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European Association of Urology



## Platinum Priority – Editorial

Referring to the article published on pp. x–y of this issue

**Re: Andrew Vickers, Sigrid V. Carlsson, Matthew Cooperberg. Routine Use of Magnetic Resonance Imaging for Early Detection of Prostate Cancer Is Not Justified by the Clinical Trial Evidence. Eur Urol. In press. <https://doi.org/10.1016/j.eururo.2020.04.016>**

### Prebiopsy MRI: Through the Looking Glass

A diagnostic test can be defined as any test used to determine the presence, nature, or severity of a particular condition. In our technology-driven era, we may like to believe that the best diagnostic test is the one that provides the most details with the highest accuracy for the condition being investigated. However, the most sophisticated and precise test is useless if its results do not change patient management or improve relevant outcomes. In other words, it is the physician's responsibility to define the right level of detail of the diagnostic test, beyond which further magnification does not result in additional clinical consequences. This dilemma applies to many diagnostic tests used in urological practice (Does ultrasensitive prostate-specific antigen [PSA] detect relevant biochemical recurrence? Does novel imaging detect relevant metastasis?). It also applies to developments in prostate biopsy indication and procedure. Is the development aimed at providing the most accurate representation of the tissue of the whole gland, and particularly of the different prostate cancer (Pca) foci that may be present? Or is it (only) aimed at retrieving the necessary information to adequately risk stratify a patient for clinical decision-making?

In their Platinum Opinion paper, Vickers et al [1] argue that routinely performing magnetic resonance imaging (MRI) before a first set of prostate biopsies is not justified, which is in contradiction to clinical practice guidelines that now recommend using MRI in this setting on the basis of level 1 evidence [2]. Two main arguments against the use of MRI are provided: systematic biopsy (SB) provides sufficient detection of clinically significant Pca (csPca), and the use of MRI lesion-targeted biopsy (TB) induces a grade migration that may lead to overtreatment. Does our new looking glass mostly cause tunnel vision?

First, although SB maintains added value in the population of biopsy-naïve patients [3–5], it seems difficult to believe that it provides adequate detection of csPca. In the Danish cohort cited by Vickers et al, among patients with negative SB, the true 20-yr Pca-specific mortality at 20 yr was 5.2% [6]. The rate of 0.7% cited must be interpreted with caution, as these data only relate to a subgroup of patients with PSA < 10 ng/mL, and PSA measurements at diagnosis were available for only 22% of the cohort. In the Göteborg screening trial, for men with negative SB in the first screening round and PSA levels of 3–10 ng/ml the 20-yr cumulative Pca mortality was 0.6%; for those with PSA > 10 ng/mL the Pca mortality was 21.4% [7]. Metastasis and Pca mortality do occur after negative SB and an imperfect diagnostic strategy may be a cause.

Second, there is no doubt that use of MRI and TB increases the detection of grade group  $\geq 2$  cancers [3–5,8,9]. We agree with Vickers et al that the use of a more sensitive test may induce stage/grade migration due to the Will Rogers effect (Fig. 1). A grade group 2 cancer only detected at TB is on average a different tumour to a grade group 2 lesion already found at SB; it is likely to be on average smaller (and if risk is a combination of grade and tumour size, also of lower risk). Notably, stage/grade migration constantly occurred during the last 50 yr as the biopsy indication and technique evolved from digital rectal examination-guided biopsy to PSA-based transrectal ultrasound (TRUS)-guided six-core (sextant) lateralised biopsy, to TRUS-guided 12-core (or more) biopsy. The 2005 International Society of Urological Pathology (ISUP) reclassification of the Gleason grading system into grade groups led to another grade migration.

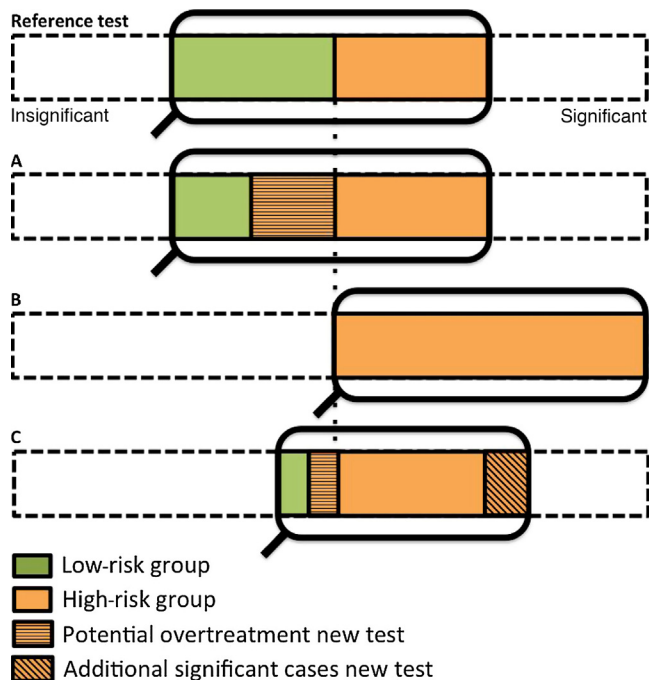
But a stage/grade shift is not a reason to abandon the MRI looking glass and stick to blind sampling of the gland, because it does not rule out the chance that additional csPca will also be detected after MRI and TB. Not all grade group  $\geq 2$  cancers detected by MRI/TB and missed by SB are insignificant cancers. Improved prostate mapping using MRI and TB, by providing a more sensitive test for ISUP score (one of the most robust predictors of clinical outcomes), is

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**Fig. 1 – Schematic representation of different scenarios for a new diagnostic test versus a reference test. The low-risk group is considered for expectant management, while high-risk cases are considered for treatment. Reference test: established risk groups represent the significance of the disease. Insignificant cases are overdetected and significant cases are underdetected. Scenario A for the new test: stage shift only for the risk groups with no difference in the significance of the disease and a risk of overtreatment. Scenario B for the new test: no detection of insignificant disease and detection of only significant disease, which represents a perfect test. Scenario C for the new test: combined effect, with a lower rate of testing, a reduction in overdetected insignificant disease, and improved detection of significant disease.**

likely to provide additional parameters and allow further refinement of current risk groups using clinical outcomes of MRI-based diagnosed PCa [10].

While waiting for data for patients with TB-diagnosed PCa to mature, we believe that rather than rejecting MRI for biopsy-naïve patients, the urological community should adopt a pragmatic approach by mitigating the potential consequences of stage/grade migration. Thus, recognising that improved targeting could artificially inflate the ISUP grade of the tumours by focusing the sampling at areas of high-grade cancer, a recent ISUP consensus conference has already suggested the use of an aggregated ISUP grade summarising the results of all the targeted biopsy cores rather than the worst core from the same MRI-identified lesion [11]. In addition, results from TB should also not be interpreted as stand-alone but in the light of the clinical context, MRI parameters such as the apparent diffusion coefficient and tumour size, PSA density, and SB results. As a result, a greater proportion of grade group 2 cancers may become eligible for active surveillance [12].

An essential point not addressed by Vickers et al is that concordant studies suggest that a biopsy indication strategy combining high-quality MRI and clinical and biochemical data (such as PSA density) improves the selection for

prostate biopsy [2]. TB has the potential to dramatically decrease the number of unnecessary biopsies and resulting postbiopsy complications. Although SB is currently still recommended in addition to TB, the strategy has the potential to also reduce diagnosis of grade group 1 cancers [2].

In conclusion, there is clear evidence that MRI and TB improve the detection of grade group  $\geq 2$  cancer over SB. This higher rate should be interpreted with care. Some detected cancers may correspond to small cancers as a result of stage/grade migration, while others may be aggressive tumours that would otherwise have been missed. The urological community should adapt risk classification in order to correctly separate the wheat from the chaff in the MRI era. Importantly, growing evidence suggests that MRI, in combination with clinical data, could also help in selecting patients with very low-risk cancer who do not need to undergo biopsy at all. The advantages of using prebiopsy MRI clearly outweigh the suggested harms.

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