

Could FAP-Targeted Molecular Imaging Replace ^{18}F -FDG for Standard-of-Care Oncologic PET?

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See the associated article on page 618.

The predominant radiotracer in oncologic PET is ^{18}F -FDG, to the point that many clinicians refer to ^{18}F -FDG PET scans simply as "PET scans." Numerous other radiotracers have been studied but only somatostatin receptor-targeted agents and prostate-specific membrane antigen (PSMA) have been widely adopted, specific tracers largely used in neuroendocrine and prostate cancers, respectively.

^{18}F -FDG uptake is not simply a marker of tumor glucose metabolism but also reflects a complex interplay of metabolism in the stroma and immune infiltrate, hypoxic microenvironment, and other dysregulated metabolic pathways. Despite the complex and variable etiology of ^{18}F -FDG uptake, ^{18}F -FDG PET has a definite place in the staging, prognostication, and treatment response assessment in a broad range of malignancies. With precision medicine and molecularly targeted therapies, an unmet need exists for functional imaging techniques to provide biologic insights beyond glucose metabolism. Several malignancies have intrinsically low ^{18}F -FDG avidity or are poorly imaged with ^{18}F -FDG PET due to high background uptake, for example, in the brain.

Malignant tissues are complex and heterogeneous, consisting of neoplastic cells and tumor microenvironment comprising stroma (including several types of fibroblasts), neovasculature, and immunomodulatory cells. Tumor microenvironment may play a vital role in invasiveness, metastatic potential, and evading immune regulation. Imaging stromal components of tumors is very attractive, not only in overcoming some limitations of ^{18}F -FDG PET, but also in providing complementary or new biologic insights. Among targets that image tumor microenvironment, a particularly exciting one is fibroblast activation protein (FAP), a quinolone-based compound that is overexpressed in a subpopulation of cancer-associated fibroblasts (CAFs) in a wide range of malignancies (1).

There are several FAP inhibitor (FAPI) compounds available. A comparison among a few of these showed that FAPI-46 showed higher tumor-to-background ratio and higher uptake in malignant and inflammatory lesions (2). In the recent study, Naeimi et al. (3)

performed FAPI-46 PET in various tumor types and confirmed early uptake of FAPI-46. Uptake in malignant lesions occurred early but also demonstrated some heterogeneity, with no significant difference in the SUV_{\max} log at 10 min and 3 h for uptake in primary but nodal uptake increased at 1 h, and uptake in the metastases was highest at 10 min. The rapid FAPI uptake in a variety of tumors with low background tissue uptake leads to the attractive possibility that FAPI PET may potentially complement or replace conventional ^{18}F -FDG PET in the future.

Another practical advantage to FAPI PET over conventional ^{18}F -FDG PET is lack of dietary requirements and uptake independent of blood glucose levels, a particular advantage for imaging of diabetic patients. The possibility of early imaging if combined with simultaneous whole-body PET technology is attractive for patient convenience and throughput with a favorable dosimetry (4).

FAPI may have a major complementary role in tumor types and anatomic sites at which ^{18}F -FDG is known to have reduced sensitivity, not least in the diagnostic setting in which lesion detection is of paramount importance. High FAPI radiopharmaceutical uptake has been demonstrated in certain tumors of the gastrointestinal tract (5,6), peritoneal disease (7), and biliary tract tumors (8) in contrast to ^{18}F -FDG. A significant strength of FAPI imaging is low physiologic uptake in most organs, leading to high target to background even if these lesions do not show absolute higher avidity for FAP than ^{18}F -FDG. This is especially true for cerebral lesions where physiologic uptake limits lesion detection with ^{18}F -FDG PET.

FAPI imaging is not without pitfalls. There is high uptake and similar retention of FAPI in inflammatory and malignant processes, leading to potential false-positive interpretations without careful attention to the clinical context and accompanying anatomic information of the CT component of the scan. With ^{18}F -FDG, this could be partly overcome with delayed imaging where inflammatory processes show washout and in general lower avidity. FAPI uptake in inflammatory lesions appears mostly stable over time (2). A crucial aspect that needs to be addressed is the extent and duration of FAPI uptake after surgery or radiation. Differentiation of viable tumor from inflammatory or fibrotic processes could be challenging when undertaking FAPI posttherapy assessments.

There is vast literature supporting ^{18}F -FDG PET, particularly in treatment response assessment and prognosis. There are early data on the prognostic value of FAPI avidity (9), but clearly larger studies in multiple tumor types are needed. Response assessment on ^{18}F -FDG PET is a major prognostic factor and guides adaptive management in many conditions such as lymphomas. There are a dearth of response assessment data with FAPI.

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Oncologic ^{18}F -FDG PET is broadly accepted in the clinical community and reimbursed by health-care providing agencies. It would be meaningful to generate evidence for FAP-targeted PET to better characterize tumor biology or in areas in which ^{18}F -FDG has shortcomings rather than replicating the entire volume of data available with ^{18}F -FDG. The economics of FAP-based tracers is bound to have an influence in its acceptance in routine practice. There is currently no literature on cost-benefit analysis of FAPI-based imaging.

Interestingly, FAP-targeted imaging is also being evaluated in nonmalignant cardiac, pulmonary, and rheumatologic conditions and early data appear promising.

Unlike ^{18}F -FDG, FAP-targeting radiopharmaceuticals have therapeutic potential. The newer cyclic peptide compound FAP-2286 has higher affinity, retention, and internalization than linear compound FAPI-46 (10). Interestingly, a study by Fendler et al. (11) shows that only a minority of tumors demonstrate high FAPI avidity ($\text{SUV}_{\max} > 10$ in 18%) if this were considered as a predictor of dose delivered by radionuclide therapy. G3/4 hematologic toxicities, possibly related to the isotope, occurred in more than 30% with ^{90}Y -FAPI-mediated therapy partly attributable to the isotope (11,12). An early study with ^{177}Lu -FAP-2286 showed G3 toxicities in 3 of 11 patients and no G4 toxicity (13). The safety profile of ^{177}Lu -FAP-2286 is being evaluated further in clinical trials (14).

Simultaneous targeting of both tumor cells and CAFs (15), or delivering a cocktail of isotopes are areas for future research. Bi-specific agents could offer simultaneous targeting of tumor and microenvironment. Clinical translation is awaited.

In conclusion, FAP-targeted imaging raises exciting opportunities with ease of patient preparation and favorable radiation dosimetry. Rapid uptake and high tumor-to-background ratio allow early imaging. Given the large volume of evidence with ^{18}F -FDG in diagnosis, prognostication, and response assessment, FAP-based imaging may be better approached, at least initially, as an agent complementary to ^{18}F -FDG, with specific applications. FAP-based therapy could substantially broaden the theranostics landscape.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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