Re:Â Follow-Up of Men with PI-RADS 4 or 5 Abnormality on Prostate MRI and Nonmalignant Pathologic Findings on Initial Targeted Prostate Biopsy

Stavrinides V, Giganti F, Allen C, Kirkham A, Punwani S, Freeman A, Norris J, Pashayan N, Moore CM, Emberton M

DOI: 10.1097/JU.0000000000001589
Reference: JU-20-2653

To appear in: *The Journal of Urology*
Accepted Date: 14 December 2020

Please cite this article as: Stavrinides V, Giganti F, Allen C, Kirkham A, Punwani S, Freeman A, Norris J, Pashayan N, Moore CM, Emberton M, Re:Â Follow-Up of Men with PI-RADS 4 or 5 Abnormality on Prostate MRI and Nonmalignant Pathologic Findings on Initial Targeted Prostate Biopsy, *The Journal of Urology*® (2019), doi: 10.1097/JU.0000000000001589.

The Journal of Urology Publish Ahead of Print
DOI: 10.1097/JU.0000000000001589

Letter to editor re:

Meng X, Chao B, Chen F, Huang R, Taneja SS, Deng F

Follow-up of men with PI-RADS 4 or 5 abnormality on prostate MRI and non-malignant pathologic findings on initial targeted prostate biopsy.

DOI: 10.1097/JU.0000000000001424. Reference: JU-20-1690

Vasilis Stavrinides[1,2,3], Francesco Giganti[1,4], Clare Allen[4], Alex Kirkham[4], Shonit Punwani[4], Alex Freeman[5], Joseph Norris[1,2], Nora Pashayan[6], Caroline M Moore[1,2], Mark Emberton[1,2]

[1] Division of Surgery and Interventional Science, University College London, London, UK

[2] Department of Urology, University College London Hospital NHS Foundation Trust, London, UK

[3] The Alan Turing Institute, London, UK

[4] Department of Radiology, University College London Hospital NHS Foundation Trust, London, UK

[5] Department of Pathology, University College London Hospital NHS Foundation Trust, London, UK

[6] Department of Applied Health Research, Institute of Epidemiology & Health, University College London, London, UK

Corresponding author:

Vasilis Stavrinides

v.stavrinides@ucl.ac.uk

Division of Surgery and Interventional Science

University College London

Charles Bell House

43-45 Foley Street, W1T 7TS, London UK

Word count: 492

We would like to congratulate Meng et al. on their recent study on the follow up of men with PIRADS 4/5 prostate MRI lesions and benign pathologic findings on targeted biopsy (TB). This paper adds to substantial recent efforts to understand the mechanism of false positive MRI phenotypes in the prostate. Although relationships between non-cancerous pathologies (especially inflammation) and false positive MRI are often discussed in somewhat definitive terms, very few studies previously provided evidence justifying this level of certainty.[1,2] Fortunately, this landscape changed in the last couple of years: on review of targeted biopsies from 98 PIRADS 5 lesions Sheridan and colleagues found that, in 18 benign ones, 39% (7/18) contained benign prostatic hyperplasia changes and 28% (5/18) inflammation.[3] Interestingly, a negative biopsy result from such lesions was associated with lower PSA density, something our group also corroborated in a diagnostic context.[4] Gordetsky and colleagues reviewed 62 lesions in 41 patients who had initial negative systematic biopsy (SB) and a subsequent combined TB/SB procedure with a negative TB component.[5] The mean percentage of stroma, basal cell hyperplasia and inflammation were increased in TB tissue compared to SB-derived material, while atrophic glands and chronic inflammation showed a positive correlation with higher PIRADS scores. More recently, Hupe and colleagues also looked at 34 PIRADS 4/5 cancer-negative lesions and used contralateral cancer-negative SBs as control.[6] The frequency of any stromal, glandular and inflammatory alterations was substantially higher in tissue from cancer-negative TBs compared to control SBs, while vascular changes were almost exclusive in TB tissue.

In this paper Meng and colleagues not only corroborate similar relationships of non-cancerous pathology with false positive MRIs, but go a step further by looking at the evolution of false positive lesions over time. The first finding, a 73% decrease from PI-RADS 4/5 to PI-RADS ≤3 (including 35% complete resolution), might reflect the high volatility of microenvironmental perturbations engendering false positive phenotypes and implies that a reasonable strategy for biopsy-negative lesions is repeat imaging to confirm their resolution.

The extent to which these processes are influenced - or govern for that matter - the natural history of prostate cancer is undetermined, but lesion regression was not equally evident in men with HGPIN or ASAP at their initial TB. It is certainly plausible that MRI-TB captures premalignancy in tissue where cancer initiation is destined to happen, but this finding could also be underestimation of tumour burden if one considers that entities like PIN have a spatial (not just temporal) association with established tumours[7]. Missed malignant tissue can of course exist within a lesion, but the additional possibility of adjacent MRI-invisible disease should always be considered, especially in the context of random, non-imaging-based SB which misses a substantial proportion of significant

tumours.[8,9] The study results have to be interpreted with caution due to the small sample size and the influence of radiologist experience on a false positive MRI reading, particularly in the PZ.[4,10] However, such research should be actively encouraged.

References

1. Panebianco, V. *et al.* Pitfalls in Interpreting mp-MRI of the Prostate: A Pictorial Review with Pathologic Correlation. *Insights Imaging* **6**, 611–630 (2015).
2. Panebianco, V. *et al.* An update of pitfalls in prostate mpMRI: a practical approach through the lens of PI-RADS v. 2 guidelines. *Insights Imaging* **9**, 87–101 (2018).
3. Sheridan, A. D. *et al.* MRI-Ultrasound Fusion Targeted Biopsy of Prostate Imaging Reporting and Data System Version 2 Category 5 Lesions Found False-Positive at Multiparametric Prostate MRI. *Am. J. Roentgenol.* **210**, W218–W225 (2018).
4. Stavrinides, V. *et al.* False Positive Multiparametric Magnetic Resonance Imaging Phenotypes in the Biopsy-naïve Prostate: Are They Distinct from Significant Cancer-associated Lesions? Lessons from PROMIS. *Eur. Urol.* S0302283820307703 (2020) doi:10.1016/j.eururo.2020.09.043.
5. Gordetsky, J. B. *et al.* Histologic findings associated with false-positive multiparametric magnetic resonance imaging performed for prostate cancer detection. *Hum. Pathol.* **83**, 159–165 (2019).
6. Hupe, M. C. *et al.* Histomorphological analysis of false positive PI-RADS 4 and 5 lesions. *Urol. Oncol. Semin. Orig. Investig.* (2020) doi:10.1016/j.urolonc.2020.01.017.
7. Sakr, W. A. *et al.* High grade prostatic intraepithelial neoplasia (HGPIN) and prostatic adenocarcinoma between the ages of 20-69: an autopsy study of 249 cases. *Vivo Athens Greece* **8**, 439–443 (1994).
8. Ahmed, H. U. *et al.* Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *The Lancet* **389**, 815–822 (2017).
9. Norris, J. M. *et al.* What Type of Prostate Cancer Is Systematically Overlooked by Multiparametric Magnetic Resonance Imaging? An Analysis from the PROMIS Cohort. *Eur. Urol.* **78**, 163–170 (2020).
10. Stolk, T. T. *et al.* False positives in PIRADS (V2) 3, 4, and 5 lesions: relationship with reader experience and zonal location. *Abdom. Radiol.* **44**, 1044–1051 (2019).

Disclosures:

VS is supported by an MRC Clinical Research Training Fellowship (MR/S005897/1) and acknowledges support from The Alan Turing Institute under the EPSRC grant EP/N510129/1, as well as previous support from EACR (EACR Travel Fellowship) and UCL (Bogue Fellowship). Francesco Giganti is

funded by the UCL Graduate Research Scholarship and the Brahm PhD scholarship in memory of Chris Adams. Caroline Moore acknowledges funding from the NIHR, the MRC, CRUK, Movember, PCUK and the EAU Research Foundation. Mark Emberton receives research support from the United Kingdom's National Institute of Health Research (NIHR) UCLH/UCL Biomedical Research Centre. He was awarded NIHR Senior Investigator in 2013.