Radiology: Imaging Cancer

COMMENTARY

PET/MRI for Primary Breast Cancer: A Match Made Better by PET Quantification?

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In current clinical practice, both breast MRI and body fluorine 18 fluorodeoxyglucose (FDG) PET are widely used for breast cancer. Breast MRI is an important part of primary breast cancer detection (for high-risk patients), diagnosis, and local staging. Breast MRI has also been applied with good success to response evaluation for patients treated with neoadjuvant (presurgical) systemic therapy (1). FDG PET, on the other hand, has shown its greatest utility in application to more advanced disease, including staging and response assessment for locally advanced and metastatic breast cancer. For assessing response of a primary tumor to neoadjuvant therapy, the two modalities are complementary. Contrast-enhanced breast MRI, which primarily measures tumor-associated capillary permeability and perfusion, has been shown to provide good estimates of disease extent after therapy (2). FDG PET, on the other hand, measures tumor glucose metabolism and can provide an early indication of response to systemic therapy, including targeted therapy such as HER2-directed agents (3). There is evidence that the combination of perfusion and metabolism measurements yields valuable information that can both predict and measure response to therapy in a primary breast tumor better than either modality alone (4). Thus, primary breast cancer response assessment is a task for which combined breast MRI and FDG PET by PET/MRI could be quite helpful. However, the accuracy of FDG uptake measures—a key component of FDG PET response assessment—has been a concern for PET/MRI, largely due to challenges in photon attenuation correction for the PET component (5). Unlike PET/CT, where CT directly measures photon attenuation and provides robust correction, photon attenuation for PET/MRI is inferred more indirectly using anatomy and tissue characteristics from MRI. Attenuation correction—and PET quantitative accuracy—may even be more problematic for primary breast tumor imaging, where dedicated breast coils for MRI provide an additional challenge for attenuation correction. This topic, namely the accuracy of FDG uptake measures for prone breast PET/MRI with dedicated breast coils is the subject of a study published by Fowler and colleagues in the current issue of *Radiology: Imaging Cancer* (6).

In this study, Fowler et al performed prone FDG PET/CT followed by prone PET/MRI using gadolinium-based contrast enhancement and breast coils in 23 women with 24 primary invasive cancers ranging from 1.1 to 8.8 cm in size. Both imaging systems employ fast detectors and time-of-flight PET reconstruction, a PET technology that improves the accuracy and consistency of PET quantification (7). Of note, the tumors included had lower histologic grade (grade 1 or 2) and were estrogen receptor (ER) positive, both of which are associated with lower FDG uptake compared with higher grade or ER-negative tumors (8). The authors found a good correlation for standardized uptake value (SUV) measures for PET/CT versus PET/MRI ($r_s > 0.95$) and a small bias toward higher SUV measures by PET/MRI ascribed in good part to later timing after FDG injection. The authors introduced a normalized SUV measure that uses uptake in normal contralateral breast fibroglandular tissue as reference tissue to adjust breast tumor FDG estimates for differences in technique and attenuation correction accuracy compared with PET/CT. The authors concluded that the results support good quantitative agreement between FDG PET/MRI and PET/CT, supporting the use of PET/MRI for applications requiring quantitative accuracy for PET, such as response assessment.

This study adds to the body of literature supporting the use of PET/MRI for imaging primary breast cancer. The time-of-flight PET imaging capabilities of the

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See also the article by Fowler et al in this issue. Conflicts of interest are listed at the end of this article.

PET/MRI system used in this study are on par with modern clinical PET/CT. This study demonstrates that attenuation correction using the MR image is accurate enough to generate SUV measures that correlate well with PET/CT SUVs, enabling simultaneous and coregistered PET and MRI for primary breast cancer imaging with an advantage of radiation dose reduction by omission of CT. Coregistration of PET with MRI, a modality that accurately depicts tumor extent, may help improve the accuracy of PET uptake measures by more accurate correction of PET partial-volume recovery loss for smaller tumors. The introduction of the contralateral normal breast SUV as a normalizing measure for primary breast cancer PET imaging is a novel feature, akin to the liver and blood pool measures used in the PERCIST criteria, that deserves further study.

One limitation of the study relates to the kinetics of FDG uptake that lead to variable FDG uptake over time. In contrast to the article's title, FDG uptake late after injection reflects more than simple glucose uptake and rather reflects glucose metabolism through *hexokinase* as depicted by the retention of phosphorylated FDG (FDG-6-phosphate [FDG-6P]). Because FDG persists in the blood pool for several hours, tracer uptake continues to rise over time with increasing trapping of FDG-6P in the tumor, resulting in a positive bias in SUV over time in tissues with active glucose metabolism. This feature of FDG kinetics likely accounts for much of the bias in SUV measures for PET/MRI (which came after PET/CT in all patients) versus PET/CT. An additional complicating factor is that the rate of SUV rise over time depends on the level of tracer uptake (ie, the SUV itself) (9). Tumors with high glucose metabolic rates (and thus high SUV) trap available FDG as FDG-6P at a high rate, resulting in SUVs that can increase by 15%–20% in as little as 15 minutes. Conversely, for less FDG-avid tumors (and normal breast tissue), progressive clearance of nonphosphorylated FDG and FDG-6P accumulation are closer to equal, resulting in flat tracer uptake curves with little change or even a decline in SUV over time. As such, the inclusion of largely ER positive, lower grade tumors is fortuitous in that the impact of time delay between PET/CT and PET/MRI for this study was modest compared with what might have been the case for higher grade, ER-negative tumors. (This factor may help account for the variability in FDG uptake bias noted by the authors in the Discussion section.) Variable changes in uptake over time, however, impact the normal contralateral breast SUV differently than for breast cancers, especially for those cancers with more high-grade, less-differentiated features that are associated with elevated glucose metabolism, high rates of FDG-6P generation, and high FDG SUV. Thus, normalizing to contralateral normal breast SUV might help as a measure to adjust for body habitus and attenuation correction errors but cannot compensate for variable uptake time. Consistent uptake times are still needed to assure consistent quantitative data for FDG PET.

Prone PET/MRI with breast coils provides accurate coregistration of tumor molecular characteristics measured by using PET with the higher spatial resolution for anatomic and functional features offered by MRI. This, as noted, has important advantages for primary breast cancer imaging that include MRI guidance for biopsy based in part on PET features, the ability to combine MRI-based measures of perfusion with PET measures of molecular features, and better partial-volume correction of PET uptake measures for small primary breast tumors. It should be noted, however, that the accuracy of PET imaging for small primary tumors is fundamentally limited by the modest spatial resolution of body PET, which typically has reconstructed spatial resolution on the order of 4–6 mm. Dedicated breast PET systems have been developed either as stand-alone devices, in combination with CT or tomosynthesis, or as a PET insert for PET/MRI (10). With their higher spatial resolution (and sensitivity), these systems provide more accurate uptake measurements for smaller tumors, especially those less than 1 cm (excluded in this work), at potentially lower tracer dose (and thus radiation exposure) and lower cost. These dedicated systems may provide an alternative approach for PET imaging of primary breast tumors, and they will require the same rigorous tests of PET quantitative accuracy used in the Fowler et al study to be useful for quantitative biomarker and response assessment applications.

Overall, the study by Fowler et al is an important contribution to the literature on breast cancer PET/MRI that provides an impetus for future use of PET/MRI for primary breast cancer imaging for both clinical practice and research where PET quantification is needed.

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