Re: "Overcoming Challenges Associated with 18F-DCFPyL PET Imaging in Prostate Cancer"

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ROWE SP, VOTER AF, WERNER RA, ZUKOTYNSKI KA, POMPER MG, GORIN MA, SOLNES LB. Re: "Overcoming Challenges Associated with 18F-DCFPyL PET Imaging in Prostate Cancer". *Can J Urol* 2023;30(2): 11465-11466.

Dear Editor

We were gratified to read the recent letter-to-the-editor from Dr. Perera Molligoda Arachchige, "Overcoming Challenges Associated with ^{18}F-DCFPyL PET Imaging in Prostate Cancer",[1] which referenced and commented upon our previous manuscript, "Image Acquisition and Interpretation of ^{18}F-DCFPyL (Piflufolastat F 18) PET/CT: How We Do It".[2] As ^{18}F-DCFPyL and other prostate-specific membrane antigen (PSMA)-targeted positron emission tomography (PET) radiotracers come to dominate imaging of men being staged or restaged for prostate cancer, it is increasingly important to recognize potential limitations of this new modality.

In our estimation, Dr. Perera Molligoda Arachchige focused on two broad aspects of PSMA PET that can create challenges for optimized implementation and interpretation. First, he correctly points out that there are a number of different potential false-positive findings and/or interpretive pitfalls. We wholeheartedly agree that this is important to recognize; our group has published extensively on the idea of interpretive pitfalls, including both false-positive and false-negative findings,[3,4] and we believe those manuscripts are key resources for anyone who is going to begin reading PSMA PET. Perhaps the most important pitfalls that readers will encounter are PSMA-avid non-prostate malignancies,[5] which must be recognized in order to guide appropriate tissue sampling and eventual optimized therapeutic approaches. Overall, navigating pitfalls on PSMA PET can be challenging, although the PSMA reporting and data system (PSMA-RADS) provides a systematic framework for the characterization of individual lesions and their placement into actionable categories.[6,7]

Secondly, Dr. Perera Molligoda Arachchige advocates for the use of dual time-point imaging for characterization of lesions into benign versus malignant categories.[1] This is based on data from Tian et al that malignant lesions will continue to accumulate radiotracer at a later time-point, leading to significantly higher uptake in those lesions relative to benign tissues.[8] Dr. Perera Molligoda Arachchige also notes that later time-point scans have improved target-to-background and he advocates for starting the scan acquisition at least 90 minutes after injection.[1] We were the first to demonstrate that later time-

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point imaging at 2 hours post-injection improves tumor-to-background and can occasionally lead to the visualization of additional lesions,[9] so we would agree with him that it would be reasonable to try to extend the time from injection to imaging to the extent possible. We also agree with him that other maneuvers, such as the administration of furosemide or the use of dynamic imaging, may add diagnostic value in certain subsets of patients.

Of note, at our PET centers, we do not carry out any of the suggested protocol alterations suggested by Dr. Perera Molligoda Arachchige. Although there are a number of ways to troubleshoot an indeterminate scan, all of those ways ultimately require perturbations in the clinical work-flow. In an ideal world, such changes could be made on a case-by-case basis and imaging of patients could be personalized based on their clinical situations. However, at the respective PET centers at which the authors of the original paper work,[2] there is tremendous demand for scanner time slots, and the successful completion of the day's work relies on a carefully choreographed routine of patient prep, radiotracer injection, placement of the patient on the scanner, and execution of the appropriate imaging protocol. Even a minor change to any of those steps can completely unravel the efficient processes on which a busy PET center relies. Hewing closely to the typical 2-deoxy-2-[^{18}F]fluoro-D-glucose protocol used in many cancer patients (typically 1 hour from injection to imaging acquisition) provides tremendous advantages in work-flow and in avoiding mistakes in a busy PET center.

As opposed to specific and personalized changes in work-flow at the present time, we believe that the implementation of artificial intelligence (AI) will gradually solve many of the issues brought up by Dr. Perera Molligoda Arachchige. For example, we are beginning to be able to automate the process of assigning PSMA-RADS scores, potentially being able to derive certainty about the nature of lesions from their single-time-point imaging features and alleviating the need for multi-time-point imaging.[10] Even before algorithms reach that level of sophistication, we can expect them to increasingly be used to balance complicated work-flows,[11] which may then allow for personalized imaging protocols, even in the busiest of PET centers.

We thank Dr. Perera Molligoda Arachchige for bringing up important limitations and challenges associated with ^{18}F-DCFPyL imaging. If we differ at all in our opinions from him, it is only in that we believe AI will be helpful in navigating pitfalls and that it will need to be employed to effectively personalize PSMA PET work-flows. We look forward to seeing those challenges overcome as PSMA-targeted PET imaging is increasingly utilized to provide high-value imaging in men with prostate cancer.

Disclosure/Conflict of interest

Under a license agreement between Progenics (a wholly-owned subsidiary of Lantheus) and the Johns Hopkins University, MGP and the University are entitled to royalties on an invention described in this article. This arrangement has been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policies. SPR and MAG are consultants for Progenics Pharmaceuticals, Inc. All other authors declare that there is no conflict of interest as well as consent for scientific analysis and publication. □

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