. After 3 Weeks of Paclitaxel, MRI Was Repeated Followed by MAMMI dbPET After Carboplatin Was Included in the Regimen. Two Weeks After the Initiation of Carboplatin Treatment, the Patient Had a Follow-up With MRI. The Last 2 MRI Scans Were Performed Between the Regimen and Before Surgery. In the Illustration, MR Indicates Breast MRI Examination and dbPET Indicates MAMMI dbPET Examination



Abbreviation: AC = doxorubicin (anthracycline) and cyclophosphamide.

negative (PR^-), and $HER2^-$, and the other triple negative (TN) for ER, PR, and HER2. In the left breast, she was also found to have a Grade 3 TN invasive ductal carcinoma.

The patient was enrolled in the Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging And moLecular Analysis 2 (I-SPY 2 TRIAL).[8] She was recruited to participate in a separate study involving imaging with dbPET before and after chemotherapy. The dbPET imaging study was a Health Insurance Portability and Accountability Act-compliant study protocol that was reviewed by the institutional review board and approved by the Committee of Human Research under the institutional Human Research Protection Program. Written informed consent was provided by the patient to participate. I-SPY 2 is a multicenter adaptive phase II treatment trial design in the neoadjuvant setting to compare the effect of investigational regimens with standard chemotherapy. The primary end point is pathological complete response (pCR).

The patient was randomized to the standard chemotherapy arm, involving 12 weeks of paclitaxel, followed by 4 weeks of doxorubicin and cyclophosphamide (AC). As part of the I-SPY 2 protocol, the patient underwent breast MRI (1.5 T Signa LX, GE Healthcare) before and after the initiation of neoadjuvant chemotherapy. In addition, she received imaging with a US Food and Drug Administration-approved high-resolution dbPET scanner (MAMMI, OncoVision). Both imaging examinations were performed with the patient in the prone position. Standard bilateral breast dynamic contrast-enhanced (DCE) MRI was obtained with and without contrast (Gadavist, 0.1 mmol/kg of body weight, 1.5 mL/s) using T1- and T2-weighted sequences. The patient received a low dose of fluorodeoxyglucose (FDG; 5 mCi) and underwent dbPET imaging at 45 minutes after injection. MRI was performed before and twice during neoadjuvant paclitaxel chemotherapy (at weeks 3 and 5 of a 12-week treatment schedule), as well as between regimen and at completion of chemotherapy (Figure 1). DbPET was performed before and after 4 weeks of paclitaxel treatment. Of note, carboplatin (also considered a standard, noninvestigational agent) was combined with the chemotherapy regimen during the third week because of clinical suspicion of disease progression, and therefore dbPET was performed 1 week after the introduction of this agent to the treatment regimen.

Before treatment, breast MRI showed 2 malignant masses in the right breast measuring 4.0 cm (ER^+) and 5.3 cm (TN), respectively, in longest diameter. Overall functional tumor volume (FTV) of both masses, defined as the volume of enhancing tumor exceeding an early enhancement threshold of 70% above baseline, was 73.2 cm^3 (Figure 2A).[5] DbPET imaging showed 2 FDG-avid lesions with the maximum standard uptake value (SUV_{max}) of 19.2 for the ER^+ tumor and 19.5 for the TN tumor (Figure 2B).

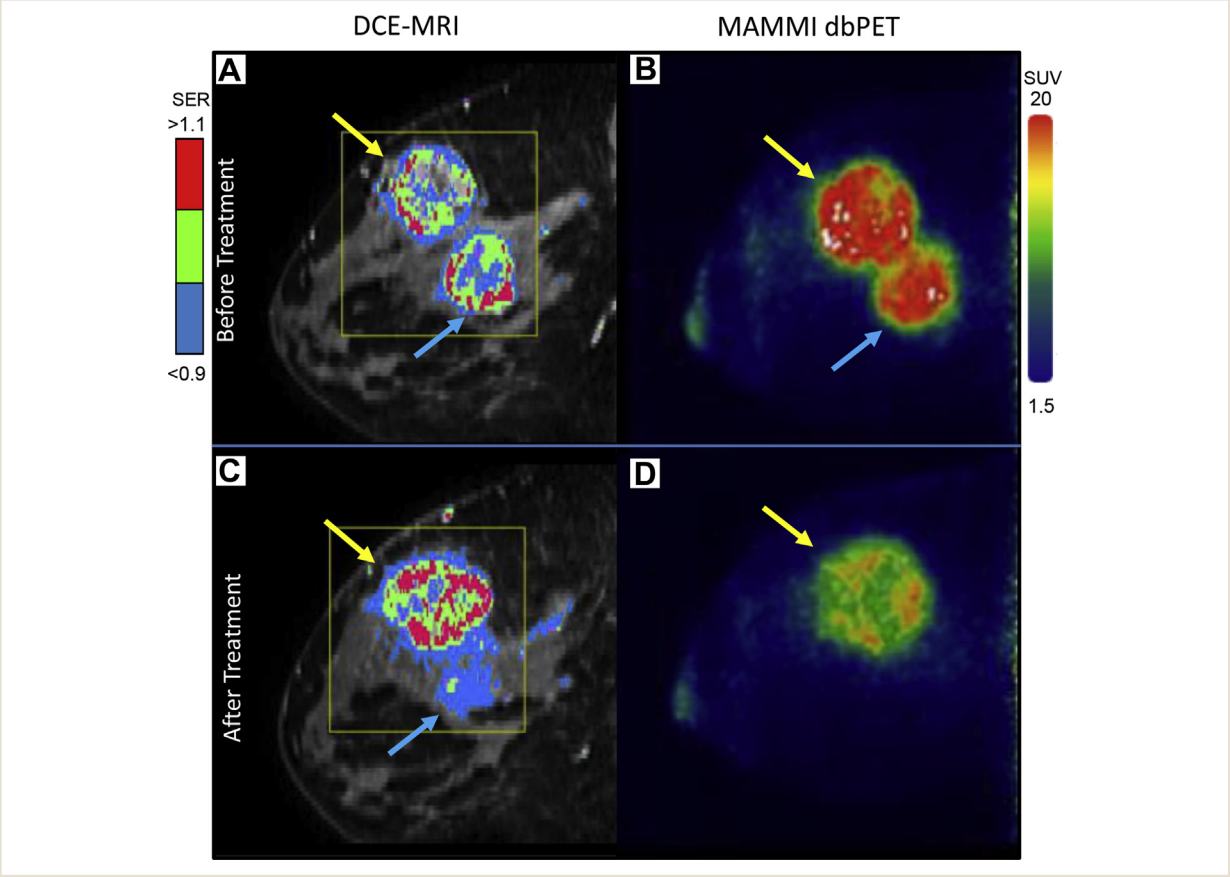
After 3 weeks of paclitaxel treatment, MRI showed a decrease in size of the ER^+ tumor to 3.2 cm, but there was slight enlargement of the TN tumor to 5.8 cm. Overall FTV of both masses also increased to 89.5 cm^3 (Figure 2C). Because MRI appeared to show disease progression, carboplatin was added to the regimen and dbPET was obtained 1 week later. DbPET showed a complete resolution of FDG uptake in the ER^+ tumor and a 22% reduction of SUV_{max} in the TN tumor (SUV_{max} at 15.3) (Figure 2D). Repeat MRI obtained 1 week later showed a minimal decrease in size of the right breast TN tumor to 5.2 cm and further decrease in the right ER^+ tumor to 2.3 cm.

Within the left breast, baseline MRI showed a 1.2-cm malignant mass with overall FTV of 0.67 cm^3 (Figure 3A) and MAMMI dbPET showed an FDG-avid mass with an SUV_{max} of 6.7 (Figure 3B). After 3 weeks of chemotherapy, MRI showed residual disease (measuring 0.7 cm with FTV at 0.12 cm^3) (Figure 3C), whereas dbPET showed no FDG uptake in the left breast mass after 4 weeks of treatment (Figure 3D).

After 12 weeks of paclitaxel chemotherapy, MRI showed marked improvement at all 3 sites with a residual ill-defined 3.8-cm TN mass and a 2.2-cm ER^+ mass in the right breast with combined FTV at 1.82 cm^3. The left breast mass had resolved completely on MRI. The patient subsequently completed 4 weeks of AC. The final MRI before surgery showed a residual 0.8-cm TN mass with surrounding faint nonmass enhancement and faint nonmass enhancement at the site of the ER^+ cancer (overall FTV at 0.22 cm^3; Figure 4).

Pathology from the subsequent right mastectomy revealed 2 residual foci of weakly ER^+, $HER2^-$, high-grade invasive ductal

Figure 2 Breast Imaging of a 32-year-old Female Patient With Biopsy Confirmed Estrogen Receptor (ER)$^{+}$/Progesterone Receptor (PR)$^{-}$/HER2^{-} (Blue Arrow) and Triple-negative (TN, Yellow Arrow) Invasive Carcinomas in the Right Breast. (A) Before Treatment Dynamic Contrast-enhanced (DCE)-magnetic Resonance Imaging (MRI) Scan Showing the Malignant Lesions With the Mapping of Contrast Signal Enhancement Ratio (SER) and Overall Functional Tumor Volume (FTV) at 73.2 cm^3. (B) Before Treatment MAMMI (OncoVision) Dedicated Breast Positron Emission Tomography (dbPET) Imaging With Fluorodeoxyglucose (FDG) Confirmed MRI Findings, Showing High FDG Avidity in Estrogen Receptor-positive (ER^{+}; Blue Arrow; Maximum Standard Uptake Value [SUVmax] = 19.2) and TN (Yellow Arrow; SUVmax = 19.5) Tumors. (C) At Week 3, DCE-MRI Showed Residual Disease in the ER^{+} Tumor and Progression of the TN Tumor With the Overall FTV at 89.5 cm^3, Whereas (D) at Week 4, MAMMI dbPET Showed a Complete Resolution of FDG Uptake in the ER^{+} Tumor and Reduction of SUVmax by 22% in the TN Tumor



carcinoma measuring 1.5 cm and 0.7 cm. There was also residual high-grade ductal carcinoma in situ, which was present as scattered microscopic foci <1 mm each. The left mastectomy specimen showed no evidence of residual disease, which was consistent with a pCR.

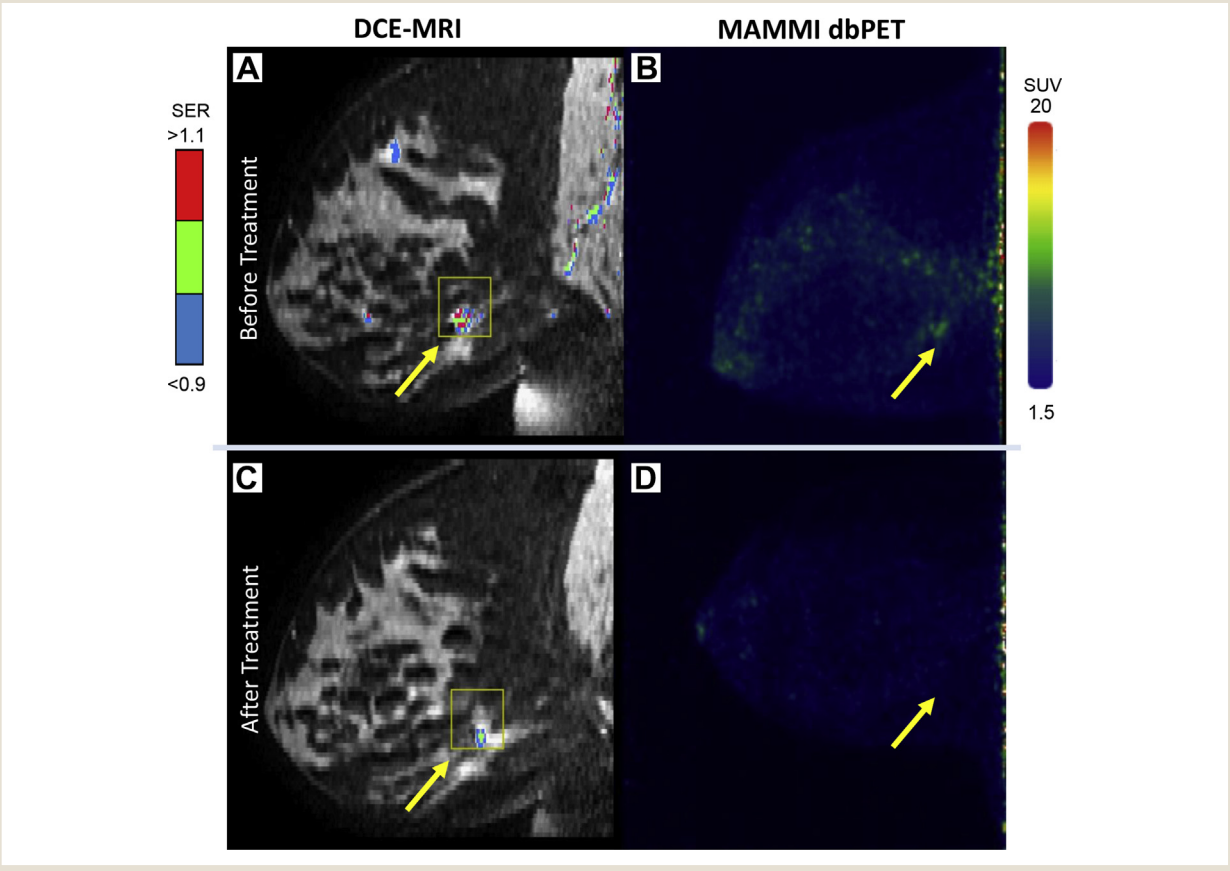
Discussion

Early assessment of response to neoadjuvant chemotherapy is essential to spare patients from undergoing prolonged courses of ineffective, toxic, and costly therapies. In the clinical trial setting, early determination of treatment response also permits the accelerated evaluation of novel targeted therapies, presenting vital prognostic information, because the response of the primary tumor has been shown to predict long-term survival outcome.[3,4]

Multiple studies have shown the ability of whole body PET and PET/computed tomography (CT) imaging to assess the early response of locally advanced breast cancer to neoadjuvant chemotherapy.[9] In a meta-analysis, Wang et al reported that the accuracy of PET was greater when performed early (after 1-2 cycles of chemotherapy) rather than late.[9] Another recent meta-analysis[10] of studies that compared FDG-PET imaging with DCE-MRI showed that PET imaging outperformed MRI in assessing early treatment response, with similar sensitivity, but higher specificity.

Whole body PET is hampered by the poor spatial resolution (approximately 5-10 mm full width at half maximum) and associated partial volume error in small lesions. Moreover, most PET examinations are performed with the patient in the supine position, which is suboptimal because of collapse of the breast and blurring from respiratory motion.[11] Increasing interest in functional evaluation of the primary breast tumor has led to the development of a dbPET imaging scanner. MAMMI dbPET is specially tailored for imaging of the breast at high spatial resolution (2 mm). It has a ring

Figure 3 Imaging of the Triple-negative (TN, Yellow Arrow) Invasive Carcinoma in the Left Breast of the Same Patient Shown in Figure 2. (A) Before Treatment Using Dynamic Contrast-enhanced (DCE)-magnetic Resonance Imaging (MRI) Showing the Malignant Lesions With the Mapping of Contrast Signal Enhancement Ratio (SER) and Overall Functional Tumor Volume (FTV) at 0.67 cm^3. (B) Before Treatment MAMMI (OncoVision) Dedicated Breast Positron Emission Tomography (dbPET) Imaging With Fluorodeoxyglucose (FDG) Showed Mild FDG Avidity in the TN Tumor (Yellow Arrow; Maximum Standard Uptake Value = 6.7). (C) At Week 3, DCE-MRI Showed Residual Disease in the TN Tumor With the Overall FTV at 0.12 cm^3, Whereas (D) at Week 4, MAMMI dbPET Showed a Complete Resolution of FDG Uptake



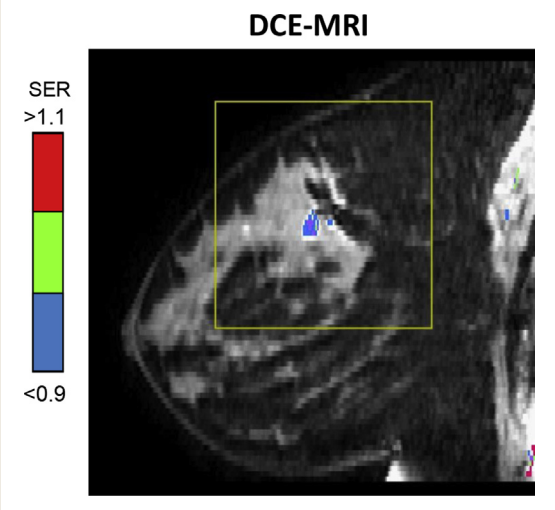
structure with 12 detector modules containing lutetium yttrium silicate scintillators for improved timing resolution and sensitivity focused on imaging the breast volume.[12] Patients are examined in the prone position. Images obtained are true 3-D[13] and spatially analogous to breast MRI.

In a case series of 234 proven breast cancers, dbPET had a higher sensitivity for the detection of subcentimeter lesions than whole-body PET/CT imaging.[14] Because of its high sensitivity, dbPET can be performed at half the dose of FDG relative to conventional PET, which is desirable for repeated imaging during treatment. Another study of 35 patients showed greater visualization of intratumoral heterogeneity with dbPET than conventional PET/CT imaging.[15] The increased sensitivity of dbPET for small lesions as well as its more detailed depiction of intratumoral FDG uptake patterns could improve our ability to accurately assess treatment response, particularly in cases of multifocal disease and heterogeneous tumors, both of which were encountered in our case example.

Prone imaging in dbPET facilitates correlation with breast MRI. In this case example, DCE-MRI and dbPET imaging exhibited similar imaging patterns (Figure 2) that might suggest a potential correlation. The signal enhancement ratio map, with rapid early enhancement and delayed contrast washout within the bilateral breast tumors, reflects the robust angiogenic property of the high-grade tumors.[16] FDG avidity is the direct measurement of active tumor metabolism. High FDG uptake is known to be associated with higher tumor Grade.[17] As shown in other studies,[18,19] the concordance of MRI and PET imaging measurements suggest that tumor angiogenic/metabolic properties are highly coupled, especially in high-grade tumors and more aggressive subtypes. Further prospective study is needed to explore this correlation.

In our case study of 1 patient, MAMMI dbPET proved to be highly sensitive for depicting early treatment response, showing resolution of FDG uptake in 2 of 3 tumors (right ER^+ tumor and left TN tumor) at the week 4 scan, whereas MRI did not show resolution of these masses until 12 to 16 weeks. Final pathology from the bilateral mastectomies showed 2 foci of residual high-grade ER^+ disease in the right breast measuring 1.5 cm and 0.7 cm, respectively, and pCR in the left breast. Thus, whereas both

Figure 4 The Final Dynamic Contrast-enhanced (DCE)-magnetic Resonance Imaging (MRI) of the Right Breast of the Same Patient in Figure 2, Showing a Faint Nonmass Enhancement at the Estrogen Receptor-Positive Cancer With the Overall Functional Tumor Volume at 0.22 cm^3



Abbreviation: SER = signal enhancement ratio.

modalities correctly predicted a very favorable treatment response, they also both overestimated the degree of response in the ER^+ tumor and failed to predict small foci of residual disease.

For the right TN tumor, MRI suggested lack of early treatment response, whereas dbPET showed a favorable response. One hypothesis for the discordant early findings between MRI and dbPET imaging for the TN tumor relates to tumor necrosis. Treatment-related tumor necrosis could have caused a paradoxical increase in enhancement and hence tumor volume at MRI. In contrast, reduced FDG avidity at PET imaging might have more accurately reflected a decrease in the viable tumor burden. Interpretation of our findings is somewhat confounded by the performance of MAMMI dbPET 1 week after carboplatin was combined with the chemotherapy regimen, whereas MRI was performed before this change. However, a subsequent MRI performed 2 weeks after the initiation of carboplatin therapy showed only a minimal decrease in tumor size, suggesting that dbPET imaging was in fact more sensitive for detecting early treatment response. Subsequent MRI examinations showed a much more dramatic response to therapy of the right TN tumor and complete pathologic response was documented at mastectomy, further validating the early dbPET imaging findings.

Conclusion

In conclusion, this feasibility study shows that dbPET imaging can capture the early response of primary breast cancer to neoadjuvant chemotherapy and reveal functional changes that precede anatomic changes at MRI. Further studies involving larger numbers of patients are needed to validate our initial observations. We are currently recruiting additional patients already enrolled in I-SPY 2 to undergo a pilot study of FDG dbPET imaging. In addition, we plan to use ^{18}F-fluoroestradiol, a novel tracer that targets ERs, enabling more precise characterization of breast tumor subtypes, heterogeneity, and treatment response to targeted therapies. When these pilot studies show robustness of dbPET for monitoring treatment response, we hope to incorporate this technique into the I-SPY 2 imaging protocol, because this will permit prospective comparisons of dbPET with MRI in a large cohort of patients with locally advanced breast cancer with a diversity of molecular profiles.

Disclosure

The authors have stated that they have no conflicts of interest.

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