



The value of routinely combining the Rotterdam European Randomized Study of Screening for Prostate Cancer Risk Calculators with multiparametric magnetic resonance imaging to predict clinically significant prostate cancer remains uncertain

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Multiparametric magnetic resonance imaging (mpMRI) has emerged as a most useful tool for triaging patients with a suspicion of harbouring prostate cancer (PCa). mpMRI findings are ranked by the Prostate Imaging Reporting and Data System (PI-RADS) which has been refined into the current PI-RADS 2 version, this topic having been reviewed recently by Roberts *et al.* in 2018 (1). mpMRI also has the ability to localise non-palpable cancer within the prostate, which if performed before a prostate biopsy will increase the diagnosis of significant PCa (2-4).

It is therefore appropriate that Alberts *et al.* (5) reviewed the ability of mpMRI to improve the prediction of high grade PCa from the Rotterdam European Randomised Study of Screening for the Prostate Cancer Risk Calculator (ERSPC-RC). These well-validated ERSPC-RC models have been reported to enable 20–33% of transrectal ultrasound-guided systematic biopsies (TRUS-Bx) to be avoided (5).

It is accepted that mpMRI is a costly investigation. In most countries, including the United States, mpMRI is only indicated after a prior benign prostate biopsy, due in a large part to insurance policies (6). However, mpMRI prior to a prostate biopsy is an effective strategy with costs only moderately higher than for a standard biopsy pathway

(7,8). The European Association of Urology (EAU) PCa guidelines recommend mpMRI following a prior negative biopsy and prior to re-biopsy in men who continue to be suspected of harbouring PCa (7,8).

Alberts *et al.* sought to determine whether the addition of the PI-RADS system and age to ERSPC-RC would improve prediction of high grade clinically-significant PCa (defined as Gleason $\geq 3+4$) for both this group (MRI-ERSPC-RC4) and for biopsy-naïve patients (MRI-ERSPC-RC3). Because the ERSPC-RC3 and ERSPC-RC4 prediction models for PCa are based on sextant biopsies from the first round (3,624 men) and second round (2,896 men) of the ERSPC Rotterdam, they constructed combination calculators from data accrued from 504 biopsy-naïve men and 457 previously biopsied men to adjust the MRI-ERSPC-RC3 and the MRI-ERSPC-RC4, respectively (5).

The authors of this manuscript reported that the addition of mpMRI resulted in a significantly higher area under the curve (AUC) for high-grade PCa for the biopsy naïve MRI-ERSPC-RC3 cohort at 0.84 compared with 0.76 for the ERSPC-RC3 group and for those men with a prior negative biopsy (AUC of 0.85 *vs.* 0.74). However, decision curve analyses showed a greater net benefit for the previously

biopsied cohort at a high-grade risk-benefit threshold of $\geq 5\%$. The authors concluded that, for those men who had previously undergone a negative prostatic biopsy, combining MRI findings with ERSPC calculator data would enable one third of these patients to avoid proceeding to have a further biopsy. This is of importance in avoiding unnecessary biopsies in men with a low risk of significant PCa and also for decreased burden on increasingly strained health budgets.

Of the 1,353 consecutive men (suspected of having but not diagnosed with PCa) enrolled who received mpMRI followed by TRUS-Bx and /or targeted biopsy (Tx), the numbers of patients contributed by the five participating institutions varied considerably ranging from 723 in Düsseldorf to 82 at Den Bosch. This is of major concern as, in the Dusseldorf institution which contributed 53% of the men to the study, only 1% of men were diagnosed with normal PIRADS 1–2 mpMRI scans. This irregularity casts significant doubt on the credibility of the data and the absence of a centralised MRI review is a notable deficiency. A similar criticism is valid in relation to the absence of a central review for histopathology. Benign biopsies varied between institutions from 38–51% (median 49%) and Gleason 3+3 carcinoma varied between 11–29% (median 16%).

The biopsy technique was heterogeneous with variation in biopsy protocols between institutions. Although MRI-TBx was performed on all PI-RADS ≥ 3 lesions, only 961 out of the 1,353 men received a TRUS-Bx, with (for PI-RADS ≥ 3) or without (for PI-RADS 1–2) additional MRI-TBx. Furthermore, it is unknown if there has been any provisional forethought for collection of any type of bodily fluid for molecular markers/metabolomics, or other analyses so relevant in an era of emerging personalised medicine through liquid biopsy profiling (9). Because of these deficiencies, this manuscript is a collation of information and is best regarded as a published audit rather than a research study that provides reliable data for meaningful insight for future clinical practice.

In many countries such as Australia, mpMRI is increasingly being performed routinely before a prostate biopsy. This has two main advantages for men viz. triaging and localisation of significant PCa. Firstly, if an abnormal (PIRADS 3–5) lesion is identified by MRI, then targeted biopsies of the MRI lesion combined with systematic biopsies increases the diagnosis of significant PCa above random systematic TRUS biopsies alone (3). For PIRADS 4–5 lesions in our institution, the risk of PCa is 73–95% (10) and therefore risk calculators are of limited benefit for

this cohort, as almost all will proceed to prostate biopsy. Secondly, if the MRI is normal (PIRADS 1–2) then most of these men do not have PCa, with only a 6–24%, risk of significant malignancy depending on the definition of significant cancer, the number of biopsy cores and, of course, the expertise of the diagnosing radiologist (2,3,6).

Performing a prostate biopsy on all these (PIRADS 1–2) men will over-investigate the majority, however not proceeding to biopsy anyone in the PIRADS 1–2 cohort will result in delaying diagnosis and treatment for some men who do have significant PCa. Therefore, risk calculators in the PIRADS 1–2 cohort hopefully will help to identify men at increased risk of PCa and avoid the delay in diagnosis. When improving technology, such as artificial intelligence interpretation of PI-RADS mpMRI scans combined with data from molecular profiling of bodily fluids, and personalized medicine become included in risk calculators validated for the population in question, we are likely to better identify men at risk of PCa in this (PIRADS 1–2) cohort.

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References

1. Roberts MJ, Teloken P, Chambers SK, et al. Prostate Cancer Detection. In: De Groot LJ, Chrousos G, Dungan K, et al. (eds). *Endotext*. South Dartmouth (MA): MDText.com, Inc., 2000–2018.
2. Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet* 2017;389:815-22.
3. Pokorny MR, de Rooij M, Duncan E, et al. Prospective study of diagnostic accuracy comparing prostate cancer detection by transrectal ultrasound-guided biopsy versus magnetic resonance (MR) imaging with subsequent MR-guided biopsy in men without previous prostate biopsies. *Eur Urol* 2014;66:22-9.
4. Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *N Engl J Med* 2018;378:1767-77.
5. Alberts AR, Roobol MJ, Verbeek JFM, et al. Prediction of High-grade Prostate Cancer Following Multiparametric Magnetic Resonance Imaging: Improving the Rotterdam European Randomized Study of Screening for Prostate Cancer Risk Calculators. *Eur Urol* 2018. [Epub ahead of print].
6. Gorin MA, Walsh PC. Magnetic Resonance Imaging Prior to First Prostate Biopsy-Are we there yet? *Eur Urol* 2018;74:409-10.
7. Moldovan PC, Van den Broeck T, Sylvester R, et al. What Is the Negative Predictive Value of Multiparametric Magnetic Resonance Imaging in Excluding Prostate Cancer at Biopsy? A Systematic Review and Meta-analysis from the European Association of Urology Prostate Cancer Guidelines Panel. *Eur Urol* 2017;72:250-66.
8. Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol* 2017;71:618-29.
9. Koo KM, Wang J, Richards RS, et al. Design and Clinical Verification of Surface-Enhanced Raman Spectroscopy Diagnostic Technology for Individual Cancer Risk Prediction. *ACS Nano* 2018;12:8362-71.
10. Yaxley AJ, Yaxley JW, Thangasamy IA, et al. Comparison between target magnetic resonance imaging (MRI) in-gantry and cognitively directed transperineal or transrectal-guided prostate biopsies for Prostate Imaging-Reporting and Data System (PI-RADS) 3-5 MRI lesions. *BJU Int* 2017;120 Suppl 3:43-50.

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