What to expect from a non-suspicious prostate MRI? A review

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Abbreviations
mpMRI   Multiparametric Magnetic Resonance Imaging
NPV   Negative Predictive Value

Résumé

Contexte : La réalisation d'une IRM multiparamétrique (IRMmp) est désormais recommandée avant la réalisation de biopsies prostatiques. En revanche, la conduite à tenir en présence d'une IRMmp non-suspecte (Score Likert ou PIRADS 1-2) est toujours débattue.

Objectifs : Faire une synthèse de la littérature récente pour répondre à trois questions. 1) Faut-il réaliser des biopsies systématisées en présence d'une IRMmp non suspecte ? 2) Quels facteurs prédictifs permettent de définir les patients candidats à une biopsie systématisée ? 3) Le manque de visibilité de certains cancers peut-elle être expliquée et quelles en sont les conséquences cliniques ?

Sources : Une revue narrative de la littérature a été réalisée à partir des bases de données Medline utilisant deux recherches avec les termes "MRI" AND "prostate cancer" AND ("diagnosis" OR "biopsy") AND ("non-suspicious" OR "negative" OR "invisible") ; "prostate cancer MRI visible". Les références des articles sélectionnés ont été analysées à la recherche d'articles supplémentaires.

Sélection des études : Les études publiées dans les 5 dernières années en anglais ont été analysées et retenues si les données disponibles permettaient de répondre à l'une des 3 questions posées.

Résultats : Considérant les cancers de grade ISUP $\geq$ 2 cliniquement significatifs, la valeur prédictive négative (VPN) de l'IRMmp était comprise entre 76% et 99%, dépendante de la prévalence du cancer et du type de test de référence utilisé. La VPN était plus élevée chez les patients aux antécédents de biopsie négative (88-96%), et plus faible chez les patients en surveillance active (85-90%). La densité de PSA (PSAd) avec un seuil de PSAd<0.15ng/ml/ml était le facteur prédictif le plus étudié et le plus pertinent associé à l'IRMmp pour éliminer un cancer significatif. Enfin, les tumeurs non visibles à l'IRMmp présentaient des différences au niveau histopathologique et génétique, conférant un intérêt clinique à la visibilité IRM.

Limites du travail : La plupart des données proviennent de centres experts et les résultats peuvent ne pas être reproductibles en dehors.

Conclusion : L'IRMmp fait preuve de performances diagnostiques élevées pour éliminer un cancer cliniquement significatif. La densité de PSA peut être utilisée pour sélectionner patients devant avoir une biopsie. Une meilleure connaissance des mécanismes à l'origine de la visibilité du cancer devrait aider le développement de nomogrammes et biomarqueurs plus précis.

Abstract

Background: Many guidelines now recommend multiparametric MRI (mpMRI) prior to an initial or repeat prostate biopsy. However, clinical decision making for men with a non-suspicious mpMRI (Likert or PIRADS score 1-2) varies.

Objectives: To review the most recent literature to answer three questions. 1) Should we consider systematic biopsy if mpMRI is not suspicious? 2) Are there additional predictive

factors that can help decide which patient should have a biopsy? 3) Can the low visibility of some cancers be explained and what are the implications?

Sources: A narrative review was performed in Medline databases using two searches with the terms "MRI" AND "prostate cancer" AND ("diagnosis" OR "biopsy") AND ("non-suspicious" OR "negative" OR "invisible"); "prostate cancer MRI visible". References of the selected articles were screened for additional articles.

Study selection: Studies published in the last 5 years in English language were assessed for eligibility and selected if data was available to answer one of the three study questions.

Results: Considering clinically significant cancer as ISUP grade $\geq$ 2, the negative predictive value (NPV) of mpMRI in various settings and populations ranges from 76% to 99%, depending on cancer prevalence and the type of confirmatory reference test used. NPV is higher among patients with prior negative biopsy (88-96%), and lower for active surveillance patients (85-90%). The PSA density (PSAd) with a threshold of PSAd<0.15ng/ml/ml was the most studied and relevant predictive factor used in combination with mpMRI to rule out clinically significant cancer. Finally, mpMRI-invisible tumours appear to differ from a histopathological and genetic point of view, conferring clinical advantage to invisibility.

Limitations: Most published data come from expert centres and results may not be reproducible in all settings.

Conclusion: mpMRI has high diagnostic accuracy and in cases of negative mpMRI, PSA density can be used to determine which patient should have a biopsy. Growing knowledge of the mechanisms and genetics underlying MRI visibility will help develop more accurate risk calculators and biomarkers.

Introduction

Prostate cancer diagnosis has considerably evolved in the past decade thanks to the progress of multiparametric magnetic resonance imaging (mpMRI) and the development of MRI-targeted prostate biopsies. In the presence of level 1 evidence, there is now consensus toward using mpMRI before the initial or repeat biopsy [1].

However, there is still disagreement on the attitude toward non-suspicious mpMRI (PI-RADS or Likert score 1-2). Therefore, systematic biopsies are still often used, driving a potential for overdetection of insignificant cancers [1]. Some centres have already chosen to biopsy only in case of mpMRI-visible lesion, but this attitude is not supported by all recommendations [2].

A systematic review and meta-analysis from the European Association of Urology Prostate Cancer Guidelines Panel including studies published between 2005 and 2015 estimated a combined negative predictive value between 67% and 88%, depending on the overall prostate cancer prevalence [3]. A very recent review considering various definitions of non-suspicious mpMRI and clinically significant cancer provided an estimated NPV of 90.8% of a PIRADS/Likert 1-2 MRI for ISUP grade ≥ 2 disease in biopsy-naïve patients [4].

Should we offer biopsy to patients with a non-suspicious mpMRI? What additional factors might help in deciding which patients should still have a biopsy? Can the non-visibility of the cancer be explained and what are the implications? We conducted a review of the most recent literature to help provide answers to these questions.

Materials and methods

Search strategy

We conducted a narrative review of the literature based on a non-structured search strategy in Medline databases, going back to 2015. The initial search terms were ("Magnetic Resonance Imaging" OR "MRI") AND "prostate cancer" AND ("diagnosis" OR "biopsy") AND ("non-suspicious" OR "negative" OR "invisible"). For the section on mpMRI invisible cancer, a second search including the terms "prostate cancer MRI visible" was performed. All English titles and abstracts were reviewed and included if providing sufficient available data to

answer the study questions. References of the selected articles were screened for additional articles.

Definition of clinically significant cancer

Unless stated otherwise, clinically significant cancer was defined as ISUP ≥ 2.

Results

Should we continue to offer biopsy to patients with a non-suspicious mpMRI?

To answer to this question, we will look at the negative predictive value of mpMRI, taking into account that it will vary depending on the population considered (biopsy-naïve versus previous negative biopsy, prostate cancer prevalence), the definition of clinically significant cancer used, and the type of confirmatory exam (density of biopsy sampling) performed.

Transperineal template biopsy as reference test: NPV 76-92%

Transperineal biopsy has been used as a confirmatory reference test to evaluate the performance of mpMRI to diagnose clinically significant prostate cancer. Details are provided in **Table 1**.

Biopsy-naïve patients

Two prospective multicentre studies provide us with a high level of evidence in this population. In the PROMIS study, 576 biopsy-naïve patients had a systematic pre-biopsy mpMRI. Multiparametric MRI findings were compared to a 5-millimetre transperineal template biopsy mapping (reference test), and a 12-core transrectal systematic biopsy. Using such an extensive and thorough confirmatory measure, the negative predictive value of a non-suspicious mpMRI (Likert 1-2; n=158) was 76% (95% CI: 69-82) to rule out any cancer with ISUP grade ≥ 2 [5]. Reassuringly, a recent post-hoc analysis of the PROMIS data showed that cancers overlooked by MRI were of lower grade and volume [6].

Hansen and colleagues recruited 807 consecutive biopsy-naïve patients in a multicentre prospective outcome study. Among them, 236 had no suspicious lesion on multiparametric mpMRI. Comparison with systematic sampling according to the Ginsburg protocol (median: 22 cores) demonstrated an NPV of 80% for mpMRI [7].

Another retrospective study, looking at 288 patients, including 131 with non-suspicious mpMRIs biopsied by a transperineal approach, reported an NPV of 84%, where clinically significant cancer included any grade with a maximum cancer core length of $\geq$ 4 mm. These results have to be interpreted in light of a lower number of cores taken (14 cores) [8]. Similarly, the NPV of 85% demonstrated by Otti and colleagues accounts for the fact that transperineal biopsies (10 cores) were taken to sample anterior regions only, otherwise, transrectal sextant biopsies were performed [9].

Thompson and colleagues included 364 patients in a prospective cohort study including 79 men with a non-suspicious mpMRI, demonstrating an NPV of 92% for ISUP grade $\geq$ 2 disease with transperineal template mapping (median 30 cores) as reference test. Of note, double reporting of all mpMRIs was done by two expert radiologists (> 1000 prostate mpMRIs each) [10].

Biopsy-naïve men and those who have had a previous negative TRUS biopsy

Distler and colleagues retrospectively analysed the performance of mpMRI in a mixed population (42% previous negative biopsy) using transperineal template biopsy mapping with a median of 27 cores as reference test. Based on the analysis of 1040 patients including 344 with non-suspicious mpMRIs (PIRADS 1-2), the NPV was 79% [11].

Repeat biopsy (including prior positive biopsies)

In a population with a high prevalence of prostate cancer, Simmons and colleagues reported an NPV of 91.4% of a non-suspicious mpMRI in ruling out clinically significant disease (ISUP grade $\geq$ 2) using transperineal template biopsy mapping as a reference test (median 49 cores) in the PICTURE trial [12].

Transrectal systematic biopsy as reference test: NPV 82-99%

Looking at studies using a less extensive reference test numbers logically provides higher NPVs as non-visible cancer is less likely to be found where the sampling density is lower. Detailed results are presented in **Table 2** (biopsy-naïve and prior negative biopsy) and **Table 3** (prior positive biopsy).

Biopsy-naïve patients

In the French MRI-FIRST trial, 45 of the 275 men enrolled had no suspicious lesion on mpMRI (PIRADSv2 or Likert 1-2) and transrectal systematic biopsy led to the diagnosis of clinically significant prostate cancer (ISUP grade $\geq$ 2) in 5 (11%) [13]. Among the 643 patients recruited in the 4M study, 309 received systematic biopsies (12 cores) following a non-suspicious mpMRI. The NPV of mpMRI, taking into account one significant cancer diagnosed at 1-year follow-up, was 96% [14].

In another recent cohort of 833 biopsy-naïve men undergoing upfront mpMRI, systematic sampling was performed for 140 patients with a Likert 1-2 score using a transrectal (12 cores - 65%) or transperineal (24 cores – 35%) approach. The NPV of a non-suspicious mpMRI was 92.8%. Of note, 344 patients with a non-suspicious mpMRI did not undergo biopsy [15].

Very similar results were obtained by Falagario and colleagues based on a retrospective cohort of 266 men among whom 117 had non-suspicious mpMRIs (PIRADS 1-2). A clinically significant cancer was detected in 9 patients (NPV 92%) [16]. Similarly, an NPV of 92% was calculated by Zhang and colleagues looking at 273 non-suspicious mpMRIs in patients undergoing 24-core systematic biopsy [17].

Prior negative biopsy

Higher NPVs are achieved in this category of patients, presumably because they are at lower risk of prostate cancer, especially in the most recent studies where patients likely had an MRI before their initial biopsy.

Boesen and colleagues focused their retrospective analysis on the 3-year follow-up of 194 patients with a history of negative biopsy. Patients were included if the mpMRI performed at the beginning of the study was non-suspicious. In this population (prior negative biopsy + non-suspicious mpMRI), the NPV was 95% [18]. Kotb and colleagues in another study including 81 non-suspicious mpMRIs found an NPV of 87.6% calculated [19].

Lo and colleagues retrospectively reviewed the mpMRIs of 138 patients including 73 that were non-suspicious. Even with long-term follow-up (median 6.7 years), the NPV remained at 96% [20]. Subgroups of patients with previous history of negative biopsy in studies reporting the results of mixed populations showed respective NPVs of 83.3%, 92%, 97%, 100% and 100% [21–25].

Mixed populations

The results of studies including biopsy-naïve, prior negative biopsy and prior positive biopsy/active surveillance patients are difficult to interpret. Nonetheless, these studies provide us with pooled NPVs reflecting daily practice. Of note, all data shown here are retrospective.

Two recent retrospective studies including 222 and 391 cancer-naïve patients with non-suspicious mpMRIs reported NPVs of 96% and 89.8%, respectively [21,26] . Interestingly, in the second study by De Visschere and colleagues, only 47% of mpMRIs were still classified as non-suspicious in retrospect, in light of clinical data revealing a diagnosis of prostate cancer at 2-year follow-up in 124/391 (32%) patients [26]. With 4-year follow-up, Panebianco and colleagues from a large series comprising 1255 non-suspicious MRIs provided an NPV of 96% among patients with a previous history of prostate biopsy and 91% in biopsy-naïve patients [27].

Adding patients with prior positive biopsy, the retrospective evaluation of a mixed cohort including 27/135 patients with prior positive biopsy performed by Oishi and colleagues provided an NPV of 82% [22]. Wang and colleagues similarly assessed a mixed cohort of 464 patients including 84 negative mpMRIs whose NPV was 87% [23].

Conversely, three retrospective studies reported NPVs ranging from 96.5% to 99% [24,25,28]. However, although all three studies included a significant number of men with non-suspicious mpMRIs (114, 100 and 201, respectively), the NPVs described were likely

driven by the majority of patients with previous negative biopsies and the very low rate of significant cancers diagnosed among them.

Active surveillance

In patients on active surveillance for ISUP 1 prostate cancer, the NPV of mpMRI to rule out clinically significant prostate cancer is lower, presumably because this is a population with a higher prevalence of prostate cancer.

The ASIST trial randomised patients between confirmatory biopsy versus mpMRI plus confirmatory biopsy. Among the 137 men in the mpMRI arm, 45 had a non-suspicious mpMRI and the NPV was 85% [29]. The same estimate was obtained by Chesnut and colleagues in a retrospective evaluation including 207 men with a 3-year follow-up. Multiparametric MRI at 3 years was non-suspicious in 72 men, and a clinically significant cancer was detected in 11 (15%) [30].

In a recent retrospective study including 111 patients on active surveillance, 48 had a non-suspicious mpMRI and a significant cancer was detected by systematic transrectal biopsy in 5 (10%) [31].

What predictive factors can we use to help decide which patients with a non-suspicious mpMRI should have a biopsy?

Patients with non-suspicious mpMRIs may avoid prostate biopsy, but 5-20% of clinically significant prostate cancer may be missed [1,5]. The NPV of a non-suspicious mpMRI is dependent on the prevalence of the disease, therefore the performance of MRI can be deceiving in a very high-risk population and risk-stratification appears critical before omitting biopsy [3]. The prevalence of significant cancer will vary by patient group (biopsy naïve> active surveillance or previous negative biopsy), but also will vary within the health care context eg. whether PSA testing is commonly done at a population level or not.

The NPV will also vary with the threshold set for clinical significance, with a higher NPV as the threshold is raised. Some groups use ISUP grade alone to set a significance threshold, whilst others will also incorporate a proxy for tumour volume, such as maximum cancer core length.

The optimal approach to identify patients with non-suspicious mpMRI but a higher risk of significant prostate cancer is not yet well established. In an editorial on PRECISION, Nzenza and colleagues proposed that in case of non-suspicious mpMRI, "systematic biopsy still has a role in patients with red flags based on factors such as family history, PSA density, PSA velocity, BRCA mutation, and abnormal digital rectal exam" [32]. Combining mpMRI score with additional predictive factors may increase the negative predictive value (NPV) of mpMRI and reduce the number of prostate biopsies for men whose risk of significant cancer is low, as well as detecting cancers in men with equivocal or non-suspicious MRIs. Few studies reported predictive factors of clinically significant cancer in patients with non-suspicious mpMRIs.

Clinical factors and PSA density

Factors like family history, abnormal digital rectal exam or ethnicity have been studied and failed to prove significant predictive factor of clinically significant cancer in non-suspicious mpMRI populations [22,24,27,33]. Studies looking at age, PSA and prostate volume showed conflicting results [22–24,27,33]. It is acknowledged that the prostate changes with age. Young men often have 'bright young prostates' which can harbour low volume ISUP 2 disease, which is less readily seen than in older men with greater differentiation between the transition and peripheral zones. Age, total PSA and prostate volume alone were found to be significant predictive factor of clinically significant prostate cancer in only one study [27], 2 studies [23,27] and 2 studies [22,33] respectively.

Previous negative biopsy status was reported as a significant predictive factor of clinically significant cancer in 2 studies [22,27]. Oishi and colleagues reported an OR = 5.2(1.6-16.5), p = 0.005 when no previous negative biopsy has been done [22].

Conversely, PSA density (PSAd) <0.15ng/ml/ml was found to be a significant predictive factor in 8 studies [7–9,11,19,22,34,35]. The NPV of the combination of mpMRI and PSAd <0.15ng/ml/ml ranged from 84% to 100% in these studies. Panebianco and colleagues found that PSAd >0.15ng/ml/ml had a hazard ratio >7 for the diagnosis of clinically significant disease in patients with a non-suspicious mpMRI [27].

A recent meta-analysis by Pagniez and colleagues showed that PSAd was the most studied and relevant predictive factor of clinically significant cancer. Indeed, when associated

with a PSAd <0.15ng/ml/ml, the NPV of mpMRI in cancer-naïve, biopsy-naïve and previous negative biopsy groups increased from 83.7%, 82.7%, 88.2% to 90.4%, 88.7% and 94.1%, respectively [36].

Biomarkers and risk calculators

Biomarkers such as PCA3, PHI, 4K score or risk calculators have been studied as potential prognostic factors. Perlis and colleagues presented results based on 128 non-suspicious mpMRIs. No patient with a non-suspicious mpMRI and a normal PCA3 score had significant cancer on biopsy (NPV=100% (p <0.0001)) [37]. Gnanapragasam and colleagues reported the results of a PHI test combined with a non-suspicious mpMRI in 94 patients. In patients with a PHI score ≥35, the NPV for significant disease was 97% (84–100%) whereas the NPV of mpMRI alone was 75.5% [38]. Falagario and colleagues presented results of the 4K score combined with non-suspicious mpMRI in 117 patients. NPV was 96.9% and 97.1% for patients with low or intermediate 4Kscore risk [16]. These biomarkers seem interesting when combined with mpMRI to increase the NPV, but further validation studies are needed before they can be established in clinical practice.

Risk calculators also appear of interest to determine the individual risk of each patient. On multivariate analysis, the Prostate Cancer Prevention Trial Risk Calculator (PCPT-RC) was a significant predictive factor of clinically significant cancer in the study conducted by Wang and colleagues (OR 1.01, p <0.01) [23]. A new tool from the European Randomized Study of Screening for Prostate Cancer risk calculator (ERSPC-RC) comprising mpMRI results has been published recently and may help selecting patients for biopsy. Falagario and colleagues presented the results of ERSPC-RC in 117 patients. Negative predictive value was 98.7% for ERSPC-RC <2% [16].

How does mpMRI-invisible prostate cancer differ from mpMRI-visible cancer (and is this clinically useful)?

Perhaps the most intriguing question about prostate cancer undetected by mpMRI is – how does this differ from disease that we detect? Early evidence suggests that mpMRI-

invisible cancer differs from its visible counterpart in almost every way, from the molecular-level through to the population-level. Furthermore, these differences may account for the mechanisms that underpin mpMRI-visibility and potentially the clinical utility afforded by mpMRI-invisibility.

Firstly, and reassuringly, tumour visibility on mpMRI is positively associated with cancer grade, volume and stage. In other words, the larger and more aggressive the cancer, the greater the probability of detection [5,27,39–41]. This characteristic of prostate mpMRI is fundamental and is likely the reason for incorporation of mpMRI into national guidelines [2]. In a post hoc analysis of PROMIS, mpMRI-invisible cancers had significantly lower overall and maximum Gleason scores ($p = 0.0007$ and $p < 0.0001$, respectively) and shorter maximum cancer core lengths (median difference: 3mm [5 vs. 8], $p < 0.0001$; 95% CI 1–3) compared to mpMRI-visible cancers [6]. Indeed, this makes radiobiological sense; smaller tumours are likely to fall below the threshold of spatial resolution of mpMRI (and therefore, will be invisible) and lower grade peripheral zone tumours are likely to have sparse tissue density (and therefore, less restricted diffusion on mpMRI).

Secondly, there are additional histopathological features (beyond tumour grade and size) that account for mpMRI conspicuity [42]. Miyai and colleagues recently compared mpMRI-visible and mpMRI-invisible tumours on whole-mount radical prostatectomy; they found that visible tumours had higher architectural density with increased proportions of cancer cells (60.9% vs. 42.7%, $p < 0.0001$), decreased stromal proportions (33.8% vs. 45.1%, $p = 0.00089$) and decreased luminal proportions (5.2% vs. 12.2%, $p < 0.0001$) [39]. These results confirm previous findings demonstrating that restricted diffusion was more strongly linked to the distribution of epithelial, luminal and stromal components than to glandular differentiation [43,44]. Again, association of increased tissue density and tumour visibility has biological plausibility – diffusion of water on mpMRI would be further restricted in tissue with higher density, thus increasing tumor conspicuity on diffusion. In a similar study, Borren and colleagues found that mpMRI-visible tumours had higher cellular and microvessel density compared to mpMRI-invisible tumours (cell density: 3560 cells/mm2 vs. 2910 cells/mm2; microvessel density: 115 vessels/mm2 vs. 90 vessels/mm2) [40]. In this case, tumour visibility is explained by higher microvessel density, which would generate higher dynamic contrast

enhanced signal through higher tissue concentrations of gadolinium within microvessels. Interestingly, there are two (potentially aggressive) prostate cancer sub-types that have reduced detection on mpMRI, namely ductal and cribriform [45,46]. However, this claim is contested; Tonttila and colleagues recently examined a cohort of men undergoing radical prostatectomy and found that preoperative mpMRI identified 90.5% (86/95) of tumours containing any cribriform or ductal pattern (95% CI 82.5–95.6), and so clearly this area warrants future research [47].

Thirdly, there has been significant recent interest in uncovering the genetics that underpin different mpMRI phenotypes [48]. Purysko and colleagues correlated the Decipher Genomic Classifier with mpMRI appearances for men undergoing radical prostatectomy and found significantly higher Decipher scores in mpMRI-visible tumours (mean difference 0.22, 95% CI 0.13–0.32; p < 0.001). This suggests enrichment of high-risk cancer genes (for early metastasis) in mpMRI-visible disease; however, the authors, crucially, did not control for tumour grade and size [49]. In contrast, Houlahan and colleagues specified inclusion of only 'clinically significant cancer' (in their case, above Gleason grade 3+4 and 1.5 cm diameter) and through genomic and transcriptomic profiling showed again, that even in a matched cohort comparison, mpMRI-visible tumours were enriched with aggressive molecular and microenvironmental features, which they described as "nimbosus" (gathering of stormy clouds, Latin) [41,50]. However, not all of the extant genomic evidence has confirmed lack of aggressive molecular features in invisible disease. For example, Parry and colleagues compared mpMRI-visible and mpMRI-invisible tumours (obtained at radical prostatectomy) using low-pass whole genome sequencing, methylation arrays and RNAseq. Somewhat concerningly, they found that three of six cores obtained from mpMRI-invisible tumours harboured genetic alterations observed in metastatic castration-resistant prostate cancer, however, this finding was heavily limited by the associated biases of radical prostatectomy and their small sample size (n = 6) [51].

Lastly, and possibly most importantly, tumour visibility (and invisibility) on mpMRI appears to confer clinical utility. PROMIS demonstrated this, in that the most significant cancers (i.e. aggressive disease, that we wish to detect and treat) were visible, and the least significant cancers (i.e. indolent disease, that we do not wish to detect and treat) were

invisible [5,6]. This was then validated in the randomised PRECISION trial, in which men who were assigned to the mpMRI-directed arm had favourable diagnostic pathological outcomes [1]. In a longitudinal trial, Panebianco and colleagues grouped men with baseline negative mpMRI according to their biopsy status; firstly, biopsy-naïve men, and secondly, men with prior negative biopsy. They showed that 95% of biopsy-naïve men, and 96% of men with previous negative biopsy, remained free of clinically significant prostate cancer after four years of follow-up; showing the important utility held by negative mpMRI [27] . Finally, it is worth noting that we may soon be in a position in which our threshold for 'significant cancer' (liable to cause cancer-specific death) actually aligns with mpMRI visibility phenotypes. In a large cohort study of MRI-based active surveillance, Stavrinides and colleagues showed that the outcomes of non-visible Gleason grade 2 (3+4) cancers were similar to Gleason grade 1 (3+3) lesions, whilst visible Gleason 3 + 4 cancers were more likely to progress. [52].

In the 29-year follow-up of the SPCG-4 trial, Bill-Axelson and colleagues found that in men treated with radical prostatectomy, Gleason score 3 + 4 disease was not associated with prostate-cancer-related death; however, they found that Gleason score 4 + 3 disease (or worse) was in fact associated with a prostate-cancer-related death (adjusted relative risk 5.73; 95% CI 1.59–20.67). This potentially suggests a new threshold for clinically significant disease, which remarkably aligns with conspicuity of prostate cancer on mpMRI, given that in PROMIS, no men with overall Gleason score 4+3 had mpMRI-invisible disease [53]. Therefore, peripheral evidence suggests that there is utility in invisibility, however, this does need further validation with bespoke MRI-correlated longitudinal studies.

Discussion

Upfront mpMRI has been included in clinical practice by many institutions, often in anticipation with the latest guidelines, and is now supported by the results of high-quality international studies.

The negative predictive value of non-suspicious mpMRI has proven to be excellent (90-95% in biopsy-naïve patients), and it is fascinating to see the initial results obtained by small retrospective studies confirmed in large, multicentre cohorts and randomised control trials [14,27,54]. Those who still doubt the ability of MRI to rule out clinically significant prostate cancer and put a higher confidence in systematic transrectal biopsy must remember that this

biopsy scheme has been proven inferior to MRI in a randomised clinical trial [1]. However, as often in clinical practice, uncertainty remains, and the answer to the question -should we biopsy in the presence of a non-suspicious mpMRI?- depends on how well we are dealing with this uncertainty. And how confident we are in explaining this uncertainty to our patients and not turn it into anxiety.

We are in an opening era of personalised medicine, and the field of prostate cancer diagnosis makes no exception. No test is perfect, particularly when applied in very "extreme" conditions, i.e. in populations with a very high prevalence of the disease considered. The accuracy of MRI is such that many clinical factors, biomarkers and risk calculators have failed to demonstrate a significant added value, especially when assessed in a population with a low prostate cancer prevalence. The PSA density with a threshold at PSAd<0.15ng/ml/ml was able to increase the performances of mpMRI in biopsy-naïve patients and patients with previous negative prostate biopsies. Known biomarkers (PCA3, PHI, 4Kscore) and risk calculators (PCPT-RC, ERSPC-RC) still have to be validated prospectively in multicentric larger cohorts before considering their inclusion in clinical practice. New blood or urine biomarkers are crucially needed to better define each patient's individualised risk and document the decision to avoid -or proceed with- biopsy. When deciding to proceed with biopsy, in these patients deemed at higher risk of prostate cancer despite a non-suspicious mpMRI, an adjustment of the biopsy strategy should be considered. Indeed, this review also outlines the superior diagnostic yield of a transperineal mapping biopsy approach compared to systematic transrectal biopsy, suggesting that it may be useful in these patients to increase sampling density.

The progress made in understanding the biology and genetics behind mpMRI visibility is still in its early phase, and future data obtained from MRI-correlated longitudinal studies will prove critical in determining the potential impact of this knowledge and translating the findings into clinical practice.

There are limitations of our review. The majority of included studies were conducted after mpMRI was already introduced in daily practice with many men already avoiding biopsy. It is therefore very likely that all retrospective studies reporting results of biopsies performed in patients with non-suspicious mpMRIs suffer of a degree of selection bias as these patients had already been judged at higher risk to warrant biopsy rather than surveillance. Furthermore, evidence cited here has frequently been produced by highly-trained, expert centres, which potentially limits generalisability to smaller centres. However, we believe that

every centre can become expert with a strong collaboration between urologists, radiologists, pathologists, and the possibility for those who report mpMRIs to obtain feedback and discuss cases with those who do the biopsies.

Conclusion

Non-suspicious mpMRI has a high negative predictive value in ruling out significant cancer, especially in patients with previous negative biopsies. Recent studies support that mpMRI-invisible tumours differ from a histopathological and genetic point of view and we are getting closer to understanding the mechanisms of mpMRI visibility. Biopsy-naïve men with increased PSA density over 0.15 should be offered biopsy as they are at higher risk of harbouring mpMRI-invisible lesions. Further work is needed to validate the best sampling approach and strategy in this situation.

Conflict of interest None

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