Published in final edited form as:

BJU Int. 2012 September ; 110(5): 651–657. doi:10.1111/j.1464-410X.2011.10875.x.

Effect of treatment with 5- α reductase inhibitors on progression in monitored men with favourable-risk prostate cancer

Ashley E. Ross, Zhaoyong Feng, Phillip M. Pierorazio, Patricia Landis, Patrick C. Walsh, H. Ballentine Carter, Bruce J. Trock, and Edward M. Schaeffer

James Buchanan Brady Urological Institute and Department of Urology, Johns Hopkins Medicinal Institutions, Baltimore, MD, USA

Abstract

- To determine whether 5- α reductase inhibitor (5-ARI) use delays cancer reclassification in an active surveillance (AS) cohort.
- We performed a retrospective study of 587 men enrolled in an AS programme, who had no history of 5-ARI use.
- Chi-squared and *t*-tests were used to compare characteristics of 5-ARI users and non-users.
- Univariable and multivariable proportional hazards models, treating 5-ARI use as a time-dependent covariate, were used to evaluate the influence of 5-ARIs on the risk of a subsequent biopsy no longer meeting criteria for continued AS (i.e. reclassification).
- 5-ARI use was initiated in 47 men while on AS.
- Men using 5-ARIs had larger prostates and higher PSA levels at diagnosis.
- During 5-ARI use, PSA levels and prostate volume decreased by mean values of 47% and 11%, respectively.
- Men using 5-ARIs had a mean of 2.5 surveillance biopsies while on the drug. Reclassification occurred in 17% of 5-ARI users compared with 31% of non-users ($P=0.04$).
- Multivariable models (adjusting for age, α -blocker use, PSA level, % free PSA, PSA density, prostate volume and number/percent biopsy core involvement at diagnosis) showed nonsignificant risk reductions for reclassification in 5-ARI users as determined by either tumour extent (hazard ratio [HR] = 0.37 (95% confidence interval [CI] 0.12 to 1.13), $P=0.08$) or grade (HR = 0.8 (95% CI 0.25–2.59), $P=0.7$).
- Treatment with 5-ARIs did not significantly alter the outcome of biopsy reclassification by grade in men with very low-risk prostate cancer.

Correspondence: Edward M. Schaeffer, Johns Hopkins University School of Medicine, Brady Urological Institute, 600 N Wolfe Street, Marburg 146, Baltimore, MD 21287, USA. eschaeffer@jhmi.edu.

CONFLICT OF INTEREST

None declared.

Keywords

5- α reductase inhibitor; very-low risk prostate cancer; active surveillance

INTRODUCTION

Widespread PSA screening has resulted in decreased prostate cancer mortality but is also associated with increases in the diagnosis of very low-risk prostate cancers that may not be clinically significant [1]. As such, active surveillance (AS) with curative intent has gained popularity as a management strategy, particularly for older men with low volume and low grade disease [2]. AS is not without risk, however, as non-invasive means of following men with prostate cancer have not proved adequate, leaving serial transrectal biopsy as the cornerstone of AS [3,4]. Accordingly, efforts to decrease the need for frequent serial biopsies have centered around: (i) the use of patient data during AS to modify follow-up schemes; (ii) the discovery and improvement of non-invasive markers for disease progression; and (iii) the evaluation of treatment methods with favourable risk profiles that might treat low grade prostate cancer or decrease disease progression, thus allowing less intensive monitoring.

5- α reductase inhibitors (5-ARIs) inhibit the conversion of testosterone to dihydrotestosterone, thus lowering the intracellular level of dihydrotestosterone in the prostate. Two large randomized controlled trials have shown a reduction in the detection of low grade prostate cancer with the use of 5-ARIs, implying that they treat or prevent the growth of low grade lesions [5,6]. These studies prompted a randomized placebo-controlled trial of dutasteride in the AS setting [7]. In addition, a recent, retrospective report has suggested that 5-ARI use might decrease pathological progression during AS [8]. In the present study, in a carefully followed AS cohort, we examine whether 5-ARI use is related to the risk that a repeat biopsy will find a more extensive or higher grade cancer when compared with the results of diagnostic biopsy.

PATIENTS AND METHODS

From 1994 to May 2010, 792 men were enrolled in an institutional review board-approved AS programme for low-risk prostate cancer [9]. Of these, 616 met all of Epstein's criteria for very low-risk prostate cancer at diagnosis (T1c, PSA density <0.15 ng/mL/cc, Gleason score ≤ 6 , <3 cancer-containing biopsy cores and $\leq 50\%$ cancer involvement of any core) with the remainder of the participants primarily having PSA densities ≥ 0.15 ng/mL/cc. Follow-up included serum PSA measurement and DRE every 6 months and annual extended (12) core prostate biopsy (with biopsies performed in the last several years typically including two additional cores to better sample anterior tissue). Curative intervention was recommended if a follow-up surveillance biopsy no longer met the criteria for AS (biopsy reclassification by either Gleason pattern ≥ 4 or cancer involving ≥ 3 cores, or $>50\%$ of any individual core).

Eight of the men had not yet had a surveillance biopsy after diagnosis and were excluded. Eighteen men who had a history of 5-ARI use before cancer diagnosis and three who had a history of Casodex (bicalutamide) use before enrolment were also excluded, leaving a final

study population of 587 men. Follow-up for each man was censored at the time of their last surveillance biopsy or first biopsy requiring reclassification. For men undergoing transurethral procedures for BPH (three men) follow-up was censored at the last biopsy before intervention. No man who started to use a 5-ARI discontinued the drug before his last surveillance or first reclassification biopsy.

Data regarding 5-ARI use were collected prospectively. PSA velocity (PSAV) was determined for men taking 5-ARIs who had at least two serial PSA measurements after drug initiation (32 men) and was calculated as the linear slope of PSA.

The outcome of interest was the risk of biopsy reclassification among those exposed or not exposed to 5-ARIs. Covariates were age, α -blocker use, PSA level, %free PSA, PSA density, prostate volume and number/percent biopsy core involvement by cancer at diagnosis. Covariates were compared using a chi-squared test in cases of equal variance and Cochran *t*-tests in cases of unequal variance. A *P* value of <0.05 was considered to indicate statistical significance. Univariable and multivariable proportional hazards models, treating 5-ARI use as a time-dependent covariate, were used to evaluate the influence of 5-ARIs on subsequent biopsy reclassification.

RESULTS

Of the 587 men in the present study, 47 initiated 5-ARIs, almost exclusively for LUTS, with the majority of men placed on finasteride (76%). Men starting 5-ARIs had significantly larger prostates and higher PSA levels at the time of cancer diagnosis (Table 1). Age, PSA density and the number and percent core involvement at diagnosis were similar between 5-ARI users and non-users (Table 1). Men placed on 5-ARIs were more likely to use α -blockers during AS (64.4% vs 18.5% of non users, $P < 0.001$).

Most men started 5-ARIs after an initial period of AS with a mean of 2.4 (SD 2.7, median 1.2, range 0–10) years. The mean (SD) duration of exposure to 5-ARIs while on AS was 2.4 (2.1) years, with men having a mean (SD) of 2.6 (2.0) surveillance biopsies while on this medication (Table 2). During exposure to 5-ARIs, PSA levels decreased by a median of 46.9% (ranging from a 1.7% increase to a 81.2% decrease). By contrast, PSA levels increased by a median of 18.6% in those not using 5-ARIs (ranging from a 437.0% decrease to a 75.0% increase [Table 2]). Prostate volume also decreased during 5-ARI use with a median decrease of 11.0% (ranging from a 61.5% increase to a 57.3% decrease) compared with a median increase of 6.9% (ranging from a 77.8% decrease to a 161.8% increase) in those not using 5-ARIs (Table 2).

When considering the crude proportion of men with an unfavourable surveillance biopsy (i.e. ignoring time to progression), 5-ARI users were significantly less likely than non-users to require reclassification by tumour extent on biopsy ($P = 0.025$), but there was no significant difference in reclassification by biopsy upgrading ($P = 0.345$ [Table 2]). Such an analysis is flawed as it ignores the fact that, for most 5-ARI users, there was an appreciable time lag between enrolling in the AS programme and their initiation of 5-ARI use. To correct for this bias in biopsy progression-free survival, 5-ARI use was treated as a time-

dependent covariate in univariable and multivariable analyses for biopsy reclassification. When considering reclassification by either biopsy upgrading or increased tumour extent, there was a nonsignificant reduction in reclassification associated with 5-ARI use, adjusted hazard ratio [HR] = 0.55 (95% CI 0.23–1.28), $P = 0.164$ (Table 3). When reclassification was restricted to either biopsy upgrading, or to increased tumour extent, associations with 5-ARI use remained statistically nonsignificant with larger protective effects seen for reclassification by tumour extent, adjusted HR = 0.80 (95% CI 0.25–2.59), $P = 0.71$ for reclassification by grade, and 0.37 (95% CI 0.12–1.13), $P = 0.08$ for reclassification by tumour extent, respectively (Tables 4 and 5). Age, %free PSA, and maximum percentage core involved with tumour (all measured at diagnosis) were consistently associated with reclassification in the multivariable models [10].

We also monitored the PSA kinetics of 5-ARI users in our AS cohort (Fig. 1). Of the 32 men for whom PSAV could be calculated (at least two PSA values available during 5-ARI use), four had an unfavourable biopsy on AS (two with disease upgrading and two with increased tumour extent). Mean PSAVs while on 5-ARIs were -0.23 ng/mL/year and -0.20 ng/mL/year among men with favourable biopsies and those whose cancers were reclassified owing to unfavourable biopsy, respectively ($P = 0.95$; Fig. 1B). The PSAVs of the two men reclassified by upgrading were -1.42 and -0.33 ng/mL/year.

DISCUSSION

Since the early 1940s, androgens have been recognized as key regulators in the growth of both benign and malignant prostate tissue. In an effort to provide selective androgen deprivation, and thus treat BPH while not lowering serum testosterone, 5-ARIs were developed and tested in large randomized controlled trials [11,12]. These trials showed favourable toxicity profiles of 5-ARIs and efficacy in the treatment of BPH. Subsequently, efforts to evaluate 5-ARIs in the setting of primary prostate cancer prevention have been undertaken through the Prostate Cancer Prevention Trial (PCPT) and Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trials using finasteride and dutasteride, respectively [5,6]. While both of these studies showed reductions in the diagnosis of low grade cancer associated with 5-ARI use, they also showed increases in the incidence of high grade disease among 5-ARI users. Owing to their association with the development of high-risk disease and because re-evaluation of the PCPT trial data showed a far more modest effect of finasteride on low grade prostate cancer, the US Food and Drug Administration (FDA) rejected the use of 5-ARIs in the setting of primary prevention [13,14].

The role of 5-ARIs in men with existing prostate cancer has been less clear. As these drugs have been shown to decrease the diagnosis of low grade prostate cancer, it is reasonable to hypothesize that 5-ARIs might also delay the progression of very low-risk prostate cancer into clinically significant disease. Nevertheless, the increased incidence of high-risk disease seen in previous trials may make clinicians think carefully about using these medications in men with diagnosed low-risk prostate cancer. Accordingly, we analysed the effects of 5-ARI use in men diagnosed with very low-risk prostate cancer to determine whether the initiation of 5-ARI treatment during AS would influence the risk of prostate cancer progression using biopsy reclassification as a proxy. We observed that 5-ARI use had a protective but

nonsignificant effect on biopsy reclassification during AS. Consistent with their effects on prostate cancer diagnosis, the protective effect of 5-ARIs was primarily seen in the prevention of reclassification by increased extent of low grade tumours over time (HR 0.37, $P=0.08$ for reclassification by extent vs 0.80, $P=0.71$ for reclassification by grade). As the present study is limited by a relatively small sample size, the effects on low grade tumour extent might be predicted to reach significance if more men could be analysed; however, this is far less likely for the marginally protective HR seen with grade reclassification. Importantly, although 5-ARI use is associated with the increased diagnosis of high grade prostate cancer, our findings suggest that the use of 5-ARIs in carefully followed men with LUTS and very-low risk prostate cancer is oncologically safe.

In contrast to our findings, a recent similarly powered study by Finelli *et al.* [8] reported that 5-ARI use in men with low-risk prostate cancer was the factor most associated with reduced risk of biopsy reclassification. Importantly, their study did not account for the variable time lag between enrolling in AS and initiation of 5-ARI use. In both the Finelli *et al.* study and the present study, to be included among the 5-ARI users in the AS cohort, men must have had no reclassification for a period of months to years *before* starting 5-ARIs. Thus, by definition, the total reclassification-free time for each 5-ARI user is artificially increased. The mean time from enrolling in AS to initiating 5-ARI use was not documented in the study by Finelli *et al.*, but in the present study the mean time was 2.4 (median 1.2) years, and for 28% (13/47 men) it was >4 years. This time lag in 5-ARI users translated into a mean of 3 biopsies (SD 2.4, median 2, range 0–9) that did not require reclassification before drug initiation, and thus introduced a substantial bias. 5-ARI use must therefore be modelled as a time-dependent covariate to control this artifact in reclassification-free survival. In fact, when we analysed our data using a standard Cox proportional hazards model (without considering 5-ARI use as a time-dependent covariate), we also saw a dramatic significant increase in reclassification-free survival among 5-ARI users, HR = 0.18 (95% CI 0.07 to 0.45, $P<0.001$), results that were similar to those of Finelli *et al.* [8].

Results from the PCPT trial have suggested that any rise in PSA level while on 5-ARIs may indicate the presence of prostate cancer, particularly high grade disease [6]. It has been proposed, therefore, that 5-ARIs might allow for elevated PSA levels to be more specific for the development of clinically significant prostate cancer and thus could allow AS protocols with increased interval between biopsies. For this reason, we describe the PSAV of men on 5-ARIs. Roughly one third of men taking 5-ARIs without biopsy reclassification had positive PSAVs and two of the four men with biopsy reclassification had negative PSAVs, both with high grade disease on biopsy. These results are consistent with those of van Leeuwen *et al.* [15], who found that 43% of men taking dutasteride and diagnosed with Gleason 7–10 disease in the REDUCE trial had stable or falling PSAs.

A major limitation of the present study is its retrospective nature. To attempt to control for this, we performed multivariable analysis using variables known to be associated with disease reclassification while on AS. Importantly, as stated above, we adjusted for the lead time before initiation of 5-ARI treatment and duration of drug use by treating 5-ARI use as a time-dependent covariate. The present study also had relatively short periods of drug

exposure to 5-ARIs with a mean time on 5-ARIs of 2.4 years. Finally, a minority of men in our AS programme used 5-ARIs which limited the study's power.

Currently, REDEEM, a randomized, double blind, placebo controlled trial for the effects of dutasteride use on 'progression' of low-risk prostate cancer has been completed with results not yet published, but presented at a recent FDA hearing and at a meeting of the Society for Urologic Oncology [13,16]. Importantly, the REDEEM study used disease 'progression' as an endpoint that included either biopsy reclassification or simply patient decision to pursue treatment, 'therapeutic progression'. Unfortunately the use of therapeutic progression confounds objective analysis of the effects of these drugs on low-risk prostate cancer and these endpoints were not separately analysed. Nevertheless, the REDEEM study showed no significant reduction in biopsy reclassification by grade in patients followed by scheduled biopsies, consistent with results seen in the present retrospective analysis.

In conclusion, in the present cohort of men with very low-risk prostate cancer, treatment with 5-ARIs had modest, nonsignificant effects on the time to prostate biopsy reclassification by increased grade with a more substantial, albeit still nonsignificant, protective effect on low grade tumour extent. As grade is the key predictor of prognosis, the present study does not support a role for 5-ARI use in the secondary prevention of clinically significant prostate cancer. Men with very low-risk prostate cancer taking 5-ARIs for LUTS are unlikely to be at increased risk for the occurrence of high grade disease.

Acknowledgments

A.E.R. was supported by Award Number T32DK007552 from the National Institute of Diabetes and Digestive Kidney Diseases. E.M.S. is an AUA Astellas Rising Star and has been given the Howard Hughes Medical Institute Physician Scientist Early Careers award.

Abbreviations

5-ARI	5- α reductase inhibitor
HR	hazard ratio
AS	active surveillance
PSAV	PSA velocity
FDA	US Food and Drug Administration

REFERENCES

1. Draisma G, Boer R, Otto SJ, et al. Lead times and overdiagnosis due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. *J Natl Cancer Inst.* 2003; 95 :868–78. [PubMed: 12813170]
2. Cooperberg MR, Broering JM, Kantoff PW, Carroll PR. Contemporary trends in low risk prostate cancer: risk assessment and treatment. *J Urol.* 2007; 178:S14–9. [PubMed: 17644125]
3. Ross AE, Loeb S, Landis P, et al. Prostate-specific antigen kinetics during follow-up are an unreliable trigger for intervention in a prostate cancer surveillance program. *J Clin Oncol.* 2010; 28 : 2810–6. [PubMed: 20439642]

4. Whitson JM, Porten SP, Hilton JF, et al. The relationship between prostate specific antigen change and biopsy progression in patients on active surveillance for prostate cancer. *J Urol*. 2011; 185:1656–60. [PubMed: 21419438]
5. Andriole GL, Bostwick DG, Brawley OW, et al. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med*. 2010; 362:1192–202. [PubMed: 20357281]
6. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med*. 2003; 349:215–24. [PubMed: 12824459]
7. Fleshner N, Gomella LG, Cookson MS, et al. Delay in the progression of low-risk prostate cancer: rationale and design of the Reduction by Dutasteride of Clinical Progression Events in Expectant Management (REDEEM) trial. *Contemp Clin Trials*. 2007; 28:763–9. [PubMed: 17573244]
8. Finelli A, Trottier G, Lawrentschuk N, et al. Impact of 5alpha-reductase inhibitors on men followed by active surveillance for prostate cancer. *Eur Urol*. 2011; 59:509–14. [PubMed: 21211899]
9. Tosoian JJ, Trock BJ, Landis P, et al. Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. *J Clin Oncol*. 2011; 29:2185–90. [PubMed: 21464416]
10. Tseng KS, Landis P, Epstein JI, Trock BJ, Carter HB. Risk stratification of men choosing surveillance for low risk prostate cancer. *J Urol*. 2010; 183:1779–85. [PubMed: 20304433]
11. McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med*. 2003; 349:2387–98. [PubMed: 14681504]
12. Roehrborn CG, Marks LS, Fenter T, et al. Efficacy and safety of dutasteride in the four-year treatment of men with benign prostatic hyperplasia. *Urology*. 2004; 63:709–15. [PubMed: 15072886]
13. FDA. [Accessed December 2010] Oncologic Drugs Advisory Committee Meeting regarding AVODART (dutasteride) NDA 21319/S0024. 2010. Available at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM234934>
14. FDA. [Accessed December 2010] Oncologic Drugs Advisory Committee Meeting regarding PROSCAR (finasteride) NDA 20180/S034. 2010. Available at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM234934>
15. van Leeuwen PJ, Kolble K, Huland H, Hambroek T, Barentsz J, Schroder FH. Prostate cancer detection and dutasteride: utility and limitations of prostate-specific antigen in men with previous negative biopsies. *Eur Urol*. 2011; 59:183–90. [PubMed: 21130560]
16. Fleshner N, Lucia M, Melich K, Nandy I, Black L, Rittmaster R. Dutasteride reduces prostate cancer progression and cancer diagnosis on re-biopsy in the REDEEM active surveillance study. *SUO*. 2011

What's known on the subject? and What does the study add?

Finasteride (Proscar) and dutasteride (Avodart) are 5- α reductase inhibitors (5-ARIs) used to treat LUTS in men with benign prostatic enlargement. Because these drugs suppress androgens, the theory has been put forward that 5-ARIs might prevent the development of prostate cancer. Careful analysis of two randomized controlled trials, however, showed that, in the clinical setting, this was not the case, and that these drugs can increase the occurrence of more aggressive high-grade disease. Because of this, the U.S. Food and Drug Administration did not approve 5-ARIs for the primary prevention of prostate cancer and notified healthcare professionals about a change in the 'Warnings and Precautions' for these drugs.

Interest remains among some for using 5-ARIs in men diagnosed with very low-risk prostate cancer to delay the progression from clinically indolent disease to clinically significant disease requiring treatment. The present study investigated whether 5-ARI use among men with very low-risk prostate cancer in an active surveillance (AS) programme would reduce the number of cancers reclassified to clinically significant disease on surveillance biopsy. Our results do not support the use of 5-ARIs for slowing or preventing cancer progression in men with low-risk prostate cancer, but do suggest that men with very low-risk prostate cancer who take 5-ARIs for LUTS are unlikely to be at increased risk for the development of high grade disease during AS.

FIG. 1.

Influence of 5-ARI use on PSA level during AS. **A**, PSA level plotted as a function of time of 5-ARI use. PSAs of men with subsequent biopsy reclassification are shown in solid red. **B**, Comparison of PSAV between men without and with biopsy reclassification as defined by unfavourable surveillance biopsy criteria.

TABLE 1

Characteristics at diagnosis of men without and with a history of 5-ARI use while on AS

Characteristic	All men	No 5-ARI use	5-ARI use	<i>P</i>
No. of men	587	540	47	
Age, years				
Median (range)	65 (45–82)	65 (45–82)	66 (54–79)	
Mean (SD)	65 (5.8)	65 (5.8)	66 (5.6)	0.265
%free PSA				
Median (range)	19.1 (1.2–55.7)	19.1 (1.2–55.7)	19.1 (8.7–37.2)	
Mean (SD)	20.4 (8.2)	20.4 (8.4)	20.0 (5.6)	0.924
PSA level (ng/mL)				
Median (range)	4.5 (0.2–19.0)	4.4 (0.2–19.0)	5.6 (1.5–11.9)	
Mean (SD)	4.7 (2.3)	4.6 (2.3)	5.7 (2.2)	<0.001
Prostate volume, mL				
Median (range)	47.9 (7.7–211.0)	46.3 (7.7–211.0)	67.0 (29.5–151.0)	
Mean (SD)	53.3 (24.9)	51.8 (24.2)	70.6 (26.8)	<0.001
PSA density				
Median (range)	0.09 (0.004–0.15)	0.09 (0.004–0.15)	0.08 (0.04–0.15)	
Mean (SD)	0.09 (0.03)	0.09 (0.03)	0.08 (0.03)	0.199
No. of cores with cancer				
Median (range)	1 (1–2)	1 (1–2)	1 (1–2)	
Mean (SD)	1.2 (0.4)	1.2 (0.4)	1.1 (0.3)	0.101
Maximum % core involvement with cancer				
Median (range)	1.0 (1.0–50.0)	4.5 (1.0–50.0)	1.0 (1.0–50.0)	
Mean (SD)	8.5 (11.3)	8.6 (11.3)	7.4 (11.7)	0.092

TABLE 2

Characteristics during AS of men without and with a history of 5-ARI use while on AS

Characteristic	All men	No 5-ARI use	5-ARI use	<i>P</i>
Time on AS, years				
Median (range)	2.0 (0–12.1)	2.0 (0–12.1)	4.2 (1.0–10.6)	
Mean (SD)	2.7 (2.3)	2.6 (2.1)	4.8 (3.0)	<0.001
No. of biopsies				
Median (range)	3 (1–12)	3 (1–12)	5.0 (2–12)	
Mean (SD)	3.7 (2.1)	3.5 (1.9)	5.5 (2.8)	<0.001
No. of biopsies while on 5-ARI				
Median (range)			2 (1–9)	
Mean (SD)			2.6(2.0)	NA
PSA (ng/mL) at last follow-up				
Median (range)	4.5 (0.3–22.0)	4.6 (0.3–22.0)	3.6 (1.1–9.7)	
Mean (SD)	5.0 (3.1)	5.1(3.1)	3.7 (2.0)	0.004
Last PSA level before 5-ARI use				
Median (range)		NA	6.0 (1.4–14.0)	
Mean (SD)			6.5 (3.0)	NA
Last PSA level while on 5-ARI				
Median (range)		NA	3.6 (1.1–10.4)	
Mean (SD)			3.7 (2.1)	NA
Prostate volume at last follow-up				
Median (range)	50.6 (8.0–184.0)	50.0 (8.0–184.0)	64.0 (30.0–175.0)	
Mean (SD)	57.7 (28.9)	56.8 (28.4)	67.8 (32.1)	0.014
Prostate volume before 5-ARI use				
Median (range)		NA	75.0 (29.5–151.0)	
Mean (SD)			76.9 (29.4)	NA
Last prostate volume on 5-ARI				
Median (range)		NA	64.5 (30.0–171.0)	
Mean (SD)			68.7 (31.0)	NA
Cancer progression, <i>n</i> (%)	177 (30.2)	169 (31.3)	8 (17.0)	0.041
Cancer progression by grade, <i>n</i> (%)	76 (13.0)	72 (13.3)	4 (8.5)	0.345
Cancer progression by volume, <i>n</i> (%)	141 (24.0)	136 (25.2)	5 (10.6)	0.025

TABLE 3

Univariable and multivariable Cox proportional hazards models for any biopsy reclassification during AS according to 5-ARI use and clinical findings at diagnosis, with 5-ARI use treated as a time-dependent covariate

Covariate	Univariate analysis	Multivariable analysis
	HR (95% CI)	HR (95% CI)
	<i>N</i> = 587; biopsy reclassification: <i>n</i> = 177	<i>N</i> = 587; biopsy reclassification: <i>n</i> = 177)
5-ARI use	0.58 (0.28–1.20), <i>P</i> = 0.140	0.55 (0.23–1.28), <i>P</i> = 0.164
α-blocker use	0.71 (0.48–1.05), <i>P</i> = 0.086	0.84 (0.54–1.30), <i>P</i> = 0.439
Age at diagnosis	1.05 (1.03–1.09), <i>P</i> = 0.0007	1.08 (1.04–1.11), <i>P</i> < 0.0001
PSA level at diagnosis	1.06 (0.998–1.12), <i>P</i> = 0.061	0.95 (0.83–1.09), <i>P</i> = 0.469
% free PSA at diagnosis	0.94 (0.92–0.96), <i>P</i> < 0.0001	0.94 (0.91–0.96), <i>P</i> < 0.0001
PSA density at diagnosis		
<0.090 (reference)	1	1
0.090	1.74 (1.28–2.38), <i>P</i> = 0.0004	1.70 (1.02–2.84), <i>P</i> = 0.043
2 positive cores at diagnosis	1.72 (1.23–2.42), <i>P</i> = 0.002	1.52 (1.04–2.23), <i>P</i> = 0.031
Maximum % of core involvement	1.02 (1.01–1.03), <i>P</i> = 0.0005	1.02 (1.01–1.04), <i>P</i> = 0.0005
Volume at diagnosis	1.00 (0.995–1.01), <i>P</i> = 0.809	1.01 (0.997–1.02), <i>P</i> = 0.152

TABLE 4

Univariable and multivariable Cox proportional hazards models for grade reclassification (Gleason pattern 4) on surveillance biopsy according to 5-ARI use and clinical findings at diagnosis, with 5-ARI use treated as a time-dependent covariate

Covariate	Univariate analysis	Multivariable analysis
	HR (95% CI)	HR (95% CI)
	<i>N</i> = 587; grade reclassification: <i>n</i> = 76	<i>N</i> = 587; grade reclassification: <i>n</i> = 76
5-ARI use	0.63 (0.22–1.76), <i>P</i> = 0.373	0.80 (0.25–2.59), <i>P</i> = 0.710
α-blocker use	0.38 (0.19–0.78), <i>P</i> = 0.008	0.53 (0.25–1.12), <i>P</i> = 0.094
Age at diagnosis	1.11 (1.06–1.16), <i>P</i> < 0.0001	1.13 (1.07–1.19), <i>P</i> < 0.0001
PSA level at diagnosis	1.11 (1.02–1.20), <i>P</i> = 0.014	0.98 (0.77–1.24), <i>P</i> = 0.840
% free PSA at diagnosis	0.92 (0.89–0.96), <i>P</i> < 0.0001	0.91 (0.87–0.95), <i>P</i> < 0.0001
PSA density at diagnosis		
<0.090 (reference)	1	1
0.090	3.09 (1.82–5.27), <i>P</i> < 0.0001	2.12 (0.90–5.02), <i>P</i> = 0.087
2 positive cores at diagnosis	1.50 (0.87–2.58), <i>P</i> = 0.141	1.14 (0.62–2.10), <i>P</i> = 0.675
Maximum % of core involvement	1.03 (1.01–1.05), <i>P</i> = 0.0011	1.03 (1.01–1.05), <i>P</i> = 0.002
Volume at diagnosis	1.00 (0.99–1.01), <i>P</i> = 0.785	1.00 (0.98–1.02), <i>P</i> = 0.894

TABLE 5

Univariable and multivariable Cox proportional hazards models for reclassification by cancer extent (>2 positive cores or >50% core involvement) on surveillance biopsy according to 5-ARI use and clinical findings at diagnosis, with 5-ARI use treated as a time-dependent covariate

Covariate	Univariate analysis	Multivariable analysis
	HR (95% CI)	HR(95% CI)
	<i>N</i> = 587; reclassification: <i>n</i> = 141	<i>N</i> = 587; reclassification: <i>n</i> = 141
5-ARI use	0.45 (0.18–1.11), <i>P</i> = 0.083	0.37 (0.12–1.13), <i>P</i> = 0.082
α-blocker use	0.72 (0.46–1.12), <i>P</i> = 0.141	0.94 (0.57–1.53), <i>P</i> = 0.793
Age at diagnosis	1.04 (1.01–1.08), <i>P</i> = 0.015	1.06 (1.02–1.11), <i>P</i> = 0.002
PSA level at diagnosis	1.03 (0.97–1.10), <i>P</i> = 0.346	0.88 (0.76–1.03), <i>P</i> = 0.107
% free PSA at diagnosis	0.94 (0.92–0.97), <i>P</i> < 0.0001	0.94 (0.91–0.96), <i>P</i> < 0.0001
PSA density at diagnosis		
<0.090 (reference)	1	1
0.090	1.63 (1.15–2.30), <i>P</i> = 0.005	1.86 (1.04–3.30), <i>P</i> = 0.036
2 positive cores at diagnosis	1.74 (1.19–2.54), <i>P</i> = 0.005	1.57 (1.02–2.42), <i>P</i> = 0.042
Maximum % of core involvement	1.02 (1.01–1.04), <i>P</i> = 0.001	1.03 (1.01–1.04), <i>P</i> = 0.001
Volume at diagnosis	1.00 (0.99–1.01), <i>P</i> = 0.922	1.01 (1.00–1.02), <i>P</i> = 0.038