MRI in prostate cancer diagnosis – do we need to add standard sampling? A review of the last 5 years

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Abstract

Introduction: In recent years, evidence has accrued to support the introduction of multiparametric magnetic resonance imaging (mpMRI) in the prostate cancer diagnostic pathway. The exact role of mpMRI in different settings is not widely agreed. In this review, we look at the use of MRI in three groups of men: biopsy naive men, those with a previous negative biopsy and those with a previous positive biopsy suitable for active surveillance.

Material and methods: An electronic MEDLINE/PubMed search up to 24th January 2018 was performed, using the search terms (*prostate cancer* OR *prostate adenocarcinoma*) AND (*MRI* OR *magnetic resonance*) AND (*biopsy naïve* OR *active surveillance* OR *prior negative biopsy* OR *no prior biopsy*). Only those studies which reported detection rates of standard biopsy and MRI-targeted biopsy, where all men had both an MRI and standard biopsy were included.

Results: Thirty-four articles were included (14 biopsy naïve, 10 prior negative biopsy and 10 prior positive biopsy). MRI-targeted biopsy consistently resulted in greater detection of clinically significant prostate cancer, and a lower detection of clinically insignificant prostate cancer, across all three patient populations. This effect was most prominent in men with at least one previous negative biopsy, and least prominent in men on active surveillance. In the presence of a negative mpMRI detection of csPCa found at systematic biopsy ranged from 0% to 20%.

Conclusions: MRI-targeted biopsy is more efficient than standard biopsy in detecting clinically significant disease in men with a positive MRI, and results in less detection of

clinically insignificant cancer. In men with a negative MRI, a significant minority of men will have clinically significant cancer detected on systematic biopsy.

1. Introduction

The current diagnostic pathway for PCa is based on the use of prostatic specific antigen (PSA) and digital rectal examination (DRE) to inform the decision to undertake systematic transrectal ultrasound-guided biopsy (TRUS-Bx). This diagnostic pathway has led, over the years, to an increase in PCa incidence and a slight reduction in cancer-specific mortality[1]. Overdiagnosis and overtreatment of indolent prostate cancer represent important drawbacks of this approach, that have not been adequately addressed by the use of active surveillance for men with low risk disease [2].

The typical sampling strategy is a 10-12 core TRUS- biopsy with cores directed principally at the base, mid-gland and apex of the peripheral zone of each of the left and right lobes of the prostate. The use of anteriorly directed cores is not recommended at first biopsy, according to the most recent European Association of Urology guidelines[3].

Although this biopsy strategy is superior to the initial 'random systematic' 6-core TRUS-Bx as reported by Stamey & Hodge, a meta-analysis that investigated the comparison between 12-core TRUS-Bx and whole gland radical prostatectomy specimens, found false negative rates for TRUS-Bx of up to 49% [4–6]. The PROMIS trial[7] in a diagnostic population of men with a raised PSA or suspicious digital rectal examination used 5mm transperineal template mapping biopsy as the gold standard and showed a negative predictive value of TRUS-Bx in detecting GS $\geq$ 3+4 PCa of 63%. When efforts are made to improve the negative predictive value of TRUS-Bx by increasing the sampling density, there is a higher probability of detecting clinically insignificant PCa [8,9].

There is growing interest in the use of multiparametric magnetic resonance

imaging (mpMRI) of the prostate to refine the diagnostic pathway of PCa, improve risk stratification, and diagnose only those men who could benefit from active treatment. Prostate MRI was initially introduced in the late 1980s as an imaging technique for local staging of PCa, identifying extracapsular extension and seminal vesicle invasion [10]. In the last decade, recent advances in imaging have enabled more accurate detection and characterization of suspicious lesions within the prostate. In addition to conventional T2-weighted anatomical sequences, mpMRI combines functional techniques such as diffusion-weighted MRI (DWI), dynamic contrast enhanced MRI (DCE) and MR spectroscopy (MRSI). The combination of these sequences in detecting PCa has been extensively studied in recent years. The PROMIS trial[7], using T2-weighted imaging with DWI and DCE, showed a sensitivity and negative predictive value of mpMRI in detecting GS $\geq$ 3+4 of 88% and 76%, respectively.

So far, three approaches have emerged to perform MRI-TBx: I) visual registration (also referred to as "cognitive" registration in the literature); II) software-assisted registration (fusion) and III) direct in-bore biopsy. There is still no consensus on which technique is the best [11].

Despite the promising role of mpMRI in the diagnostic pathway of PCa, international panels of experts are cautious in advising the use of MRI and subsequent MRI-TBx in every setting of PCa diagnosis. In particular there is much debate about the need for systematic cores in men having MRI-targeted biopsies, and in those men with a negative MRI.

The European Association of Urology and National Comprehensive Cancer network (NCCN) guidelines stated that is too early to make recommendations on

routinely using mpMRI for biopsy naïve patients. The UK NICE guidelines 2014 recommend mpMRI for men with a positive biopsy in whom radical treatment or active surveillance are considered, and in those men with a negative TRUS-Bx where a clinical suspicion of prostate cancer remains. Because of the approach that men fit for radical treatment in whom the biopsy is positive or negative, there is a growing tendency in the UK to use mpMRI before biopsy. This is particularly the case in those men who are referred on the UK timed cancer pathway, where a diagnosis of, or exclusion of prostate cancer must be made within 31 days of a referral for assessment. There is a financial penalty of £5000 per patient for exceeding this timeframe. This financial imperative has contributed to the rapid uptake of pre-biopsy MRI in the UK, in order to shorten time to diagnosis, and subsequent treatment, where referral to treatment must not exceed 62 days[12]. The approach of using mpMRI before biopsy in all men fit for active treatment has recently been mandated by NHS England[13].

For men with an initial negative TRUS biopsy, both the EAU and the NCCN guidelines recommend MRI in men with a clinical suspicion of prostate cancer[3,14].

The UK is the only national guideline to mandate the use of MRI at the start of active surveillance, whilst the EAU has suggested its use in active surveillance with a grade B recommendation [3] and the NCCN considers the inclusion of mpMRI in active surveillance protocol still debatable [14].

Previous analyses of MRI-targeted biopsies have not always clearly differentiated between the desired outcome of the detection of clinically significant disease, and the undesired outcome of the detection of clinically insignificant disease. One of the challenges in reviewing the literature here is the lack of a consistently applied definition

for clinically significant disease.

The recent PRECISION study has assessed this in a randomized controlled trial where men either had a standard biopsy or an MRI-targeted biopsy[15]. Men in the standard biopsy arm had 26% clinically significant cancer and 22% clinically insignificant cancer (with significance deemed as any Gleason 7 or above), whilst in the MRI arm 28% of men avoided biopsy, 38% had clinically significant disease and 9% had clinically insignificant disease. PRECISION was an analysis of 2 different pathway approaches, showing clear advantages to the MRI-targeted pathway. However, questions have been raised about the potential advantage of adding standard cores to MRI targeted cores, and in using standard sampling in men with a negative MRI[15].

2. Evidence acquisition

2.1. Objective

The objective of this review was to compare the diagnostic efficiency of a targeted biopsy strategy with a standard biopsy strategy in three patient populations (initial biopsy, previous negative biopsy and previous positive biopsy), with reference to the desired outcome of the detection of clinically significant prostate cancer, and the undesired outcome of the detection of clinically insignificant prostate cancer. Specifically we aimed to compare the targeted strategy alone with the combined strategy, to assess the value of adding standard cores to targeted cores.

2.2. Search strategy

MEDLINE/PubMed was searched from inception to 24th January 2018. The search terms used were (*prostate cancer* OR *prostate adenocarcinoma*) AND (*MRI* OR *magnetic resonance*) AND (*biopsy naïve* OR *active surveillance* OR *prior negative biopsy* OR *no prior biopsy*).

We selected only those studies in which the detection rates had been compared between MRI-targeted biopsy and standard biopsy in each individual man, with each patient acting as his own control (paired cohort), and where results were available separately for any one of the defined population groups. Data of men with a negative MRI who had standard biopsy alone were also reported, where available. As we know that MRI has improved over time and in order to provide updated data, we excluded all papers published before 2012.

3. Evidence synthesis

Overall, 911 publications were found. If it was not clear from the abstract whether the paper might contain relevant data, the full paper was assessed. Thirty-four papers were included in the final analysis (Table 1). The literature search and flow-chart of studies selection is depicted in Figure 1. Fourteen studies addressed no prior biopsy, 10 addressed prior negative biopsy and 10 addressed prior positive biopsy (active surveillance).

Table 1 shows the main characteristics of the included studies. Data regarding detection rate and relative sensitivities are depicted in Figure 2 and Figure 3, and supplementary Table 1, with data regarding PCa in patients with negative mpMRI depicted in Figure 4.

To compare the sensitivity of an MR-targeted approach to a standard approach we calculated the relative sensitivity of MRI targeted biopsy to standard biopsy. The relative sensitivity of MRI-TBx is the result of the ratio between individual sensitivity of MRI-TBx and individual sensitivity of TRUS-Bx. The individual sensitivity, is the number of cancers detected by a technique divided by the number of cancers detected by the combination of both techniques. A value of one would show equal sensitivity, a value of > 1 would show greater sensitivity for an MRI-targeted approach and a value of <1 shows lower sensitivity of MRI-targeted biopsies compared to standard biopsies. For clinically significant prostate cancer a higher relative sensitivity is desirable and for clinically insignificant prostate cancer a low relative sensitivity is desirable. Definition of csPCa reflected the definitions used in each included study, reported in Table 1. Due to the lack of definitions for clinically significant disease and disease progression in the studies included in the prior positive biopsy group, detection rates and sensitivities referred to Gleason score ≥ 3+4 and GS = 3+3.

3.1. How does MRI-targeted biopsy compare to standard biopsy in each patient population?

Biopsy naïve men (figure 2a)

Fourteen studies were included in this group. Use of the combined strategy resulted in the highest detection rate of clinically significant disease at 48% (CI: 42-58), vs 43% (CI: 38-49) and 37% (CI: 31-44) for MRI-TBx and TRUS-Bx alone, respectively. No statistically significant differences were found comparing the combined approach to

targeted approach alone (p = 0.21).

In terms of the diagnosis of clinically insignificant disease, MRI-TBx detected less than standard biopsy with 9% (CI: 7-12) men detected with MRI-TBx, 15% (CI: 10-20) with standard biopsy alone and 17% (CI: 12-22) with a combined approach. The combined approach was statistically significantly superior in detecting insignificant PCa compared to MRI-TBx alone (p < 0.01).

Prior negative biopsy (Figure 2b)

Ten studies were included in this group. MRI-targeted biopsy alone resulted in csPCa detection in 23% (CI: 18-28) of men, with standard biopsy detecting 17% (CI: 11-26) and the combined approach 29% (CI: 22-36). No significant differences were found comparing the combined approach to the targeted approach alone (p = 0.14).

For clinically insignificant prostate cancer MRI-targeted biopsy detected 8% (CI: 5-10), compared to 15% (CI: 9-22) for standard biopsy and 17% (CI: 13-25) for the combined approach. The combined approach was significantly statistically superior to MRI-TBx alone (p <0.01).

Prior positive biopsy (active surveillance) (Figure 2c)

Ten studies were included for this group. MRI-targeted biopsy alone resulted in the detection of Gleason 3+4 cancer in 29% (CI: 13-43), vs 24% (CI: 14-37) for standard biopsy alone and 37% (CI: 24-49) for a combined approach. No significant differences were found comparing the combined approach to the targeted approach alone (p = 0.26).

Detection of Gleason 3+3 in the group of men already diagnosed with low risk

disease was 20% (CI: 13-25) for MRI-targeted biopsy alone vs 33% (CI: 25-44) for standard biopsy and 37% (CI: 28-50) for the combined approach. The combined approach was significantly statistically superior in detecting Gleason 3+3 compared to a targeted strategy alone (p = 0.04).

3.2. What is the relative sensitivity of MRI-targeted biopsy across different populations?

Biopsy naïve

MRI-TBx performed better than TRUS-Bx in detecting csPCa in twelve out of fourteen studies of biopsy naïve men (Figure 3a), with a median relative sensitivity of 1.15 (CI: 1.07-1.31) and median individual sensitivity of 0.88 (CI: 0.85-0.92) and 0.76 (CI: 0.71-0.80), respectively. MRI-TBx and TRUS-Bx missed csPCa in 12% and 24% of the cases, respectively.

Prior negative biopsy

MRI-TBx was superior to TRUS-Bx in the detection of clinically significant disease in 7 out of 9 studies with an overall median relative sensitivity of 1.45 (CI: 1.08-1.69). Median individual sensitivity for MRI-TBx and TRUS-Bx was 0.84 (CI: 0.70-0.88) and 0.61 (CI: 0.52-0.73), respectively. In other words, MRI-TBx and TRUS-Bx would have missed 16% and 39% of csPCa cases respectively.

Prior positive biopsy (active surveillance)

In the detection of GS ≥ 3+4 PCa, MRI-TBx was superior to TRUS-Bx in 6 out of 9 studies with an overall median relative sensitivity of 1.25; CI: 1.02-1.75). Median individual sensitivity for MRI-TBx and TRUS-Bx was 0.85 (CI: 0.59-0.96) and 0.73 (CI: 0.53-0.80), respectively. In other words, MRI-TBx and TRUS-Bx would have missed 15% and 27% of the cases.

3.3. Does MRI-TBx, compared to TRUS-Bx, result in a lower insignificant PCa detection?

In all the groups analyzed (biopsy naïve, previous negative and active surveillance), MRI-TBx showed lower detection rates of insignificant PCa (Figure 3a-b-c).

In the biopsy naïve group, the median relative sensitivity of MRI-TBx for insignificant PCa was 0.67 (CI: 0.46-0.86). Median individual sensitivity for MRI-TBx and TRUS-Bx were 0.59 (CI: 0.37-0.76) and 0.86 (CI: 0.77-0.99), respectively. MRI-TBx would have detected 33% less insignificant PCa compared to TRUS-Bx alone.

In prior negative biopsy group, the median relative sensitivity of MRI-TBx for PCa GS 3+3 was 0.55 (CI: 0.34-0.82). Median individual sensitivity for MRI-TBx and TRUS-Bx were 0.45 (CI: 0.30-0.59) and 0.80 (CI: 0.70-0.92), respectively. MRI-TBx would have detected 45% less GS 3+3 PCa compared to TRUS-Bx alone.

In the active surveillance group, the median relative sensitivity of MRI-TBx for GS 3+3 was 0.62 (CI: 0.39-0.67). Median individual sensitivity for MRI-TBx and TRUS-Bx were 0.52 (CI: 0.32-0.60) and 0.87 (CI: 0.82-0.94), respectively. MRI-TBx would have detected 38% less GS 3+3 PCa compared to TRUS-Bx alone.

3.4. Does negative mpMRI reliably rule out presence of PCa and csPCa?

A minority of the included studies report the detection rate of standard biopsy in men with a negative MRI. In biopsy naïve, prior negative and prior positive biopsy patients, three out of fourteen, four out of ten and three out of ten studies provided biopsy results in negative mpMRI series, respectively (Figure 4).

Detection rate of csPCa in biopsy naïve patients with negative mpMRI ranged from 13% to 20%, respectively.

In patients with at least one prior negative biopsy, with negative mpMRI, the detection rate of csPCa ranged from 0% to 13%, respectively.

In patients with prior positive biopsy (active surveillance), with negative mpMRI, the detection rate of csPCa ranged from 0% to 21%, respectively.

3.5. Discussion

3.5.1. Summary of findings

Role of positive mpMRI in biopsy naïve patients

In this review, fourteen studies investigating biopsy naïve patients were included. Overall, in all the series, the use of the combination of TRUS-Bx and MRI-TBx provided the highest detection of csPCa (48%, vs 43% and 37% for MRI-TBx and TRUS-Bx alone) (Figure 2a). Interestingly, the use of the combination of the two biopsy strategies, compared to the use of targeted strategy alone, did not significantly increase the detection of csPCa (p=0.21), but it did significantly increase the detection of insignificant disease

($p<0.01$). The direct comparison between MRI-TBx and TRUS-Bx showed higher accuracy of MRI-TBx in detecting csPCa (relative sensitivity 1.15, thus 15% better than TRUS-Bx) and greater ability to avoid a diagnosis of insignificant disease (relative sensitivity 0.67, thus TRUS-Bx was 49% better than MRI-TBx to detect insignificant disease [1/0.67]) (Figure 3a).

In this analysis, in the presence of a suspicion of PCa and a subsequent positive mpMRI, the addition of targeted samples to standard biopsies always increased the likelihood of detecting significant disease, without a significant increase in the diagnosis of insignificant PCa. The use of MRI-TBx alone would have led to a slightly lower likelihood of csPCa detection but a reduction of 41% in detection of non significant disease compared to the combined approach.

The role of mpMRI in the setting of initial biopsy has been already investigated in several studies and not all the results are concordant[16,17]. Specifically, this review focused on studies providing data regarding each single biopsy strategy, thus mostly based on series of men with a positive mpMRI. This could have affected the overall PCa prevalence and overestimated the usefulness of the targeted approach. Nonetheless, these findings are supported by the PROMIS trial[7], which has shown the effectiveness of mpMRI as a triage test using as reference test the 5-mm template transperineal prostate biopsy. In this trial, the authors demonstrated that mpMRI detection of csPCa (defined as GS $\geq$ 3+4 or core length $\geq$ 4mm) in biopsy naïve men was significantly superior compared to TRUS-Bx (51% vs. 22%). It should be remembered that this study did not use a targeted biopsy approach, as it compared the 'gold standard' of 5mm sampling versus a standard TRUS biopsy[7]. In addition, the results from PRECISION, where men

were randomised between either standard biopsy or MRI-targeted biopsy, with detection of clinically significant and insignificant cancer of 38% and 9% in the MRI-targeted arm, and 26% and 22% in the standard biopsy arm, was broadly similar to the studies of biopsy naïve men included here[15].

Role of positive mpMRI in prior negative patients

In this review, ten articles have been included for this subset. Overall, adding the MRI-TBx to TRUS-Bx allowed an increase in the detection of csPCa (Figure 2b). Specifically, the combination of the two techniques detected 29% of csPCa compared to 17% and 23% for TRUS-Bx and MRI-TBx alone respectively. It is noteworthy that the median corrected relative sensitivity of MRI-TBx was 1.45, which means that the targeted strategy detected an additional 45% csPCa compared to TRUS-Bx alone, again similar to the 38% vs 28% clinically significant cancer in the MRI-targeted and standard arms of PRECISION, where men were biopsy naive. In this analysis of prior negative biopsy men, MRI-TBx alone would have detected 55% less insignificant PCa and missed 16% of csPCa compared to the combined approach[15].

These promising findings are not surprising as, in men with a prior negative biopsy and a subsequent positive mpMRI, it is likely that the systematic approach used might have failed to accurately sample the prostate gland, and in particular could have missed tumours in the anterior prostate, midline, and extreme base and apex.

Even though in this review we assessed the ability of mpMRI in finding PCa, there is growing evidence supporting the introduction of mpMRI in the setting of repeat biopsy, both for its ability to detect or rule out csPCa. The PICTURE study reported a

sensitivity and negative predictive value for mpMRI of 94% and 69%, respectively. The authors referred to Likert score ≥ 3, using transperineal mapping biopsies as reference test[18]. A meta-analysis of 14 studies including 698 patients, reported a per-site negative predictive value ranged from 92% to 98%[19]. Furthermore, in a meta-analysis, MRI-TBx showed to detect 18% less insignificant PCa compared to the standard of care in patients with previous negative biopsy [16].

Role of positive mpMRI in prior positive patients (active surveillance)

Ten studies were included in this review. All patients had been previously diagnosed with low risk PCa according to different criteria.

Similar to the other populations, the addition of MRI-TBx to the standard of care, allowed to detect a higher number of GS ≥ 3+4 compared to the standard of care alone (37% vs. 24% and 29%, for TRUS-Bx and MRI-TBx alone, respectively). Interestingly, in contrast to that seen in other populations, the increase of GS ≥ 3+4 detection in combined approach compared to MRI-TBx was not significant (p=0.14). This could be explained by the small number of the studies included and by the fact that GS ≥ 3+4 detection rates differed markedly among the different studies. In addition, men may have been offered radical treatment rather than active surveillance if they had other risk factors such as a high PSA or a high PSA density, which would have reduced the pool of missed disease in those formally on active surveillance. Schoots et al. reported a rate of reclassification of 47% in patients with positive mpMRI submitted to MRI-TBx, whilst on active surveillance[20].

When we directly compared MRI-TBx to TRUS-Bx the former detected 25%

more GS ≥ 3+4 (corrected median relative sensitivity 1.25) and 38% less PCa with GS 3+3. It is noteworthy that MRI-TBx alone would have missed 15% of GS ≥ 3+4 and detected 48% less insignificant disease if compared to the combination of both biopsy strategies.

The introduction of mpMRI in AS protocols is so far still controversial, and international guidelines suggest its use but with an intermediate grade of recommendations [3,14]. The UK National Institute for Health and Care Excellence (NICE) guidelines recommend the use of mpMRI at the start of active surveillance, and that it can be used either in addition to or instead of biopsy for repeat assessment during follow up[12].

In this review we observed that the addition of mpMRI and, in particular, the use of MRI-TBx, increases the detection of PCa with GS 3+4, which is considered in the most cases as disease progression which might trigger active treatment. Nonetheless, there is still a lack of standardization both in AS protocols and in the definition of disease progression; moreover, the number of studies included was small. Abdi et al, in a series of 603 patients on AS, demonstrated that the use of mpMRI combined with MRI-TBx could improve the detection of PCa progression during active surveillance [21]. Furthermore, Siddiqui et al, demonstrated that the use of a mpMRI based nomogram could decrease the number of repeat biopsies by as much as 68%[22]. In the context of the role of mpMRI within AS protocols, Schoots et al concluded that an mpMRI could detect csPCa in one third of patients at the start of AS, but data supporting the use of mpMRI within the follow up were still lacking and derive from non-standardized studies[20].

Negative mpMRI and prostate cancer

In this study we focused on the value of positive mpMRI in order to more objectively compare the systematic vs targeted biopsy approach. Nonetheless, while assessing the role of mpMRI in the diagnostic pathway of PCa, it is important to take into account the value of negative mpMRI, since up to one third of patients with a clinical suspicion of PCa may have no visible lesions at mpMRI [7,18]. Recent systematic reviews assessing the diagnostic accuracy of mpMRI found a negative predictive value (NPV) for csPCa ranging from 63% to 98% [23,24]. The clinical implication of a high NPV is the possibility to spare prostate biopsies in patients with negative mpMRI.

In our analysis, in biopsy naïve patients, the presence of csPCa in patients with negative mpMRI ranged from 13% to 20% (Figure 4) which is in line with the literature, in particuar the PROMIS trial which reported a NPV of 72% for csPCa (defined as GS ≥ 3+4)[7].

In the prior negative biopsy cohort, csPCa was found in 0% to 13% of men with a negative mpMRI (Figure 4). The PICTURE study in men with a prior negative biopsy reported a NPV for csPCa (defined as GS ≥ 3+4 and/or CCL ≥ 4mm) of 69%[18].

Patients on active surveillance with a negative mpMRI, harbored PCa with GS ≥ 3+4 in 0% to 21% of cases (Figure 4), across the studies. In a recent systematic review addressing the role of mpMRI in active surveillance patients, a reclassification rate of 17% at repeat biopsy following a negative mpMRI was seen[20]. This leads many to the conclusion that standard sampling should still be undertaken in men with a negative MRI, although others will use a combination of MRI and PSA kinetics or PSA density to reduce biopsies in men on active surveillance.

Clinical implications

These findings, have significant clinical implications, particularly in light of recent studies such as PROMIS[7] and PRECION[15], which were not included in the review as they did not fit our review criteria of comparing MRI-targeted with a combined approach using standard and targeted cores in the same man.

To summarise our finding in all men due to undergo biopsy, irrespective of previous biopsy status, MRI-TBx is of value in increasing the diagnosis of csPCa, with greatest benefit in men with prior negative biopsies. The addition of MRI-TBx did not increase the detection of insignificant PCa.

Second, in the presence of a positive mpMRI, MRI-TBx was superior to standard TRUS-Bx in csPCa detection in all men. In this review, when considering the addition of standard sampling to MRI-TBx alone, there is a statistically non-significant increase in the csPCa detection rate (39% vs 34% which means an increase range of 12-16% of all csPCa diagnosed across the studies) but a sharp increase in the detection of non significant disease (23% vs 11% which means an increase range of 41-55% of all non significant PCa diagnosed across the studies). In order to decrease the overdiagnosis of indolent disease and do this at least harm to the patient, MRI can be used.

Finally, mpMRI is characterized by a high NPV and few csPCa are missed by this approach, although this does vary across studies (range 0-21%). Those wishing to further increase the negative predictive value of a negative MRI could use PSA density, where a PSA density of ≥0.15 has been shown to identify the majority of men who have clinically significant disease in the presence of an equivocal MRI, in the diagnostic setting and in active surveillance[25,26].

Guidelines panels are still cautious in advising the introduction of mpMRI in every setting of PCa diagnosis[3,12,14]. The limitations related to the use of mpMRI in clinical practice are its limited availability, relatively high cost in some healthcare settings, and the presence of inter-observer variability amongst differently experienced radiologists. A recent analysis demonstrated that the total cost of the mpMRI strategy across the care pathway is similar to the cost of standard of care, due to a reduction in overdiagnosis and overtreatment offsetting the initial costs of MRI[27]. The advent of PI-RADS score v.2[28] is expected to significantly improve the standardization and decrease the variability in interpretation and reporting, and further confirmation of this is awaited. Rosenkrantz et al, recently reported a moderate reproducibility of PI-RADS v.2 with a percentage of agreement of 79% for PI-RADS assessment category ≥ 3[29].

3.5.2 Strength and limitations

The aim of this review was to compare targeted biopsy strategies (MRI-TBx) and standard of care (TRUS-Bx), analyzing studies of the last 5 years, where men had both approaches, and their status prior to MRI was clearly defined (biopsy naïve, prior negative or prior positive biopsy). The results were presented as comparison between descriptive corrected medians of detection rates and relative sensitivities of the individual studies included. In order to assess the value of mpMRI in the whole diagnostic pathway, we provided, where available, data regarding negative mpMRI patients.

The major strength of this report is the focus on series of men submitted to both targeted and systematic biopsies. This has resulted in a reliable comparison between the two techniques alone and the combination of both.

Furthermore, the inclusion of studies exclusively published in the last 5 years helps to provide an accurate assessment of the role of modern mpMRI in PCa diagnosis.

Nonetheless, the limitations of this review should be reported. First, the definition of csPCa varied among the studies. Consequently, the comparison between the results are affected by a bias of definition. The greatest variability in the definition of csPCa was in the prior positive biopsy group, where some centres only include men with Gleason 3 + 3 disease, and others also include men with lower volume Gleason 3+4.

Second, not all studies reported explicit adoption of the STAndards of Reporting for MRI-Targeted biopsy studies (START) recommendations[30] and of the PRECISE recommendations for reporting mpMRI in men in active surveillance[31]. Consequently, for some studies, data regarding PCa detection rate are the results of an interpretation and extraction from the text of the study itself.

Third, there was a wide heterogeneity among the included studies, regarding the mpMRI cut-off used to trigger a targeted biopsy. The reason for this diversity is the lack of evidence regarding the management of the so called "indeterminate lesions" (i.e. PI-RADS score 3 or Likert score 3). A recently published systematic review regarding this topic reported a rate of csPCa ranging from 4.4% to 11.3% among men with a PI-RADS 3 lesion detected by mpMRI[32]. Interestingly, van der Sar et al., in a series of 168 biopsy naïve men with Likert score 3/5 lesions on mpMRI were given the possibility to choose between immediate targeted biopsy and monitoring with a delayed biopsy, if indicated[33]. The majority of patients (57%; 95/168) chose monitoring. After 20 months of follow-up, only 11% (10/95) of men who chose monitoring underwent prostate biopsy due to rising PSA and/or mpMRI progression, and only 4% (4/95) were diagnosed with PCa[33]. In

order to decrease the number of biopsies and the risk of overdiagnosis, a strategy based on close surveillance using PSA monitoring and mpMRI for a rising PSA might be considered in the management of patients with indeterminate mpMRI lesions[32]. Nonetheless, with the aim to more accurately inform the patient discussion, larger studies with longer follow-up would be helpful.

Fourth, the present study relied exclusively on non-randomized series, to evaluate the utility of adding standard biopsies to MRI-TBx. There is a lack of randomized data to answer this specific question and whilst the recent PRECISION publication[15] gives a clear answer to the greater utility of MRI-TBx compared to TRUS-Bx, the utility of adding standard biopsy to MRI-TBx was not addressed.

Finally, we focused on studies providing data regarding patients submitted to both the biopsy strategies, which relies on series where the majority of men have a positive mpMRI. This might have introduced selection bias affecting the prevalence of PCa in the populations considered. For the sake of completeness we provided biopsy results in patients with negative mpMRI submitted to TRUS-Bx, where reported, in order to provide a wider description of the role of mpMRI within the diagnostic pathway. Nonetheless, results provided regarding presence of disease missed by mpMRI should be carefully considered. A very helpful paper on this subject has been published by Panebianco and colleagues, suggesting that men with a negative MRI defined as PIRADS score 1 or 2, have at least 95% freedom from clinically significant disease in the 4 years after the negative MRI[34].

The practical implications of the growing body of evidence for the use of MRI, are that we need to address the challenges of providing high quality MRI in a cost

effective manner, in order to achieve the goals of increasing the detection of clinically significant disease, reducing the overdiagnosis of clinically insignificant disease and reducing the harms of biopsy in those men who can safely avoid it. This will require a comprehensive training programme for both urologists, radiologists and support staff, as well as negotiations with those paying for diagnostic pathways in different health care settings.

4. Conclusions

This review confirms that the addition of MRI-TBx in patients with a positive mpMRI detects more csPCa in men with no prior biopsy and with at least one previous negative biopsy, compared to the use of standard biopsy alone. The role of mpMRI seems to be promising in increasing the detection rate of intermediate risk PCa in men with a previous diagnosis of low risk prostate cancer.

MRI-TBx was superior to TRUS-Bx alone in detecting csPCa in all the biopsy settings. The targeted approach alone also reduces the likelihood of a diagnosis of clinically insignificant disease, with a non-significant reduction in the detection of clinically significant disease. The presence of a negative MRI is associated with a significantly lower likelihood of prostate cancer, and, in a highly expert centre has been associated with 95% freedom from clinically significant disease at 4 years.

In summary, we recommend that the use of mpMRI is considered before biopsy in each clinical situation, to increase the detection of significant cancers. Addition of standard cores to targeted cores can be associated with an increase of clinically significant cancer detection ranging from 12% to 16% but a corresponding increase in the

detection of clinically insignificant disease from 41% to 55%. The decision to add standard cores to targeted cores should therefore be considered in the light of the results of a given centre and individual patient preference.

In the presence of a negative mpMRI there is a risk up to 20% of finding csPCa. Patients with a story of previous negative biopsy have the lowest risk. An additional way to risk stratify men with a negative biopsy is to use PSA density, offering standard biopsy to men with an equivocal MRI and a PSA density of >0.15.

These data should encourage a pathway which incorporates MRI, and addresses the challenges of ensuring that high quality MRI is available more widely.

Figure legend

Figure 1: Flow diagram showing the outcome of the initial searches resulting in the full studies included in the review.

Figure 2: Prevalence of detected PCa for individual studies included. a) Biopsy naïve b) Prior negative biopsy c) Prior positive biopsy. On the y-axis the percentage on overall number of patients included in each single study submitted to both MRI-TBx and TRUS-Bx. NA = the value could not be calculated.

Figure 3: Relative sensitivity of MRI-TBx compared to TRUS-Bx for individual studies included. a) Biopsy naïve b) Prior negative biopsy c) Prior positive biopsy. Relative sensitivity > 1 indicates that MRI-TBx detects more cancers than TRUS-Bx, conversely relative sensitivity < 1 indicates that MRI-TBx detects less cancers than TRUS-Bx.

Figure 4: Prevalence of detected PCa for men with negative mpMRI in the studies included.

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