Journal of Nuclear Medicine, published on February 2, 2023 as doi:10.2967/jnumed.122.265003

Could FAP-targeted molecular imaging replace FDG for standard-of-care oncologic PET?

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Word count: 1592

Financial support: none

Disclosures: none

No potential conflicts of interest relevant to this article exist.

Short running title: Is FAP based PET imaging the future?

The predominant radiotracer in oncologic PET is FDG, to the point that many clinicians refer to 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 cancer respectively.

FDG uptake is not simply a marker of tumour 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 aetiology of FDG uptake, 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 biological insights beyond glucose metabolism. There are also a range of malignancies with intrinsically low FDG avidity or are poorly imaged with FDG PET due to high background uptake e.g. brain.

Malignant tissues are complex and heterogeneous, consisting of neoplastic cells and tumour 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 tumours is very attractive, not only in overcoming some limitations of FDG PET, but also to provide complementary or new biological insights. Among targets that image tumour microenvironment, a particularly exciting one is fibroblast activating protein, FAP (Fibroblast Activation Protein), a quinolone-based compound which is overexpressed in a subpopulation of cancer associated fibroblasts (CAF’s) in a wide range of malignancies (*1*).

There are several FAP inhibitor (FAPI) compounds available. A comparison amongst a few of these showed that FAPI-46 showed higher tumor to background ratio (TBR) and higher uptake in malignant as well as

inflammatory lesions(*2*). In the recent study, Naeimi et al (JNM staff to please insert appropriate reference here as this paper will be published alongside this commentary) performed FAPI-46 PET in various tumor types and confirm early uptake of FAPI-46. Uptake in malignant lesions occurred early but also demonstrated some heterogeneity, with no significant difference in the SUVmax log at 10 minutes and 3 hours for uptake in primary but nodal uptake increased at 1 hour, and uptake in the metastases was highest at 10 minutes. The rapid FAPI uptake in a variety of tumours with low background tissue uptake leads to the attractive possibility that FAPI PET may potentially complement or replace conventional FDG PET in the future.

Another practical advantages to FAPI PET over conventional FDG PET is lack of dietary requirements and uptake independent of blood glucose levels, a particular advantage for imaging of diabetic patients. Possibility of early imaging if combined with simultaneous whole body PET technology is attractive for patient convenience and throughput with a favourable dosimetry (*3*).

FAPI may have a major complementary role in tumor types and anatomic sites where FDG is known to have reduced sensitivity, not least in the diagnostic setting where lesion detection is of paramount importance. High FAPI radiopharmaceutical uptake has been demonstrated in certain tumors of the GI tract (*4*) (*5*) peritoneal disease (*6*,*7*) and biliary tract tumors (*8*) in contrast to FDG. A significant strength of FAPI imaging is low physiological uptake in most organs leading to high target to background even if these lesions do not show absolute higher avidity for FAP compared to FDG. This is especially true for cerebral lesions where physiological uptake limits lesion detection with 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 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 post-surgery or radiation. Differentiation of viable tumour from inflammatory or fibrotic processes could be challenging when undertaking FAPI post-therapy assessments.

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

Oncologic FDG PET is broadly accepted in the clinical community and reimbursed by healthcare providing agencies. It would be meaningful to generate evidence for FAP targeted PET to better characterize tumor biology or in areas where FDG has shortcomings rather than replicating the entire volume of data available with 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 FAP inhibitor-based imaging.

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

Unlike FDG, FAP targeting radiopharmaceuticals have theranostic potential. The newer cyclic peptide compound FAP-2286 has higher affinity, retention and internalization compared to linear compound FAPI 46 (*10*). Interestingly, a study by Fendler et al. (*11*) shows that only a minority of tumors demonstrate high FAP Inhibitor avidity (SUVmax >10 in 18%) if this were considered as a predictor of dose delivered by radionuclide therapy. G3/4 hematological toxicities, possibly related to the isotope, occurred in >30% with 90Y-FAPI mediated therapy partly attributable to the isotope(*12*) (*11*). An early study with 177Lu-FAP-2286 showed no G4 and 3/11 G3 toxicites (*13*). Safety profile of 177Lu-FAP-2286 is being evaluated further in clinical trials (*14*).

Simultaneous targeting of both tumor cells and CAF's (*15*), and/or delivering a cocktail of isotopes are areas for future research. Bispecific agents could offer simultaneous targeting of tumor and micro-environment. Clinical translation is awaited.

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

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