



## Opinion: Open Science

# Diagnosis of Clinically Significant Prostate Cancer Diagnosis Without Histological Proof in the Prostate-specific Membrane Antigen Era: The Jury Is Still Out

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We read with great interest the article by Heetman et al [1] analyzing the reliability of the imaging combination of prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) and multiparametric magnetic resonance imaging (mpMRI) to safely predict the presence of clinically significant prostate cancer (csPC) to omit the need for histopathological verification via prostate biopsy. Of note, csPC at prostate biopsy was defined as International Society of Urological Pathology (ISUP) grade  $\geq 2$ .

The authors must be commended for their study. They used a large retrospective cohort of 459 patients with a suspicion for the presence of PC. Interestingly, every individual underwent PSMA PET/CT and mpMRT, as well as fusion and randomized prostate biopsy. The authors showed that the specific combination of these innovative imaging techniques with a csPC definition of high tracer uptake (maximum standardized uptake value [SUVmax]  $\geq 8$  mSV) on PSMA PET/CT and a Prostate Imaging-Reporting and Data System (PI-RADS) 4–5 lesion on mpMRI had an impressive detection rate of 98%. This finding may suggest that biopsy confirmation will no longer be needed in the near future. However, for more conflicting radiographic scenarios (eg, lower SUVmax thresholds and/or PI-RADS 1–3 lesions) this does not hold true. For example, for patients with tracer uptake on PSMA PET/CT with SUVmax  $\geq 4$  mSV and a PI-RADS 1–3 lesion, the image-based detection rate for csPC dropped to approximately 69%. While the authors need to be congratulated for their efforts and important results, their conclusion that PSMA PET/CT in combination with

mpMRI may replace prostate biopsies deserves to be put into perspective.

First, the proportion of false-positive image-detected/confirmed (PSMA PET/CT and mpMRI) cases for men harboring either insignificant or no PC is non-negligible. In the current study, as many as one in four image-detected/confirmed cases (25%) harbored insignificant PC (defined as ISUP grade 1) at biopsy, which aggravates the ongoing debate regarding overdiagnosis and specifically overtreatment. This proportion is in line with the current prospective PRIMARY trial, in which approximately one in five men (18%) had ISUP grade 1 disease at biopsy [2]. Even more importantly, the PRIMARY trial also showed that 26% of all men did not harbor any PC. Unfortunately, Heetman et al did not report the negative biopsy rate in their study.

Second, we believe that besides the findings reported from this study, practical and economic aspects should also be considered. We are already facing crowded radiological departments trying to schedule patients for mpMRI. Moreover, even more limited schedules would be available for wider and more general utilization of PSMA PET/CT if used for initial PC detection. Keeping changing demographics in mind, and thus rising PC incidence within the next decades, it is questionable and currently unimaginable that the majority of our patients would omit prostate biopsy and be diagnosed only with PSMA PET/CTs and mpMRI because of high costs, timely procedures, and tight schedules and resources. Furthermore, as mentioned above, the 18–25% rate of insignificant PC (ISUP grade 1) related to this combined diagnostic technique needs to be kept in mind [3,4].

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Similarly, the added benefit of csPC detection of 98% for the combination of PSMA PET/CT and a PI-RADS 4–5 lesion on mpMRI should be carefully compared to the csPC detection rates of PI-RADS 4 (60%) or 5 (83%) scores without additional PSMA PET/CT according to the PROMIS and PRECISION trials [5,6]. Taking all this evidence together, we do not believe that the innovative image-based approach without biopsy is ready for prime time. On the contrary, a reliable, standardized, widely available, inexpensive, and low-comorbidity procedure such as prostate biopsy compares rather favorably and efficiently in comparison. However, further technological developments are on the radar to improve aspects such as MRI examination time (eg, biparametric MRI) and the cost of PSMA PET/CT.

Third, to thoroughly investigate the impact of mpMRI in combination with PSMA PET/CT in csPC detection, final pathological results after radical prostatectomy are helpful in evaluating upgrading/upstaging effects on biopsy for patients with low-risk and favorable intermediate-risk PC [7,8]. If PSMA PET/CT favorably correlates with prediction and accurate diagnosis of csPC on final pathology, it might be an even more interesting diagnostic tool rather than just for omitting prostate biopsy. Looking in more detail at the literature, only a few studies have addressed upstaging/upgrading on PSMA PET/CT after radical prostatectomy as an endpoint. Thus, in comparison to mpMRI, with an overload of papers addressing this endpoint [9–11], the data for upstaging/upgrading on PSMA PET/CT seem to be very immature and missing standardized cutoffs such as a specific tracer uptake threshold to reliably predict csPC on final pathology for clinician use in daily patient counseling.

Finally, prostate biopsies do provide important information beyond diagnosis for the treating urologist. For example, active surveillance criteria are mainly based on (immuno-) histological outcomes (eg, number of cores, percentage of positive cores) and strongly influence treatment decisions [12,13]. Moreover, how should urologists proceed for patients with clinical characteristics suspicious for prostate cancer (eg, digital rectal examination [DRE]) and a low prostate-specific antigen (PSA) level in a setting in which biopsies are omitted and diagnosis is via a combination of PSMA PET/CT and mpMRI? These patients do not have high tracer uptake in the prostate, and PC diagnosis and aggressiveness might be underestimated [14]. Furthermore, the same issue applies to prostate histologies other than adenocarcinoma [15].

Many open questions and problems must be answered before prostate biopsies can be safely omitted in daily urological routine. In the meantime, risk stratification is an option for validation of this imaging approach. Thus, patients with high-risk disease (high PSA, suspicious DRE, high PSA density, and positive family history) for whom surgery is recommended may be potential candidates for this innovative approach for treatment planning with more accurate local and distant staging.

**Conflicts of interest:** The authors have nothing to disclose.

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