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ARTICLE

For men enrolled in active surveillance, pre-biopsy biparametric magnetic resonance imaging significantly reduces the risk of reclassification and disease progression after 1 year

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ABSTRACT

Aims: To assess the level of disease progression at confirmatory staging biopsies after 1 year of active surveillance (AS) and compare the detection rate of significant prostate cancers (PCas) in patients who underwent pre-biopsy biparametric magnetic resonance imaging (bpMRI) before the first set of diagnostic transrectal ultrasonography-guided biopsies (TRUS-bx) with the detection rate in patients who did not undergo pre-biopsy bpMRI.

Materials and methods: Comparison of two patient groups enrolled in AS. Patients in Group A ($n = 127$) underwent pre-biopsy bpMRI followed by TRUS-bx ± targeted biopsies. Patients in Group B ($n = 127$) were enrolled in AS based on biopsy results from TRUS-bx only.

Results: Overall, 6% of the patients in Group A and 20% of the patients in Group B had an upgrade in Gleason grade from insignificant to significant PCa at confirmatory staging biopsies (odds ratio [OR], 3.5; $p = .002$; 95% confidence interval [CI], 1.6–7.9).

Conclusions: Patients who underwent pre-biopsy bpMRI before the first set of diagnostic biopsies had a reduced risk of reclassification and disease progression after 1 year of AS. Thus, pre-biopsy bpMRI improves the selection of men who should be enrolled in AS.

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Introduction

Prostate cancer (PCa) comprises a continuum of neoplasms ranging in aggressiveness from insignificant cancers with no effect on patient morbidity or mortality to highly aggressive significant cancers. PCa diagnosis is not traditionally based on imaging, but biopsies are systematically obtained for screening from predefined regions of the prostate gland using transrectal ultrasonography (TRUS). Diagnoses, treatment regimens or surveillance programs are offered to patients, depending on the severity of the disease. One approach is active surveillance (AS), which is offered to men with low-risk PCa who will probably never develop cancer-related symptoms [1]. The purpose of AS is to reduce over-treatment and avoid or delay invasive interventions with their inherent side effects, such as impotence and incontinence [1]. Men enrolled in AS are monitored closely using prostate-specific-antigen (PSA) measurements, digital rectal examinations and confirmatory biopsies 1 year after inclusion. Active treatment can then be initiated in response to disease progression [1]. Thus, AS is heavily dependent on accurate risk assessments including tumour localisation, volume and Gleason grade group (GG). However, TRUS-guided biopsies (TRUS-bx) are prone to sampling errors, and clinically significant PCas may be missed by the random untargeted sampling method [2]. Convincing evidence shows that multiparametric (mp) magnetic resonance imaging (MRI) has a high sensitivity and a high negative predictive value (NPV) in detecting and ruling out significant PCa [3,4]. Thus, for men enrolled in AS, a mpMRI may be used to identify those with a missed clinically significant PCa, leading to reclassification after a confirmatory biopsy or excluding the presence of aggressive disease and confirming that the patient is eligible for AS [5–8]. Such a strategy is currently recommended by the European Association of Urology guidelines for all men enrolled in AS [9], but there is no clear consensus on at what time point during follow-up a mpMRI should be performed. Furthermore, recent studies have shown that a simple biparametric (bp) MRI can also improve PCa risk stratification, has a high NPV for ruling out significant disease in biopsy-naïve men, and may be used to avoid unnecessary biopsies [3,10–12]. Compared with mpMRI, bpMRI is rapid involves fewer scan sequences and does not require contrast agent, which reduces both magnet-time and costs. Recent assessment of the diagnostic performance of pre-biopsy bpMRI in identifying men eligible for AS showed that a confirmatory mpMRI shortly after inclusion was unnecessary [13]. The purpose of this study is to assess the level of disease progression at confirmatory staging biopsies after 1 year of AS and compare the detection rate of significant PCas in patients who underwent pre-biopsy bpMRI before the first set of

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diagnostic TRUS-bx with the detection rate in patients who did not undergo pre-biopsy bpMRI.

Material and methods

We identified two patient groups (A and B). Group A patients were derived from a prospective database used to assess the diagnostic accuracy of bpMRI for PCa detection in biopsy-naïve men [3]. This database included 1020 biopsy-naïve men with clinical suspicion of PCa who underwent bpMRI followed by TRUS-bx and targeted biopsies of any lesion with a prostate imaging reporting and data system (PI-RADS) score $\geq$ 3 during the period November 2015 to June 2017. Of these men, 144 were subsequently enrolled in AS, based on the national guidelines [14]. The primary inclusion criterion for AS was men with low-risk PCa (i.e. tumour stage $\leq$ T2a, PSA $\leq$ 10 ng/mL, and GG $\leq$ 1). However, well-informed men with limited intermediate-risk PCa (cT2b, PSA = 10–20 ng/mL or GG2 in only 1–2 biopsy cores) could be enrolled based on patient preference. All men enrolled in AS underwent a control mpMRI followed by confirmatory TRUS-bx and targeted biopsies of any lesion with a PI-RADS score $\geq$ 3 after 1 year, as part of the standard AS follow-up regime. However, 17 patients were excluded from our study because they refused to undergo TRUS-bx or did not have a control mpMRI for various reasons. Thus, the final Group A consisted of 127 men (Figure 1). Group B consisted of 127 men enrolled in AS based on national guidelines [14] who had conventional TRUS-bx without pre-biopsy bpMRI. These patients were obtained from our departmental patient register for the period December 2013 to August 2018 (Figure 2). Group B patients were not obtained from the same time period as those from Group A (Figure 2) because all biopsy-naïve men from the Group A time period had undergone pre-biopsy bpMRI as part of our prospective study [3].

Magnetic resonance imaging

All MRI examinations (bpMRI and mpMRI) were performed using a 3-T MRI magnet (Ingenia version 5.3.1; Philips Healthcare, Best, the Netherlands) with a 16-channel surface coil and a built-in table coil (Philips Healthcare) positioned over the pelvis. No post-acquisition filtering was applied outside what is denoted 'default' by the scanner vendor (Philips Healthcare). The bpMRI protocol included axial T2-weighted and diffusion-weighted imaging with reconstructions of the corresponding apparent diffusion coefficient maps and image acquisition times of approximately 15 min. In addition to the bpMRI protocol, the mpMRI protocol also included triplanar T2-weighted imaging and dynamic contrast-enhanced (0.2 mL/kg gadoteric acid [15–20 mL 279.3 mg/mL Dotarem injection fluid; Guerbet B. P., Villepinte, France]) T1-weighted imaging sequences in the axial plane. Furthermore, anti-peristaltic drugs (1 mL hyoscine butylbromid [20 mg/mL Buscopan injection fluid; Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany] and 1 mL glucagon [1 mg/mL GlucaGen; Novo Nordisk A/S, Bagsvaerd, Denmark]) were administered if tolerated. The mpMRI and bpMRI protocol details are listed in Table 1 in Thestrup et al. [13]. All MRIs were reviewed by the same prostate MRI physician (>8 years of experience), who registered and scored any suspicious lesions on a 5-point scale according to their likelihood of being significant PCa (1, highly unlikely; 2, unlikely; 3, equivocal; 4, likely; and 5, highly likely) using the PI-RADS version 2 criteria [15]. Patients with no suspicious lesions were assigned a PI-RADS score of 1. The reader was aware of the bpMRI results when reporting the mpMRI results from Group A patients. However, because the bpMRI protocol did not include dynamic contrast-enhanced imaging, scoring of lesions in the peripheral zone relied solely on diffusion-weighted image findings (i.e. the dominant sequence). Therefore, an equivocal score of 3 was not upgraded to a score of 4 due to a lack of positive dynamic contrast-enhanced findings. For patients in Group A, the mpMRI results were compared to the initial bpMRI results and deemed equivalent if no new lesions were detected, or if a lesion did not increase in PI-RADS score. Equivocal cases were discussed at a multidisciplinary conference that included urologists and radiologists. Here, biopsy and MRI results were analysed together. If there was a mismatch between the PI-RADS assessment category/MRI suspicion level (e.g. large tumour, low apparent diffusion coefficient value and invasive behaviour) and the biopsy results (e.g. benign targeted biopsy or limited Gleason score 6 tumour), then biopsy targeting error was suspected and a re-biopsy was recommended. Similarly, any patient with a new suspicious lesion on mpMRI was referred for re-biopsy if the result could potentially change clinical management. Unfortunately, because our fusion-biopsy system does not record the needle tracks, prior biopsy sites could not be retrospectively checked.

Histopathological evaluation

The same genitourinary pathologist (>16 years of experience) reviewed all biopsy samples. For each PCa-positive biopsy core, the location, the Gleason Score and the percentage of cancerous tissue per core were determined based on the International Society of Urological Pathology 2005 consensus guidelines [16]. In addition, based on the global Gleason scores from all of the tumour-containing biopsies, patients were assigned to a GG in accordance with the International Society of Urological Pathology 2014 consensus guidelines [17]. Repeat biopsy results were compared to the original diagnostic biopsies. Both GG and volume were included in the definition of a significant PCa, which was any core with high-grade PCa (GG $\geq$ 3) or a maximum cancerous core length greater than 50% (MCCL > 50%) of GG 2 PCa. The same definition is used in the database and the PROMIS Study [3,5].

Statistical analysis

Descriptive statistics were used to present patient characteristics. Continuous variables (i.e. age, PSA level, PSA density and prostate volume) were described using means and

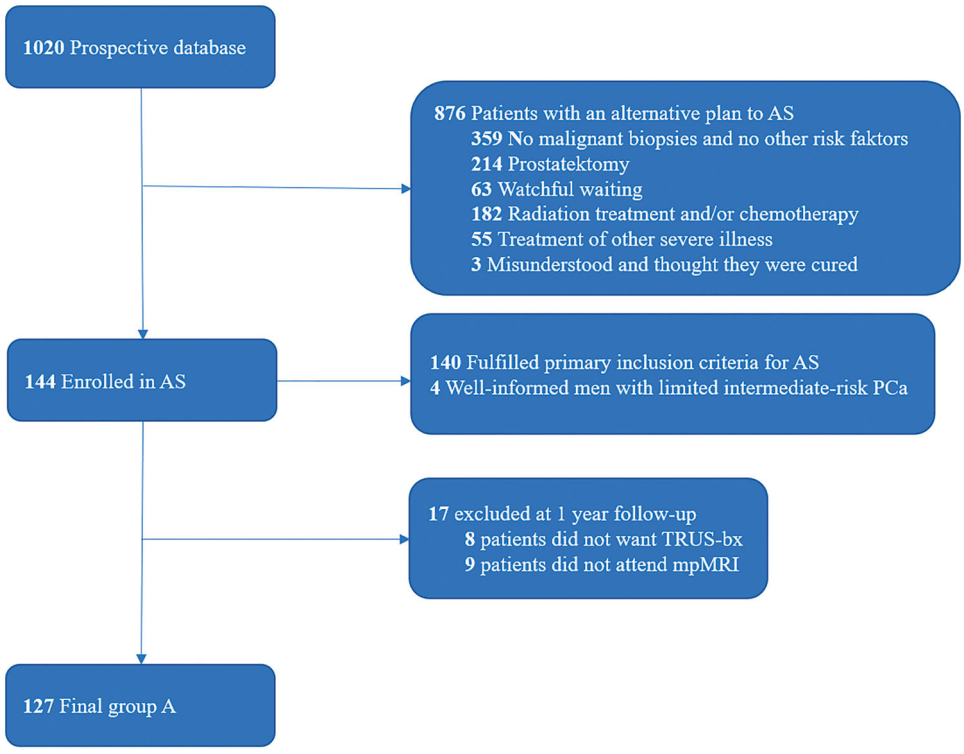

Figure 1. Flowchart of showing patients included in the study population for Group A. AS: active surveillance; PCa: prostate cancer; mpMRI: multiparametric magnetic resonance imaging; TRUS-bx: systematic transrectal ultrasonography-guided biopsies.

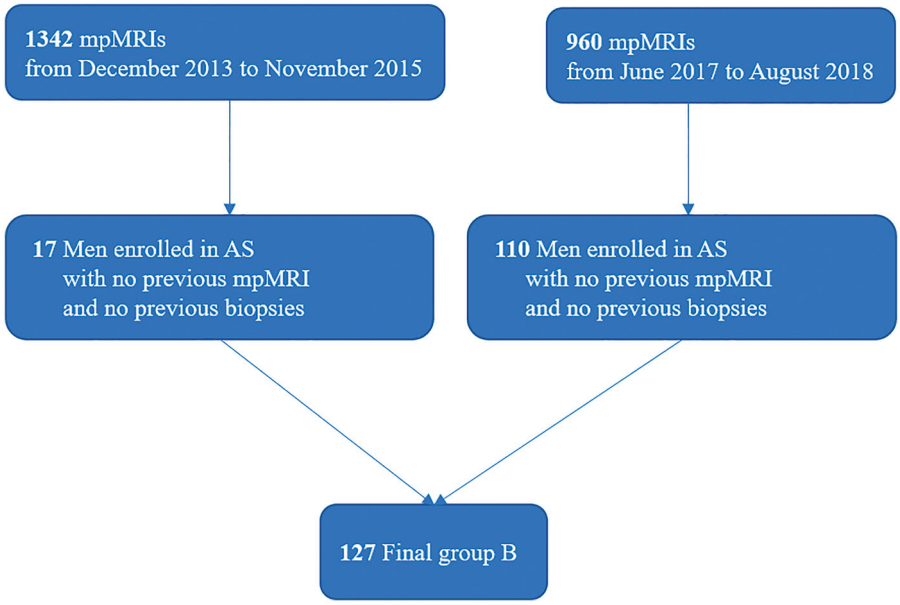

Figure 2. Flowchart showing patients included in the study population for Group B. AS: active surveillance; mpMRI: multiparametric magnetic resonance imaging.

standard deviation, and normality was tested using the Shapiro–Wilk method. Differences between the two groups were tested using an unpaired *t*-test. Clinical tumour stage data were pooled in non-palpable and palpable tumour groups and Fisher's exact test was used to compare clinical tumour stages determined by digital rectal examinations. Odds ratios were calculated using a 2×2 contingency table and a two-sample test for equality of proportions with continuity correction followed by epidemiological tabulation. Statistical analysis was performed using Rstudio software version 1.1.5 (RStudio, Inc., Boston, MA) and a p value $< .05$ was considered statistically significant [18].

Results

There were no significant differences in clinical parameters between groups A and B. The patients' demographic data and baseline characteristics are listed in Table 1. Overall, 6% of patients in Group A (7/127) and 20% of patients in Group

Table 1. Patient characteristics.

Clinical characteristic	Group A ($n = 127$)	Group B ($n = 127$)	p Value	Normality (Group A/Group B)
Age, mean (SD), years	65 (±6)	64 (±7)	.8	<0.001/<0.001
PSA, mean (SD), ng/mL	7.5 (±6)	6.9 (±2.8)	.5	<0.001/<0.001
Prostate volume, mean (SD), cm^3	57.2 (±27.9)	56 (±23.1)	.7	<0.001/<0.001
PSA density, mean (SD), $ng/mL/cm^3$	0.1 (±0.1)	0.1 (±0.1)	.5	<0.001/<0.001
Time from biopsy to bp/mpMRI, mean (SD), days	398 (±51)	391 (±60)	.6	<0.001/<0.001
cTDRE stage, number (%)				
Non-palpable tumour				
Tx	17 (13.4)	17 (13.4)	–	
T1c	94 (74)	96 (75.6)	–	
Palpable tumour			<.001	
T2	16 (12.6)	14 (11)	–	

bpMRI: biparametric magnetic resonance imaging; mpMRI: multiparametric magnetic resonance imaging; cTDRE: tumour stage determined by digital rectal examination; SD: standard deviation; PSA: prostate-specific-antigen.
SI conversion factor: To convert PSA to micrograms per litre, multiply by 1.0.

Table 2. Upgrade in biopsy Gleason scores and Gleason grade groups from first to second set of biopsies.

Upgrades resulting in significant prostate cancer[a]	Group A ($n = 127$)	Group B ($n = 127$)
GG1 to GG2 MCCL > 50%	1 (0.8%)	11 (8.7%)
Cancer core length/core length, mm	6/12 and 9/15	6/12 and 12/20 and 13/19 and 12/16 10/17 and 6/10 and 10/15 8/10 and 15/20 and 8/15 9/18 and 12/20 and 9/19 9/15 and 10/14 and 10/16 10/18 and 9/19 5/12 and 11/19 and 9/15 9/18 and 11/15 12/20 and 10/15 and 9/18 5/11 and 10/18 7/14 and 12/20 and 10/17
GG2 MCCL ≤ 50% to GG2 MCCL > 50%	2 (1.6%)	9 (7.1%)
Cancer core length/core length, mm	9/18 and 12/20 and 10/19 10/18 and 10/19	8/15 and 7/15 and 10/15 9/17 and 11/19 9/15 and 12/19 and 9/15 10/15 and 12/20 and 10/14 9/15 and 6/11 7/15 and 5/10 and 10/15 2/5 and 12/20 and 13/19 and 12/16 8/14 and 9/15 6/12 and 12/20 and 13/19 and 12/16
GG1 to GG3	1 (0.8%)	3 (2.4%)
Cancer core length/core length, mm	2/16 and 9/15 and 11/15	6/10 and 7/15 and 5/10 and 7/17 3/5 and 10/18 7/13 and 10/20 and 8/15 and 9/15
GG2 MCCL ≤ 50% to GG3	2 (1.6%)	
Cancer core length/core length, mm	7/14 11/14 and 9/13 and 6/15	
No prostate cancer to GG4		1 (0.8%)
Cancer core length/core length, mm		7/11 and 9/15 and 8/15 and 12/16
GG1 to GG4	1 (0.8%)	
Cancer core length/core length, mm	3/10	
GG1 to GG5		1 (0.8%)
Cancer core length/core length, mm		10/15 and 7/14
Total upgrades, number (%)	7 (5.5%)	25 (19.7%)

[a]Significant prostate cancer definition: Any core with high-grade prostate cancer (GG ≥ 3) or maximum cancerous core length greater than 50% (MCCL > 50%) of GG2 prostate cancer.
GG: Gleason grade group; MCCL: maximum cancerous core length; PI-RADS: prostate imaging reporting and data system.

B (25/127) had an upgrade in GG from insignificant to significant cancer at 1-year confirmatory biopsies (Table 2). The odds ratio for a patient in Group B having a GG upgrade from insignificant to significant PCa was 3.5-fold higher than for a patient in Group A ($p = .002$; 95% confidence interval [CI], 1.6–7.9). Mean core length for upgrades in Group A *versus* B was 15.5 ± 2.7 *versus* 15.3 ± 3.4 mm ($p = 0.77$; 95% CI, −2.3–8.7). Mean cancer core length for upgrades in Group A *versus* B was 9 ± 2.8 *versus* 9.1 ± 2.5 mm ($p = .35$; 95% CI, −1.4–1.9). Of the seven patients in Group A who exhibited disease progression at 1-year confirmatory biopsies, five (71%) were identified by targeted biopsies, whereas the remaining two patients were identified by TRUS-bx because they had no suspicious lesions on the confirmatory mpMRI. All seven of these patients advanced to active treatment. Similarly, of the 25 patients in Group B who exhibited disease progression, 23 (92%) were identified by targeted biopsies, whereas the remaining two patients were identified by TRUS-bx because they had no suspicious lesions on the confirmatory mpMRI. Of these 25 Group B patients, 19 (76%) advanced to active treatment. At 1-year confirmatory biopsies, 76 patients in Group A (60%) and 79 patients in Group

B (62%) had a mpMRI with a suspicious lesion, which led to targeted biopsies.

Discussion

We found that significantly more men who did not undergo pre-biopsy bpMRI before enrolment in AS were diagnosed with significant PCa after 1 year (20% *versus* 6%), leading to active treatment. This illustrates that performing a bpMRI before diagnostic biopsies improves risk stratification and selection of men who should be enrolled in AS, because it reduces the risk of reclassification significantly (odds ratio [OR], 3.5). This was highlighted in a review by Giganti and Moore who emphasised the potential benefits of using bpMRI to identify men with higher grade cancer who have been misclassified by standard biopsies as having low-risk disease suitable for AS [19]. Furthermore, our findings are consistent with a previous study by Tran et al. that described how systematic sampling with MRI-ultrasound fusion biopsies detected a cancer upgrade in 14% (30/207) of men enrolled in AS [20].

Only 6% of patients in Group A had an upgrade in GG to significant PCa. In total, 71% of these cases were identified by mpMRI targeted biopsies and all of the upgrades had therapeutic consequences. Although our numbers are limited, standard biopsies had an added value of only 2% (2/127) in both Group A and Group B. Because this added value is minimal, performing standard biopsies at follow-up may be unnecessary. The DETECTIVE study concluded that for patients enrolled in AS, repeat biopsies should be performed in response to a change in mpMRI findings, and this conclusion is supported by the minimal added value we observed for standard biopsies at follow-up [21]. Therefore, instead of biopsies, serial MRI could be implemented in the future and guided by the PRECISE recommendations [22]. If we had measured lesion volumes, this may have increased the detection rate of MRI. In particular, the DETECTIVE study noted that the volume of the dominant lesion should be considered an indicator of tumour volume [21]. The PRECISE recommendations state that a significant increase in size and/or conspicuity of features associated with PCa should be assessed as radiological progression [22].

Our study had some limitations. It was performed at a single centre with one dedicated MRI physician reading all the MRI scans and two highly experienced TRUS operators performing all the biopsies. As a result, no inter-reader analysis was possible. However, we previously found a high intra- (Cohen's Kappa = 0.94) and inter- (Cohen's Kappa = 0.84–0.87) reader agreement when comparing bpMRI with mpMRI [12,23]. Less experienced readers and operators might not achieve the same diagnostic yield. Importantly, Stavrinides et al. suggested that mpMRI results for patients enrolled in AS should always be interpreted in the context of MRI performance at a particular centre [4].

Because we used biopsy results as standard reference, PCa lesions may have been missed by bpMRI, mpMRI and biopsies. Thus, this was a retrospective study with no prostatectomy specimens to confirm the presence or absence of PCa lesions. Consequently, the diagnostic- and staging-accuracy could not be evaluated precisely. Because all patients underwent standard biopsies following initial bpMRI, including those with low-suspicion bpMRI results, using biopsies as standard reference allowed us to compare outcomes that reflect clinical practice.

Our patient numbers were limited and larger prospective studies are needed to confirm our conclusions. However, although the PROMIS study was performed in biopsy-naïve men and not in an AS cohort, it found a strong correlation between suspicious mpMRI results and significant PCas. The PROMIS study used 5-mm template sampling as standard reference and only 17/158 significant PCas were missed [5].

We cannot exclude the possibility that some cancers may have developed into significant disease during the observational year. However, progression resulting in upgrade is uncommon, and undetected co-existing higher-grade disease at inclusion is often the cause of reclassification at confirmatory biopsies [24].

Finally, because the bpMRI scans were scored using a modified PI-RADS score, equivocal PI-RADS scores of 3 in the peripheral zone were not upgraded to PI-RADS 4 due to the lack of positive dynamic contrast-enhanced evidence. However, this limitation would only affect biopsy results stratified by PI-RADS scores and not overall outcomes, because all PI-RADS 3 lesions were biopsied.

In conclusion, patients who underwent pre-biopsy bpMRI before the first set of diagnostic biopsies had a significantly reduced risk of reclassification and disease progression after 1 year of AS. Thus, a simple bpMRI may be used to select men who should be enrolled in AS.

Disclosure statement

The authors declare that they have no conflicts of interest with respect to the research, authorship and/or publication of this article.

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