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Title: Molecular Imaging of Prostate Cancer: Choosing the Right Agent

Running Title: Choosing A Prostate Cancer Imaging Agent

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Main Text

The well-recognized limitations of conventional imaging with computed tomography (CT), magnetic resonance imaging (MRI), and ^{99m}Tc-methylene diphosphonate bone scan (BS) have contributed to a revolution in PET imaging of prostate cancer (PCa). A plethora of PET radiotracers have entered preclinical and early clinical development and in fact two compounds have been approved by the United States Food and Drug Administration (FDA) for PCa imaging (^{11}C-choline (*1*) and ^{18}F-FACBC/^{18}F-fluciclovine (*2*)). Furthermore, at least two different radiotracers targeting prostate-specific membrane antigen (PSMA) are likely to undergo the New Drug Application (NDA) process at the FDA within the next few years (^{68}Ga-PSMA-11 (*3*) and ^{18}F-DCFPyL (*4*)).

However, as these multiple radiotracers become more widely available, it will become necessary for clinicians who treat men with PCa to choose among these agents in an informed manner. That is not a trivial matter, as different radiotracers may have advantages or disadvantages that affect their utility in different clinical scenarios (*5*), and all radiotracers have pitfalls to interpretation that may be more salient in some patients than in others (*6*). Understanding these nuances and being able to recommend the appropriate radiotracer in different circumstances will undoubtedly be important foundational knowledge for nuclear imaging specialists.

This precept underlies the importance of the manuscript by Calais *et al.* that appears in this issue of *Journal of Nuclear Medicine*: *Head-to-head comparison of ^{68}Ga-PSMA-11 PET/CT and ^{18}F-Fluciclovine PET/CT in a case series of 10 patients with prostate cancer recurrence* (*7*). In this study, the authors reviewed the records of 288

patients with recurrent PCa who participated in a prospective study examining the use of ^{68}Ga-PSMA-11 PET/CT for disease localization. Ten patients were retrospectively identified who had also undergone imaging with ^{18}F-fluciclovine PET/CT a median of 2.3 months prior to study enrollment. The median serum prostate specific antigen (PSA) level of these patients was quite low (1.0 ng/mL at the time of ^{18}F-fluciclovine imaging and 1.1 ng/mL at the time of ^{68}Ga-PSMA-11 imaging), thus tested the limits of sensitivity of these two radiotracers.

The authors observed starkly different detection efficiencies with the two radiotracers. More specifically, ^{18}F-fluciclovine was able to identify putative sites of disease in 2/10 (20%) patients, while ^{68}Ga-PSMA-11-avid foci in 7/10 (70%) patients. Of the eight patients with negative ^{18}F-fluciclovine scans, 5/8 (63%) had suspicious findings with ^{68}Ga-PSMA-11 PET/CT. In both patients with a positive ^{18}F-fluciclovine PET/CT, additional sites of suspected disease were noted with ^{68}Ga-PSMA-11. As noted by the authors, the markedly higher sensitivity of the PSMA-targeted agent led to changes in clinical decision-making.

Calais, et al. acknowledge that the inherent shortcomings of their small retrospective study limit the conclusions that can be drawn regarding the performance of these two radiotracers. The authors' findings, however, are in keeping with the available literature that would have predicted higher sensitivity for PSMA-targeted agents at low PSA values (*8-10*). Indeed, prospective trials are needed in which patients are imaged with both ^{18}F-fluciclovine and a PSMA-targeted radiotracer within a short time interval (one to seven days). Additionally, these study should aim to compare these radiotracers across a range of clinical contexts (*11,12*) including the staging of

men presenting with newly diagnosed PCa who are at risk for harboring occult metastatic disease as well as in the setting of castration resistance among patients being considered for endoradiotherapy with PSMA-targeted therapeutic agents (*13,14*). This latter clinical context is of particular importance as PSMA expression is known to decrease with neuroendocrine differentiation (*15,16*) and therefore imaging with ^{18}F-fluciclovine or other agents in combination with a PSMA-targeted compound may help identify patients who are poor candidates for endoradiotherapy.

The manuscript by Calais, et al. is an important step forward in comparing two of the most widely studied PCa radiotracers. It is incumbent upon the field of molecular imaging to ensure that additional comparative studies are undertaken to firmly establish the roles of different PCa radiotracers in various clinical settings – only then can we select the right tool for the job. Without these data, we have nothing more than an embarrassment of riches / radiotracers.

Conflict-of-Interest Statement

M.G.P. is a coinventor on a U.S. Patent covering ^{18}F-DCFPyL, and as such is entitled to a portion of any licensing fees and royalties generated by this technology. This arrangement has been reviewed and approved by the Johns Hopkins University in accordance with its conflict-of-interest policies. M.A.G. has served as a consultant to Progenics Pharmaceuticals, the licensee of ^{18}F-DCFPyL. M.A.G., M.G.P., and S.P.R. have received research support from Progenics Pharmaceuticals.

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