Radiology

PET of Fibroblast-Activation Protein for Breast Cancer Diagnosis and Staging

David A. Mankoff, MD, PhD • Mark A. Sellmyer, MD, PhD

Dr Mankoff is Matthew J. Wilson professor and vice chair for research in the University of Pennsylvania Department of Radiology. His research focuses on translational molecular cancer imaging, especially breast cancer, and quantitative imaging methods.

Dr Sellmyer is an assistant professor in the University of Pennsylvania Department of Radiology. His research is at the intersection of molecular imaging and translational chemical biology.

PET molecular imaging has had a remarkable impact on cancer identification and localization, particularly in application to systemic staging (1). An important need for this task is a molecular imaging target that is more highly expressed in tumors compared with normal tissue to ensure adequate sensitivity and specificity for identifying cancer sites. Defining the ubiquitous characteristics of cancer has been a longstanding goal of cancer research. In a landmark set of articles, Hanahan and Weinberg (2) defined classic hallmarks of cancer that include sustaining proliferative signaling, evading growth suppressors, activating invasion and metastasis, enabling replicative immortality, inducing angiogenesis, and resisting cell death. At the time these advances in basic cancer research were occurring, the molecular imaging community was developing the instrumentation and infrastructure for widespread adoption of PET with CT and exploring targets for molecular cancer imaging. Over the next 2 decades, PET/CT using the glucose analog fluorine 18 (^{18}F) fluorodeoxyglucose (FDG) became a clinical standard for cancer detection and staging (3). FDG enables the measurement of regional glucose metabolism, and its success highlighted the recognition that aberrant metabolism is a hallmark of cancer (2). ^{18}F-FDG PET/CT provides a great example of how the basic cancer biology and cancer molecular imaging communities can work together to inform both areas of research. In this issue of *Radiology*, Backhaus and Burg et al (4) highlight early results of imaging breast cancer with PET using another cancer feature identified through basic research, namely the co-localization of cancer cells with cancer-associated fibroblasts.

Although glucose metabolism has been a powerful target for cancer molecular imaging, past experience identified some important limitations that include reduced sensitivity for well-differentiated tumors—for example, lobular breast cancer (5)—that typically have lower glucose metabolism than less well-differentiated and more aggressive cancers and limited specificity with regard to other nonmalignant processes that rely heavily on glucose metabolism, such as inflammation (3). These limitations spurred a search by the molecular imaging community for other pan-tumor imaging probes that could help report on hallmarks of cancer beside glucose metabolism. Basic science again provided an important clue. The tissue surrounding the tumor undergoes reactive changes that are specific to the presence of the tumor. In macroscopic terms, radiologists are familiar with such reactions in the form of spiculation from a lung carcinoma or desmoplastic reaction from a small bowel neuroendocrine tumor. Examination of this reaction at the histopathologic and molecular levels developed into an entire cancer subfield studying the tumor microenvironment and identified a mix of contributing cell types that included cancer-associated fibroblasts. Cancer-associated fibroblasts were known to upregulate a protein called fibroblast-activation protein (FAP) (6,7). FAP is a membrane-bound gelatinase, a nonclassical serine protease that takes several forms, including a secreted, truncated form. Under normal physiologic conditions, FAP expression is quite low in most adult tissues; however, reactive stromal fibroblasts upregulate FAP in response to wound healing, tissue repair, and many different types of cancer. Given the upregulation of FAP during carcinogenesis, small-molecule FAP inhibitors (FAPIs) (eg, talabostat), monoclonal antibodies (sibrotuzumab), and even chimeric antigen receptor T cells using an anti-FAP single-chain fragment variable have been developed for FAP therapeutic targeting (6). Leveraging the inherent characteristics of small-molecule biodistribution, which can show rapid clearance and can provide high-contrast imaging for highly expressed targets, small-molecule FAPI PET radiopharmaceuticals have been developed, including those using the radioisotopes, gallium 68 (^{68}Ga)

From the Department of Radiology (D.A.M., M.A.S.) and Department of Biochemistry and Biophysics (M.A.S.), 1 Donner Building, Hospital of the University of Pennsylvania, 3400 Spruce St, Philadelphia, PA 19104-4283. Received August 16, 2021; revision requested August 25; revision received August 26; accepted August 30. **Address correspondence to** D.A.M. (e-mail: *david.mankoff@pennmedicine.upenn.edu*).

Conflicts of interest are listed at the end of this article.

See also the article by Backhaus and Burg et al in this issue.

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and ^{18}F (8,9). These PET radiopharmaceuticals have produced striking clinical images of cancer, including tumors difficult to image using FDG PET, such as prostate and thyroid cancer.

In this issue of *Radiology*, Backhaus and Burg et al (4) present a retrospective analysis of ^{68}Ga-FAPI-46 breast PET/MRI followed by whole-body scanning to show the capability of this approach to image local breast cancer and lymph nodes and for whole-body breast cancer staging. Nineteen women were evaluated, with 18 examinations performed to complement initial staging and one performed for restaging after therapy for distant metastases. All patients had histologically confirmed breast cancer, and most had larger or locally advanced breast tumors. As seen in previous studies (8,9), ^{68}Ga-FAPI showed strong tracer uptake in untreated primary tumors. The uptake in most tumors was more than 10-fold higher than that in healthy breast tissue. Unlike FDG (10), uptake of ^{68}Ga-FAPI appeared to be independent of breast phenotype (ie, there was no association between the breast cancer histologic findings [lobular or ductal] and subtype according to hormone receptor expression and human epidermal growth factor receptor 2 [HER2] expression and the level of radiotracer uptake). This observation is not that surprising based on the biologic characteristics of FAP, and it corroborates the pan-tumor marker nature of FAP-targeted imaging. The results also showed high uptake in both primary breast lesions and regional lymph nodes, including some that were not well seen or missed at MRI. ^{68}Ga-FAPI-46 PET/MRI also had high uptake in distant metastases, including in some bone lesions not seen with bone scanning. There were, however, several small false-negative lesions (eg, a 3-mm tumor in a lymph node) and false-positive findings, which included uptake suggested to be healing from biopsy residua, a hepatic lesion consistent with focal nodular hyperplasia, and a benign soft-tissue tumor. Overall, however, these results indicate considerable promise for the application of ^{68}Ga-FAPI-46 PET in breast cancer, including the ability to address FDG limitations such as low uptake in some hormone receptor–positive tumors (3,5,10).

The study had some limitations, however, including a retrospective design and the fact that the study focused on patients with larger or locally advanced breast cancer. The authors acknowledged that this cohort of patients had a much higher FAPI maximum standardized uptake value relative to published literature reports, possibly indicating a bias toward more advanced and aggressive disease. It is hard to estimate sensitivity and specificity from this early study. Without full sampling of all tissues or clinical follow-up, it is unknown which tumor sites might have been missed, and sensitivity cannot be measured. Similarly, although many of the lesions identified at FAPI PET were confirmed with biopsy, not all were. Thus, it is challenging to estimate the specificity, especially when all patients have known cancers.

Although high FAPI uptake and identification of metastases not seen at MRI or bone scanning indicate promise for ^{68}Ga-FAPI-46 PET, there is a need for more direct comparison to other such modalities used for breast cancer diagnosis and staging, including and especially FDG PET/CT. Almost all patients in this study had tumors of 2 cm or greater, and all but one patient had triple-negative, HER2-positive, or higher-grade hormone receptor–positive cancers. This is a population in which FDG PET/CT would have also performed well for detecting primary, regional lymph node, and distant sites of disease and would have likely identified lesions not seen at MRI or bone scanning (10). Future studies might focus more on patients with low-grade hormone receptor–positive, HER2-negative ductal and especially lobular breast cancers, where FDG PET/CT does not perform as well (5,10).

A second minor limitation was that the authors chose to use PET/MRI rather than the more widely used PET/CT. PET/MRI may hold advantages for imaging the primary tumor; however, limited studies directly comparing FDG PET/MRI to PET/CT for breast cancer nodal and distant disease staging do not show major advantages of PET/MRI compared with PET/CT. It may be helpful to separate the goals of primary breast cancer diagnosis and staging in future studies designed to determine the performance of FAPI PET compared with existing imaging approaches.

Overall, the study by Backhaus and Burg et al (4) indicates considerable promise for the application of ^{68}Ga-FAPI-46 PET in breast cancer for staging and possibly for primary breast cancer diagnosis. This early report supports future studies to explore both applications with a focus on tumor types and clinical scenarios where FAPI PET may provide key clinical data and insights that are not provided by current clinical imaging approaches.

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