What is the best PET target for early biochemical recurrence of prostate cancer?

Authors' reply

We thank Gerald L Andriole for his interest in our prospective study comparing ^{18}F-fluciclovine PET/CT and ^{68}Ga-PSMA-11 PET/CT in patients with early biochemical recurrence after prostatectomy.[1]

Andriole pointed out that only 50 (35%) of 143 screened patients were enrolled. Reasons for screen failure were reported in the study flowchart,[1] and patients were recruited until the prospective target enrolment was met (n=50). Pernthaler and colleagues' study,[2] to which Andriole compared our study, is not a prospective hypothesis-testing trial with a preregistered statistical analysis plan and sample size justification. The patient selection process is not provided. In our study, we selected a prostate-specific antigen (PSA) cutoff of 2·0 ng/mL because the role of imaging is much more important for treatment decision in patients with earlier disease than those with advanced disease, in whom cure cannot be achieved and systemic therapy cannot be avoided. Pernthaler and colleagues' study included 58 patients with various initial treatment strategies with a mean PSA of 14·9 ng/mL, up to 230·4 ng/mL. Thus, the two studies cannot and should not be compared.

Andriole also expressed concern that our expert fluciclovine readers were less experienced than our expert PSMA readers. This raises an interesting question: how many fluciclovine scans must one read to be considered experienced? We used three external blinded independent central readers (BICR) who have published on the use of fluciclovine PET and did reader training for fluciclovine PET. Pernthaler and colleagues did not rely on BICR, as is required by regulatory authorities. The identity and training of the readers were not disclosed. The same readers interpreted both scans 4 weeks apart (which could introduce recall bias) and "any disagreement was resolved by consensus"[2] not further specified (which could introduce a non-independent, non-masking major bias). Our study used BICR with full transparent disclosure, and a centralised majority rule (2:1) was applied for any disagreement.

As outlined in our results and further discussed, the lower target-to-background ratio of fluciclovine (up to 8-times lower than for PSMA)[1] is likely to account for differences in diagnostic performance. Because of a lower target-to-background ratio, fluciclovine PET is more difficult to interpret than PSMA PET, as also shown by low inter-reader agreement measurements.[1,3] By contrast, the high target-to-background ratio of PSMA PET results in superior sensitivity and high inter-reader agreement.[4,5]

The difference of target-to-background ratio reflects how high the biological targets (amino acid transporters *vs* PSMA expression) are upregulated in cancer-target tissue compared with background organs. Therefore, similar detection rate differences can be expected when comparing fluciclovine with any other PSMA-targeting PET agents (eg, ^{68}Ga-PSMA I&T, ^{18}F-DCFPyL, ^{18}F-PSMA-1007, and rhPSMA).

The investigational test (^{68}Ga-PSMA-11 PET) was done at the study site for all patients. It is correct that the standard-of-care index test (fluciclovine PET) was done outside the study site in 12 (24%) of 50 patients per clinical routine. However, detection rates for fluciclovine were significantly lower than those for PSMA, independent of fluciclovine PET scan acquisition site. Additionally, the mean uptake period for fluciclovine scans (2·3 min, range 1–7) was shorter (2 min average) than that recommended by guidelines (3–5 min). This could have affected pelvic image quality (which might have affected T and N staging) due to higher blood pool activity at early imaging times. This might have resulted in a small bias against fluciclovine detection rates. However, fluciclovine detection rate was 26% for both the 35 patients with a 1–2 min of uptake time and the 12 patients imaged 3–7 min after tracer injection. Detection rates of PSMA were superior in both groups (52% and 66%; p=0·019 and 0·038, respectively). Furthermore, shorter initial fluciclovine uptake times could not have affected extra-pelvic staging, which was also unequivocally superior with PSMA PET. Finally, a post-hoc multivariable logistic regression analysis was done to rule out technical bias and potential confounding factors.[1] Neither fluciclovine uptake time or any other technical parameters were a confounding factor. The only predictive factor for PET scan positivity was the PET tracer used (fluciclovine or PSMA).

In conclusion, we believe our study was not prone to any relevant bias. Our results indicate an unequivocal superior detection rate of PSMA over fluciclovine PET in patients with early biochemical recurrence after surgery. We believe that the technical concerns raised by Andriole were already appropriately addressed in our Article.

Ultimately, performance of a diagnostic PET molecular imaging test is not determined by reader training or technical aspects. Performance is driven by the biological target relevance. PSMA overexpression appears to be a superior PET imaging target than amino acids transporter upregulation for detecting early recurrent prostate cancer. PSMA also yields the possibility of theranostic applications.

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