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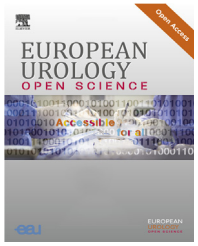

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Opinion: Open Science

Virtual Prostate Biopsy with Prostate-specific Membrane Antigen and Magnetic Resonance Imaging: Closer to Reality in a Subgroup of Prostate Cancer Patients?

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Prostate-specific membrane antigen (PSMA) is highly expressed on most prostate cancer (PC) cells, and this evidence has led to development of several PSMA ligands for positron emission tomography (PET) imaging. The nuclear medicine community has come a long way since the first in-human applications of ^{68}Ga-PSMA-11, which date back to 2012, and at present the use of PSMA PET is suggested by several international guidelines for investigating PC in different clinical settings [1]. In particular, PSMA PET is recommended for detection of recurrence in patients with biochemical recurrence, either after prostatectomy and radiation therapy or with prostate-specific antigen persistence after radical treatment [1]. PSMA PET is also indicated for staging of high-risk PC at presentation and for identifying candidates for Lu-PSMA treatment.

There are far fewer papers regarding the use of PSMA PET for detection of PC [2,3]. Technically, sensitivity may be limited owing to the spatial resolution of PET (around 5 mm) and very small focal PC lesions will be missed by PSMA PET. Furthermore, it is known that approximately 5% of PCs do not overexpress PSMA, and these may be missed. For these reasons, PSMA PET is not even mentioned in guidelines on the diagnostic workflow for patients with suspected PC, for which multiparametric magnetic resonance imaging (mpMRI) is recommended instead [1]. However, these arguments ignore the probability of PSMA overexpression in more aggressive PCs, leading to easy detection even for smaller foci, and the fact that lower expression in low-grade malignancies (ISUP1) could be a distinct advantage when trying to identify only those malignancies that need intervention [4].

The paper by Heetman and colleagues [5] in this issue of *European Urology Open Science* provides a change in perspective, suggesting the use of PSMA PET combined with MRI to avoid unnecessary biopsies. The rationale is very simple: both MRI (Prostate Imaging-Reporting and Data System [PI-RADS] score of 4 or 5) and a high maximum standardized uptake value (SUV_{max}) on PSMA PET have shown good specificity in detecting clinically significant PC. Combining the two methods using smart thresholds (high PI-RADS score and high SUV_{max}) allows such high specificity for the presence of clinically relevant PC that the need for histological confirmation may become obsolete. In summary, the combination of PI-RADS $\geq$4 with SUV_{max} $\geq$8 identified PC with a specificity of 98%, and the authors speculate that a nomogram combining predictive factors could be developed to identify patients for whom biopsy could be avoided.

Of course, the study is preliminary with a number of limitations, such as being single-center, retrospective, and small. In addition, biopsy will remain indispensable in certain patients with a risk of PC by providing important additional information (eg, Gleason score, specific tumor characteristics, DNA testing) for management decisions [6]. Nonetheless, it is very important to consider the hypothesis of whether histological confirmation of suspected lesions is still needed if mpMRI and PSMA PET, known to be the most accurate imaging techniques, are

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combined in a "virtual biopsy" [7]. Emmett et al. [8] previously confirmed the high negative predictive value and sensitivity of PSMA PET and mpMRI for identification of clinically significant PC (csPC) and showed that consideration of the intraprostatic PSMA uptake pattern improves the diagnostic accuracy for csPC [9]. Similarly, the PRIMARY trial found very high specificity (100%) for the combination of high PI-RADS score (4 or 5) and high PSMA SUV_{max} (>9). This current trial also confirms the strong association between grade group on histopathology and high PSMA SUV_{max}. It is important to note that early work demonstrated that the use of PSMA PET SUV_{max} alone has limited ability to identify which prostate sextants are tumor-positive and have a Gleason score of 7–10 [10]. In addition, recent data from the PEDAL study indicate that fixed SUV_{max} cutoffs are potentially not the way forward for optimizing identification of csPC via PSMA PET, and should be investigated in conjunction with other characteristics such as the patterns of tracer distribution, volume, and background/signal ratio [11]. Taken together, the evidence suggests that the first likely subgroup of patients who could safely avoid prostate biopsy are those with negative PSMA PET and negative MRI. A second possible group are the patients for whom a definitive therapy has already been determined, such as radical prostatectomy. In these patients, biopsy before surgical excision could be unnecessary and this potential warrants evaluation in future trials. Using these strategies, the morbidity and discomfort of patients [12] exposed to biopsies can be reduced. Furthermore, there are favorable financial implications for society if modern imaging technologies succeed in replacing biopsies in a subgroup of patients with PC.

From a philosophical point of view, it can be added that with virtual biopsy the concept of diagnosis itself changes from foundationalism to coherentism. Foundationalism holds that knowledge (in this case, diagnostic judgment) should ultimately be based on evidence that cannot be justified further. Assuming that biopsy and histopathology are the gold standard fits the foundationalist agenda. Coherentism is the view that knowledge requires convergence of many items of evidence, none of which is taken as the bedrock [13]. Acknowledged limitations of traditional biopsies in terms of reliability and partiality, together with the good prospects of imaging and artificial intelligence (AI)-supported biopsies, speak in favor of a conceptual shift from foundationalism to coherentism.

In conclusion, the study by Heetman and colleagues [5], although preliminary, brings to light a very interesting prospect. Prostate biopsy is an invasive procedure associated with patient morbidity and a financial burden on society. So far, the emphasis has been on reducing unnecessary biopsies via risk stratification for patients with low incidence of PC; however, if the chance of PC is close to 100% and treatment with radical prostatectomy is planned, a biopsy for histological confirmation could be seen as redundant. This pathway for diagnosing PC without histological proof could be an option for reducing the 1 million prostate biopsies performed in Europe each year [4]. Therapy without histological confirmation is already in practice for other malignancies such as renal cell carcinoma, for which histological proof is only used for radiologically indeterminate renal masses [4]. Lastly, there are potential further opportunities to improve on the method for imaging-based virtual biopsies using AI and radiomics [7].

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References

[1] Mottet N, Cornford P, van den Bergh RCN, et al. EAU guidelines on prostate cancer. Arnhem, The Netherlands; 2021. https://uroweb.org/guideline/prostate-cancer/.
[2] Hu X, Wu Y, Yang P, Wang J, Wang P, Cai J. Performance of ^{68}Ga-labeled prostate-specific membrane antigen ligand positron emission tomography/computed tomography in the diagnosis of primary prostate cancer: a systematic review and meta-analysis. Int Braz J Urol. In press. https://doi.org/10.1590/S1677-5538.IBJU.2020.0986.
[3] Fendler WP, Schmidt DF, Wenter V, et al. ^{68}Ga-PSMA PET/CT detects the location and extent of primary prostate cancer. J Nucl Med 2016;57:1720–5. https://doi.org/10.2967/jnumed.116.172627.
[4] Kaittanis C, Andreou C, Hieronymus H, et al. Prostate-specific membrane antigen cleavage of vitamin B9 stimulates oncogenic signaling through metabotropic glutamate receptors. J Exp Med 2018;215:159–75. https://doi.org/10.1084/jem.20171052.
[5] Heetman JG, Wever L, Pereira LJP, van den Bergh RC. Clinically significant prostate cancer diagnosis without histological proof: a possibility in the prostate-specific membrane antigen era? Eur Urol Open Sci 2022;44. https://doi.org/10.1016/j.euros.2022.06.013.
[6] Parker C, Castro E, Fizazi K, et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020;31:1119–34. https://doi.org/10.1016/j.annonc.2020.06.011.
[7] Murray JM, Wiegand B, Hadaschik B, Herrmann K, Kleesiek J. Virtual biopsy: just an AI software or a medical procedure? J Nucl Med 2022;63:511–3. https://doi.org/10.2967/jnumed.121.263749.
[8] Emmett L, Buteau J, Papa N, et al. The additive diagnostic value of prostate-specific membrane antigen positron emission tomography computed tomography to multiparametric magnetic resonance imaging triage in the diagnosis of prostate cancer (PRIMARY): a prospective multicentre study. Eur Urol 2021;80:682–9. https://doi.org/10.1016/j.eururo.2021.08.002.
[9] Emmett LM, Papa N, Buteau J, et al. The PRIMARY Score: using intraprostatic PSMA PET/CT patterns to optimise prostate cancer diagnosis. J Nucl Med. In press. https://doi.org/10.2967/jnumed.121.263448.
[10] Pomykala K, Fendler W, Calais J, Eiber M, Czernin J. Accuracy of ^{68}Ga-PSMA PET/CT to localize cancer in the prostate gland and to predict Gleason score. J Nucl Med 2018;59:1468.
[11] Wong LM. PEDAL: a phase III study comparing diagnostic accuracy of mpMRI prostate to ^{18}F-DCPyL PSMA PET/CT. Presented at the 37th annual European Association of Urology Congress, Amsterdam, The Netherlands, July 1–4, 2022.
[12] Tops SCM, Grootenhuis JGA, Derksen AM, et al. The effect of different types of prostate biopsy techniques on post-biopsy infectious complications. J Urol 2022;208:109–18. https://doi.org/10.1097/JU.0000000000002497.
[13] BonJour L. The dialectic of foundationalism and coherentism. In: Greco J, Sosa E, editors. The Blackwell guide to epistemology. Oxford, UK: Blackwell Publishing; 2017. p. 117–42. https://doi.org/10.1002/9781405164863.ch4.