

How imaging is changing prostate cancer management

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Abstract (/250)

In this paper we look at how imaging has changed the management of prostate cancer. We start evaluating the shift from systematic to magnetic resonance imaging - targeted biopsies and discuss the most relevant papers published at this regard.

Then, we discuss the past and ongoing studies that evaluate the role of MRI as a triage and screening tool and the application of this technique during active surveillance, including its role in the biopsy setting.

Growing evidence supports the use of MRI in the prostate cancer pathway, but only in the presence of images of optimal diagnostic quality and experience in prostate MRI reporting and biopsy execution.

Keywords: 3 to 6

Prostate cancer, prostate biopsy, magnetic resonance imaging, screening, active surveillance

Introduction (Gaelle)

The last decade has witnessed major changes in prostate cancer management. Among these, the advent of magnetic resonance imaging (MRI), by allowing the visualisation of the cancerous lesion inside the prostatic gland, opened new management horizons. The former prostate cancer early detection pathway, based on prostate specific antigen (PSA), digital rectal examination and systematic biopsies, resulted in a significant uncertainty in ruling out clinically significant prostate cancer, and, in many cases, to overtreatment [1]. Active surveillance has been demonstrated as a validated treatment option, with the possibility to address the risk of overtreatment by close monitoring of cancer characteristics, limiting active treatments and their consequences to men harbouring clinically significant cancers [2]. Still, the uptake of active surveillance by patients and urologists remained insufficient. A significant number of patients were only presented with radical treatment options, while many chose to withdraw from active surveillance because of anxiety [3]. In parallel, many men under active surveillance failed to adhere to the proposed surveillance protocol, mostly because of the burden of repeat prostate biopsies [4].

The present review aims at summarising the evidence demonstrating how magnetic resonance imaging addressed these concerns and transformed prostate cancer management, focusing on the early detection and active surveillance settings.

How has imaging changed prostate cancer diagnosis?

From systematic to MRI-guided biopsies: moving from darkness to light

For decades, prostate biopsies, the cornerstone of prostate cancer diagnosis and management, have been performed according to various systematic templates, hoping that the needles steered as evenly as possible would allow for the detection of clinically significant disease. This strategy resulted in poor sensitivity, even with saturation templates, and a significant degree of uncertainty, driving physicians and patients to prefer radical treatment over conservative options, even in the presence of Gleason 6 disease [1]. Furthermore, up to 20-30% of tumours, anteriorly-located, were neglected by this approach, and only diagnosed at an advanced stage [5].

The first application of prostate MRI dates back to nearly 40 years ago. The correlation between MR images and radical prostatectomy specimens (n=20) soon resulted in the description of a low T2 signal intensity in the region of the prostatic tumour [6]. However, the diagnostic performances of this newly discovered imaging modality did not immediately compare favourably with DRE and ultrasound, notably for the detection of extraprostatic disease, with a predictive value of 100% by rectal examination, 83% by ultrasound and 66% by MRI in a series of 25 patients treated by retropubic radical prostatectomy [7].

The technological advances and improvement of MR scanners rapidly allowed the acquisition of images of diagnostic quality. In parallel, the concept of MRI-targeted biopsies emerged, and effort was put into the development and validation of the first MRI-ultrasound fusion devices as an alternative to cognitive registration and in-bore targeting [8]. Still, the urological community was divided around the interest of MRI

prior to biopsy, in part owing to the lack of standardisation and reproducibility of MRI interpretation. The description and publication of the Prostate Imaging Reporting and Data System (PI-RADS) classification in 2012, and its subsequent revisions (PI-RADS v2.0 and v2.1) proved decisive in the uptake of MRI, allowing the setup of large multicentre trials [9].

A fast-growing body of evidence

The PROMIS study, is, to date, the only study providing a direct comparison between MRI and systematic biopsy results, using as ground truth, an ethically-acceptable alternative to radical prostatectomy for patients without prostate cancer (i.e. systematic sampling of the entire gland through a 5-mm brachytherapy grid with a transperineal approach) [10]. This prospective study including 740 biopsy-naïve men demonstrated a greater sensitivity of MRI compared to a standard, 10-12 core systematic biopsy protocol, for the detection of clinically-significant (Gleason $\geq 3+4$) prostate cancer (MRI sensitivity 93%, 95% CI 88–96%; systematic biopsy sensitivity 48%, 95%CI 42–55%; $p < 0.0001$).

Adding to this, high-quality evidence from several randomised clinical trials and prospective, within-patient comparative studies further established the added-value of MRI and MRI-targeted biopsies in biopsy-naïve men (**Table 1**).

The PRECISION multicentre trial randomised 500 men from 25 centres and 11 countries between MRI and targeted biopsies (in case of a suspicious lesion on MRI) or 10-12 core systematic biopsies without MRI. The detection rate for clinically significant disease was 38% in the MRI + targeted biopsy vs 26% in the systematic biopsy arm ($p=0.005$). Of note, men with a non-suspicious MRI did not undergo biopsy and follow-up data of this group of patients will be of particular interest to estimate the

proportion of significant cancers missed and how follow-up can play a safety net role in mitigating the consequences of delayed diagnosis [11].

The French multicentre prospective MRI-FIRST trial allowed for a direct, within-patient comparison of 2 biopsy strategies, among 251 patients recruited before MRI, and systematic biopsy performed independently of MRI results. The detection rate of targeted biopsies was higher than that of systematic biopsies (32.3% vs 29.9%), without reaching statistical significance [12]. A combined biopsy strategy (targeted + systematic) was found to outperform targeted biopsies alone. Of interest, significant prostate cancer was detected in 5/45 (11%) men with non-suspicious MRI (Likert 1-2) [12].

In the 4M study, 626 men were enrolled prospectively to have an MRI, targeted biopsies under direct MRI, in-bore guidance, and systematic 12-core transrectal biopsies. The detection rate of both biopsy modalities proved remarkably high, in a possibly selected population, in which targeted biopsies also outperformed systematic biopsies in spite of a relatively low number of targeted cores (detection rate 50% for targeted biopsies with a mean 2.7 targeted cores vs 45% for systematic biopsies) [13]. The superiority of a combination of MRI-targeted and systematic biopsies compared to systematic biopsies alone was recently demonstrated to hold in a screening setting. A total of 12,750 men were invited by mail to participate and 1532 with PSA levels ≥ 3 ng/ml were randomised in a 2:3 ratio between MRI+MRI-targeted biopsies (in case of a suspicious lesion on MRI, PI-RADS 3-5)+systematic biopsies, or standard 10-12-core systematic biopsies. The detection rate of the combination biopsy strategy was 21% vs 18% for systematic biopsies alone ($p < 0.001$), while 467/929 (50%) of men in the MRI group avoided biopsy [14].

MRI-based screening: ready for prime-time?

The added-value of prostatic MRI as a filter for aggressive prostate cancer was confirmed by the studies cited previously, as well as an abundant literature confirming these findings from real-life data [15]. PSA-based screening in prostate cancer is still not recommended although the control arm of the PLCO study demonstrated a large contamination with PSA-testing, and the updated results of the ERSPC trial at 13 years confirmed a rate ratio of prostate cancer mortality in men screened of 0.73 (95% CI 0.61-0.88) [16]. Limitations of large-scale PSA testing include lack of sensitivity, low specificity, and the risk of overdiagnosis and overtreatment.

The use of MRI of the prostate as a first-line screening tool is still limited by the cost, availability and duration of a conventional multiparametric MRI, including T2-weighted imaging, diffusion-weighted imaging and dynamic contrast-enhanced sequences [9]. Fast, bi-parametric MRI (i.e., by omitting contrast-enhanced sequences), and simplifying the acquisition of morphological sequences, presents an interesting, cost-effective alternative, which displayed high diagnostic performance (95% sensitivity, 65% specificity for fast bi-parametric MRI vs 69% for multiparametric MRI) in an expert centre among the 626 patients included in the 4M study [17].

A recent, single-centre non-inferiority randomised trial compared a strategy including fast MRI followed by conventional multiparametric MRI in equivocal cases to upfront standard multiparametric MRI of the prostate in 311 biopsy-naïve men. The detection rate for clinically-significant disease was 23.5% with fast MRI vs 32.7% with mpMRI, with a 9.2% difference under the predefined non-inferiority threshold. Of note, this study was conducted among patients pre-selected through PSA-testing, and does not inform on the applicability of fast MRI as a first-line screening tool [18].

The ReIMAGINE prostate cancer screening study, a prospective single-centre study, is currently recruiting in the UK and will inform the acceptability of an MRI-based screening program based on MRI protocols without contrast agent injection, and the prevalence of cancer detected in MRI-screened men [19]. The results of this study are eagerly awaited to assess the feasibility and cost-effectiveness of upfront MRI-based screening programmes.

How has imaging changed prostate cancer management during active surveillance?

We have seen that over the last decade the diagnostic pathway of prostate cancer has changed significantly by the advent of mpMRI [20]. Several randomised trials have shown that mpMRI is the best technique to detect and localise clinically significant prostate cancer and it allows performing MRI-targeted biopsy [15].

An abnormal scan is positively associated with increased tumour volume and high tumour grade and therefore the introduction of this technique into the diagnostic pathway of prostate cancer has helped reduce both overdiagnosis and underdiagnosis.

The role of mpMRI in the diagnosis of prostate cancer has been discussed in the previous section. We will now examine the role of this technique in the management of prostate cancer, with a focus on active surveillance.

Active surveillance refers to a conservative management approach for patients with low- and favourable intermediate-risk disease to avoid or delay unnecessary treatment [21].

Different active surveillance programmes are available across the world, with different eligibility criteria (mainly based on PSA, DRE and biopsy results) and different timing for confirmatory or follow up biopsies.

In detail, in order to detect misclassification, most protocols still require a confirmatory biopsy and/or mpMRI within 1 year after enrolment into active surveillance [22].

There has been increasing interest in the use of mpMRI during active surveillance due to its high negative predictive value for clinically significant prostate cancer [23]. Thus, a patient with a negative scan and favourable disease on biopsy may be advised to pursue active surveillance.

A systematic review has shown that mpMRI at the start of surveillance can detect clinically significant disease in one-third to half of men [24].

We also know that a suspicious lesion on mpMRI is seen in two-thirds of men otherwise suitable for active surveillance, and data from radical prostatectomies have shown that a positive mpMRI is more likely to be associated with upgrading (defined as Gleason score > 3+3) than a negative scan (43% vs 27%) [24].

Turkbey and colleagues reported that the incorporation of mpMRI into the D'Amico, Epstein or CAPRA scoring systems could reduce (by 85%, 75% and 91%, respectively) the number of misclassifications in assigning patients to active surveillance or treatment using radical prostatectomy as the reference standard [25].

By performing mpMRI before biopsy we know that visible lesions with suspicious radiological features (or showing signs of radiological progression during active surveillance) can now be targeted for biopsy, detecting a higher percentage of patients with clinically significant disease and reducing the number of clinically insignificant disease diagnosed if standard biopsies are omitted [11].

This is corroborated by the results from the multicentre ASIST trial, which initially showed no difference in the upgrade rate between standard re-biopsy or mpMRI with two cores targeted to a lesion (i.e. Gleason Grade Group 2 upgrade: 21% vs 23%,

p=0.9) during AS, although it should be noted that in the highly-experienced centre the upgrading rate was much higher in the MRI arm (i.e. 20% for 12-core vs 33% for MRI-targeted bx) (p=0.09). At 2-year follow up, baseline mpMRI before confirmatory biopsy resulted in 50% fewer failures of AS and less progression to higher-grade prostate cancer, confirming the value of mpMRI in the AS setting. However, significant differences (p= 0.019) were observed between sites for the 98 patients in progression rate in the MRI arm, with 2/48 (4.2%) at one centre, 7/26 (27%) at another, and 4/24 (17%) at the third centre.

However, robust data support the use of mpMRI instead of repeating standard biopsy for monitoring men on active surveillance are still lacking and there is a need to define significant disease on MRI and significant changes over time [26].

We know that the two most relevant questions during active surveillance are:

- *What constitutes a radiologically significant lesion during active surveillance?*
- *What is a significant (clinically meaningful) change on mpMRI?*

In 2016 the European School of Oncology convened a taskforce of different experts (radiologists, urologists and radiation oncologists) to make recommendations on serial mpMRI reporting during AS in order to collect data across different centres in a robust and systematic manner.

The Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) recommendations were created [27].

This scoring system is a 1-to-5 Likert scale that assesses the likelihood of radiological change over time (such as mpMRI sequences and scoring) from the previous or baseline mpMRI scan. **(Table 1)**

A PRECISE score of 1 means that there has been complete radiological regression, a PRECISE score of 3 implies that the MR features are stable over time while a PRECISE score of 5 indicates that there has been definitive stage progression. The radiologists should take absolute measurements of visible lesions at each time point to enable accurate assessment of change, using a dedicated case report [27].

Over the last three years, there have been different groups that have applied the PRECISE recommendations in their active surveillance cohorts [28–32] and their results have been pooled together in a recent systematic review and meta-analysis that has shown that serial MRI of the prostate using the PRECISE score (not alone but in addition to other clinical factors and biomarkers) allows to reliably rule in and rule out prostate cancer progression [26] but further studies on larger cohorts are needed before recommending MRI as a stand-alone tool to avoid biopsies.

Discussion

We have seen through this review how MRI has changed – or has the potential to change – early prostate cancer management, from population screening to active surveillance. A few questions remain unanswered and warrant further discussion.

Will we ever get rid of systematic biopsies in prostate cancer diagnosis?

So far, the combination of systematic and targeted biopsies has been recommended as the biopsy strategy of choice, minimising the risk of underdetection of around 5-10% clinically significant prostate cancers that would be missed by targeted biopsies alone [12]. Still, the discussion around biopsy templates is actively ongoing, and a new strategy of “focal saturation”, including biopsies of the “penumbra” around the MRI lesion, is proving very promising in order to better estimate the tumour volume, grade, without increasing the detection of non-clinically significant prostate cancers. In a retrospective study looking at the location of 3552 cancerous cores from 927 men, 90% of positive cores were located within a radius of 10 mm from the nearest MRI lesion [33].

Prostatic MRI demonstrated excellent accuracy in ruling out significant prostate cancer, and is an excellent filter for aggressive cancers, thus limiting the overdiagnosis of non-clinically significant prostate cancer. New targeting modalities, and the increase in the number of targeted cores are two interesting strategies to limit targeting errors. Taking a step back, it is probably time to ask ourselves why we are still putting more trust in a diagnostic modality (systematic biopsy) that proved inferior to MRI and targeted biopsies in a randomised control trial, and still largely contributes to the detection of non-clinically significant cancers. And time to realise that by doing this,

we, collectively as urologists, choose to transfer the uncertainty we cannot handle on patients who have to deal with the uncertainty of active surveillance.

Can MRI replace biopsy in active surveillance?

We acknowledge that prostate MRI, like any other tests, is not perfect and we know that it can sometimes miss high-grade disease.

However, an important aspect of the application of prostate MRI during AS is tumour visibility. The medium-term outcomes from an imaging-based AS cohort that includes patients with up to Gleason 3+4 disease at entry biopsy and a baseline + serial MRI have shown a significant difference (in terms of treatment, transition to watchful waiting, Gleason $\geq 4 + 3$ on follow-up biopsy or death) between MR-visible and non-visible lesions for both low and intermediate-risk disease.

Most patients, particularly those with Gleason 3 + 3 cancer and non-visible disease at baseline, remained on imaging-based surveillance at five years and the treatment rate was similar to that reported from other AS cohorts with comparable follow-up but pre-defined follow up biopsies.

Therefore, given the growing interest in the delivery of personalised medicine, we believe that routine re-biopsy in the presence of stable findings on serial MRI (especially when there is no visible lesion) associated with stable PSA kinetics could be avoided.

Will imaging render prostate biopsy obsolete?

To date, despite excellent sensitivity, the specificity of MRI in the detection of prostate cancer does not support a biopsy-free diagnostic pathway. However, the high specificity of novel imaging modalities, and in particular that of prostate-specific membrane antigen positron emission tomography (PSMA-PET) supported the setup of clinical trials exploring this possibility. In a recent report, 25 patients with a high suspicion of clinically significant prostate cancer on MRI (PI-RADS score ≥ 4) and PSMA-PET (PET score ≥ 4 on a five-point Likert scale and maximum standardized uptake value ≥ 4.0) were treated by radical prostatectomy without prior biopsy confirmation. All patients had clinically-significant prostate cancer on final pathology, the positive surgical margin rate was 20%. Fifteen patients (60%) had organ-confined disease, and lymph node involvement was detected in 4/25 (16%), unsuspected from imaging in 3/4 cases [34]. Those results based on a limited retrospective study are exploratory, but set the basis for a possible future where prostate cancer initial evaluation would rely solely on imaging. For now, (targeted) prostate biopsies will remain the cornerstone of prostate cancer diagnosis and management, through the confirmation of prostate cancer diagnosis, but also by informing risk-stratification and clinical decision still relying heavily on the estimation of the tumour grade and volume obtained from prostate biopsies.

Conclusion

In conclusion, prostate MRI will definitely help us define each patient's individualised risk but only in the presence of images of optimal diagnostic quality and expertise in prostate MR reporting and biopsy conduct.

Declaration of conflict of interest (30 to 50)

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