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A Multivariable Approach Using Magnetic Resonance Imaging to Avoid a Protocol-based Prostate Biopsy in Men on Active Surveillance for Prostate Cancer—Data from the International Multicenter Prospective PRIAS Study

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Abstract

Background: There is ongoing discussion whether a multivariable approach including magnetic resonance imaging (MRI) can safely prevent unnecessary protocol-advised repeat biopsy during active surveillance (AS).
Objective: To determine predictors for grade group (GG) reclassification in patients undergoing an MRI-informed prostate biopsy (MRI-Bx) during AS and to evaluate whether a confirmatory biopsy can be omitted in patients diagnosed with upfront MRI.
Design, setting, and participants: The Prostate cancer Research International: Active Surveillance (PRIAS) study is a multicenter prospective study of patients on AS (www.prias-project.org). We selected all patients undergoing MRI-Bx (targeted ± systematic biopsy) during AS.
Outcome measurements and statistical analysis: A time-dependent Cox regression analysis was used to determine the predictors of GG progression/reclassification in patients undergoing MRI-Bx. A sensitivity analysis and a multivariable logistic regression analysis were also performed.
Results and limitations: A total of 1185 patients underwent 1488 MRI-Bx sessions. The time-dependent Cox regression analysis showed that age (per 10 yr, hazard ratio [HR] 0.84 [95% confidence interval {CI} 0.71–0.99]), MRI outcome (Prostate Imaging Reporting and Data System [PIRADS] 3 vs negative HR 2.46 [95% CI 1.56–3.88], PIRADS 4 vs negative HR 3.39 [95% CI 2.28–5.05], and PIRADS 5 vs negative HR 4.95 [95% CI 3.25–7.56]), prostate-specific antigen (PSA) density (per 0.1 ng/ml cm^3, HR 1.20 [95% CI 1.12–1.30]), and percentage positive cores on the last systematic biopsy (per 10%, HR 1.16 [95% CI 1.10–1.23]) were significant predictors of GG reclassification. Of the patients with negative MRI and a PSA density of <0.15 ng/ml cm^3 (n = 315), 3% were reclassified to GG ≥2 and 0.6% to GG ≥3. At the confirmatory biopsy, reclassification

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to GG ≥2 and ≥3 was observed in 23% and 7% of the patients diagnosed without upfront MRI and in 19% and 6% of the patients diagnosed with upfront MRI, respectively. The multivariable analysis showed no significant difference in upgrading at the confirmatory biopsy between patients diagnosed with or without upfront MRI.

Conclusions: Age, MRI outcome, PSA density, and percentage positive cores are significant predictors of reclassification at an MRI-informed biopsy. Patients with negative MRI and a PSA density of <0.15 ng/ml cm^3 can safely omit a protocol-based prostate biopsy, whereas in other patients, a multivariable approach is advised. Being diagnosed with upfront MRI appears not to significantly affect reclassification risk; hence, a confirmatory MRI-Bx cannot totally be omitted yet.

Patient summary: A protocol-based prostate biopsy while on active surveillance can be omitted in patients with negative magnetic resonance imaging (MRI) and prostate-specific antigen density <0.15 ng/ml cm^3. A confirmatory biopsy cannot simply be omitted in all patients diagnosed with upfront MRI.

1. Introduction

Active surveillance(AS) is a strategy for prostate cancer (PCa) patients aiming to avoid unnecessary active treatment of indolent PCa while detecting aggressive cancers before harm ensues [1,2]. As a recommended strategy for patients with low and specially selected intermediate-risk PCa, AS has excellent long-term (cancer-specific) survival rates [3,4]. Most AS protocols and international guidelines recommend a prostate biopsy according to predetermined schedules [5]. A prostate biopsy may be burdensome and possibly associated with side effects [5]. Magnetic resonance imaging (MRI) in AS increases the detection rate of grade group (GG) reclassification [6–8]. There is, however, an ongoing debate whether or not a prostate biopsy can safely be omitted in patients with negative MRI during AS [9–13]. Therefore, a one-size-fits-all AS protocol, requiring a repeat prostate biopsy at fixed time points, is often used in daily clinical practice.

In the 2021 European Association of Urology (EAU) guidelines, the recommendation to omit a protocol-based biopsy in patients with negative MRI and a low clinical suspicion of PCa progression has been removed [2,11]. This uncertainty is, among others, related to a significant institutional variation in the negative predictive value of the MRI [13–15]. On the contrary, in patients diagnosed with upfront MRI, the EAU guidelines now recommend omitting the confirmatory biopsy (ie, the biopsy following the diagnostic biopsy, typically performed within 12 mo after diagnosis; strength rating: weak) [2,11]. Data from a multicenter setting might help reduce the current knowledge gap [13,14]. In 2013, the Prostate cancer Research International: Active Surveillance (PRIAS) study started to collect data to analyze the ability of MRI to reduce the number of protocol-based biopsy sessions. In an initial analysis in 2017, no patient with a Prostate Imaging Reporting and Data System (PIRADS) score of ≤3 and a prostate-specific antigen (PSA) density of <0.15 ng/ml cm^3 showed GG progression/reclassification [16]. Hence, a protocol-based biopsy might safely be omitted in this subgroup of patients. However, the sample size of the initial cohort was too small to give a strong recommendation.

In the current analysis, we aim to determine the predictors of GG progression/reclassification in patients undergoing an MRI-informed prostate biopsy (MRI-Bx) during AS, enabling the identification of patients who could potentially skip a protocol-based biopsy. In addition, we evaluated whether it is safe to omit the confirmatory biopsy in patients diagnosed with upfront MRI.

2. Patients and methods

The PRIAS study is a multicenter prospective study that aims to provide an evidence-based recommendation on which patients to include in AS and how to perform the follow-up. Clinicians from all over the world can include PCa patients who opted for an AS strategy and provided informed consent. Based on the online entered patient characteristics, the PRIAS website automatically displays how to continue AS according to the fixed PRIAS follow-up schedule. In the period 2013–2021 (reflecting our current study cohort), the inclusion criteria for patients' follow-up using MRI were the following: PCa GG1, no evidence of extracapsular extension on digital rectal examination (DRE), PSA <10 ng/ml, a PSA density of <0.2 ng/ml cm^3, and fitness for definitive treatment. Patients aged over 70 yr with GG2, with a maximum of 10% involvement per biopsy core and two or fewer positive cores, were also allowed to be included. The follow-up schedule recommends that if no upfront MRI is performed, perform MRI with targeted biopsy (TBx) 3 mo after inclusion. Furthermore, the schedule recommends performing MRI with TBx and systematic biopsy (SBx) after 1, 4, 7, and 10 yr, and every 5 yr thereafter. Recently, the inclusion criteria were updated to allow for the inclusion of more patients with intermediate-risk PCa (without invasive cribriform and intraductal carcinoma). The complete inclusion criteria and complete follow-up schedule are available on www.prias-project.org.

2.1. Study population

To determine the predictors of GG reclassification after MRI-Bx, we included all patients in the PRIAS study under-

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going MRI-Bx during AS, irrespective of the time of biopsy. We excluded patients with a lesion (PIRADS ≥3) on MRI who did not undergo TBx. Patients who underwent multiple subsequent MRI-Bx sessions while on AS were included as separate events.

To determine the need to perform MRI-Bx early during AS and to determine the effect of upfront MRI on the risk of reclassification at MRI-Bx while on AS, we selected two subgroups of patients: group A consists of patients diagnosed without upfront MRI and group B consists of patients diagnosed with upfront MRI. The PRIAS protocol recommends MRI with possible TBx 3 mo after inclusion in patients diagnosed without upfront MRI. If these patients subsequently underwent MRI-Bx, they were included in group B (see Fig. 1).

2.2. Statistical analysis

A time-dependent Cox proportional hazard regression model is considered appropriate for analyzing the time-to-event outcome and the repeated measurements of the patients included. We used the time between the last MRI and the current MRI, or in the case of the first MRI, the time between diagnosis and MRI as the time indicator. Covariates included DRE outcome, age at biopsy, PIRADS score, PSA density at the time of MRI, and percentage positive cores on the last SBx. The outcome of the analysis was reclassification, defined as a higher GG after MRI-Bx than before the procedure. As a sensitivity analysis, we performed an additional analysis with GG ≥3 as the outcome. For interpretation purposes, we rescaled the age at biopsy per 10 yr, the PSA density per 0.10 ng/ml cm^3, and the percentage positive cores per 10%. Since the PIRADS score is a categorical variable, we assessed its overall effect on reclassification using the likelihood ratio test. To assess the predictors of reclassification at the first biopsy during AS, we performed a multivariable logistic regression analysis including the same predictors as described above and the predictor of whether MRI was performed before the diagnostic biopsy. Missing data of percentage positive cores were imputed with predicting mean matching. Statistical analyses were performed with R version 4.1.0 complemented with R-package survival (R Foundation for Statistical Computing, Vienna, Austria) [17,18].

3. Results

A total of 2755 MRI scans were performed during AS, of which we excluded 629 MRI scans because no TBx was performed while the MRI showed a lesion (PIRADS ≥3) and 638 negative MRI scans because no SBx was performed (as recommended by the protocol at 3 mo). Finally, 1185 patients who underwent 1488 MRI-Bx sessions during AS were included. The median PSA at the time of MRI-Bx was 6.7 (interquartile range [IQR] 4.9–9.2) ng/ml (Table 1). The median time from inclusion to MRI-Bx was 13 (IQR 10–40) mo.

Overall, 326 (22%) and 106 (7%) patients were reclassified to GG ≥2 and ≥3 at MRI-Bx. Reclassification to GG ≥2 and ≥3 was seen in 30 (6%) and five (1%) patients with negative MRI and in 296 (29%) and 101 (10%) patients with a lesion (PIRADS ≥3) on MRI, respectively (Table 2). The time-dependent Cox analysis showed that age, MRI outcome, PSA density, and percentage positive cores on the last SBx density are significant predictors of GG reclassification, and DRE is not (Table 3). To elaborate, an increase of 10 yr results in a hazard ratio (HR) of 0.84 (95% confidence interval [CI] 0.71–0.99) for reclassification during subsequent MRI-Bx. Moreover, patients with PIRADS scores of 3, 4, and 5 have HRs of 2.46 (95% CI 1.56–3.88), 3.39 (95% CI 2.28–5.05), and 4.95 (95% CI 3.25–7.56), respectively, to reclassify compared with patients with negative MRI. For PSA density, an increase of 0.1 ng/ml cm^3 results in an HR of 1.20 (95% CI 1.12–1.30) to reclassify at a subsequent biopsy, and a 10% increase in percentage positive cores on the last SBx results in an HR of 1.16 (95% CI 1.10–1.23). The sensitivity analysis with reclassification to GG ≥3 as the outcome variable is shown in Supplementary Table 1. These results highlight the importance of MRI outcome and PSA density in predicting reclassification at MRI-BX. Figure 2 shows the upgrading-free survival over time of the cohort included in this analysis.

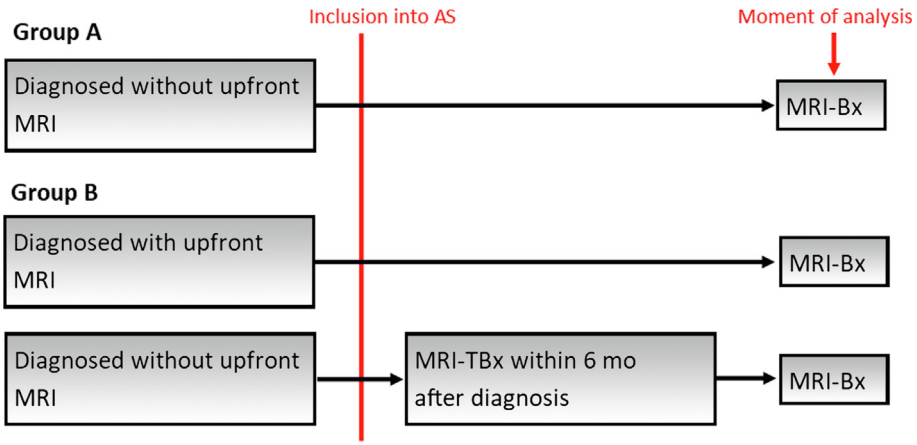

Fig. 1 – Composition of groups A and B to determine the effect of MRI-targeted biopsy on the probability of being reclassified on follow-up biopsy. AS = active surveillance; MRI = magnetic resonance imaging; MRI-Bx = MRI-informed prostate biopsy; MRI-TBx = MRI with targeted biopsy.

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Table 1 – Characteristic of patients included in the time-dependent Cox model analysis and the two group of patients included in the multivariable logistic regression analysis

	All	Confirmatory biopsy after first MRI	Confirmatory biopsy after second MRI
Number of MRI-informed biopsies	1488	553	262
Age at MRI (yr)	67 (62–72)	66 (61–71)	67 (62–72)
PSA at MRI	6.7 (4.9–9.2)	6.2 (4.7–8.3)	6.2 (4.3–8.4)
PSA density at MRI	0.14 (0.09–0.21)	0.13 (0.09–0.20)	0.13 (0.08–0.19)
DRE at MRI			
T1c	1337 (89.9%)	486 (87.9%)	238 (90.8%)
T2a	131 (8.8%)	59 (10.1%)	18 (6.9%)
T2b	10 (0.7%)	3 (0.5%)	3 (1.1%)
T2c	6 (0.4%)	3 (0.5%)	3 (1.1%)
T3	4 (0.3%)	2 (0.4%)	0 (0%)
Grade group before MRI			
1	1412 (95%)	538 (97%)	250 (95%)
2	76 (5%)	15 (3%)	12 (5%)
Time between diagnosis and MRI	13 (10–40)	11 (5–12)	12 (11–14)
Time between first and second MRI	–	–	12 (10–14)
Number of previous MRI scans			
0	902 (61%)	553 (100%)	
1	465 (31.3%)		262 (100%)
2	98 (6.6%)		
3	23 (1.5%)		
Outcome first MRI			
No lesion	467 (31.4%)	197 (36%)	92 (35%)
PIRADS 3	272 (18.3%)	100 (18%)	40 (15%)
PIRADS 4	536 (36%)	195 (35%)	93 (36%)
PIRADS 5	213 (14.3%)	61 (11%)	37 (14%)
Percentage positive cores on last SBx			
0–5%	292 (19.6%)	21 (3.8%)	27 (10.3%)
5.1–10%	495 (33.3%)	251 (45.4%)	86 (32.8%)
10.1–15%	134 (9.0%)	62 (11.2%)	30 (11.5%)
15.1%–20	274 (18.4%)	116 (21.0%)	60 (22.9%)
20.1–30%	139 (9.3%)	47 (8.5%)	32 (12.2%)
>30.1%	135 (9.1%)	56 (10.1%)	22 (8.4%)
Missing	19 (1.3%)		5 (1.9%)
Biopsies in case of a lesion			
Targeted biopsy only	338 (33%)	113 (32%)	26 (15%)
Targeted and systematic biopsy	683 (67%)	243 (68%)	144 (85%)

DRE = digital rectal examination; MRI = magnetic resonance imaging; PIRADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; SBx = systematic biopsy.

Table 2 – Outcome of biopsy stratified to PIRADS score in all patients included in the time-dependent Cox model analysis, patients diagnosed with systematic biopsy who underwent first MRI before confirmatory biopsy (group A), and patients who underwent second MRI before confirmatory biopsy and were included with MRI with targeted biopsy in case of a lesion (group B)

		Grade group at biopsy					
		0	1	2 (no reclassification)	2 (reclassification)	≥3	Total
	All patients						
Outcome MRI	PIRADS 3	88	129	6	37	12	272
	PIRADS 4	123	242	19	103	49	536
	PIRADS 5	23	88	7	55	40	213
	No lesion	171	262	4	25	5	467
	Total	405	721	36	220	106	1488
Group A							
Outcome first MRI	PIRADS 3	33	42	1	18	6	100
	PIRADS 4	37	99	5	39	15	195
	PIRADS 5	5	20	1	22	13	61
	No lesion	57	125	1	10	4	197
	Total	132	286	8	89	38	553
Group B							
Outcome second MRI	PIRADS 3	10	24	1	4	1	40
	PIRADS 4	22	42	1	17	11	93
	PIRADS 5	4	18	3	8	4	37
	No lesion	40	47	0	5	0	92
	Total	76	131	5	34	16	262

MRI = magnetic resonance imaging; PIRADS = Prostate Imaging Reporting and Data System.

The risk of GG reclassification at MRI-Bx during AS stratified to MRI outcome and PSA density is displayed in Figure 3. Figure 3 shows that all patients with a PIRADS score of ≥4 have a high risk of being reclassified at a prostate biopsy even with a low PSA density. Of the 315 patients with negative MRI and a PSA density of <0.15 ng/ml cm^3, eight (3%) were reclassified to GG ≥2 and two (0.6%) to GG ≥3. These numbers are, respectively, 20 (13%) and 3

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Table 3 – Outcome of the time-dependent Cox analysis considering upgrading to grade group ≥2 as upgrading for all patients undergoing MRI-informed prostate biopsy during AS

	Hazard ratio (95% confidence interval)	*p* value
DRE		0.052
≤T1c	Ref	
≥T2a	1.35 (1.00–1.84)	
Age (per 10 yr)	0.84 (0.71–0.99)	0.032
MRI outcome		<0.001
Negative	Ref	
PIRADS 3	2.46 (1.56–3.88)	
PIRADS 4	3.39 (2.28–5.05)	
PIRADS 5	4.95 (3.25–7.56)	
PSA density (per 0.1 ng/ml cm^3)	1.20 (1.12–1.30)	<0.001
Percentage positive cores on last SBx (per 10%)	1.16 (1.10–1.23)	<0.001

AS = active surveillance; DRE = digital rectal examination; MRI = magnetic resonance imaging; PIRADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; Ref = reference; SBx = systematic biopsy.

(2%) for patients with negative MRI and a PSA density of ≥0.15 ng/ml cm^3, 21 (17%) and 6 (4%) for patients with a PIRADS score of 3 and a PSA density of <0.15 ng/ml cm^3, and 28 (22%) and 6 (5%) for patients with a PIRADS score of 3 and a PSA density of ≥0.15 ng/ml cm^3.

The subgroup analysis included 553 patients diagnosed without upfront MRI (group A) and 262 patients diagnosed with upfront MRI (group B; Table 1 and Fig. 1). The median time to MRI-Bx was 11 (IQR 5–12) and 12 (IQR 11–14) mo for groups A and B, respectively. In group A, 127 (23%) patients were reclassified to GG ≥2 and 38 (7%) to GG ≥3 (Table 2). Omitting the first biopsy procedure in patients with negative MRI would have reduced the number of biopsy sessions by 36%, at the cost of missing 11% of the patients who were reclassified to GG ≥2 and 11% of those reclassified to GG ≥3. In group B, 50 (19%) patients were reclassified to GG ≥2 and 16 (6%) to GG ≥3. Omitting a biopsy in patients with negative MRI would have reduced the number of biopsy procedures by 35%, at the cost of missing 10% of the patients who were reclassified to GG ≥2 and no reclassification to GG ≥3. There was no significant difference in the risk of being reclassified to groups A and B (group B vs group A: odds ratio [OR] 1.32 [95% CI 0.89–1.98], p = 0.2), whereas MRI outcome, DRE outcome, and PSA density were significant predictors of reclassification (Table 4).

4. Discussion

The available evidence and the resulting guideline recommendations to (temporarily) forgo a prostate biopsy during AS with the use of MRI remain heavily debated in the literature [9–15]. Our results from the multicenter PRIAS study show that upgrading at MRI-Bx during AS is fairly common (22% to GG ≥2 and 7% to GG ≥3). Moreover, age, MRI outcome, PSA density, and percentage positive cores at a previous biopsy are significant predictors of GG reclassification. Overall, MRI outcome seems to be the strongest predictor of GG reclassification. In patients with a PIRADS score of 3 or negative MRI, a multivariable approach is recommended to determine the importance of a protocol-advised biopsy. Patients with negative MRI and a PSA density of <0.15 ng/ml cm^3 represent a very-low-risk group and can safely postpone a protocol-based biopsy. Finally, reclassification rates at the first biopsy while on AS is similar between patients diagnosed with and without upfront MRI (23% to GG ≥2 and 7% to GG ≥3 vs 19% and 6%, respectively). Our results

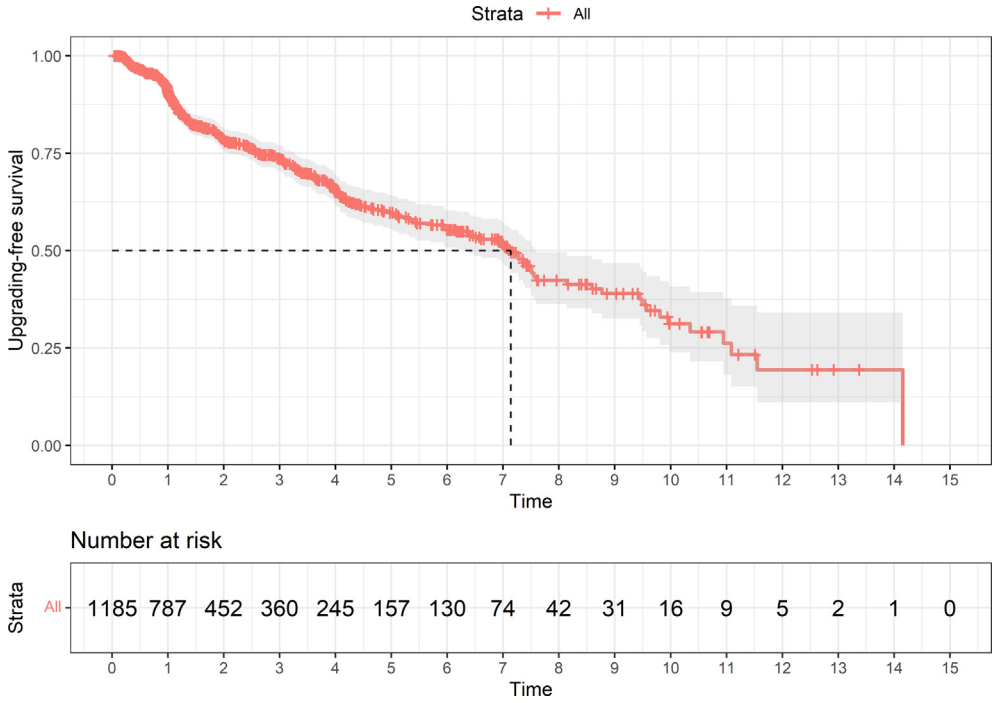

Fig. 2 – Upgrading-free survival over time.

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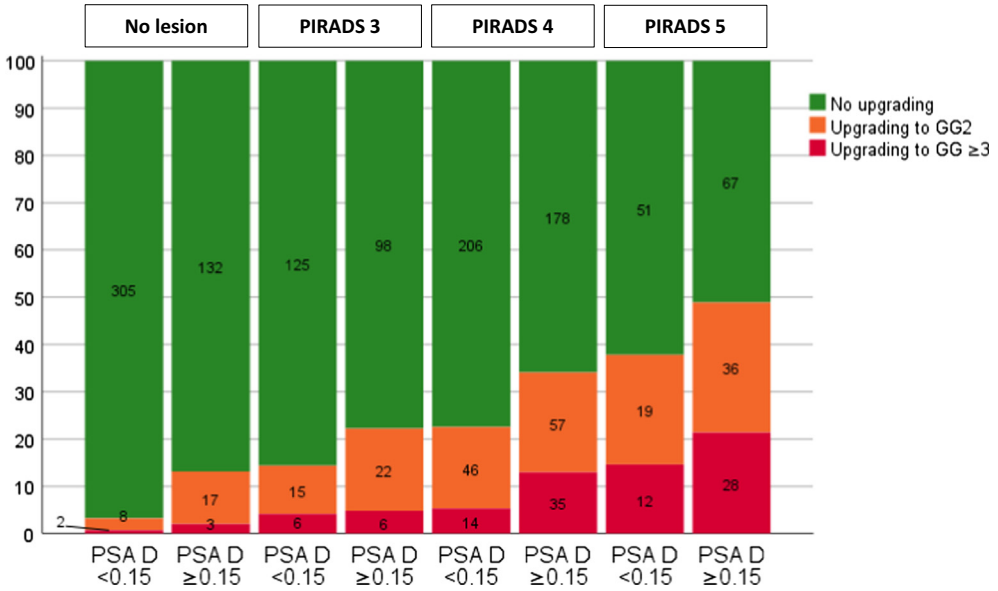

Fig. 3 – The percentage of upgrading after MRI-informed biopsy stratified to MRI outcome and PSA density. The exact number of patients are shown in the bars. GG = grade group; MRI = magnetic resonance imaging; PIRADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; PSA D = PSA density.

Table 4 – Outcome of the multivariable logistic regression analysis considering upgrading to grade group 2 as upgrading for all patients undergoing the first biopsy during AS after their first or second MRI

	Odds ratio (95% CI)	*p* value
DRE		
Benign	Ref	
Suspicious	1.81 (1.08–3.01)	0.02
Age at biopsies (per 10 yr)	1.10 (0.85–1.43)	0.47
MRI outcome		
No lesion	Ref	<0.001
PIRADS 3	3.18 (1.70–6.06)	
PIRADS 4	4.50 (2.66–7.93)	
PIRADS 5	10.14 (5.45–19.47)	
PSA density at MRI (per 0.1 ng/ml cm^3)	1.40 (1.17–1.69)	<0.001
Percentage positive cores on last SBx (per 10%)	1.14 (1.00–1.31)	0.055
With upfront MRI	Ref	
Without upfront MRI	1.32 (0.89–1.98)	0.17

AS = active surveillance; CI = confidence interval; DRE = digital rectal examination; MRI = magnetic resonance imaging; PIRADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; Ref = reference; SBx = systematic biopsy.

highlight the importance of a multivariable approach instead of a one-size-fits-all protocol to determine the most crucial biopsy moments while on AS.

In a recent systematic review, Hettiarachchi et al [13] concluded that "there is significant institutional variation in the diagnostic performance of mp-MRI during AS". In other words, the negative predictive value of MRI during AS differs significantly between centers [9,13,19]. This is likely caused by the different risk characteristics of the cohort described and the quality of the MRI (evaluation) [15,20,21]. All this makes it debatable whether or not it is necessary to perform a protocol-based biopsy in patients with negative MRI during AS. The PIRADS version 2.1 aims to reduce the inter-rater variability and the Prostate Imaging Quality score to assess whether the quality of the MRI is sufficient to exclude significant disease [22,23]. In our multicenter study, we included DRE, age at biopsy, MRI outcome, PSA density, and percentage positive cores on the last SBx to predict GG reclassification at MRI-Bx. Overall, our reclassification rates are similar to those reported in the literature [13,14]. Our results confirm that negative MRI cannot exclude reclassification to GG ≥2(6%); reclassification to GG ≥3 is, however, rare (1%) [9,19,24]. A multivariable risk assessment should be used to determine whether or not prostate biopsies are indicated. We propose to skip a protocol-based prostate biopsy in patients with negative MRI and a PSA density of <0.15 ng/ml cm^3, to use shared decision-making to discuss the need for a prostate biopsy in patients with a PIRADS score of 3 or a PSA density of >0.15 ng/ml cm^3, and not to skip a protocol-based prostate biopsy in all patients with a PIRADS ≥4 lesion. Nevertheless, as described above, it is important to investigate the negative predictive value of the MRI in one's own institutional AS cohort.

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The DETECTIVE consensus meeting agreed that a confirmatory biopsy can be omitted in patients diagnosed with upfront MRI [12]. Tosoian et al [3] and Dieffenbacher et al [27] showed that patients diagnosed with upfront MRI were significantly less likely to be reclassified during AS. In the ASIST trial, the reported risk reduction was, however, reported only in patients treated in experienced centers [15]. Moreover, a risk reduction does not automatically mean that the protocol-based biopsy can safely be omitted. Our results showed no significant difference in reclassification rates between patients diagnosed with and without upfront MRI. Since PRIAS represents the daily clinical practice and as such is a mix of centers with a highly variable number of patients treated with AS, this calls for awareness of one's clinical setting when implementing guidelines into practice. As such, we feel that the EAU recommendation to omit the confirmatory prostate biopsy in all patients diagnosed with upfront MRI might be premature.

Our study has several limitations. First, no data were available on MRI and biopsy route, and the technique and experience of the radiologists and physicians performing the biopsy. In addition, there is no central reading of MRI and pathology in the PRIAS study. This study, however, is a multicenter trial, making the results most representative of daily clinical practice. Second, not all patients and clinicians strictly followed the recommended follow-up schedule, creating a possible selection bias. This group of patients, however, represents a clinical cohort that includes both high- and low-risk patients. Moreover, although all patients with a lesion on MRI underwent TBx, not all patients underwent SBx simultaneously. Earlier research showed that TBx and SBx complement each other [14]. This, however, does not influence our recommendation to omit a biopsy in patients with negative MRI and a low PSA density. Third, it can be debated whether reclassification to GG $\geq$2 is a suitable endpoint for the time-dependent Cox regression analysis. Our sensitivity analysis, however, showed similar outcomes for reclassification to GG $\geq$3. Fourth, we only included easily available predictors (PSA density, MRI outcome, DRE, age, and percentage positive cores on the last SBx). This could potentially flaw the predictive capability of the model. Moreover, no data were available on the racial characteristics of the patients included. The PRIAS study is, however, a worldwide study. Fifth, we did not study the effect of the Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) score on the risk of upgrading in patients with sequential MRI scans. Finally, the median follow-up time to MRI-Bx was 13 mo. These results can therefore not be extrapolated to MRI-Bx after multiple MRI-Bx sessions.

Future studies should focus on further reducing the number of unnecessary protocol-based prostate biopsies during AS. The added value of prostate-specific membrane antigen positron emission tomography/computed tomography and microultrasound in preventing biopsy, especially in patients with equivocal (PIRADS 3) lesions, should be investigated [25]. A recently published personalized prediction model for the risk of reclassification on AS showed promising results for the ability to prevent unnecessary prostate biopsies using, among others, PSA velocity [26]. These models should be extended with, among others, the MRI outcome and prostate volume to evaluate the possibility of further reducing unnecessary prostate biopsies in the MRI era.

5. Conclusions

Analyses of this multicenter large cohort of PCa patients on AS undergoing MRI-Bx showed the following. First, reclassification at MRI-Bx is fairly common while on AS. Second, age, DRE outcome, MRI outcome, PSA density, and percentage positive cores on the last SBx are important predictors of GG upgrading at MRI-Bx during AS. A protocol-based prostate biopsy can safely be omitted in patients with negative MRI and a PSA density of <0.15 ng/ml cm^3. For patients with a PIRADS 3 lesion, a multivariable approach and shared decision-making seem appropriate to determine the need for a protocol-based biopsy, whereas patients with a PIRADS $\geq$4 lesion should be recommended to undergo a protocol-based biopsy. Third, upgrading at biopsy early during AS is similar between patients included with or without MRI. For clinical practice, this implies that the confirmatory biopsy cannot (yet) be omitted in patients diagnosed with upfront MRI. Future studies should focus on developing personalized models to replace the one-size-fits-all protocols used currently.

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Study concept and design: Luiting, Roobol, Remmers.
Acquisition of data: All authors.
Analysis and interpretation of data: Luiting, Roobol, Remmers.
Drafting of the manuscript: Luiting, Roobol, Remmers.
Critical revision of the manuscript for important intellectual content: Boevé, Valdagni, Chiu, Semjonow, Berge, Tully, Rannikko, Staerman.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2022.03.007.

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