EDITORIAL COMMENT

Balancing the benefits and harms of MRI-directed biopsy pathways

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Key Points

- *Before a prostate biopsy, the likely benefits and the harms emanating from true and false test MRI results need to be balanced. Prioritizing patients' preferences and their tolerance to potential harms are essential to assess.*
- *The decision curve analysis method is an analytical framework where the net clinical benefit is plotted against a range of risk thresholds of having important cancers, helping patients and their physicians to decide between cancer averse (important cancers being detected) and biopsy averse (biopsies avoided) strategies.*
- *The decision curve analysis method showed that the incorporation of clinical risk factors with MRI findings optimizes biopsy outcomes over a range of clinically relevant risk thresholds, compared to other biopsy strategies.*

Prostate cancer diagnoses in the MRI-directed biopsy era are fraught with the need to make choices, in order to strike the appropriate balance between the benefits and harms for patients in their biopsy decisions. Diagnostic and patient impacts of both true and false test results should influence who and how to conduct a biopsy. Combining in all men with suspected cancer, systematic biopsies and targeted biopsy after a positive MRI scan seems like a safe choice, because it maximizes the detection of important cancers. However, the use of systematic biopsies is associated with an increase in the detection of low-grade cancers that may submit patients, at best, to the extra cost and anxiety of active

surveillance and, at worst, to overtreatment. In addition, a prostate biopsy is associated with discomfort and morbidity, and it seems desirable to try to avoid it in patients whose risk of important cancers is reasonably low.

The MRI-directed pathway's ability of rule out cancer (its true-negative test result) is commonly emphasized because it is substantial and most robust. Sathianathen et al. in a meta-analysis of 42 studies reported a negative predictive value of 91% which varied a little between studies [1], and centres with similar demographic mix show higher degrees of agreement [2]. It is, therefore, reasonable to conclude that MRI, when negative, could help avoid unnecessary biopsies. Nonetheless, attention should be paid to the MRI facility, and to standardizing MRI techniques and radiological assessments [3]. In addition, because the negative predictive value of MRI is dependent on prevalence [4], estimating the patient's likely risk should help assess whether or not we can trust negative MRI findings.

What to do with men with MRI positive findings is more difficult for multiple reasons. Overall, the specificity of MRI is intermediate and is highly variable between studies [5] and centres [6], so it seems desirable to be highly selective on who and how to biopsy men with positive results. Here also, estimating the likely patient risk should help since the positive predictive value is also dependent on prevalence [5]. Although the PI-RADS score is a good predictor of the likelihood of the presence of important cancers, success is dependent on the suspicion category. Therefore, the ideal

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diagnostic method for biopsy should not be the same for category PI-RADS 3 or PI-RADS 5 lesions, provided, of course, that radiological assessments are made using the PI-RADS recommendations [7].

We must also not forget the patient impact of false results after an MRI assessment. Fortunately, the high NPV means that there are few men harbouring important cancers after negative MRI; therefore, appropriate safety nets are needed to find these men as their cancers emerge during observations. Some men with positive MRI have biopsies that do not have important cancers on targeted cores but are discovered on accompanying systematic cores [8]. Contributing factors include targeting errors and histologic interpretation variability. The need for quality control and quality assurance procedures through the accreditation of team working and certification of the team members is needed to decrease biopsy yields variability [3].

With these complexities in mind, there are multiple ways to optimize the balance of MRI-directed biopsy results, weighing the benefits versus the harms (Fig. 1). Firstly, it is possible to adjust patient selections by incorporating PSA-density values with positive and negative MRI scan results [9], with or without additional clinical factors that informing on the risk of having an important cancer [10, 11]. Secondly, by thresholding on a different PI-RADS assessment category for biopsy decisions (e.g. score 4 instead of 3), or taking the radiological stability into account in men on active surveillance. Thirdly, the biopsy approach for men with a 'positive MRI scan' result

may be altered to ensure that the target has been optimally sampled, for example by increasing the number of targeted cores employed. Fourthly, to compensate for possible histologic grade shifts of targeted biopsy cores, by increasing the core numbers, adjusting the histologic evaluations of the targeted cores [12], or employing a higher histologic grade for clinical significance [8].

When employing these methods, it is necessary to judge the equilibrium between the benefits and harms using a common analytical framework. The decision curve analysis method, in which net clinical benefit is plotted against a range of relevant risk thresholds of having cancer, can give insights into the balance [13]. The net benefit quantifies the net true positives or true negatives corrected for the harm of false positives or false negatives, whereas the risk threshold indicates the maximum acceptable risk of missing a clinically important cancer. If a patient or their physician is particularly worried about missing disease (cancer averse) and/or there is no excess risk of biopsy complications, then a low-risk threshold for biopsy would be reasonable. If, by contrast, a patient or their physician is more worried about the potential harms of biopsy (biopsy averse), then a higher risk threshold may be adopted.

Bittencourt et al. [11] retrospectively evaluated the impact of different diagnostic pathways, in a cohort of biopsy-naïve men at high risk for prostate cancer, who came to their reference centre for MRI-ultrasound fusion prostate biopsy. They compared systematic biopsies in all patients, with different
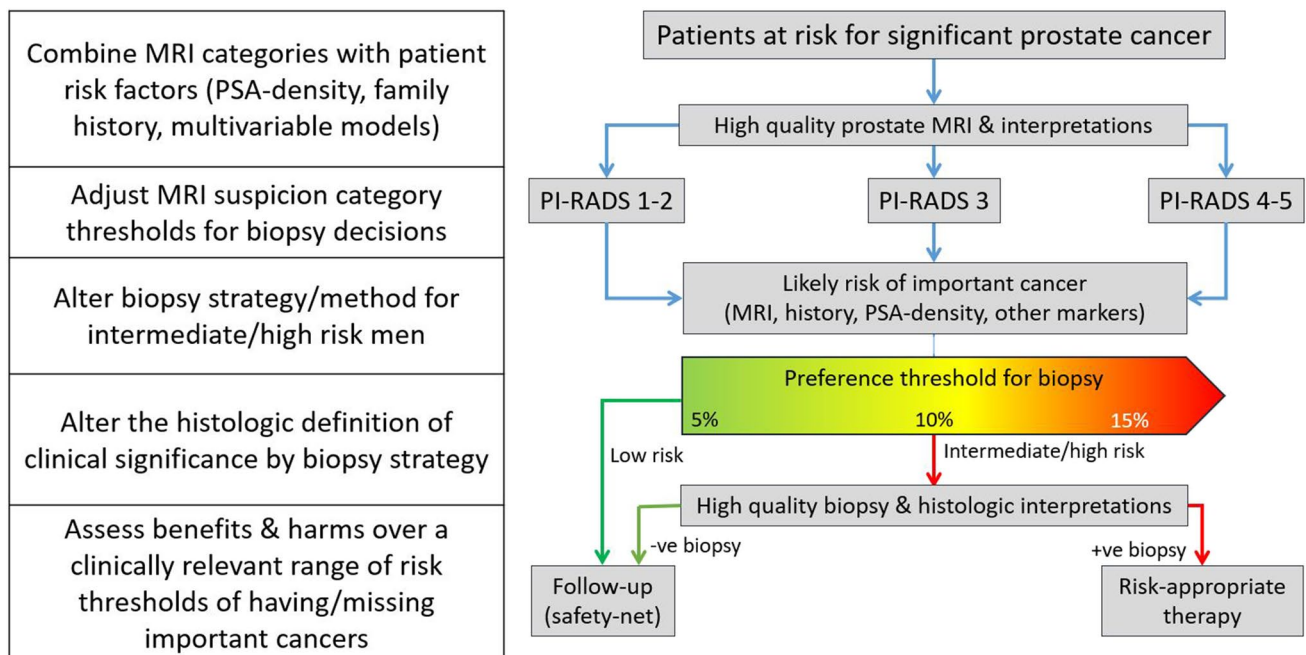

Fig. 1 Balancing the benefits and harms of MRI-directed biopsy results. Legend: There are multiple ways to optimize the balance of MRI-directed true and false results, weighing the benefits versus the harms. PI-RADS, Prostate Imaging–Reporting and Data System

MRI-based strategies, including a clinical risk-based strategy where no biopsy was done in lower risk men with PI-RADS category 1–3 scores. Here, the clinical risk was assessed clinically by incorporating PSA-density values, DRE findings and family history with the MRI results. The reference standard was systematic biopsy for all patients plus targeted biopsies for MRI-identified lesions. They found that systematic and targeted biopsies only in men with positive MRI (MRI-focused) and the risk-based pathways showed the highest detection of International Society of Urological Pathology grade group (GG) ≥ 2 cancers. Moreover, the risk-based pathway was associated with a higher number of biopsies avoided. They noted that any MRI-directed pathways performed better than the systematic biopsies for the detection of GG ≥ 2 cancers while reducing the detection of GG $= 1$ tumours.

Based on the decision curve analysis, the net benefit of the risk-based pathway outperformed the other pathways within the typical range of "cancer averse" and "biopsy averse" clinical decision scenarios (5–30%). These results are in line with the analysis of Deniffel et al. who also showed reductions in unnecessary biopsies in men with positive MRI by incorporating PSA-density values in cancer-averse scenarios, and additionally the potential superiority of PI-RADS + PSA density compared to other non-calibrated logistic regression models [10]. The current study validates the extrapolations of Schoots et al. [14], on the likely benefit and harms of different MRI-based pathways. However, the current study results are not practice-changing for several reasons: the retrospective design of the study, the fact that the patients were highly selected (overall prevalence of cancer of 76%) and were only biopsy-naïve, and the fact that all MRIs and biopsies were performed by the same operator. Additional retrospective and prospective studies are necessary to assess the consistency of the observations over a wider range of disease prevalence, populations and with radiologists and biopsy operators of varying experience. Only then can the risk-based MRI pathway be adopted as the default 'best practice' method of diagnosing men with suspected clinically important prostate cancers.

Declarations

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