Editorial Commentary

^{68}Ga-PSMA-11 PET accuracy in recurrent prostate cancer

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The role of conventional imaging in the management of prostate cancer (PCa) is confined. In nuclear medicine the use of different radiopharmaceuticals allows to successfully evaluate *in vivo* PCa, with a safe and non-invasive approach. Scientific data are rapidly growing in this field, especially in the clinical setting of biochemical recurrence. (1) Results from an interesting prospective single-arm clinical trial by Fendler *et al.* about the assessment of ^{68}Ga-PSMA-11 PET accuracy in recurrent PCa were recently published (2).

Choline-based tracers have been used because of their affinity to PCa. Despite significant advances regarding these compounds, their diagnostic capability is limited, as, sometimes, they cannot reliably identify local recurrence, lymph node involvement, or soft-tissue deposits (3).

^{18}F-Fluciclovine, which recently received FDA approval, represents an interesting radiopharmaceutical in the PCa management for its low urinary excretion and its favourable dosimetry (4).

In the last years the introduction of radiolabeled prostate-specific mebran antigen (PSMA) ligands, showed promising results for PCa imaging. Although PSMA is not specific for PCa and is expressed in several normal and neoplastic tissues, PSMA-ligand PET detects PCa metastases with superior accuracy when compared to conventional imaging (1,5,6). Among other imaging techniques PSMA-ligand PET has an improved detection rate (DR) for smaller lesions and, compared to conventional imaging, may be able to identify nodal metastatic disease at earlier stages, even when PSA levels are low (7).

In a meta-analysis of 15 studies (n=1,163), although there was wide heterogeneity in the inclusion criteria, it was shown that PSMA-ligand PET/CT changed clinical management of patients in more than half of the cases (8).

PSMA-ligand PET/CT outperforms conventional imaging also in staging PCa (9). Furthermore, with the recent advent of PSMA-targeted radioligand therapy, PSMA-ligand PET/CT has the peculiar feature to serve not only as a diagnostic imaging tool, which can modify treatment strategies, but also as a therapeutic one. Recent studies demonstrated that ^{177}Lu-labeled PSMA ligand therapy is safe, effective and determines decreasing PSA levels in patients with metastatic castration-resistant PCa (10).

It is well known that there are some limitations in conducting diagnostic randomized prospective studies, but prospective proof of accuracy of a diagnostic tool is essential for its approval.

In the single-arm prospective multicenter trial carried out by Fendler *et al.* (2) patients underwent ^{68}Ga-PSMA-11 PET/CT or PET/MRI for restaging PCa after radical therapy. Patients were eligible if they had a history of PCa and biochemical recurrence after radical surgery, radical radiotherapy (RT) or both. Included patients had biochemically recurrent, hormone-sensitive or castration-resistant PCa. Exclusion criteria were investigational therapy for PCa, inability to tolerate a PET scan, and another concurrent malignant condition. Presence of PCa was recorded by 3 blinded readers on a per-patient and per-region base.

Lesions were validated by a composite reference standard including, in descending priority, histopathologic analysis, imaging, and PSA follow-up after local/focal therapy.

Obtaining a positive predictive value (PPV) equal or

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higher than 0.70 was the primary endpoint, which was met resulting in a PPV of 0.84 on a per-patient and per-region basis of ^{68}Ga-PSMA-11 PET for detection of tumor location confirmed by histopathologic analysis.

Discussing secondary endpoints, 92% of PET-positive patients and 92% of PET-positive regions were characterized as true positive (PPV =0.92) in cases with composite validation. In cases with histopathologic validation, 73 of 79 (92%) confirmed patients and 76 of 84 (90%) confirmed regions were PET positive resulting in a sensitivity of 0.92 on a per-patient and 0.90 on a per-region basis.

A significant correlation between DR and PSA ranges was found with DR improving as PSA values increase (P<0.001). Whereas, no significant association was found between the PSA doubling time and PSA nadir with PET DR.

Furthermore, this study showed a substantial inter-reader reproducibility employing three different independent blinded readers for each PET scan, demonstrating a reproducibility of PET interpretation.

This study also demonstrated to be safe for patients. In fact, no serious adverse events, even post examination, were noted.

Despite it is known that developing a reference standard in terms of validation of results in biochemically recurrent PCa patients is complex, among 475 (75%) PET-positive patients, PPV based on histopathological confirmation was assessed in a minority of patients (n=87; 18%). Imaging follow up and PSA monitoring were used as results validation techniques in the majority of cases with a follow up duration ranging between 1 and 12 months.

Within the optimal therapeutic window (PSA 0.5–<1.0 ng/mL) DR was 57% (38% with PSA values <0.5 ng/mL) highlighting the potential change in clinical management when other conventional imaging modalities are often inconclusive. Moreover, a PSA decline ≥50% is seen in 31/39 patients (79%) after focal therapy directed to PSMA-positive lesions. The authors did not report PSA declines for patients with PET-negative findings after salvage therapy, focusing on patients with PET-positive lesions. This would have been of interest considering previous studies showing a high chance of a PSA decline among PET-negative patients and proposing a limited sensitivity of PSMA PET in local recurrences (11).

These data are encouraging, nevertheless we should take them carefully as long as a real improvement of overall survival (OS) and metastasis-free survival is not proven (12).

Furthermore, neither OS nor progression free survival (PFS) are calculated.

Nuclear medicine imaging with ^{68}Ga-PSMA is gaining more and more interest in detection and assessment of metastatic disease burden of PCa. To date ^{68}Ga-PSMA PET affects management in about half of PCa patients.

The manuscript in question is the first report of a well-designed prospective and multicenter study focusing on ^{68}Ga-PSMA PET/CT or PET/MRI in recurrent PCa including a great numerosity of patients (635) and certainly represents a step forward in the prostate scenario.

The overall DR of PSMA PET in this study (75%) is similar to detection rates reported in literature as in in the study of Verburg *et al.* in which diagnostic performance of ^{68}Ga-PSMA PET/CT was evaluated in 155 patients (median PSA in positive scans: 5.2 ng/mL; median PSA in negative scans: 1.17 ng/mL) (13).

Per-patient and per-region PPV confirmed by composite validation and histopathologic validation and per-patient and per-region sensitivity, confirmed by histopathologic validation, are concordant with previously published data. This confirms that ^{68}Ga-PSMA PET/CT is significantly more sensitive than standard restaging imaging and may be useful in identifying patients for subsequent targeted therapy (8,14).

McCarthy *et al.* investigated patients with early biochemical recurrence after radical surgery or radiotherapy with PSMA PET/CT imaging in a prospective multicentre clinical trial. All patients included had no lesions or oligometastatic disease on CT and BS. This study highlighted a similar overall prevalence of PSMA PET/CT positive disease. In 199 patients with no lesions on restaging CT and BS, 148 patients (74%) who underwent radical surgery or RT (median PSA 2.55 ng/mL), demonstrated PSMA-positive lesions (15).

Further research and prospective clinical studies are mandatory to improve non-invasive PCa management. It may be interesting to carry out a study with a control arm of patients who didn't undergo PSMA PET/CT and compare the 2 populations' results. Moreover, it may be very interesting to obtain data like OS and PFS to assess the prognostic impact of PET/CT on PCa patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest

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to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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