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Original Article

# Long-term outcomes of active surveillance for Grade Group 1 prostate cancer and the impact of the use of MRI on overtreatment

Ivo I. de Vos[1], Cristina Marenghi[4], Fabio Badenchini[4], Egbert R. Boevé[2], Francisco Lozano-Uruñuela[5], Markus Graefen[6], Antti S. Rannikko[7,8], Frederic Staerman[9], Mikio Sugimoto[10], Takuma Kato[10], Diederik M. Somford[3], Mark Frydenberg[11,12], Chris H. Bangma[1], Sebastiaan Remmers[1], Monique J. Roobol[1], and Prostate Cancer Research International: Active Surveillance (PRIAS) consortium[†]

*[1]Department of Urology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, [2]Department of Urology, Sint Franciscus Hospital, Rotterdam, [3]Department of Urology, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands, [4]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [5]Department of Urology, Hospital Universitario de Navarra, Pamplona, Spain, [6]Department of Urology, Martini Klinik, Hamburg, Germany, [7]Helsinki University Hospital, [8]Department of Urology and Research Program in Systems Oncology, University of Helsinki, Helsinki, Finland, [9]Department of Urology, Polyclinique Reims-Bezannes, Bezannes, France, [10]Department of Urology, Faculty of Medicine, Kagawa University, Kagawa, Japan, [11]Department of Surgery, Faculty of Medicine, Nursing and Health Sciences, Monash University, and [12]Department of Urology, Cabrini Institute, Cabrini Health, Melbourne, Australia*

[†]The Prostate Cancer Research International: Active Surveillance (PRIAS) consortium members are presented in Data S1.

## Objectives

To present the long-term outcomes of men with Grade Group (GG) 1 prostate cancer (PCa), included in the Prostate Cancer Research International Active Surveillance (PRIAS) study, and to assess the effect of the inclusion of magnetic resonance imaging (MRI) within the active surveillance (AS) protocol.

## Patients and Methods

The PRIAS study is a multicentre, prospective, web-based cohort study monitoring patients on AS. In total, 8910 men with GG1 PCa were followed in 169 centres worldwide. The cumulative incidences of definitive treatment, metastasis and PCa-specific mortality (PCSM) were estimated using competing risk analyses. Additionally, multivariable analysis was performed to assess the risk of reclassification, stratified by MRI performed around the time of diagnosis.

## Results

The cumulative incidence of definitive treatment 15 years post-diagnosis was 55% (95% confidence interval [CI] 53–57). For metastasis, the 15-year cumulative incidence was 2.7% (95% CI 1.5–4.4). Eight men of died from PCa, resulting in a 15-year cumulative PCSM incidence of 0.23% (95% CI 0.09–0.54). Compared to men with no MRI around the time of diagnosis, those who underwent MRI during the first 18 months of AS were associated with a significantly higher risk of reclassification to ≥GG2, while men with a positive MRI before diagnosis were associated with a higher risk of reclassification to GG2, but not to ≥GG3. Men with GG2 PCa on MRI-targeted rebiopsy who underwent definitive treatment did not show a statistically significant higher risk of 5-year disease recurrence compared to those who had GG1 PCa on last biopsy during AS.

## Conclusions

Our study confirms the safety of AS for GG1 PCa, with low metastasis and PCSM rates over 15 years. Furthermore, the inclusion of MRI in AS prompts increased detection of GG2, leading to increased treatment rates despite similar short-term risks. To minimise overtreatment, expanding eligibility for AS and the uptake of AS in men with favourable GG2 PCa is crucial to address the stage shift resulting from the increased accuracy of MRI.

## Keywords

active surveillance, magnetic resonance imaging, metastatic disease, mortality, prostatic neoplasms

## Introduction

Active surveillance (AS) is a monitoring approach for low- to intermediate-risk prostate cancer (PCa) to counter overtreatment by postponing or avoiding unnecessary definitive treatment, such as radical prostatectomy (RP) and radiotherapy (RT), and its associated side effects. In 2006, the Prostate Cancer Research International Active Surveillance (PRIAS) study was initiated as an observational web-based study with the objectives of validating AS as a treatment option and providing evidence-based guidance for the selection and follow-up of AS [1]. Since then, long-term outcomes from the PRIAS study and other prospective, protocol-managed AS studies have consistently demonstrated the safety of AS [2–7], which has led to its establishment as the preferred treatment option for low-risk PCa in most international guidelines [8].

Nevertheless, ongoing assessment of long-term outcomes of AS remains vital, given that low-risk, localised PCa tends to progress slowly and could result in morbidity and PCa-specific mortality (PCSM) beyond 10 years after diagnosis, especially for those with a long life expectancy [6,9]. Moreover, in the past decade, there has been a notable trend towards incorporating MRI and additional MRI-targeted biopsies in both the diagnostic setting and follow-up strategy for AS. The use of additional MRI-targeted biopsies, with their improved accuracy compared to systematic biopsies alone [10], aims to improve patient selection for AS by reducing the issue of undersampling at baseline, and to ensure timely detection of clinically significant PCa during follow-up. In 2013, the PRIAS study integrated MRI as part of a side protocol, and it has been fully incorporated into the main protocol since 2020. While prior studies have reported on the short- and medium-term outcomes of MRI utilisation in AS [11–13], these have been predominantly derived from single academic expert centres, which can limit the generalisability of their results. The PRIAS study, in contrast, aims to offer a reflection of worldwide clinical practice by including AS patients from academic, non-academic, and private practices.

Here, we report the long-term oncological outcomes of almost 9000 men with Grade Group (GG) 1 PCa managed with AS in the PRIAS study. Furthermore, we aimed to provide a contemporary perspective by comparing the outcomes of men diagnosed via systematic biopsies with those of men managed with current AS practices that incorporate MRI and MRI-targeted biopsies. This includes an evaluation of medium-term outcomes such as GG reclassification, progression to definitive treatment, and disease recurrence after definitive treatment.

## Patients and Methods

The PRIAS study is a multicentre, prospective cohort study that maintains a web-based register (https://prias-project.org) initiated in 2006, where participating centres submit data on PCa patients who opted for AS after diagnosis. The medical ethics committee of the Erasmus University Medical Centre and, dependent on local regulations, local committees, approved the PRIAS study (MEC number 2004-339). All participants provided written informed consent. The study involves academic, non-academic and private practices across 23 countries worldwide. Based on the individual's previously entered data, the PRIAS website automatically provides recommendations on how to continue AS according to the follow-up protocol.

The original PRIAS study protocol and changes to this up to 2015 have been described previously [1,2]. In short, the initial inclusion criteria were GG1, clinical stage ≤T2c, PSA level ≤10 ng/mL, ≤2 cores positive for PCa, PSA density ≤0.2 ng/mL$^2$, and fitness for curative treatment. Since 2020, men with a higher PSA level (≤20 ng/mL) and PSA density (≤0.25 ng/mL$^2$) have been eligible if MRI was performed at the time of inclusion. Men with GG2 disease are also eligible, as long as less than 50% of cores are positive for GG2, and there is no cribriform growth pattern or intraductal carcinoma found on biopsy. All changes to the PRIAS protocol are presented in Table S1.

The follow-up schedule consists of PSA tests, DRE, MRI (if available), and repeat biopsies (Table S2). The initial criteria used to recommend a switch to definitive treatment were GG1 with three or more positive cores, evidence of extracapsular extension on DRE (≥cT3), or a PSA doubling time of <3 years (provided at least four PSA values were available). Since 2015, ≥GG2 and/or ≥cT3 have been the only recommended reasons for definitive treatment.

### Primary Analyses

All men with GG1 disease at initial diagnosis were included in this report. Primary analyses focused on the long-term outcomes of the whole cohort. Outcomes of interest were definitive treatment, metastasis and PCSM. Cumulative incidences of the outcomes were calculated using competing risk analysis according to the Fine-Grey method [14]. Regarding definitive treatment, a switch to watchful waiting (recommended for patients with a life expectancy of <10 years), or other-cause death during AS were considered as competing events. For metastasis and PCSM, other-cause death was defined as the competing event.

### Secondary Analyses

Secondary analyses focused on medium-term outcomes stratified according to the use of MRI around the time of diagnosis. Outcomes of interest were grade reclassification and metastatic disease at 5 years post-diagnosis. To reflect on periods with different contemporary practice regarding the

use of MRI, four different subpopulations were defined based on the utilisation of MRI around the time of diagnosis: men who did not undergo MRI before diagnosis or confirmatory biopsy (Group A); men who underwent MRI between diagnosis and confirmatory biopsy (Group B; defined as the first biopsy within 18 months after diagnosis); those who underwent MRI before diagnosis and had suspicious lesion (Prostate Imaging Reporting and Data System [PI-RADS] or Likert ≥3; Group C); and those who underwent MRI before diagnosis and had no suspicious lesion (Group D).

Furthermore, to assess the association between the use of MRI around the time of diagnosis and the risk of reclassification to GG2 or ≥GG3 during AS, a competing risk regression was performed, adjusting for characteristics at the time of diagnosis, including age, PSA level, prostate volume, and clinical stage. Discontinuation of AS without reclassification was considered a competing event and patients still on AS without reclassification were censored. Follow-up time was calculated from the date of diagnosis to the date of reclassification, discontinuation of AS, or censoring date.

### Tertiary Analyses

Finally, to assess how the method of detecting GG2 disease (through systematic biopsies, MRI-targeted biopsies, or both) related to disease recurrence, we conducted a competing risk regression analysis to assess disease recurrence at 5 years after RP or RT. This analysis was stratified by highest GG found on last biopsy during AS before switching to definitive treatment, with GG2 disease further categorised based on detection method: systematic biopsies, MRI-targeted biopsies, or both. We truncated follow-up in this analysis at 5 years to account for differences in follow-up duration between groups due to the later introduction of MRI within the study period. Disease recurrence was defined as either local recurrence, biochemical recurrence (defined as a PSA level ≥0.2 ng/mL after RP or a PSA level 2.0 ng/mL above the nadir after RT), or secondary treatment. To account for other factors at the time of discontinuation, age, PSA, prostate volume, PSA doubling time, and duration on AS were included as covariates.

Follow-up for the current analysis was truncated at December 2023. *P* values were two-sided, and statistical significance was set at $P \leq 0.05$. All statistical analyses were performed in R statistical software version 4.1.2.

## Results

### Primary Analyses

In total, 9252 men were prospectively followed in the PRIAS study across 169 centres worldwide. Of these men, 8910 men had GG1 PCa, with a median (interquartile range [IQR]) age of 66 (61–71) years and a median (IQR) PSA level of 5.7 (4.6–7.3) ng/mL at the time of diagnosis (Table 1). Most men (94%) had low-risk disease. Adherence to the fixed biopsies recommended by the follow-up protocol was 81% (95% CI 79–82) at 1 year, 69% (95% CI 67–70) at 4 years, 54% (95% CI 51–56) at 7 years, and 29% (95% CI 26–33) at 10 years.

Throughout the follow-up period, 2914 men switched to definitive treatment, 519 men switched to watchful waiting, and 156 men died during AS (Fig. 1). The cumulative incidence of definitive treatment at 2, 5, 10 and 15 years post-diagnosis was 22% (95% CI 21–23), 38% (95% CI 37–40), 50% (95% CI 48–51) and 56% (95% CI 53–57), respectively. The cumulative incidence of remaining on AS at 2, 5, 10 and 15 years post-diagnosis was 76% (95% CI 75–77), 56% (95% CI 54–58), 36% (95% CI 33–39) and 19% (95% CI 13–25), respectively.

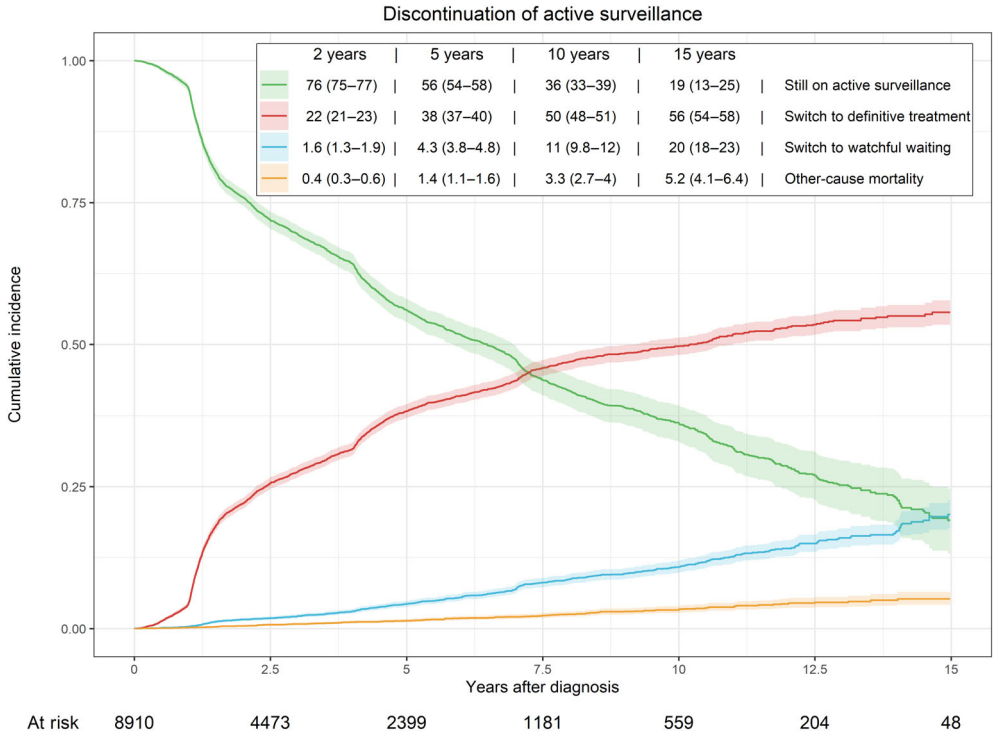
At 2, 5, 10 and 15 years, 5843, 3231, 882 and 108 men were still alive (i.e., still at risk for PCa death), respectively. A total of 36 patients developed metastasis, resulting in a cumulative incidence of 0.93% (95% CI 0.60–1.4) at 10 years and 2.7%

**Table 1** Characteristics at diagnosis of men with Grade Group 1 disease included in the PRIAS study.

| Patient characteristics | *n* = 8910 |
|---|---|
| Age, years, median (IQR) | 66 (61, 71) |
| PSA, ng/mL, median (IQR) | 5.7 (4.6, 7.3) |
| PSA ≥10 ng/mL, *n* (%) | 412 (4.6) |
| PSA density, ng/mL$^2$, median (IQR) | 0.13 (0.09, 0.16) |
| Number of positive cores, *n* (%) | |
| 1 | 5580 (63) |
| 2 | 2543 (29) |
| ≥3 | 787 (8.8) |
| Percentage of cores positive, median (IQR) | 10 (8, 17) |
| Clinical tumour stage, *n* (%) | |
| T1a/b | 67 (0.8) |
| T1c | 7823 (88) |
| T2a | 906 (10) |
| T2b | 83 (0.9) |
| T2c | 33 (0.4) |
| MRI before diagnosis, *n* (%) | 1977 (22) |
| Method of detection, *n* (%) | |
| Systematic biopsy | 8250 (93) |
| Systematic and target biopsy | 403 (4.5) |
| Target biopsy | 190 (2.1) |
| TURP | 67 (0.8) |
| EAU risk group, *n* (%) | |
| Low | 8386 (94) |
| Intermediate | 489 (5.5) |
| High | 35 (3.9) |
| Year of diagnosis, *n* (%) | |
| Before 2010 | 1574 (18) |
| 2010–2014 | 2417 (27) |
| 2015–2019 | 3165 (35) |
| 2020 and later | 1754 (20) |
| Charlson comorbidity score, *n* (%) | |
| 0 | 4833 (54) |
| 1 | 628 (7.0) |
| 2 | 1768 (20) |
| ≥3 | 1681 (19) |

*EAU, European Association of Urology; IQR, interquartile range.*

**Fig. 1** Discontinuation of active surveillance over time.




(95% CI 1.5–4.3) at 15 years after diagnosis. Eight men died from PCa (clinical characteristics are presented in Table S3), which represents a cumulative incidence of 0.23% (95% CI 0.08–0.53) at 15 years after diagnosis. The cumulative incidence for other-cause mortality was 8.2% (95% CI 7.1–9.5) at 10 years and 21% (95% CI 17–25) at 15 years after diagnosis.

## Secondary Analyses Stratified for the Use of MRI around the Time of Diagnosis

After stratifying for the use of MRI around the time of diagnosis, Group A consisted of 5844 men, Group B of 1089 men, Group C of 1246 men, and Group D of 731 men (Table S4). The baseline tumour characteristics were not comparable among these groups. Group A included a lower proportion (3.0%) of patients with intermediate-risk PCa at diagnosis compared to Groups B (8.2%), C (11%), and D (11%).

At 5 years post-diagnosis, the cumulative incidence of reclassification to GG2 was 16% (95% CI 15–17) in Group A, 24% (95% CI 22–27) in Group B, 24% (95% CI 20–28) in Group C, and 17% (95% CI 14–22) in Group D (Fig. 2A). The cumulative incidence of reclassification to GG3 or higher was 7.5% (95% CI 6.8–8.3) in Group A, 11% (95% CI 8.8–13) in Group B, 11% (95% CI 7.8–14) in Group C, and 3.7% (95% CI 2.1–5.9) in Group D (Fig. 2B). The cumulative incidence of metastatic disease at 5 years was 0.41% (95% CI 0.24–0.67) in Group A and 0.15% (95% CI 0.02–0.82) in Group B. There were no metastatic events in Group C and D.

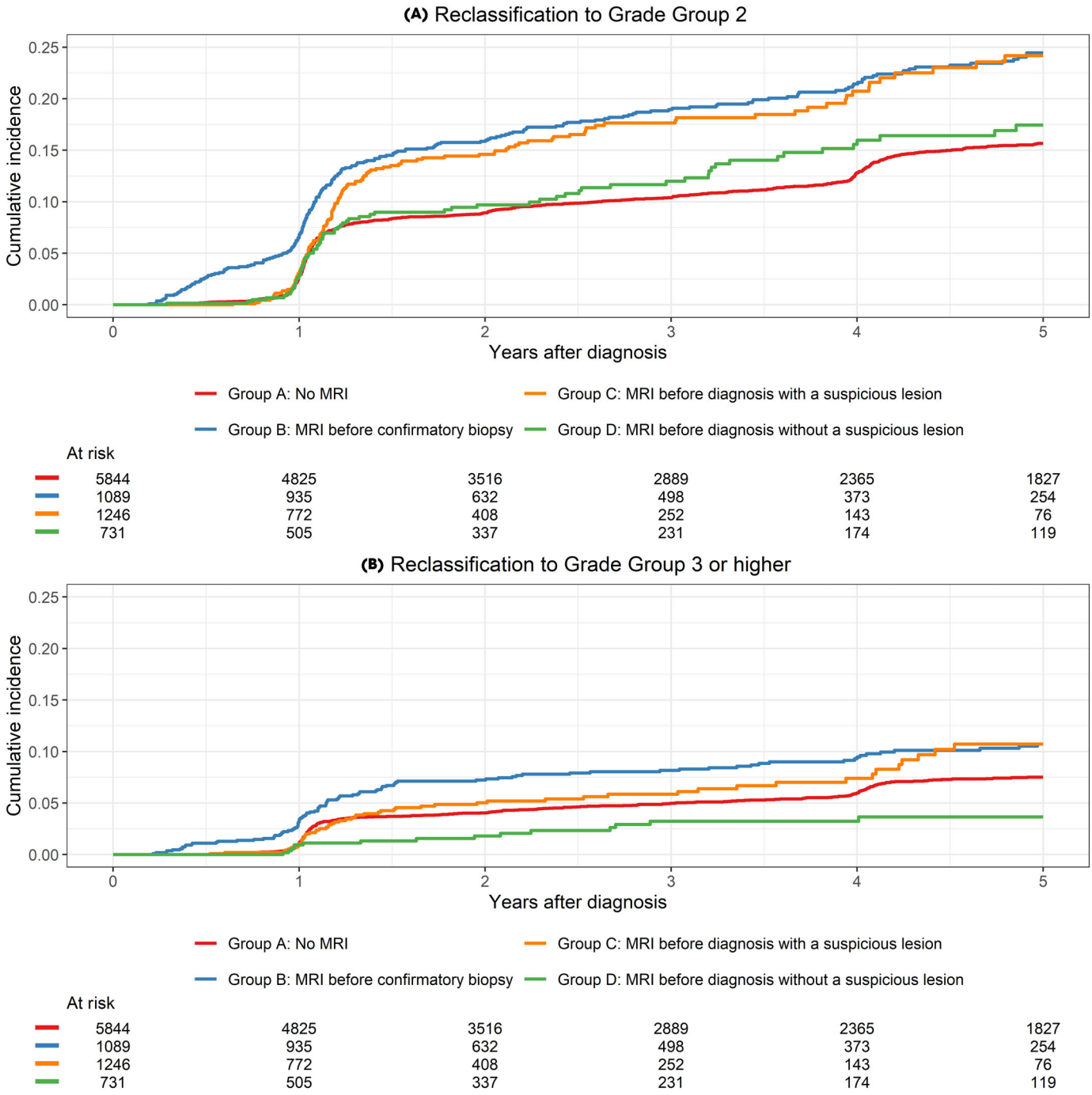
After adjusting for baseline characteristics, compared to Group A, Group B (subdistribution hazard ratio [sHR] 1.71, 95% CI 1.47–1.99) and Group C (sHR 1.55, 95% CI 1.30–1.85) were associated with a statistically significant higher risk of reclassification to GG2, while Group D (sHR 1.12, 95% CI 0.88–1.42) did not show a statistically significant different risk (Table 3). Regarding reclassification to GG3 or higher, Group B (sHR 1.57, 95% CI 1.25–1.96) was still associated with a statistically significant higher risk than Group A, Group C (sHR 1.22, 95% CI 0.92–1.62) did not show a statistically significant different risk, and Group D (sHR 0.50, 95% CI 0.30–0.85) demonstrated a statistically significant lower risk compared to Group A (Table 2). Similar trends in sHRs were observed in the additional analysis assessing men who switched to definitive treatment following reclassification to GG2 or ≥GG3 PCa (Table S5).

## Tertiary Analyses of Disease Recurrence after Definitive Therapy Stratified for GG Found on Last Biopsy during AS

Statistically significant predictors associated with disease recurrence at 5 years after switching from AS to RP or RT were last PSA value (sHR 1.09, 95% CI 1.05–1.13), and GG3 vs GG1 on last biopsy during AS (sHR 2.37, 95% CI 1.35–4.16; Table 3).

**Fig. 2** Reclassification during active surveillance stratified by the use of MRI around the time of diagnosis.




Presence of GG2 PCa on systematic biopsy, MRI-targeted biopsy, or both showed no statistically significant difference in risk compared to GG1 PCa on last biopsy.

## Discussion

Based on its consistently proven safety in various studies, AS has become a guideline-endorsed treatment strategy for GG1 PCa, with the aim of minimising unnecessary overtreatment while retaining the window of cure. However, given the long natural history of low-risk PCa, evaluating the long-term outcomes beyond 10 years after diagnosis remains essential. In this study, comprising academic, non-academic and private practices, and thus reflecting worldwide clinical practice, 882 men were followed for >10 years, and 108 men at >15 years after initial diagnosis.

**Table 2** Competing risk regression of reclassification to Grade Group 2 and Grade Group 3 or higher.

| | sHR | 95% CI | *P* value |
|---|---|---|---|
| Reclassification to GG2 | | | |
| Age at diagnosis (per year) | 1.02 | 1.01, 1.03 | <0.001 |
| PSA at diagnosis (per doubling) | 1.30 | 1.19, 1.43 | <0.001 |
| Prostate volume at diagnosis (per 10 cc) | 0.88 | 0.85, 0.91 | <0.001 |
| **Clinical stage at diagnosis** | | | |
| T1 | Reference | | |
| T2 | 1.13 | 0.95, 1.35 | 0.2 |
| **Use of MRI around time of diagnosis (group)** | | | |
| No MRI (A) | Reference | | |
| MRI between diagnosis and confirmatory biopsy (B) | 1.71 | 1.47, 1.99 | <0.001 |
| MRI before diagnosis with a suspicious lesion (C) | 1.55 | 1.30, 1.85 | <0.001 |
| MRI before diagnosis with no suspicious lesion (D) | 1.12 | 0.88, 1.42 | 0.4 |
| Reclassification to ≥GG3 | | | |
| Age at diagnosis (per year) | 1.05 | 1.04, 1.06 | <0.001 |
| PSA at diagnosis (per doubling) | 1.31 | 1.14, 1.50 | <0.001 |
| Prostate volume at diagnosis (per 10 cc) | 0.81 | 0.77, 0.86 | <0.001 |
| **Clinical stage at diagnosis** | | | |
| T1 | Reference | | |
| T2 | 0.72 | 0.53, 0.97 | 0.032 |
| **Use of MRI around time of diagnosis (group)** | | | |
| No MRI (A) | Reference | | |
| MRI between diagnosis and confirmatory biopsy (B) | 1.57 | 1.25, 1.96 | <0.001 |
| MRI before diagnosis with a suspicious lesion (C) | 1.22 | 0.92, 1.62 | 0.2 |
| MRI before diagnosis with no suspicious lesion (D) | 0.50 | 0.30, 0.85 | 0.010 |

*sHR, subdistribution hazard ratio.*

**Table 3** Competing risk regression of disease recurrence at 5 years after switching from active surveillance to radical prostatectomy or radiotherapy.

| Characteristic | sHR | 95% CI | *P* value |
|---|---|---|---|
| Age at discontinuation (per year) | 0.97 | 0.95, 1.00 | 0.028 |
| Last PSA (per doubling, ng/mL) | 2.25 | 1.65, 3.07 | <0.001 |
| Last prostate volume (per 10 cc) | 0.92 | 0.75, 1.13 | 0.4 |
| **PSA doubling time** | | | |
| >3 years | Reference | | |
| 0–3 years | 0.92 | 0.56, 1.48 | 0.7 |
| Time on AS (years) | 1.0 | 0.90, 1.10 | >0.9 |
| **GG on last biopsy during AS** | | | |
| 1 | Reference | | |
| 2 (+ on systematic cores) | 1.16 | 0.66, 2.04 | 0.6 |
| 2 (+ on MRI-targeted cores) | 0.82 | 0.27, 2.48 | 0.7 |
| 2 (+ on systematic and MRI-targeted cores) | 1.94 | 0.70, 5.38 | 0.2 |
| ≥3 | 2.57 | 1.50, 4.41 | <0.001 |

*AS, active surveillance; GG, grade group; sHR, subdistribution hazard ratio.*

We observed a 15-year cumulative incidence of 2.7% for metastasis and 0.23% for PCSM for men with GG1 at initial diagnosis. To put this mortality rate into perspective, this probability is over five times lower than has been reported for a cohort of 13 481 men (1.3% at 15 years) who had a negative prostate biopsy, with a similar median age (66 years) and PSA level (<10.0 ng/mL) [15]. Additionally, it is nearly 10 times lower than the lifetime risk of PCSM of 1.5%–2% before the age of 80 years [16]. Rates of metastasis and PCSM for men with GG1 have also been reported in long-term results from other large AS cohorts, each with distinct inclusion criteria and follow-up schedules. The Canary Prostate Active Surveillance Study cohort, a large US multicentre study, recently reported a 10-year incidence of 1.4% for metastasis and 0.1% for PCSM [7]. The Memorial Sloan Kettering Cancer Center found a somewhat lower 15-year probability of 1.5% for metastasis and only one death from PCa [3]. The Johns Hopkins cohort showed a lower 15-year risk of 0.1% for both metastasis and PCSM [5]. Moreover, findings from the Sunnybrook Hospital, which also included men with a higher PSA level (<20 ng/mL), demonstrated a higher 15-year metastasis risk of 6% for men with PSA <20 ng/mL, and a 15-year PCSM risk of 3% for men with PSA <10 ng/mL [17]. Differences in metastasis and PCSM rates can be attributed to differences in protocols and inclusion criteria across the cohorts. For example, Johns Hopkins employed more stringent inclusion criteria, while Sunnybrook used broader criteria such as a higher PSA level [18]. Additionally, the PRIAS study is a global multicentre study, unlike the cohorts from single, experienced centres, which may influence factors such as baseline undersampling. Nonetheless, when considering the collective results of these cohorts, the findings consistently reaffirm the safety and curative potential of AS in patients with GG1 PCa. Moreover, our results, derived from centres with varying levels of experience and clinical practices in pathology, radiology and biopsy techniques, further reinforce the safety of AS beyond just experienced centres [19].

Nevertheless, our findings also demonstrate that half of men switch to definitive treatment within 10 years. Similar 10-year treatment probabilities ranging from 48% to 64% were observed in other AS cohorts [3,5,7,20–22]. Thus, even though definitive treatment and its associated burden are postponed for over a decade or even avoided altogether for almost 50% of men who start AS, 50% of men still undergo definitive treatment. Considering the excellent long-term oncological outcomes, this raises the question of how to further reduce any unnecessary definitive treatment.

Additionally, it is important to note that these long-term oncological outcomes are mainly based on men who were diagnosed with systematic prostate biopsies. Over the last

decade, AS practice has evolved considerably with the introduction of MRI and MRI-targeted biopsies, with the aim of detecting tumours that are missed by systematic biopsies based on the improved accuracy of the former. The results of our secondary analysis indicate that this effect is achieved, as our findings show that the use of MRI shortly after diagnosis was associated with a significantly higher risk of reclassification to GG2 and ≥GG3 PCa compared to non-use of MRI around the time of diagnosis, also after adjusting for other clinical characteristics at the time of diagnosis. Interestingly, when MRI was performed before diagnosis, those with a suspicious lesion were also significantly associated with an increased risk of reclassification to GG2, but not to ≥GG3, compared with those who did not undergo MRI around the time of diagnosis. Additionally, men who underwent an MRI before diagnosis, on which no suspicious lesion was observed, even had a lower risk of reclassification to ≥GG3. Although these findings should be interpreted with caution given the wide confidence intervals due to the low number of events, particularly for reclassification to ≥GG3, they indicate that the use of MRI before diagnosis is primarily associated with an increased detection of GG2 tumours rather than more aggressive ≥GG3 tumours. This raises the question of whether this improved detection of GG2 PCa through the use of MRI is clinically relevant. Our multivariable competing risk regression in the tertiary analysis demonstrated that men who underwent RP or RT due to reclassification to GG2 on MRI-targeted biopsies showed no statistically significant higher risk in 5-year disease recurrence compared to those who had GG1 on last biopsy during AS. Similarly, the analysis by Batouche et al. [23] of a large tertiary centre registry also found no significant difference in 5-year disease recurrence risk between treated individuals with MRI-detected GG2 PCa and those with GG1 PCa without MRI. Additionally, considering the already excellent long-term oncological outcomes of men on AS without the use of MRI, alongside the presumption that GG2 disease was likely undersampled in this population, these results support the hypothesis that the improved accuracy of MRI-targeted biopsies has led to a grade shift, especially from GG1 to GG2. For instance, patients diagnosed with GG1 disease though systematic biopsies in the pre-MRI era would, in contemporary practice, be at significant risk of being reclassified to GG2 and discontinuing AS due the finding of a low amount of Gleason 4 on MRI-targeted biopsy, even though they may essentially be the same patients. The major downside of this grade shift is that it can result in increased overtreatment, as previously demonstrated by higher rates of definitive treatment both in biopsy-naïve patients [23,24] and, based on our results, in those initially diagnosed with GG1 who are on AS. Although current guidelines support offering AS to men with favourable intermediate-risk GG2 disease, the actual uptake of AS in these patients remains suboptimal, with less than 20% of men being selected for initial conservative management [25]. Our data contribute additional evidence supporting the need to further extend the eligibility and uptake of AS in men with GG2 PCa in the current MRI era to prevent unnecessary overtreatment of these men [26,27].

Our study has some limitations. Firstly, the PRIAS study, being prospective in nature, did not randomise for the use of MRI. Therefore, it is possible that confounding factors present during the follow-up period may have influenced the current outcomes. However, other than the recommendation to use MRI in the follow-up schedule, the timing and frequency of biopsies at fixed intervals remained unchanged in the protocol, as reflected by comparable biopsy rates between the groups (Table S4). Additionally, although a small fraction of Group A men eventually underwent MRI during follow-up, this occurred at a rate of only 0.06 per person-year and after a median of 4.1 years post-diagnosis, suggesting a minimal impact of MRI on the reclassification and treatment rates in this group. Finally, the use of reclassification as an endpoint in the secondary analysis may be subject to ascertainment bias, as it relies on follow-up biopsies being performed. Although adherence to fixed biopsies declined over time, at least 83% of men had at least one repeat biopsy within 5 years (Table S4), suggesting a low risk of ascertainment bias.

In conclusion, our findings, reflecting global clinical practice, affirm the safety and effectiveness of AS in patients with GG1 PCa, as evidenced by low rates of metastasis and PCSM observed over a significant follow-up period of 15 years. In addition, our results demonstrate that the introduction of MRI in AS protocols can lead to a stage shift of GG1–GG2 disease with a subsequent increase in definitive treatment, despite comparable short-term oncological risks between MRI-detected GG2 and GG1. Given the already outstanding long-term outcomes of AS, we argue that it is essential to further extend the eligibility and uptake of AS in men with favourable GG2 PCa to adjust for the increased accuracy of MRI and to prevent unnecessary overtreatment of these men.

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## Disclosure of Interests

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Correspondence: Ivo I. de Vos, Department of Urology, Erasmus MC Cancer Institute, Doctor Molewaterplein 40, 3015 GD Rotterdam (Room number NA-1524), The Netherlands.
e-mail: i.devos@erasmusmc.nl

Abbreviations: AS, active surveillance; PCa, prostate cancer; PCSM, prostate cancer-specific mortality; PRIAS, Prostate Cancer Research International Active Surveillance; RP, radical prostatectomy; RT, radiotherapy; sHR, ubdistribution hazard ratio.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Data S1.** Members of PRIAS consortium.

**Table S1.** Updates from PRIAS protocol.

**Table S2.** Timetable of current PRIAS protocol follow-up schedule.

**Table S3.** Clinical characteristics of men who died of prostate cancer.

**Table S4.** Baseline characteristics stratified for the use of MRI around time of diagnosis.

**Table S5.** Competing risk regression of switching to definitive treatment following reclassification to Grade Group 2 and Grade Group 3 or higher.

 