Original Article

Early experience in avoiding biopsies for biopsy-naïve men with clinical suspicion of prostate cancer but non-suspicious biparametric magnetic resonance imaging results and prostate-specific antigen density < 0.15 ng/mL^2: A 2-year follow-up study

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Abstract

Background: Only limited data have been published on the diagnostic accuracy of combining biparametric (bp) magnetic resonance imaging (MRI) and prostate-specific antigen density (PSAd) to rule out biopsies.

Purpose: The purpose is to assess the 2-year risk of being diagnosed with sPCa following the strategy of avoiding immediate biopsies in men with non-suspicious bp MRIs and a PSAd <0.15 ng/mL^2.

Material and Methods: Two hundred biopsy-naïve men with clinical suspicion of PCa underwent a pre-biopsy bp MRI from March to July 2019. Of these, 109 men had a Prostate Imaging Reporting and Data System (PI-RADS) score of 1–3 including 77 men with calculated PSAd <0.15 ng/mL^2. As a result, no biopsies were performed in these 77 men, who were clinically followed up for at least 2 years and re-examined in case of rising suspicion of sPCa. The remaining 32 men with a calculated PSAd ≥0.15 ng/mL^2 underwent systematic biopsies and targeted biopsies of any PI-RADS 3 lesion.

Results: One of the 77 men (1.3%) had an sPCa diagnosed within 2 years of follow-up. All men were referred back to their general practitioner within 1 year and 9% (7/77) were re-referred to the urology department during follow-up. Among these men, 43% (3/7) continued to have PSA levels that were above their individual thresholds at confirmatory testing and underwent secondary MRI scans.

Conclusions: No biopsies for men with bpMRI results exhibiting maximum PI-RADS 3 and with a PSAd <0.15 ng/mL^2 resulted in a 2-year risk of being diagnosed with sPCa of 1.3%.

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Introduction

Previously, all men with clinical suspicion of prostate cancer (PCa) underwent twelve systematic transrectal ultrasound-guided prostate biopsies (TRUS-bx). This approach led to men without PCa undergoing unnecessary biopsies and to many men being diagnosed and treated for clinically insignificant PCa.[1] Furthermore, prostate biopsies are uncomfortable, invasive and can lead to complications such as serious infections and rectal bleeding.[2–4] Transrectal ultrasound is a very effective tool for identifying the prostate and its anatomical structures but it cannot accurately distinguish between normal tissue and cancerous lesions.[5] The development of multiparametric (mp) magnetic resonance imaging (MRI) has led to improved risk assessments and mpMRI can be used to determine the likelihood of cancer and show its location within the prostate.[6–10]. mpMRI may be used to guide a biopsy needle and improve the detection of significant (s) PCa, compared with TRUS-bx alone.[6–10] In addition, a normal mpMRI scan result may be used to rule out significant disease, avoiding the need for biopsies. Consequently, mpMRI combined with TRUS-bx can decrease both the number of unnecessary biopsies, with their inherent complications, and the detection rate of insignificant PCa. Therefore, clinical guidelines now recommend pre-biopsy mpMRI.[11,12] However, because mpMRI utilizes three-plane T2-weighted, diffusion-weighted and dynamic contrast-enhanced sequences and uses contrast media, it is time consuming and costly.[11,12] Recent studies have shown that an abbreviated biparametric (bp) MRI procedure may be more cost effective than mpMRI because the former is

faster and requires fewer scan sequences and no contrast media but exhibits similar sPCa detection rates.[9,13–20] Furthermore, risk stratification can be further improved if bpMRI scores are combined with other biomarkers such as prostate-specific antigen density (PSAd).[21,22] Because prostate-specific antigen (PSA) is produced by both PCa cells and normal and benign hyperplastic prostatic epithelia, PSA levels are greatly influenced by the volume of benign prostatic hyperplasia. One method for improving the cancer-specific resolution of PSA measurements is to combine PSA levels with the volume of the prostate to generate a ratio called the PSA density (PSAd).[23] Only a few studies have reported the diagnostic accuracy of combining bpMRI and PSAd, but these found that combining bpMRI with either PSA or PSAd improved the diagnostic accuracy of detecting PCa compared with using either parameter alone.[22,24,25] Thus, there are limited data on combining bpMRI with PSAd as a risk stratification strategy, and no follow-up data have been published on men with clinical low-risk findings avoiding biopsies.

Our department has introduced a strategy that is based on published studies[20,22] and updated recommendations from the 2019 European Association of Urology guidelines.[11] From March 2019, all men with suspicion of localized PCa undergo pre-biopsy bpMRI and their PSAd is calculated (Figure 1). If bpMRI shows no suspicious lesions and PSAd is <0.15 ng/mL^2, no biopsies are performed (green boxes, Figure 1). This study evaluates our strategy and early experience of avoiding immediate biopsies in men with non-suspicious bpMRI results and a PSAd <0.15 ng/mL^2 by quantifying the 2-year risk of an sPCa diagnosis.
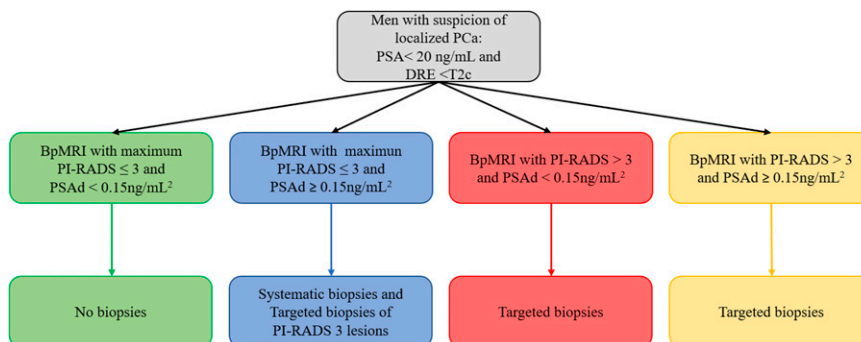

Figure 1. Departmental strategy for diagnosis of PCa in men with suspicion of localized PCa. Notes: PCa: prostate cancer; DRE: digital rectal examination; bpMRI: biparametric magnetic resonance imaging; PI-RADS: Prostate Imaging Reporting and Data System; PSA: prostate-specific antigen; PSAd: prostate-specific antigen density.
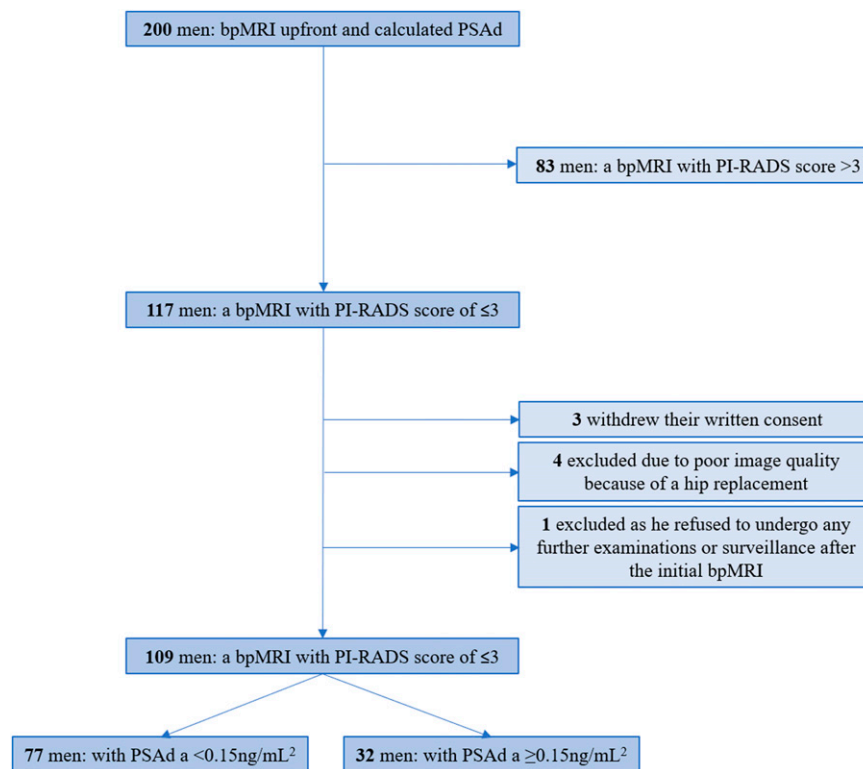
Figure 2. Men excluded from study. Notes: bpMRI: biparametric magnetic resonance imaging; PI-RADS: Prostate Imaging Reporting and Data System; PSAd: prostate-specific antigen density.

Materials and methods

Our institutional database had 200 biopsy-naïve men with clinical suspicion of PCa (PSA <20 ng/mL and digital rectal examination [DRE] <T2c) who had an initial bpMRI scan and PSAd calculated between March and July 2019. Of these, 117 men had bpMRI scan results exhibiting a maximum Prostate Imaging Reporting and Data System (PI-RADS) score of 3.[26] Eight of the 117 men were excluded for various reasons (Figure 2). The final study population consisted of 109. Of these, 77 with a calculated PSAd >0.15 ng/mL^2 avoided initial prostate biopsies and were clinically followed-up for at least 2 years. The remaining 32 men with a calculated PSAd ≥0.15 ng/mL^2 underwent systematic biopsies and targeted biopsies of any PI-RADS 3 lesion. Inclusion was between March and July 2019 and the follow-up deadline was in August 2021. The database was approved by the Danish Data Protection Agency and participants provided written informed consent.

Departmental strategy

As of March 2019, our department offers all men with suspicion of localized PCa a pre-biopsy bpMRI and their PSAd is calculated (Figure 1). If the bpMRI is normal or equivocal (PI-RADS 1–3) and the PSAd is < 0.15 ng/mL^2 with no other risk factors (e.g. familiar or genetic disposition), these men can forego biopsies (green boxes, Figure 1) and are referred back for clinical surveillance (routine PSA and DRE measurements) in primary care. However, if the bpMRI score is 1–3, but PSAd ≥0.15 ng/mL^2, systematic biopsies are offered due to the increased risk of sPCa and targeted biopsies of any PI-RADS 3 lesion (blue boxes, Figure 1). If the bpMRI has one or more suspicious lesions (score 4–5), targeted biopsies of the lesions plus systematic biopsies are offered regardless of PSAd level (red and yellow boxes, Figure 1).

The men included in this study with bpMRI scores of 1–3 and PSAd <0.15 ng/mL^2 were referred back to their general practitioner (GP) or underwent treatment for lower urinary tract symptoms or remained under clinical surveillance in-house. The general structure of the follow-up procedure is shown in Figure 3. In-house clinical surveillance consisted of PSA measurements plus DREs by a urologist every 6 months. Repeated biopsies were performed at the discretion of the treating urologist when there was clinical suspicion of missed sPCa, based on either PSA above the individual threshold (prostate volume multiplied by 0.15 ng/mL) or a suspect DRE. If a man repeatedly exhibited PSA levels that were below his individual threshold, he was referred back to his GP.

This strategy also includes a safety net for all men who are referred back to their GP for surveillance. The GPs are
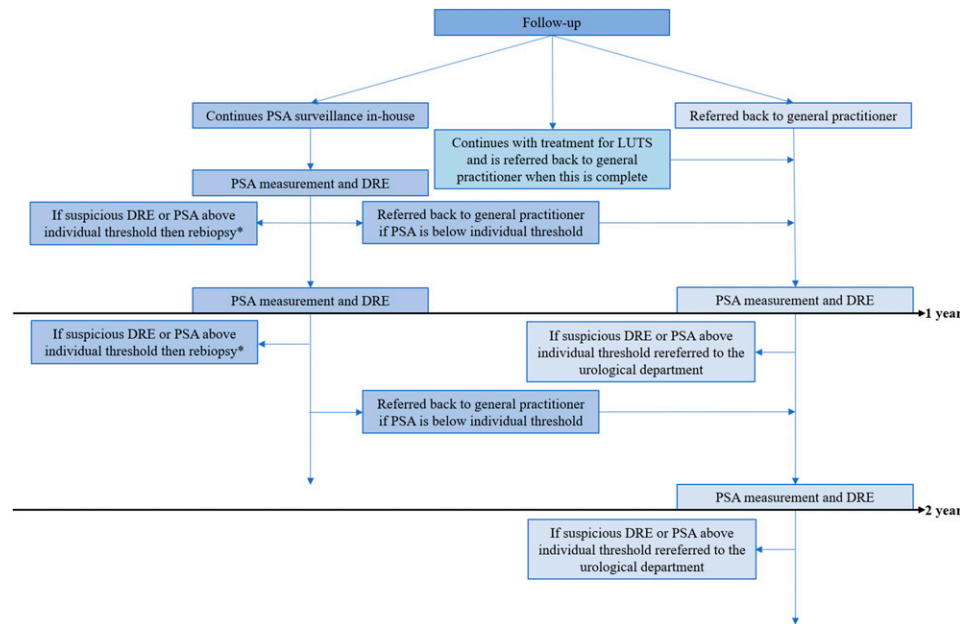
Figure 3. Follow-up structure. *The biopsy result determines whether each man proceeds to the next step in the flow chart or is offered appropriate treatment. Notes: PSA: prostate-specific antigen; LUTS: lower urinary tract symptoms; DRE: digital rectal examination.

instructed to measure PSA levels annually. If PSA levels increase above the calculated individual threshold, then the man is re-referred due to suspicion of PCa. The individual PSA levels were calculated from prostate volumes multiplied by 0.15 ng/mL.

In case of re-referrals from the GP, a confirmatory PSA measurement was performed at the urology department and benign reasons for increased PSA levels, such as urinary tract infections and urinary retention, were excluded. If PSA levels continued to be elevated, the urologist would order an mpMRI scan. All men underwent systematic biopsies plus additional targeted biopsies of any suspicious lesions (PI-RADS ≥ 3).

MRI

All MRI scans were read by specialized dedicated prostate MRI radiologists. A Philips Ingenia Elition 3.0T scanner (Philips Healthcare, Best, the Netherlands) with an anterior coil was used for all MRI examinations. The mpMRI and bpMRI protocols are provided in the Supplementary Information. All lesions on MRI scans were scored on a 5-point scale according to their likelihood of being sPCa (1, highly unlikely; 2, unlikely; 3, equivocal; 4, likely and 5, highly likely) using the PI-RADS version 2.1 criteria [26]. Prostate volume was measured according to the ellipsoid method as described in PI-RADS version 2.1 [26].

Histopathological evaluation

All biopsy samples were reviewed by a genitourinary pathologist and the location, Gleason Score (GS) and

percentage of cancerous tissue of each PCa-positive biopsy core were based on the International Society of Urological Pathology 2005 consensus guidelines.[27] In addition, a Gleason grade group (GG) was assigned to men with tumour-containing biopsies in accordance with the International Society of Urological Pathology 2014 consensus guidelines.[28] The definition of sPCa was any core with PCa GG ≥ 2.

Statistical analysis

RStudio software was used to perform all statistical analyses.[29] Patient characteristics are presented using descriptive statistics, with medians and interquartile ranges used to report continuous variables (e.g. age, PSA level, PSAd, prostate volume and number of days).

Results

Demographic and baseline characteristics of the study population are presented in Table 1 and Table 2. All men with PSAd <0.15 ng/mL^2 were referred back to their GP within 1 year of their initial assessment and 9% (7/77) were re-referred to the urology department during the 2-year follow-up period. Of these, 43% (3/7) continued to have PSA levels that were above their individual threshold levels at confirmatory testing, with no obvious benign explanation; these men each underwent a secondary mpMRI scan. For two of the men, the MRI results showed no lesions,

Table 1. Demographic and baseline characteristics PSA density < 0.15 ng/mL^2.

Clinical characteristic	Population (n = 77)
Age, median (IQR), years	66 (71–59)
PSA, median (IQR), ng/mL	6.1 (7.6–5.1)
Prostate volume, median (IQR), mL	68 (89–57)
PSA density, median (IQR), ng/mL^2	0.1 (0.1–0.06)
Time from bpMRI to follow-up end, median (IQR), days	841 (877–812)
cTDRE stage, number (%)	
Non-palpable tumour	
Tx	7 (9.1)
T1c	59 (76.6)
Palpable tumour	
T2a	11 (14.3)
PI-RADS, number (%)	
1	42 (54.5)
2	31 (40.3)
3	4 (5.2)

Notes: bpMRI: biparametric magnetic resonance imaging; cTDRE: tumour stage determined by digital rectal examination; IQR: interquartile range; PI-RADS: Prostate Imaging Reporting and Data System; PSA: prostate-specific antigen.
SI conversion factor: To convert PSA to micrograms per litre, multiply by 1.0.

Table 2. Demographic and baseline characteristics PSA density ≥ 0.15 ng/mL^2.

Clinical characteristic	Population (n = 32)
Age, median (IQR), years	66 (72–58)
PSA, median (IQR), ng/mL	8.2 (10.1–6)
Prostate volume, median (IQR), mL	40 (56–31)
PSA density, median (IQR), ng/mL^2	0.2 (0.25–0.2)
cTDRE stage, number (%)	
Non-palpable tumour	
Tx	1 (3.1)
T1c	23 (71.9)
Palpable tumour	
T2a	3 (9.4)
T2b	5 (15.6)
PI-RADS, number (%)	
1	16 (50)
2	9 (28.1)
3	7 (21.9)

Notes: bpMRI: biparametric magnetic resonance imaging; cTDRE: tumour stage determined by digital rectal examination; IQR: interquartile range; PI-RADS: Prostate Imaging Reporting and Data System; PSA: prostate-specific antigen.
SI conversion factor: To convert PSA to micrograms per litre, multiply by 1.0.

whereas the other man had a PI-RADS 4 lesion. The two men who had normal MRI results underwent systematic biopsies, which were all benign. The man with the PI-RADS 4 lesion was re-referred with a PSA level of 5 ng/mL, which was above his individual threshold of 4.8 ng/mL. At the urology department, this man's PSA level was recorded as 5.9 ng/mL and he accepted the offer of an mpMRI. The mpMRI revealed a PI-RADS 4 lesion with an apparent diffusion coefficient score of 0.56. In retrospect, the reader was able to locate the lesion on the initial bpMRI, but the lesion had grown. Targeted biopsies of the lesion revealed sPCa with GS7 (4+3) representing GG3. The man accepted the offer of radical prostatectomy and after the procedure he exhibited no positive margins and no positive lymph nodes and was staged pT2cN0M0.

All re-referrals to the urology department were due to increases in PSA levels rather than changes in DRE findings. Only one of the 77 men (1.3%) had sPCa diagnosed within 2 years after their initial evaluation (Figure 4).

The men with PSAd ≥0.15 ng/mL^2 who underwent biopsies are presented in Table 3. Overall, 63% had no cancer in their biopsies and 37% had cancer ranging from GG 1 to 5 (Table 3).

The proportion of men with PI-RADS score 3 lesions were 10% (11/109). Of these, four men (4/11) had a PSAd <0.15 ng/mL^2. The other seven men with elevated PSAd ≥0.15 ng/mL^2 underwent systematic-plus targeted biopsies of the PI-RADS 3 lesion and detected four men with GS7 (3+4) representing GG2, one man with GS9 (5+4) representing GG5 and two men who had no cancer in their biopsies. The four men with PSAd <0.15 ng/mL^2 avoided biopsies and were referred back to the GP for surveillance. Of these, two men were re-referred back from the GP during surveillance due to rising PSA above their individual threshold. However, one man did not have PSA-elevation at confirmatory testing, while the other underwent confirmatory diagnostic mpMRI. This mpMRI was without any suspicious lesions and both men were referred back to their GP for continued PSA-surveillance.
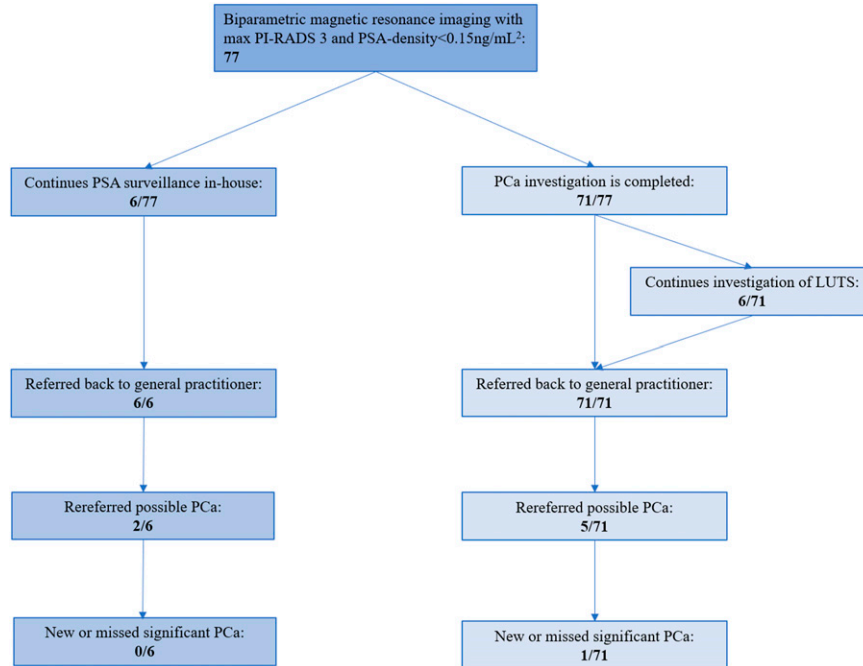
Figure 4. Outcomes. Notes: PI-RADS: Prostate Imaging Reporting and Data System; PSA: prostate-specific antigen; PCa: prostate cancer; LUTS: lower urinary tract symptoms.

Table 3. Systematic biopsy results and treatment options for PI-RADS 1-3 and PSA density ≥ 0.15 ng/mL^2.

GG (%)	Population ($n = 32$)
No cancer	19 (59.4)
Inflammation	1 (3.1)
1	4 (12.5)
2	7 (21.9)
3	0 (0)
4	0 (0)
5	1 (3.1)
Treatment option (%)	
Re-referred to general practitioner	19 (59.4)
Active surveillance	6 (18.8)
Radical prostatectomi	5 (15.6)
Brachyterapi	1 (3.1)
Discontinued	1 (3.1)

Notes: GS: Gleason score; GG: Gleason grade group; PI-RADS: Prostate Imaging Reporting and Data System; PSA: prostate-specific antigen.
SI conversion factor: To convert PSA to micrograms per litre, multiply by 1.0.

Discussion

In this preliminary study, we assessed our early experience of avoiding biopsies for men with PI-RADS scores ≤ 3 on bpMRI and a PSAd <0.15 ng/mL^2, and instead initiating an individual PSA-monitoring safety net for re-referrals. Using this strategy, we found that 77 of 200 men (39%) avoided

biopsies and only one man (1.3%) was diagnosed with sPCa within 2 years of follow-up. However, because only men with increased PSA levels were re-referred, we do not know the prevalence of missed sPCa in men who did not undergo confirmatory biopsies. Nonetheless, when following the initial strategy, the only man known to have a missed sPCa was identified by the safety net while the disease was still localized and remedial treatment remained possible. Furthermore, of the men with PI-RADS scores ≤ 3 on bpMRI and PSAd ≥ 0.15 ng/mL^2, only 19% had more than GG2 PCa detected by systematic biopsies. If looking isolated at all the men with PI-RADS 3, only one of them (1/11) had more than a GG2 PCa.

Previously, a study by Boesen et al. also combined bpMRI and PSAd.[22] This assessed the diagnostic accuracy, predictive values and best biopsy strategy for detecting and ruling out sPCa.[26] Boesen et al. assessed 808 men and found that 283 of them (35%) had sPCa.[22] These researchers concluded that the best strategy was restricting biopsies to men with highly suspicious bpMRI findings (score ≥ 4) or PSAd ≥ 0.15 ng/mL^2, which is the strategy our department has subsequently introduced.[22] Boesen et al. found that this strategy reduced the number of men requiring biopsies by 41% and overdiagnoses of insignificant PCa by 45%, while missing only 5% of men with sPCa.[22]

A retrospective study by Venderink et al. investigated the proportion of men who could avoid biopsies based on negative mpMRI findings (PI-RADS ≤ 2) and assessed the number of sPCa detected during follow-up.[30] Of 4259 men

who were scanned, 2281 had negative MRI results, and 320 of the 2281 men with negative MRI results had a follow-up mpMRI scan after a median of 57 months.[30] Among these men, sPCa diagnosis-free survival was 99.6% after 3 years and 94.1% after 6 years.[30] Biopsies were performed in men with PI-RADS scores ≥3, and sPCa was detected in 15.8%, 43.2% and 74.5% of men with PI-RADS scores of 3, 4 and 5, respectively.[30] In contrast to the study described by Venderink et al., our patient population was very limited. However, although we used bpMRI instead of mpMRI, our results are similar. In addition, in accordance with the findings reported by Boesen et al., we do not perform biopsies on men with PI-RADS scores of 3 if their PSAd is <0.15 ng/mL^2.[22] In the group studied by Venderink et al., the median PSAd was 0.13 ng/mL^2, and 274 of those men with a PI-RADS score of 3 had a PSAd of ≥0.15 ng/mL^2.[30] Unfortunately, Venderink et al. do not report the GS of all men with PI-RADS scores of 3 but many of these men probably had sPCa if they had PSAd values of ≥0.15 ng/mL^2. The decision on whether to perform biopsies on men with PI-RADS scores of 3 depends on weighing the risk of missing sPCa against the benefits of avoiding unnecessary biopsies, as well as reducing costs and the possibility of complications.[3,4] Similar to our study, Venderink et al. stress the need to follow-up men with negative MRI results.[30] They do not report individual thresholds for PSA levels and did not use PSAd measurements as part of their initial screening strategy.[30]

Panebianco et al. separated 1255 men with negative mpMRI results (PI-RADS ≤ 2) into two groups. They followed up the biopsy-naïve group for a median of 38 months and the group with a previous negative TRUS-bx for a median of 60 months and found that the likelihood of PCa was similar in both groups.[31] They also found that the likelihood of being sPCa diagnosis-free at 48 months was 95% for biopsy-naïve men but 96% for men who had a previous negative TRUS-bx.[31] This shows that the negative TRUS-bx improved sPCa diagnosis-free survival from 95% to 96%.[31] However, multivariable analysis showed that a previous negative TRUS-bx did not independently predict the likelihood of a subsequent sPCa diagnosis, whereas age, PSA level and PSAd did, with PSAd being the strongest independent predictor.[31] This finding supports our decision to use PSAd as a biomarker for risk stratification.

A systematic review by Moldovan et al. assessed the negative predictive value (NPV) of mpMRI in men with a suspicion of PCa in 48 eligible studies.[32] For sPCa, the prevalence was 32.9% and the median mpMRI NPV was 88.1%.[32] NPV significantly decreased when cancer prevalence increased.[32] The NPV of mpMRI varied greatly depending on study design, cancer prevalence, and definitions of positive mpMRI and sPCa.[32] These authors concluded that risk stratification of men should be the first step in the sPCa screening procedure.[32] Their results are supported by a meta-analysis by Villers et al., who showed

that mpMRI had a median NPV of 88% for sPCa.[33] These studies highlight the importance of improving risk stratification, which is the focus of our departmental strategy.

Overall, our 2-year follow-up study is consistent with these previous studies and confirms that bpMRI can be combined safely with PSAd in a short-term follow-up strategy with an individualized PSA-surveillance 'safety net' in place. This strategy minimizes biopsy cores, financial costs and the risk of post-biopsy complications.[34] Further stratification could include having different PSAd cut-offs for each PI-RADS score.[34] Increasing the values of PSAd cut-offs may reduce the number of biopsies but increase the risk of missed sPCa. Decreasing the values of PSAd cut-offs may reduce the risk of missed sPCa but increase the number of biopsies.[34] Whether other physicians and/or patients find our threshold range acceptable depends on the level of risk that they are ready to accept. We do not know the frequency of missed sPCa associated with our strategy as not all are biopsied. In the Biparametric MRI for Detection of Prostate Cancer study, which also used bpMRI as a pre-biopsy strategy, Boesen et al. found that 5% sPCa were missed if systematic biopsies in MRI negative men were avoided.[20] Missing 5% of GS7 PCa on immediate prostate biopsies is deemed acceptable.[22] Decreasing the PSAd cut-off would conflict with our goal of performing fewer unnecessary biopsies. Despite our low percentage of missed sPCa, we encourage clinicians to be cautious when MRI results suggest that prostate biopsies are unnecessary. Our results are dependent on the extensive experience of our reporting radiologists, high image qualities and local disease prevalence. Consequently, we urge every institution to understand their particular test performance statistics when making clinical decisions based on MRI findings.

The main limitation of our study was the small study population; we would need a larger sample to provide more definite results. However, our early experience provides a good overview and justifies a larger study, which we will perform when enough men have reached a later follow-up stage. A second limitation is our follow-up period of 2 years. PCa is a slow-growing cancer and we need to increase our follow-up period beyond 2 years.[35] A third limitation is our study's retrospective design. This means we lack direct pathological confirmation of negative mpMRI results, and no uniform follow-up protocol was planned. Therefore, interval lengths varied between PSA measurements, MRI scans and re-biopsies. However, this approach reflects our everyday clinical practice, and the results may be generally relevant.

In conclusion, our clinical strategy of no biopsies for men with bpMRI results exhibiting maximum PI-RADS scores of 3 and with a PSAd <0.15 ng/mL^2 resulted in a 2-year risk of being diagnosed with sPCa of 1.3%. However, larger studies with longer follow-up periods are needed to support our findings.

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