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Re: Assessment of ^{68}Ga-PSMA-11 PET Accuracy in Localizing Recurrent Prostate Cancer: A Prospective Single-Arm Clinical Trial

Fendler WP, Calais J, Eiber M, et al

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Experts' summary:
This prospective, multicentre, single-arm trial among 635 men with biochemically recurrent prostate cancer (PC) revealed high PC detection rates for positron emission tomography (PET) with the ^{68}Ga-labelled prostate-specific membrane antigen ligand PSMA-11. Using histopathology and a composite reference standard of follow-up imaging and prostate-specific antigen (PSA) measurements after focal salvage therapy, PSMA-PET had a positive predictive value of 84–92%. The overall PC detection rate in this cohort with median PSA of 2.1 ng/ml was 75%. Detection rates significantly increased with higher PSA levels. At PSA of $<$0.5 ng/ml (n = 136), PC recurrence was visualized in 38% of men. Importantly, no serious adverse events were noted and inter-reader agreement was substantial.

Experts' comments:
In this study randomly assigned blinded readers prospectively confirmed data from recent meta-analyses [1,2]. The study included a mix of patients, including hormone-sensitive and castration-resistant PCs. The high PC detection rates for men with low PSA levels highlight the potential for early detection and changes in clinical management. PET-directed focal therapy led to PSA declines of $>$50% in 31 of 39 men. However, it cannot be emphasized enough that it is still unclear if more sensitive imaging is really improving relevant oncological endpoints such as overall and metastasis-free survival [3]. Therefore, we have to reflect before initiation of PET imaging if the results are going to influence subsequent PC management decisions for individual patients [4]. For men with hormone-sensitive PC experiencing early relapse, a great concern is the omission of timely salvage radiotherapy for men without PET findings. The current study only reports PSA declines for patients with PET-positive findings, and it would have been of interest to see the response in patients with PET-negative findings receiving salvage radiotherapy. Previous reports showed a high chance of a PSA decline among these men, suggesting poor sensitivity of PSMA-PET in detecting local recurrences at low PSA levels [5]. Improvement in outcome by adapting the radiotherapy field to imaging findings is likely, but prospectively unproven [3]. For men with high-risk M0 castration-resistant PC, by contrast, high rates of N1 and M1 PC detection with PSMA-PET imaging should not be a surprise and these men need systemic treatment [4,6]. Whether localized salvage therapy is useful in patients with short PSA doubling times remains questionable.

Taken together, data indicate that PSMA-PET is a great advance in imaging and most certainly will help in curing more men with advanced PC. This hypothesis must now be tested in prospective studies with adequate oncological endpoints. Identifying the optimal target populations for image-guided salvage approaches is the next step in therapy optimization.

Conflicts of interest: Boris Hadaschik reports grants from German Cancer Aid, German Research Foundation, and Profound Medical; grants, personal fees, and nonfinancial support from Janssen; and personal fees and nonfinancial support from Astellas, AstraZeneca, Bayer, BMS, Lightpoint Medical, Sanofi, and Uromed. Piet Ost reports institutional grants from Merck and Varian and institutional consultancy fees from Ferring, BMS, Janssen, Sanofi, and Bayer.

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