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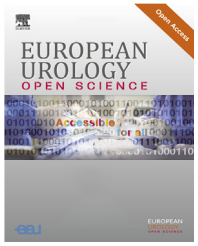

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Open to Debate: For

Prostate-specific Membrane Antigen Positron Emission Tomography, Not Conventional Imaging, Should Be Performed for Primary Staging of High-risk Prostate Cancer

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The staging of high-risk prostate cancer (PCa) historically relied on contrast-enhanced computed tomography (CT) and bone scintigraphy in addition to pelvic magnetic resonance imaging. These techniques have been extensively used in clinical trials to assess the burden of disease. Accordingly, data for patient survival in relation to specific treatments rely on conventional imaging only for the definition of M0 versus M1 patient groups. However, PCa imaging has rapidly evolved in recent years and is moving towards a more personalised approach. Comprehensive evaluation of tumour biology together with evaluation of different patterns of expression by cancer clones has become an attractive field of investigation for molecular imaging. Even if data on overall survival and disease progression for patients who have undergone prostate-specific membrane antigen (PSMA) positron emission tomography (PET) during diagnostic work-up are still pending, the superior diagnostic accuracy of PSMA PET can no longer be ignored.

Here we evaluate the efficacy of PSMA PET for staging of high-risk PCa and its impact in the clinical decision-making process.

The proPSMA study [1], a randomised controlled phase 3 trial in high-risk PCa, proved the higher diagnostic accuracy, lower radiation exposure, and better inter-reader agreement of PSMA PET in comparison to the present standard-of-care imaging, represented by bone scans and CT. Furthermore, the study demonstrated a significantly higher management change for patients before curative primary therapy. Similar results have been obtained in two other recently published phase3 trials [2,3]. In the UCLA/UCSF trial [3], distant metastasis (M1a, M1b, or M1c) was observed in approximately 20% of the nonsurgical cohort (intermediate- to high-risk PCa), highlighting the importance of accurate disease staging before primary therapy.

A cost-effectiveness analysis was recently conducted using data from the proPSMA trial [4]. From an Australian societal perspective, PSMA PET is the dominant strategy, with both better accuracy and lower costs, compared to the standard of care. By improving the detection accuracy for metastatic disease, PSMA PET could significantly impact the downstream treatment of PCa, potentially reducing health care service use and improving quality of life. These results provide a compelling case for adopting PSMA PET in clinical practice. However, results derived from health technology assessments may not be broadly generalisable considering the high variability among geographical regions in terms of resources availability, costs, disease morbidity/mortality, and standards of practice. Accordingly, further evaluations of the cost-effectiveness of PSMA PET in different health care settings are needed [5].

One of the main criticisms of PSMA PET is that data regarding its impact on patient survival are still pending

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[6]. This is a relatively new technique with the first-in-human applications dating back to only 2012. Nevertheless, PSMA PET has already gained approval in the USA and Europe [7]. The US Food and Drug Administration approved ^{68}Ga-PSMA-11 in 2020 and ^{18}F-DCFPyL in 2021, and monographs for ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007 were published in the European Pharmacopoeia in 2021. Hence, the rapid introduction of small-molecule PSMA ligands into daily practice is a very good example of how translational imaging should work.

When new techniques are first introduced into clinical practice, inaccurate reports are frequent, which is especially true when considering the diagnostic pitfalls for typical metastatic locations (eg, bones and lymph nodes). Discrepancies among readers in centres with limited experience in uro-oncological malignancies should also be considered. In this context, the recent implementation of a standardised interpretation guideline [8] could contribute to uniform and reproducible image interpretation and more consistent reporting in clinical practice, which should reduce the incidence of misinterpretation and increase the data reproducibility within clinical trials. Several studies have already confirmed the optimal inter-reader agreement for PSMA PET [9] and the optimal positive predictive value and specificity [2,3,10]. Accordingly, the clinical relevance of diagnostic pitfalls in the interpretation of PSMA PET images has been substantially reduced.

Finally, targeting of PSMA also represents a therapeutic opportunity. PSMA PET has ground-breaking potential as a more accurate diagnostic procedure that can also identify specific targets for radioligand therapy. The theranostic approach (therapy and diagnosis using the same probe) probably represents one of the most important innovations in the management of PCa. The VISION trial recently revealed a 40% reduction in the risk of death when PSMA-based radioligand therapy was added to standard-of-care therapy for patients with PSMA-positive metastatic castration-resistant PCa [11]. In the near future, PSMA radioligand therapy, alone or in combination with other synergistic therapies [12] (ENZA-p, NCT04419402), will be tested in early stages of PCa, including high-volume disease at presentation (PSMAfore, NCT04689828).

In conclusion, PSMA PET has the potential to save time and reduce costs from both patient and health care perspectives by providing more accurate disease staging and more effective, personalised imaging-guided approaches.

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