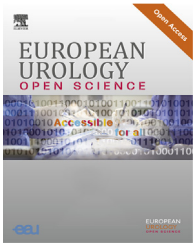
available at www.sciencedirect.com
journal homepage: www.eu-openscience.europeanurology.com



European Association of Urology

Prostate Cancer

Magnetic Resonance Imaging-guided Active Surveillance Without Annual Rebiopsy in Patients with Grade Group 1 or 2 Prostate Cancer: The Prospective PROMM-AS Study

Birte Valentin[a], *Christian Arsov*[b,c], *Tim Ullrich*[a], *Rouvier Al-Monajjed*[b], *Matthias Boschheidgen*[a], *Boris A. Hadaschik*[d], *Francesco Giganti*[e,f], *Markus Giessing*[b], *Cristina Lopez-Cotarelo*[g], *Irene Esposito*[g], *Gerald Antoch*[a], *Peter Albers*[b,h], *Jan Philipp Radtke*[b,i,†,*], *Lars Schimmöller*[a,j,†]

[a] *Department of Diagnostic and Interventional Radiology, University of Düsseldorf, Düsseldorf, Germany;* [b] *Department of Urology, University of Düsseldorf, Düsseldorf, Germany;* [c] *Elisabeth-Krankenhaus Rheydt, Department of Urology and Paediatric Urology, Staedtische Kliniken Moenchengladbach GmbH, Moenchengladbach, Germany;* [d] *Department of Urology, University Hospital Essen, Essen, Germany;* [e] *Department of Radiology, University College London Hospitals NHS Foundation Trust, London, UK;* [f] *Division of Surgery and Interventional Science, University College London, London, UK;* [g] *Institute of Pathology, Medical Faculty, University of Düsseldorf, Düsseldorf, Germany;* [h] *Division of Personalized Early Detection of Prostate Cancer, German Cancer Research Center, Heidelberg, Germany;* [i] *Department of Radiology, German Cancer Research Center, Heidelberg, Germany;* [j] *Department of Diagnostic, Interventional Radiology and Nuclear Medicine, Marien Hospital Herne, University Hospital of the Ruhr-University Bochum, Herne, Germany*

Article info

Article history:
Accepted October 16, 2023

Associate Editor:
Roderick van den Bergh

Keywords:
Prostate cancer
Magnetic resonance imaging
Transrectal ultrasound fusion-guided biopsy
Active surveillance
Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE)

Abstract

Background: Multiparametric magnetic resonance imaging (mpMRI) may allow patients with prostate cancer (PC) on active surveillance (AS) to avoid repeat prostate biopsies during monitoring.

Objective: To assess the ability of mpMRI to reduce guideline-mandated biopsy and to predict grade group upgrading in patients with International Society of Urological Pathology grade group (GG) 1 or GG 2 PC using Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) scores. The hypothesis was that the AS disqualification rate (ASDQ) rate could be reduced to 15%.

Design, setting and participants: PROMM-AS was a prospective study assessing 2-yr outcomes for an mpMRI-guided AS protocol. A 12 mo after AS inclusion on the basis of MRI/transrectal ultrasound fusion-guided biopsy (FBx), all patients underwent mpMRI. For patients with stable mpMRI (PRECISE 1–3), repeat biopsy was deferred and follow-up mpMRI was scheduled for 12 mo later. Patients with mpMRI progression (PRECISE 4–5) underwent FBx. At the end of the study, follow-up FBx was indicated for all patients.

Outcome measurements and statistical analysis: We calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for upgrading to GG 2 in the GG 1 group, and to GG 3 in the GG 2 group on MRI. We performed regression analyses that included clinical variables.

† These authors are joint senior authors.
* Corresponding author. Department of Radiology, German Cancer Research Center, Heidelberg, Germany.

https://doi.org/10.1016/j.euros.2023.10.005

Results and limitations: The study included 101 patients with PC (60 GG 1 and 41 GG 2). Histopathological progression occurred in 31 patients, 18 in the GG 1 group and 13 in the GG 2 group. Thus, the aim of reducing the ASDQ rate to 15% was not achieved. The sensitivity, specificity, PPV, and NPV for PRECISE scoring of MRI were 94%, 64%, 81%, and 88% in the GG 1 group, and 92%, 50%, 92%, and 50%, respectively, in the GG 2 group. On regression analysis, initial prostate-specific antigen ($p < 0.001$) and higher PRECISE score (4–5; $p = 0.005$) were significant predictors of histological progression of GG 1 PC. Higher PRECISE score ($p = 0.009$), initial Prostate Imaging-Reporting and Data System score ($p = 0.009$), previous negative biopsy ($p = 0.02$), and percentage Gleason pattern 4 ($p = 0.04$) were significant predictors of histological progression of GG 2 PC. Limitations include extensive MRI reading experience, the small sample size, and limited follow-up.
Conclusions: MRI-guided monitoring of patients on AS using PRECISE scores avoided unnecessary follow-up biopsies in 88% of patients with GG 1 PC and predicted upgrading during 2-yr follow-up in both GG 1 and GG 2 PC.
Patient summary: We investigated whether MRI (magnetic resonance imaging) scores can be used to guide whether patients with lower-risk prostate cancer who are on active surveillance (AS) need to undergo repeat biopsies. Follow-up biopsy was deferred for 1 year for patients with a stable score and performed for patients whose score progressed. After 24 months on AS, all men underwent MRI and biopsy. Among patients with grade group 1 cancer and a stable MRI score, 88% avoided biopsy. For patients with MRI score progression, AS termination was correctly recommended in 81% of grade group 1 and 92% of grade group 2 cases.

1. Introduction

For patients with low-risk International Society of Urological Pathology grade group 1 (GG 1) prostate cancer (PC) and selected cases with favorable intermediate-risk PC, active surveillance (AS) is recommended, which avoids unnecessary, potentially harmful, active treatments in patients with indolent disease [1–3]. It has been shown that AS is safe in terms of cancer-specific survival over long-term follow-up [3].

Most AS protocols, including the Prostate Cancer Research International Active Surveillance (PRIAS) protocol, recommend follow-up biopsies to justify a switch to active treatment based on histological progression [2]. However, protocol adherence to repeat biopsies on AS reduces over time [4]. Thus, whether or not a follow-up biopsy can be safely omitted in patients with clinically histopathological stable PC is still debated [5–7]. In addition, it remains unclear whether histological progression can be predicted by multiparametric magnetic resonance imaging (mpMRI) [8].

One approach to improve risk stratification in AS patients is structured reporting of sequential mpMRI scans using Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) criteria [9]. On internal and external validation, the negative predictive value (NPV) of PRECISE (score 1–2) in ruling out upgrading was nearly 100% [8,10]. In addition, the European Association of Urology (EAU) guidelines have removed the recommendation for early reclassification biopsies when AS inclusion is based on upfront mpMRI and MRI/transrectal ultrasound (TRUS) fusion-guided biopsy (FBx) [3]. AS might be also feasible in GG 2 PC, with metastasis-free 5-yr survival rates of approximately 64–68% [11,12]. However, data on MRI and PRECISE criteria are sparse in GG 2 PC [13].

Here we present 2-yr follow-up data from PROMM-AS, a prospective evaluation of mpMRI and MRI-guided biopsy for AS in PC. mpMRI was used as a stratification tool for patients with GG 1 or GG 2 PC managed with AS after initial FBx that included targeted and systematic cores. The aim of the trial was to use MRI for stratification to correctly predict patients without clinical progression who could avoid repeat biopsies during AS to guide treatment decisions.

2. Patients and methods

2.1. Study design

After institutional review board approval (ID 2017034168), the PROMM-AS study included patients with low-risk (GG 1) or favorable intermediate-risk (GG 2) PC. This prospective, single-arm, phase 2 study evaluated mpMRI and MRI-guided biopsies for AS with the primary endpoint of reducing AS discontinuation on the basis of histology reclassification at 24-mo follow-up FBx. We proposed that the results would allow definition of an MRI-based pathway to identify and monitor patients suitable for AS. Our hypothesis was that the high rate of discontinuation due to misclassification at initial diagnosis would be reduced. We investigated if follow-up MRI scans at 12 and 24 mo after AS inclusion based on initial mpMRI and FBx can reliably guide immediate or deferred follow-up biopsy. FBx included both targeted and systematic cores. In our center, only men with at least one Prostate Imaging-Recording and Data System (PI-RADS) $\geq$3 lesion undergo biopsy. Thus, only men with visible lesions were included. The study design included follow-up mpMRI at 12 mo, and another follow-up mpMRI and FBx at 24 mo after enrollment (Fig. 1). Prostate-specific antigen (PSA) levels were

measured every 3 mo throughout the entire study period. In the event of a PSA increase exceeding ≥0.75 ng/ml/yr, patients underwent additional follow-up mpMRI [2]. Progression was assessed using the PRECISE score. If the follow-up mpMRI was stable (PRECISE score 1–3), the patient did not undergo repeat biopsy at 12 mo or at additional follow-up mpMRI triggered by a PSA increase. If there was evidence of mpMRI progression (PRECISE score 4–5), FBx was carried out immediately. In cases of confirmed histopathological progression, participation in the study was terminated. If no histopathological progression occurred, the study protocol continued as originally planned and concluded with follow-up mpMRI and FBx at 24 mo.

As detailed in the protocol (NCT03979573), the sample size was determined with reference to a 95% confidence interval (CI) for the primary endpoint, which was a reduction in the AS discontinuation rate after 24 mo because of histopathological disqualification (upgrading to GG ≥2 in the GG 1 group or to GG ≥3 in the GG 2 group) from 25%, as reported by Tosoian et al [14], to the 15% reported by Hoeks et al [15]. Assuming an expected proportion of 15% in this study, the CI excluded the (at time of study conception) observed proportion of 22% [14,15]. Thus, the sample size was calculated as 150 patients.

2.2. *Imaging and image analysis*

Patients underwent baseline and protocol-mandated mpMRI after 12 and 24 mo and in cases of PSA progression. Contrast medium–supported mpMRI (ProHance; Bracco Imaging, Konstanz, Germany) examinations

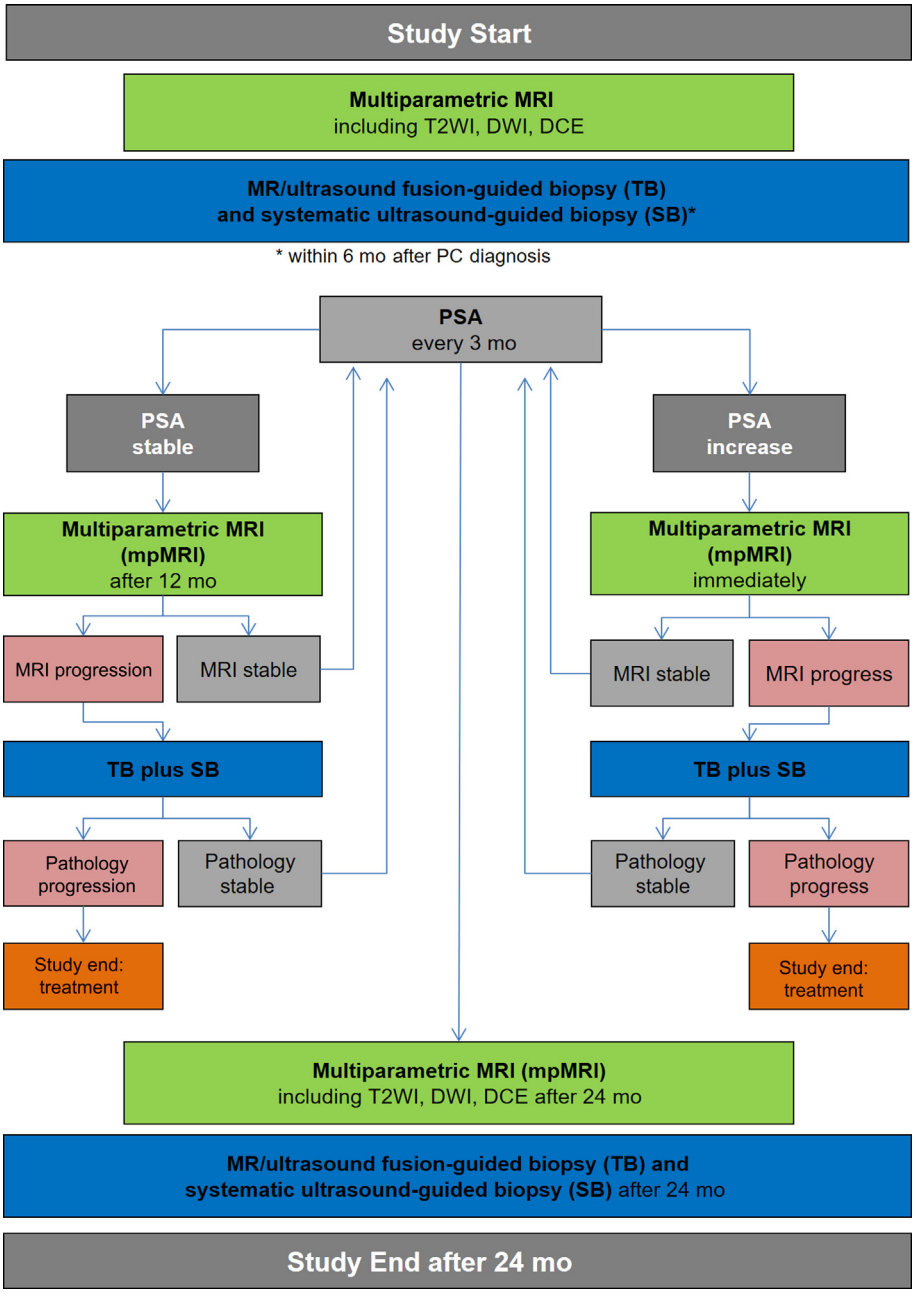


Fig. 1 – Flowchart of the study design. MRI = magnetic resonance imaging; T2WI = T2-weighted imaging; DWI = diffusion-weighted imaging; DCE = dynamic contrast enhancement; PC = prostate cancer; PSA = prostate-specific antigen.

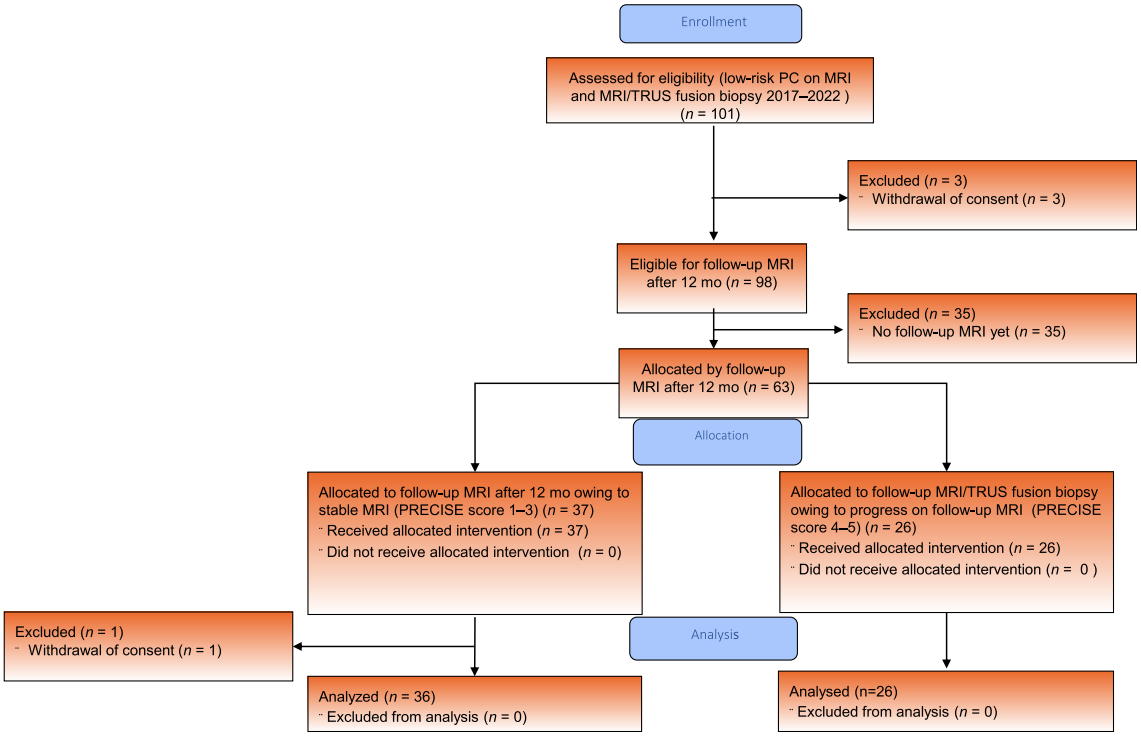


Fig. 2 – Consolidated Standards of Reporting Trials (CONSORT) flow chart. MRI = magnetic resonance imaging; PC = prostate cancer; PRECISE = Prostate Cancer Radiological Estimation of Change in Sequential Evaluation; TRUS = transrectal ultrasound.

Table 1 – Patient demographics

Parameter	Initial GG 1	Initial GG 2
Patients (*n*)	60	41
Withdrew consent before 12-mo follow-up MRI (*n*)	1	2
Patients included in the analysis (*n*)	59	39
Withdrew consent after 12-mo follow-up MRI (*n*)	1	0
Median age, yr (IQR)	60 (52–70)	68 (58–73)
Median prebiopsy PSA, ng/ml (IQR)	5.0 (3.7–7.6)	6.3 (5.0–8.9)
Suspicious DRE findings (cT2a), *n* (%)	9 (15)	5 (13)
Median prostate volume, ml (IQR)	38 (30–53)	39 (25–46)
Prior prostate biopsy, *n* (%)	10 (17)	9 (23)
Biopsy-naïve, *n* (%)	49 (83)	30 (77)
Median PSA density, ng/ml/ml (IQR)	0.14 (0.11–0.19)	0.20 (0.11–0.30)
Initial PI-RADS 3 score, *n* (%)	14 (23)	4 (10)
Initial PI-RADS 4 score, *n* (%)	37 (63)	27 (69)
Initial PI-RADS 5 score, *n* (%)	8 (14)	8 (21)
Median number of biopsies per patient, *n* (IQR)	14 (14–14)	14 (14–14)

GG = International Society of Urological Pathology grade group; MRI = magnetic resonance imaging; PSA = prostate-specific antigen, DRE = digital rectal examination; PI-RADS = Prostate Imaging-Reporting and Data System.

were performed on a 3-T MRI scanner (Magnetom PRISMA, Siemens, Erlangen, Germany). The mpMRI protocol was in accordance with PI-RADS v2.1 recommendations [16].

All examinations were prospectively evaluated by or under the supervision of a board-certified radiologist (L.S.) with >10 yr of experience in reading prostate MRI (600 scans/yr). PI-RADS and PRECISE scores were assigned according to PI-RADS v2.1 and PRECISE recommendations [9,17]. Prostate volume was measured on MRI using DynaCAD software. Lesions were reported using the PI-RADS scoring sheet including the sectors [17]. Reflecting routine clinical practice, radiologists and urologists were not blinded to clinical data. Lesion contours were drawn by uroradiologists using UroNAV. All scans were of high MRI quality, defined as a Prostate Imaging Quality (PI-QUAL) score of 4 or 5 [18].

In accordance with PRECISE criteria, MRI progression was defined as a reduction in apparent diffusion coefficient (ADC) of $\leq$20% for the tumor on equitable region-of-interest measurements, or lesion size progression $\geq$20% on T2-weighted imaging or ADC maps, or detection of a new lesion with a PI-RADS score of 4 or 5 [9].

2.3. *Biopsy and histopathology*

The UroNAV platform was used for transrectal FBx, including targeted cores (TB, median 2 per lesion) and systematic cores (SB, median 12) [19]. Each procedure was performed by board-certified urologists with >4 yr of experience in FBx. The operator had access to all mpMRI data. TB and SB cores were placed in containers and reported separately. His-

tological tissue samples were examined according to International Society of Urological Pathology guidelines by or under the supervision of a uropathologist with >10 yr of experience in prostate pathology (C.L.C.) [20].

2.4. Statistical analyses

Patient demographic data are reported using descriptive statistics. The sensitivity, specificity, positive predictive value (PPV), and NPV were calculated for PRECISE scores for serial MRI scans and follow-up biopsies with 95% CI. Regression analyses for AS disqualification were performed for clinical and MRI parameters. Continuous-variable effects were modeled nonparametrically using linear tail-restricted cubic splines or with simple transformations (log transformation, polynomials). Log-transformed PSA was used. To account for nonlinearity between PRECISE categories (especially between categories 1–3 and 4–5), PRECISE was modeled using cubic splines. All tests were two-sided with a significance level of 5%. Statistical analyses were performed using PRISM 9.4.1 (GraphPad, San Diego, CA, USA). Reporting followed the Standards of Reporting of Diagnostic Accuracy (Supplementary Table 1) and were in accordance with the CONSORT statement [21]. The CONSORT checklist is provided in Supplementary Table 2.

3. Results

Between September 2017 and September 2022, 101 patients were prospectively included in the study. After three patients withdrew consent, a total of 98 patients with GG 1 or GG 2 PC with initial mpMRI and FBx were available for analysis (Fig. 2). Imaging and histopathological outcomes were analyzed continuously. After recognizing that the primary endpoint of reducing the histopathological upgrading rate to 15% could not be achieved, as upgrading occurred in 31 patients, an interim intention-to-treat analysis was performed.

The demographic parameters and the distribution of initial mpMRI PI-RADS scores, PRECISE scores, and biopsy results are given in Table 1. Results stratified according to MRI stability versus MRI progression according to PRECISE scores (1–3 vs 4–5) are shown in Figures 3 and 4, Table 2, and Supplementary Table 3. Overall, 18/60 patients initially diagnosed with GG 1 PC via FBx were disqualified from AS because of histopathological upgrading, as were 13/41 patients with initial GG 2 PC. Details for these 18 patients in the GG 1 group are listed in Supplementary Table 4. Supplementary Tables 5 and 6 give an overview of patient, biopsy, and MRI characteristics for disqualified and nondisqualified cases.

At 12-mo follow-up, 26/63 patients overall experienced MRI progression and 37 had stable MRI findings. After 24 mo, 12/24 patients overall showed MRI progression and 12 had stable MRI. MRI progression occurred in 37% of the GG 1 group and 50% of the GG 2 group at 12-mo follow-up, and in 47% of the GG 1 group and 60% of the GG 2 group at 24 mo (Figs. 3 and 4). A total of 59% of patients with GG 1 PC and 64% of patients with GG 2 PC showed MRI progression over the 24-mo study period. Details on the sensitivity, specificity, PPV, and NPV for MRI scoring are given in Table 2. In the group with initial GG 1 PC, the sensitivity was 94% and the NPV for ruling out disqualification was 88%. The specificity was 64% and the PPV was 81%. In the

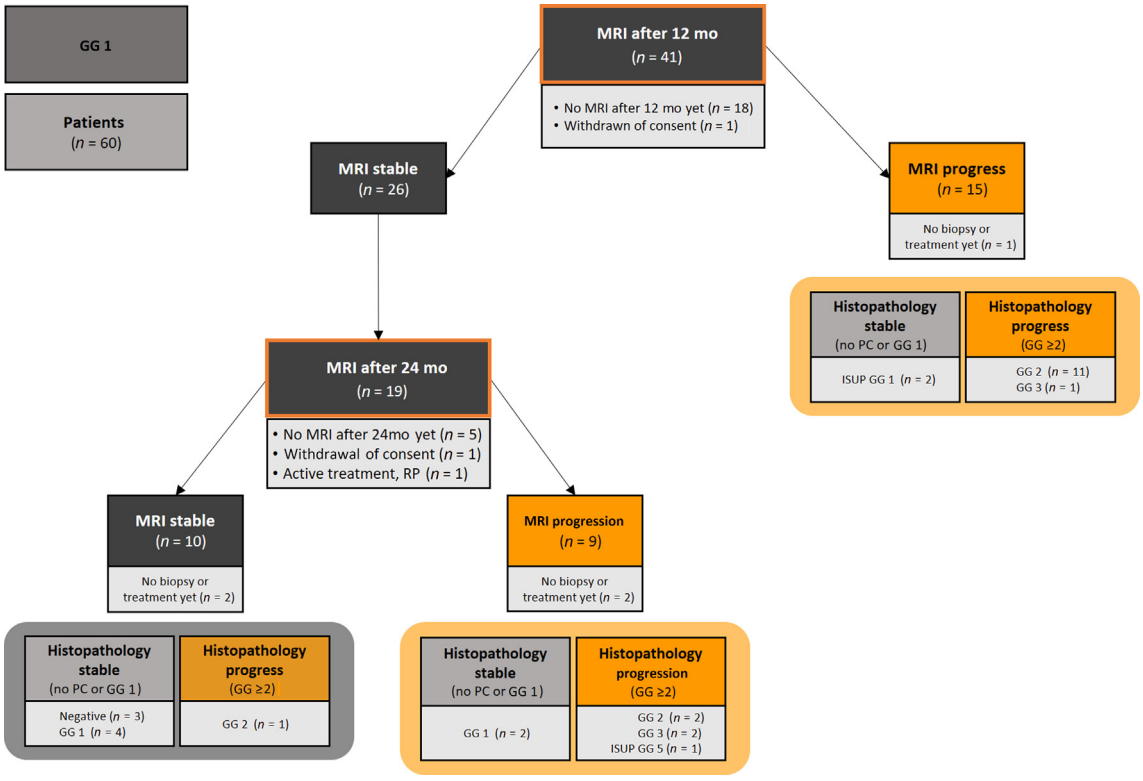


Fig. 3 – Flowchart of follow-up MRI and MRI/transrectal ultrasound fusion biopsy in the group with International Society of Urological Pathology grade group 1 (GG 1) PC. MRI = magnetic resonance imaging; PC = prostate cancer; RP = radical prostatectomy.

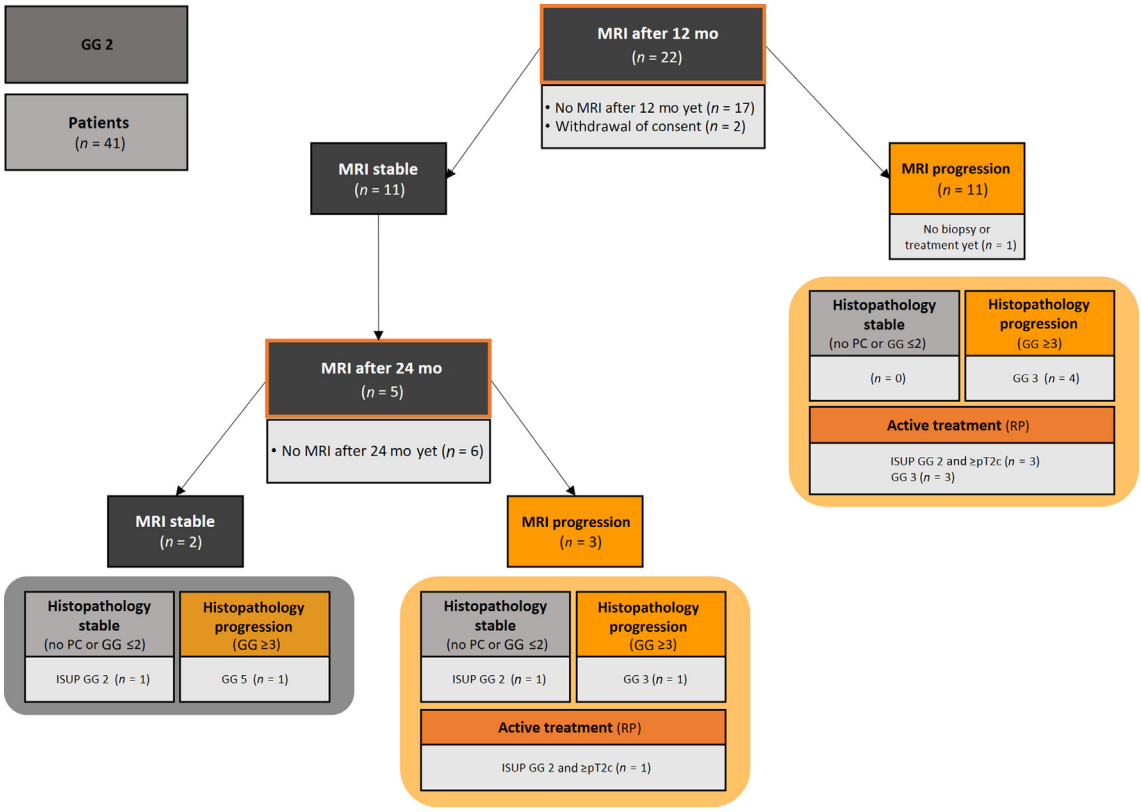


Fig. 4 – Flowchart of follow-up MRI and MRI/transrectal ultrasound fusion biopsy in the group with International Society of Urological Pathology grade group 2 (GG 2) PC. MRI = magnetic resonance imaging; PC = prostate cancer; RP = radical prostatectomy.

Table 2 – Cross tabulation of MRI and histopathology findings, with sensitivity, specificity, PPV, and NPV results for the GG 1 and GG 2 subgroups

MRI findings	Histopathology			Specificity, % (95% CI)	Sensitivity, % (95% CI)	Accuracy (95% CI)	NPV, % (95% CI)	PPV, % (95% CI)
	Stable	PG	Total					
GG 1 subgroup								
Stable [a]	7	1	8					
PG [b]	4	17	21					
Total	11	18	29	64 (31–89)	94 (73–100)	83 (64–94)	88 (50–98)	81 (66–90)
GG 2 subgroup								
Stable [a]	1	1	2					
Progression [b]	1	12	13					
Total	2	13	15	50 (1.3–99)	92 (64–100)	87 (60–98)	50 (8.9–91)	92 (75–98)

GG = International Society of Urological Pathology grade group; PG = progression; PPV = positive predictive value; NPV = negative predictive value; CI = confidence interval; MRI = magnetic resonance imaging; PRECISE = Prostate Cancer Radiological Estimation of Change in Sequential Evaluation.
[a] PRECISE score 1–3.
[b] PRECISE score 4–5.

GG 2 group, the sensitivity was 92%, specificity was 50%, PPV was 92%, and NPV was 50%.

Clinical and MRI parameters were analyzed for their ability to predict histopathological upgrading. A PRECISE score of 4–5 was a significant predictor of AS disqualification in both groups (p = 0.005 for GG 1 and p = 0.009 for GG 2; Table 3). Initial PSA was a significant predictor in the GG 1 group (p < 0.001), whereas initial PI-RADS classification (p = 0.007), percentage Gleason pattern 4 (p = 0.04), and previous biopsy status (p = 0.02) were significant predictors in the GG 2 group.

4. Discussion

Overall, our study showed upgrading in 31% of patients despite initial MRI and FBx. Of note, the overall reclassification rates within the 2-yr AS period were higher than initially expected. In part this was because of the relatively high proportion of patients with GG 2 PC on FBx. The reclassification rate for initial GG 1 PC is comparable to follow-up biopsy results in the study by (34%) Stavrinides et al [8]. In general, reclassification rates of 19–23% are expected [8,10,22]. This difference might be explained by our cohort,

Table 3 – Regression analyses using cubic splines and polynomials for prediction of active surveillance disqualification in the GG 1 and GG 2 subgroups

Parameter	OR	95% CI	*p* value
GG1 subgroup			
PRECISE score for sequential MRI scans (4–5 vs 1–3)	2.80 (2.18–4.03)		**0.005**
Initial PSA	1.33 (5.13–8.10)		**<0.001**
Initial PSA density	2.29 (0.96–2.78)		0.83
Initial PI-RADS category (4–5 vs 3)	1.71 (0.55–6.35)		0.38
Negative prebiopsy (yes vs no)	4.95 (−3.37 to 13.28)		0.06
Prostate volume (per 10-ml increment)	0.95 (0.90–1.00)		0.06
Digital rectal examination (<cT2 vs ≥cT2)	1.09 (−3.85 to 5.91)		0.28
Age (per 5-yr increment)	1.14 (0.98–1.09)		0.25
PSA kinetics (>0.75 ng/ml/yr)	0.06 (−1.93 to 2.05)		0.90
Median number of positive cores	2.42 (0.71–10.52)		0.18
Median percentage of positive cores	0.89 (0.72–1.07)		0.24
Median maximal percentage core infiltration	1.03 (0.99–1.07)		0.12
GG 2 subgroup			
PRECISE score for sequential MRI scans (4–5 vs 1–3)	7.80 (2.08–34.15)		**0.009**
Initial PSA	0.02 (−0.03 to 0.07)		0.52
Initial PSA density	0.61 (−2.04 to 5.94)		0.70
Initial PI-RADS category (4–5 vs 3)	4.09 (3.53–4.64)		**0.007**
Negative prebiopsy (yes vs no)	0.97 (−0.93 to 3.12)		**0.02**
Prostate volume (per 10-ml)	0.08 (−0.35 to 0.50)		0.71
Digital rectal examination (<cT2 vs ≥cT2)	0.10 (−3.10 to 8.13)		0.84
Age (per 5-yr increment)	0.05 (0.10–0.20)		0.49
PSA kinetics (>0.75 ng/ml/yr)	0.06 (−1.93 to 2.05)		0.90
Percentage of positive cores	1.05 (0.88–1.28)		0.6
Maximal percentage core infiltration	1.05 (0.99–1.24)		0.33
Percentage Gleason pattern 4	1.16 (1.03–1.39)		**0.04**
Cribriform pattern	3.50 (0.29–82.58)		0.34

CI = confidence interval; GG = International Society of Urological Pathology grade group; MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging-Reporting and Data System; PRECISE = Prostate Cancer Radiological Estimation of Change in Sequential Evaluation; PSA = prostate-specific antigen.

which exclusively comprised patients with MRI-visible lesions, with a PI-RADS score of 4 or 5 in 77% of patients in the GG 1 group and 90% in the GG 2 group, and thus representing a cohort at risk of harboring more aggressive tumor than in low-risk PC cohort with mostly negative MRI findings.

In terms of the reliability of MRI as a stratification tool in AS, our results for the GG 1 group suggests that follow-up MRI outcomes seem to be a reliable predictor of grade group reclassification. In particular, when follow-up MRI examinations were stable (PRECISE 1–3) the NPV for ruling out AS disqualification in low-risk PC was 88% over the 2-yr period after AS inclusion. This study is one of the first to prospectively analyze the ability of MRI to detect upgrading of GG 2 PC during AS. The PPV of 92% suggests that MRI progression is a strong predictor of histopathological reclassification and might indicate that follow-up biopsies can be avoided, and such patients could directly proceed to active treatment. Conversely, the low NPV of 50% may mean it would be unwise to skip (or at least defer) repeat biopsies in these patients. However, the low NPV for this subgroup is a result of the low number of cases. In the GG 1 group the NPV of 88% for ruling out AS disqualification is higher than the 80% reported by Chu et al [5] and comparable to findings by Doan et al [23]. In spite of different inclusion criteria and AS protocols across institutions, the diagnostic performance of MRI during AS in terms of the NPV is remarkable [7]. A meta-analysis by Rajwa et al [6] supports this, with pooled NPVs of 83–88%. Another issue worthy of consideration is correct detection of PC upgrading on serial mpMRI. In the GG 1 group, 81% of the patients with progression on MRI (PRECISE 4–5) also had histopathological progression to GG 2. This PPV is considerably higher than the pooled PPV from other series [5–7]. The necessity to perform protocol-mandated biopsy in patients with follow-up mpMRI during AS is debatable. According to our results, an MRI-mandated AS pathway could safely prevent or defer follow-up biopsy for 2 yr, particularly when MRI progression occurs in AS patients with GG 2 PC.

More than 75% of the participants progressed from GG 1 to only GG 2 and initial PI-RADS classification of this patients was predominately 4. Nonetheless, a disqualification rate of 30% for GG 1 PC should lead to at least yearly follow-up MRI in the first 2–3 yr, at least in a cohort with exclusively visible lesions at baseline. Of note, the 94% sensitivity of MRI for predicting AS disqualification for the 18 patients in the GG 1 group who were upgraded is a strong argument for using MRI with PRECISE scoring instead of biopsies. In the GG 2 group, the reclassification rate was similar (32%) and most of these patients were upgraded to GG 3 on final pathology without adverse features in their radical prostatectomy specimen (Fig. 4 and Supplementary Table 6). In total, only 13 patients progressed to GG 3 and developed unfavorable pathology. However, not all recruited patients could be followed up (Supplementary Table 5).

In summary, our results raise questions about the inclusion of patients with GG 2 PC in AS programs. On the one hand, the disqualification rate in our cohort over a short follow-up period was high for GG 2 disease. It is notable that disqualification in this group was associated with the initial percentage Gleason pattern 4 on regression analysis. Among the patients with GG 2 who were disqualified, the median percentage Gleason pattern 4 was 30% on first

biopsy and 40% on follow-up biopsy. On the other hand, serial standardized MRI was sufficient for detection of upgrading. The high disqualification rate in our study, similar to that of Stavrinides et al [8], should also be discussed in the context of FBx. In one-third of cases, the grade group upgrading was detected in SB cores and not on TB alone (with 2 cores). This mirrors the current EAU recommendations [3] and research results [24,25]: TB and SB should complement each other for accurate detection of upgrading for AS disqualification, and/or might indicate a need to increase the number of TB cores.

Our study has some limitations. First, serial mpMRI scans were read by a single experienced radiologist, with all imaging performed at a single institution, which might influence the generalizability of the results. However, as Rajwa et al [6] reported higher accuracy rates for standardized PRECISE scoring, the PRECISE score should, in our opinion, be used for follow-up mpMRI during AS. In addition, this is the first study to prospectively use PRECISE scoring as the main trigger for an individualized AS protocol. However, our study lacks analysis of inter-reader variability, as in the study by Giganti et al [26], or central MRI reading.

Second, it is debatable whether upgrading to GG 2 is a suitable endpoint for time-dependent analysis in the GG 1 group, whereas persistent GG 2 disease is tolerated for patients with GG 2 PC at diagnosis. In addition, long-term 15-yr data from the ProtecT trial demonstrated comparable metastasis-free survival (MFS) rates for low- and intermediate-risk PC [27]. Choice of MFS as an endpoint in a group of patients who underwent curative-intent treatment (radical prostatectomy vs AS) before eventually developing metastatic disease and subsequently dying would be reasonable, as this prompts initiation of antihormonal treatment, with potential side effects besides tumor response [28].

Third, follow-up was limited to 2 yr. Thus, our results cannot be extrapolated to longer AS time periods and recommendations to forgo biopsy. Future studies should focus on further reducing the number of unnecessary protocol-based prostate biopsies during AS over longer time spans. In addition, our interim intention-to-treat analysis because the 15% disqualification rate was not reached led to attrition of participants who reached 12- or 24-mo follow-up. This resulted in a rather small sample size of 101 patients. However, characteristics of the subgroups after 12 and 24 mo were representative of the entire cohort.

Lastly, we acknowledge that our cohort had a relatively high risk of disqualification, as all men had visible lesions on MRI at baseline. This should be taken into account when comparing our relatively high disqualification rate to cohorts with low-risk disease and patients without MRI at inclusion or without lesions on MRI.

5. Conclusions

This study on mpMRI-guided, individualized AS failed to reach a low upgrading rate, which was the primary endpoint. However, mpMRI was able to reliably predict histopathological progression, with a PPV of 81% for GG 1 upgrading and 92% for GG 2 upgrading. PRECISE scores also had a high NPV of 88% for ruling out progression in patients with low-risk PC. On the basis of these results, follow-up biopsies could be omitted for patients with stable MRI (PRECISE 1–3) in a 2-yr AS period. However, these results need further evaluation in prospective and larger cohorts and in particular with a new study design regarding endpoints for different subgroups.

Author contributions: Jan Philipp Radtke had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Schimmöller, Arsov, Albers, Antoch.
Acquisition of data: Valentin, Arsov, Ullrich, Al-Monajjed, Boschheidgen, Giessing, Lopez-Cotarelo, Antoch, Albers, Radtke, Schimmöller.
Analysis and interpretation of data: Valentin, Schimmöller, Albers, Hadaschik, Antoch, Radtke.
Drafting of the manuscript: Valentin, Schimmöller, Radtke.
Critical revision of the manuscript for important intellectual content: Valentin, Arsov, Ullrich, Al-Monajjed, Hadaschik, Giganti, Boschheidgen, Giessing, Lopez-Cotarelo, Antoch, Albers, Radtke, Schimmöller.
Statistical analysis: Schimmöller, Radtke.
Obtaining funding: None.
Administrative, technical, or material support: Albers, Antoch, Lopez-Cotarelo.
Supervision: Albers, Antoch, Schimmöller.
Other: None.

Financial disclosures: Jan Philipp Radtke certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Jan Philipp Radtke reports personal fees from Bayer, Siemens Healthineers, Saegeling Medizintechnik, Bender Gruppe, Janssen Pharmaceuticals, Dr. Wolf, Beckelmann und Partner, Astellas Pharma, Philips, MedCom, Apogepha, Astra Zeneca, and SPL. The remaining authors have nothing to disclose.

Funding/Support and role of the sponsor: None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2023.10.005.

References

[1] Cooperberg MR, Meeks W, Fang R, Gaylis FD, Catalona WJ, Makarov DV. Time trends and variation in the use of active surveillance for management of low-risk prostate cancer in the US. JAMA Netw Open 2023;6:e231439.
[2] Bul M, Zhu X, Valdagni R, et al. Active surveillance for low-risk prostate cancer worldwide: the PRIAS study. Eur Urol 2013;63:597–603. https://doi.org/10.1016/j.eururo.2012.11.005.
[3] Mottet N, Cornford P, van den Bergh RCN, et al. EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on prostate cancer. Arnhem, The Netherlands: European Association of Urology; 2023.
[4] Bokhorst LP, Alberts AR, Rannikko A, et al. Compliance rates with the Prostate Cancer Research International Active Surveillance (PRIAS) protocol and disease reclassification in noncompliers. Eur Urol 2015;68:814–21. https://doi.org/10.1016/j.eururo.2015.06.012.

[5] Chu CE, Lonergan PE, Washington SL, et al. Multiparametric magnetic resonance imaging alone is insufficient to detect grade reclassification in active surveillance for prostate cancer. Eur Urol 2020;78:515–7. https://doi.org/10.1016/j.eururo.2020.06.030.
[6] Rajwa P, Pradere B, Quhal F, et al. Reliability of serial prostate magnetic resonance imaging to detect prostate cancer progression during active surveillance: a systematic review and meta-analysis. Eur Urol 2021;80:549–63. https://doi.org/10.1016/j.eururo.2021.05.001.
[7] Hettiarachchi D, Geraghty R, Rice P, et al. Can the use of serial multiparametric magnetic resonance imaging during active surveillance of prostate cancer avoid the need for prostate biopsies? A systematic diagnostic test accuracy review. Eur Urol Oncol 2021;4:426–36. https://doi.org/10.1016/j.euo.2020.09.002.
[8] Stavrinides V, Giganti F, Trock B, et al. Five-year outcomes of magnetic resonance imaging–based active surveillance for prostate cancer : a large cohort study. Eur Urol 2020;78:43–5. https://doi.org/10.1016/j.eururo.2020.03.035.
[9] Moore CM, Giganti F, Albertsen P, et al. Reporting magnetic resonance imaging in men on active surveillance for prostate cancer: the PRECISE recommendations — a report of a European School of Oncology Task Force. Eur Urol 2017;71:648–55.
[10] Dieffenbacher S, Nyarangi-Dix J, Giganti F, et al. Standardized magnetic resonance imaging reporting using the Prostate Cancer Radiological Estimation of Change in Sequential Evaluation criteria and magnetic resonance imaging/transrectal ultrasound fusion with transperineal saturation biopsy to select men. Eur Urol Focus 2019;7:102–10. https://doi.org/10.1016/j.euf.2019.03.001.
[11] Baboudjian M, Breda A, Rajwa P, et al. Active surveillance for intermediate-risk prostate cancer: a systematic review, meta-analysis, and metaregression. Eur Urol Oncol 2022;5:617–27. https://doi.org/10.1016/j.euo.2022.07.004.
[12] Richard PO, Timilshina N, Komisarenko M, et al. The long-term outcomes of Gleason grade groups 2 and 3 prostate cancer managed by active surveillance: results from a large population-based cohort. Can Urol Assoc J 2020;14:174–81. https://doi.org/10.5489/cuaj.6328.
[13] Giganti F, Stabile A, Stavrinides V, et al. Natural history of prostate cancer on active surveillance: stratification by MRI using the PRECISE recommendations in a UK cohort. Eur Radiol 2021;31:1644–55. https://doi.org/10.1007/s00330-020-07256-z.
[14] Tosoian JJ, Johnbull E, Trock BJ, et al. Pathological outcomes in men with low risk and very low risk prostate cancer: implications on the practice of active surveillance. J Urol 2013;190:1218–23. https://doi.org/10.1016/j.juro.2013.04.071.
[15] Hoeks CMA, Somford DM, Van Oort IM, et al. Value of 3-T multiparametric magnetic resonance imaging and magnetic resonance-guided biopsy for early risk restratification in active surveillance of low-risk prostate cancer a prospective multicenter cohort study. Invest Radiol 2014;49:165–72.
[16] Turkbey B, Rosenkrantz AB, Haider MA, et al. Prostate Imaging Reporting and Data System version 2.1: 2019 update of Prostate Imaging Reporting and Data System version 2. Eur Urol 2019;76:340–51. https://doi.org/10.1016/j.eururo.2019.02.033.
[17] Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS Prostate Imaging-Reporting and Data System: 2015, version 2. Eur Urol 2016;69:16–40. https://doi.org/10.1016/j.eururo.2015.08.052.
[18] Giganti F, Allen C, Emberton M, Moore CM, Kasivisvanathan V. Prostate Imaging Quality (PI-QUAL): a new quality control scoring system for multiparametric magnetic resonance imaging of the prostate from the PRECISION trial. Eur Urol Oncol 2020;3:615–9. https://doi.org/10.1016/j.euo.2020.06.007.
[19] Arsov C, Rabenalt R, Blondin D, et al. Prospective randomized trial comparing magnetic resonance imaging (MRI)-guided in-bore biopsy to MRI-ultrasound fusion and transrectal ultrasound-guided prostate biopsy in patients with prior negative biopsies. Eur Urol 2015;68:713–20. https://doi.org/10.1016/j.eururo.2015.06.008.
[20] Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA. The 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma definition of grading patterns and proposal for a new grading system. Am J Surg Pathol 2016;40:244–52. https://doi.org/10.1097/PAS.0000000000000530.
[21] Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. J Clin Epidemiol 2010;63:834–40. https://doi.org/10.1016/j.jclinepi.2010.02.005.
[22] Luiting HB, Remmers S, Boeve ER, et al. 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. Eur Urol Oncol 2022;5:651–8. https://doi.org/10.1016/j.euo.2022.03.007.
[23] Doan P, Scheltema MJ, Amin A, et al. Final analysis of the Magnetic Resonance Imaging in Active Surveillance trial. J Urol 2022;208:1028–36. https://doi.org/10.1097/ju.0000000000002885.
[24] Tschirdewahn S, Wiesenfarth M, Bonekamp D, et al. Detection of significant prostate cancer using target saturation in transperineal magnetic resonance imaging/transrectal ultrasonography-fusion biopsy. Eur Urol Focus 2021;7:1300–7. https://doi.org/10.1016/j.euf.2020.06.020.
[25] Klotz L, Pond G, Loblaw A, et al. Randomized study of systematic biopsy versus magnetic resonance imaging and targeted and systematic biopsy in men on active surveillance (ASIST): 2-year postbiopsy follow-up. Eur Urol 2020;77:311–7. https://doi.org/10.1016/j.eururo.2019.10.007.
[26] Giganti F, Pecoraro M, Stavrinides V, et al. Interobserver reproducibility of the PRECISE scoring system for prostate MRI on active surveillance: results from a two-centre pilot study. Eur Radiol 2020;30:2082–90. https://doi.org/10.1007/s00330-019-06557-2.
[27] Hamdy FC, Donovan JL, Lane JA, et al. Fifteen-year outcomes after monitoring, surgery, or radiotherapy for prostate cancer. N Engl J Med 2023;388:1547–58. https://doi.org/10.1056/nejmoa2214122.
[28] Xie W, Regan MM, Buyse M, et al. Metastasis-free survival is a strong surrogate of overall survival in localized prostate cancer. J Clin Oncol 2017;35:3097–104. https://doi.org/10.1200/jco.2017.73.9987.