Should men undergo MRI before prostate biopsy? (Pro)

1,500 - 2,000 words with up to 50 references

(2,064 words)
1. Introduction

In the last three years, several urological societies have updated their guidelines and expanded the indication for multiparametric magnetic resonance imaging (MRI) to biopsy-naïve individuals with suspicion of prostate cancer prior to performing prostate biopsy [1,2]. This recommendation had previously been limited to patients with persistent prostate cancer suspicion despite previous negative biopsies [3].

The adoption of an MRI-based approach in the early work-up of prostate cancer constitutes a radical change in the diagnostic pathway to prostate cancer, that is traditionally based on transrectal ultrasound (TRUS)-guided prostate biopsy in response to an elevated prostate-specific antigen (PSA) and/or abnormal digital rectal examination (DRE). A PSA-based approach has been shown to have significant limitations due to its unsatisfactory sensitivity and specificity for clinically significant prostate cancer (csPCa), leading to a number of unnecessary biopsies. The lack of cost-effectiveness has prevented societies from developing effective population-based screening programmes for the early detection of prostate cancer.

In the last decade, several high-quality randomised studies have demonstrated the benefits of an MRI-led pathway, namely an increase in the detection of csPCa while reducing diagnosis of insignificant prostate cancer, and potentially allowing patients with non-suspicious MR scans to avoid biopsy [4-7].

In this Seminar, we give an overview of the current data supporting the application of MRI in patients prior to performing prostate biopsy.
1.1 PSA screening

Despite its lack of reliability in identifying prostate cancer, total PSA remains the single-most important trigger for prostate biopsy today and early identification of prostate cancer.

PSA concentrations in men 50-70 years old have furthermore been shown to be strong predictors of prostate cancer metastasis and prostate cancer-related death [8].

PSA alterations commonly occur in a variety of benign conditions and even low PSA levels cannot exclude the presence of csPCa, with up to 50% csPCa patients having PSA levels below 3ng/mL [9-11]. On the other hand, the commonly adopted threshold of 4ng/mL leads to detection of prostate cancer in down to 21% patients, thus potentially leading to 4 out of 5 unnecessary biopsies [12-13]. Furthermore, a PSA-based screening approach is severely limited by the overdetection of nonsignificant prostate cancer in up to 50% of all newly diagnosed patients [4], with significant implications for patients and healthcare systems in terms of quality of life, potential side effects of unnecessary treatments and healthcare expenditure. Attempts to increase the PSA diagnostic accuracy have been made by the adjustment for prostate volume with PSA density [14-15] and kinetics [16], the association with other biomarkers (such as PHI, 4K score, urinary PCa3) [17-19] and stratification based on genetic testing [20,21], as well as the incorporation into risk stratification tools (e.g., European Randomised Study of Screening for Prostate Cancer - ERSPC -) [22,23]. Despite some evidence from the ERSPC study for the benefit of PSA-led screening protocols thanks to progressive decrease over time of the number-needed-to-treat to avoid once prostate cancer-related death, several large population screening studies have yet failed to confirm a positive impact on prostate cancer-specific mortality [24-29].
In this scenario, no population-level screening protocols using PSA can be offered and international societies recommend adequate patient counselling before requesting PSA testing for the early detection of PCa [1,2,30,31].

2. MRI before prostate biopsy

2.1 Is MRI useful in men with a raised PSA?

One of the most important questions in the diagnostic pathway of prostate cancer is if MRI can be used as the first assessment tool of patients with a raised PSA or abnormal digital rectal examination. In other words, if an MRI-led pathway compares to a standard biopsy pathway and if a biopsy can be safely avoided if the MRI is negative.


This approach has been driven by some key publications that have been published over the last 5 years.

The first work was the PROstate Mr Imaging Study (PROMIS) study [4], which compared MRI and standard TRUS biopsies in biopsy-naive men using 5mm template mapping prostate biopsies as a reference test. The study showed that TRUS biopsy detects around 50% and MRI 93% of csPCa, defined as any Gleason primary pattern 4 or 6 mm of any cancer at 5mm template mapping biopsy. This means that around one in four men could safely
avoid a biopsy when the MRI is low risk. Although PROMIS showed that MRI can detect csPCa more accurately than standard TRUS biopsy, it is important to highlight that no MRI-targeted biopsies had been performed in this study and the reference standard was 5mm sampling.

The second key publication was the PRECISION trial [5], a multicentre randomised trial in which biopsy-naïve men were randomised to standard or MRI-targeted biopsy. Sixty-four out of 248 patients (26%) in the standard biopsy arm had csPCa (defined as Gleason score ≥ 7), whilst 55/248 (22%) had clinically insignificant cancer (i.e., they had been overdiagnosed). Conversely, 95/252 (38%) patients in the MRI arm had csPCa and only 23/252 (9%) had clinically insignificant disease.

The third study (4M) [6] was a prospective multicentre Dutch study in 626 biopsy-naïve men who underwent pre-biopsy MRI followed by TRUS-biopsy and targeted biopsy (in-bore) if MRI was suspicious. The Authors showed a similar detection rate of csPCa (defined as Gleason score ≥ 7) for the MRI and TRUS pathway (25% and 23% respectively), with 49% of patients who could avoid biopsy.

The fourth study (MRI-FIRST) [7] was a prospective multicentre study comparing systematic vs targeted biopsies in 251 patients. Only 14% of men could avoid a biopsy and the detection rates of csPCa (defined as Gleason 3+4) were similar with each technique (29.9% with systematic and 32.3% with targeted biopsy; p = 0.38).
In addition to the aforementioned studies, a systematic review by Drost and colleagues [32] sought to determine the diagnostic accuracy of MRI-only, MRI-targeted biopsy, the MRI pathway (i.e., MRI with or without MRI-targeted biopsy) and systematic biopsy as compared to template-guided biopsy (reference standard) in detecting csPCa (defined as Gleason Grade Group ≥ 2). The MRI pathway was the most accurate strategy to detect csPCa, although the studies included had different criteria for patient selection.

**2.2 Could community screening for prostate cancer using MRI be helpful?**

Screening for prostate cancer has generated considerable debate within the medical community.

The ideal screening test should be both effective (i.e., detect cancer before any signs or symptoms become apparent) and cost-effective.

A review by Ilic and colleagues [33] analysed all randomised controlled trials of screening vs no screening for prostate cancer that included PSA testing, with or without digital rectal examination.

Overall, in a population aged from 45 to 80 years and a follow-up ranging from 7 to 20 years, the Authors observed that there was no statistically significant difference in prostate cancer-specific mortality between patients randomised to screening and control groups (risk ratio 1.00), although the ERSPC study was the only one reporting a 21% significant reduction of prostate cancer-specific mortality in a pre-specified subgroup of men aged 55 to 69 years (risk ratio 0.84) [33], and these results have been corroborated at 16 years of follow up meaning that there is a larger benefit in the use of PSA testing as the time goes on. [28]
Another clinical trial that needs to be mentioned is the CAP trial [9], in which no difference in prostate cancer death was observed at 10 years between the intervention (i.e., PSA monitoring) and the control (i.e., no PSA monitoring) group (0.31 vs 0.30 per 1,000 person-years) with an increase in the number of low-risk (i.e., Gleason 3+3) cases (1.7 % vs 1.1 %).

We have seen that MRI is better than standard biopsy at diagnosing cancer in patients with a raised PSA [32] and that PSA and other traditional tools (e.g., digital rectal examination and TRUS biopsy) are not accurate enough as a screening method in the detection of csPCa, it is reasonable to investigate if MRI can be used as a community screening tool.

There has been much interest at this regard in different countries across the world.

A group from Toronto [34] was the first to evaluate the feasibility of prostate MRI as the primary screening test for prostate cancer. Volunteers to undergo an MRI for prostate cancer screening followed by a prostate biopsy irrespective of their PSA level were recruited by a news advertisement in a local newspaper within the Greater Toronto Area.

The final population comprised 47 men. Eighteen of them (38 %) had cancer, six (33 %), eight (45 %) and four (22 %) of which had Gleason Score 6, 7 and 9, respectively.

When comparing the performance between MRI and PSA in predicting the presence of prostate cancer, MRI scores had a higher area under of the curve (0.81) than PSA level (0.67) and the adjusted odds ratio for having prostate cancer was significantly higher for MRI score (2.7; p=0.004) than PSA level (1.1; p=0.21).
A more recent study [35] from the UK was compared the performance of PSA testing, MRI and ultrasonography as screening tests for prostate cancer at different sites. Men aged 50 to 69 years were invited for prostate cancer screening and the final population comprised 408 patients. The proportion of men with positive MRI results (scores from 3 to 5) was higher than the proportion with positive PSA test results (72 % vs 40 %; p < 0.001) and MRI (using a score of 4 or 5 to define a positive test result) was associated with more men (n = 11) diagnosed with clinically significant cancer than PSA alone (≥ 3 ng/mL) (n = 7), without an increase in the number of men advised to undergo biopsy or overdiagnosed with clinically non-significant cancer. The proportion of men with positive ultrasonography results (scores from 3 to 5) was higher than the proportion of those with positive PSA test results (96 % vs 40 %; p < 0.001) but ultrasonography (using again a score of 4 or 5 to define a positive test result) was not superior in detecting csPCa (n = 4) compared with PSA testing alone.

There are also two ongoing studies that need to be mentioned.

In the first study [36] a random sample of men aged 50 to 60 years in the Göteborg area (Sweden) are being randomised to either a screening or control group. Participants in the screening group are further randomised into one of three Arms: (1) PSA-test; if PSA ≥ 3 ng/mL, then MRI and systematic biopsy, plus targeted biopsy to suspicious lesions; (2) PSA-test; if PSA ≥ ng/mL, then MRI and targeted biopsy to suspicious lesions; (3) PSA-test; same as the first Arm but with a lower PSA-cut-off (≥1.8 ng/ml). The primary outcome is the detection rate of clinically insignificant prostate cancer (defined as Gleason Grade Group 1) comparing all men with PSA ≥ 3 ng/mL in Arm 1 vs Arm 2 + 3. The results from this trial will definitely help us expand our knowledge about the role of prostate MRI for screening.
The second study is being carried out in the UK [37] in collaboration with general practitioners and members of the public who have been affected by or have experience of prostate cancer. In this study biopsy-naïve patients aged 50-75 years have been invited to undergo prostate cancer screening using PSA and MRI. The primary endpoints of the study are the acceptance rate for invitations to screening prostate MRI, the prevalence of MRI-defined suspicious lesions in a screening population, and the presence of cancer for those patients undergoing biopsy as a result of MR-visible lesions.

3. Conclusion

In conclusion, there is compelling evidence to support the use of prebiopsy MRI as a standard part of the assessment for all patients at risk of prostate cancer. Patients with a raised PSA and no clear lesions on MRI should have a risk assessment including other factors (e.g., PSA density, PSA kinetics, family history), and a tailored discussion of the risks and benefits before considering biopsy.

Initial results have also shown that MRI represents a promising community screening tool for prostate cancer, but currently this technique cannot be recommended as a screening tool by national/international guidelines. Future research, including the Re-IMAGINE study and other studies targeting specific populations (e.g., age, ethnicity, genetic testing), will definitely help us answer this question.
References


